CLINICAL STUDY PROTOCOL

Study Title:	**A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears (OPUS-2)**
SARcode Bioscience Protocol Number:	**1118–DRY–300**
Investigational Product:	**Lifitegrast ophthalmic solution**
IND Number:	**077885**
Indication:	**Dry eye disease**
Sponsor:	**SARcode Bioscience, Inc.** **1000 Marina Blvd, Suite 250** **Brisbane, CA 94005**
Development Phase:	**Phase 3**
SARcode Bioscience's Responsible Medical Officer:	[redacted], **MD**
Date of Amendment 1:	**September 6, 2013**
Date of Protocol:	**November 6, 2012**

Clinical Study Protocol Amendment Summary, Amendment 1

A description of protocol changes has been provided below. Note that the protocol synopsis (Section 2) was updated to be consistent with the changes made in the body of the protocol. The changes are **bolded** throughout the protocol document.

Section 2.1 – Schedule of Events

Footnote 14 was updated to correct the required timing of the final study drug dose at Visit 5.

Previous Language:

At Visit 5, subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 15 ± 5 minutes following the last study assessment.

Revised Language:

At Visit 5, subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 15 ± **15** minutes following the last study assessment.

Section 4 – LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

MedDRA acronym corrected.

Previous Language:

MedDRA Medical Dictionary for Regulatory Authorities

Revised Language:

MedDRA Medical Dictionary for Regulatory **Activities**

Section 8 – STUDY OBJECTIVES

Study objectives were updated to clarify that objectives will be measured in the designated study eye where appropriate. Symptom score objectives were updated to reflect that the measurement will be mean change from baseline rather than the Day 84 score.

Previous Language:

The co-primary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of:
    - Sign – inferior corneal fluorescein staining score (0 – 4 point scale) measured by mean change from baseline to Day 84
    - Symptom – eye dryness score (0 – 100 point visual analogue scale, OU) measured at Day 84
- To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered BID for 84 days.

The secondary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the secondary endpoints of:
    - Sign: total corneal staining score (0 – 12 point scale), mean change from baseline to Day 84.
    - Sign: nasal lissamine staining score (0 – 4 point scale), mean change from baseline to Day 84
    - Symptom: eye discomfort score (0 – 100 point VAS scale, OU), at Day 84
    - Symptom: ocular discomfort score (0 – 4 point scale), at Day 84

Revised Language:

The co-primary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of:
    - Sign – inferior corneal fluorescein staining score (0 – 4 point scale) measured by mean change from baseline to Day 84 **in the designated study eye**
    - Symptom – eye dryness score (0 – 100 point visual analogue scale, OU) measured **by mean change from baseline to** Day 84
- To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered BID for 84 days.

The secondary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the secondary endpoints of:
    - Sign: total corneal staining score (0 – 12 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye**.
    - Sign: nasal lissamine staining score (0 – 4 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye.**
    - Symptom: eye discomfort score (0 – 100 point VAS scale, OU), **measured by mean change from baseline to** Day 84.
    - Symptom: ocular discomfort score (0 – 4 point scale), **measured by mean change from baseline to** Day 84 **in the designated study eye.**

Section 9.7.1 – Primary Efficacy Outcome Measures

The co-primary ocular symptom outcome measure was changed to reflect that the measurement will be mean change from baseline rather than the Day 84 eye dryness score.

Previous Language:

Ocular Symptom

The subjective co-primary efficacy outcome measure is the eye dryness score (0 – 100 point VAS scale, OU) at Day 84.

Revised Language:

Ocular Symptom

The subjective co-primary efficacy outcome measure is the **mean change from baseline to Day 84 in** eye dryness score (0 – 100 point VAS scale, OU).

Section 9.7.2 – Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures related to ocular symptoms were changed to reflect that the measurement will be mean change from baseline rather than the Day 84 scores.

Previous Language:

Ocular Symptoms

- Eye discomfort score (0 – 100 point VAS scale, OU) – at Day 84
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye – at Day 84

Revised Language:

Ocular Symptoms

- Eye discomfort score (0 – 100 point VAS scale, OU) – **mean change from baseline to** Day 84
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye – **mean change from baseline to** Day 84

Section 9.7.3 – Tertiary Efficacy Outcome Measures

The tertiary efficacy outcome measures were updated to specify the fields for the corneal fluorescein staining score and the lissamine green staining score under Ocular Signs. The Ocular Symptoms were updated to specify that the trigger subscale is based on environmental triggers.

Previous Language:

Ocular Signs

The following ocular signs will be measured at every visit and mean change from baseline at every visit in the designated study eye:

- Corneal fluorescein staining score – all fields
- Lissamine green staining score – all fields
- Conjunctival redness score
- Schirmer tear test without anesthesia

Ocular Symptoms

The following ocular symptoms will be measured at every visit and mean change from baseline at every visit:

- 7-item VAS (0 – 100 scale, OU; burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, pain), each item scored individually
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye
- Total OSDI score (0 – 100 scale)
- Symptoms subscale OSDI score (0 – 4 scale; mean of Questions 1-5)
- Visual-related function subscale OSDI score (0 – 4 scale; mean of items from Questions 6-9)
- Trigger subscale OSDI score (0 – 4 scale; mean of items from Questions 10-12)

Revised Language:

Ocular Signs

The following ocular signs will be measured at every visit and mean change from baseline at every visit in the designated study eye:

- Corneal fluorescein staining score – **inferior, superior, central, and total (derived from the sum of the regions)**
- Lissamine green staining score – **nasal, temporal, and total (derived from the sum of the regions)**
- Conjunctival redness score
- Schirmer tear test without anesthesia

Ocular Symptoms

The following ocular symptoms will be measured at every visit and mean change from baseline at every visit:

- 7-item VAS (0 – 100 scale, OU; burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, pain), each item scored individually
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye
- Total OSDI score (0 – 100 scale)
- Symptoms subscale OSDI score (0 – 4 scale; mean of Questions 1-5)
- Visual-related function subscale OSDI score (0 – 4 scale; mean of items from Questions 6-9)
- **Environmental t**rigger subscale OSDI score (0 – 4 scale; mean of items from Questions 10-12)

Section 9.7.4 – Safety Outcome Measures

The t-test analysis to compare average drop comfort scores was removed.

Previous Language:

The incidence and severity of ocular adverse events and the incidence and severity of non-ocular adverse events will be reported.

The following safety assessments will be measured at every visit, except as noted. Descriptive analyses of these safety measures will be summarized by treatment at all time points:

- Best corrected visual acuity (BCVA)
- Slit lamp biomicroscopy
- Dilated fundoscopy (Visits 1 and 5 only)

A two-sample t–test will be used to compare the average drop comfort (0 – 10 scale; Visits 2 – 5 only) rating of 5.0% lifitegrast concentration to placebo. This test will be performed using the same methodology as used for the primary efficacy analysis.

Revised Language:

The incidence and severity of ocular adverse events and the incidence and severity of non-ocular adverse events will be reported.

The following safety assessments will be measured at every visit, except as noted. Descriptive analyses of these safety measures will be summarized by treatment at all time points:

- Best corrected visual acuity (BCVA)
- Slit lamp biomicroscopy
- Dilated fundoscopy (Visits 1 and 5 only)

Section 10 – ADVERSE EVENTS

The requirements for the follow-up of persisting adverse events was clarified and revised to only require discussion of ongoing ocular non-serious adverse events at study completion with the medical monitor.

Previous Language:

The reporting period for non–serious and serious AEs is the period from the subject signing the ICF continuing through the through the last study visit (Day 84, Visit 5). Events recorded prior to the use of IP will be distinguished from events recorded after starting the use of IP. The latter will be referred to as treatment-emergent AEs. If a non-serious AE remains unresolved at the conclusion of the study, the PI and Medical Monitor or designee will make a joint clinical assessment as to whether continued follow–up of the AE is warranted, and the results of this assessment must be documented. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Revised Language:

The reporting period for non–serious and serious AEs is the period from the subject signing the ICF continuing through the last study visit (Day 84, Visit 5). Events recorded prior to the use of IP will be distinguished from events recorded after starting the use of IP. The latter will be referred to as treatment-emergent AEs. If a non-serious**, ocular** AE remains unresolved at the conclusion of the **subject's participation in the** study, the PI **or designee should contact the** Medical Monitor **and** make a joint clinical assessment as to whether continued follow–up of the AE is warranted, and the results of this assessment must be documented. **All other non-serious AEs which remain unresolved at the conclusion of the subject's participation in the study should be assessed by the PI or physician designee and followed to resolution at his/her discretion.** Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Section 10.1 – Serious Adverse Events

The title and email address for [redacted] was updated.

Previous Language:

[redacted] MD, [redacted]
SARcode Bioscience, Inc.
1000 Marina Blvd, Suite 250
Brisbane, CA 94005

Office: [redacted]
Cell: [redacted]
Fax: [redacted]
Email: [redacted]

Revised Language:

[redacted], MD
SARcode Bioscience, Inc.
1000 Marina Blvd, Suite 250
Brisbane, CA 94005

Office: [redacted]
Cell: [redacted]
Fax: [redacted]
Email: [redacted]

Section 14.2 – Study Populations

The randomized study population was added.

Previous Language:

- Intent-to-Treat (ITT) – The ITT population includes all randomized subjects who receive at least one dose of study medication. Imputation methods will be used to address missing data for efficacy analyses.
- Safety Population – The Safety population includes all randomized subjects who receive at least one dose of study medication.

Revised Language:

- **Randomized – The Randomized population includes all subjects who are randomized.**
- Intent-to-Treat (ITT) – The ITT population includes all randomized subjects who receive at least one dose of study medication. Imputation methods will be used to address missing data for efficacy analyses.
- Safety Population – The Safety population includes all randomized subjects who receive at least one dose of study medication.

Section 14.6 – Primary Efficacy Analysis

The primary efficacy analysis of the inferior corneal fluorscein staining was clarified to reflect that the change from baseline is measured to Day 84. The primary efficacy analysis of the eye dryness score was updated to reflect that the analysis will be the mean change from baseline to Day 84 rather than at Day 84. The testing and stratification were specified.

Previous Language:

The primary analysis of the objective efficacy endpoint of mean change from baseline in inferior corneal fluorescein staining will be performed using a stratified two-sample t-test (i.e., analysis of variance) comparing lifitegrast ophthalmic solution to placebo in the Intent to-Treat (ITT) population with Last Observation Carried Forward (LOCF). The stratification factors used for randomization will be used for this analysis. The individual strata will contribute to the overall analysis proportionate to their size as suggested by Anello (2005).

The primary analysis of the subjective efficacy endpoint of the eye dryness score, at Day 84, will be performed using a two-sample t-test comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF).

Revised Language:

The primary analysis of the objective efficacy endpoint of mean change from baseline **to Day 84** in inferior corneal fluorescein staining will be performed using a stratified two-sample t-test (i.e., **ANOVA**) comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). The stratification factors used for randomization will be used for this analysis. **The ANOVA model will include treatment, strata and the interaction between treatment and strata.**

The primary analysis of the subjective efficacy endpoint of the eye dryness score, **mean change from baseline to** Day 84, will be performed using a **stratified** two-sample t-test **(i.e., ANOVA)** comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). **The stratification**

factors used for randomization will be used for this analysis. The ANOVA model will include treatment, strata and the interaction between treatment and strata.

The stratified, two-sample t-test will be performed using the LSMEANS statement in PROC MIXED with the option to specify weights for combining the between-treatment group estimate from each stratum. The between-treatment group estimates from each stratum will be combined using the number of subjects in each stratum as the weights as proposed by Lin (1999). The individual strata will contribute to the overall analysis proportionate to their size as suggested by Anello (2005).

Section 14.9 – Safety Analysis

The t-test analysis to compare average drop comfort scores was removed.

Previous Language:

All safety analyses will be performed on the safety population. Descriptive analyses of safety measures including visual acuity, slit lamp biomicroscopy and dilated fundoscopy will be summarized by treatment at all time points. For analyses of treatment emergent AEs, descriptive summaries will be based upon AEs with the greatest severity. A two-sample t-test will be used to compare the average drop comfort rating of 5.0% lifitegrast concentration to placebo.

Revised Language:

All safety analyses will be performed on the safety population. Descriptive analyses of safety measures including visual acuity, slit lamp biomicroscopy and dilated fundoscopy will be summarized by treatment at all time points. For analyses of treatment emergent AEs, descriptive summaries will be based upon AEs with the greatest severity.

Section 19 – REFERENCES

Reference citation for Lin (1999) inserted in response to new text in Section 14.6 Primary Efficacy Analysis.

Section 21 – SIGNATURE PAGE

SARcode Bioscience protocol number updated to Amendment 1. The title on the Sponsor signature line was updated.

Previous Language:

SARcode Bioscience Protocol Number: 1118-DRY-300

Accepted for the Sponsor:

On behalf of SARcode Bioscience, Inc., I confirm that SARcode Bioscience, Inc., as a Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the PI is informed of all relevant information that becomes available during the conduct of this study.

[redacted] Medical Monitor's Signature Date

Printed name: [redacted] MD

Revised Language:

SARcode Bioscience Protocol Number: 1118-DRY-300**, Amendment 1**

Accepted for the Sponsor:

On behalf of SARcode Bioscience, Inc., I confirm that SARcode Bioscience, Inc., as a Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the PI is informed of all relevant information that becomes available during the conduct of this study.

Medical Monitor's Signature Date

Printed name: [redacted] MD

Section 22 – APPENDICES

Appendix 3: Procedure for the Ocular Discomfort Score (ODS) Assessment

The instructions were updated to clarify that the ocular discomfort score assessment should be conducted by site personnel and subjectively graded by the subject.

Previous Language:

Ocular discomfort scores will be subjectively graded by the subjects according to the following scale (rating each eye separately):

Revised Language:

Assessment of ocular discomfort scores will be **conducted by site personnel and will be** subjectively graded by the subjects according to the following scale (rating each eye separately):

Section 22 – APPENDICES

Appendix 10: Procedure for Evaluating Conjunctival Staining with Lissamine Green

The instructions were corrected to reflect that two regions of both eyes are scored rather than three.

Previous Language:

Score each of the three regions of both eyes using the modified grading scale of 0–4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

Revised Language:

Score each of the **two** regions of both eyes using the modified grading scale of 0–4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

2 SYNOPSIS

NAME OF COMPANY SARcode Bioscience, Inc. 1000 Marina Blvd, Suite 250 Brisbane, CA 94005 **NAME OF FINISHED PRODUCT:** Lifitegrast ophthalmic solution, 5.0% **NAME OF ACTIVE INGREDIENT:** (S)–2–(2–benzofuran–6–carbonyl) –5,7–dichloro–1,2,3,4–tetrahydroisoquinoline–6–carboxamido)–3–(3–(methylsulfonyl) phenyl) propanoic acid	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE OF STUDY:

A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears (OPUS-2)

PROTOCOL NUMBER:

1118–DRY–300

STUDY SITES:

Multicenter study involving approximately 20 sites located in the United States

STUDY PERIOD:	**PHASE OF DEVELOPMENT:**
Approximately 14 weeks	Phase 3

OBJECTIVES:

The primary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of:
    - Sign – inferior corneal fluorescein staining score (0 – 4 point scale) measured by mean change from baseline to Day 84 **in the designated study eye**
    - Symptom – eye dryness score (0 – 100 point visual analogue scale, OU) measured **by mean change from baseline to** Day 84
- To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered BID for 84 days.

