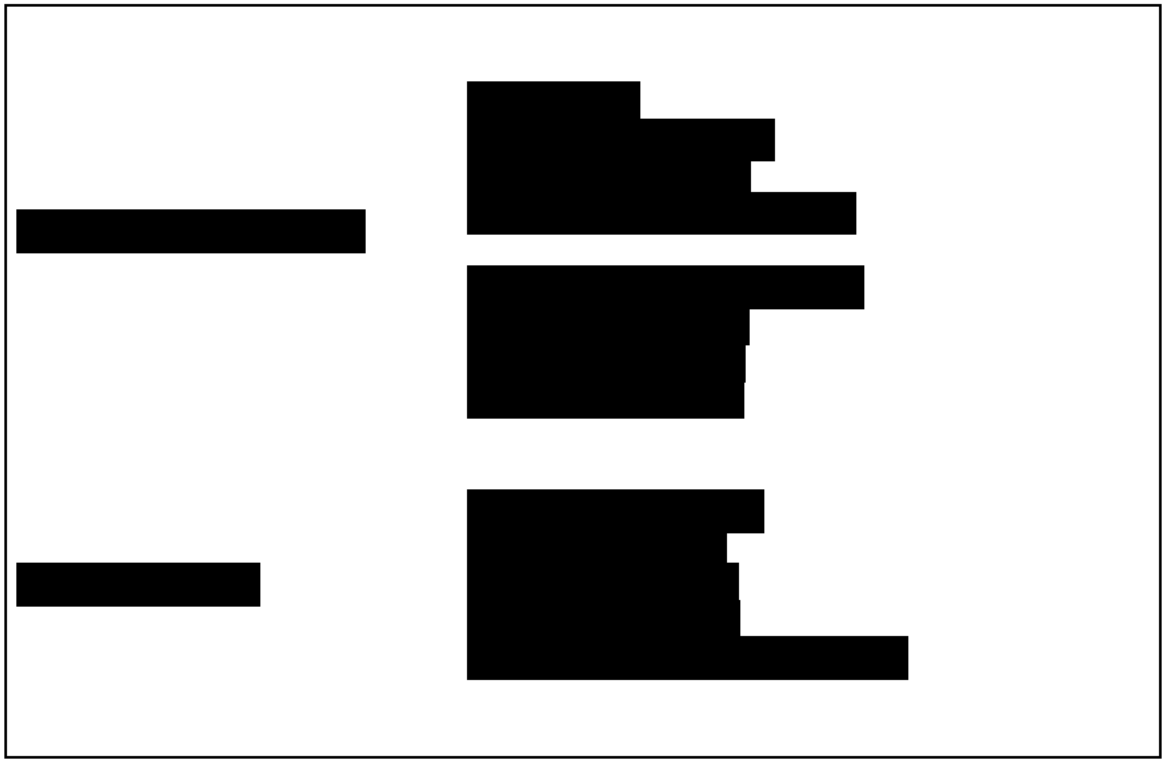
Clinical Trial Protocol: VISTA-2 / 19-110-0011

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of SkQ1 Ophthalmic Solution in the Environment and During Challenge in the Controlled Adverse Environmental (CAE®) Model for the Treatment of Dry Eye Syndrome
Protocol Number:	VISTA-2 / 19-110-0011
Study Phase:	3
Product Name:	SkQ1 Ophthalmic Solution
IND Number:	113433
Indication:	Dry Eye Syndrome (DES)
Investigators:	Multi-Center
Sponsor:	Mitotech, SA 42, rue de la Vallée L-2661 Luxembourg
Contract Research Organization:	Ora. Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673

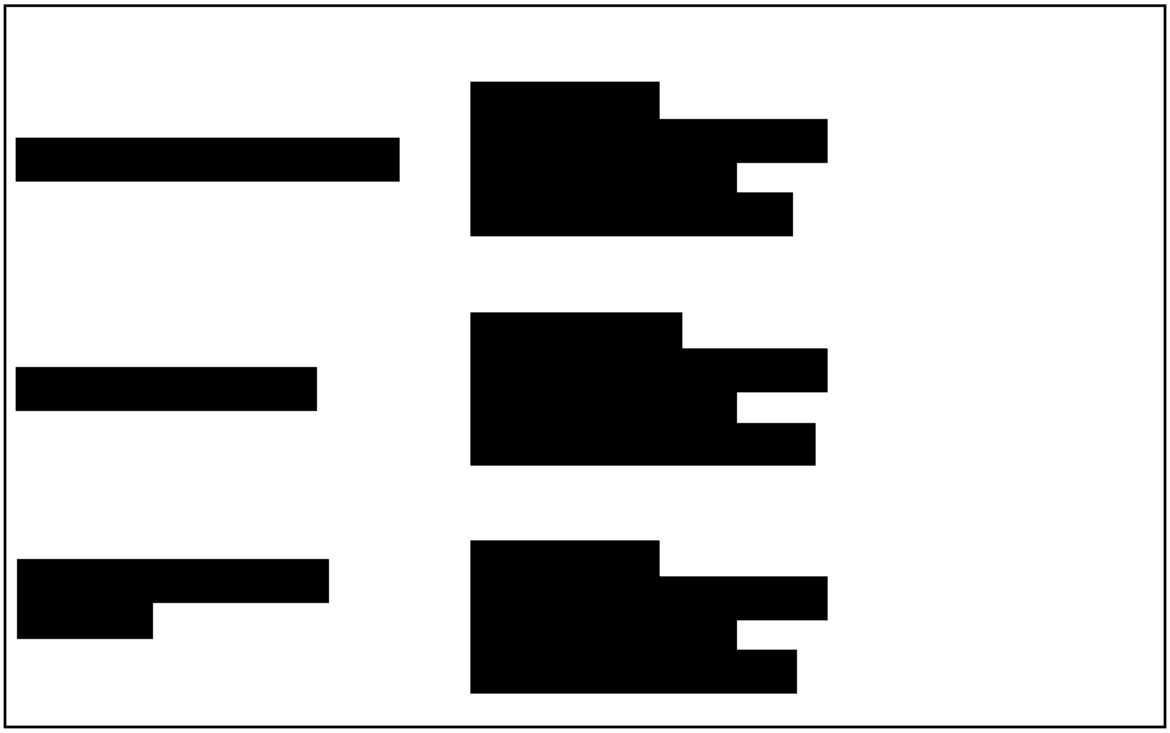
	Date
Original Protocol:	Version 1.0 4 November 2019

