Clinical Trial Protocol

A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry Eye (The SIDE Study)

Version 1.0 23MAR2022

NCT05411367

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Protocol Title:	A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry Eye (The SIDE Study)
Protocol Number:	614/1132
Study Phase:	3
Product Name:	SI-614 ophthalmic solution
IND Number:	112,592
Indication:	Keratoconjunctivitis sicca (Dry Eye)
Investigators:	Multi-Center
Sponsor:	Seikagaku Corporation 6-1, Marunouchi 1-chome Chiyoda-ku, Tokyo 100-0005, Japan
Contract Research Organization:	[redacted]
IRB:	[redacted]

Original Protocol:	March 23, 2022/Version 1.0
Amendment 1:	Not applicable

Confidentiality Statement

MEDICAL MONITOR

[redacted]	Responsible for medical management, safety surveillance, confirming patient eligibility, and reviewing safety data and clinical study report

SPONSOR PERSONNEL

[redacted]	Responsible for supervision of planning, management of clinical trial
[redacted]	Responsible for study management

[redacted] PERSONNEL

[redacted]	Responsible for oversight and coordination of clinical trial and administrative follow-up
[redacted]	Responsible for oversight of clinical planning, management and conduct of the clinical trial.
[redacted]	Responsible for planning, management, conduct, and monitoring of clinical trial

SYNOPSIS

Protocol Title:	A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry Eye (The SIDE Study)
Protocol Number:	614/1132
Study Drug:	• 0.3% SI-614 ophthalmic solution • Placebo (vehicle of SI-614 ophthalmic solution)
Study Phase:	3
Study Objective:	To evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution compared with placebo when administered 4 times daily for 84 days in patients with dry eye
Overall Study Design	
Structure:	Multi-center, double-masked, randomized, placebo-controlled study
Duration:	2 weeks of run-in period and 12 weeks of treatment period
Controls:	Placebo
Dosage/Dose Regimen:	One drop of study drug will be instilled in each eye 4 times daily (morning, noon, afternoon, evening before bedtime) for 84 days. Patients will be randomized in a 1:1 ratio into one of the 2 arms of the study: • 0.3% SI-614 • Placebo
Summary of Visit Schedule:	7 visits and 3 phone calls over the course of approximately 14 weeks • Visit 1, Day -14 ± 3 • Visit 2, Day 1 • Visit 3, Day 8 ± 2 • Visit 4, Day 15 ± 2 • Phone Call for Drug Compliance, Day 22 ± 2 • Visit 5, Day 29 ± 3 • Phone Call for Drug Compliance, Day 43 ± 2 • Visit 6, Day 57 ± 3 • Phone Call for Drug Compliance, Day 71 ± 2 • Visit 7, Day 85 ± 3

Measures Taken to Reduce Bias:	This is a randomized and double-masked study.
Study Population Characteristics	
Number of Patients:	Approximately 230 (115 per treatment arm) patients will be enrolled at up to 10 sites.
Condition/Disease:	Keratoconjunctivitis sicca (Dry Eye)
Inclusion Criteria:	**Patients must:** 1. Be male or female of any race, at least 18 years of age at Visit 1. 2. Have provided verbal and written informed consent. 3. Be able and willing to use eye drops 4 times daily with a compliance rate of 80% or greater during the run-in period and follow instructions, including participation in all study assessments and visits. 4. Have a patient-reported history of dry eye in both eyes for at least 6 months prior to Visit 1. 5. Have used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1. 6. Have a best-corrected visual acuity score of +0.70 logarithm of the minimum angle of resolution (logMAR) or better in both eyes at Visit 1, as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. 7. Report an average score of 2.0 or higher in at least 1 of the 5 symptoms over the 7 days prior to Visit 2 as measured by the [redacted] Ocular Discomfort and 4-Symptom Questionnaire from the patient daily diary 8. Have ALL of the following in the qualifying eye(s), [redacted] at Visits 1 and 2: a) A tear film break-up time (TFBUT) of ≤ 5 seconds and ≥ 1 second b) A fluorescein staining score of ≥ 2 in at least 1 region [redacted]

	c) A conjunctival redness score of ≥ 1 [redacted] d) A total lissamine green staining score of ≥ 2 [redacted] 9. Demonstrate a response to the [redacted] at Visits 1 and 2 in the qualifying eye(s), as defined as meeting ALL of the following criteria: a) Have an increase of ≥ 3 in fluorescein staining score in the cornea [redacted] b) Report a score of ≥ 3 [redacted] Ocular Discomfort Scale [redacted] 10. If a female of childbearing potential, have a negative urine pregnancy test at Visit 1 and will be using an adequate method of birth control throughout the study period. [Females are considered of childbearing potential unless they are surgically sterilized (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) or post-menopausal (at least 12 months since last menses). Adequate birth control is defined as use of hormonal contraceptives (oral, implantable, injectable or transdermal), spermicide in conjunction with a barrier such as condom or diaphragm, or an intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the patient becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study.]
Exclusion Criteria:	**Patients must not:** 1. Have any clinically significant slit lamp findings at Visit 1 or Visit 2, including active blepharitis, meibomian gland dysfunction, lid margin inflammation or ocular allergies that

	requires therapeutic treatment and/or, in the opinion of the investigator, may interfere with the study parameters. 2. Be diagnosed with an ongoing ocular infection (bacterial, viral or fungal), or active ocular inflammation (eg, follicular conjunctivitis) at Visit 1 or Visit 2. 3. Have a history of laser in situ keratomileusis (LASIK) surgery in either eye within 12 months prior to Visit 1, or have any scheduled LASIK surgery during the study period. 4. Have had any ocular surgical procedure within 12 months prior to Visit 1, or have any scheduled ocular surgical procedure during the study period. 5. Have used contact lenses within 30 days prior to Visit 1 or anticipates use of contact lenses during the study period. 6. Have used punctal plugs within 3 months prior to Visit 1 or anticipates use of punctal plugs during the study period. 7. Have used nasal spray for dry eye (i.e. TYRVAYA®) within 30 days prior to Visit 1 or anticipates use of nasal spray for dry eye during the study period. 8. Have used topical ocular cyclosporine (i.e., Restasis® or Cequa™) or topical lifitegrast (i.e. Xiidra®) within 45 days prior to Visit 1. 9. Have used any topical ocular prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tear substitutes, gels or scrubs within 24 hours prior to Visit 1 or during the study period. 10. Be currently using any medication known to cause ocular drying or increased lacrimation that has not been used on a stable dosing regimen for at least 30 days prior to Visit 1, or anticipates a change in such medication during the study period. 11. Have a current malignancy or has received treatment of malignancy within the past 5 years prior to Visit 1. Patients who have undergone

	successful resection of a basal cell or squamous cell carcinoma of the skin may be enrolled even if the resection was within 5 years. 12. Have an uncontrolled systemic disease including, but not limited to clinically significant cardiovascular disease, pulmonary disease, or metabolic disease or any other systemic disease/symptoms that, in the opinion of the investigator, would interfere with study parameters. 13. Have an uncontrolled psychiatric condition that required a change in medication in the 30 days prior to Visit 1, or anticipates hospitalization or change in such medication during the study period, or substance or alcohol abuse. 14. Be a female who is pregnant, nursing an infant, or planning a pregnancy. 15. Have a known allergy and/or sensitivity to the study drug or its components. 16. Have a condition or is in a situation that, in the opinion of the investigator, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patients' participation in the study. 17. Be currently enrolled in an investigational drug or device study, have used an investigational drug or device within 45 days prior to Visit 1, or have been previously randomized to receive SI-614 ophthalmic solutions or placebo.
Evaluation Criteria	
Efficacy Measures:	**Primary Efficacy Measures:** The following primary endpoint will be evaluated: • Change from baseline [redacted] in total corneal fluorescein staining score [redacted] in the study eye. **Secondary Efficacy Measures:** The following secondary endpoint will be used: • Change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14.

	Exploratory Efficacy Measures: The following exploratory efficacy measures will be used: **Signs** • Fluorescein staining score [redacted] • Lissamine green staining score [redacted] • TFBUT • Conjunctival redness [redacted] **Symptoms** • Patient daily diary during dosing period • Ocular Surface Disease Index© (OSDI)© questionnaire • [redacted] Ocular Discomfort and 4-Symptom Questionnaire • [redacted] Ocular Discomfort Scale
Safety Measures:	• Best-corrected visual acuity • Slit lamp biomicroscopy • Adverse event (AE) query
Other Measures:	• Urine pregnancy test

General Statistical Methods and Types of Analyses

Analysis Populations

- Intention-to-Treat Population
  The intention-to-treat (ITT) population includes all randomized patients. Subjects in the ITT population will be analyzed as randomized. The primary analysis will be performed on the ITT population with the primary estimand.
- Per-Protocol Population

  The per-protocol (PP) population is defined as all ITT patients who have no major protocol deviations and completed the trial. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

  Safety Population – The safety population will include all patients who receive at least 1 dose of randomized study drug. Subjects in the Safety population will be analyzed as treated.

Sample Size

Difference and standard deviation (SD) estimates are derived from the Phase 2 and Phase 2/3 study.

The primary endpoint is the change from baseline [redacted] Day 29 [redacted] in total corneal fluorescein staining. The study will be considered successful if and only if this endpoint is met. In order to have 90% power to detect a difference of -0.75 between SI-614 and placebo, 109 patients per treatment arm are required to be randomized. This assumes a two-sided test at alpha = 0.05 and a common SD of 1.7 in both treatment arms.

Accounting for up to 5% dropouts in the study, 115 patients per treatment arm, or 230 total patients are required to have 90% power for the primary endpoint.

The hierarchical, secondary endpoint of the change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 will have 51% power with this sample size, assuming a difference between SI-614 and placebo of -0.13. This endpoint will be tested conditional upon the primary endpoint being successful, thereby maintaining the study-wide type I error rate for both endpoints. The sample size calculation assumes a two-sided test at alpha = 0.05 and a common SD of 0.48 in both treatment arms.

Multiplicity

Hierarchical fixed sequence testing will be used in the analysis of the primary dry eye sign endpoint and the secondary dry eye symptom endpoint to maintain study wide type I error. The primary endpoint of change from baseline [redacted] at Day 29 [redacted] of the corneal total fluorescein staining score will be evaluated at a two-sided study wide alpha level of 0.05. If the primary endpoint is statistically significant, then the secondary endpoint of change from baseline of the bedtime assessment from the patient daily diary during Day 1 through Day 14 will be evaluated at a two-sided study wide alpha level of 0.05. If the primary endpoint is not statistically significant, no further formal hypothesis testing will proceed and the analyses of the secondary endpoint will be conducted as an exploratory analyses.

Exploratory endpoints will not be type I error controlled and thus, considered exploratory and hypothesis generating.

Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the "study eye" as defined by the following:

Study Eye: Eyes are eligible for analysis if they meet all "inclusion criteria" as specified in Section 5.3. In the case that both eyes are eligible for analysis, the study eye will be the eye with the largest change [redacted] in corneal total fluorescein staining score [redacted] at baseline (Visit 2). If the baseline change [redacted] in corneal total fluorescein staining score is the same in both eyes, then the right eye will be used as the study eye. If only one eye meets all inclusion criteria, then the single qualifying eye is the study eye.