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The secondary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the secondary endpoints of:
    - Sign: total corneal staining score (0 – 12 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye**.
    - Sign: nasal lissamine staining score (0 – 4 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye**.
    - Symptom: eye discomfort score (0 – 100 point VAS scale, OU), **measured by mean change from baseline to** Day 84.
    - Symptom: ocular discomfort score (0 – 4 point scale), **measured by mean change from baseline to** Day 84 **in the designated study eye**.

METHODOLOGY:

Study Design

Multicenter, randomized, prospective, double–masked, placebo–controlled, parallel–arm design with block enrollment stratified by inferior corneal staining score ($\leq$ / $>$ 1.5) and eye dryness score ($<$ / $\geq$ 60). Approximately 700 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either lifitegrast ophthalmic solution (5.0%) or placebo solution as topical ophthalmic drops administered bilaterally BID for 84 days (12 weeks). Subjects, Sponsor, CROs and site personnel will be masked to treatment assignments.

The total number of expected participants, including screen failures, is approximately 1,300 subjects.

Screening Period (Day –14 ± 3 to Day 0)

The screening period consists of two visits (Visit 1, Day -14 ± 3) and a confirmatory visit (Visit 2, Day 0). Subjects must have an inferior corneal staining (ICS) score of $\geq$ 0.5 point (0 – 4 point scale with allowance for 0.5 point increments) in at least one eye at Visit 1 (screening #1) and replicate

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the score of ≥ 0.5 point in the *same eye* at Visit 2 (confirmatory screening #2) in order to continue to be eligible for the study. The worst (highest ICS score) eye meeting these requirements will be designated as the **study eye**.

Visit 1: Day –14 ± 3 – Screening #1

- **Evaluation** After informed consent is obtained from study subjects, subjects will undergo preliminary screening that includes obtaining demographic data, subject-reported height and weight, medical and medication history, inclusion/exclusion criteria evaluation, urine pregnancy test (as appropriate), completion of subject questionnaires [visual analogue scale (VAS), ocular discomfort score (ODS), and ocular surface disease index (OSDI)], undergo ocular examination assessments [best corrected visual acuity (BCVA), slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), Schirmer tear test (STT) without anesthesia] and collection of adverse events (AEs).
- Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)
- Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the <u>*same eye*</u>:

  (1) Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)

  (2) STT (without anesthesia) ≥ 1 and ≤ 10 mm

Following the screening procedures at this visit, all subjects who meet all eligibility criteria and have a positive response (as defined above) will undergo dilated fundoscopy.

Subjects who continue to meet eligibility criteria will ***self-administer*** their initial dose of placebo drops (open–label, single drop, approximately 50 µL/drop volume, OU, from the same vial), for training purposes, at the study site under supervision of trained study personnel **30 ± 15 minutes** following the last study assessment. **Only a single dose of placebo drops will be administered OU from the same vial on Day –14.**

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Prior to discharge from the study site on Day –14 (Visit 1), subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated on self-administration of placebo. Subjects will be instructed to self–administer one drop BID in each eye in the morning and the evening just prior to bedtime until screening Visit 2. Subjects will be scheduled for Visit 2 during Visit 1. Subjects will be instructed NOT to instill placebo drops on the morning of their next scheduled study visit (Visit 2, Day 0).

Days –13 thru Day –1

Subjects will begin out–patient self–administered open–label BID placebo treatment in the morning and the evening just prior to bedtime of Day –13 and continue through Day –1 (the day prior to Visit 2).

Placebo will be provided in single–use unit dose vials. Subjects will administer a single drop (approximately 50 µL/drop volume, OU, from the same vial) in the morning and the evening just prior to bedtime and report adverse events.

Visit 2: ***Day 0 – Confirmatory Screening, Randomization and Baseline Visit***

- Baseline values for efficacy measures will be established at this visit.
- Open-label placebo vials will be collected.
- Site staff must confirm subjects have NOT administered their morning placebo dose at home.
- **Evaluation (Screening #2)** Subjects will undergo preliminary screening that includes inclusion/exclusion criteria evaluation, AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires [visual analogue scale (VAS), ocular discomfort score (ODS), ocular surface disease index (OSDI)] and undergo ocular examination assessments [best corrected visual acuity (BCVA), slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and Schirmer tear test (STT) without anesthesia].
- Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)

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- Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:

  (1) Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)

  (2) STT (without anesthesia) ≥ 1 and ≤ 10 mm

  If both eyes meet the two criteria above, the eye with the greater score in inferior corneal staining at Visit 2 will be selected as the study eye. If both eyes have equal scores in inferior corneal staining at Visit 2, then the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal inferior corneal staining and STT scores at Visit 2, the right eye (OD) will be selected as the study eye.

Following a **20 ± 15-minute** waiting period after the screening procedures at this visit, all subjects will receive their last dose of placebo drops (open–label, 2 drops *each* eye, approximately 50 µL/drop volume, OU) at the study site by trained study personnel.

All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria for Visit 2 will be randomized to one of two treatment arms.

Treatment Period (Day 0 to Day 84 ± 8; Visits 2–5)

Day 0 (Visit 2): Randomized subjects will receive their initial dose of study drug (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel **30 ± 15 minutes** following the last dose of placebo drops administered by trained study personnel. **Only a single dose of randomized study drug will be administered OU from the same vial on Day 0.** A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following initial dosing (post–randomization) at Visit 2.

Prior to discharge from the study site on Visit 2 (Day 0), randomized subjects will be educated on self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self-administer study drug on the morning of their next scheduled study visit (Visit 3, Day 14). Subjects will be scheduled for Visit 3 during Visit 2.

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Day 1 to 13: Subjects will begin out–patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 1 and continue through Day 13 (the day prior to Visit 3). Study drug will be provided in single–use unit dose vials. Subjects will administer a single drop (approximately 50 µL /drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs.

Day 14 ± 3 (Visit 3): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) for Day 14 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 3. The subject, just prior to bedtime, will administer the evening dose at home.

Prior to discharge from the study site on Visit 3 (Day 14), subjects will be educated on self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 4 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4, Day 42). Subjects will be scheduled for Visit 4 during Visit 3.

Day 15 thru 41: Subjects will continue out-patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 15 and continue through Day 41 (the day prior to Visit 4). Study drug will be provided in single–use unit dose vials. Subjects will administer a single drop, (approximately 50 µL/drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs.

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Day 42 ± 4 (Visit 4): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) for Day 42 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 4. The subject, just prior to bedtime, will administer the evening dose at home.

Prior to discharge from the study site on Visit 4 (Day 42), subjects will be educated on self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5, Day 84). Subjects will be scheduled for Visit 5 during Visit 4.

Day 43 thru 83: Subjects will continue out–patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 43 and continue through Day 83 (the day prior to Visit 5). Study drug will be provided in single–use unit dose vials. Subjects will self-administer a single drop, (approximately 50 µL/drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs.

Day 84 ± 8 (Visit 5): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

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Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 5.

Following drop comfort evaluation, subjects will undergo final ocular examination assessments (BCVA and slit lamp biomicroscopy) and then dilated fundoscopy at the end of the visit. Subjects will then exit the study treatment. The total duration of study participation including screening and treatment is anticipated to be approximately 100 days (~14 weeks).

NUMBER OF SUBJECTS PLANNED:

Approximately 700 subjects with history of active artificial tear use (within 30 days prior to Visit 1) will be enrolled in the study. The total number of expected participants, including screen failures, is approximately 1,300 subjects.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

INCLUSION CRITERIA:

Individuals eligible to participate in this study must meet all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and HIPAA documents after the nature of the study has been explained and prior to initiation of Visit 1 procedures or exams
2. Willing and able to comply with all study procedures
3. Be at least 18 years of age at the time of enrollment
4. Male or female

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5. PRN or scheduled use of non-prescription (over-the-counter) artificial tear substitute for symptoms of dry eye within past 30days prior to Visit 1 and willing to suspend use of tear substitutes 72 hours prior to Visit 1 until completion of the study
6. Best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1
7. Patient–reported history of dry eye in both eyes
8. Corneal fluorescein staining score ≥ 2 (0–4 point scale) in at least one region in at least one eye at Visits 1 and 2
9. Conjunctival redness score ≥ 1 (0–4 point scale with allowance for 0.5 point increments) in at least one eye at Visits 1 and 2
10. Eye dryness score ≥ 40 (0-100 point VAS scale, OU) at Visits 1 and 2
11. A positive response in at least one eye, defined as meeting ALL of the following criteria in the *same eye* at both Visits 1 and 2:
    (1) Inferior corneal fluorescein staining score ≥ 0.5 (0–4 point scale with allowance for 0.5 point increments)
    (2) STT (without anesthesia) ≥ 1 and ≤ 10 mm
12. A negative urine pregnancy test if female of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal–oral, implantable, injectable, or transdermal contraceptives; mechanical–spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner.
13. Subjects with secondary Sjögren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosis) or other autoimmune diseases (e.g., multiple sclerosis, inflammatory bowel disease) are eligible for enrollment consideration provided the subject meets all other inclusion and exclusion criteria, AND, are not in a medical state – in the opinion of the Principal Investigator – that could interfere with study parameters, are not taking

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systemic/ocular steroids, and are not immunodeficient/immunosuppressed (e.g., receiving systemic immunomodulating or immunosuppressive drugs to manage their baseline medical state).

EXCLUSION CRITERIA:

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Contraindications to the use of the study drug(s)
2. Known hypersensitivity to study drug or its components
3. Received treatment with any concentration of lifitegrast ophthalmic solution, not including lifitegrast vehicle (placebo), in a previous clinical trial.
4. Any ocular condition that, in the opinion of the Investigator, could affect study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation.
5. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
6. Active or history of ocular herpes; any other ocular infection within the last 30 days
7. Unwilling to avoid wearing contact lenses for 7 days prior to and for duration of the study period
8. Positive urine pregnancy test or nursing an infant
9. Any blood donation or significant loss of blood within 56 days of Visit 1
10. Any history of immunodeficiency disorder, HIV, positive hepatitis B, C, or evidence of acute active hepatitis A (anti–HAV IgM), or organ or bone marrow transplant

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11. Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre–study washout period (see below) and during the study. Prohibited medications include topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti–inflammatory eye drops) for the duration of the study. The appropriate pre–study washout period is as follows:

    (1) Antihistamines (including ocular): 72 hours prior to Visit 1

    (2) Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period

    (3) Topical cyclosporine: 6 weeks prior to Visit 1

    (4) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

    (5) Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study; antihistamines are not allowed at any time during the study

    (6) All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1

12. Any significant chronic illness that, in the opinion of the Investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes
13. Use of any investigational product or device within 30 days prior to Visit 1 or during the study period
14. History of laser–assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any scheduled ocular surgical procedure during the study period
15. History of YAG-laser posterior capsulotomy in past 6 months prior to Visit 1

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16. Known history of alcohol and/or drug abuse within the past 12 months, that in the opinion of the Principal Investigator, may interfere with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject
17. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatrical pemphigoid) or destruction of conjunctival goblet cells (as with Vitamin A deficiency) are not eligible for the study. Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that, in the opinion of the Principal Investigator, will not interfere with study compliance and/or outcome measures are not excluded from the study.

DOSE, ROUTE AND REGIMEN:

Screening: Between Visits 1 and 2, all subjects will receive 14 consecutive days (± 3 days) of open-label placebo ocular drops self–administered BID in both eyes in the morning and the evening just prior to bedtime.

Treatment: During the 12–week (84 ± 8 days) treatment period, lifitegrast ophthalmic solution 5.0% concentration or placebo solution will be administered BID by bilateral topical ocular dosing. Subjects will be randomized to one of two treatment arms (1:1) and receive study drug following the last dose of placebo drops administered by trained study personnel after assessments at Visit 2.

DURATION OF TREATMENT:

Approximately 84 days (12 weeks)

REFERENCE THERAPY, DOSE, ROUTE AND REGIMEN:

Open–label placebo solution (placebo) will be provided to subjects from Day –14 to Day 0. Placebo ocular drops will be self–administered BID in both eyes in the morning and the evening just prior to bedtime.

Following randomization at Visit 2, subjects assigned to receive placebo will be dosed according to the same schedule as the lifitegrast ophthalmic solution concentration.

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OUTCOME MEASURES:

Primary Efficacy Outcome Measures:

The co-primary efficacy outcome measures are:

- Sign: inferior corneal fluorescein staining score (0 – 4 point scale with allowance for 0.5 point increments) in the designated study eye – mean change from baseline to Day 84
- Symptom: eye dryness score (0 – 100 point VAS scale, OU) – **mean change from baseline to** Day 84

Secondary Efficacy Outcome Measures:

The secondary efficacy outcome measures are:

- Sign: total corneal staining score (0 – 12 point scale) – in the designated study eye – mean change from baseline to Day 84
- Sign: nasal lissamine score (0 – 4 point scale) – in the designated study eye – mean change from baseline to Day 84
- Symptom: eye discomfort score (0 – 100 point VAS scale, OU) – **mean change from baseline to** Day 84
- Symptom: ocular discomfort score (0 – 4 point scale) – in the designated study eye – **mean change from baseline to** Day 84

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Tertiary Efficacy Outcome Measures:

Ocular Signs

The following ocular signs will be measured at every visit and mean change from baseline at every visit in the designated study eye:

- Corneal fluorescein staining score – **inferior, superior, central, and total (derived from the sum of the regions)**
- Lissamine green staining score – **nasal, temporal, and total (derived from the sum of the regions)**
- Conjunctival redness score
- Schirmer tear test without anesthesia

Ocular Symptoms

The following ocular symptoms will be measured at every visit and mean change from baseline at every visit:

- 7-item VAS (0 – 100 scale, OU; burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, pain), each item scored individually
- Ocular discomfort score (ODS, 0 – 4 scale) – in the designated study eye
- Total OSDI score (0 – 100 scale)
- Symptoms subscale OSDI score (0 – 4 scale; mean of Questions 1-5)
- Visual-related function subscale OSDI score (0 – 4 scale; mean of items from Questions 6-9)
- **Environmental t**rigger subscale OSDI score (0 – 4 scale; mean of items from Questions 10-12)

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Safety Outcome Measures:

- Incidence and severity of ocular adverse events
- Incidence and severity of non-ocular adverse events
- Best corrected visual acuity at all visits
- Slit lamp biomicroscopy at all visits
- Drop comfort assessment (0 – 10 scale; Visits 2 – 5)
- Dilated fundoscopy (Visits 1 and 5)

STATISTICAL METHODS:

Analysis Populations

Randomized: all randomized subjects.

Intent-to-Treat (ITT): all subjects randomized that receive at least one dose of study medication.

Safety: all subjects randomized that receive **at least one dose of** study medication.