Confidentiality Statement

SPONSOR PERSONNEL



ORA PERSONNEL



SYNOPSIS

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of SkQ1 Ophthalmic Solution in the Environment and During Challenge in the Controlled Adverse Environmental (CAE®) Model for the Treatment of Dry Eye Syndrome
Protocol Number:	VISTA-2 / 19-110-0011
Study Drug:	1) 1.55 µg/mL SkQ1 ophthalmic solution 2) Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)
Study Phase:	3
Study Objective:	The objective of this study is to compare the safety and efficacy of SkQ1 ophthalmic solution to placebo for the treatment of the signs and symptoms of dry eye syndrome.
Overall Study Design	
Structure:	Multi-center, double-masked, randomized, placebo-controlled study
Duration:	An individual subject's participation is estimated to be approximately 9 weeks (63 days)
Controls:	Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)
Dosage/Dose Regimen:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally as 1-2 drops [redacted] for 56 days (from Visit 2 to Visit 5): 1) 1.55 µg/mL SkQ1 ophthalmic solution 2) Placebo SkQ1 ophthalmic solution (Vehicle) During a 7-day study run-in period (beginning at the end of Visit 1 for the purpose of subject selection) prior to randomization, all subjects will receive 1-2 drops of Placebo SkQ1 ophthalmic solution (Vehicle) bilaterally [redacted]
Summary of Visit Schedule:	5 visits over the course of approximately 9 weeks • Visit 1 = Day -7 -2/+1 days, Screening • Visit 2 = Day 1, Baseline, Screening Confirmation, Randomization and Initiation of Double-Masked Treatment • Visit 3 = Day 29 ± 2 days • Visit 4 = Day 43 ± 2 days

	• Visit 5 = Day 57 ± 4 days, 8-Week CAE® Test, End of Double-Masked Treatment • [redacted]
Measures Taken to Reduce Bias:	This is a double-masked study. Subjects will be assigned to treatment groups using stratified random sampling [redacted]
Study Population Characteristics	
Number of Subjects:	Approximately [redacted] subjects will be screened to enroll approximately 600 (300 active : 300 placebo) subjects
Condition/Disease:	Dry Eye Syndrome
Inclusion Criteria:	**Subjects must:** a. Be at least 18 years of age; b. Provide written informed consent; c. Have a subject-reported history of dry eye for at least 6 months prior to Visit 1; d. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; e. [redacted] f. [redacted] g. [redacted] h. [redacted] i. [redacted]

	j. [redacted] k. Have at least one eye (the same eye) satisfy all criteria for f, g, h, i, and j above.
Exclusion Criteria:	**Subjects must <u>not</u>:** a. Have previously been exposed to SkQ1 ophthalmic; b. Have any clinically significant slit-lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; c. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation (e.g. follicular conjunctivitis) at Visit 1; d. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; e. Have used any eye drops within 2 hours of Visit 1; f. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months; g. Have used Restasis®, Xiidra® or CEQUA™ within 60 days of Visit 1; h. Have had any ocular and/or lid surgeries within 6 months of Visit 1 or any planned over the study period; i. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; j. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); k. Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study

	(ETDRS) scale in both eyes at Visit 1; l. Have an uncontrolled systemic disease; m. Be a woman who is pregnant, nursing or planning a pregnancy; n. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy), or is post-menopausal (without menses for 12 consecutive months); o. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study; p. [redacted] q. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study; r. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; s. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1; t. Be currently using any hormone replacement therapy that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 and during the study;

	u. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.
Study Formulations and Formulation Numbers:	Run-in: Placebo to be supplied by the sponsor. Study Drug: Batch/lot information for SkQ1 ophthalmic solution (1.55µg/mL and Placebo) to be supplied by the sponsor.
Evaluation Criteria	
Efficacy Measures:	**Primary Efficacy Measures:** The primary endpoints will be tested in a hierarchical fixed sequence in the following order: • Change from baseline (Visit 2) in Ocular Discomfort at Visit 5 (Day 57) [redacted] • Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted] **Key Secondary Efficacy Measures:** The key secondary efficacy endpoints will be tested in a hierarchical fixed sequence in the following order: 1. Change from baseline (Visit 2) in Ocular Discomfort at Visit 3 (Day 29) [redacted] 2. Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 4 (Day 43) [redacted]

3. Tear film break-up time pre- to post-CAE® change at Visit 5 (Day 57) in the worst eye at baseline;
4. Change from baseline (Visit 2) in corneal fluorescein staining in central region at Visit 3 (Day 29) [redacted]

Exploratory Efficacy Measures:

- [redacted]

For efficacy endpoints collected at the eye level, the unit of analysis will be the worst eye, as defined by the following:

[redacted]

	[redacted]
Safety Measures:	• Visual acuity (ETDRS); • Slit-lamp biomicroscopy; • Adverse event query; • Dilated fundoscopy • Intraocular pressure
Other:	• N/A

General Statistical Methods and Types of Analyses

Analysis Populations

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed on the ITT population. Subjects in the ITT population will be analyzed as randomized.
- Per-Protocol Population – The per-protocol (PP) population excludes subjects with significant protocol deviations or who do not complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.
- Safety Population – The safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

In addition, the following populations are defined for the primary and key secondary analysis of conjunctival fluorescein staining:

ITTCFS Population – [redacted]

PPCFS Population – [redacted]

Sample Size

To address the multiple primary efficacy variables employed in this study, the sample size calculations have been based on a hierarchical structure. In order to test a variable,

the preceding variable(s) must have shown statistically significant improvements versus placebo using a two-sided significance level of 0.05. Using these strategies, the Type I error rate will be maintained at the 0.05 significance level for the primary efficacy variables.

This study is expected to enroll 300 subjects in the active treatment arm and 300 subjects in the placebo grou [redacted] enrollment of 284 patients per group would be required for 90% power for each endpoint to detect the differences between the active treatment group and placebo group.

Primary Efficacy Analyses

Efficacy analyses will be performed on the ITT and ITTCFS populations, for Ocular Discomfort and conjunctival fluorescein staining endpoints, respectively. Supportive analyses will be performed on the PP and PPCFS populations, for Ocular Discomfort and conjunctival fluorescein staining endpoints, respectively.