Primary Efficacy Analysis

For the primary efficacy endpoint, change from baseline [redacted] will be calculated as visit – (minus) baseline [redacted] such that a positive difference indicates a

worsening of dry eye signs or symptoms. In addition, treatment comparisons between active and placebo will be calculated as 0.3% SI-614 – (minus) placebo, such that a negative result indicates a better score for the 0.3% SI-614 (i.e., 0.3% SI-614 demonstrated less severity in dry eye signs or symptoms than the placebo group).

The primary analysis of the primary endpoint will use the ITT population with multiple imputation methodology as specified in Estimand 1 (defined in Section 11.4.4) using Analysis of Covariance (ANCOVA) if the rate of missing data for an endpoint is balanced between the two treatment groups (as evaluated by the Fisher's exact test at an alpha level of 0.05) or the rate of missing data for an endpoint is ≤ 5% in all subjects. If the rate of missing data for an endpoint is imbalanced between treatment groups (as demonstrated by the Fisher's exact test with a p-value < 0.05) and the rate of missing data for an endpoint is greater than 5% in all subjects, then the primary analyses will utilize the ITT population with observed data only using the permutation test with trimmed means methodology with Estimand 2 (defined in Section 11.4.4).[1]

The ANCOVA model used to compare the change from baseline [redacted] to Day 29 [redacted] in corneal total fluorescein staining score in the study eye between 0.3% SI-614 and placebo will include baseline [redacted] in corneal total fluorescein staining score in the study eye at Visit 2 and treatment group as covariates.

As supportive analyses, two-sample t-tests and a Wilcoxon rank sum test will be conducted to compare the change from baseline [redacted] at Day 29 [redacted] between the two treatment groups. Additional exploratory comparisons of the mean raw scores of corneal total fluorescein staining score at Day 29 [redacted] and baseline [redacted] (Visit 2, Day 1) between the treatment groups will be conducted using two-sample t-tests and Wilcoxon rank sum tests. Quantitative summary statistics will be provided for baseline Day 1 [redacted], Day 29 [redacted], and change from baseline [redacted] at Day 29 [redacted].

Sensitivity analyses will include multiple imputation by placebo group-based pattern mixture models (PMM), multiple imputation via randomized treatment group-based Markov Chain Monte Carlo (MCMC), single imputation by Last Observation Carried Forward (LOCF), tipping point analyses, and analyses of observed data only using the ITT and PP populations.

Secondary Efficacy Analyses

Analyses of the secondary efficacy endpoint of the change from baseline (Day -7 through Day -1) in average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 will use a Mixed-Model Repeated Measures (MMRM). The model will include the baseline average score of ocular discomfort and dryness (average of Day -7 through Day -1), treatment group, study day (Day 1 to Day 14 as categorical variables), and the interaction between treatment group and study day as fixed effects with correlated errors due to study day. The overall treatment differences (0.3% SI-614 versus placebo) and the corresponding p-values will be estimated based on the MMRM. As

a sensitivity analysis, the above model will also be run without including the baseline average score of ocular discomfort and dryness symptom as a covariate.

As an additional sensitivity analysis of the average score of ocular discomfort and dryness symptom, the change from baseline in average ocular discomfort and dryness score from Day 1 to Day 14 will also be compared between the 2 treatment groups using two-sample t-tests and Wilcoxon rank sum tests for each individual day. In addition, an ANCOVA model using the baseline average score of ocular discomfort and dryness and treatment group will be used to examine change from baseline at each day.

Analyses of the secondary endpoint will utilize the ITT population using observed data only. Sensitivity analyses will include multiple imputation as described in Estimand 1, multiple imputation by placebo group-based PMM, multiple imputation via randomized treatment group-based MCMC, single imputation by LOCF, and analyses of observed data only using the PP population.

Exploratory Efficacy Analyses

Exploratory efficacy variables will generally be analyzed on the ITT population using observed data.

For signs [redacted] (including fluorescein staining, lissamine green staining, TFBUT, and conjunctival redness), the change [redacted] at each visit will be compared between the 2 treatment groups using a two-sample t-test, a Wilcoxon rank sum test, as well as an ANCOVA model adjusting for baseline [redacted] value. In addition, change from time point-matched baseline ([redacted]) will be analyzed similarly.

For symptom measures (including OSDI, [redacted] Ocular Discomfort and 4-symptom Questionnaire), each individual symptom score as well as the change from baseline ([redacted] at Visit 2) will be compared between 0.3% SI-614 and placebo for each visit using a two-sample t-test, a Wilcoxon rank sum test, and an ANCOVA model adjusting for baseline.

[redacted] Ocular Discomfort Scale [redacted] is measured every 5 minutes [redacted] The area under the curve will be calculated for each patient using the trapezoidal rule, and compared between treatment groups using a two-sample t-test, as well as an ANCOVA model adjusting for baseline (Visit 2 area under the curve).

Safety Variables

Frequencies and percentages of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of patients with TEAEs by system organ class (SOC), by SOC and preferred term (PT), by SOC, PT and maximal severity, by SOC, PT and strongest relationship, and by

SOC, PT, maximal severity, and strongest relationship. Separate analyses will be performed for ocular and non-ocular TEAEs.

Other safety endpoints including visual acuity, slit lamp biomicroscopy, and corneal sensitivity will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized. All safety endpoints will be assessed using the Safety population.

Summary of Known and Potential Risks and Benefits to Human Patients

SI-614 ophthalmic solution appears to be safe and well-tolerated. In a Phase 2 clinical trial of SI-614 with 150 dry eye patients, a subgroup of more symptomatic dry eye patients treated with 0.3% SI-614 showed statistically significantly reduced corneal fluorescein staining and statistically significantly improved dry eye symptoms. The most common ocular TEAEs were instillation site reactions (24.7% of TEAEs), and possibly but less likely, ocular hyperemia or reduced visual acuity (each of which were 1.3% of TEAEs). In a Phase 2/3 study in 240 patients with dry eye, 0.3% SI-614 showed statistically significant improvement in the dry eye symptom primary efficacy endpoint, reproducing the results of the Phase 2 study subgroup analysis. The most frequently reported acute AE was instillation site pain: 16 patients (13.1%) in the 0.3% SI-614 group and 8 patients (6.8%) in the placebo group, and all of these events were mild in severity and were resolved by the end of the study. Overall, the incidence of TEAEs in the 0.3% SI-614 group was comparable with that in the placebo group.

Potential Risks: Phase 2 and Phase 2/3 data indicate that SI-614 has an acceptable safety profile.

Potential Benefits: Patients may experience a reduction in various signs and symptoms of dry eye disease.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
[redacted]	[redacted]
CFR	Code of Federal Regulations
eCRF	electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HA	sodium hyaluronate
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional/independent review board
ITT	intention-to-treat
IVRS/IWRS	Interactive Voice/Web Response System
LASIK	laser *in situ* keratomileusis
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
LS	least squares
MCMC	Markov Chain Monte Carlo
OSDI	Ocular Surface Disease Index
OTC	over-the-counter
PMM	pattern mixture models
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ class
TFBUT	tear film break-up time
TEAE	treatment-emergent adverse event
US	United States
WOCBP	women of childbearing potential

1 INTRODUCTION

Dry eye is a multifactorial condition characterized by tear hyperosmolarity and tear film instability, which can lead to corneal surface damage and an inflammatory component that worsens the condition. Patients with dry eye experience symptoms of discomfort and visual disturbance. The first line of therapy for patients with mild to moderate dry eye is tear supplementation with products generally categorized as artificial tears. These products, however, do not accurately mimic the unique physical and chemical properties of natural tear films, which are a complex mixture of lipids, an aqueous solution of proteins and electrolytes, and a mucous component. Most artificial tear products are hypotonic or isotonic buffered solutions containing electrolytes, surfactants and various types of viscosity agents. Macromolecular complexes added to artificial tear solutions act as viscosity agents for the aqueous layer; carboxymethylcellulose is the most commonly used agent in the United States (US). Most artificial tear solutions are minimally effective and must be instilled many times per day.

SI-614 is a chemically modified sodium hyaluronate (HA). HA is a biopolymer that is present in the vitreous body of the eye, extracellular matrix of the skin, and synovial fluid within joints. HA is composed of linear chains of disaccharide units (N-acetyl-glucosamine and glucuronate) in varying molecular weights. HA molecules possess unique physical and chemical properties such as viscoelasticity and water retention. HA is used in a variety of medical applications, including ocular surgery, arthritis treatment and dermatology applications. In most of these applications, the product utilizing HA is classified as a medical device based on the viscoelastic properties. HA is the active ingredient in several contact lens wetting solutions.

HA has been investigated as a viscosity agent in artificial tear formulations for the treatment of dry eye. 0.2% HA demonstrated significantly longer ocular surface residence times than 0.3% hydroxypropylmethylcellulose or 1.4% polyvinyl alcohol.[2] Some early clinical studies reported improvement of dry eye signs and symptoms in patients treated with HA-containing solutions compared to other lubricant solutions, whereas others did not.[3-6] Recent clinical studies have demonstrated improvement in dry eye signs and symptoms.[7-10]

Lubricant preparations containing HA as the active ingredient have been approved for use in the treatment of dry eye in multiple countries, but not in the US. HA ophthalmic solution 0.1% and 0.3% has been marketed in Japan since 1995 and in some other Asian countries under the trade names Hyalein®. Current usage is over 40 million units per year. HA ophthalmic solution 0.18% has also been marketed in Europe, Australia, and parts of Asia under the trade names Vismed®, Vislube®, and Hylovis®. In the US, HA is listed as an inactive ingredient in an over-the-counter (OTC) artificial tear product (Blink® Tears).

SI-614 has demonstrated improved tear film stabilization compared to HA in pre-clinical studies, and in Phase 2 and Phase 2/3 clinical studies. In the Phase 2 study, statistically significant reductions in corneal fluorescein staining and improved dry eye symptoms were seen. In the Phase 2/3 study, SI-614 demonstrated statistically significant improvements for dry eye symptoms (ocular discomfort and dryness) and secondary analyses supported indicated that statistically significant improvements in all symptoms began within the first 5 days of dosing and remained efficacious for the entire 28 days

treatment period. Despite its effect on symptomatology, 0.3% SI-614 ophthalmic solution failed to show a statistically significant reduction in corneal fluorescein staining score in the study eye at Day 28 (primary sign). The detailed results from nonclinical and prior clinical stuies can be found in the latest version of the investigator's brochure.

The objective of the current Phase 3 study is to evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution compared to placebo when administered 4 times daily for 84 days in patients with dry eye.

1.1 Risks and Benefits

Treatment with SI-614 appeared to be safe and well-tolerated in Phase 2 and Phase 2/3 studies conducted in patients with dry eye.

