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12 June 2023

A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects Diagnosed with Dry Eye Disease

Clinical Trial Protocol

Protocol Title:	A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects Diagnosed with Dry Eye Disease
Protocol Number:	23-110-0002
Study Phase:	2
Investigational Product Name:	IC265 Ophthalmic Solution
IND Number:	130141
Indication:	Dry Eye Disease
Investigators:	Single-Center
Sponsor:	IACTA Pharmaceuticals, Inc 19900 MacArthur Blvd, Suite 550 Irvine, CA 92612
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Version	1.0
Original Protocol (Version 1.0):	12 Jun 2023

Confidentiality Statement

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SYNOPSIS

Protocol Title:	A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects with Dry Eye Disease
Protocol Number:	23-110-0002
Investigational Product:	1. IC265 Ophthalmic Solution 1% 2. Placebo Ophthalmic Solution
Study Phase:	2
Objective(s):	The objective of this study is to compare the safety and efficacy of IC265 Ophthalmic Solution 1% to placebo for the treatment of the signs and symptoms of dry eye disease.
Overall Study Design:	
Structure:	Single-center, randomized, double-masked, placebo-controlled
Duration:	An individual subject's participation is estimated to be approximately 14 weeks (84 days)
Controls:	Placebo (vehicle minus active) Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally BID for 84 days (from Visit 2 to Visit 5). 1) IC265 Ophthalmic Solution 1% 2) Placebo Ophthalmic Solution (Vehicle) During a 14 -day study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID.
Summary of Visit Schedule:	5 visits over the course of approximately 14 weeks • Visit 1 = Day -14 ± 2, Screening (CAE® visit) • Visit 2 = Day 1, CAE Confirmation/Baseline (CAE® visit) • Day 8, Safety Phone Follow Up • Visit 3 = Day 15 ± 2, 2-Week Follow Up (CAE® visit) • Day 29, Safety Phone Follow Up • Visit 4 = Day 43 ± 2, 6-Week Follow Up (CAE® visit) • Day 64, Safety Phone Follow Up • Visit 5 = Day 85 ± 4, 12-Week Follow-Up/Study Exit (CAE® visit)
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double-masked study
Study Population Characteristics:	
Number of Subjects:	Approximately 80 subjects will be screened to enroll 40 subjects (20 randomized subjects in each treatment group)
Condition/Disease:	Dry Eye Disease
Inclusion Criteria:	
Subjects must: 1. Be at least 18 years of age; 2. Provide written informed consent; 3. Have a reported or documented history of dry eye for at least 6 months prior to Visit 1; 4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; 5. Report a score of ≥ 2 on the Ora Calibra Ocular Discomfort & 4-symptom questionnaire in at least one symptom at Visits 1 and 2; 6. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1 and 2; 7. Have a pre-CAE conjunctival redness score ≥ 1 according to the Ora Calibra Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1 and 2; 8. Have a corneal fluorescein staining score of ≥ 2 in at least one region (e.g. inferior, superior, or central) at Visits 1 and 2; 9. Have a sum corneal fluorescein staining score of ≥ 4, based on the sum of the inferior, superior, and central regions, at Visits 1 and 2; 10. Have a total lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions at Visits 1 and 2; 11. Demonstrate a response to the CAE at Visits 1 and 2 as defined by:	

a. Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least one eye following CAE exposure
b. Reporting an Ora Calibra Ocular Discomfort Score ≥3 at 2 or more consecutive time points in at least one eye during CAE exposure (if a subject has an ocular discomfort rating of 3 at time = 0 for an eye, s/he must report an ocular discomfort rating of 4 for two consecutive measurements for that eye) Note: a subject cannot have an ocular discomfort score of 4 at time = 0);

12. Have at least one single eye satisfy all criteria for for 6, 7, 8, 9, 10, and 11 above.

Exclusion Criteria:

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

1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, ocular rosacea, lid margin inflammation, or active ocular allergies that require therapeutic treatment;
2. Have any clinically significant (CS) posterior chamber findings, or a history of such findings/disorders, that may include exudative (i.e., wet) age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, glaucoma, ocular hypertension, or any other retinal or optic nerve disease/disorder that require therapeutic treatment and/or in the opinion of the Investigator may interfere with study parameters;
3. Have worn contact lenses within 48 hours prior to Visit 1 or anticipate using contact lenses during the study;
4. Have laser-assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery and/or any other ocular surgical procedure within 12 months prior to Visit 1; or have any ocular surgical procedure scheduled to be conducted during the study period;
5. Have had any surgeries of the ocular surface or lid in the past 6 months;
6. Have a history of lacrimal duct obstruction in either eye within 12 months prior to Visit 1;
7. Have used temporary (i.e., collagen) punctal plugs within 12 weeks prior to Visit 1 or anticipate their use during the study period;
8. Have permanent punctal plugs inserted or removed – including falling out – or have had surgical punctal occlusion within 12 weeks prior to Visit 1 or anticipate any such event at any time during the study period;
9. Use any of the following treatments in the period indicated before Visit 1 or anticipate their use at any time during the study.

<u>24 hours prior to Visit 1</u>

10. All topical ophthalmic preparations (e.g., medications for glaucoma, over-the counter-solutions, artificial tears, gels, scrubs, ointments)

<u>72 hours prior to Visit 1</u>

11. Antihistamines (including topical ophthalmic and nasal antihistamines)

<u>30 days prior to Visit 1</u>

12. Topical ophthalmic non-steroidal anti-inflammatories
13. Topical ophthalmic corticosteroids
14. Topical ophthalmic autologous serum
15. Topical ophthalmic antibiotics
16. Mast cell stabilizers
17. Oral aspirin or aspirin-containing products except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
18. Any other medication known to cause ocular drying (e.g., antidepressants, beta blockers) except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
19. Restasis®
20. Xiidra®
21. CEQUA™
22. LipiFlow® or other similar meibomian gland dysfunction (MGD) therapy
23. TrueTear®
24. Corticosteroids (e.g., systemic steroids including intravenous, intramuscular, intraarticular, and oral steroids; nasal steroids; facial topical steroids; dermatological steroids with high potency or large treatment areas);
25. Tetracyclines (tetracycline, doxycycline, minocycline, etc.);
26. Be monocular or have best corrected visual acuity greater than or equal to logMAR +0.7 in either eye as assessed by the ETDRS scale at Visit 1;