Primary efficacy endpoints are:

- Change from baseline (Visit 2) in Ocular Discomfort in the worst eye at Visit 5 (Day 57) [redacted]
- Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) in the worst eye at Visit 5 (Day 57) [redacted]

The primary efficacy endpoint of conjunctival fluorescein staining (sum of temporal and nasal regions) will be tested in the pre-specified subgroup [redacted]

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model [redacted] The adjusted least squares means and their

standard errors (SEs) will be presented along with their two-sided 95% confidence intervals (CIs) for each treatment group and the difference between the active treatment group and the placebo treatment group. In addition, a two-sample t-test will be used to compare the active and placebo groups in the change from baseline at Visit 5 [redacted] The mean difference, SD for the difference, and the 95% CI for the difference will be presented. A two-sided p-value < 0.05 will be considered statistically significant.

The primary analyses for both primary endpoints will be conducted on the ITT and ITTCFS populations for Ocular Discomfort and conjunctival fluorescein staining, respectively, using the Markov Chain Monte Carlo (MCMC) multiple imputation method to impute missing data. [redacted] Sensitivity analyses for the ocular discomfort endpoint will also be performed using Last Observation Carried Forward (LOCF) method on the ITT population as well as with the observed data only for both the ITT and PP populations. Sensitivity analyses for the conjunctival fluorescein staining endpoint will be performed using LOCF on the ITTCFS population as well as with the observed data only for both the ITTCFS and PPCFS populations. Sensitivity analyses using LOCF and observed data only will include Wilcoxon rank sum tests.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoint of conjunctival fluorescein staining at Visit 4 (Day 43) will be tested in the ITTCFS population; other key secondary efficacy endpoints will be tested in the full ITT population.

Imputation will not be applied for any missing data in the key secondary efficacy endpoints.

Analyses will use ANCOVA models with baseline values included as covariates. Two-sample t-tests and Wilcoxon rank sum tests will be performed as sensitivity analyses.

Sensitivity analyses of the conjunctival fluorescein staining endpoint will be performed using the PPCFS population with observed data only. Sensitivity analyses of the other key secondary endpoints will be performed using the PP population with observed data only.

Exploratory Efficacy Analyses

Exploratory efficacy analyses will be analyzed on the ITT population using observed data. Imputation will not be applied for any missing data in the exploratory efficacy endpoints.

Analyses will use ANCOVA models with baseline values included as covariates, two-sample t-tests, and Wilcoxon rank sum tests. [redacted]

Safety Variables

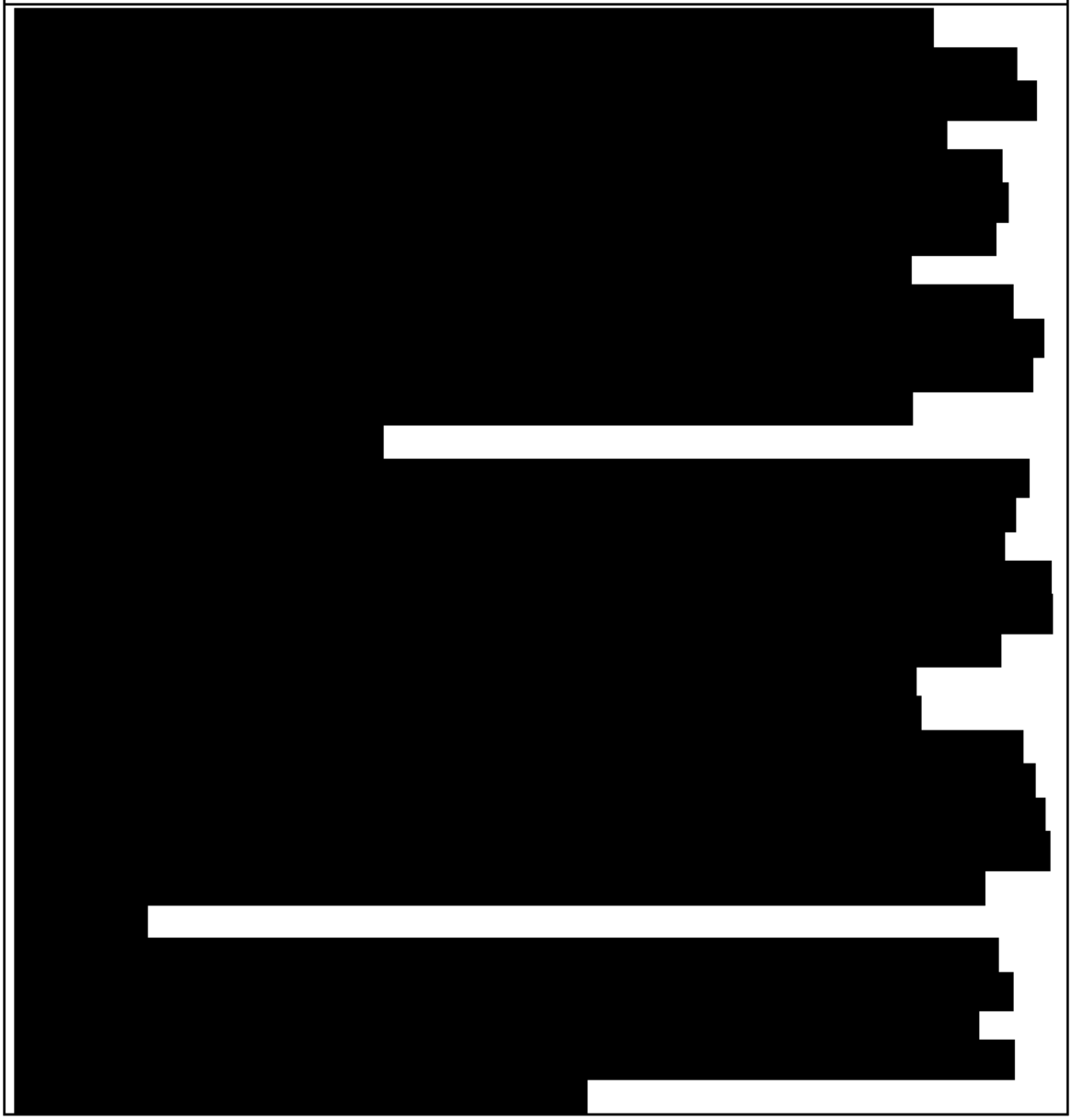
Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens

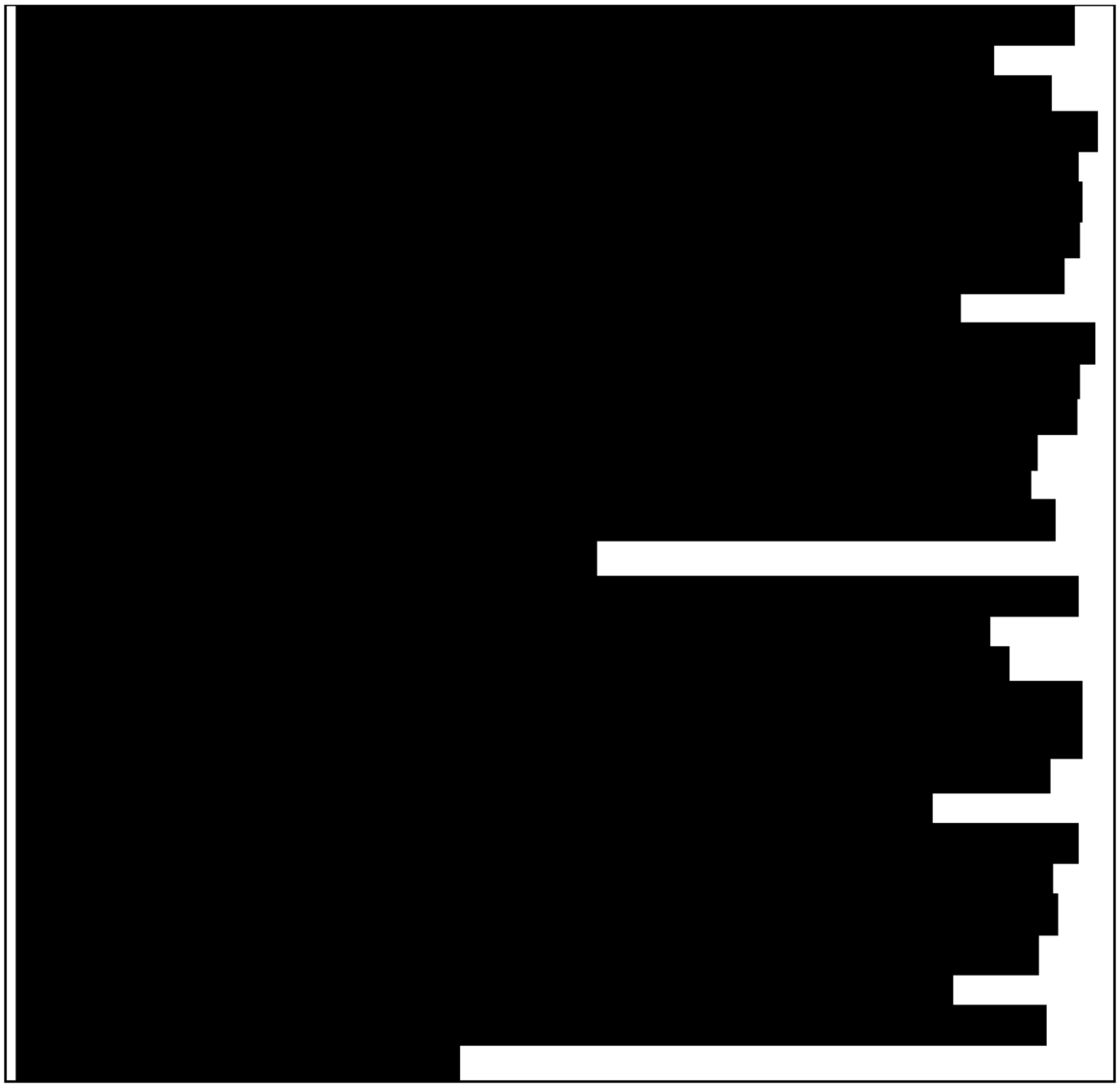
after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs (SAEs)
- By maximal severity
- By study day of onset

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

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate.





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LIST OF ABBREVIATIONS

AE	adverse event
[redacted]	[redacted]
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	electrocardiograph
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IP	investigational product
IOP	intraocular pressure
IRB	institutional/independent review board
ITT	intent-to-treat
IUD	intra uterine device
KCS	keratoconjunctivitis sicca
kg	kilogram
LASIK	laser *in situ* keratomileusis
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mL	milliliter
mm	millimeter
µg	microgram
mmHg	millimeters of mercury
[redacted]	[redacted]
VA	visual acuity

1 INTRODUCTION

Dry eye syndrome (DES), also known as Keratoconjunctivitis sicca (KCS), is a multifactorial disease of the tears and ocular surface; symptoms include discomfort, visual disturbance, and tear film instability, with the potential for exposure of and damage to the ocular surface. The condition is accompanied by increased osmolarity of tears and inflammation of the ocular surface. Symptoms can be caused by defects in the aqueous, lipid, and/or mucin layers of the tear film[1]. Current therapies for dry eye are only palliative, mostly focusing on replacement of tears to reduce symptoms. Only three approved products are available in the USA currently: Restasis® (Cyclosporine Ophthalmic Emulsion, Allergan, Irvine, California, USA), CEQUA™ (cyclosporine ophthalmic solution, Sun Pharma, Princeton, NJ, USA) and Xiidra® (lifitigrast ophthalmic solution, Shire US, Inc., Lexington, MA, USA).

Oxidative mechanisms are also believed to play an important role in the pathogenesis of age-related eye disease such as DES. Consequently, many investigations have focused on whether vitamins and trace minerals with antioxidant properties help prevent the onset or progression of DES.

SkQ1 is a novel compound and powerful antioxidant. Given its chemical properties, SkQ1 and related compounds have been shown to be active in a variety of animal models of illness believed to involve free radical damage. These include rat models of H_20_2 and ischemia-induced heart arrhythmia, heart infarction, kidney ischemia, and stroke studied both ex vivo and in vivo.[1] In addition, SkQ1 has been found to provide benefit in a number of models of eye diseases, including DES[2-6].

[redacted]

2 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of SkQ1 ophthalmic solutions to placebo for the treatment of the signs and symptoms of DES.