A Phase 2, multicenter, randomized, double-masked, parallel-group study was conducted to evaluate the efficacy and safety of 2 concentrations (0.3% and 0.5%) of SI-614 ophthalmic solution compared to placebo (vehicle) when administered 4 times daily for 28 days in 150 patients with dry eye. Neither SI-614 concentration met the protocol-defined efficacy objectives. However, treatment with 0.3% SI-614 statistically significantly reduced corneal fluorescein staining at Day 28 and statistically significantly improved dry eye symptoms during Day 0 through Day 13 compared to placebo in a subgroup of more symptomatic patients (ie, those who had a worst symptom score ≥ 2.5 during Day -7 through Day -1). The 0.3% SI-614 appeared to be more effective in reducing dry eye symptoms rapidly than 0.5% SI-614. Both concentrations of SI-614 were safe and well-tolerated. Most of the adverse events (AEs) were of mild severity, with no severe AEs. The most common ocular treatment-emergent adverse events (TEAEs) were instillation site reactions (37 [24.7%], of which 25 were in the SI-614 treatment groups and 12 were in the placebo group), ocular hyperemia (2 [1.3%], 1 in each of the SI-614 groups), and reduced visual acuity (2 [1.3%], 1 in each of the SI-614 groups).

A Phase 2/3 study was conducted to evaluate the efficacy and safety of 0.3% SI-614 compared to placebo (vehicle) when administered 4 times daily for 28 days int 240 patiens with dry eye. Statistically significant improvements were seen for the primary efficacy symptom objective of mean change from baseline in average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 0 through Day 13. SI-614 failed to meet the primary sign endpoint of mean change [redacted] in the study eye at Day 28. The majority of AEs were mild in severity and no AEs were severe. No serious adverse events (SAEs) were reported. The most frequently reported ocular TEAE and non-ocular TEAE were instillation site pain (20 [16.4%] patients in the 0.3% SI-614 group and 16 [13.6%] patients in the placebo group) and nosopharyngitis (4 [3.3%] patients in the 0.3% SI-614 group and 3 [2.5%] patients in the placebo group). Four TEAEs led to the premature discontinuation of 2 patients; 1 patient in the 0.3% SI-614 group (conjunctivitis right eye, conjunctivitis left eye) and 1 patient in the placebo group (conjunctivitis right eye, conjunctivitis left eye). No safety concerns were raised in terms of visual acuity and slit lamp biomicroscopy assessments.

Potential Risks: Based on the results of Phase 2 and Phase 2/3 studies with SI-614, the most likely AEs that patients may experience include instillation site reactions, and, possibly but less likely, reduced visual acuity. AEs reported in published safety data from clinical trials of HA ophthalmic solutions in dry eye patients included worsening of dry eye symptoms, eye pain, or foreign body sensation. Additionally, based on results from animal studies with SI-614, patients may also experience discharge and redness of the eye.

Potential Benefits: Patients may experience a reduction in various signs and symptoms of dry eye.

2 STUDY OBJECTIVES

To evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution compared with placebo when administered 4 times daily for 84 days in patients with dry eye

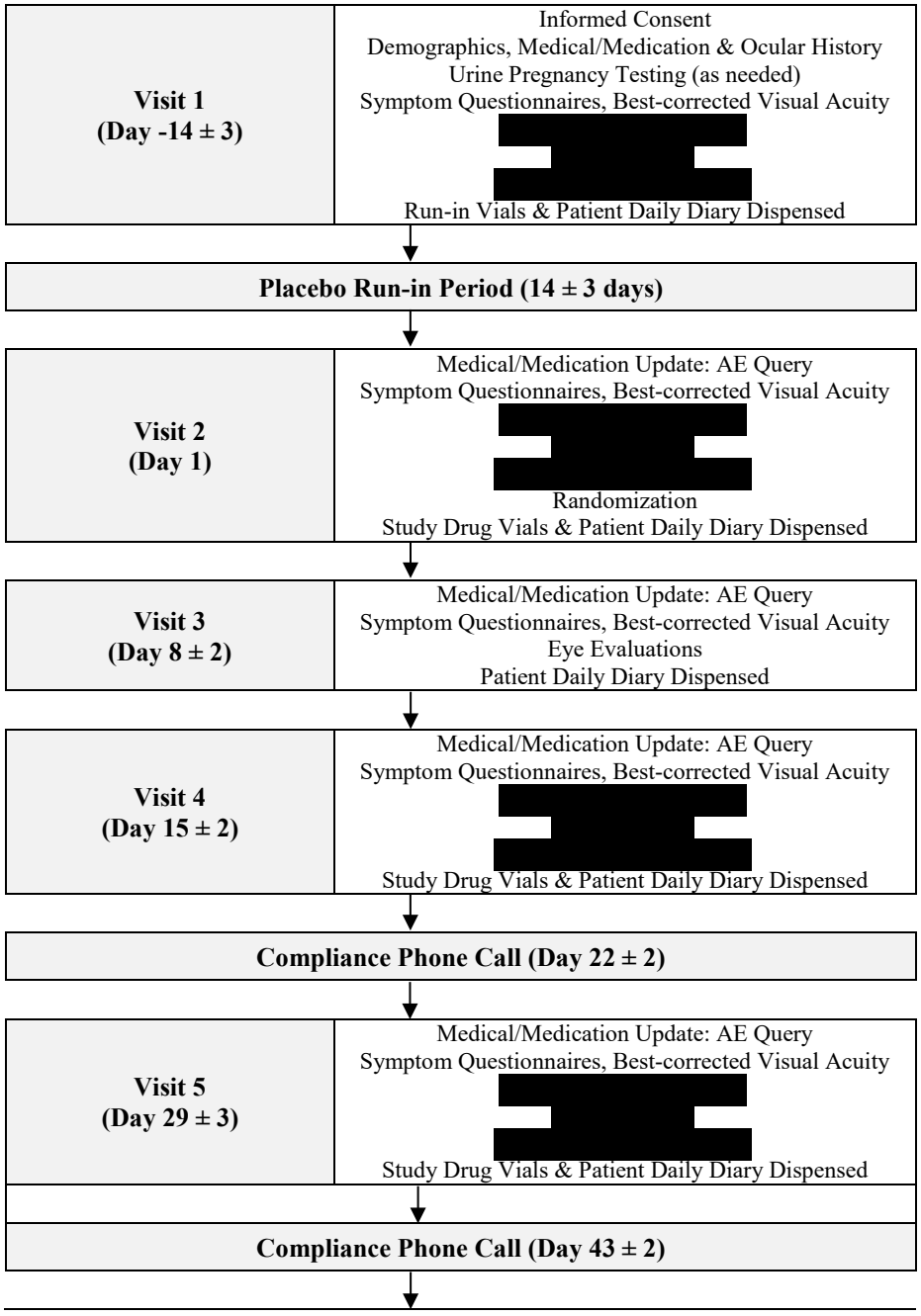
3 CLINICAL HYPOTHESES

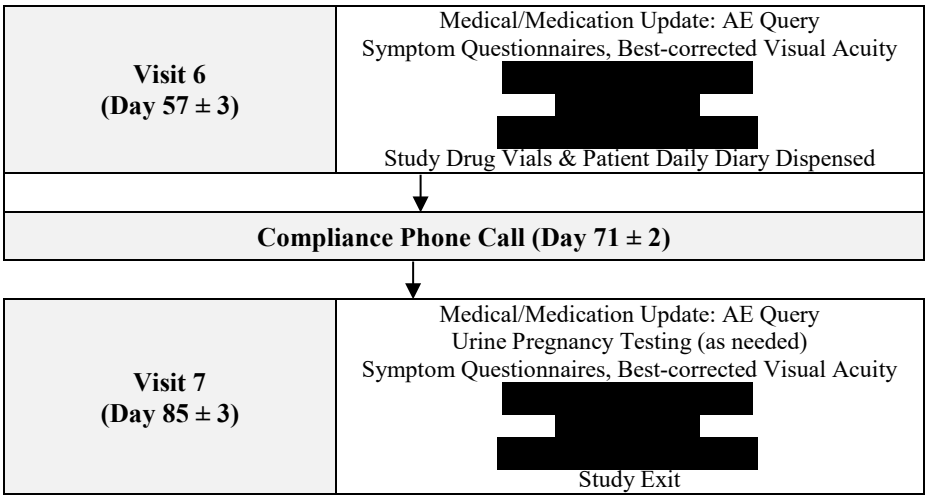
The clinical hypotheses for this study are that 0.3% SI-614 ophthalmic solution is superior to placebo for the primary endpoints of signs, as follows:

- Patients receiving 0.3% SI-614 ophthalmic solution will have a statistically significantly smaller increase in total corneal fluorescein staining score at Day 29 (Visit 5) [redacted] compared with patients receiving placebo (primary sign).

4 OVERALL STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-masked study designed to evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution compared to placebo in patients with dry eye. Approximately 230 male and female patients at least 18 years of age with a patient-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized to receive treatment with 0.3% SI-614 or placebo in a 1:1 ratio (approximately 115 patients in each treatment group). This study will consist of 2 periods: a 14-day run-in period and a 84-day treatment period. A study flow chart appears below:





Patients who terminate early during the treatment period will be asked to complete safety and efficacy assessments prior to commencement of any alternative dry eye therapy (if at all possible). Patients who are terminated early from the study will not be replaced.

In this study, the vehicle of SI-614 ophthalmic solution has been selected as the placebo control to objectively evaluate the efficacy and safety of 0.3% SI-614 ophthalmic solution. In addition, randomized assignment and double-masked design features has been implemented to minimize any bias for patient selection and data evaluation.

5 STUDY POPULATION

5.1 Number of Patients

It is estimated that approximately 230 patients (115 in each arm) will be enrolled. Patients will be randomized in a 1:1 ratio of 0.3% SI-614 to placebo.

5.2 Study Population Characteristics

All patients must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Patients must:

1. Be male or female of any race, at least 18 years of age at Visit 1.
2. Have provided verbal and written informed consent.
3. Be able and willing to use eye drops 4 times daily with a compliance rate of 80% or greater during the run-in period and follow instructions, including participation in all study assessments and visits.
4. Have a patient-reported history of dry eye in both eyes for at least 6 months prior to Visit 1.
5. Have used and/or desired to use an artificial tear substitute for dry eye symptoms within 6 months prior to Visit 1.
6. Have a best-corrected visual acuity score of +0.70 logarithm of the minimum angle of resolution (logMAR) or better in both eyes at Visit 1, as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart
7. Report an average score of 2.0 or higher in at least 1 of the 5 symptoms over the 7 days prior to Visit 2 as measured by the [redacted] Ocular Discomfort and 4-Symptom Questionnaire from the patient daily diary
8. Have ALL of the following in the qualifying eye(s), [redacted] at Visits 1 and 2:
   a) A tear film break-up time (TFBUT) of ≤ 5 seconds and ≥ 1 second
   b) A fluorescein staining score of ≥ 2 in at least 1 region [redacted]
   c) A conjunctival redness score of ≥ 1 [redacted]
   d) A total lissamine green staining score of ≥ 2 [redacted]
9. Demonstrate [redacted] at Visits 1 and 2 in the qualifying eye(s), as defined as meeting ALL of the following criteria:
   a) Have an increase of ≥ 3 in fluorescein staining score in the cornea [redacted]
   b) Report a score of ≥ 3 [redacted] Ocular Discomfort Scale at 2 or more consecutive time points [redacted] (if patient reports a score of 3 at Time 0, the patient must have a score of 4 at 2 or more consecutive time points)

10. If a female of childbearing potential, have a negative urine pregnancy test at Visit 1 and will be using an adequate method of birth control throughout the study period. [Females are considered of childbearing potential unless they are surgically sterilized (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) or post-menopausal (at least 12 months since last menses). Adequate birth control is defined as use of hormonal contraceptives (oral, implantable, injectable or transdermal), spermicide in conjunction with a barrier such as condom or diaphragm, or an intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the patient becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study.]