<table>
<tr><td colspan="2">27. Have a severe systemic disease, chronic illness or uncontrolled medical condition including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, poorly controlled diabetes and/or clinically significant (CS) hematologic, renal or liver disease that in the opinion of the Investigator could interfere with study assessments or limit compliance;
28. Be a woman who is pregnant, nursing or planning a pregnancy;
29. 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, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e., without menses for 12 consecutive months);
30. Be a woman of childbearing potential who is not using an acceptable means of birth control. Acceptable methods of contraception include hormonal (e.g., oral, implantable, injectable, or transdermal contraceptives), mechanical (e.g., spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine device (IUD), or surgical sterilization of partner. For non-sexually active females, abstinence might be regarded as an adequate method of birth control; however, if the subject became sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
31. Have a known hypersensitivity or contraindication to the investigational products (IPs) or their components;
32. 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 (e.g., any planned procedure or surgery during the study period);
33. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days prior to Visit 1;
34. Have previously participated in a clinical trial with IC265 (previously called PRT-2761);
35. Be, in the opinion of the Investigator, unable or unwilling to comply with the study protocol, including participation in all study assessments, visits, and dosing, or be unable to instill eye drops successfully. Subject non-compliance with dosing during the run-in period, defined as < 80% or > 125% of expected doses taken, might be exclusionary if, in the opinion of the Investigator, the subject is likely to be non-compliant with subsequent dosing regimens or other study assessments; or
36. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.</td></tr>
<tr><td colspan="2">Evaluation Criteria:</td></tr>
<tr><td>Efficacy Measures and Endpoints:</td><td><u>Efficacy Measures:</u>
The following endpoints will be tested in the study eye:
• Fluorescein staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
• Ocular discomfort and dry eye symptoms at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
• Lissamine green staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
• Tear film break-up time at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
• Conjunctival Redness at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE), and mean change from baseline Visit 2 (Day 1) pre-CAE to Visit 5 (Day 84) pre-CAE
• Ocular Surface Disease Index (OSDI) at Visits 3, 4, and 5 (pre-CAE)
• Schirmer's test at Visit 3, 4, and 5
• Ocular discomfort during CAE at Visits 4 and 5
• Daily Diary Symptom Score</td></tr>
<tr><td>Safety/Tolerability Measures:</td><td>• Visual acuity
• Slit-lamp evaluation
• Adverse event query
• Intraocular pressure</td></tr>
</table>

	• Undilated fundoscopy • Drop comfort assessment after randomization at Visit 2, 3, 4, and 5

General Statistical Methods and Types of Analyses

Analysis Populations

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Efficacy analyses will be performed on the ITT population with observed data only. The ITT population may also be analyzed using the Last Observation Carried Forward (LOCF) imputation method and multiple imputation to assess sensitivity. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. 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 includes all randomized subjects who have received at least one dose of the investigational product. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

Unit of Analysis

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

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with the worst (higher) total corneal fluorescein staining, based on the sum of the inferior, superior, and central regions, at baseline (Visit 2) pre-CAE. If the total corneal staining is the same in both eyes, then the right eye will be selected as the study eye.

Sample Size

Approximately 80 subjects will be screened to enroll 40 subjects (20 subjects in each group). This is a Phase 2 study for which no formal sample size calculation has been performed. The sample size chosen was not based on statistical considerations, but is based on historical experience.

Multiplicity Considerations

As this is an exploratory study with no primary or secondary endpoints, there will be no multiplicity adjustments and all analyses are considered hypothesis-generating.

Efficacy Endpoints Analysis

The method of analysis for efficacy endpoints will be based on the distribution of the individual variable for analysis. Variables recorded on a continuous scale will be analyzed at each visit using two-sample t-tests and Wilcoxon rank sum tests. Each visit and treatment group will be summarized using descriptive statistics for the ITT population with observed data only. Changes from baseline will be summarized by visit and treatment using descriptive statistics and analyzed by visit using ANCOVA models with baseline value and treatment group, two sample t-tests and Wilcoxon rank sum tests on the ITT population with observed data only.

For multinomial outcome variables, a generalized linear model will be used, and the distribution will be specified as multinomial.

The ITT population will be analyzed using LOCF imputation for the primary efficacy analysis. For sensitivity analyses on the primary and key secondary endpoints, observed data will be used on the ITT and PP population, and multiple imputation will be used on the ITT population. Further details will be included in the statistical analysis plan (SAP). Analyses using ANCOVA or generalized linear models including data from both regions will include a fixed effect of region.

Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequencies and percentages will be provided per treatment group of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An adverse event is treatment emergent if it occurs or worsens after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term for treatment-related adverse events (AEs), by system organ class and preferred term for serious adverse events (SAEs); and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular and non-ocular adverse events.

The incidence of patients who experience a TEAE of interest over the 12-week post-treatment observation period will be compared between the IC265 and placebo groups. A generalized linear model will be used.

The incidence of patients who experience a composite of one or more MedDRA preferred terms of interest over the 12-week post-treatment observation period will be compared between the IC265 and placebo groups. A generalized linear model will be used, and the distribution will be specified as binomial.
Other safety endpoints will be summarized by treatment and visit using descriptive statistics. Change or shift from baseline will also be summarized where appropriate. For assessments performed by eye, both eyes will be summarized separately.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
BID	Twice Daily
CAE	Controlled Adverse Environment
CDs	Compact Discs
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DED	Dry Eye Disease
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent To Treat
IWRS	Interactive Web Response System
LASIK	Laser In Situ Keratomileusis
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OCT	Optical Coherent Tomography
OSDI	Ocular Surface Disease Index
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TFBUT	Tear Film Break-Up time
TEAEs	Treatment-Emergent Adverse Events
VA	Visual Acuity
VAS	Visual Analog Scale
WHO	World Health Organization

1.0 INTRODUCTION

Dry eye disease (DED) is a prevalent chronic eye condition affecting between 5% and 34% of the population worldwide, and approximately 1 million to 4 million Americans between 65 to 84 years of age (Fiscella 2011, Messmer 2015). This multifactorial disease has considerable socio-economic implications, including daily activities, visual function, social and physical functioning, workplace productivity, and quality of life (Pflugfelder 2008). According to the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II, "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig, Nichols et al. 2017). Recurrent corneal erosion and ocular surface inflammation are often painful and cause visual function impairment, significantly reducing the quality of life of patients.

Treatment approaches vary but generally employ the use of artificial tears to combat dryness or target the inflammatory aspect of the disease. While artificial tears often relieve some of the symptoms in the short term, many doses are required throughout the day and the underlying cause is left untreated. The Food and Drug Administration (FDA)-approved treatments that focus on inflammation for dry eye disease are 0.05% cyclosporine-A ophthalmic emulsion (Restasis®, Allergan), 0.09% cyclosporine ophthalmic solution (CEQUA™, Sun Pharmaceutical Industries, Inc), and lifitegrast 5% ophthalmic solution (Xiidra®, Shire US, Inc.).

To target the inflammatory aspect of DED, IACTA Pharmaceuticals, Inc. is currently developing IC265 ophthalmic solution with drug substance previously known as PRT-2761, a potent inhibitor of Syk. PRT-2761 is a small molecule in the pyrimidine carboxamide class that functions as a specific inhibitor to spleen tyrosine kinase (Syk). Syk is a non-receptor protein tyrosine kinase critical for B-cell activation and development and for signaling through the activating class of Fc receptors that are expressed on a wide range of hematopoietic cells including mast cells, macrophages, and neutrophils. Upon Fc receptor ligation, Syk binds to the di-phosphorylated immunomodulatory tyrosine-based activation motif (ITAM) harboring adaptor protein FcRγ, resulting in tyrosine phosphorylation of multiple downstream substrates that ultimately regulates cell survival, functional activation, differentiation, and clonal expansion (Ulanova, Duta et al. 2005). Syk is critical to the regulation of immune cell activation in response to ligation of a variety of receptors, making it an intriguing target for the treatment of inflammatory and autoimmune disorders. Inhibitors of Syk are currently in development for a number of diseases including heparin-induced thrombocytopenia, idiopathic thrombocytopenia, and chronic lymphocytic leukemia (Reilly, Sinha et al. 2011, Hoellenriegel, Coffey et al. 2012, Markham 2018).