Primary Efficacy Analysis

The primary analysis of the objective efficacy endpoint of mean change from baseline **to Day 84 in** inferior corneal fluorescein staining will be performed using a stratified two-sample t-test (i.e., analysis of variance **[ANOVA]**) comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). The stratification factors used for randomization will be used for this analysis. **The ANOVA model will include treatment, strata and the interaction between treatment and strata.**

The primary analysis of the subjective efficacy endpoint of **the eye dryness score, mean change from baseline to Day 84,** will be performed using a **stratified** two-sample t-test **(i.e., ANOVA)** comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). **The stratification factors used for randomization will be used for this analysis. The ANOVA model will include treatment, strata and the interaction between treatment and strata.**

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Secondary Efficacy Analysis

The co-primary efficacy endpoints will also be analyzed using additional statistical methods, including a non-parametric Wilcoxon rank sum test (LOCF) and repeated measures ANOVA for confirmation (no imputation). Secondary efficacy endpoints will be analyzed similarly to the primary analysis for the co-primary efficacy endpoints.

Tertiary Efficacy Analysis

Tertiary efficacy endpoints will be analyzed using the same statistical methods as the primary and secondary efficacy endpoints. However, tertiary analyses will only be performed on the ITT population with LOCF.

Safety Analysis

All safety analyses will be performed on the safety population. All safety measures including visual acuity, slit lamp biomicroscopy, and dilated fundoscopy will be summarized descriptively by treatment at all time points.

Power and Sample Size

For the primary ocular sign, based on the results of the OPUS-1 Phase 3 study, it is reasonable to expect a 0.25 unit difference in lifitegrast ophthalmic solution and placebo in the mean change from baseline to Day 84 in inferior corneal staining, with a common standard deviation of 0.95 units. Under these assumptions, a sample size of 350 per group will yield approximately 93% power to show a significant difference at the $\alpha = 0.05$ level using a two-sample t-test.

For the primary ocular symptom, based on the results of the OPUS-1 Phase 3 study, it is reasonable to expect a 10.0 unit difference in lifitegrast ophthalmic solution and placebo at Day 84 in the mean eye dryness score, with a common standard deviation of 40 units. Under these assumptions, a sample size of 350 per group will yield approximately 91% power to show a significant difference at the $\alpha = 0.05$ level using a two-sample t-test.

It is expected that no subjects will be excluded from the primary analysis due to missing data given the proposed primary analysis method.

2.1 Schedule of Events

Procedure	Visit 1 Day – 14 ± 3	Days –13 – –1	Visit 2 Day 0			Days 1–13	Visit 3 Day 14 ± 3	Days 15–41	Visit 4 Day 42 ± 4	Days 43–83	Visit 5 Day 84 ± 8	ET/ UNS[1]
			Pre-Random-ization	Random-ization	Post-Random-ization							
Informed Consent	X											
Demographic data	X											
Height and Weight (Subject-reported)	X											
Medical History/Medication History[2]	X											
Concomitant Medication Review			X				X		X		X	X
Inclusion/Exclusion Criteria[3]	X		X									
Urine Pregnancy Test[4]	X		X				X		X		X	X
Subjective Measures												
Visual Analogue Scale (VAS)[5]	X		X				X		X		X	X
Ocular Discomfort Score (ODS)[6]	X		X				X		X		X	X
Ocular Surface Disease Index (OSDI)	X		X				X		X		X	X
Drop Comfort[7]					X		X		X		X	
Objective Measures												
Best Corrected Visual Acuity (BCVA)[8]	X		X				X		X		2X	X
Slit lamp Biomicroscopy[9]	X		X				X		X		2X	X
Conjunctival Redness Score[10]	X		X				X		X		X	X
Corneal Staining (fluorescein)[11]	X		X				X		X		X	X
Conjunctival Staining (lissamine)[12]	X		X				X		X		X	X
Schirmer Tear Test (w/o anesthesia)	X		X				X		X		X	X
Dilated Fundoscopy[13]	X										X	X

Procedure	Visit 1 Day – 14 ± 3	Days –13 – –1	Visit 2 Day 0			Days 1–13	Visit 3 Day 14 ± 3	Days 15–41	Visit 4 Day 42 ± 4	Days 43–83	Visit 5 Day 84 ± 8	ET/ UNS[1]
			Pre-Random-ization	Random-ization	Post-Random-ization							
Study Therapy												
Open-label Placebo Administration at Study Site[14]	X		X									
Placebo Dispensation (Open–label) [15]	X											
Open-label Placebo Administration at Home [14]		X										
Placebo Vial Collection[16]			X									X
Randomization[17]				X								
Study Drug Administration at Study Site[14]					X		X		X		X	
Study Drug Dispensation[18]					X		X		X			
Study Drug Administration at Home [18]						X	X	X	X	X		
Study Drug Collection[18]							X		X		X	X
Adverse Event Assessment[19]	X	X	X		X	X	X	X	X	X	X	X
Study Exit											X	X

[1] ET/UNS: Early Termination and Unscheduled Visit Assessments.

[2] Only significant non–ocular medical history during the past year; only medications taken within the past 60 days. Artificial Tear Use should be within the past 30 days prior to Visit 1.

[3] Subjects must replicate the following findings in the *same eye* at Visits 1 and 2 in order to be considered for further study eligibility:

(1) Inferior corneal fluorescein staining score ≥ 0.5 points (0 – 4 point scale with allowance for 0.5 point increments), and

(2) STT without anesthesia ≥ 1 and ≤ 10 mm, at Visits 1 and 2

If both eyes meet the two criteria above, the eye with the greater in inferior corneal staining at Visit 2 will be selected as the study eye. If both eyes have an equal inferior corneal staining score at Visit 2, the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal score in inferior corneal staining and equal STT scores at Visit 2, the right eye (OD) will be selected as the study eye.

[4] Women of childbearing potential only.

[5] 7-item Visual Analogue Scale (0 – 100 point scale, OU): burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, pain.

[6] Ocular discomfort score (0 – 4 point scale).

[7] Drop comfort assessments (0 – 10 scale) are obtained in each eye immediately, then at 1, 2, and 3 minutes following instillation of the study drug. At Visits 2, 3, 4, and 5 – drop comfort assessments will be conducted following the initial dosing of the day. For all drop comfort assessments, subjects will be administered study drug by trained study personnel.

[8] A Best Corrected Visual Acuity (BCVA) assessment will be measured prior to open-label placebo administration at Visit 1 and prior to study drug administration at Visits 2, 3, 4 and 5. At Visit 5, a second BCVA assessment will also be measured after the final study drug dose has been administered at the site by trained study personnel.

[9] A slit lamp examination will be performed prior to open-label placebo administration at Visit 1 and prior to study drug administration at Visits 2, 3, 4 & 5. At Visit 5, a second slit lamp examination will be performed after the final study drug dose has been administered at the site by trained study personnel.

[10] 0 – 4 point scale with allowance for 0.5 point increments.

[11] 0 – 4 point scale with allowance for 0.5 point increments using 3 corneal regions (superior, central, inferior).

[12] 0 – 4 point scale with allowance for 0.5 point increments using 2 conjunctival regions (nasal, temporal).

[13] Dilated fundoscopy should be performed at the end of Visits 1 and 5.

[14] At Visit 1, after achieving a positive response, as defined by the protocol and noted above in footnote #4, subjects will self-administer open–label placebo drops in both eyes, for training purposes, at the study site under the supervision of trained study personnel **30 ± 15 minutes** following the last study assessment. **Only a single dose of placebo drops will be administered OU, from the same vial, on Day –14 (Visit 1).**

Following the screening procedures at Visit 2, all subjects will receive their last dose of placebo drops (open–label, 2 drops *each* eye, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel **20 ± 15 minutes** following the last study assessment. All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria for Visit 2 will be randomized to one of two treatment arms.

At Visit 2, following randomization, subjects will be administered the initial dose of randomized study drug **30 ± 15 minutes** after the last dose of placebo drops administered by trained study personnel. **Only a single dose of randomized study drug will be administered OU on Day 0 (Visit 2).**

At Visits 3 and 4, subjects will receive their first dose of the day by trained study personnel following a **15 ± 15 minutes** after **the last study assessment**; the second dose of the day will be administered at home, by the subject, in the evening just prior to bedtime.

At Visit 5, subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 15 ± 15 minutes following the last study assessment.

Subjects will then perform a drop comfort assessment immediately and then at 1, 2 and 3 minutes following initial dosing at Visit 2 (post-randomization study drug dosing) and Visit 3, 4 and 5.

[15] Open-label placebo vials will be dispensed at Visit 1 and will be self–administered by the subjects at home on Days –13 – –1. The open-label placebo vials will be collected at Visit 2. Upon return of the open-label placebo vials, site staff must confirm subjects have NOT administered their morning dose at home for Visit 2.

[16] Placebo vials will be collected at Visit 2. Site staff must confirm subjects have NOT administered their morning placebo dose at home for Visit 2.

[17] All subjects having a positive response (as defined above in footnote #3) and meeting all other screening eligibility criteria after Visit 2 will be randomized.

[18] Randomized study drug vials will be dispensed post-randomization at Visits 2, 3 and 4. The study drug will be collected at the visit following the visit when they were dispensed. Upon study drug return, site staff must confirm subjects have NOT administered their morning dose at home for Visits 3, 4 and 5. Study drug will be self–administered by the subjects at home on Days 1–13, Days 15–41 and Days 43–83.

[19] Adverse Event reporting will begin after each subject signs an Informed Consent Form and continue through the end of the last study visit, Visit 5 (Day 84), or early termination assessment.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredients
BCVA	Best Corrected Visual Acuity
BID	Bis In Die (Two Times Daily)
CAE	Controlled Adverse Environment
CD	Compact Disk
CDA	Clinical Data Analyst
CDM	Clinical Data Manager
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HAV	Hepatitis A
HIV	Human Immunodeficiency Virus
ICAM	Intercellular Adhesion Molecule
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inferior Corneal Staining
IgM	Immunoglobulin M
IL	Interleukin
IND	Investigational New Drug
IOP	Intraocular Pressure

IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web-based Response System
KCS	Keratoconjunctivitis Sicca
LASIK	Laser–assisted in situ keratomileusis
LDPE	Low Density Polyethylene
LFA–1	Lymphocyte Function–associated Antigen–1
LIF	Lifitegrast
LOCF	Last Observation Carried Forward
LogMAR	Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory **Activities**
MW	Molecular Weight
N	Number
NA	Not Applicable
ND	Not Done
OSDI	Ocular Surface Disease Index
OU	Oculus Uterque (Each eye or Both eyes)
PI	Principal Investigator
PK	Pharmacokinetics
PRN	Pro Re Nata - use as needed
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR 1118	Lifitegrast
SD	Standard Deviation
STT	Schirmer Tear Test
STZ	Streptozotocin
TEAE	Treatment Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TID	Ter In Die (Three Times Daily)

TNF	Tumor Necrosis Factor
UNK	Unknown
UNS	Unscheduled study visit
US	United States
USA	United States of America
VA	Visual Acuity
VAS	Visual Analogue Scale
YAG-laser	yttirum aluminum garnet laser (synonymous term, Nd:YAG - neodymium doped)

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use." (from E6 ICH)

The terms "IP" and "study drug" may be used interchangeably in the protocol.

5 ETHICS

5.1 Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation that the Institutional Review Board (IRB) or Ethics Committee (EC) is properly constituted and compliant with ICH Guidelines and GCP requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/EC will be provided to SARcode Bioscience or designee. The Principal Investigator (PI) will provide the IRB/EC with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all consent forms translated to a language other than the native language of the clinical site. The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/EC confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the PI and copies are received at SARcode Bioscience or designee. The approval document should refer to the study by protocol title and SARcode Bioscience 1118–DRY–300 (if possible), identify the documents reviewed, and include the date of the review and approval. SARcode Bioscience or designee will ensure that the appropriate reports on the progress of the study were made to the IRB/EC and SARcode Bioscience by the PI in accordance with applicable governmental regulations.

5.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

1. US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
2. E6 International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice

Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject, or his/her legally authorized representative will provide written, informed consent before any study–related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with E6 ICH (GCP Guideline, Section 4.8) and 21 CFR §50 and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to SARcode Bioscience for approval prior to submission to the IRB/EC. SARcode Bioscience and the IRB/EC must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet, and all ICFs translated to a language other than the native language of the clinical site must also be received by SARcode Bioscience prior to the delivery of IP.

The Investigator will provide copies of the signed ICF to each subject and will maintain the original in the subject's file.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the PI at each site must provide to SARcode Bioscience or designee a fully executed and signed Form FDA 1572 and a Financial Disclosure Form. All sub–Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub–Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of research subjects in this study.

The study will be administered by and monitored by employees or representatives of SARcode Bioscience or designee. Clinical Research Associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. SARcode Bioscience's Regulatory Affairs Department or designee will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

7 INTRODUCTION

Lifitegrast (formerly "SAR 1118") is a potent and selective small molecule LFA–1 antagonist (MW 615.4) that is formulated as an unpreserved, buffered sterile eye drop intended for the treatment of patients with signs and symptoms of dry eye disease.

A comprehensive review of lifitegrast is contained in the Investigator's Brochure supplied by SARcode Bioscience; the Investigator must review this document and confirm receipt prior to initiating the study.

7.1 Nonclinical Studies

The nonclinical program for lifitegrast was designed to characterize the pharmacology, pharmacokinetics and toxicology of the compound in vitro and in vivo. The in vivo characterization includes the intended clinical route of administration, ocular drops, to assess local effects on ocular tissue. In addition, studies using the intravenous (IV) route of administration assessed the systemic effects of lifitegrast.

Both in vitro and in vivo data support the potential for lifitegrast to be safe and effective in humans. In vitro pharmacology studies showed that lifitegrast inhibited Jurkat immortalized human T–cell line's attachment to ICAM–1 with increasing dose. A side–by–side comparison of lifitegrast and a known direct competitive LFA–1 antagonist in this assay demonstrated comparable dose dependent inhibition of cell attachment and LFA–1 antagonism by lifitegrast (Gadek, 2002, Science), (Keating, 2006, Protein Sci). In a study with stimulated human peripheral blood mononucleocytes (PBMC), lifitegrast demonstrated potent inhibition of the release of a panel of inflammatory cytokines [Interleukins (IL) 1, 2, 3, 4, 5, 13; Interferon γ, TNFα), particularly the T–cell regulating cytokines, IL–2 and IL–4, with increasing dose (Murphy, 2011, Invest Ophthalmol Vis Sci). Results from a clinical pharmacology trial in dogs with spontaneously occurring keratoconjunctivitis sicca (KCS) showed that treating dogs for 12 weeks with ocular drops of lifitegrast (3x/day; 1% concentration) produced symptomatic improvements and significantly improved a key clinical endpoint in KCS patients, the Schirmer's tear test ($p<0.05$; ANCOVA) (Murphy, 2011, Invest Ophthalmol Vis Sci). Lifitegrast inhibition of retinal leukostasis and vascular leakiness following topical ocular administration (1 and 5% dose strengths TID for 2 months) was assessed in a rodent streptozotocin (STZ)-induced diabetic retinopathy model (Rao, 2010, Invest Ophthalmol Vis Sci), which showed that lifitegrast eye drops (1% and 5% TID) significantly reduced leukostasis and blood-retinal barrier leakage in a dose-dependent manner. Topical administration of lifitegrast (0.1% and 1.0% TID) resulted in significant inhibition (~50% reduction in neutrophil count) of corneal inflammation in a murine model of corneal inflammation.