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study is that SkQ1 ophthalmic solution 1.55µg/mL is superior to placebo for the primary endpoints of signs and symptoms, as follows:

- Subjects receiving SkQ1 ophthalmic solution will have a statistically significantly lower mean change from baseline (Visit 2) in Ocular Discomfort at Visit 5 (Day 57) [redacted]
- Subjects receiving SkQ1 ophthalmic solution will have a statistically significantly lower mean change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted]

4 OVERALL STUDY DESIGN

See synopsis.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

It is estimated that approximately [redacted] subjects will be screened to enroll approximately 600 (300 active: 300 placebo) subjects. Subjects will be randomized in a 1:1 ratio to 1.55 µg/mL SkQ1 or placebo.

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, of either gender, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Subjects must:

a. Be at least 18 years of age;

b. Provide written informed consent;

c. Have a subject-reported history of dry eye for at least 6 months prior to Visit 1;

d. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;

e. [redacted]

f. [redacted]

g. [redacted]

h. [redacted]

i. [redacted]

j. [redacted]

k. Have at least one eye (the same eye) satisfy all criteria for f, g, h, i, and j above.

5.4 Exclusion Criteria

Subjects must not:

a. Have been exposed to SkQ1 ophthalmic solution;

b. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;

c. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation (e.g. follicular conjunctivitis) at Visit 1;

d. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;

e. Have used any eye drops within 2 hours of Visit 1;

f. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;

g. Have used Restasis®, Xiidra® or CEQUA™ within 60 days of Visit 1;

h. Have had any ocular and/or lid surgeries within 6 months of Visit 1 or any planned over the study period;

i. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

j. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);

k. Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;

l. Have an uncontrolled systemic disease;

m. Be a woman who is pregnant, nursing or planning a pregnancy;

n. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has

had a hysterectomy or bilateral tubal ligation or bilateral oophorectomy), or is post-menopausal (without menses for 12 consecutive months);

o. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;

p. [redacted]

q. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;

r. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;

s. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;

t. Be currently using any hormone replacement therapy that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 and during the study;

u. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

Sponsor and/or investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measures

The primary endpoints will be tested in a hierarchical fixed sequence in the following order:

1. Change from baseline (Visit 2) in Ocular Discomfort at Visit 5 (Day 57) [redacted]
2. Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted]

6.1.2 Key Secondary Efficacy Measures

The key secondary efficacy endpoints will be tested in a hierarchical fixed sequence in the following order:

1. Change from baseline (Visit 2) in Ocular Discomfort at Visit 3 (Day 29) [redacted]
2. Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 4 (Day 43). [redacted]
3. Tear film break-up time pre- to post- CAE® at Visit 5 (Day 57) in the worst eye at baseline;
4. Change from baseline (Visit 2) in corneal fluorescein staining in central region at Visit 3 (Day 29) [redacted]

6.1.3 Criteria for Effectiveness

The primary efficacy variables will be evaluated to assess effectiveness. For this phase 3 study, the primary analyses will each be evaluated at two-sided alpha levels of 0.05 (SkQ1 ophthalmic solution versus placebo) to determine evidence of efficacy. Testing will follow a hierarchical testing strategy, where efficacy for each endpoint and comparison to placebo will be determined only if the preceding test(s) are statistically significant.

6.2 Safety Measures

- Visual acuity (ETDRS);

- Slit-lamp biomicroscopy;
- Adverse event query;
- Dilated fundoscopy;
- Intraocular pressure.

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Run-In

Placebo SkQ1 ophthalmic solution (Vehicle of SkQ1 ophthalmic solution)

7.1.2 Study Drug(s)/ Formulation(s)

- 1.55 µg/mL SkQ1 ophthalmic solution
- Placebo SkQ1 ophthalmic solution (Vehicle)

7.1.3 Study Drug Packaging Configuration

[redacted] All study drug will be labeled according to applicable regulatory requirements.

7.1.4 Study Drug Storage and Accountability

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. [redacted]

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 subjects 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 subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

7.1.5 Instructions for Dispensation, Use, and Administration

At the end of Visit 1, qualified subjects will receive a kit [redacted]

At Visit 2, the run-in kit will be collected from subjects for drug accountability. At the end of Visit 2, qualified subjects will be randomized [redacted]

At Visit 3, the study drug kit will be collected from subjects for drug accountability. [redacted]

At Visit 4, the study drug kit will be collected from subjects for drug accountability. [redacted]

At Visits 5 the study drug kit will be collected from subjects for drug accountability.

[redacted]

If needed, replacement kits are also available to be dispensed to a subject.

7.2 Other Study Supplies

Ora to provide sites with urine pregnancy tests, Schirmer's test strips, sodium fluorescein, lissamine green, tear collection supplies.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

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

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., prior to changes in a subject's medical treatment and/or prior to study related procedures), the study will be discussed with each subject, and subjects wishing to

participate must give written informed consent using an informed consent form (ICF). The informed consent form 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).

8.1.4 Procedures for Final Study Entry

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

8.1.5 Methods for Assignment to Treatment Groups:

Prior to initiation of study run-in (at Visit 1), each subject who signs the informed consent will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at each site and no numbers will be skipped or omitted.

At Visit 2, a patient who meets all the eligibility criteria will be randomized to receive treatment with1.55 µg/mL SkQ1 Ophthalmic Solution or placebo in a 1:1 ratio [redacted]

Subjects will be assigned to treatment groups using stratified random sampling and stratification [redacted]

[redacted] 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. Kit numbers for returned bottles will also be recorded for each visit.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken.

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).

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 2 for description):

Visit 1 (Day -7 -2/+1 days): Screening

- Informed consent / Health Information Portability and Accountability Act (HIPAA);
- Demographic data and medical / medication history;
- Urine pregnancy test (for females of childbearing potential);
- [redacted] Ocular Discomfort Scale;
- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [redacted]
- Visual acuity;
- Review of qualification criteria;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- Tear Film Break-up Time (TFBUT);
- Fluorescein staining [redacted]

- [redacted];
- [redacted]
- [redacted]
- Intraocular pressure;
- Dilated fundoscopy;
- Review of qualification criteria;
- Adverse event query;
- Dispensation of run-in (RUN-IN) for [redacted] until Visit 2;
  - [redacted]
- [redacted]
  - [redacted]
- Dispensation of diaries and subject instructions;
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Qualified subjects will be scheduled for Visit 2.