The non-clinical program for PRT-2761 (drug substance of IC265 ophthalmic solution) consisted of: proof-of concept studies in a murine conjunctival allergen challenge (CAC) model, non-Good Laboratory Practice (GLP) pharmacokinetic studies in rats and rabbits, 28 days GLP oral toxicity and toxicokinetic studies in rats, and 28 days GLP ocular toxicity and toxicokinetic studies in Dutch Belted rabbits and beagle dogs. No clinical studies for the treatment of DED have been conducted with PRT-2761. However, clinical experience and safety with PRT-2761 has been demonstrated for the treatment of acute and chronic allergic conjunctivitis in a single-center phase 2 study.

2.0 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of IC265 Ophthalmic Solution 1% to placebo for the treatment of the signs and symptoms of dry eye disease.

3.0 CLINICAL HYPOTHESIS

The clinical hypotheses for this study is that IC265 Ophthalmic Solution 1% twice daily (BID) is superior to its vehicle (BID) for the following endpoints of signs and symptoms of dry eye, as follows:

- Fluorescein staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Ocular discomfort and dry eye symptoms at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Lissamine green staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Tear film break-up time at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Conjunctival Redness at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE), and mean change from baseline Visit 2 (Day 1) pre-CAE to Visit 5 (Day 85) pre-CAE
- Ocular Surface Disease Index (OSDI) at Visits 3, 4, and 5
- Schirmer's test at Visit 3, 4, and 5
- Ocular discomfort during CAE at Visits 4 and 5
- Daily diary symptom score

4.0 OVERALL STUDY DESIGN

This is a Phase 2, single-center, double-masked, randomized, placebo-controlled clinical study. Subjects will be randomized to one of the following treatment arms at Visit 2 (Day 1):

- IC265 Ophthalmic Solution 1%: 1 drop BID bilaterally (N=~20)
- Placebo Ophthalmic Solution (Vehicle): 1 drop BID bilaterally (N=~20)

Approximately 40 subjects will be randomly assigned to one of the two groups (1:1) to receive either IC265 Ophthalmic Solution 1% or placebo solution as topical ophthalmic drops administered bilaterally BID for 12 weeks. Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment.

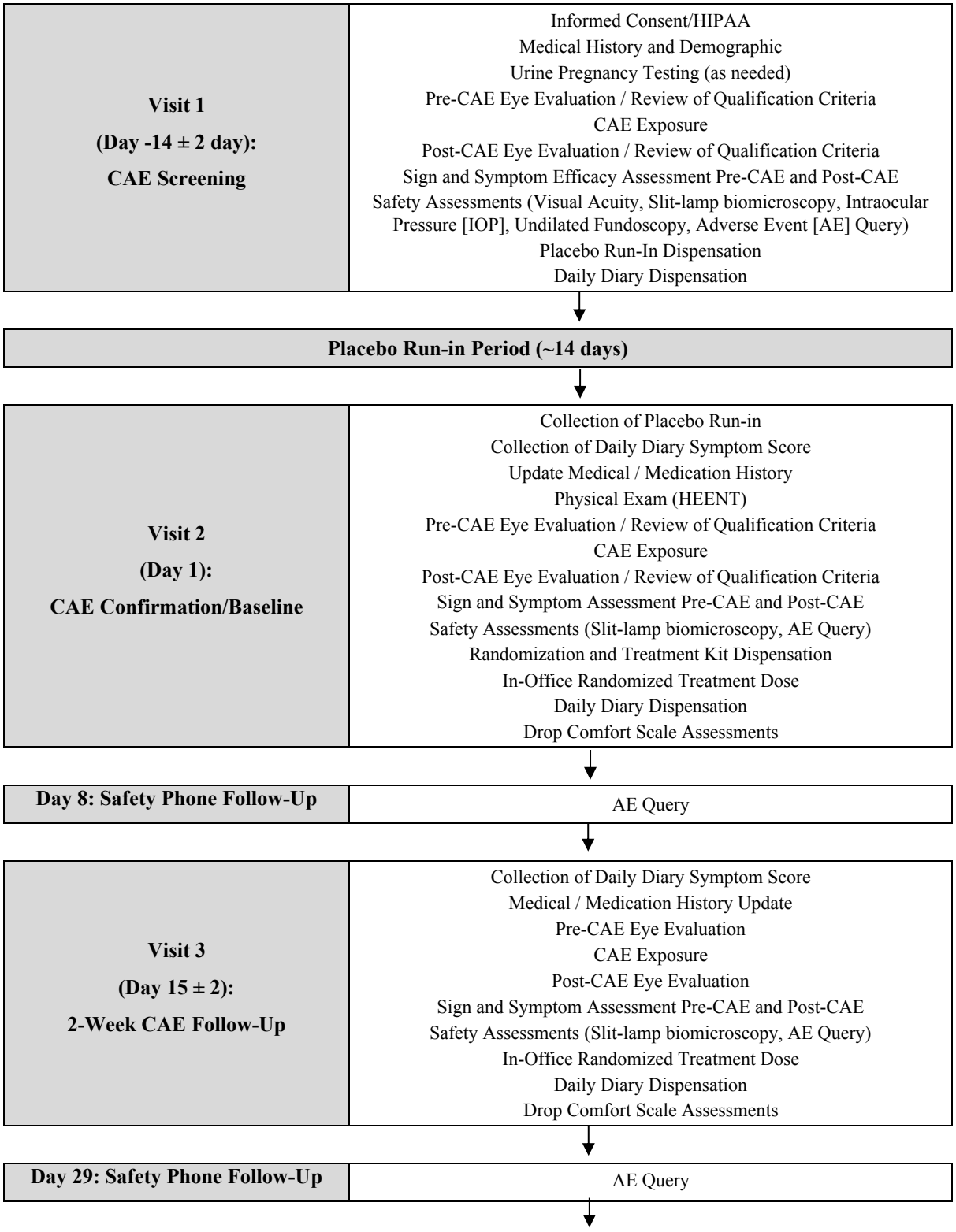
During the 14-day study run-in period prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID.

During the screening period, two 90-minute exposures to the CAE will be conducted to ascertain eligibility to enter the study at Visit 1 (Day -14 ± 2) and Visit 2 (Day 1). Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle BID for approximately 14 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double-masked fashion for 84 days. Subjects will

self-administer drops BID and will complete Daily diary symptom score assessments as instructed.

The CAE exposure will occur at Visit 1 (Day -14 ± 2), Visit 2 (Day 1), Visit 3 (Day 15 ± 2), Visit 4 (Day 43 ± 2), and Visit 5 (Day 85 ± 4), with Pre-CAE, during CAE and Post-CAE assessments of ocular signs and symptoms. Study drug will be discontinued at Visit 5. Subjects will exit from the study at this visit.