Results from safety pharmacology studies to evaluate the effects of lifitegrast on the respiratory, cardiovascular and central nervous system were unremarkable, as were those

from three genotoxicity studies. Ocular administration of lifitegrast (up to 3.15 mg/eye/day) for up to 13 weeks to rabbits and dogs produced no treatment–related adverse findings in clinical chemistry or histopathologic analyses. The most notable treatment–related findings from these studies were blepharospasm (squinting) noted sporadically in a few rabbits given 3.15 mg/eye/day shortly following dosing and a dose–related transient irritative response characterized by squinting, blinking and tearing that was observed in the 28–day dog study, to which all affected animals acclimated (i.e., clinical signs resolved despite repeated exposure to lifitegrast). In a 9-month study of TID ocular administration to rabbits, the frequency of squinting, tearing and blinking tended to diminish with repeated administration of lifitegrast, such that after Day 29, these symptoms were infrequent in animals given the highest dose (1.75 mg/eye/dose, TID; 5.25mg/eye/day). There were no adverse lifitegrast treatment-related findings in clinical ocular examinations (including intraocular pressure [IOPs], pachymetry measurements, and electroretinography [ERGs]) across all toxicology studies nor were adverse lifitegrast-related effects noted in clinical or anatomic pathology or histopathology parameters.

These nonclinical findings support the continued clinical evaluation of lifitegrast in human subjects.

7.2 Previous Clinical Studies

7.2.1 Phase 1 Safety and Pharmacokinetics in Healthy Adult Subjects

A Phase 1 multicenter, randomized, prospective, double–masked, placebo–controlled study of escalating doses of topical lifitegrast ophthalmic solution was conducted in 4 cohorts (0.1%, 0.3%, 1%, 5%) in 28 healthy adults (7 subjects per cohort: 5 received lifitegrast ophthalmic solution and 2 received placebo solution) (Semba, 2010, J Ocul Pharmacol Ther). The dosing schedule (OU) was divided into 3 periods, each separated by a 72-hour wash–out interval: once/day x 1 day, twice/day x 10 days, and thrice/day x 10 days. Slit lamp, BCVA, Schirmer tear tests, TFBUT, IOP were assessed at screening and the beginning and end of each period. For each cohort, masked safety data was reviewed by a Safety Committee prior to allowing dose-escalation of the next cohort. A total of 2856 doses (102 drops/subject) were administered over 1148 subject study days (41 study days/subject) in 56 eyes.

No serious or severe ocular or non–ocular AEs occurred during the study; there were 38 ocular (N=11 subjects) and 21 non–ocular (N=11 subjects) adverse events, respectively. All subjects in all cohorts completed the study and no study drug doses were missed. AEs were generally transient and mild in severity. No overall dose–related safety trends were observed when analyzed by cohort or by period.

Ocular Adverse Events: Most of the ocular adverse events (87%) occurred in placebo and 0.3% lifitegrast groups. The distribution of ocular adverse events is outlined in Table 7.2.1.1.

Table 7.2.1.1: Ocular Adverse Events

		0.1%	0.3%	1.0%	5.0%	Placebo	Total
Period 1 Single dose	Event(s)	0	5	0	0	6	11
	Subject(s)	0	2	0	0	3	3*
Period 2 BID dosing 10 days	Event(s)	1	6	1	2	4	14
	Subject(s)	1	2	1	1	1	6*
Period 3 TID dosing 10 days	Event(s)	0	8	0	1	4	13
	Subject(s)	0	3	0	1	1	5*
Total	Event(s)	1	19	1	3	14	38
	Subject(s)	1	5	1	1	5	11*

* Unique subjects; some subjects assigned to lifitegrast reported an adverse event in eye receiving placebo drop in Period 1

The most commonly reported ocular AEs considered possibly related to lifitegrast administration were (in descending frequency): eye irritation (N=3; 2 subjects), ocular hyperemia (N=3; 2 subjects), eyelid pain (N=2; 2 subjects), eye pruritus (N=2; 2 subjects), asthenopia (N=2; 1 subject), dark circles under the eye (N=2; 1 subject), dry eye (N=2; 1 subject), eye discharge (N=1), and blurred vision (N=1).

Non–Ocular Adverse Events: Most of the non–ocular adverse events (76%) occurred in the placebo (N=5 events; 3 subjects) and 0.3% lifitegrast (N=11; 4 subjects) groups. The most commonly reported non–ocular AEs considered related to study drug treatment were (by frequency): headache (N=5; 4 subjects) and dysgeusia (N=1; 1 subject).

The pharmacokinetic profile demonstrated adequate exposure for all lifitegrast doses when administered BID. There was no evidence of drug accumulation in tear or plasma. A comprehensive summary of the Phase 1 study is provided in the Investigator's Brochure. Overall, topical lifitegrast ophthalmic solution administered to healthy adult subjects up to 5.0% TID appears safe and well–tolerated.

7.2.2 Phase 2 Study in Subjects with Dry Eye

A Phase 2 multicenter, randomized, double-masked, placebo-controlled study was conducted in 230 dry eye subjects (M 51: F 179; mean age 62.3 yrs) selected with the Controlled Adverse Environmental (CAE) Model (Semba, 2012, Am J Ophthalmol). Principle eligibility criteria included exacerbation in corneal staining and ocular symptoms with CAE exposure, no active meibomian gland disease/blepharitis, and Schirmer tear test (STT; mm) > 1 and < 10. After a 2-week open-label vehicle wash-out, eligible subjects were randomized 1:1:1:1 to lifitegrast (0.1%, 1.0%, 5.0%) or placebo (vehicle) administered BID for 12 wks. Ocular

signs and symptoms (OSDI) were assessed at 2, 6, and 12 weeks. No supplemental artificial tears were allowed during the course of treatment. Primary outcome variable was inferior corneal staining (ICS; environmental).

The study demonstrated clinically relevant dose-responses for lifitegrast in ICS at Week 12 ($p=0.0566$, repeat measures). Mean change from baseline to Week 12 analysis showed significant improvement ($p<0.05$) and dose-response in ICS and OSDI visual-related functions (ability to read, drive at night, use computer, watch television). Statistical significance and/or statistical trends with dose-response were observed with other variables including total OSDI score (visual-related functions, triggers, symptoms), STT, and total corneal staining score. STT showed improved tear production at 2 weeks ($p<0.05$) and a consistent dose-response through Week 12 ($p=0.09$) for lifitegrast subjects vs. placebo. Adverse events (AEs) were mostly mild and transient in nature with no severe ocular AEs. Lifitegrast 5.0% showed increased instillation site AEs relative to placebo but events appear limited only to the initial dose of drug.

Lifitegrast topical ophthalmic solution demonstrated improvements ($p<0.05$; 1.0, 5.0%) in signs (corneal staining) and symptoms (visual-related function OSDI sub-scale) compared to placebo and appears safe and well-tolerated when administered BID over 12 weeks.

7.2.3 Phase 3 Study in Subjects with Dry Eye (OPUS-1)

A Phase 3 multicenter, randomized, double-masked, placebo-controlled study was conducted in 588 dry eye subjects (M 142: F 446; mean age 60.6 yrs) selected with the Controlled Adverse Environmental (CAE) Model; 565 subjects completed the study (96.1%). The design and study population was similar to the prior Phase 2 except the CAE was utilized only during subject screening (Visits 1 and 2). Principle eligibility criteria included exacerbation in corneal staining and ocular symptoms with CAE exposure, no active meibomian gland disease/blepharitis, and Schirmer tear test (STT; mm) ≥ 1 and ≤ 10. After a 2-week open-label vehicle wash-out, eligible subjects were randomized 1:1 to lifitegrast (5.0%) or placebo (vehicle) administered BID for 12 wks. Ocular signs and symptoms (OSDI) were assessed at 2, 6, and 12 weeks. No supplemental artificial tears were allowed during the course of treatment. The co-primary efficacy outcome variables were inferior corneal staining (ICS; environmental), and visual-related function subscale of the OSDI.

Statistically significant results were observed for the primary efficacy variable of inferior corneal fluorescein staining score and key symptoms.

There were no serious ocular AEs. A total of 415 ocular AEs occurred in 245 subjects as follows (AEs [subjects]): 113[73] placebo and 302[172] 5.0% LIF. The most frequently reported ocular events for 5.0% LIF were instillation site irritation (23.5%), pain (21.5%), and reaction (17.1%); the majority of these events were mild and transient in nature and occurred only on the initial administration of 5.0% LIF (“first dose reaction”).

7.3 Study Rationale

The purpose of this study is to confirm the efficacy and safety of a 5.0% concentration of lifitegrast ophthalmic solution as compared to placebo in the treatment of the signs and symptoms of dry eye following 12 weeks of BID dosing in an adequate and well-controlled Phase 3 study.

Lifitegrast ophthalmic solution is a potent antagonist of LFA–1 and is under investigation for the treatment of the signs and symptoms in symptomatic dry eye patients. The Phase 2 and 3 studies of lifitegrast in dry eye subjects demonstrated statistically significant improvements in both inferior corneal staining and key ocular symptoms.

7.4 Summary of Overall Risks and Benefits

Lifitegrast has been safe and well-tolerated across all clinical studies (refer to the Investigator's Brochure) involving a total of 906 adult subjects. No severe ocular adverse events (AEs) have been observed. Most ocular AEs are transient and mild to moderate in nature. The most commonly reported ocular AEs are transient instillation site irritation pain and reaction, particularly with 5.0% lifitegrast. This appears to be associated only with the initial dose.

Non-ocular AEs appear to be transient and mild to moderate in nature. The most commonly reported non-ocular AEs are dysgeusia and headache. A total of 12 SAEs have occurred (all non-ocular); none were reported as drug-related and no pattern has emerged to suggest a relationship to lifitegrast.

Overall, in the dry eye population, the benefits of lifitegrast appear to outweigh the risks. The Phase 3 program will collect further confirmatory evidence in a large sample size and establish the efficacy and safety profile of lifitegrast ophthalmic solution (5.0%) for dry eye.

8 STUDY OBJECTIVES

The co-primary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of:
    - Sign – inferior corneal fluorescein staining score (0 – 4 point scale) measured by mean change from baseline to Day 84 **in the designated study eye**
    - Symptom – eye dryness score (0 – 100 point visual analogue scale, OU) measured **by mean change from baseline to** Day 84
- To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered BID for 84 days.

The secondary objectives of the study are:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in subjects currently using artificial tears as assessed by the secondary endpoints of:
    - Sign: total corneal staining score (0 – 12 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye**.
    - Sign: nasal lissamine staining score (0 – 4 point scale), **measured by** mean change from baseline to Day 84 **in the designated study eye.**
    - Symptom: eye discomfort score (0 – 100 point VAS scale, OU), **measured by mean change from baseline to** Day 84.
    - Symptom: ocular discomfort score (0 – 4 point scale), **measured by mean change from baseline to** Day 84 **in the designated study eye.**

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, prospective, double–masked, placebo-controlled, parallel-arm design. Subjects will be randomized to one of the following treatment arms at Visit 2 and will be instructed to follow a BID-dosing regimen for 12 weeks:

- Lifitegrast 5.0% ophthalmic solution (N~350)
- Placebo, (lifitegrast vehicle) ophthalmic solution (N~350)

Study Design

Multicenter, randomized, prospective, double–masked, placebo–controlled, parallel–arm design with block enrollment stratified by inferior corneal staining score (≤ / > 1.5) and eye dryness score (< / ≥ 60). Approximately 700 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either lifitegrast ophthalmic solution (5.0%) or placebo solution as topical ophthalmic drops administered bilaterally BID for 84 days (12 weeks). Subjects, Sponsor, CROs and site personnel will be masked to treatment assignments.

The study will be conducted in two periods: screening and treatment.

The total number of expected participants, including screen failures, is approximately 1,300 subjects

Screening Period (Day –14 ± 3 to Day 0)

The screening period consists of two visits (Visit 1, Day -14 ± 3) and a confirmatory visit (Visit 2, Day 0). Subjects must have an inferior corneal staining (ICS) score of ≥ 0.5 point (0 – 4 point scale with allowance for 0.5 point increments) in at least one eye at Visit 1 (screening #1) and replicate the score of ≥ 0.5 point in the *same eye* at Visit 2 (confirmatory screening #2) in order to continue to be eligible for the study. The worst (highest ICS score) eye meeting these requirements will be designated as the **study eye**.

Visit 1: Day –14 ± 3 – Screening #1

- **Evaluation** After informed consent is obtained from study subjects, subjects will undergo preliminary screening that includes obtaining demographic data, subject-reported height and weight, medical and medication history, inclusion/exclusion criteria evaluation, urine pregnancy test (as appropriate), completion of subject questionnaires [visual analogue scale (VAS), ocular discomfort score (ODS), and ocular surface disease index (OSDI)], undergo ocular examination assessments [best corrected visual acuity (BCVA), slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), Schirmer tear test (STT) without anesthesia] and collection of adverse events (AEs).

Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)

Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:

1. Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)
2. STT (without anesthesia) ≥ 1 and ≤ 10 mm

Following the screening procedures at this visit, all subjects who meet all eligibility criteria and have a positive response (as defined above) will undergo dilated fundoscopy.

Subjects who continue to meet eligibility criteria will ***self-administer*** their initial dose of placebo drops (open–label, single drop, approximately 50 µL/drop volume, OU, from the same vial), for training purposes, at the study site under supervision of trained study personnel **30 ± 15 minutes** following the last study assessment. **Only a single dose of placebo drops will be administered OU from the same vial on Day –14.**

Prior to discharge from the study site on Day –14 (Visit 1), subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated on self-administration of placebo. Subjects will be instructed to self–administer one drop BID in each eye in the morning and the evening just prior to bedtime until screening Visit 2. Subjects will be scheduled for Visit 2 during Visit 1. Subjects will be instructed NOT to instill placebo drops on the morning of their next scheduled study visit (Visit 2, Day 0).

Days –13 thru Day –1

Subjects will begin out–patient self–administered open–label BID placebo treatment in the morning and the evening just prior to bedtime of Day –13 and continue through Day –1 (the day prior to Visit 2).

Placebo will be provided in single–use unit dose vials. Subjects will administer a single drop (approximately 50 µL/drop volume, OU, from the same vial) in the morning and the evening just prior to bedtime and report adverse events.

Visit 2: Day 0 – Confirmatory Screening, Randomization and Baseline Visit

- Baseline values for efficacy measures will be established at this visit.
- Open-label placebo vials will be collected.
- Site staff must confirm subjects have NOT administered their morning placebo dose at home.
- **Evaluation (Screening #2)** Subjects will undergo preliminary screening that includes inclusion/exclusion criteria evaluation, AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires [visual analogue scale (VAS), ocular discomfort score (ODS), ocular surface disease index (OSDI)] and

undergo ocular examination assessments [best corrected visual acuity (BCVA), slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and Schirmer tear test (STT) without anesthesia].

Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)

Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:

1. Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)
2. STT (without anesthesia) ≥ 1 and ≤ 10 mm

   If both eyes meet the two criteria above, the eye with the greater score in inferior corneal staining at Visit 2 will be selected as the study eye. If both eyes have equal scores in inferior corneal staining at Visit 2, then the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal inferior corneal staining and STT scores at Visit 2, the right eye (OD) will be selected as the study eye.

Following a **20 ± 15-minute** waiting period after the screening procedures at this visit, all subjects will receive their last dose of placebo drops (open–label, 2 drops *each* eye, approximately 50 µL/drop volume, OU) at the study site by trained study personnel.

All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria for Visit 2 will be randomized to one of two treatment arms.

Treatment Period (Day 0 to Day 84 ± 8; Visits 2–5)

Day 0 (Visit 2): Randomized subjects will receive their initial dose of study drug (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel **30 ± 15 minutes** following the last dose of placebo drops administered by trained study personnel. **Only a single dose of randomized study drug will be administered OU from the same vial on Day 0.** A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following initial dosing (post-randomization) at Visit 2.

Prior to discharge from the study site on Visit 2 (Day 0), randomized subjects will be educated on self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self-administer study drug on the morning of their next scheduled study visit (Visit 3, Day 14). Subjects will be scheduled for Visit 3 during Visit 2.

Day 1 to 13: Subjects will begin out–patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 1 and continue through Day 13 (the day prior to Visit 3). Study drug will be provided in single–use unit dose vials. Subjects will

administer a single drop (approximately 50 µL /drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs.

Day 14 ± 3 (Visit 3): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) for Day 14 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 3. The subject, just prior to bedtime, will administer the evening dose at home.

Prior to discharge from the study site on Visit 3 (Day 14), subjects will be educated on self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 4 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4, Day 42). Subjects will be scheduled for Visit 4 during Visit 3.

Day 15 thru 41: Subjects will continue out-patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 15 and continue through Day 41 (the day prior to Visit 4). Study drug will be provided in single–use unit dose vials. Subjects will administer a single drop, (approximately 50 µL/drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs

Day 42 ± 4 (Visit 4): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) for Day 42 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be

performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 4. The subject, just prior to bedtime, will administer the evening dose at home.

Prior to discharge from the study site on Visit 4 (Day 42), subjects will be educated on self-administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5, Day 84). Subjects will be scheduled for Visit 5 during Visit 4.

Day 43 thru 83: Subjects will continue out–patient self–administered study drug treatment (BID) in the morning and the evening just prior to bedtime of Day 43 and continue through Day 83 (the day prior to Visit 5). Study drug will be provided in single–use unit dose vials. Subjects will self–administer a single drop, (approximately 50 µL/drop volume, OU, from the same vial) during waking hours in the morning and the evening just prior to bedtime. Subjects will be instructed to report AEs.

Day 84 ± 8 (Visit 5): Study drug vials will be collected. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows:

Subjects will undergo AE and concomitant medication review, urine pregnancy test (as appropriate), completion of subject questionnaires (VAS, ODS, OSDI), and undergo ocular examination assessments [BCVA, slit lamp biomicroscopy, conjunctival redness scoring, corneal and conjunctival staining (with fluorescein and lissamine green, respectively), and STT without anesthesia].

Subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 5.

Following drop comfort evaluation, subjects will undergo final ocular examination assessments (BCVA and slit lamp biomicroscopy) and then dilated fundoscopy at the end of the visit. Subjects will then exit the study treatment. The total duration of study participation including screening and treatment is anticipated to be approximately 100 days (~14 weeks).

9.2 Discussion of Study Design, Including Choice of Control Group

The proposed study design is common for Phase 3 studies assessing safety in dry eye subjects. A placebo control is included to aid in distinguishing study drug–related adverse effects from study drug–unrelated effects, and to confirm the efficacy and safety of lifitegrast ophthalmic solution (5.0%) vs. placebo in the treatment of the signs and symptoms of dry eye.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and HIPAA documents after the nature of the study has been explained and prior to initiation of Visit 1 procedures or exams
2. Willing and able to comply with all study procedures
3. Be at least 18 years of age at the time of enrollment
4. Male or female
5. PRN or scheduled use of non-prescription (over-the-counter) artificial tear substitute for symptoms of dry eye within past 30days prior to Visit 1 and willing to suspend use of tear substitutes 72 hours prior to Visit 1 until completion of the study
6. Best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1
7. Patient–reported history of dry eye in both eyes
8. Corneal fluorescein staining score ≥ 2 (0–4 point scale) in at least one region in at least one eye at Visits 1 and 2
9. Conjunctival redness score ≥ 1 (0–4 point scale with allowance for 0.5 point increments) in at least one eye at Visits 1 and 2
10. Eye dryness score ≥ 40 (0-100 point VAS scale, OU) at Visits 1 and 2
11. A positive response in at least one eye, defined as meeting ALL of the following criteria in the *same eye* at both Visits 1 and 2:
    (1) Inferior corneal fluorescein staining score ≥ 0.5 (0–4 point scale with allowance for 0.5 point increments)
    (2) STT (without anesthesia) ≥ 1 and ≤ 10 mm
12. A negative urine pregnancy test if female of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post–menopausal [12 months after last menses]) and must use adequate birth control throughout the study period. Adequate birth control is defined as hormonal–oral, implantable, injectable, or transdermal contraceptives; mechanical–spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner.
13. Subjects with secondary Sjögren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosis) or other autoimmune diseases (e.g., multiple sclerosis, inflammatory

bowel disease) are eligible for enrollment consideration provided the subject meets all other inclusion and exclusion criteria, AND, are not in a medical state – in the opinion of the Principal Investigator – that could interfere with study parameters, are not taking systemic/ocular steroids, and are not immunodeficient/immunosuppressed (e.g., receiving systemic immunomodulating or immunosuppressive drugs to manage their baseline medical state).

9.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Contraindications to the use of the study drug(s)
2. Known hypersensitivity to study drug or its components
3. Received treatment with any concentration of lifitegrast ophthalmic solution, not including lifitegrast vehicle (placebo), in a previous clinical trial.
4. Any ocular condition that, in the opinion of the Investigator, could affect study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation.
5. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
6. Active or history of ocular herpes; any other ocular infection within the last 30 days
7. Unwilling to avoid wearing contact lenses for 7 days prior to and for duration of the study period
8. Positive urine pregnancy test or nursing an infant
9. Any blood donation or significant loss of blood within 56 days of Visit 1
10. Any history of immunodeficiency disorder, HIV, positive hepatitis B, C, or evidence of acute active hepatitis A (anti–HAV IgM), or organ or bone marrow transplant
11. Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre–study washout period (see below) and during the study. Prohibited medications include topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti–inflammatory eye drops) for the duration of the study. The appropriate pre–study washout period is as follows:

    (1) Antihistamines (including ocular): 72 hours prior to Visit 1

(2) Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period

(3) Topical cyclosporine: 6 weeks prior to Visit 1

(4) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

(5) Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study; antihistamines are not allowed at any time during the study

(6) All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1

12. Any significant chronic illness that, in the opinion of the Investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes
13. Use of any investigational product or device within 30 days prior to Visit 1 or during the study period
14. History of laser–assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any scheduled ocular surgical procedure during the study period
15. History of YAG-laser posterior capsulotomy in past 6 months prior to Visit 1
16. Known history of alcohol and/or drug abuse within the past 12 months, that in the opinion of the Principal Investigator, may interfere with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject
17. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatrical pemphigoid) or destruction of conjunctival goblet cells (as with Vitamin A deficiency) are not eligible for the study. Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that, in the opinion of the Principal Investigator, will not interfere with study compliance and/or outcome measures are not excluded from the study.

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects (or their legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and/or Sponsor and in accordance with his/her clinical judgment. However, it is encouraged that the Investigator contact the Sponsor, when possible, to discuss possible reasons for discontinuation prior to

withdrawing a subject from the study. When possible, the tests and evaluations listed for the early termination (ET) visit should be carried out (see Section 12.4).

SARcode Bioscience must be notified of all subject withdrawals as soon as possible. SARcode Bioscience also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or SARcode Bioscience may withdraw a subject from the study include, but are not limited to the following:

- Subject experiences a serious or intolerable AE
- Subject requires medication prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow–up
- Subject becomes pregnant

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after two attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor (or designee), regulatory agencies, and IRB/EC. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country–specific regulations, such as HIPAA in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. At Visit 1, each subject will be assigned a screening (subject) number upon signing the informed consent. All screening numbers will be assigned by the site in strict numerical sequence and no numbers will be skipped or omitted (e.g., each subject will be assigned to the lowest screening number available). Prior to initiation of study drug treatment, all qualified subjects will be assigned a randomization number. All subject numbers will be assigned using an Interactive Web

Response System (IWRS), accounting for the stratification factors of the subject's baseline inferior corneal fluorescein staining and eye dryness scores. Subject numbers will be assigned in a strict numerical sequence and no numbers will be skipped or omitted.

This unique identifier will be on all eCRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Randomized subjects that drop–out from the study will not be replaced.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will receive twice-daily doses (BID) of either 5.0% lifitegrast ophthalmic solution or placebo administered to the ocular surface as an eye drop.

9.4.2 Identity of Investigational Product (IP)

Lifitegrast is a small molecule inhibitor of LFA–1.

9.4.2.1 Product Characteristics and Labeling

Study drug will be supplied as a sterile, clear, colorless liquid solution containing 5.0% API (lifitegrast) concentration in 5 cavity single dose, 0.99 mL low–density polyethylene (LDPE) unit dose vials with a fill volume of approximately 0.2 mL. Each mL of a 5.0% solution contains 50 mg of the API. In addition to lifitegrast, the components of the drug product solution are: sodium chloride, sodium thiosulfate, dibasic sodium phosphate, sodium hydroxide and sterile water.

The placebo solution consists of all components of the drug product solution with the exception of lifitegrast.

9.4.3 Storage and Labeling

At the study site, all IP must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated qualified clinical site personnel. All IP must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, ICH Guidelines, GCPs and study procedures.

Lifitegrast and placebo solutions may be stored at room temperature (59 to 77°F or 15 to 25°C). Sterile drug product and placebo solutions are packaged into single–use 0.99 mL LDPE unit dose vials that deliver an approximate per drop volume of 50 µL. Five cavity unit dose vials are packaged in aluminum foil pouches under nitrogen. Unit dose vials are for SINGLE USE ONLY.

At a minimum, the immediate or secondary study drug packaging will provide the following information: study sponsor identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), study identification and manufacture date.

9.4.4 Directions for Administration

During the treatment period of 12 weeks (± 8 days), the study drug will be administered as single drops (approximately 50 µL/drop volume) in both eyes BID schedule, OU, from the same vial, in the morning and the evening just prior to bedtime according to the following schedule:

- **Day –14 ± 3 (Visit 1):** For training purposes, the initial dose of open–label placebo drops will be self-administered OU by the subject at the study site under the supervision of trained study personnel 30 ± 15 minutes following the last study assessment after the Post–CAE. **Only a single dose of placebo drops will be administered OU from the same vial on Day –14.**
- **Days –13 to –1:** BID schedule (OU, in the morning and the evening just prior to bedtime) of placebo drops administered by subject at home.
- **Day 0 (Visit 2):** The final dose of open–label placebo (2 drops *each* eye, approximately 50 µL/drop volume, OU) will be administered following a 20 ± 15–minute waiting period after the screening procedures at this visit. Randomized subjects will be administered their initial dose of randomized study drug (a single drop, approximately 50 µL/drop volume, OU, from the same vial) at the study site by trained study personnel 30 ± 15 minutes following last dose of placebo drops administered by trained study personnel. **Only a single dose of randomized study drug will be administered OU on Day 0.**
- **Days 1 to 13:** BID schedule (OU, in the morning and the evening just prior to bedtime) of randomized study drug administered by subject at home
- **Day 14 ± 3 (Visit 3)**: Subjects will receive their first study drug dose (a single drop, OU, from the same vial) for Day 14 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. The subject, just prior to bedtime, will administer the evening dose at home.
- **Day 15 to 41**: BID schedule (OU, in the morning and the evening just prior to bedtime) of randomized study drug administered by subject at home**.**
- **Day 42 ± 4 (Visit 4)**: The first study drug dose for Day 42 will be administered OU, from the same vial, at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. The subject, just prior to bedtime, will administer the evening dose at home.

- **Day 43 to 83**: BID schedule (OU, in the morning and the evening just prior to bedtime) of randomized study drug administered by subject at home**.**
- **Day 84 ± 8 (Visit 5)**: The final study drug dose (Day 84) will be administered OU, from the same vial at the study site by trained study personnel at least 15 ± 15 minutes following the last study assessment.

The individual instilling the study drug dose may not be the clinical evaluator conducting Investigator assessments of the primary and secondary efficacy and safety endpoints.

After randomization, subjects will be dispensed the same study drug for BID administration at home (in the morning and the evening just prior to bedtime), OU, between Visits 2, 3, 4 and 5.

IP solutions should be administered at room (ambient) temperature throughout the study period.

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to receive 5.0% lifitegrast ophthalmic solution or placebo solution based on a 1:1 ratio [lifitegrast (5.0%):placebo] within the randomization strata using permuted blocks.

Randomization will be centralized across study centers, stratified by Visit 2 inferior corneal fluorescein staining score ($\leq$ / > 1.5) and by eye dryness score (< / $\geq$ 60) in the study eye in order to ensure balance amongst the treatment groups. An IWRS will be used to facilitate subject randomization accounting for the stratification factors. Upon a subject's qualification to enter the study, his/her Visit 2 inferior corneal staining score and dry eye score will be input into the IWRS system to classify the subject into one of the following strata:

- Visit 2 inferior corneal staining score $\leq$ 1.5 in the study eye and dry eye score < 60
- Visit 2 inferior corneal staining score $\leq$ 1.5 in the study eye and dry eye score $\geq$ 60
- Visit 2 inferior corneal staining score > 1.5 in the study eye and dry eye score < 60
- Visit 2 inferior corneal staining score > 1.5 in the study eye and dry eye score $\geq$ 60

The IWRS will be used at Visit 2 to assign a randomization number and a study drug kit number to each subject. The randomization number will be used by the IWRS at Visit 3 and Visit 4 to obtain an appropriate study drug kit number for drug resupply.

9.4.6 Selection of Doses Used in the Study

The dose selection for this study is based upon results from both nonclinical toxicology studies, a Phase 1 clinical study in healthy subjects, a Phase 2 and Phase 3 study in dry eye subjects. The selected study dose will provide an exposure considered likely to have a therapeutic effect while maintaining a margin of safety.

9.4.6.1 Selection of Timing of Dose for Each Subject

A BID schedule was selected based upon the pharmacokinetic results of both tear and plasma conducted during Phase 1. BID dosing is a commonly used regimen in clinical investigations of topical ophthalmic medications.