Visit 2 (Day 1): Baseline/Screening Confirmation/ Randomization and Initiation of Double-Masked Treatment

- Collection and review of run-in (RUN-IN) and subject diaries;
- [redacted]
- Medical/medication history update;
- Adverse event query;
- [redacted] Ocular Discomfort Scale;

- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [redacted]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- TFBUT;
- Fluorescein staining [redacted]
- [redacted]
- [redacted]
- [redacted]
- Review of qualification criteria;
- Randomization;
- Dispensation of study drug kit according to randomization for [redacted] until Visit 3;
- [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Adverse event query;
- Schedule subjects for Visit 3.

[redacted]

[redacted]

Visit 3 (Day 29 ± 2 days): 2-Week Follow-Up

- Collection and review of study drug and subject diaries;
- [redacted]
- Medical / medication history update;
- Adverse event query;
- [redacted] Ocular Discomfort Scale;
- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [redacted]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- TFBUT;
- Fluorescein staining [redacted]
- [redacted]
- [redacted]
- [redacted]
- Dispensation of study drug kit according to randomization for [redacted] until Visit 4;
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- Adverse event query;
- Schedule subjects for Visit 4.

[redacted]

[redacted]

Visit 4 (Day 43 ± 2 days): 4-Week Follow-up

- Collection and review of study drug and subject diaries;
- [redacted]
- Medical / medication history update;
- Adverse event query;
- [redacted] Ocular Discomfort Scale;
- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [redacted]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- TFBUT;
- Fluorescein staining – [redacted] Scale;
- [redacted] Scale;
- [redacted]
- [redacted]
- Dispensation of study drug kit according to randomization for [redacted] until Visit 5;
- [redacted]
- [redacted]
- [redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Adverse event query;
- Schedule subjects for Visit 5.

[redacted]

- [redacted]

Visit 5 (Day 57 ± 4): 8-Week CAE® Test/ End of Double-Masked Treatment

- Collection and review of study drug and subject diaries;
- Medical / medication history update;
- Adverse event query;
- Urine pregnancy test (for females of childbearing potential);
- [redacted] Ocular Discomfort Scale;
- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- [redacted]
- Visual acuity;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- TFBUT;
- Fluorescein staining [redacted]
- Lissamine Green staining [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]

- [redacted] Ocular Discomfort Scale;
- [redacted] Ocular Discomfort Scale & 4-Symptom Questionnaire;
- Slit-lamp biomicroscopy;
- [redacted]
- [redacted]
- TFBUT;
- Fluorescein staining [redacted]
- [redacted]
- Intraocular pressure;
- Dilated fundoscopy;
- Adverse event query;
- Study Exit.

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 5 (Day 57 ± 4), then all safety evaluations and [redacted] that are to be performed at Visit 5 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

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

If a female reports a pregnancy or has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall instruct the patient to immediately stop the study medication and request from the subject and/or the subject'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 subject's source documents and will provide a copy of all documentation to Ora.

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 subject 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;
- Visual Acuity;
- Intraocular Pressure;
- Pregnancy Test;
- Dilated Fundoscopy;
- Assessment of Adverse Events;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper [redacted] instillation and storage of study drug at the end of Visits 1, 2, 3, and 4 and given written instructions. [redacted] These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

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

- adverse events;
- protocol violations;

- administrative reasons (e.g., inability to continue due to scheduling changes);
- lost to follow up;
- sponsor termination of study;
- subject choice (e.g. withdrawal of consent); and
- other

Note: In addition, any subject may be discontinued for any sound medical reason at the discretion of the investigator.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or study sponsor and will be clearly documented on the eCRF.

8.7 Study Termination

The study may be stopped at any time by the investigator, the sponsor, and/or Ora with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve 5 visits over approximately a 9-week period (63 days).

8.9 Monitoring and Quality Assurance

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

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

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered IP-related. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the IP,

without any judgment about causality. Any pre-existing medical condition that worsens after administration of the IP will also be considered a new adverse event.

If there is a worsening of a medical condition that was present prior to the administration of the IP, this should also be considered a new adverse event and reported. Any medical condition present prior to the administration of the IP that remains unchanged or improved should not be recorded as a treatment emergent adverse event at subsequent visits unless it worsens during treatment.

Investigational Product (IP) includes the investigational drug under evaluation and placebo, or any other medications required by the protocol given during any stage of the study.

Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, relationship to IP, 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 adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as determined by the investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

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

9.1.2 Relationship to Investigational Product

The relationship of each adverse event to the Investigational Product (IP) should be determined by the investigator using these explanations:

- *Definite*: When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE;
- *Probable*: When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.
- *Possible*: When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example, due to missing data or insufficient evidence.
  None: When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.

- *Unclassified*: When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the IP caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the adverse event. Types of evidence that would suggest a causal relationship between the IP and the adverse event include: a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one 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 (e.g., 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.

9.1.3 Expectedness

The expectedness of an adverse event should be determined based upon existing safety information about the IP using these explanations:

- *Unexpected*: An adverse event that is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed.
- *Expected*: An adverse event that is listed in the Investigator's brochure at the specificity and severity that has been observed.
- *Not Applicable*: Any adverse event that is unrelated to the IP.

Adverse events that are mentioned in the Investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an adverse event, but the final classification is subject to the Medical Monitor's determination.

9.2 Serious Adverse Events

An adverse event 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 adverse event;

Note: An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event 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 serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., 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 or subject 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 adverse events and their outcomes must be reported to Ora, 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 Suspected Unexpected Adverse Reaction