A study design flow chart is provided below:



Visit 4 **(Day 43 ± 2):** **6-Week CAE Follow Up**	Collection of Daily Diary Symptom Score Update Medical / Medication History Pre-CAE Eye Evaluation CAE Exposure Post-CAE Eye Evaluation Sign and Symptom Assessment Pre-CAE and Post-CAE Safety Assessments (Slit-lamp biomicroscopy, AE Query) Treatment Kit Dispensation In-Office Randomized Treatment Dose Daily Diary Dispensation Drop Comfort Scale Assessments
↓	
Day 64: Safety Phone Follow-Up	AE Query
↓	
Visit 5 **(Day 85 ± 4)/Early Termination:** **12-Week CAE Follow Up and Study Exit**	Collection of Daily Diary Symptom Score Update Medical / Medication History Pre-CAE Eye Evaluation CAE Exposure Post-CAE Eye Evaluation Sign and Symptom Assessment Pre-CAE and Post-CAE Safety Assessments (Slit-lamp biomicroscopy, IOP, Undilated Fundoscopy, AE Query) Study Exit

5.0 STUDY POPULATION

5.1 NUMBER OF SUBJECTS (APPROXIMATE)

Approximately 80 subjects will be screened to enroll 40 subjects (20 in each group). Subjects will be randomized in each treatment arm. Subjects will be randomized in a 1:1 ratio of

- IC265 Ophthalmic Solution 1%
- Placebo Ophthalmic Solution (Vehicle)

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

Each subject must:

1. Be at least 18 years of age;
2. Provide written informed consent;
3. Have a reported or documented history of dry eye for at least 6 months prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1, except as noted below in Section 5.4(**Error! Reference source not found.**);
5. Report a score of ≥ 2 on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom at Visits 1 and 2;

6. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1 and 2;
7. Have a pre-CAE conjunctival redness score ≥ 1 according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1 and 2;
8. Have a corneal fluorescein staining score of ≥ 2 in at least one region (e.g. inferior, superior, or central) at Visits 1 and 2;
9. Have a sum corneal fluorescein staining score of ≥ 4, based on the sum of the inferior, superior, and central regions, at Visits 1 and 2;
10. Have a total lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions at Visits 1 and 2;
11. Demonstrate a response to the CAE® at Visits 1 and 2 as defined by:
    a. Having at least a ≥1 point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure
    b. Reporting an Ora Calibra® Ocular Discomfort Score ≥3 at 2 or more consecutive time points in at least one eye during CAE® exposure (if a subject has an ocular discomfort rating of 3 at time = 0 for an eye, s/he must report an ocular discomfort rating of 4 for two consecutive measurements for that eye) Note: a subject cannot have an ocular discomfort score of 4 at time = 0);
12. Have at least one single eye satisfy all criteria for 6, 7, 8, 9, 10, and 11 above.

5.4 EXCLUSION CRITERIA

Each subject may <u>not</u>:

1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, ocular rosacea, lid margin inflammation, or active ocular allergies that require therapeutic treatment;
2. Have any clinically significant (CS) posterior chamber findings, or a history of such findings/disorders, that may include exudative (i.e., wet) age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, glaucoma, ocular hypertension, or any other retinal or optic nerve disease/disorder that require therapeutic treatment and/or in the opinion of the Investigator may interfere with study parameters;
3. Have worn contact lenses within 48 hours prior to Visit 1 or anticipate using contact lenses during the study;
4. Have laser-assisted in situ keratomileusis (LASIK) or similar type of corneal refractive surgery and/or any other ocular surgical procedure within 12 months prior to Visit 1; or have any ocular surgical procedure scheduled to be conducted during the study period;
5. Have had any surgeries of the ocular surface or lid in the past 6 months;
6. Have a history of lacrimal duct obstruction in either eye within 12 months prior to Visit 1;
7. Have used temporary (i.e., collagen) punctal plugs within 12 weeks prior to Visit 1 or anticipate their use during the study period;
8. Have permanent punctal plugs inserted or removed – including falling out – or have had surgical punctal occlusion within 12 weeks prior to Visit 1 or anticipate any such event at any time during the study period;

9. Use any of the following treatments in the period indicated before Visit 1 or anticipate their use at any time during the study.

24 hours prior to Visit 1

   a. All topical ophthalmic preparations (e.g., medications for glaucoma, over-the counter-solutions, artificial tears, gels, scrubs, ointments)

72 hours prior to Visit 1

   b. Antihistamines (including topical ophthalmic and nasal antihistamines)

30 days prior to Visit 1

   c. Topical ophthalmic non-steroidal anti-inflammatories
   d. Topical ophthalmic corticosteroids
   e. Topical ophthalmic autologous serum
   f. Topical ophthalmic antibiotics
   g. Mast cell stabilizers
   h. Oral aspirin or aspirin-containing products except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
   i. Any other medication known to cause ocular drying (e.g., antidepressants, beta blockers) except in the case that it was taken on a stable dosing regimen for at least 30 days prior to Visit 1 and is expected to be taken on the same regimen throughout the study period
   j. Restasis®
   k. Xiidra®
   l. CEQUA™
   m. LipiFlow® or other similar meibomian gland dysfunction (MGD) therapy
   n. TrueTear®
   o. Corticosteroids (e.g., systemic steroids including intravenous, intramuscular, intraarticular, oral steroids; nasal steroids; facial topical steroids; dermatological steroids with high potency or large treatment areas);
   p. Tetracyclines (tetracycline, doxycycline, minocycline, etc.)

10. Be monocular or have best corrected visual acuity greater than or equal to logMAR+0.7 in either eye as assessed by the ETDRS scale at Visit 1;
11. Have a severe/serious systemic disease, chronic illness or uncontrolled medical condition including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, poorly controlled diabetes and/or clinically significant (CS) hematologic, renal or liver disease that in the opinion of the Investigator could interfere with study assessments or limit compliance;
12. Be a woman who is pregnant, nursing or planning a pregnancy;
13. 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, bilateral tubal ligation, or bilateral oophorectomy), or is post-menopausal (i.e., without menses for 12 consecutive months);

14. Be a woman of childbearing potential who is not using an acceptable means of birth control. Acceptable methods of contraception include hormonal (e.g., oral, implantable, injectable, or transdermal contraceptives), mechanical (e.g., spermicide in conjunction with a barrier such as a diaphragm or a condom), intrauterine device (IUD), or surgical sterilization of partner. For non-sexually active females, abstinence might be regarded as an adequate method of birth control; however, if the subject became sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
15. Have a known hypersensitivity or contraindication to the investigational products (IPs) or their components;
16. Have a condition or be in a situation which the Investigator felt may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study (e.g., any planned procedure or surgery during the study period);
17. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days prior to Visit 1;
18. Have previously participated in a clinical trial with IC265 (previously called PRT-2761);
19. Be, in the opinion of the Investigator, unable or unwilling to comply with the study protocol, including participation in all study assessments, visits, and dosing, or be unable to instill eye drops successfully. Subject non-compliance with dosing during the run-in period, defined as < 80% or > 125% of expected doses taken, might be exclusionary if, in the opinion of the Investigator, the subject is likely to be non-compliant with subsequent dosing regimens or other study assessments; or
20. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.

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).

If a subject discontinues participation in the study early, every attempt will be made to complete the exit procedures required at the final study visit (Visit 5).