5.4 Exclusion Criteria

Patients must not:

1. Have any clinically significant slit lamp findings at Visit 1 or Visit 2, including active blepharitis, meibomian gland dysfunction, lid margin inflammation or ocular allergies that requires therapeutic treatment and/or, in the opinion of the investigator, may interfere with the study parameters.
2. Be diagnosed with an ongoing ocular infection (bacterial, viral or fungal), or active ocular inflammation (eg, follicular conjunctivitis) at Visit 1 or Visit 2.
3. Have a history of laser in situ keratomileusis (LASIK) surgery in either eye within 12 months prior to Visit 1, or have any scheduled LASIK surgery during the study period.
4. Have had any ocular surgical procedure within 12 months prior to Visit 1, or have any scheduled ocular surgical procedure during the study period.
5. Have used contact lenses within 30 days prior to Visit 1 or anticipates use of contact lenses during the study period.
6. Have used punctal plugs within 3 months prior to Visit 1 or anticipates use of punctal plugs during the study period.
7. Have used nasal spray for dry eye (i.e. TYRVAYA®) within 30 days prior to Visit 1 or anticipates use of nasal spray for dry eye during the study period.
8. Have used topical ocular cyclosporine (ie, Restasis® or Cequa™) or topical lifitegrast (i.e. Xiidra®) within 45 days prior to Visit 1.
9. Have used any topical ocular prescription (including medications for glaucoma) or OTC solutions, artificial tear substitutes, gels or scrubs within 24 hours prior to Visit 1 or during the study period.
10. Be currently using any medication known to cause ocular drying or increased lacrimation that has not been used on a stable dosing regimen for at least 30 days prior to Visit 1, or anticipates a change in such medication during the study period.
11. Have a current malignancy or has received treatment of malignancy within the past 5 years prior to Visit 1. Patients who have undergone successful resection of a basal

cell or squamous cell carcinoma of the skin may be enrolled even if the resection was within 5 years.

12. Have an uncontrolled systemic disease including, but not limited to clinically significant cardiovascular disease, pulmonary disease, or metabolic disease or any other systemic disease/symptoms that, in the opinion of the investigator, would interfere with study parameters.
13. Have an uncontrolled psychiatric condition that required a change in medication in the 30 days prior to Visit 1, or anticipates hospitalization or change in such medication during the study period, or substance or alcohol abuse.
14. Be a female who is pregnant, nursing an infant, or planning a pregnancy.
15. Have a known allergy and/or sensitivity to the study drug or its components.
16. Have a condition or is in a situation that, in the opinion of the investigator, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patients' participation in the study.
17. Be currently enrolled in an investigational drug or device study, have used an investigational drug or device within 45 days prior to Visit 1, or have been previously randomized to receive SI-614 ophthalmic solutions or placebo.

5.5 Withdrawal Criteria (if applicable)

Patients are free to discontinue their participation in this study at any time and for any reason, specified or unspecified, without prejudice. In addition, the Investigator may decide to discontinue a patient from the study for safety reasons or when it is in the best interest of the patient. No constraints will be placed on ordinary patient management, and patients (when appropriate) will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.

Reasons for patient withdrawal may include but are not limited to the following:

- Either at the Investigator's request, for safety reasons (eg, serious or severe AE), or at the patient's request.
- Non-compliance (eg, failure to follow dosing instructions, missing visits, using prohibited medications).
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the patient (the Investigator will report all such information on the source documents/electronic case report forms (eCRFs) and decide, in accordance with the Sponsor, whether the patient is to be withdrawn).
- A confirmed positive pregnancy test at any time during the study.
- When a patient is lost to follow-up. The Investigator (or designee) will attempt 3 times to reach the patient by telephone, and will send a follow-up letter by certified mail before considering the patient as lost to follow-up. These actions will be documented in the source document and recorded on the End of Study eCRF, and a copy of the follow-up letter maintained in the Investigator's file.

- When a patient is erroneously admitted into the study or does not meet eligibility criteria.

In addition, the Sponsor also reserves the right to discontinue the study at any time for either clinical or administrative reasons.

Patients not completing the entire study should be fully evaluated when possible. If, for any reason, a patient is discontinued before completing Visit 5, the patient should return to the clinic to return all used and unused study drug vials and patient daily diary and perform all the safety assessments scheduled for Visit 5 including but not limited to AE query, pregnancy test, best-corrected visual acuity and slit lamp biomicroscopy evaluation, and the reason for termination entered in the source document and End of Study eCRF.

All early terminations and their reasons must be carefully documented by the Investigator on the End of Study eCRF and, if applicable, on the Adverse Event eCRF. No patient who has been randomized can be replaced by another if the patient is discontinued prematurely for any reason.

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measures

The following primary endpoint will be evaluated:

- Change from baseline [redacted] to Day 29 [redacted] in total corneal fluorescein staining score [redacted]

6.1.2 Secondary Efficacy Measures

The following secondary endpoint will be evaluated:

- Change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14.

6.1.3 Exploratory Efficacy Measures

The following exploratory efficacy measures will be used:

Signs

- Fluorescein staining score [redacted]
- Lissamine green staining score [redacted]
- TFBUT
- Conjunctival redness [redacted]

Symptoms

- Patient daily diary during dosing period
- Ocular Surface Disease Index (OSDI) questionnaire
- [redacted] Ocular Discomfort and 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale

6.2 Safety Measures

- Best-corrected visual acuity
- Slit lamp biomicroscopy
- AE query

6.3 Other Measures

- Urine pregnancy test

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Run-In

The placebo (vehicle) solution is formulated as a clear, colorless, sterile, aqueous solution for topical ocular administration. The solution is composed of the same formulation as SI-614 ophthalmic solution but does not contain the active ingredient, SI-614. The placebo container is identical to the SI-614 ophthalmic solution vials.

7.1.2 Study Drug(s)/Formulation(s)

- 0.3% SI-614 ophthalmic solution
  SI-614 ophthalmic solution is formulated as a clear, colorless, sterile aqueous solution for topical ocular administration containing: the active ingredient (SI-614 0.3% w/v), sodium chloride, potassium chloride, dibasic sodium phosphate, sodium dihydrogen phosphate and water for injection, adjusted to pH 5.0 to 6.0. It is packaged in low-density polyethylene vials.
- Placebo ophthalmic solution
  The placebo ophthalmic solution is formulated as a clear, colorless, sterile aqueous solution for topical ocular administration. The solution is composed of the same formulation as SI-614 ophthalmic solution but does not contain the active ingredient, SI-614. The placebo container is identical to the SI-614 ophthalmic solution vials.

7.1.3 Study Drug Packaging Configuration

Nineteen pouches will be packed in a two-week clinical kit. Each pouch will contain 1 day's supply of study medication for 4 times daily dosing. Each pouch contains of 5 vials. Pouches will be labeled and the two-week clinical kits will be labeled.

7.1.4 Study Drug Storage and Accountability

Study drug(s) must be stored at controlled room temperature (25°C or less, Do Not Freeze), protected from light, and secured at the investigational site in a locked container, with access limited to the Investigator and designated study personnel.

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to patients properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to patients, amount returned to the site by the patients, and the amount returned to the Sponsor or destroyed upon the completion of the study.

7.1.5 Instructions for Dispensation, Use, and Administration

Patients will instill 1 drop of study drug (0.3% SI-614 or placebo) into each eye 4 times daily (morning, noon, afternoon, evening before bedtime) for 84 days. Study drug will be

stored in light protective foil pouches, which will contain 5 vials. Four vials of study drug will be insilled daily, one vial for back-up. Unused vial will be returned to the site. Patients should not open a foil pouch until they are ready to use the first vial of the pouch. Patients will be instructed to dose both eyes with 1 vial, as each vial is for single-use dosing.

7.2 Other Study Supplies

Urine pregnancy test kits, fluorescein sodium solution and lissamine green strips will also be required for the study.

8 STUDY METHODS AND PROCEDURES

8.1 Patient Entry Procedures

8.1.1 Overview

Patients as defined by the criteria in Section 5.2, 5.3 and 5.4 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a patient's participation in the trial (ie, prior to changes in a patient's medical treatment and/or prior to study related procedures), the study will be discussed with each patient, and patients wishing to participate must give written informed consent using an informed consent form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board (IRB).

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4). They include:

- LASIK – 12 months prior to Visit 1 and throughout study period
- Ocular surgery – 12 months prior to Visit 1 and throughout study period
- Contact lenses – 30 days prior to Visit 1 and throughout study period
- Punctal Plugs – 3 months prior to Visit 1 and throughout study period
- Nasal spray (TYRVAYA®) – 30 days prior to Visit 1 and throughout study period
- Topical ocular cyclosporine (Restasis® or Cequa™) – 45 days prior to Visit 1 and throughout study period
- Topical lifitigrast (Xiidra®) – 45 days prior to Visit 1 and throughout study period
- Topical Eyedrops – 24 hours prior to Visit 1 and throughout study period
- Unstable medication causing ocular drying or increased lacrimation – 30 days prior to Visit 1 and throughout study period
- Investigational drug or device – 45 days prior to Visit 1 and throughout study period

8.1.4 Procedures for Final Study Entry

Patients must meet all inclusion and none of the exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups:

At Visit 1, patients who provide written informed consent will be assigned a unique 5-digit screening number, which includes the 2-digit site number plus a unique 3-digit screening number beginning with 001 (eg, 11-001, 11-002, 11-003, etc.). Screening numbers must be assigned in ascending consecutive order.

Prior to Visit 2, the Medical Monitor will review the medical and medication history, screening results and screening eligibility criteria for each patient who enters the run-in period, and confirm the patient's eligibility for the study. If there is a change in medical or medication status between Visits 1 and 2, the Medical Monitor will review and confirm the patient's eligibility for the study prior to randomization at Visit 2 (if possible) or as soon as possible after Visit 2.

At Visit 2, a patient who meets all the eligibility criteria will be randomized to receive treatment with 0.3% SI-614 or placebo in a 1:1 ratio. The Interactive Voice/Web Response System (IVRS/IWRS) will be used to account for the stratification factors.