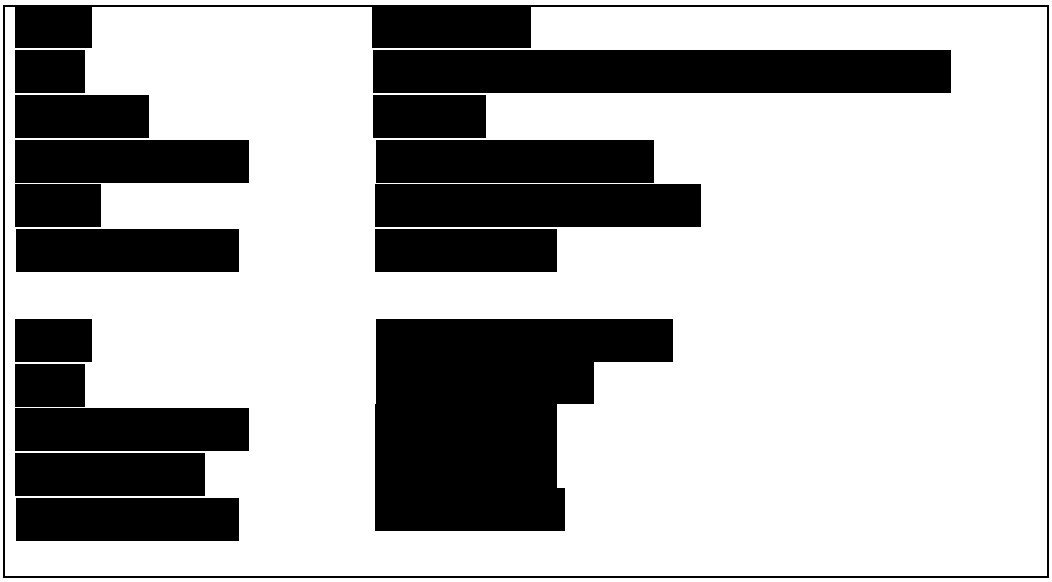
All adverse events that are 'suspected' and 'unexpected' are to be reported to Ora, the study sponsor and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the study drug, must be immediately reported. All information relevant to the serious adverse event must be recorded on the appropriate eCRF. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious adverse event must be followed up and the outcome reported.

In the event of a serious adverse event, the investigator must notify Ora and the sponsor immediately (within 24 hours); 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 subject; provide Ora 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 adverse event within their guidelines for reporting serious adverse events.

Serious adverse events should be reported within one day to the contacts listed below:



9.4 Procedures for Unmasking of Study Drug

All subjects, 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 arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified, when possible, before unmasking study drug as described in the following paragraph.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should, if possible, contact Ora and/or the medical monitor prior to unmasking the identity of the IP. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify Mitotech and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using [redacted]. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file.

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

Adverse events that are ongoing at the end of the study visit will be followed. Phone calls will be placed with any subject who experiences an adverse event until the issue is resolved or the condition is considered ongoing and stable.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed on the ITT population. Subjects in the ITT population will be analyzed as randomized.

Per-Protocol Population – The per protocol (PP) population excludes subjects with significant protocol deviations or who do not complete the study. Protocol deviations will be assessed and the per protocol population identified prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

Safety Population – The safety population will include all subjects receiving treatment from whom at least one safety measurement is obtained following the first dose of study drug. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

In addition, the following populations are defined for the primary and key secondary analyses of conjunctival fluorescein staining:

ITTCFS Population – The ITTCFS population includes all subjects in the ITT population with [redacted]

PPCFS Population – The PPCFS population includes all subjects in the PP population with [redacted]

The statistical analysis of safety data will be performed for the safety population. The primary efficacy analysis of Ocular Discomfort will be performed on the ITT population. The primary efficacy analysis of conjunctival fluorescein staining will be performed on

the ITTCFS population. Key secondary efficacy analyses will be performed on the ITT population, except for analysis of conjunctival fluorescein staining, which will be performed on the ITTCFS population. Exploratory efficacy analyses will be performed on the ITT population. The primary efficacy analysis procedures will also be performed on the PP and PPCFS populations as sensitivity analyses, for Ocular Discomfort and conjunctival fluorescein staining, respectively.

10.2 Statistical Hypotheses

The following statistical hypotheses will be tested, with H_{01}, H_{02}, H_{03}, H_{04}, H_{05}, H_{06} tested (in that order) comparing SkQ1 ophthalmic solution versus placebo. Each hypothesis test will be conditional upon the prior test(s) rejecting the null hypothesis. The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided. Each test is therefore successful with respect to efficacy if the corresponding null hypothesis is rejected using a two-sided significance level of 0.05.

Primary Efficacy

H_{01}: There is no difference between SkQ1 ophthalmic solution and placebo for the change from baseline in Ocular Discomfort at Visit 5 (Day 57) [redacted]

H_{11}: The change from baseline in Ocular Discomfort at Visit 5 (Day 57) [redacted] is less with SkQ1 ophthalmic solution than with placebo.

H_{02}: There is no difference between SkQ1 ophthalmic solution and placebo for the change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted]

H_{12}: The change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted] is less with SkQ1 ophthalmic solution than with placebo [redacted]

Key Secondary Efficacy

H_{03}: There is no difference between SkQ1 ophthalmic solution and placebo for the change from baseline in Ocular Discomfort at Visit 3 (Day 29), [redacted]

H_{13}: The change from baseline in Ocular Discomfort at Visit 3 (Day 29), [redacted] is less with SkQ1 ophthalmic solution than with placebo.

H_{04}: There is no difference between SkQ1 ophthalmic solution and placebo for the change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 4 (Day 43), [redacted]

H_{14}: The change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 4 (Day 43), [redacted] is less with SkQ1 ophthalmic solution than with placebo [redacted]

H_{05}: There is no difference between SkQ1 ophthalmic solution and placebo for the pre- to post-CAE® change in tear film break-up time at Visit 5 (Day 57) in the worst eye.

H_{15}: The pre- to post-CAE® change in tear film break-up time at Visit 5 (Day 57) in the worst eye is greater with SkQ1 ophthalmic solution than with placebo.

H_{06}: There is no difference between SkQ1 ophthalmic solution and placebo for the change from baseline in corneal fluorescein staining in the central region at Visit 3 (Day 29), [redacted]

H_{16}: The change from baseline in corneal fluorescein staining in the central region at Visit 3 (Day 29), [redacted] is less with SkQ1 ophthalmic solution than with placebo.

10.3 Sample Size

To address the multiple primary efficacy variables employed in this study, the sample size calculations have been based on a hierarchical structure. In order to test a variable, the preceding variable(s) must have shown statistically significant improvements versus placebo using a two-sided significance level of 0.05. Using these strategies, the Type I error rate will be maintained at the 0.05 significance level for the primary efficacy variables.

[redacted] enrollment of 284 patients per group would be required for 90% power for each endpoint to detect the differences between the active treatment group and placebo group.

10.4 Statistical Analysis

10.4.1 General Considerations

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

All efficacy analyses will be evaluated at a two-sided alpha = 0.05 and two-sided 95% CIs around the difference between treatments (SkQ1 – placebo) as well as two-sided 95% CIs around the point estimates within each treatment group.

All summaries will be presented by treatment group. Summaries will be provided for demographics, baseline medical history, and subject disposition.