9.4.7 Masking

All study personnel will be masked with regard to treatment assignments. Unmasking will take place only if the Principal Investigator and Sponsor's Medical Monitor or designee agrees that knowledge of the treatment assignment is important to the medical care of the subject. Unmasking will take place only following a formal written request by the Principal Investigator and agreement by the Sponsor's Medical Monitor, unless the treatment information is needed by the Principal Investigator in an emergency situation.

9.4.8 Prior and Concomitant Medications

All prescription and over–the–counter medications taken by a subject for 60 days prior to Day –14 (Visit 1) through the end of the study, Day 84 (Visit 5) will be recorded on the designated eCRF. The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Medical Monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.4.9 Treatment Compliance

IP will be administered to subjects by trained study personnel during study site visits. When subjects take IP home between visits, they will be instructed to return all used and unused IP containers at each subsequent study visit. Subject compliance with the dosing regimen will be assessed by reconciliation of the used and unused IP. The quantity of dispensed, returned, used, lost, etc. IP containers must be recorded on the study medication dosing log provided for the study. Non-compliance with dosing will be recorded as a protocol deviation if >20% of the expected number of doses since the last visit have been missed or if > 120% of the expected number of doses since the last visit have been taken. Compliance will also be calculated across the full duration of the treatment period following the subjects' study completion.

9.5 Investigational Product Accountability

The PI or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, subjects to whom IP is dispensed (subject–by–subject dose

specific accounting), and IP lost or accidentally or deliberately destroyed. The PI or designee must retain all unused or expired study supplies until the study monitor (on–site CRA) has confirmed the accountability data.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after SARcode Bioscience has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to SARcode Bioscience and retained in the PIs study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to SARcode Bioscience or designee upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by SARcode Bioscience.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

No dietary restrictions will be imposed on study subjects.

9.7 Outcome Measures

The Schedule of Events in the Synopsis (Section 2.1) describes the timing of required evaluations.

9.7.1 Primary Efficacy Outcome Measures

Ocular Sign

The objective co-primary efficacy outcome measure is the mean change from baseline to Day 84 in inferior corneal fluorescein staining score (0 – 4 point scale with allowance for 0.5 point increments) in the designated study eye.

Ocular Symptom

The subjective co-primary efficacy outcome measure is the **mean change from baseline to Day 84 in** eye dryness score (0 – 100 point VAS scale, OU).

9.7.2 Secondary Efficacy Outcome Measures

Ocular Signs

- Total corneal staining score (0 – 12 point scale) – in the designated study eye – mean change from baseline to Day 84
- Nasal lissamine score (0 – 4 point scale) – in the designated study eye – mean change from baseline to Day 84

Ocular Symptoms

- Eye discomfort score (0 – 100 point VAS scale, OU) – **mean change from baseline to** Day 84
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye – **mean change from baseline to** Day 84

9.7.3 Tertiary Efficacy Outcome Measures

Ocular Signs

The following ocular signs will be measured at every visit and mean change from baseline at every visit in the designated study eye:

- Corneal fluorescein staining score – **inferior, superior, central, and total (derived from the sum of the regions)**
- Lissamine green staining score – **nasal, temporal, and total (derived from the sum of the regions)**
- Conjunctival redness score
- Schirmer tear test without anesthesia

Ocular Symptoms

The following ocular symptoms will be measured at every visit and mean change from baseline at every visit:

- 7-item VAS (0 – 100 scale, OU; burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, pain), each item scored individually
- Ocular discomfort score (0 – 4 point scale) – in the designated study eye
- Total OSDI score (0 – 100 scale)
- Symptoms subscale OSDI score (0 – 4 scale; mean of Questions 1-5)

- Visual-related function subscale OSDI score (0 – 4 scale; mean of items from Questions 6-9)
- **Environmental t**rigger subscale OSDI score (0 – 4 scale; mean of items from Questions 10-12)

9.7.4 Safety Outcome Measures

The incidence and severity of ocular adverse events and the incidence and severity of non-ocular adverse events will be reported.

The following safety assessments will be measured at every visit, except as noted. Descriptive analyses of these safety measures will be summarized by treatment at all time points:

- Best corrected visual acuity (BCVA)
- Slit lamp biomicroscopy
- Dilated fundoscopy (Visits 1 and 5 only)

10 ADVERSE EVENTS

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product (IP), whether or not considered related to the IP.

An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre–existing conditions (e.g., worsening of asthma). Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

The reporting period for non–serious and serious AEs is the period from the subject signing the ICF continuing through the last study visit (Day 84, Visit 5). Events recorded prior to the use of IP will be distinguished from events recorded after starting the use of IP. The latter will be referred to as treatment-emergent AEs. If a non-serious**, ocular** AE remains unresolved at the conclusion of the **subject's participation in the** study, the PI **or designee should contact the** Medical Monitor **and** make a joint clinical assessment as to whether continued follow–up of the AE is warranted, and the results of this assessment must be documented. **All other non-serious AEs which remain unresolved at the conclusion of the subject's participation in the study should be assessed by the PI or physician designee and followed to resolution at his/her discretion.** Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will assess AEs for severity, for relationship to IP or placebo solution, and as to whether the event meets one or more of the definitions of an SAE (see Section 10.1).

The Investigator will determine the severity of each AE and will record it on the source documents and AE eCRF, using the categories defined below.

Grade	**Description**
Mild	No limitation of usual activities
Moderate	Some limitation of usual activities
Severe	Inability to carry out usual activities

The Investigator will determine the relationship of an AE to the IP and will record it on the source documents and AE eCRF, using the categories defined below.

Relationship	**Description**
Not Related	Exposure to the IP has not occurred. OR The administration of the IP and the occurrence of the AE are not reasonably related in time. OR The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts [evidence] or arguments to suggest a causal relationship to the IP.
Possibly Related	The administration of the IP and the occurrence of the AE are reasonably related in time. AND The AE could not be explained equally well by factors or causes other than exposure to the IP.
Probably Related	The administration of IP and the occurrence of the AE are reasonably related in time. AND The AE is more likely explained by exposure to the IP than by other factors or causes.

In order to classify adverse events and diseases, preferred terms will be assigned by the Sponsor or CRO to the original terms entered on the eCRF, using MedDRA (Medical Dictionary for Regulatory Activities terminology).

10.1 Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that:

- Results in death
- Is life threatening, that is, places the subject at immediate risk of death from the event as it occurred. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires in–patient hospitalization or prolongation of an existing in–patient hospitalization

- Results in persistent or significant disability or incapacity. An event qualifies as resulting in a persistent or significant disability or incapacity if it involves a substantial disruption of the subject's ability to carry out usual life functions. This definition is not intended to include experiences of relatively minor or temporary medical significance.
- Is a congenital anomaly or birth defect, that is, an AE that occurs in the child or fetus of a subject exposed to IP prior to conception or during pregnancy
- Is an important medical event or serious medical condition that does not meet any of the above criteria, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in the emergency room, allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

More than one of the above criteria may apply to any specific event.

The reporting period for SAEs is the period from the time of the subject signing of the ICF through the last study visit (Day 84, Visit 5). SAEs reported to the Investigator outside of this reporting period will be reported to SARcode Bioscience and the Medical Monitor if, in good medical judgment, the event has any bearing on the study data. SAEs must be followed by the Investigator until resolution, even if this extends beyond the study–reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Any SAE, whether or not considered related to study drug, will be reported immediately (within 24 hours) to [redacted] by fax or scanned and emailed using the study–specific SAE Report Form. In addition to the outcome of the SAE, any medication or other therapeutic measures used to treat the event will be recorded on the appropriate eCRF page(s). Investigators should not wait to collect additional information that fully documents the event before notifying [redacted] of an SAE. SARcode Bioscience may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by SARcode Bioscience, the Medical Monitor [redacted] as soon as it becomes available.

Reporting of SAEs to the IRB/EC will be done in compliance with the standard operating procedures and policies of the IRB/EC and with applicable regulatory requirements. Adequate documentation must be obtained by SARcode Bioscience showing that the IRB/EC was properly and promptly notified as required.

Contact information for SARcode Bioscience is as follows:

[redacted] MD
SARcode Bioscience, Inc.
1000 Marina Blvd, Suite 250
Brisbane, CA 94005

Office: [redacted]
Cell: [redacted]
Fax: [redacted]
Email: [redacted]

Contact information for [redacted] is as follows:

A completed SAE Report form signed by the Investigator must be faxed to the [redacted] Safety number: [redacted] or scanned and emailed to [redacted]. [redacted] will forward the SAE Report form to SARcode Bioscience and the Medical Monitor.

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is as follows:

[redacted], MD
SARcode Bioscience, Inc.
1000 Marina Blvd, Suite 250
Brisbane, CA 94005

Office: [redacted]
Cell: [redacted]
Fax: [redacted]
Email: [redacted]

11 APPROPRIATENESS OF MEASUREMENTS

Efficacy: Standard measures of efficacy in the evaluation of potential therapeutics for dry eye will be collected. These include assessments of both signs (objective measures) and symptoms (subjective measures) of dry eye at every study visit. Objective efficacy measures include: conjunctival redness, corneal staining, conjunctival staining and STT. Subjective efficacy measures include: VAS, ODS and OSDI.

Safety: Both ocular and non–ocular AEs will be collected. The measures of safety used in this study are standard clinical procedures for dry eye studies including drop comfort, BCVA, slit lamp biomicroscopy, corneal fluorescein staining and dilated fundoscopy.

11.1 Pharmacokinetics

No pharmacokinetic (PK) samples will be collected.

12 STUDY PROCEDURES

12.1 Prestudy

An ICF must be signed and dated by the subject, the PI or designee obtaining informed consent and witness (if required) before any study–related procedures are performed.

12.2 Screening Visit – Visit 1: Day –14 ± 3

All subjects will undergo the following screening assessments:

- Informed Consent/HIPAA Prior to any changes in a subject's medical treatment and/or invasive procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.
- Demographic Data and Medical/Medication/Ocular History Collect and record all demographic data (including self-reported height and weight), medical history, any medications and any underlying condition(s). Significant ocular and non–ocular medical history only within the past year and medications within the past 60 days will be captured. Artificial Tear Use should be within the past 30 days prior to Visit 1.
- Review of Inclusion/Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential) Women of childbearing potential must have a negative urine pregnancy test to continue in the study.
- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart Subjects must have a score of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1.
- Slit Lamp Biomicroscopy A slit lamp exam will be performed at the beginning of the visit to exclude subjects with disallowed ocular conditions.
- Conjunctival Redness Score An objective measure used to score redness on a 0 – 4 point scale. Half point increments (0.5) may be used.
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)
- STT (w/o anesthesia)
- Monitor Adverse Events (report any AEs that occur after signing the ICF)

Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)

Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:

1. Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)
2. STT (without anesthesia) ≥ 1 and ≤ 10 mm

- Dilated Fundoscopy (following screening eligibility)
- Placebo Instillation at the Study Site Following a **30 ± 15-minute** waiting period after the last study assessment, subjects will ***self-administer*** their first dose of placebo drops (open-label, single drop, approximately 50 µL/drop volume, OU) for training purposes, at the study site under supervision of trained study personnel for Day -14. **Only a single dose of placebo drops will be administered OU, from the same vial on Day -14.**
- Monitor Adverse Events (report any AEs that occur after signing the ICF)
- Open-Label Placebo Vial Dispensation Prior to discharge from the site on Day –14 (Visit 1), subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated in self–administration of placebo. Subjects will be instructed NOT to instill open-label placebo on the morning of their next scheduled study visit (Visit 2, Day 0).
- Schedule Next Visit Subjects will be scheduled for Visit 2, and reminded to bring their corrective glasses, if applicable, to Visit 2.

12.3 Treatment Visit(s)

12.3.1 Visit 2: Day 0 – Confirmatory Screening, Randomization and Baseline Visit

Baseline values for primary and secondary efficacy and safety measures will be established at this visit.

Confirmatory Screening

- Placebo Vial Collection All open-label placebo vials dispensed for Days -13 to -1 should be collected and inventoried by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning placebo dose at home
- Review of Inclusion/Exclusion Criteria
- Monitor and Query Adverse Events (report any AEs)
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)

- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival Redness Score
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)
- STT (w/o anesthesia)

Eligible subjects must have an eye dryness score ≥ 40 (0 – 100 point VAS scale, OU)

Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:

1. Inferior corneal fluorescein staining score ≥ 0.5 (0 – 4 point scale with allowance for 0.5 point increments)
2. STT (without anesthesia) ≥ 1 and ≤ 10 mm

   If both eyes meet the two criteria above, the eye with the greater score in inferior corneal staining at Visit 2 will be selected as the study eye. If both eyes have equal scores in inferior corneal staining at Visit 2, then the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal inferior corneal staining and STT scores at Visit 2, the right eye (OD) will be selected as the study eye.

- Placebo Instillation at the Study Site Following a **20 ± 15-minute** waiting period after the screening procedures at this visit, all subjects will receive their last dose of placebo drops (open-label, 2 drops each eye, approximately 50 µL/drop volume) at the study site by trained study personnel.

Randomization

- Following Visit 2 Confirmatory Screening procedures, all subjects having a positive response (as defined above) and meeting all other screening eligibility criteria will be randomized to one of two treatment arms (1:1) to receive either lifitegrast ophthalmic solution (5.0%) or placebo solution as topical ophthalmic drops administered bilaterally BID for 84 days (12 weeks).

Treatment Period

- Study Drug Instillation at the Study Site Randomized subjects will be administered their initial dose of randomized study drug (a single drop, approximately 50 µL/drop volume,

OU, from the same vial) at the study site by trained study personnel **30 ± 15 minutes** following the last dose of placebo drops administered by trained study personnel. **Only a single dose of randomized study drug will be administered OU from the same vial on Day 0.**

- Drop Comfort Assessment A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following initial dosing (post–randomization) at Visit 2.
- Monitor and Query Adverse Events (report any AEs)
- Study Drug Dispensation Prior to discharge from the study site on Visit 2 (Day 0), randomized subjects will be educated in self-administration of study drug and will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 3, Day 14).
- Schedule Next Visit Subjects will be scheduled for Visit 3, and reminded to bring their corrective glasses, if applicable, to Visit 3.

12.3.2 Visit 3: Day 14 ± 3

- Study Drug Collection All used/unused study drug vials dispensed for Days 1 to 13 should be collected and inventoried by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home.
- Monitor and Query Adverse Events (report any AEs)
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival Redness Score
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)
- STT (w/o anesthesia)

- Study Medication Instillation at the Study Site Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU) for Day 14 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. The evening dose will be administered at home, by the subject, just prior to bedtime.
- Drop Comfort Assessment A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 3.
- Monitor and Query Adverse Events (report any AEs)
- Study Drug Dispensation Prior to discharge from the study site on Visit 3 (Day 14), randomized subjects will be educated in self-administration of study drug and will receive their assigned study drug kit with sufficient supply to last until Visit 4 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 4, Day 42).
- Schedule Next Visit Subjects will be scheduled for Visit 4, and reminded to bring their corrective glasses, if applicable, to Visit 4.