6.0 STUDY PARAMETERS

6.1 EFFICACY ENDPOINTS

The following endpoints will be tested in the study eye:

- Fluorescein staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score

- Ocular discomfort and dry eye symptoms at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Lissamine green staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Tear film break-up time at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Conjunctival Redness at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE), and mean change from baseline Visit 2 (Day 1) pre-CAE to Visit 5 (Day 85) pre-CAE
- Ocular Surface Disease Index (OSDI) at Visits 3, 4, and 5 (pre-CAE)
- Schirmer's test at Visit 3, 4, and 5
- Ocular discomfort during CAE at Visits 4 and 5
- Daily diary symptom score

6.2 SAFETY MEASURES

The following safety measures will be evaluated in both eyes:

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular pressure
- Undilated fundoscopy
- Drop comfort assessment after randomization at Visit 2, 3, 4, and 5

7.0 STUDY MATERIALS

7.1 STUDY TREATMENTS

7.1.1 Study Drug Formulation

All arms will be double-masked. Subjects will be randomized 1:1 into:

- IC265 Ophthalmic Solution 1%; BID
- Placebo Ophthalmic Solution (Vehicle); BID

IC265 Ophthalmic Solution will be formulated as a sterile, non-preserved solution around pH 6 for topical ophthalmic administration and is intended for clinical use. The study drug will be supplied in blow-fill seal ampoules, which allow for product administration directly to the eye. Each ampoule will contain a nominal volume of 0.27 mL.

The excipients which will be used to manufacture IC265 Ophthalmic Solution will be standard excipients for use in ophthalmic solutions that comply with their respective USP / EP monographs.

The placebo for IC265 Ophthalmic Solution contains all the same excipients used in the active formulation without the API.

7.1.2 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period.

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen were selected based on positive efficacy results in the proof-of-concept nonclinical studies. The proposed treatment period is 12 weeks.

7.1.3 Instructions for Use and Administration

- Subjects will receive placebo ophthalmic solution at Visit 1, and assigned a study drug kit at Visit 2, 3, and 4.
- Subjects who are randomized must administer study drug bilaterally BID. At Visit 2, 3, and 4, subjects will self-administer one dose of study drug in office.

7.2 LABELING, PACKAGING, STORAGE, ACCOUNTABILITY, AND RETURN OR DISPOSAL OF INVESTIGATIONAL PRODUCT

7.2.1 Labeling/Packaging

Investigational product (IP) will be packaged and labeled into clinical kits. The primary packaging of the IC265 will be blow-fill-seal ampules with a fill volume of 0.27 mL. The secondary packaging is a foil pouch that contains three ampules in each pouch.

Run-in Period

For the run-in period, 6 pouches will be packaged in a 1-week clinical kit. Each subject will receive 2 kits.

Treatment Period

BID Dosing: For the treatment period, 6 pouches will be packaged in a 1-week clinical kit. Each subject will receive 12 kits.

7.2.2 Storage of Investigational Product

Ampoules must be stored at controlled room temperature from 15 ^{o}C to 25^{o}C until the day of use. Any material remaining in the ampoule after use should be discarded. IC265 Ophthalmic Solution should be kept out of reach of children. Drug administration instructions and discarding information will be provided with each study.

7.2.3 Accountability of Investigational Product

The IP is to only be prescribed by the Principal Investigator (PI) or his/her named sub-investigator(s), and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

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

7.2.4 Return or Disposal of Investigational Product

All IP (used or unused) will be returned to the sponsor or their designee. The return of IP will be specified in writing.

7.3 OTHER STUDY SUPPLIES

Other study supplies include Schirmer's test strips, sodium fluorescein, lissamine green, Fluress, Tropicamide, Daily diary.

8.0 STUDY METHODS AND PROCEDURES

8.1 SUBJECT ENTRY PROCEDURES

8.1.1 Overview

Subjects as defined by the criteria in Section 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 study (i.e., changes in a subject's medical treatment and/or 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. 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 (Section 5.3 and 5.4).

8.1.5 Methods for Assignment to Treatment Groups:

Before the initiation of study run-in at Visit 1, each subject who provides written informed consent will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 and Visit 2 will be assigned a randomization number at the end of Visit 2. Randomization number will be assigned manually and entered in the Screening and Enrollment log or automatically assigned using the Interactive Web Response System (IWRS).

The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). Subjects, Sponsor, CRO, and site personnel will be masked to treatment assignment.

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 eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical 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

An Informed Consent Form (ICF) must be signed and dated by the subject, the PI or designee and witness (if required) before any study-related procedures are performed.

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objectives

Procedures listed below should be performed in the given order. See Appendix 1 for the Schedule of Visits and Measurements Appendix 2 for details on methodologies and grading systems.

8.3.2 Visit 1: Day –14 ± 2 – CAE Screening

All subjects will undergo the following screening assessments:

Pre–CAE

- Informed Consent/Health Insurance Portability and Accountability Act (HIPAA)
- Demographic Data and Medical/Medication/Ocular History
- Review of Inclusion/Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study
- Adverse Event (AE) Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- Visual Analog Scale (VAS) Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- At least 15 minute wait between Schirmer's test and CAE exposure
- 90-minute CAE exposure
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE and every 5 minutes thereafter

Post–CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Intraocular Pressure (IOP)
- Undilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
- Run-in (Vehicle) and Diary Dispensation: Prior to discharge from the study site on Visit 1, subjects will be dispensed sufficient Run-in supply to last until Visit 2 and will be educated in diary recording and self–administration of vehicle run-in. Subjects will be instructed to self–administer one drop BID bilaterally until Visit 2. Subjects will be instructed NOT to instill run-in on the morning of their next scheduled study visit (Visit 2).
- Subjects will be scheduled for Visit 2.

8.3.3 Visit 2: Day 1 – CAE® Confirmation and Baseline

Pre–CAE

- Study Diary/Run-in Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- Medical/medication history update
- Physical Exam (HEENT)
- AE query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer’s test
- Schirmer’s test

- At least 15 minute wait between Schirmer's test and CAE exposure
- 90-minute CAE exposure;
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE and every 5 minutes thereafter

Post–CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Slit Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Review of Inclusion/Exclusion Criteria
- Randomization
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3
- Study Drug Instillation at the Study Site: Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician
- Ora Calibra® Drop Comfort Scale
- Subjects will be scheduled for Visit 3

8.3.4 Safety Phone Follow-Up: Day 8, Day 29, and Day 64

- AE Query

8.3.5 Visit 3: Day 15 ± 2

Pre–CAE

- Study Diary Collection
- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness

- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- 90-minute CAE exposure
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE and every 5 minutes thereafter

Post–CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 3, subjects will be re-educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 4.
- Study Drug Instillation at the Study Site: Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician
- Ora Calibra® Drop Comfort Scale
- Subjects will be scheduled for Visit 4

8.3.6 Visit 4: Day 43 ± 2

Pre–CAE

- Study Diary Collection
- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy

- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- 90-minute CAE exposure
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE and every 5 minutes thereafter

Post–CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 4, subjects will be re-educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5.
- Study Drug Instillation at the Study Site: Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician
- Ora Calibra® Drop Comfort Scale
- Subjects will be scheduled for Visit 5

8.3.7 Visit 5: Day 85 ± 4

Pre–CAE

- Study Drug/Study Diary Collection
- Medical and Medication History Update
- Pregnancy Test (if applicable)
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy

- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- At least 15 minute wait between Schirmer's test and CAE exposure
- 90-minute CAE exposure;
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE and every 5 minutes thereafter

Post–CAE

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- IOP
- Undilated Fundoscopy
- Study Exit

8.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

8.4.1 Scheduled Visits

Refer to Appendix 1: Schedule of Visits and Measurements 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
- IOP
- Urine Pregnancy Test
- Undilated Fundoscopy
- Assessment of AEs

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

8.5 COMPLIANCE WITH PROTOCOL

Subjects will be instructed on proper use of the subject Daily diary and proper instillation and storage of study drug at the end of Visits 1 through 4 and given written instructions. To assess dosing and symptom assessment compliance, the subject daily diaries will be collected at Visit 2, 3, 4, 5, and the subject's used and unused study drug ampules will be collected at Visit 3, 4, and 5. Dosing compliance will be based on the used and unused ampule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded. Subjects will be reinstructed on dosing compliance and this will be documented in the source documents. 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.