Patient's will be stratified by the following factors and cut-offs:

1. Average of dryness and ocular discomfort at bedtime assessment for Run-in patient daily diary mean (Day -7 through Day -1).
    a. ≤ 2.5
    b. > 2.5

2. Change [redacted] in total corneal fluorescein staining at Visit 2
    a. ≤ 3.5
    b. > 3.5

Both strata will be entered into the IVRS/IWRS, which will assign the randomization number and the assigned kit number for the patient. The site staff will dispense to the patient the study kit labeled with the corresponding kit number. Both the randomization number and the dispensed study drug kit number will be recorded on the patient's source document and eCRF.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or OTC, is to be recorded on the patient's source document and corresponding eCRF along with the reason the medication was taken. Concomitant medications that are considered necessary for the patient's welfare, but will not interfere with study assessments and evaluations, will be allowed during the study at the Investigator's discretion.

Use of medications known to cause ocular drying or increased lacrimation (see Appendix 3) is allowed; however, any use of medications known to cause ocular drying or increased lacrimation must be on a stable dosing regimen for at least 30 days prior to Visit 1, and should remain stable during the study period. A change in the use of a medication known to cause ocular drying or increased lacrimation during the study period will be recorded as a protocol deviation.

Concurrent enrollment in another investigational drug or device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.4).

If a specific medication/therapy has the potential to interfere with the treatment effect of the study drug or interpretation of the study results, the Investigator should contact the Medical Monitor prior to use.

Any patient using a prohibited medication/therapy during the course of the study that could interfere with the treatment effect of the study drug or interpretation of the study results may be withdrawn from the study at the discretion of the Investigator and/or Sponsor. However, the Investigator should not withdraw a patient without first confirming it with the Medical Monitor and/or Sponsor. Use of a prohibited medication during the applicable washout period or during the study period will be recorded as a protocol deviation.

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objective(s)

The following procedures will be performed (see Appendix 1 for description):

Visit 1 (Day -14 ±3)

- Informed consent/Health Information Portability and Accountability Act (HIPAA)
- Demographic data and medical/medication & ocular history
- Urine pregnancy test (for females of childbearing potential)
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Review of qualification criteria
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes

- Run-in solution instillation
    - A trained study technician will instill the first dose of run-in solution (1 drop in each eye) in-office.
- Waiting period of up to 10 minutes following dose of run-in solution
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Review of qualification criteria
- AE query
- Patient instillation of run-in solution
    - Qualified patient will self-administer 1 drop of run-in solution in both eyes under study staff observation.
- Run-in solution dispensation
    - Qualified patients will be instructed to instill 1 drop of run-in solution 4 times daily in each eye starting in the evening of Visit 1 and continuing through the morning of Visit 2.
- Dispensation of diaries and patient instructions
    - Qualified patients will also be dispensed a patient daily diary to be completed 4 times daily, and instructed to record each dose of run-in solution taken. Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with run-in solution.
- Schedule patients for Visit 2
    - Qualified patients will be scheduled to return for Visit 2, and will be instructed to instill the morning dose of run-in solution at least 1 hour before the start of Visit 2.

Visit 2 (Day 1)

- Collection and review of run-in vials and patient diaries for qualification and compliance
- Medical/medication & ocular history updates

- AE query
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Review of qualification criteria
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes
- Run-in solution instillation
    - A trained study technician will instill a dose of run-in solution (1 drop in each eye) in-office.
- Waiting period of up to 10 minutes following dose of run-in solution
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Review of qualification criteria
- Randomization
- Study drug dispensation and instillation
    - Randomized patients will be dispensed 1 treatment kit assigned by IVRS/IWRS, and a trained study technician will instill the first dose of study drug (1 drop in each eye) in-office.
    - Randomized patients will be instructed to instill 1 drop of study drug 4 times daily in each eye starting in the evening of Visit 2 and continuing through the morning of Visit 3.

- Patient daily diary dispensation
    - Randomized patients will also be dispensed a new patient daily diary to be completed 4 times daily, and instructed to record each dose of study drug taken. Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with study drug.
- AE query;
- Schedule patients for Visit 3
    - Randomized patients will be scheduled to return for Visit 3 and will be instructed to instill the morning dose of study drug at least 1 hour before the start of Visit 3.

Visit 3 (Day 8 ± 2): 1-Week Follow-Up

- Collection and review of study drug and patient diaries for compliance
- Medical/medication & ocular history updates
- AE query
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Study drug dispensation and instillation
    - Patients will not be dispensed new treatment kit at Visit 3, and a trained study technician will instill a dose of study drug (1 drop in each eye) in-office from the kit dispensed at Visit 2.
    - Patients will be instructed to instill 1 drop of study drug 4 times daily in each eye starting in the evening of Visit 3 and continuing through the morning of Visit 4.
- Patient daily diary dispensation
    - Patients will also be dispensed a new patient daily diary to be completed 4 times daily, and instructed to record each dose of study drug taken.

Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with study drug.

- AE query
- Schedule patients for Visit 4
    - Patients will be scheduled to return for Visit 4 and will be instructed to instill the morning dose of study drug at least 1 hour before the start of Visit 4.

Visit 4 (Day 15 ± 2): 2-Week Follow-Up

- Collection and review of study drug and patient diaries for compliance
- Medical/medication & ocular history updates
- AE query
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes
- Study drug instillation
    - A trained study technician will instill a dose of study drug (1 drop in each eye) in-office from returned kit.
- Waiting period of up to 10 minutes following dose of study drug
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]

- Lissamine green staining [redacted]
- Study drug dispensation and instillation
    - Patients will be dispensed 1 new treatment kits assigned by IVRS/IWRS, and a trained study technician will instill the first dose of study drug (1 drop in each eye) in-office from a new kit.
    - Patients will be instructed to instill 1 drop of study drug 4 times daily in each eye starting in the evening of Visit 4 and continuing through the morning of Visit 5.
- Patient daily diary dispensation
    - Patients will also be dispensed a new patient daily diary to be completed 4 times daily, and instructed to record each dose of study drug taken. Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with study drug.
- AE query
- Schedule patients for Phone Call and Visit 5
    - Patients will be scheduled for a phone call at around week 3 (Day 22 ± 2) and return for Visit 5 and will be instructed to instill the morning dose of study drug at least 1 hour before the start of Visit 5.

Phone Call for Drug Compliance: Day 22 ± 2

- The patient will be contacted by telephone and told the following:
    - Patients will be reminded to continue instilling 1 drop of study drug 4 times daily in each eye; and to complete the symptom assessments before dosing with study drug and to record each dose of study drug taken.
- AE query

Visit 5 (Day 29 ± 2): 4-Week Follow-Up

- Collection and review of study drug and patient diaries for compliance
- Medical/medication & ocular history updates
- AE query
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]

- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes
- Study drug instillation
    - A trained study technician will instill a dose of study drug (1 drop in each eye) in-office from returned kit.
- Waiting period of up to 10 minutes following dose of study drug
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Study drug dispensation and instillation
    - Patients will be dispensed 2 new treatment kits assigned by IVRS/IWRS, and a trained study technician will instill the first dose of study drug (1 drop in each eye) in-office from a new kit.
    - Patients will be instructed to instill 1 drop of study drug 4 times daily in each eye starting in the evening of Visit 5 and continuing through the morning of Visit 6.
- Patient daily diary dispensation
    - Patients will also be dispensed a new patient daily diary to be completed 4 times daily, and instructed to record each dose of study drug taken. Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with study drug.
- AE query
- Schedule patients for Phone Call and Visit 6

Patients will be scheduled for a phone call at around week 6 (Day 43 ± 2) and return for Visit 6 and will be instructed to instill the morning dose of study drug at least 1 hour before the start of Visit 6.

Phone Call for Drug Compliance: Day 43 ± 2

- The patient will be contacted by telephone and told the following:
    - Patients will be reminded to continue instilling 1 drop of study drug 4 times daily in each eye; and to complete the symptom assessments before dosing with study drug and to record each dose of study drug taken.
- AE query

Visit 6 (Day 57 ± 3): 8-Week Follow-Up

- Collection and review of study drug and patient diaries for compliance
- Medical/medication & ocular history updates
- AE query
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes
- Study drug instillation
    - A trained study technician will instill a dose of study drug (1 drop in each eye) in-office from returned kit.
- Waiting period of up to 10 minutes following dose of study drug.
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Study drug dispensation and instillation

  - Patients will be dispensed 2 new treatment kits assigned by IVRS/IWRS, and a trained study technician will instill the first dose of study drug (1 drop in each eye) in-office from a new kit.
  - Patients will be instructed to instill 1 drop of study drug 4 times daily in each eye starting in the evening of Visit 5 and continuing through the morning of Visit 6.
- Patient daily diary dispensation
  - Patients will also be dispensed a new patient daily diary to be completed 4 times daily, and instructed to record each dose of study drug taken. Patients will also be instructed to complete the symptom assessments in the morning and in the evening before dosing with study drug.
- AE query

Phone Call for Drug Compliance: Day 71 ± 2

- The patient will be contacted by telephone and told the following:
  - Patients will be reminded to continue instilling 1 drop of study drug 4 times daily in each eye; and to complete the symptom assessments before dosing with study drug and to record each dose of study drug taken.
- AE query

Visit 7 (Day 85 ± 3): 12-Week Follow-Up

- Collection and review of study drug and patient diaries for compliance
- Medical/medication & ocular history updates
- AE query
- Urine pregnancy test (for females of childbearing potential)
- [redacted] Ocular Discomfort & 4-Symptom Questionnaire
- [redacted] Ocular Discomfort Scale
- OSDI
- Best-corrected visual acuity
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Waiting period of at least 20 minutes

- Study drug instillation
    - A trained study technician will instill a dose of study drug (1 drop in each eye) in-office from returned kit.
- Waiting period of up to 10 minutes following dose of study drug.
- [redacted]
- Slit-lamp biomicroscopy
- Conjunctival redness [redacted]
- TFBUT
- Fluorescein staining [redacted]
- Lissamine green staining [redacted]
- Best-corrected visual acuity
- AE query
- Study exit

Early Termination/Discontinuation

If a patient is discontinued from the study prior to Visit 7, then all safety evaluations and efficacy evaluations that are to be performed at Visit 7 should be performed on the day of discontinuation (early termination) prior to commencement of any alternative dry eye therapy (if at all possible).

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure patient safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as “Not done.”

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp biomicroscopy;
- Best-corrected visual acuity;
- Pregnancy test;
- Assessment of AEs;

- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Patients will be instructed on proper use of the patient daily diary and proper instillation and storage of study drug at the end of Visits 1, 2, 3, 4, 5, and 6, and given written instructions. The patient daily diaries and used and unused study drug vials will be collected at each visit from Visit 2 up to and including Visit 7 to assess dosing and symptom assessment compliance. Dosing compliance will be based off of the used and unused vial count. If the patient is less than 75% or more than 125% compliant with dosing based on the expected number of used vials, then the patient will be deemed non-compliant and a deviation should be recorded.

In the patient daily diary, if more than 25% of Dose Taken boxes are checked "no", left blank, or missing for a diary period, a patient will be deemed non-compliant and a diary deviation will be recorded. If more than 25% of the total diary symptom assessments for that dosing period are missed, these patients will be deemed non-compliant and a diary symptom assessment deviation will be recorded. These guidelines will be used by the Investigator for determining the patient's necessary compliance for the study and for recording deviations from this compliance.

8.6 Patient Disposition

8.6.1 Completed Patients

A completed patient is one who has not been discontinued from the study and has successfully completed Visit 7.

8.6.2 Discontinued Patients

Patients may be discontinued prior to their completion of the study due to:

- AE
- Protocol violation
- Administrative reasons (eg, inability to continue)
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Sponsor termination of study
- Other

Note: In addition, any patient may be discontinued for any sound medical reason.

Notification of a patient discontinuation and the reason for discontinuation will be made to [redacted] and/or Sponsor and will be clearly documented on the patient's source documents and eCRF.

8.7 Study Termination

The study may be stopped at any time by the investigator, the Sponsor, and/or [redacted] with appropriate notification.

8.8 Study Duration

An individual patient's participation will involve 7 visits over approximately a 14-week period (98 days).

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, sponsor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, patient safety, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the patients' medical records will be performed in a manner that adequately maintains patient confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, [redacted]/sponsor quality assurance and or its designees may carry out on-site inspections and/or audits, which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as patient confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease occurring after the patient started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug will be considered a new AE, but exacerbation of conditions related to the signs and symptoms of dry eye will not be reported as an AE unless they persist and/or result in the discontinuation of the patient.

Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as an AE at subsequent visits.

AEs (both elicited and observed) and SAEs will be monitored throughout the study. The investigator will promptly review all AEs (both elicited and observed) for accuracy and completeness. All AEs will be documented on the appropriate source document and eCRF.

A worsening in best-corrected visual acuity from Visit 1 [redacted] of greater than or equal to 0.22 logMAR units is considered an AE.

Pregnancy is not to be considered an AE, but it is an important medical event that must be followed up as described in Section 10.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the patient. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the patient, but is easily tolerated and does not interfere with the patient's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

9.1.2 Relationship to Study Drug

The relationship of each AE to the study drug should be determined by the investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. Types of evidence that would suggest a causal relationship between the study drug and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome); 1 or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Note: A SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the patient's eyes (eg, hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

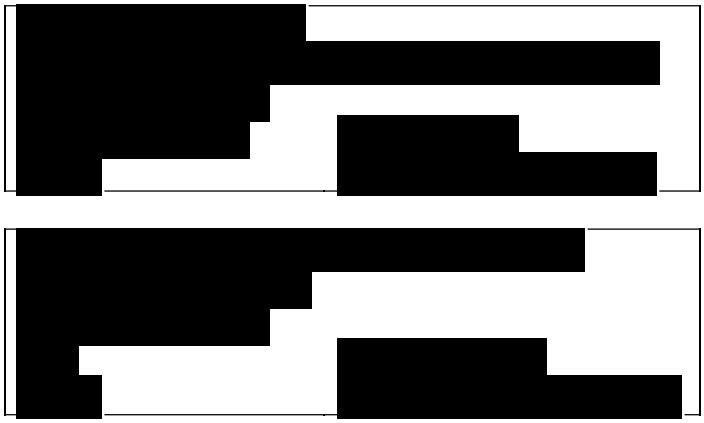
All AEs and their outcomes must be reported to [redacted] the study sponsor, and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Serious Adverse Event

To ensure patient safety, all SAEs, regardless of relationship to the study drug, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate eCRF. The investigator is obligated to pursue and obtain information requested by [redacted] and/or the sponsor in addition to that information reported on the eCRF. All patients experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify [redacted] and the sponsor immediately; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient; provide [redacted] and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:



9.4 Procedures for Unmasking of Study Drug

All patients, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment has been assigned to a patient. When possible (ie, in non-emergent situations), [redacted] and/or Sponsor should be notified before unmasking study drug.

Serious unexpected suspected adverse reactions, which are patient to expedited reporting, will be unmasked before submission to the Regulatory Authorities. The procedure for unmasking will be described in a separate Safety Plan for this study.

9.5 Type and Duration of the Follow-up of Patients after Adverse Events

The investigator will follow unresolved suspected AEs to resolution until the patient is lost to follow-up or until the AE is otherwise explained. Resolution means the patient has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the AE.

Non-SAEs identified on the last scheduled contact must be recorded on the Adverse Event eCRF with the status noted.

SAEs identified on the last scheduled contact must be recorded on the Adverse Event eCRF and reported to [redacted] and the Sponsor according to the procedure outlined in Section 9.3.1. These events may include previously reported or new SAEs. Any new SAEs reported by the patient to the investigator that occurred after the last scheduled visit and are determined by the investigator to be reasonably associated with the use of the study drug will be reported to the Sponsor. These events may include SAEs that are captured on follow-up telephone contact or at any other time after the defined study period. The investigator should follow serious related AEs identified after the last scheduled contact until the events are resolved or the patient is lost to follow-up. The investigator should continue to report any significant follow-up information to the Sponsor until the event is resolved.

10 Pregnancy

Women of Childbearing Potential (WOCBP) include any females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or are not postmenopausal at least 12 months since last menses. WOCBP will be required to use designated methods of birth control during the course of the study, all women who are pregnant, nursing an infant, or planning a pregnancy will be excluded from participation.

During the study, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a patient or Investigator suspects that the patient may be pregnant prior to study drug administration, the study drug must be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the patient must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the patient is receiving study drug treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued, and patient will be withdrawn from the study and followed until the pregnancy comes to term.

If a female has a positive pregnancy test during the study, then the investigator will notify [redacted] immediately. The investigator shall request from the patient and/or the patient's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the patient's source documents and will provide a copy of all documentation to [redacted] A Pregnancy Report form will be submitted to the Sponsor and [redacted] at a minimum initially and at the end of the pregnancy. The Investigator is also encouraged to submit to the Sponsor and [redacted] trimester follow up reports during the pregnancy. The outcome of the pregnancy and any complications occurring during the pregnancy or the delivery must be reported to the Sponsor and [redacted]

The contact person at [redacted] to report a pregnancy is:

[redacted]

[redacted]

11 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 Analysis Populations

Intention-to-Treat Population (ITT) – The intention-to-treat (ITT) population includes all randomized patients. Subjects in the ITT population will be analzyed as randomized. The primary analysis will be performed on the ITT population with the primary estimand.

Per-Protocol (PP) Population – The PP population is defined as all ITT patients who have no major protocol deviations and completed the trial. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

Safety Population – The safety population will include all patients who receive at least 1 dose of randomized study drug. Subjects in the Safety population will be analyzed as treated.

11.2 Statistical Hypotheses

The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided at a significance level of 0.05. The primary and secondary endpoints will be tested in a hierarchical fixed sequence in the following order:

H_{01}: There is no difference between 0.3% SI-614 and placebo in the change [redacted] in corneal total fluorescein staining score [redacted] in the study eye at Visit 5 (Day 29).

H_{A1}: Change from baseline [redacted] to Day 29 [redacted] in corneal total fluorescein staining score [redacted] in the study eye is less with 0.3% SI-614 than with placebo.

H_{02}: There is no difference between 0.3% SI-614 and placebo in the change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14.

H_{A2}: Change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 is less with 0.3% SI-614 than with placebo.

11.3 Sample Size

The power and sample size for this study were calculated based on the results from the previous Phase 2 and Phase 2/3 study.

In order to have 90% power to detect a difference of -0.75 between SI-614 and placebo, 109 patients per treatment arm are required to be randomized. This assumes a two-sided test at alpha = 0.05 and a common standard deviation (SD) of 1.7 in both treatment arms.

Accounting for up to 5% dropouts in the study, 115 patients per treatment arm, or 230 total patients are required to have 90% power for the primary endpoint.

The hierarchical, secondary endpoint of the change from baseline in the average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 will have 51% power with this sample size, assuming a difference between SI-614 and placebo of -0.13. This endpoint will be tested conditional upon the primary endpoint being successful, thereby maintaining the study-wide type I error rate for both endpoints. The sample size calculation assumes a two-sided test at alpha = 0.05 and a common SD of 0.48 in both treatment arms.

11.4 Statistical Analysis

11.4.1 General Considerations

The quantitative variables will be summarized using mean, median, SD, minimum, and maximum. The qualitative variables will be summarized using counts and percentages.

All efficacy analyses will present two-sided 95% confidence intervals around the difference between treatments (SI-614 – placebo).

All summaries will be presented by treatment group. Summaries will be provided for demographics and patient disposition.

Baseline measures are defined as the last time point-matched measure prior to the initiation of randomized study drug treatment unless otherwise specified. Change from baseline will be calculated as follow-up visit value minus baseline value. Treatment comparisons between active and vehicle will be calculated as active minus vehicle. For measures from daily patient diaries, baseline is defined as the average of all days during Day -7 to Day -1, calculated separately for the morning, bedtime, and daily averages. Daily scores are first obtained by averaging the AM and PM scores for that day, as applicable.

11.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the "study eye" as defined by the following:

Study Eye: Eyes are eligible for analysis if they meet all "inclusion criteria" as specified in Section 5.3. In the case that both eyes are eligible for analysis, the study eye will be the eye with the greatest change [redacted] in corneal total fluorescein staining score [redacted] at baseline (Visit 2). If the baseline change [redacted] in corneal total fluorescein staining score is the same in both eyes, then the right eye will be used as the study eye. If only one eye meets all inclusion criteria, then the single qualifying eye is the study eye.

11.4.3 Missing Data

The primary efficacy analyses will be performed using the multiple imputation methodology specified in Estimand 1 if the rate of missing data for an endpoint is balanced between the two treatment groups (as evaluated by the Fisher's exact test at an alpha level of 0.05) or the rate of missing data for an endpoint is ≤ 5% in all subjects. If the rate of missing data for an endpoint is imbalanced between treatment groups (as

demonstrated by the Fisher's exact test with a p-value < 0.05) and the rate of missing data for an endpoint is greater than 5% in all subjects, then the primary analyses will utilize the ITT population with observed data only specified in Estimand 2 using the permutation test with trimmed means methodology. Additional sensitivity analyses will be executed including:

- Multiple imputation via placebo group-based pattern mixture models (PMM) imputation with the ITT population under the assumption of missing not at random;
- Multiple imputation via randomized treatment group-based Markov Chain Monte Carlo (MCMC) with the ITT population under the assumption of missing at random;
- Last observation carried forward (LOCF) imputation methodology using the ITT population;
- Tipping point analyses;
- Observed data only using ITT and PP populations.

Secondary efficacy analyses will be conducted similarly.

Exploratory efficacy analyses will be conducted using the ITT population with observed data only.

11.4.4 Primary Efficacy Analyses

For the primary endpoint, change from baseline will be calculated as visit – baseline such that a positive difference indicates a worsening of dry eye signs. In addition, treatment comparisons between 0.3% SI-614 and placebo will be calculated as 0.3% SI-614 – placebo, such that a negative result indicates a better score for 0.3% SI-614 (i.e., 0.3% SI-614 demonstrated less severity in dry eye signs than the placebo group).