Baseline measures are defined as the last measure prior to the initiation of study treatment (Visit 2).

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints collected at the eye level, the unit of analysis will be the "worst eye"

10.4.3 Missing Data

The primary efficacy analyses will be performed using Markov Chain Monte Carlo multiple imputation to account for missing Day 57 data.

In order to show that the primary results are robust to various patterns of missing data, sensitivity models will include the following methods of handling missing data for each primary endpoint:

- Using a control-based pattern mixture for multiple imputation
- Using the last observation carried forward (LOCF) method for missing values
- Analyzing observed data only
- Analyzing observed data for the PP and PPCFS populations for ocular discomfort and conjunctival fluorescein staining, respectively.

Imputation will not be applied for any missing data in the key secondary or exploratory efficacy endpoints.

10.4.4 Multiplicity Adjustments

The primary and key secondary efficacy analyses will be tested following a hierarchical testing strategy in order to maintain a study-wide type I error rate of 0.05 while testing the primary and key secondary hypotheses. The testing strategy will proceed as follows:

1) Compare the change from baseline in Ocular Discomfort at Visit 5 (Day 57) [redacted] between SkQ1 and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 2; otherwise no further testing will be performed and all other testing is considered exploratory.
2) Compare the change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 5 (Day 57) [redacted] in the worst eye between SkQ1 and placebo. [redacted] If statistically significant at a two-sided alpha = 0.05, proceed to step 3; otherwise no further testing will be performed and all other testing is considered exploratory. Compare the change from baseline in Ocular Discomfort at Visit 3 (Day 29), [redacted] between SkQ1 and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 4; otherwise no further testing will be performed and all other testing is considered exploratory.
3) Compare the change from baseline in conjunctival fluorescein staining (sum of temporal and nasal regions) at Visit 4 (Day 43), [redacted] between SkQ1 and placebo. [redacted] f statistically significant at a two-sided alpha = 0.05, proceed to step 5; otherwise no further testing will be performed and all other testing is considered exploratory.

4) Compare the tear film break-up time pre- to post-CAE® change at Visit 5 (Day 57) in the worst eye between SkQ1 and placebo. If statistically significant at a two-sided alpha = 0.05, proceed to step 6; otherwise no further testing will be performed and all other testing is considered exploratory.
5) Compare the change from baseline in corneal fluorescein staining in the central region at Visit 3 (Day 29), [redacted] between SkQ1 and placebo. All other testing is considered exploratory.

10.4.5 Primary Efficacy Analyses

Primary efficacy endpoints are:

- Change from baseline (Visit 2) in Ocular Discomfort in the study worst eye at Visit 5 (Day 57) [redacted]
- Change from baseline (Visit 2) in conjunctival fluorescein staining (sum of temporal and nasal regions) in the study worst eye at Visit 5 (Day 57) [redacted]

[redacted].

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model, [redacted]. The adjusted least squares means and their standard errors (SEs) will be presented along with their two-sided 95% confidence intervals (CIs) for each treatment group and the difference between the active treatment group and the placebo treatment group. In addition, a two-sample t-test will be used to compare the active and placebo groups in the change from baseline at Visit 5 [redacted]. The mean difference, SD for the difference, and the 95% CI for the difference will be presented. A two-sided p-value < 0.05 will be considered statistically significant.

The primary analyses for both primary endpoints will be conducted on the ITT and ITTCFS populations for Ocular Discomfort and conjunctival fluorescein staining, respectively, using the Markov Chain Monte Carlo (MCMC) multiple imputation method to impute missing data. [redacted] Sensitivity analyses for the ocular discomfort endpoint will also be performed using Last Observation Carried Forward (LOCF) method on the ITT population as well as with the observed data only for both the ITT and PP populations. Sensitivity analyses for the conjunctival fluorescein staining endpoint will be

performed using LOCF on the ITTCFS population as well as with the observed data only for both the ITTCFS and PPCFS populations. Sensitivity analyses using LOCF and observed data only will include Wilcoxon rank sum tests.

10.4.6 Key Secondary Efficacy Variables

The key secondary efficacy endpoint of conjunctival fluorescein staining at Visit 4 (Day 43) will be tested in the ITTCFS population; other key secondary efficacy endpoints will be tested in the full ITT population.

Imputation will not be applied for any missing data in the key secondary efficacy endpoints.

Analyses will use ANCOVA models with baseline values included as covariates. Two-sample t-tests, and Wilcoxon rank sum tests will be performed as sensitivity analyses.

Sensitivity analyses of the conjunctival fluorescein staining endpoint will be performed using the PPCFS population with observed data only. Sensitivity analyses of the other key secondary endpoints will be performed using the PP population with observed data only.

10.4.7 Exploratory Efficacy Analyses

Exploratory efficacy analyses will be analyzed on the ITT population using observed data. Imputation will not be applied for any missing data in the exploratory efficacy endpoints.

Analyses will use ANCOVA models with baseline values included as covariates, two-sample t-tests, and Wilcoxon rank sum tests. [redacted]

10.4.8 Safety Variables

Adverse events will be coded using the MedDRA dictionary.

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature treatment discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term for the following categories of AEs:

- All TEAEs
- TEAEs at least possibly related to study treatment
- TEAEs leading to study treatment discontinuation
- Serious TEAEs
- By maximal severity
- By study day of onset

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

Other safety endpoints will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate.

10.4.9 Interim Analyses

There will be no interim analyses.

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

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), 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.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study.

All informed consent forms 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 (e.g., 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 Ora prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 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 informed consent form will be used.

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

All personal study subject 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 Ora, the sponsor, the IRB approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject'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 subject's identity will not be disclosed in these documents.

11.4 Documentation

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

11.4.1 Retention of Documentation

All study-related source documents, correspondence, patient records, consent forms, record of the distribution and use of all study drug and copies of case report forms should be maintained on file for at least two 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 two 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.

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

11.5.1 Labeling/Packaging

[redacted]

All run-in and study drug will be labeled according to applicable regulatory requirements.

11.5.2 Storage of Study Drug

[redacted]

11.5.3 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 subjects 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 subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed on behalf of the Sponsor following local regulations.

11.6 Recording of Data on Source Documents and electronic Case Reports Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source document, and all study-related material. 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 (e.g., 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.

11.7 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the study sponsor will have the final decision regarding the manuscript and publication.

12 REFERENCES

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