12.3.3 Visit 4: Day 42 ± 4

- Study Drug Collection All used/unused study drug vials dispensed for Days 15 to 41 should be collected and inventoried by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home.
- Monitor and Query Adverse Events (report any AEs)
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival Redness Score
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)
- STT (w/o anesthesia)

- Study Medication Instillation at the Study Site Subjects will receive their first study drug dose (a single drop, approximately 50 µL/drop volume, OU) for Day 42 at the study site by trained study personnel 15 ± 15 minutes following the last study assessment. The evening dose will be administered at home, by the subject, just prior to bedtime.
- Drop Comfort Assessment A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 4.
- Monitor and Query Adverse Events (report any AEs)
- Study Drug Dispensation Prior to discharge from the study site on Visit 4 (Day 42), randomized subjects will be educated in self-administration of study drug and will receive their assigned study drug kit with sufficient supply to last until Visit 5 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 5, Day 84).
- Schedule Next Visit Subjects will be scheduled for Visit 5, and reminded to bring their corrective glasses, if applicable, to Visit 5.

12.3.4 Visit 5: Day 84 ± 8

- Study Drug Collection All used/unused study drug vials dispensed for Days 43 to 83 should be collected and inventoried by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home.
- Monitor and Query Adverse Events (report any AEs)
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart (to be measured before and after dosing)
- Slit Lamp Biomicroscopy (to be performed before and after dosing)
- Conjunctival Redness Score
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)

- STT (w/o anesthesia)
- Study Medication Instillation at the Study Site Subjects will receive their final study drug dose (a single drop, approximately 50 µL/drop volume, OU) at the study site by trained study personnel 15 ± 15 minutes following the last study assessment.
- Drop Comfort Assessment A drop comfort evaluation will be performed immediately and then at 1, 2 and 3 minutes following dosing at Visit 5.
- Dilated Fundoscopy (at the end of the study visit)
- Monitor and Query Adverse Events (report any AEs)
- Exit Study Treatment

12.4 Screen Failures, Termination, Unscheduled Visits, and Lost to Follow Up

Subjects may voluntarily withdraw from the study at any time. Subjects who miss a scheduled visit prior to randomization or do not qualify for the study will be considered screen failures.

Every effort will be made for discontinued subjects to undergo the following procedures at their Exit visit or Early Termination visit, if possible. The following procedures may also be conducted at an Unscheduled Visit.

- Study Drug Collection All used/unused study drug vials dispensed should be collected and inventoried by a trained study technician.
- Monitor and Query Adverse Events (report any AEs)
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- VAS
- Ocular Discomfort Score (ODS)
- OSDI
- BCVA Utilizing an ETDRS Chart (to be measured before and after dosing)
- Slit Lamp Biomicroscopy (to be performed before and after dosing)
- Conjunctival Redness Score
- Corneal Staining (fluorescein)
- Conjunctival Staining (lissamine green)

- STT (w/o anesthesia)
- Dilated Fundoscopy (at the end of the study visit)
- Exit from Study Subjects will be exited from the study

The termination visit will occur on the date the subject withdraws from or completes the study, even if the date does not correspond to a protocol–specific visit.

12.4.1 Subjects Lost to Follow Up

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after two attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

13 DATA QUALITY ASSURANCE

SARcode Bioscience personnel (or designee) will visit the study site prior to initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, the Sponsor and/or designee will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on eCRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

A Sponsor-designated clinical data management group, will design and program a study database and corresponding eCRFs, and provide training for sites and CRAs on data entry and cleaning procedures. Data quality control and analysis will be performed by SARcode Bioscience (or designee), including study monitors, and the clinical data management group, based on predefined data management and statistical analysis plans.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide a detailed description of the planned statistical analyses.

14.2 Study Populations

- **Randomized – The Randomized population includes all subjects who are randomized**.
- Intent-to-Treat (ITT) – The ITT population includes all randomized subjects who receive at least one dose of study medication. Imputation methods will be used to address missing data for efficacy analyses.
- Safety Population – The Safety population includes all randomized subjects who receive at least one dose of study medication.

14.3 Missing Data Handling

The method of Last Observation Carried Forward (LOCF) will be used for the primary efficacy analysis on the ITT population. In these analyses, values recorded at Visit 2 or later will be used to replace missing data at visits where data were not recorded.

Additional imputation methods will be used for sensitivity analyses.

14.4 Unit of Analysis

The unit of analysis will be the individual eye for assessments performed by eye, or the subject for assessments performed by subject.

14.5 Data Analysis Conventions

Continuous variables will be summarized using descriptive statistics including the number of observations, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized using frequencies and percentages. Hypothesis testing, unless otherwise indicated, will be performed using two-sided tests at the $\alpha = 0.05$ significance level.

14.6 Primary Efficacy Analysis

The primary analysis of the objective efficacy endpoint of mean change from baseline **to Day 84** in inferior corneal fluorescein staining will be performed using a stratified

two-sample t-test (i.e., **ANOVA**) comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). The stratification factors used for randomization will be used for this analysis. **The ANOVA model will include treatment, strata and the interaction between treatment and strata.**

The primary analysis of the subjective efficacy endpoint of the eye dryness score, **mean change from baseline to** Day 84, will be performed using a **stratified** two-sample t-test **(i.e., ANOVA)** comparing lifitegrast ophthalmic solution to placebo in the Intent-to-Treat (ITT) population with Last Observation Carried Forward (LOCF). **The stratification factors used for randomization will be used for this analysis. The ANOVA model will include treatment, strata and the interaction between treatment and strata.**

The stratified, two-sample t-test will be performed using the LSMEANS statement in PROC MIXED with the option to specify weights for combining the between-treatment group estimate from each stratum. The between-treatment group estimates from each stratum will be combined using the number of subjects in each stratum as the weights as proposed by Lin (1999). The individual strata will contribute to the overall analysis proportionate to their size as suggested by Anello (2005).

14.7 Secondary Efficacy Analysis

The co-primary efficacy endpoints will also be analyzed using additional statistical methods, including a non-parametric Wilcoxon rank sum test (LOCF) and repeated measures ANOVA for confirmation (no imputation).

Secondary efficacy endpoints will be analyzed similarly to the primary analysis for the co-primary efficacy endpoints.

14.8 Tertiary Efficacy Analysis

Tertiary efficacy endpoints will be analyzed using the same statistical methods as the primary and secondary efficacy endpoints. However, tertiary analyses will only be performed on the ITT population with LOCF.

14.9 Safety Analysis

All safety analyses will be performed on the safety population. Descriptive analyses of safety measures including visual acuity, slit lamp biomicroscopy and dilated fundoscopy will be summarized by treatment at all time points. For analyses of treatment emergent AEs, descriptive summaries will be based upon AEs with the greatest severity.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequencies and percentages will be provided per treatment group of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation. An AE is treatment-emergent if it occurs or worsens after the first

dose of study medication. Events prior to the initiation of study treatment will be summarized separately.

Furthermore, frequencies will be given for subjects with TEAEs by:

1. system organ class and preferred term;
2. system organ class, preferred term and maximal severity;
3. system organ class, preferred term and strongest relationship;
4. system organ class, preferred term, maximal severity, and strongest relationship.

Separate analyses will be performed for ocular and non-ocular TEAEs.

14.10 Determination of Sample Size

For the primary ocular sign, based on the results of the OPUS-1 Phase 3 study, it is reasonable to expect a 0.25 unit difference in lifitegrast ophthalmic solution and placebo in the mean change from baseline to Day 84 in inferior corneal staining, with a common standard deviation of 0.95 units. Under these assumptions, a sample size of 350 per group will yield approximately 93% power to show a significant difference at the $\alpha = 0.05$ level under a two-sample t-test.

For the primary ocular symptom, based on the results of the OPUS-1 Phase 3 study, it is reasonable to expect a 10.0 unit difference in lifitegrast ophthalmic solution and placebo at Day 84 in the mean eye dryness score, with a common standard deviation of 40 units. Under these assumptions, a sample size of 350 per group will yield approximately 91% power to show a significant difference at the $\alpha = 0.05$ level under a two-sample t-test.

It is expected that no subjects will be excluded from the primary analysis due to missing data given the proposed primary analysis method.

14.11 Multiplicity Considerations

Statistical significance is required for both the sign and the symptom for treatment success, hence no multiplicity adjustment is necessary for the co-primary endpoints. Should the primary endpoints be significant, Hochberg's procedure will be applied to control the Type I error rate across the symptom secondary endpoints (i.e., eye discomfort score and ocular discomfort score). Additionally, Hochberg's procedure will be applied to the secondary sign endpoints, total corneal staining and nasal lissamine staining score. There will be no adjustments for multiplicity across the tertiary endpoints.

14.12 Changes in the Conduct of the Study or Planned Analyses

Only SARcode Bioscience may modify the protocol. Any change in study conduct considered necessary by the PI will be made only after consultation with SARcode Bioscience, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/EC must be sought, and the Investigator should inform SARcode Bioscience and the full IRB/EC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/EC must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/EC prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by SARcode Bioscience and the IRB/EC, and all active subjects must again provide informed consent.

Note: If discrepancies exist between minor features of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

15 ELECTRONIC CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic data capture (EDC) will be used. Therefore, subject data from source documents will be entered directly into the clinical database at the Investigator Sites using electronic case report forms (eCRFs). Designated site personnel must complete the applicable eCRFs as soon as possible after a subject visit, and the eCRFs must be available for review at the next scheduled monitoring visit. Prior to locking the clinical database, the Investigator must review and approve the completed eCRFs to verify their accuracy.

Electronic case report form completion guidelines that are approved by SARcode Bioscience, or designee will designate how to appropriately enter data into eCRFs from the source documents. Typically, blank fields are not acceptable. If a field is blank because the item was not done, the field will be marked "ND." If the item is unknown, the field will be marked "UNK." If the item is not applicable, the field will be marked "NA."

Discrepancies (i.e., queries) will be generated for suspect data (e.g., vital signs that are out of expected range, potential protocol compliance concerns, date discrepancies, etc.) and missing data in the clinical database. Some discrepancies will be automatically generated during data entry into the eCRFs as potential data quality issues arise. Other discrepancies will be automatically generated after batch validation is executed on the clinical database during which more advanced, cross-panel edit checks are executed. Finally, manual discrepancies may be generated by Investigators, CRAs, the clinical data manager (CDM), or clinical data analysts (CDAs) as the study data is further analyzed during monitoring visits or data listing reviews. All discrepancies will be routed within the clinical database system to the appropriate clinical study staff, typically beginning with the site coordinator and ending with either the CRA or the CDM for resolution. When these discrepancies are opened within the system on eCRF pages that have already been verified by the CRA or approved by the Investigator, the database system will automatically require the CRA to re-verify and the Investigator to reapprove the applicable pages.

SARcode Bioscience policy is that eCRF study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records (i.e., records at the Investigator Site that have previous medical history/ information), and subjects will be informed of this and will confirm their agreement when giving informed consent. If an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by SARcode Bioscience will compare the eCRFs with the original source documents at the study site and evaluate the eCRFs for completeness and accuracy. If necessary, the study site personnel will be contacted for corrections and/or clarifications.

Data that are modified in the clinical database to resolve related discrepancies must be supported in the source documents.

After the clinical database is locked, compact disks (CDs) with copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

16 STUDY MONITORING AND AUDITING

Qualified individuals designated by SARcode Bioscience will monitor all aspects of the study according to ICH/GCP and standard operating procedures for compliance with applicable government regulations. The PI agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors. The PI and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by SARcode Bioscience or CRO or its designees. The review of the subjects' medical records will be performed in a manner to ensure that subject confidentiality is adequately maintained. Further details of the study monitoring will be outlined in a Monitoring Plan.

Members of SARcode Bioscience GCP Compliance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The PI will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an audit of the study. If informed of such an inspection, the PI should notify SARcode Bioscience immediately. The PI will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state and federal laws apply.

17 RETENTION OF RECORDS

The PI must retain all study records required by SARcode Bioscience and by the applicable regulations in a secure and safe facility. The PI must consult a SARcode Bioscience representative before disposal of any study records, and must notify SARcode Bioscience of any change in the location, disposition or custody of the study files. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the USA or an ICH region and until (1) there are no pending or contemplated marketing applications in the USA or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The PI/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a SARcode Bioscience agreement. SARcode Bioscience must be notified and will assist with retention should PI/institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of SARcode Bioscience to inform the PI/institution as to when these documents no longer need to be retained.

18 USE OF INFORMATION AND PUBLICATION

SARcode Bioscience recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between SARcode Bioscience, CRO's and the PI.

Due to the confidential nature of this development program, the results of the study may not be published or publicly presented without the prior approval of SARcode Bioscience. Any Investigator wishing to publish or present any study finding must present a manuscript or abstract to SARcode Bioscience one hundred and twenty (120) days prior to submission for publication or presentation to provide SARcode Bioscience an opportunity for review and comment.

19 REFERENCES

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20 INVESTIGATOR RESPONSIBILITIES

20.1 Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/EC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/EC. Additionally, he or she will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

21 SIGNATURE PAGE

Protocol Title: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo-Controlled Study Evaluating the Efficacy of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears (OPUS-2)

SARcode Bioscience Protocol Number: 1118–DRY–300, **Amendment 1**

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator's Signature _____ Date _____

Printed Name _____

Accepted for the Sponsor:

On behalf of SARcode Bioscience, Inc., I confirm that SARcode Bioscience, Inc., as a Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the PI is informed of all relevant information that becomes available during the conduct of this study.

[redacted] 06 SEP 2013

Medical Monitor's Signature Date

[redacted]

Printed name: [redacted], MD

22 APPENDICES

Appendix 1: 1118–DRY–300 (OPUS-2) Study Schema

Appendix 2: Procedure for Symptom Assessment with the Visual Analogue Scale (VAS)

Appendix 3: Procedure for the Ocular Discomfort Score (ODS) Assessment

Appendix 4: Ocular Surface Disease Index (OSDI)

Appendix 5: Procedure for Evaluating Drop Comfort

Appendix 6: Procedure for Measuring Visual Acuity

Appendix 7: Procedure for Performing Slit Lamp Biomicroscopy

Appendix 8: Procedure for Evaluating Conjunctival Redness

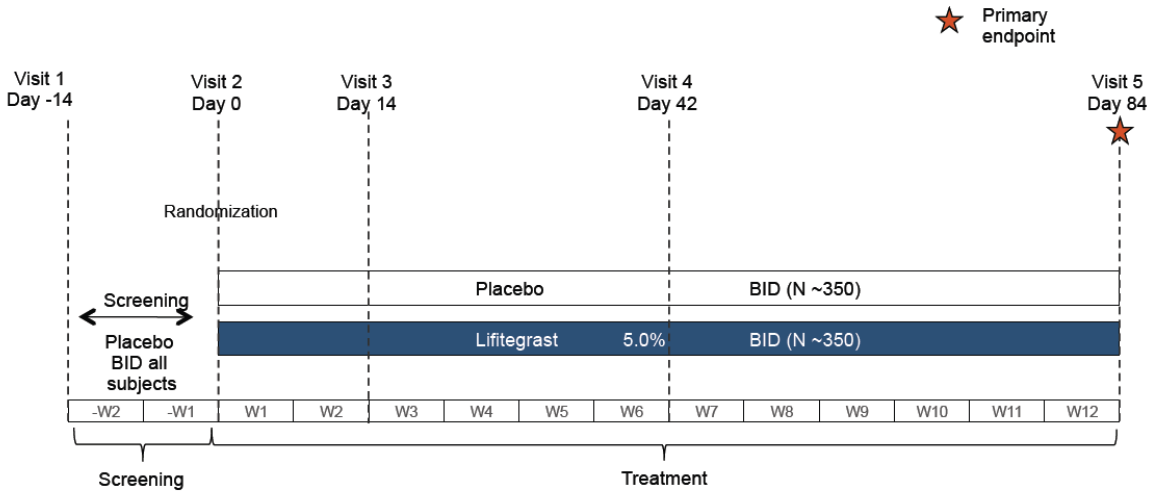
Appendix 9: Procedure for Evaluating Corneal Staining with Fluorescein

Appendix 10: Procedure for Evaluating Conjunctival Staining with Lissamine Green

Appendix 11: Procedure for Performing Schirmer Tear Test

Appendix 12: Procedure for Conducting Dilated Fundoscopy

Appendix 1: 1118–DRY–300 (OPUS-2) Study Schema



Appendix 2: Procedure for Symptom Assessment with the Visual Analogue Scale (VAS)

Subjects will be asked the following questions regarding their current ocular discomfort (unrelated to study drug instillation) at all visits.