The primary analysis of the primary endpoint will use the ITT population. If the rate of missing data for an endpoint is balanced between the two treatment groups (as evaluated by the Fisher's exact test at an alpha level of 0.05) or the rate of missing data for the endpoint is ≤ 5% in all subjects then primary analysis will be executed using ANCOVA with multiple imputation methodology using the following Estimand 1:

Estimand 1:

- Population:
    - ITT population
- Endpoint:
    - Change from baseline [redacted] in total corneal fluorescein staining score in the study eye at Day 29 [redacted] in the ITT population
- Intercurrent event:

  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed. [treatment policy strategy]
  - Withdrawal due to lack of efficacy or adverse events. Missing values assumed to be missing not at random will be multiply imputed using placebo group-based PMM imputation. [hypothetical strategy]
  - Missing data with withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events. Missing values assumed to be missing at random will be multiply imputed using randomized treatment group-based MCMC imputation. [hypothetical strategy]

- Population-level summary:
  - Difference in the mean change from baseline [redacted] in total corneal fluorescein staining score in the study eye at Day 29 [redacted] between 0.3% SI-614 and placebo in the ITT population.

The permutation test with trimmed means as specified in Estimand 2 will then be executed as additional sensitivity analyses.

If the rate of missing data for the endpoint is imbalanced between treatment groups (demonstrated by Fisher's exact test with a p-value of <0.05) and the rate of missing data for the endpoint is greater than 5% in all subjects, then the primary analyses will utilize the ITT population with observed data only using the permutation test with trimmed means methodology with Estimand 2:

Estimand 2:

- Population:
  - ITT population
- Endpoint:
  - Change from baseline [redacted] in total corneal fluorescein staining score in the study eye at Day 29 [redacted] in the ITT population
- Intercurrent event:
  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance. [treatment policy strategy]

  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed. [treatment policy strategy]
  - Withdrawal or missed assessments for any reason. Missing values will be trimmed from analyses in accordance to trimmed means methodology. [hypothetical strategy]

- Population-level summary:
  - Difference in the mean change from baseline [redacted] in total corneal fluorescein staining score in the study eye at Day 29 [redacted] between 0.3% SI-614 and placebo in the ITT population.

Analyses using the ITT population with multiple imputation with Estimand 1 will be additional sensitivity analyses.

The proportion of data trimmed in the permutation test with trimmed means analysis will be dependent on the maximum rate of missing data in any treatment group using the following:

Maximum Rate of Missing Data (%)	Data Trimmed (%)
>5% to <10%	10%
10% to <20%	20%
20% to <30%	30%

In the event that the maximum rate of missing data exceeds 30% in any treatment group, then the percentage trimmed will increase by a decile until the percentage trimmed exceeds the maximum rate of missing data in any treatment group.

The ANCOVA model used to compare the change from baseline [redacted] to Day 29 [redacted] in corneal total fluorescein staining score in the study eye between 0.3% SI-614 and placebo will include baseline [redacted] in corneal total fluorescein staining score in the study eye at Visit 2 and treatment group as covariates.

As supportive analyses, two-sample t-tests and a Wilcoxon rank sum test will be conducted to compare the change from baseline [redacted] at Day 29 [redacted] between the two treatment groups. Additional exploratory comparisons of the mean raw scores of corneal total fluorescein staining score at Day 29 [redacted] and baseline [redacted] (Visit 2, Day 1) between the treatment groups will be conducted using two-sample t-tests and Wilcoxon rank sum tests. Quantitative summary statistics will be provided for baseline Day 1 [redacted] Day 29 [redacted] and change from baseline [redacted] at Day 29 [redacted].

Least Squares (LS) means with standard errors (SEs) for each treatment group and LS mean differences between treatment groups with SEs will be presented from the

ANCOVA model together with two-sided p-values and two-sided 95% confidence intervals. Sample means, sample mean differences with SEs, two-sided 95% confidence intervals, and two-sided p-values will be reported from the two-sample t-tests. Two-sided p-values will be reported from the Wilcoxon rank sum tests for observed data only analyses and LOCF analyses only. Trimmed means of each treatment group, trimmed mean differences between treatment groups, two-sided exact p-values and two-sided exact 95% confidence intervals will be presented from the permutation test with trimmed means.

Sensitivity analyses will include multiple imputation by placebo group-based PMM, multiple imputation via randomized treatment group-based MCMC, single imputation by LOCF, and analyses of observed data only using the ITT and PP populations.

11.4.5 Secondary Efficacy Variables

Analyses of the secondary efficacy endpoint of the change from baseline (Day -7 through Day -1) in average score of ocular discomfort and dryness at the bedtime assessment from the patient daily diary during Day 1 through Day 14 will use a MMRM. The model will include the baseline average score of ocular discomfort and dryness (average of Day -7 through Day -1), treatment group, study day (Day 1 to Day 14 as categorical variables), and the interaction between treatment group and study day as fixed effects with correlated errors due to study day. The overall treatment differences (0.3% SI-614 versus placebo) and the corresponding p-values will be estimated based on the MMRM. As a sensitivity analysis, the above model will also be run without including the baseline average score of ocular discomfort and dryness symptom as a covariate.

As an additional sensitivity analysis of the average score of ocular discomfort and dryness symptom, the change from baseline in average ocular discomfort and dryness score from Day 1 to Day 14 will also be compared between the two treatment groups using two-sample t-tests and Wilcoxon rank sum tests for each individual day. In addition, an ANCOVA model using the baseline average score of ocular discomfort and dryness and treatment group will be used to examine change from baseline at each day.

Analyses of the secondary endpoint will utilize the ITT population using observed data only. Sensitivity analyses will include multiple imputation as described in Estimand 1, multiple imputation by placebo group-based PMM, multiple imputation via randomized treatment group-based MCMC, single imputation by LOCF, and analyses of observed data only using the PP population.

11.4.6 Exploratory Efficacy Variables

Exploratory efficacy variables will generally be analyzed on the ITT population using observed data.

For signs [redacted] (including fluorescein staining, lissamine green staining, TFBUT, and conjunctival redness), the change [redacted] measure at each visit and the change [redacted] at baseline [redacted] at each visit will be compared between the 2 treatment groups using a two-sample t-test, a Wilcoxon rank sum test, as well as an ANCOVA model adjusting for

baseline [redacted] value. In addition, change from time point-matched baseline [redacted] will be analyzed similarly.

For symptom measures (including OSDI, [redacted] Ocular Discomfort and 4-symptom Questionnaire), each individual symptom score as well as the change from baseline ([redacted] at Visit 2) will be compared between 0.3% SI-614 and placebo for each visit using a two-sample t-test, a Wilcoxon rank sum test, and an ANCOVA model adjusting for baseline.

[redacted] Ocular Discomfort Scale [redacted] is measured every 5 minutes [redacted] The area under the curve will be calculated for each patient using the trapezoidal rule, and compared between treatment groups using a two-sample t-test, as well as an ANCOVA model adjusting for baseline (Visit 2 area under the curve).

11.4.7 Safety Variables

AEs will be coded using the Medical Dictionary for Regulatory Activities dictionary.

Frequencies and percentages of patients with TEAEs, serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of patients with TEAEs by system organ class (SOC), by SOC and preferred term (PT), by SOC, PT and maximal severity, by SOC, PT and strongest relationship, and by SOC, PT, maximal severity, and strongest relationship. Separate analyses will be performed for ocular and non-ocular TEAEs.

Other safety endpoints including visual acuity, slit lamp biomicroscopy, and corneal sensitivity will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately. In addition, shifts from baseline to worst on-treatment value for ocular safety assessments will be summarized. All safety endpoints will be assessed using the Safety population.

11.4.8 Adjustment for Multiplicity

Hierarchical fixed sequence testing will be used in the analysis of the primary dry eye sign endpoint and the secondary dry eye symptom endpoint to maintain study wide type I error. The primary endpoint of change from baseline [redacted] at Day 29 [redacted] of the corneal total fluorescein staining score will be evaluated at a two-sided study wide alpha level of 0.05. If the primary endpoint is statistically significant, then the study will be declared a success for the primary endpoint and then the secondary endpoint of change from baseline of the bedtime assessment from the patient daily diary during Day 1 through Day 14 will be evaluated. If the primary endpoint is not statistically significant, no further formal hypothesis testing will proceed and the analyses of the secondary endpoint will be conducted as an exploratory analyses.

Exploratory endpoints will not be type I error controlled and thus, considered exploratory and hypothesis generating.

11.4.9 Interim Analyses

There will be no planned interim analyses.

12 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

12.1 Protection of Human Patients

12.1.1 Patient Informed Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each patient and/or from the patient's parent or legal guardian prior to enrollment into the study.

All ICFs must be approved for use by the sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (eg, due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Sponsor and [redacted] prior to submission to the governing IRB and that it is read, signed and dated by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by [redacted] and/or study sponsor and provided in writing by [redacted] and/or study sponsor prior to the consent process.

12.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB approved version of the ICF will be used.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

12.3 Patient Confidentiality

All personal study patient data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of [redacted] the sponsor, the IRB approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's identity will not be disclosed in these documents.

12.4 Documentation

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's study patient files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiographs. The investigator's copy of the eCRFs serves as the investigator's record of a patient's study-related data.

12.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all study drug and copies of eCRFs should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

12.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

12.5.1 Labeling/Packaging

Nineteen pouches will be packed in a two-week clinical kit. Each pouch will contain 5 vials. Pouches will be labeled and the two-week clinical kits will be labeled. The labels will include instructions for use.

12.5.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the investigator and his/her designees, and must be maintained at controlled room temperature (25°C or less, Do Not Freeze) and protected from light. The study drug will be administered only to

patients entered into the clinical study, in accordance with the conditions specified in this protocol.

12.5.3 Accountability of Study Drug

The study drug is to only be prescribed by the principal investigator or his/her named sub investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to patients properly qualified under this protocol to receive study drug.

The investigator must keep an accurate accounting of the study drug received from the supplier. This includes the amount of study drug dispensed to patients, amount of study drug returned to the investigator by the patients, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

12.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed at the study side. The return or disposal of study drug will be specified in writing.

12.6 Recording of Data on Source Documents and Case Reports Forms (CRFs)

All patient data will be captured in the patient source documents which will be transcribed in the eCRFs. The investigator is responsible for ensuring that study data is completely and accurately recorded on each patient's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (eg, by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized patients will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for screen failure patients. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs containing copies of all applicable patients' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

12.7 Handling of Biological Specimens

Not applicable.

12.8 Amendments to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the patients) must be approved by the IRB before it may be

implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

12.9 Publications

Information collected during this clinical study concerning SI-614 ophthalmic solution and results of the data obtained are proprietary and strictly confidential. The Sponsor reserves all rights to any such information. Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Sponsor and [redacted] will have the final decision regarding the manuscript and publication.

13 REFERENCES

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14 APPENDICES

Appendix 1: Schedule of Visits and Measurements

Visit Day	**Visit 1** -14±3			**Visit 2** 1			**Visit 3** 8±1	**Visit 4** 15±2			**Tel.** 22±2	**Visit 5** 29±3			**Tel.** 43±2	**Visit 6** 57±3			**Tel.** 71±2	**Visit 7** 85±3		
Placebo Run-in Administration	←	—	—	—	—	→																
Study Drug Administration							←	—	—	—	—	—	—	—	—	—	—	—	—	→		
Patient Daily Diary Symptom Assessment								←	—	—	—	—	—	—	—	—	—	—	—	→		
[redacted]	[redacted]																					
Informed Consent/HIPAA	X																					
Demographics	X																					
Medical/Medication & Ocular History Update	X			X			X	X				X				X				X		
Eligibility Criteria	X		X	X		X																
Urine Pregnancy Test[1]	X																			X		
4-Symptom Questionnaire (in-office)	X			X			X	X				X				X				X		
Ocular Discomfort (in-office)	X	X[2]		X	X[2]		X	X	X[2]			X	X[2]			X	X[2]			X	X[2]	
OSDI	X			X			X	X				X				X				X		
Best-Corrected Visual Acuity	X			X			X	X				X				X				X		X
Slit Lamp Biomicroscopy	X		X	X		X	X	X		X		X		X		X		X		X		X
Conjunctival Redness	X		X	X		X	X	X		X		X		X		X		X		X		X
TFBUT	X		X	X		X	X	X		X		X		X		X		X		X		X
Fluorescein Staining	X		X	X		X	X	X		X		X		X		X		X		X		X
Lissamine Green Staining	X		X	X		X	X	X		X		X		X		X		X		X		X
Run-in Vials Dispensed			X																			
Run-in Instilled (in office)	X		X	X																		
Run-in Vials Collected/Accountability				X																		
Randomization						X																
Study Drug Vials Dispensed						X				X				X				X				
Study Drug Instilled (in office)						X	X	X		X		X		X		X		X		X		
Study Drug Vials Collected/Accountability							X	X				X				X				X		
Daily Diary Dispensed			X			X	X			X				X				X				
Daily Diary Collected				X			X	X				X				X				X		
Adverse Event Query			X	X		X	X	X		X	X	X		X	X	X		X	X	X		X

Visit Day	**Visit 1** -14±3	**Visit 2** 1	**Visit 3** 8±1	**Visit 4** 15±2	**Tel.** 22±2	**Visit 5** 29±3	**Tel.** 43±2	**Visit 6** 57±3	**Tel.** 71±2	**Visit 7** 85±3
Placebo Run-in Administration	←	→								
Study Drug Administration			←	→						
Patient Daily Diary Symptom Assessment				←	→					
[redacted]	[redacted]									
Exit from Study										X

Abbreviations: [redacted] HIPAA. Health Insurance Portability and Accountability Act; OSDI, ocular surface disease index; Tel., Telephone call (to check drug compliance); TFBUT, tear film breakup time

[1]For females of childbearing potential

[redacted]

Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

The following examination procedures, tests, equipment and techniques are listed in this Appendix:

Visual Acuity Procedures

LogMAR Visual Acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual Acuity should be evaluated at the beginning of each visit in the study (ie, prior to slit-lamp examination). Patients should use most recent correction to attain their best-corrected visual acuity.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", eg, from Prevent Blindness) wall charts are used, the patient viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Chart 1 & 2, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The patient should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The patient should be told that the chart has letters only, no numbers. If the patient reads a number, he/she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The patient 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 patient changes a response (eg, 'that was a "C" not an "O"') before he/she has read aloud the next letter, then the change must be accepted. If the patient changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the patient says he/she cannot read a letter, he/she should be encouraged to guess. If the patient identifies a letter as 1 of 2 letters, he/she should be asked to choose 1 letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

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

For Example: Patient 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 visual acuity	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a patient forgets his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from baseline (Visit 1) will be considered an AE.

Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described. The following will be examined at each visit:

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

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

[redacted]

Ocular Surface Disease Index© (OSDI©)

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

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

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

Subtotal score for answers 1 to 5 (A)

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

Subtotal score for answers 6 to 9 (B)

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

Subtotal score for answers 10 to 12 (C)

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

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

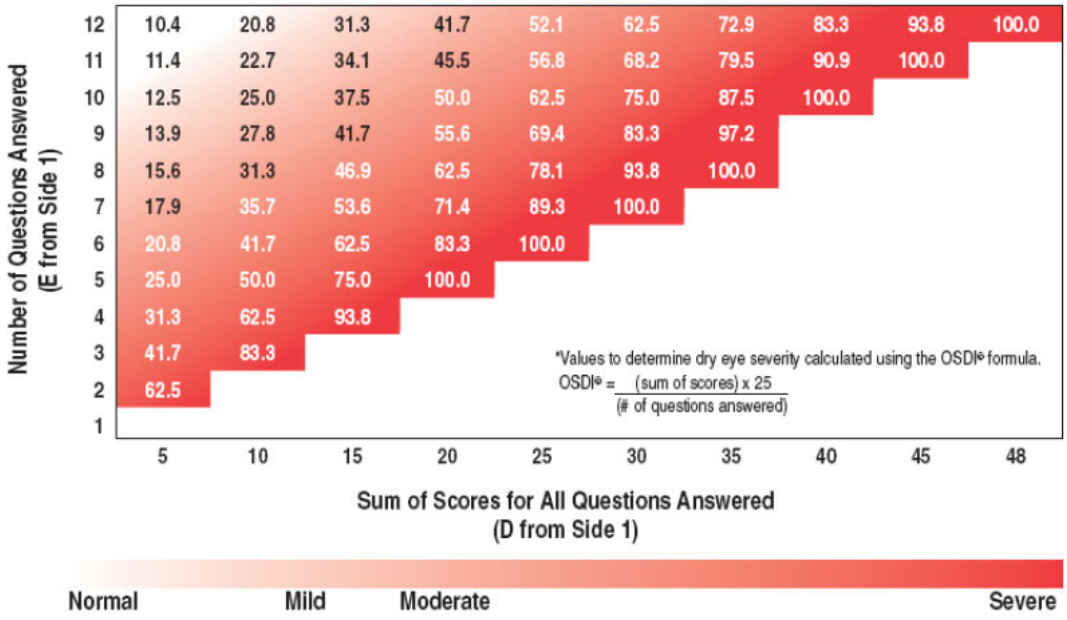
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

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

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

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



1. Data on file, Allergan, Inc.
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[redacted]

Tear Film Break-Up Time (TFBUT)

The examiner will instill 5 μL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the patient will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT.

With the aid of a slit lamp, the examiner will monitor the integrity of the tear film, noting the time it takes to form micelles from the time that the eye is opened. TFBUT will be measured in seconds using a stopwatch and a digital image recording system for the right eye followed by the left eye. A Wratten #12 yellow filter will be used to enhance the ability to grade TFBUT.

For each eye, 2 measurements will be taken and averaged unless the 2 measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement would be taken and the 2 closest of the 3 would be averaged.

Fluorescein Staining

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. In order to achieve maximum fluorescence, the examiner should wait approximately 3-5 minutes after instillation before evaluating fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the [redacted]. Digital images of fluorescein staining may be taken for digital analysis.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Lissamine Green Staining

The Investigator will instill 10 µL of lissamine green solution into the inferior conjunctival cul-de-sac and wait approximately 30 seconds before evaluating staining. The patient will be instructed to blink several times to distribute the lissamine green. The staining will be graded with the [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Patient Diary

Patients will be instructed to complete patient daily diary prior to dosing 4 times daily.

Appendix 3: List of Ocular Drying or Increased Lacrimation Medications

The following classes of concomitant medications are prohibited if the specific concomitant medication is known to cause ocular drying or increased lacrimation (i.e. ocular dryness or increased lacrimation is listed among the AEs or side effects section of the medication's labeling) and the medication has not been used at a stable dose for at least 30 days prior to Visit 1.

Ocular Drying

- Antihistamines
- Anti-depressants
- β-blockers
- Antipsychotic
- Codeine
- Decongestants
- Diuretics

Increased Lacrimation

- Cholinergic drugs

Appendix 4: Key Organizations and Personnel

Name and Contact Information	Responsibility
Seikagaku Corporation Address: 6-1, Marunouchi 1-chome Chiyoda-ku Tokyo 100-0005 JAPAN [redacted]	Sponsor - Trial design - Study management - Data management - Statistical analysis - Review of adverse events
[redacted]	CRO - Trial design - Management of the clinical study - Investigational drug management - Medical writing
[redacted]	Statistical analysis, IRT and data management
[redacted]	Medical Monitor - Medical management - Safety surveillance - Confirm the patient's eligibility for the study - Review safety data and clinical study report

Appendix 5: Amendment Summary of Changes

Not applicable

Appendix 6: Sponsor and [redacted] Approvals

Protocol Title: A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry eye (The SIDE Study)

Protocol Number: 614/1132

Final Date: March 23, 2022 / Version 1.0

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed: _____ Date: _____
[redacted]

Signed: _____ Date: _____
[redacted]

Signed: _____ Date: _____
[redacted]

Signed: _____ Date: _____
[redacted]

Signed: _____ Date: _____
[redacted]

Signed: _____ Date: _____
[redacted]

Appendix 7: Investigator's Signature

Protocol Title: A Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of SI-614 Ophthalmic Solution in Patients with Dry eye (The SIDE Study)

Protocol Number: 614/1132

Final Date: March 23, 2022 / Version 1.0

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by [redacted] and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____

Appendix 8: COVID-19 PANDEMIC AND SUGGESTED MEASURES

This section is provided in response to the "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Public Health Emergency" issued by the FDA on March 2020 and updated on August 2021. Taking the COVID-19 impact into account, this section provides guidance to Investigators and their site staff to mitigate risks and suggested measures to modify operations. Each Investigator may choose to implement different measures according to their sites' operations; which may include, but are not limited to the following items.

Screening Questions to Identify Potential COVID-19 Exposure

When scheduling an on-site visit for subjects, consider asking the subjects a few, short questions regarding potential exposure to COVID-19 before their on-site visit (in-person interactions). For example:

1. Have you had any of the following symptoms in the past 14 days without confirmation of etiology such as a positive flu test, existing chronic medical condition, etc.
    - Fever greater than 100.4 dgrees
    - Fahrenheit
    - Cough
    - Difficulty breathing
    - Sore throat
2. In the last 14 days, have you lived with, visited, cared for, or been in a room for a prolonged period of time with someone who is under investigation or has been confirmed for COVID-19?

Remote Monitoring

Due to travel restrictions, shelter in place or stay at home mandates, sites' change in operations, and a number of other reasons to try to contain the spread of the virus and minimize exposure, it is reasonable to conduct monitoring visits remotely, instead of in-person, whenever feasible. Site staff/Investigator will work with CRO and the assigned CRA to define and understand the logistics of the remote visit such as source data verification.

Data Management

In order to confirm the effect of COVID-19 on this study, the following information will be captured in eCRF.

- Missed visit due to COVID-19
- Missed assessment due to COVID-19

- Screen failed subject due to COVID-19
- Early discontinuation due to COVID-19
- AE related to COVID-19