A protocol deviation occurs when there is any non-adherence to a study procedure or schedule that is specified by the protocol. The term "protocol deviation" includes those departures from the protocol previously described by the term "protocol violation"; all departures from the protocol are now described as protocol deviations, regardless of the potential impact on subject safety. A Protocol Deviation Log shall be maintained by the site(s). Protocol deviations will be summarized in the final clinical study report.

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:

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of study

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

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or 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 14-week period (14 days pre-screening, 84 days of treatment).

8.9 MONITORING AND QUALITY ASSURANCE

During the course of the study an Ora monitor, or designee, will make routine site visits to review protocol compliance, assess IP accountability, 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, 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 subject confidentiality to the extent that local, state, and federal laws apply.

9.0 ADVERSE EVENTS

9.1 ADVERSE EVENT (AE)

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the case report form (CRF). Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the subject upon indirect questioning. Exacerbation of conditions related to the signs and symptoms of DED will not be reported as an AE.

All AEs and their outcomes, regardless of causality or expectedness, must be reported to Ora and the Sponsor as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate case report form (CRF). Adverse events will be collected after the signing of the Informed Consent).

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 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 Investigator must assess whether they consider an AE to be drug-related. In assessing this relationship, the Investigator must use information about the conditions/concurrent medication, and chronology of the event relative to drug. The investigator should initially classify the relatedness of an AE, but the final classification is subject to the Medical Monitor's determination unless revised by the Sponsor, which has the ultimate responsibility for judging relatedness. The relationship of each AE to the IP should be determined by the investigator using these explanations:

- **Definitely Related**: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
- **Probably Related**: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- **Possibly Related**: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- **Unlikely to be Related**: Relationship uncertain to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.
- **Not Related**: Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, or exposure to IP has not occurred.

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:

- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours), unless the inpatient admission was pre-planned prior to the signing of the informed consent. 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 (SAE) 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
- Death;
- Is life-threatening;

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

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

9.2.1 Expectedness

The expectedness of a SAE should be determined based upon existing safety information about the IP using these explanations:

- **Unexpected*:*** An SAE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- **Expected*:*** An SAE that is listed in the Investigational Brochure (IB) at the specificity and severity that has been observed.
- **Not applicable*:*** An SAE unrelated to the IP.

SAEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

9.3 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

All SAEs and their outcomes, regardless of causality or expectedness, must be reported to Ora and the Sponsor as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate case report form (CRF). Adverse events will be collected after the signing of the Informed Consent).

9.3.1 Reporting a Serious Unexpected Suspected Adverse Reaction

All SAEs that are both 'suspected' and 'unexpected' are to be reported to Ora, the Sponsor, and the IRB/IEC and the regulatory authorities as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the IP, must be immediately reported within 24 hours of awareness of the event. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify Ora and the Sponsor immediately using the contact information below; 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 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 IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

Name: Title: Office Telephone: Mobile Phone: Office Facsimile:	Joseph B. Ciolino, MD Medical Monitor 617-573-5575 401-935-9662 617-573- 4324
Name: Title: Office Telephone: Office Facsimile:	David Welch Clinical Project Manager (978) 685-8900 x (978) 689-0020
Ora Safety	safetygroup@oraclinical.com

9.4 PROCEDURES FOR UNMASKING (IF APPLICABLE)

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 group has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug. Ora and/or the study Sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify the Sponsor, 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 IWRS. 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.

Unmasked subjects will be discontinued from the study. Unmasked subjects will be followed for safety monitoring until resolution of the adverse event or study completion, whichever occurs last.

9.5 TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

The investigator will follow unresolved AEs to resolution or stabilization until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the investigator should make reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSIS

10.1 ANALYSIS POPULATIONS

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Efficacy analyses will be performed on the ITT population with observed data only. The ITT population may also be analyzed using the Last Observation Carried Forward (LOCF) imputation method and multiple imputation to assess sensitivity. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. 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 includes all randomized subjects who have received at least one dose of the investigational product. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of efficacy data will be performed for the ITT population and on the PP population as sensitivity analyses.

10.2 STATISTICAL HYPOTHESES

This is an exploratory study with no primary or secondary endpoints. The following endpoints will be tested in the study eye:

- Fluorescein staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Ocular discomfort and dry eye symptoms at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)

- Lissamine green staining (Ora Calibra scale) at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE) in the following regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Tear film break-up time at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE)
- Conjunctival Redness at Visits 3, 4 (pre-CAE, post-CAE, and pre- to post-CAE), and 5 (pre-CAE, post-CAE, and pre- to post-CAE), and mean change from baseline Visit 2 (Day 1) pre-CAE to Visit 5 (Day 84) pre-CAE
- Ocular Surface Disease Index (OSDI) at Visits 3, 4, and 5 (pre-CAE)
- Schirmer's test at Visit 3, 4, and 5
- Ocular discomfort during CAE at Visits 4 and 5
- Daily diary symptom score

10.3 SAMPLE SIZE

Approximately 80 subjects will be screened to enroll 40 subjects (20 subjects in each group). This is a Phase 2 study for which no formal sample size calculation has been performed. The sample size chosen was not based on statistical considerations, but is based on historical experience.

10.4 STATISTICAL ANALYSIS

10.4.1 General Considerations

Continuous variables will be summarized descriptively using number of subjects (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

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

For the purpose of summarization, medical history, concurrent therapies, and AEs will be coded to Medical Dictionary for Regulatory Authorities (MedDRA) MedDRA and World Health Organization (WHO) Drug dictionaries, as appropriate.

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment, usually at Visit 2. 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.

All analyses will be 2-sided at a significance level of 0.05 unless otherwise specified. For all efficacy analyses, 95% confidence intervals on the difference between each dose of IC265 and vehicle will be provided.

10.4.2 Unit of Analysis

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

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with the worst (higher) total corneal fluorescein staining, based on the sum of the inferior, superior, and central

regions, at baseline (Visit 2) pre-CAE. If the total corneal staining is the same in both eyes, then the right eye will be selected as the study eye.

10.4.3 Missing Data

Missing data will be imputed using Last Observation Carried Forward (LOCF) on the ITT population for primary analyses.

Sensitivity analyses of the primary analyses and important secondary comparisons will include the following in order to provide a robust understanding of the impact of missing and spurious data:

- Using observed data only on the ITT population
- Using multiple imputation on the ITT population
- Using observed data only on the PP population.

No imputation will be used for safety endpoints.

10.4.4 Multiplicity Consideration

As this is an exploratory study with no primary or secondary endpoints, there will be no multiplicity adjustments and all analyses are considered hypothesis-generating.

10.4.5 Efficacy Analyses

The method of analysis for efficacy endpoints will be based on the distribution of the individual variable for analysis. Variables recorded on a continuous scale will be analyzed at each visit using two-sample t-tests and Wilcoxon rank sum tests. Each visit and treatment group will be summarized using descriptive statistics for the ITT population with observed data only. Changes from baseline will be summarized by visit and treatment using descriptive statistics and analyzed by visit using ANCOVA models with baseline value and treatment group, two sample t-tests and Wilcoxon rank sum tests on the ITT population with observed data only.

For multinomial outcome variables, a generalized linear model will be used, and the distribution will be specified as multinomial.

The ITT population may also be analyzed using LOCF imputation and multiple imputation to assess sensitivity as detailed further in the statistical analysis plan (SAP). Analyses using the PP population with observed/recorded data only may also be conducted.

10.4.6 Safety Variables

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Frequencies and percentages will be provided per treatment group of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An adverse event is treatment emergent if it occurs or worsens after the first dose of randomized study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term for treatment-related adverse events (AEs), by system organ class and preferred term for serious adverse events (SAEs); and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular and non-ocular adverse events.

The incidence of patients who experience a TEAE of interest over the 12-week post-treatment observation period will be compared between the IC265 and placebo groups. A generalized linear model will be used, and the distribution will be specified as binomial.

The incidence of patients who experience a composite of one or more MedDRA preferred terms of interest over the 12-week post-treatment observation period will be compared between the IC265 and placebo groups. A generalized linear model will be used.

Other safety endpoints will be summarized by treatment and visit using descriptive statistics. Change or shift from baseline will also be summarized where appropriate. For assessments performed by eye, both eyes will be summarized separately.

10.4.7 Interim Analyses

There will be no interim analyses in this study.

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

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (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 IP in the countries involved will be addressed.

11.1 PROTECTION OF HUMAN SUBJECTS

11.1.1 Subject 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 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.

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

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations 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 is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, the Sponsor, the IRB/IEC approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies (when relevant) will be granted direct access to the subject's original medical and study records for verification of the data and/or clinical study 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 IP 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 electrocardiograms. The Investigator's copy of the CRFs serves as the Investigator's record of a subject's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of CRFs 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 IP. 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 RECORDING OF DATA ON SOURCE DOCUMENTS AND CASE REPORTS FORMS (CRFS)

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's CRF, 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.

Data entry of all enrolled and randomized subjects 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 be entered in eCRF for screen failure subjects. 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 (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.6 PUBLICATIONS

All data derived from the study will be the property of the sponsor and must be kept strictly confidential. The Investigator must not submit any of the data from this study for publication without prior consent of the Sponsor. The Sponsor will have the final decision regarding any manuscript and publication.

12.0 REFERENCES

Craig, J. P., K. K. Nichols, E. K. Akpek, B. Caffery, H. S. Dua, C. K. Joo, Z. Liu, J. D. Nelson, J. J. Nichols, K. Tsubota and F. Stapleton (2017). "TFOS DEWS II Definition and Classification Report." Ocul Surf **15**(3): 276-283.

Fiscella, R. G. (2011). "Understanding dry eye disease: a managed care perspective." Am J Manag Care **17 Suppl 16**: S432-439.

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13.0 APPENDICES

13.1 APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Visit 1 Day -14 ± 2		Visit 2 Day 1		Day 8	Visit 3 Day 15 ± 2		Day 29	Visit 4 Day 43 ± 2		Day 64	Visit 5 Day 85 ± 4/Early Termination	
	Pre-CAE	Post - CAE	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE	Phone Call	Pre-CAE	Post-CAE
Informed Consent / HIPAA	X												
Medical / Medication History and Demographic	X												
Run-in Collection			X										
Study drug Collection						X			X			X	
Diary Collection			X			X			X			X	
Medical / Medication History Update			X			X			X			X	
Adverse Event Query	X		X		X	X		X	X		X	X	
Pregnancy Test	X[1]											X[1]	
Physical Exam (HEENT)			X										
Ora Calibra™ Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X		X	X		X	X		X	X
OSDI© Questionnaire	X		X			X			X			X	
Visual Acuity (ETDRS)	X		X			X			X			X	
Review of Qualification Criteria	X	X	X	X									
Slit-lamp Biomicroscopy	X	X	X	X		X	X		X	X		X	X
TFBUT	X	X	X	X		X	X		X	X		X	X
Fluorescein Staining	X	X	X	X		X	X		X	X		X	X
Lissamine Green Staining	X	X	X	X		X	X		X	X		X	X
Conjunctival Redness	X	X	X	X		X	X		X	X		X	X
Tear Collection			X									X	
CAE® Exposure	X		X			X			X			X	
Ora Calibra™ Ocular Discomfort Scale	X[2]		X[2]			X[2]			X[2]			X[2]	
Unanesthetized Schirmer's Test				X									X
Intraocular Pressure		X											X
Undilated Fundus Exam		X											X

Run-in Article Dispensation		X											
Randomization				X									
Randomized Study Drug Instillation				X			X			X			
Drop Comfort Assessment				X			X			X			
Study Drug Dispensation				X			X			X			
Diary Dispensation		X		X			X			X			
Exit Subject from Study													X
X[1] = For females of childbearing potential, **X**[2] = Procedure started at time 0 and then conducted every 5 minutes thereafter during the 90 minute CAE[SM] exposure													

13.2 APPENDIX 2: EXAMINATION PROCEDURES, TESTS, & EVALUATIONS

Visual Acuity Procedures (ETDRS Chart)

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

Equipment

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

Measurement Technique

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

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

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as 1 of 2 letters, he or 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 included in the last line read. This total sum represents the logMAR VA for that eye.

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

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of VA during the study, all VA 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 (i.e., a subject forgets his glasses), the reason for the change in correction should be documented.

Slit Lamp Biomicroscopy Procedures

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). The following will be examined:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Eyelid

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

Undilated Fundoscopy

Undilated fundus exams will be performed using indirect ophthalmoscopy. The Investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

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

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

Intraocular Pressure (IOP)

Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. A single measurement is made to obtain a determination of IOP. The same tonometer employing the investigator's standard technique

will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

Unanesthetized Schirmer's Test

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

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

Ocular Surface and Disease Index© (OSDI©) for Dry Eye

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)

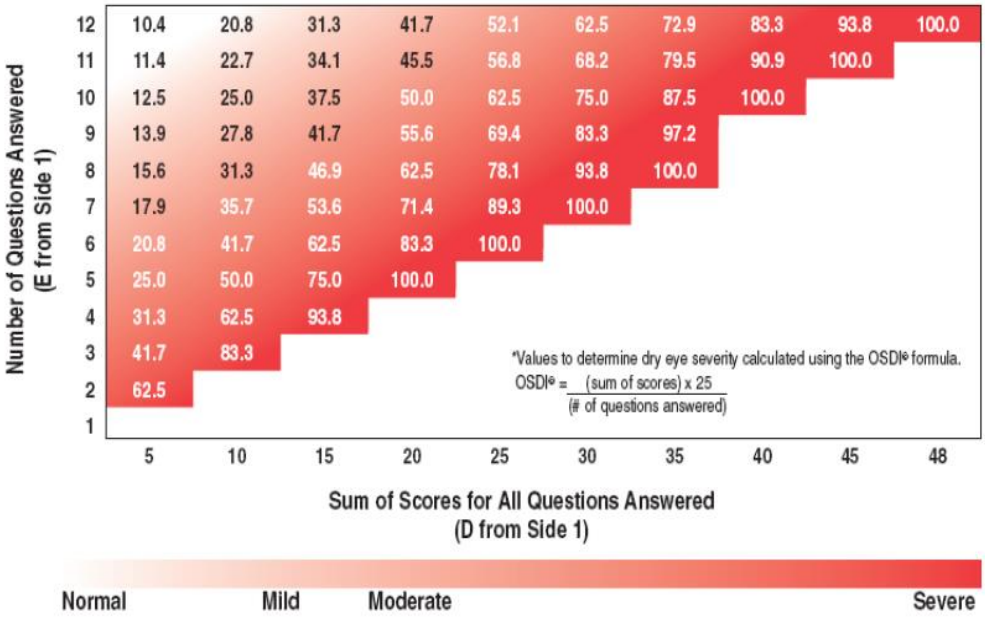
Please turn over the questionnaire to calculate the patient's final OSDI® score.

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

Visual Analog Scale (VAS)

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

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

Burning/ Stinging	0%	100%
Itching	0%	100%
Foreign Body Sensation	0%	100%
Blurred Vision	0%	100%
Eye Dryness	0%	100%
Photophobia	0%	100%
Pain	0%	100%

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 subject 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 Ora Calibra® Corneal and Conjunctival Staining Scale.

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale for Dry Eye

This procedure will be performed according to Ora, Inc. Standard Operating Procedures (SOPs) and/or guidance documents.

Ocular discomfort scores will be subjectively graded by the subjects according to the following scale, rating each eye separately.

0	No discomfort
1	Intermittent awareness
2	Constant awareness
3	Intermittent discomfort
4	Constant discomfort

Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire for Dry Eye

This procedure will be performed according to Ora, Inc. Standard Operating Procedures and/or guidance documents.

At each day during the at-home dosing period, subjects will grade the severity of their dry eye syndrome symptoms in their diary in the morning and in the evening, before instilling the study drug.

Subjects will rate the severity of each of the following symptoms, with regard to how both their eyes feel, in general – overall ocular discomfort, burning, dryness, grittiness and stinging according to the following 6-point (0 to 5) scale where 0 = none and 5 = worst.

0 1 2 3 4 5

(None) (Worst)

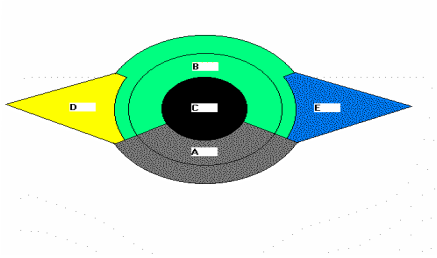
Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

The following scale will be used to grade staining of the ocular surface (areas A, B, C, D, and E). Half (0.5) grade increments may be used.

None	0 = no staining
Trace	1 = occasional
Mild	2 = countable
Moderate	3 = uncountable, but not confluent
Severe	4 = confluent

Staining areas:



Staining Areas	Ocular Structure	Position
A – Inferior	Cornea	4-8 o'clock, extending 2 mm onto the conjunctiva
	Limbus/Conjunctiva	4-8 o'clock, extending 2 mm towards the center
B – Superior	Cornea	8-4 o'clock, extending 3 mm onto the conjunctiva
	Limbus/Conjunctiva	8-10 o'clock and 2-4 o'clock, extending 1 mm onto the conjunctiva; 10-2 o'clock, extending 2 mm onto the conjunctiva
C – Central	Cornea	Central cornea
D – Temporal	Conjunctiva	Triangular wedge of temporal conjunctiva
E – Nasal	Conjunctiva	Triangular wedge of nasal conjunctiva

Lissamine Green Staining

The Investigator will instill 10 µL of lissamine green solution or place a lissamine strip into the inferior conjunctival cul-de-sac and wait approximately 30 seconds before evaluating staining. The subject will be instructed to blink several times to distribute the lissamine green. The staining will be graded with the Ora Calibra® Corneal and Conjunctival Staining Scale.

Ora Calibra® Conjunctival Redness Scale for Dry Eye

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

None	0 = Normal, without vasodilation
Trace	1 = Trace ciliary or conjunctival vasodilation
Mild	2 = Broad ciliary vasodilation;
Moderate	3 = Broad ciliary and slight, horizontal conjunctival vasodilation
Severe	4 = Broad ciliary and prominent, horizontal conjunctival vasodilation
Half (0.5) unit increments are allowed.	

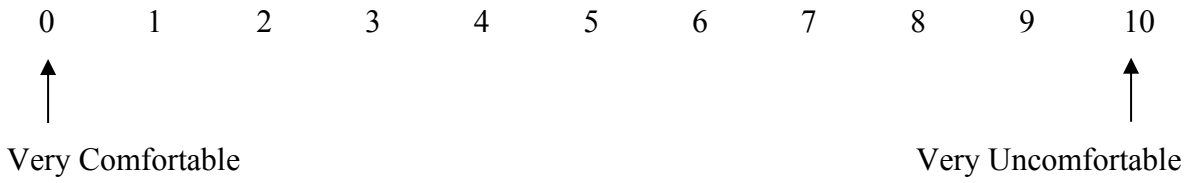
Drop Comfort Assessments

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

Subject-Reported Drop Comfort Scale

Drop comfort will be assessed for each eye immediately upon instillation, and at 1 and 2 minutes following initial dosing at Visits 1, 2, 3, and 4 using the Ora Calibra™ Drop Comfort Scale.

Ora Calibra® Drop Comfort Scale



Subject Diary

Subject will be asked to complete a dosing diary daily between Visit 1 and Visit 5.

13.3 APPENDIX 3: PROTOCOL AMENDMENT SUMMARY

Not Applicable.

13.4 APPENDIX 4: SPONSOR AND ORA APPROVALS

Protocol Title:	A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects with Dry Eye Disease
IND Number	130141
Final Date (Version 1.0):	12 Jun 2023

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:

George Ousler
Senior Vice President, Anterior Segment
Ora, Inc.

Signed:_____ Date:

Eric Carter,
Chieft Medical Officer
IACTA Pharmaceuticals, Inc.

Signed:_____ Date:

Anoshie Ratnayake,
Medical Monitor
IACTA Pharmaceuticals, Inc.

13.5 APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 2, Single-Center, Randomized, Double-Masked, Placebo-Controlled Study to Assess the Safety and Efficacy of IC265 Ophthalmic Solution 1% in Subjects with Dry Eye Disease
IND Number	130141
Final Date (Version 1.0):	12 Jun 2023

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 Ora and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) 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: _____