The subject will be asked to subjectively rate each ocular symptom **(OU)** by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort."

Burning/Stinging	0%	50%	100%
	|_____|		
Itching	0%	50%	100%
	|_____|		
Foreign body sensation	0%	50%	100%
	|_____|		
Eye Discomfort	0%	50%	100%
	|_____|		
Eye Dryness	0%	50%	100%
	|_____|		
Photophobia	0%	50%	100%
	|_____|		
Pain	0%	50%	100%
	|_____|		

Appendix 3: Procedure for the Ocular Discomfort Score (ODS) Assessment

Assessment of ocular discomfort scores will be **conducted by site personnel and will be** subjectively graded by the subjects according to the following scale (rating each eye separately):

At this moment in time - rate the discomfort level of each eye

No discomfort	0
Slight discomfort or awareness	1
Mild discomfort or awareness	2
Moderate discomfort	3
Severe discomfort	4

Reference: modified from Begley, (2003), Invest Ophthalmol Vis Sci and Caudle, (2007), Opt and Vis Sci

Appendix 4: Ocular Surface Disease Index

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

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

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

Subtotal score for answers 1 to 5 (A)

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

Subtotal score for answers 6 to 9 (B)

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

Subtotal score for answers 10 to 12 (C)

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

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

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

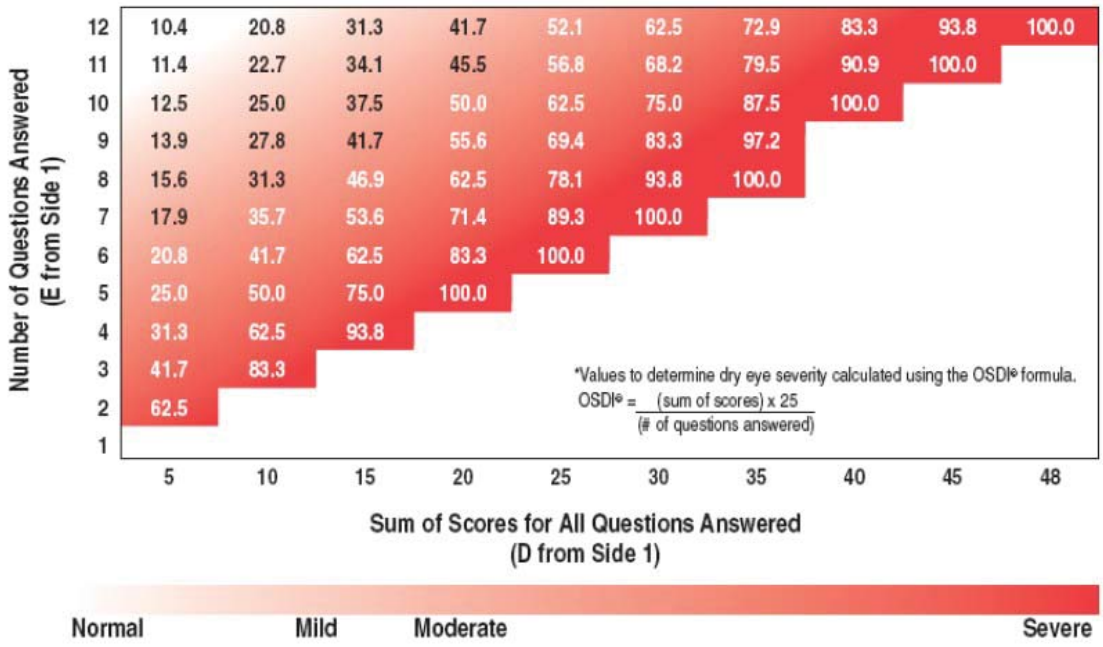
(OSDI)

Evaluating the OSDI© Score[1]

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

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

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



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

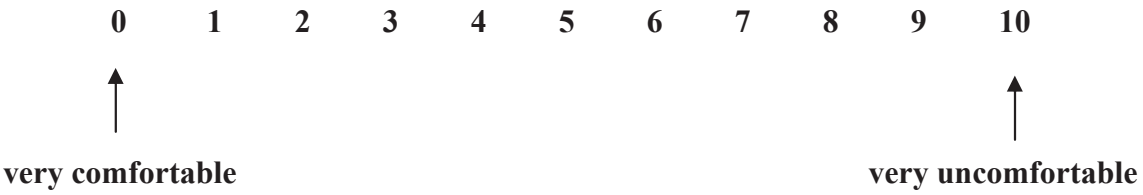
Reference: Schiffman, (2000), Arch Ophthalmol; OSDI is copyrighted by Allergan, Inc., Irvine, CA

Appendix 5: Procedure for Evaluating Drop Comfort

Reported Drop Comfort by the Subject:

The purpose of the evaluation is to assess the degree of initial comfort of the instilled eye drop (placebo versus lifitegrast).

Evaluation of the comfort of the eye drop will be conducted for each eye immediately (time 0) and at 1, 2 and 3 minutes following initial dosing at Visit 2, 3, 4 and 5:



Note: The drop comfort response is NOT considered an AE regardless of severity unless it results in an interruption of study drug treatment or discontinuation of the subject from the study. However, if the subject is experiencing discomfort symptoms 5-15 minutes after the drop comfort assessment is completed, then the site should record these symptoms as AEs.

Reference: Torkildsen, (2008), Clin Ther

Appendix 6: Procedure for Measuring Visual Acuity

General Guidance

- Visual acuity will be assessed at each visit in the study prior to slit lamp examination.
- Visual acuity will be assessed using an ETDRS format wall chart under normal room illumination using the logMAR scoring system. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. To ensure consistency in responses during the study, visual acuity assessments must be done using the same testing conditions (e.g., same lighting conditions) and same spectacle correction throughout the study; if there is a change in the testing conditions (e.g., subject forgets eyeglasses), the reason for the change should be documented.
- Visual acuity testing will be tested with the subject wearing his/her current spectacle correction, therefore, the subject should be queried as to whether he/she requires correction for distance vision (e.g., driving); if so - the subject will be tested with glasses. The subject should be reminded to bring the ***same pair*** of glasses to each study visit. If the subject forgets to bring glasses, visual acuity will be tested using the pinhole occluder and the results recorded as "with pinhole".
- If the examiner needs to repeat the visual acuity assessment (at same visit) for technical reasons (e.g., subject has difficulty reading chart and it is recognized that the eyeglasses are soiled/smudged after the test was conducted, or subject failed to understand instructions properly), the examiner, at his/her professional discretion, is allowed to choose the single set of visual acuity scores that best represents the subject's visual acuity for that visit.
- A change from baseline in visual acuity of greater than or equal to a logMAR of 0.22 is considered an Adverse Event.

Equipment

- For purposes of standardizing the testing conditions during the study, all sites must use ETDRS 2000 Series Charts 1 and 2. For reflectance (wall) charts, the chart should be placed frontally and well illuminated.

Visual Acuity Measurement Technique

- The distance from the subject's eyes to the visual acuity chart is 4 meters and the subject may sit or stand. The examiner should ensure the subject is comfortable and the head is not moving forward/backward during testing and that the eyes remain at the same distance from the chart throughout the test. If the subject requires multifocal corrective

glasses, the examiner should confirm that the subject is viewing the chart with the distance segment.

- Pre-testing instruction should include informing the subject that the chart has letters only. To achieve the best identification of each letter, the examiner should remind the subject to read the chart slowly; the subject should not proceed to the next letter until giving a definitive response.
- The left eye is occluded and testing begins with the right eye (Chart 1). The subject should attempt to read each letter, line-by-line, left-to-right, beginning with line 1 at the top of the chart. If the subject reads a number, the examiner should remind the subject that the chart contains only letters and then request a letter instead.
- 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/she 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.
- When the subject says he/she cannot read a letter, the subject should be encouraged to guess. If the subject identifies a letter as one of two letters, he/she should be asked to choose one letter. 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.
- After the test for the right eye is completed, occlude the right eye. The test is then repeated for the left eye (Chart 2).

LogMAR Visual Acuity Calculations

- The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. The examiner records a letter read incorrectly, or a letter for which the subject made no guess, by crossing the letter out with an "X". Each letter read incorrectly is scored as one (1) point.
- The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including in the last line read. This total sum represents the logMAR visual acuity for that eye.
- 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**

The following Snellen equivalents will be used to correspond to the logMAR VA:

Visual acuity scales

Foot	Meter	Decimal	LogMAR
20/200	6/60	0.10	1.00
20/160	6/48	0.13	0.90
20/120	6/36	0.17	0.78
20/100	6/30	0.20	0.70
20/80	6/24	0.25	0.60
20/60	6/18	0.33	0.48
20/50	6/15	0.40	0.40
20/40	6/12	0.50	0.30
20/30	6/9	0.63	0.18
20/25	6/7.5	0.80	0.10
20/20	6/6	1.00	0.00
20/16	6/4.8	1.25	–0.10
20/12	6/3.6	1.67	–0.22
20/10	6/3	2.00	–0.30

Appendix 7: Procedure for Performing Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as Normal or Abnormal. Abnormal findings will be described. The following will be examined at each visit:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Lid

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

Appendix 8: Procedure for Evaluating Conjunctival Redness

Conjunctival redness will be graded according to the following scale: Half (0.5) point increments may be used.

None	0 = None, no vasodilation
Trace	1 = Slight vasodilation of the ciliary or conjunctival vessels
Mild	2 = Diffuse vasodilation of ciliary vessels
Moderate	3 = Diffuse ciliary and trace horizontal vasodilation of conjunctival vessels
Severe	4 = Diffuse ciliary vasodilation with conspicuous vasodilation of horizontal conjunctival vessels

Reference: modified from Efron, (2001), Ophthal Physiol Opt

Appendix 9: Procedure for Evaluating Corneal Staining with Fluorescein

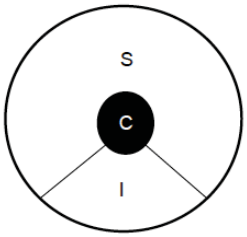
The purpose of this procedure is to grade the degree of corneal epithelial cell injury as measured by fluorescence using slit-lamp examination.

Procedure:

- A 5.0 µL volume of 2% *unpreserved* sodium fluorescein is instilled into the lower conjunctival sac using a micropipette (sterile tip) or glass capillary tube.
- After approximately 5 minutes following instillation of fluorescein, the corneal fluorescein grade is obtained of each eye using a 0-4 point scale (with 0.5 point increments).
- The upper eyelid is slightly lifted to assess the whole corneal surface
- A blue light and a #12 Wratten yellow filter must be used to view the eye.
- It is recommended that the same investigator evaluate the same subject using the same slit-lamp/settings at all study visits

Corneal Staining Score

The corneal surface is divided into three regions as diagrammed.



Outside circle includes limbal margin
S = Superior Region
C = Central Region
I = Inferior Region

Score each of the three regions of both eyes using the modified grading scale of 0–4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

None	0 = no staining
Trace	1 = few/rare punctate lesions
Mild	2 = discrete and countable lesions
Moderate	3 = lesions too numerous to count but not coalescent
Severe	4 = coalescent

Reference: modified from Lemp, (1995), CLAO and Shimmura, (1995), J Ophthalmol

Appendix 10: Procedure for Evaluating Conjunctival Staining with Lissamine Green

The purpose of this procedure is to grade the degree of conjunctival epithelial cell injury as measured by lissamine green using slit-lamp examination.

Procedure:

- A 10 µL volume of lissamine green solution is instilled into the inferior conjunctival cul-de–sac
- The subject will be instructed to blink several times to distribute the lissamine green.
- After approximately 30 seconds following instillation of lissamine, the staining will be graded using a 0-4 point scale (with 0.5 point increments)

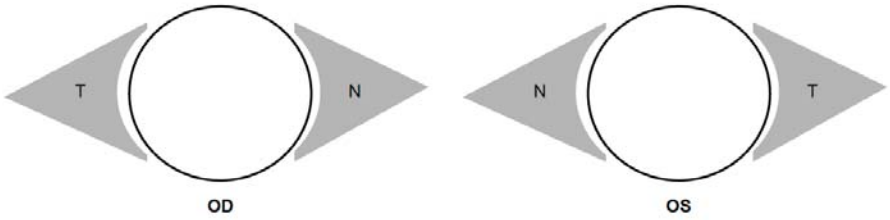
Conjunctival Staining Score:

The conjunctival surface is divided into two triangular segments (gray region) as diagrammed below.

T (Temporal Region) = wedge of temporal conjunctiva

N (Nasal Region) = wedge of nasal conjunctiva

Circle represents limbal margin of the cornea



Score each of the **two** regions of both eyes using the modified grading scale of 0–4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

None	0 = no staining
Trace	1 = few/rare punctate lesions
Mild	2 = discrete and countable lesions
Moderate	3 = lesions too numerous to count but not coalescent
Severe	4 = coalescent

Reference: modified from Lemp, (1995),CLAO and van Bijsterveld, (1969), Arch Ophthal

Appendix 11: Procedure for Performing Schirmer Tear Test

Schirmer Tear Test will be performed according to the following procedure:

- Using a sterile Tear Flo Schirmer test strip (Rose Enterprises), a bend in the strip will be made in line with the notch in the strip
- The subject will be instructed to gaze up and in
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye

Appendix 12: Procedure for Conducting Dilated Fundoscopy

A dilated fundoscopy exam will be performed during the study at Visits 1 and 5, and potentially at an Early Termination Visit. The investigator will instill 1 drop of 1% tropicamide bilaterally and wait approximately 15 minutes or when the subject's eyes are deemed sufficiently dilated in the opinion of the investigator. Observations will be graded as Normal or Abnormal. Abnormal findings will be described. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve