CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
Protocol Number:	HL036-DED-US-P301
Development Phase:	Phase 3
Investigational Product:	HL036 Ophthalmic Solution
IND Number:	135371
Indication:	Dry Eye Disease
Investigators	Multi-centered (Up to 13 sites)
Sponsor:	HanAll Biopharma Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170
Contract Research Organization	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
HanAll Biopharma's Responsible Medical Officer:	[redacted] Director, Product and Business Development HPI Inc. / HanAll Biopharma Co., Ltd 1 Church St. Suite 103 Rockville, MD 20850, USA
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673 USA
Date of Protocol: **Original Protocol:**	24 Jan 2019
Statement of Compliance with Good Clinical Practice	
This study will be performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP).	
Confidentiality Statement	
This protocol is confidential and the information available within it may not be reproduced or otherwise disseminated.	

SPONSOR PERSONNEL

Head, Bio Research Center	[redacted]
Director, Product and Business Development, HPI Inc.	[redacted]
Alliance Advisor, Product and Business Development, HPI Inc.	[redacted]
Assistant Manager, Product and Business Development, HPI Inc.	[redacted]
Medical Advisor, Product and Business Development, HPI Inc.	[redacted]
Manager, Clinical Development	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

ORA PERSONNEL

Department Vice President:	[redacted]
Department Director:	[redacted]
Clinical Project Manager:	[redacted]

SYNOPSIS

NAME OF COMPANY HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	**NAME OF DRUG PRODUCT** HL036 Ophthalmic Solution for Treatment of Dry Eye
TITLE OF STUDY: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye	
PROTOCOL NUMBER:	HL036-DED-US-P301
STUDY SITES:	Multicenter study involving up to 13 sites located in the United States
STUDY PERIOD: Approximately 70 days	**PHASE OF DEVELOPMENT:** Phase 3
STUDY FORMULATIONS:	0.25% HL036 Ophthalmic Solution Placebo Vehicle Solution
OBJECTIVE: The objective of this study is to compare the safety and efficacy of 0.25% HL036 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.	
DOSE, ROUTE AND REGIMEN: Screening: During the 14-day (± 2 days) run-in period, open–label placebo ocular drops will be self–administered twice daily (BID) in both eyes in the morning and the evening by all subjects. Treatment: During the 8–week (56 ± 2 days) treatment period, 0.25% HL036 Ophthalmic Solution or placebo ophthalmic solution will be self-administered BID by bilateral topical ocular dosing. Subjects will be randomized to one of two treatment arms (1:1) to receive study drug self-administered by subject after the Post–Ora Controlled Adverse Environment® (CAE) #2 assessments at Visit 2.	
DURATION OF TREATMENT: Approximately 56 days (8 weeks)	
REFERENCE THERAPY, DOSE, ROUTE AND REGIMEN: Open–label placebo ophthalmic solution (placebo) will be provided to subjects from Day –14 to Day -1. Placebo ocular drops will be self–administered BID in both eyes in the morning and the evening. Following randomization, placebo will be dosed according to the same schedule as the HL036 Ophthalmic Solution.	
NUMBER OF SUBJECTS PLANNED: Approximately 630 subjects will be enrolled in the study. The total number of expected participants, including screen failures, is approximately 1575 subjects.	
DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION: **INCLUSION CRITERIA:** Individuals eligible to participate in this study must meet all of the following criteria: 1. Be at least 18 years of age; 2. Provide written informed consent; 3. Be willing and able to comply with all study procedures; 4. Have a patient-reported history of dry eye for at least 6 months prior to Visit 1; 5. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1;	

NAME OF COMPANY	NAME OF DRUG PRODUCT
HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	HL036 Ophthalmic Solution for Treatment of Dry Eye

6. Have a best corrected visual acuity (BCVA) of [redacted] logMAR or better (Snellen equivalent score of [redacted]) in each eye at Visit 1;
7. Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2;
8. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm at Visits 1 and 2;
9. Have a corneal fluorescein staining score of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visits 1 and 2;
10. Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1 and 2 pre-CAE
11. Demonstrate in the same eye(s) a response to the CAE® at Visits 1 and 2 as defined by:

    [redacted]

12. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10 and 11 above.
13. A negative urine pregnancy test if female of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post–menopausal [12 months after last menses]) and must use adequate birth control through the study period. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

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, lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;
4. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;
5. Have used Restasis®, Xiidra®, or Cequa® within 60 days of Visit 1;
6. Have any previous experience using HL036;
7. Have had any ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid surgeries over the study period;
8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;
9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for the following medications:
    a) Antihistamines (including ocular): 72 hours prior to Visit 1
    b) Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period
    c) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

NAME OF COMPANY	**NAME OF DRUG PRODUCT**
HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	HL036 Ophthalmic Solution for Treatment of Dry Eye

d) Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study
e) All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1

10. Have an uncontrolled systemic disease;
11. Be a woman who is pregnant, nursing or planning a pregnancy;
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
13. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
14. Have a known allergy and/or sensitivity to the test article or its components;
15. 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;
16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
17. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

ENDPOINTS:

The primary efficacy endpoints of the study are:

- Inferior corneal staining (sign), Pre- to Post-CAE at Day 57 (Week 8)
- Ocular discomfort (symptom), Pre-CAE at Day 57 (Week 8)

The secondary efficacy endpoints of the study are:

- Fluorescein staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum and total staining
- Conjunctival lissamine green staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum and total staining
- Conjunctival redness
- Schirmer's Test
- Tear film break-up time (TFBUT)
- Ocular Surface Disease Index© (OSDI©)
- Visual Analog Score (VAS)
- Daily symptom diary (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score)
- Daily symptom diary by CAE Qualification Time
- Drop comfort

NAME OF COMPANY	**NAME OF DRUG PRODUCT**
HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	HL036 Ophthalmic Solution for Treatment of Dry Eye

The safety endpoints of the study are:

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular Pressure
- Dilated fundoscopy
- Immunogenicity to HL036 in Serum

STATISTICAL METHODS:

Analysis Populations

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary analysis will be performed on the ITT population with the Markov Chain Monte Carlo (MCMC) imputation method for missing values. The ITT population may also be analyzed with Last Observation Carried Forward (LOCF) imputation, imputation via pattern mixture models, and with observed data only 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.

Sample Size

This study is expected to enroll 315 subjects in each of the two treatment arms, for a total of 630 randomized subjects. Assuming a 10% drop out rate, 283 subjects per group are expected to complete the study.

Assuming a common standard deviation in the change from baseline for the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining of 0.74 units, a sample size of 283 subjects per group will have 99% power to detect a difference of 0.3 units between the active treatment group and the placebo group at a significance level of 0.05. A sample size of 283 subjects per treatment arm will have 93% power to detect a mean difference of 0.3 units in the change from baseline for the pre-CAE® ocular discomfort as assessed by the Ora Calibra® Ocular Discomfort Scale, assuming a standard deviation of 1.03 units. The power for both the sign and symptom endpoints is 93%, assuming independence between the endpoints.

Multiplicity Consideration:

Hierarchical fixed sequence testing will be used to maintain the type I error rate. The primary analysis will first test the difference in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of HL036, then the study will be considered a success, HL036 will be declared to be superior to placebo in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57, and the difference in the change from baseline of the pre-CAE® ocular discomfort at Day 57 will be tested at the two-sided alpha = 0.05 level.

If, in addition to a statistically significant test of the difference in change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 in favor of HL036, the test of the difference in the change from baseline of the pre-CAE® ocular discomfort at Day 57 is also statistically significant in favor of HL036, then HL036 will be declared superior to placebo in both the change from

NAME OF COMPANY	NAME OF DRUG PRODUCT
HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	HL036 Ophthalmic Solution for Treatment of Dry Eye

baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining and the change from baseline of the pre-CAE® ocular discomfort at Day 57.

Primary Efficacy Analyses:

For both endpoints, change from baseline will be calculated as visit – baseline such that a positive difference indicates a worsening of dry eye signs or symptoms. In addition, treatment comparisons between active and placebo will be calculated as active – placebo, such that a negative result indicates a better score for the active treatment (i.e., the active treatment had a smaller increase in dry eye signs or symptoms than the placebo group).

Analysis of Covariance (ANCOVA) models will be used to compare the change from baseline in the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 (Visit 6), as measured on the Ora Calibra® scale, between 0.25% HL036 Ophthalmic Solution and Placebo. The ANCOVA models will include terms for baseline pre-CAE® to post-CAE® change in inferior corneal fluorescein staining and study site. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across study sites. The primary analysis will use MCMC imputation to have a full accounting of the ITT population at the Day 57 visit, as described in Section 10.4.3. As supportive analyses, imputation by LOCF, multiple imputation by pattern mixture models and analyses of observed data only will also be conducted. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted as supportive analyses.

Ocular discomfort will be analyzed similarly. ANCOVA models will be used to compare the change from baseline in the pre-CAE® ocular discomfort score at Day 57 (Visit 6), as measured on the Ora Calibra® Ocular Discomfort Scale, between 0.25% HL036 Ophthalmic Solution and Placebo. The ANCOVA models will include terms for baseline (Visit 2) ocular discomfort and study site. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across sites.

Secondary Efficacy Analyses:

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max), and analyzed with two-sample t-tests comparing each of the active treatment groups to placebo. All visit-based data will be analyzed at each visit and change from baseline. Change scores from pre- to post-CAE® will be calculated as Post-CAE® score – Pre-CAE® score. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed where appropriate. No imputation will be performed for secondary efficacy variables.

Corneal fluorescein staining by region and total, conjunctival lissamine green staining by region, TFBUT, conjunctival redness, unanesthetized Schirmer's test, drop comfort assessment, OSDI©, ocular discomfort and dry eye symptoms, ocular discomfort during CAE®, pre- to post-CAE® changes, and changes from baseline in these measures will be analyzed by visit using two-sample t-tests and Wilcoxon rank sum tests, as appropriate.

The worst symptom for each subject will be identified as the symptom with the highest average score during the run-in period (Days -14 to -1) as recorded in the subject diary. For morning, evening and daily average assessments, the weekly averages of the worst symptom and each individual symptom will be analyzed using two-sample t-tests and Wilcoxon rank sum tests.

Safety Variables

Adverse events will be coded using the Medical Dictionary for Regulatory Authorities (MedDRA). Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class, by system organ class and preferred term, by system organ class, preferred term and maximal severity, by system organ class, preferred term and strongest

NAME OF COMPANY	**NAME OF DRUG PRODUCT**
HanAll Biopharma, Co., Ltd. DaeWoong Building 3Fl. Bongeunsaro 114-gil 12 Seoul, Gangnam-gu South Korea 06170	HL036 Ophthalmic Solution for Treatment of Dry Eye

relationship, and by system organ class, preferred term, maximal severity, and strongest relationship. Separate analyses will be performed for ocular specific and all AEs (including systemic).

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredients
BCVA	Best Corrected Visual Acuity
BID	Bis In Die (Two Times Daily)
CAE	Controlled Adverse Environment
CFR	Code of Federal Regulations
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LASIK	Laser–assisted in situ keratomileusis
LDPE	Low Density Polyethylene
LOCF	Last Observation Carried Forward
LogMAR	Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Authorities
OD	Right Eye
ODS	Ocular Discomfort Score
OSDI	Ocular Surface Disease Index
OU	Oculus Uterque (Each eye or Both eyes)
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
TFBUT	Tear Film Break Up Time
TNF	Tumor Necrosis Factor
TNFR	Tumor Necrosis Factor Receptor
VA	Visual Acuity
VAS	Visual Analog Scale

1 INTRODUCTION

Dry eye is a complex disease that results in symptoms of discomfort, visual disturbance, and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Estimates of the prevalence of dry eye vary considerably, depending on the criteria used to define the syndrome, but in the U.S., as many as 3.2 million women and 1.7 million men over the age of 50 have dry eye, with a projected 40% increase in number of patients affected by 2030[1-3]. With the aging population in the United States and other countries of the developed world, and with increasing computer use, dry eye is expected to become more prevalent and finding a treatment is becoming more important[4].

HL036 ophthalmic solution is a molecularly engineered tumor necrosis factor receptor 1 (TNFR1) fragment (HL036). Molecule fragmentation and engineering techniques are applied for enhanced tissue distribution, increased stability and potency.

HL036 is a TNFR1 fragment composed of 171 amino acids, from 41 ~ 211 residues of TNFR1 outside domain and a methionine residue added at the N-terminal. HL036 is a protein molecularly engineered by amino acid substitution of the 29th leucine, 53rd histidine, 56th histidine, 58th arginine, 59th histidine, and 122nd lysine with valine, methionine, phenylalanine, proline, glycine, and asparagine respectively.

HL036 ophthalmic solution demonstrated potent anti-inflammatory effects in a carrageenan-induced acute in vivo model of inflammation, and significant efficacy in a collagen-induced arthritis model. HL036 ophthalmic solution has also been shown to cause statistically significant clinical improvements in a dry eye animal model. HL036 ophthalmic solution significantly improved the signs and symptoms of dry eye in a Phase 2 clinical trial in one hundred-fifty subjects with a history of dry eye.

1.1 Nonclinical Studies

1.2 Previous Clinical Studies

A Phase 1 clinical study assessed the safety, local tolerance, and pharmacokinetic properties of HL036 ophthalmic solutions by topical ophthalmic instillation of HL036 twice in one day (12 hours apart) into the left eyes of healthy male volunteer, while the right eyes received vehicle placebo. A total of 20 subjects were randomized in a 8:2 ratio to receive HL036 (0.05% or 0.5%) or placebo in the left eyes.

Instillation of 0.05% or 0.5% HL036 ophthalmic solution into the left eyes of healthy male volunteers resulted in no clinically significant systemic absorption observed in any of the subjects. Blood sampling for pharmacokinetics assessment showed that one drop (40 µl) of HL036 topical instillation twice in one day resulted in no detectable systemic absorption, at either concentration. Among the AEs, conjunctival hyperemia was the most frequently reported AE, but there was no significant difference in number of subjects that had conjunctival hyperemia in the left or right eyes. Safety and local tolerance assessment results showed no clinically significant observations.

A Phase 2, multicenter, randomized, prospective, double–masked, placebo–controlled, parallel–arm study compared the safety and efficacy of 0.10% and 0.25% HL036 ophthalmic solutions to placebo for the treatment of the signs and symptoms of dry eye disease (DED). One hundred-fifty subjects were randomly assigned to one of three treatment groups (1:1:1) to receive either HL036 Ophthalmic Solution (0.10%, 0.25%) or placebo solution as topical ophthalmic drops administered bilaterally twice daily (BID) over a period of eight weeks.

HL036 ophthalmic solutions at 0.10% or 0.25% demonstrated strong efficacy to treat the signs and symptoms of DED. HL036 Ophthalmic Solution was safe and well tolerated in the majority of patients. These data support the further development of HL036 0.25% Ophthalmic Solution for the indication of DED.

1.3 Study Rationale

HL036 ophthalmic solution is a molecularly TNFR1 fragment (active pharmaceutical ingredient also denoted as HL036337). Molecule fragmentation and engineering techniques are applied for enhanced tissue distribution, increased stability and potency.

Anti-tumor necrosis factor (TNF) molecules have been approved for rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, and Crohn’s diseases. They are also prescribed for off-label use for uveitis, dry eye disease, macular degeneration, sciatic neuralgia, chronic obstructive pulmonary diseases and asthma.

The role of TNF as a major cytokine in dry eye provides a rationale for use of TNF inhibitors in this disease. However, the majority of TNF inhibitors are antibody-based with a large molecular size (~150 kDa) that limits tissue penetration. Considering the

limited ocular distribution and excessive toxicity of TNF-inhibitor therapies administered systemically, HL036 Ophthalmic Solution was developed as a TNF-inhibitor with increased penetration and distribution and minimal systemic side effects.

[redacted]

1.4 Summary of Overall Risks and Benefits

[redacted]

A double-masked Phase 2 study compared two concentrations of HL036 ophthalmic solution, 0.10% and 0.25%, to placebo in an 8-week treatment duration. Both concentrations of HL036 demonstrated significant clinical differences over placebo in at least one sign or symptom of DED. The primary endpoints of this study were mean change in inferior corneal staining (sign) at Visit 6 and mean change in ocular discomfort (symptom) at Visit 6 prior to the Ora Controlled Adverse Environment® (CAE®) analyzed by an Analysis of Covariance (ANCOVA). While no significant findings favored HL036 Ophthalmic Solution treatment prior to CAE®, it was demonstrated that the HL036 treatment significantly protected subjects from CAE® exposure. That is, at Visit 6, subjects who had been previously treated with HL036 had a significantly reduced exacerbation of ocular surface staining after the CAE®. Further, when the primary endpoint of ocular discomfort was analyzed by a t-test, significant improvement was observed.

While statistically significant findings were not identified for all endpoints, all signs and symptoms trended in favor of HL036 Ophthalmic Solution. The symptoms of DED (i.e. ocular discomfort) were most improved with HL036 0.10% Ophthalmic Solution while the signs of DED (i.e. lissamine or fluorescein staining) were better improved by HL036 0.25% Ophthalmic Solution. Post-hoc analyses showed that that while significant improvements from baseline were seen in both groups stratified by time to qualify (< 20 minutes versus ≥ 20 minutes), the most notable improvements were in the symptoms of subjects with time to qualify < 20 minutes, demonstrating that subjects who were more sensitive to the CAE® were more responsive to treatment with HL036.

In this study, 150 subjects self-administered HL036 in both eyes BID. There were no significant safety concerns caused by HL036 treatment at either concentration. There were no serious adverse events (SAEs) or deaths in this study. Eight patients developed conjunctivitis 3 to 4 weeks after start of treatment and thus were discontinued per

protocol. All AEs were limited to mild severity with 8 cases of conjunctivitis, which all resolved within 24-48 hours of treatment discontinuation. Drop comfort scalar inquires and descriptors demonstrated a favorable drop comfort profile. Immunogenicity testing is ongoing, therefore, the results will be updated in the next Protocol Amendment.

Overall, HL036 Ophthalmic Solution was safe and well tolerated in the majority of patients.

2 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of 0.25% HL036 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study are that 0.25% HL036 Ophthalmic Solution is superior to placebo for the primary endpoints of signs and symptoms, as follows:

- Pre- to Post-CAE® inferior corneal fluorescein staining score on the Ora Calibra® scale, measured by mean change from baseline (Visit 2) to Visit 6;
- Pre- CAE® ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale, measured by mean change from baseline (Visit 2) to Visit 6;

4 OVERALL STUDY DESIGN

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

- 0.25% HL036 Ophthalmic Solution (N~315)
- Placebo Solution (N~315)

Approximately 630 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either 0.25% HL036 Ophthalmic Solution or placebo solution as topical ophthalmic drops administered bilaterally BID.

Subjects, Sponsor, Clinical Research Organization and site personnel will be masked to treatment assignment.

During the screening period, two [redacted] exposures to the CAE® will be conducted to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 56 days. Subjects will self-administer drops BID and will complete daily symptom diary assessments as instructed.

At Visits 4 (Day 15), 5 (Day 29) and 6 (Day 57), CAE® exposure will occur, with pre-CAE®, during CAE® (symptoms only) and post-CAE® assessments of ocular signs and symptoms. At Visit 3 only, no CAE® exposure will occur but signs and symptoms will be assessed.

The total number of expected participants, including screen failures, is approximately 1575 subjects.

A study flow chart appears below:

Visit 1 (Day -14 ± 1): CAE® Screening	Informed Consent Demographics, Medical/Medication & Ocular History Review of Qualification Criteria Adverse Event Query Urine Pregnancy Testing[1] Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure, with discomfort grading Post-CAE® Discomfort Questionnaires Post-CAE® Eye Evaluations Safety Assessments (Intraocular Pressure [IOP] and Dilated Fundoscopy) Review of Qualification Criteria and AE Query Run-in & Subject Daily symptom diary Dispensed
↓	
Placebo Run-in Period (14 ± 1 day)	
↓	
Visit 2 (Day 1): CAE® Confirmation/ Baseline	Collection of Run-in/Diary Medical/Medication Update: AE Query Review of Qualification Criteria Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure, with discomfort grading Post-CAE® Discomfort Questionnaires Post-CAE® Eye Evaluations Review of Qualification Criteria and AE Query Randomization Blood sampling for Immunogenicity testing In-Office Dose & Drop Comfort Questionnaire Study Drug & Subject Daily symptom diary Dispensed
↓	
Visit 3 (Day 8±1): 1-Week Follow Up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Eye Evaluations In office Dose Study Drug Dispensation Daily symptom diary Dispensed
↓	

Visit 4 (Day 15 ± 2): 2-Week CAE® Follow Up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure, with discomfort grading Post-CAE® Discomfort Questionnaires Post-CAE® Eye Evaluations AE Query Study Drug & Subject Daily symptom diary Dispensed
↓	
Visit 5 (Day 29 ± 2): 4-Week CAE® Follow Up	Collection of Study Drug/Diary Medical/Medication Update: AE Query Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure, with discomfort grading Post-CAE® Discomfort Questionnaires Blood sampling for Immunogenicity testing Post-CAE® Eye Evaluations AE Query Study Drug & Subject Daily symptom diary Dispensed
↓	
Visit 6 (Day 57 ± 3): 8-Week CAE® Follow-Up and Study Exit for Subjects with Negative Immunogenicity Results	Collection of Study Drug/Diary Medical/Medication Update: AE Query Urine Pregnancy Testing[1] Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure, with discomfort grading Post-CAE® Discomfort Questionnaires Blood sampling for Immunogenicity testing Post-CAE® Eye Evaluations Safety Assessments (IOP and Dilated Fundoscopy) AE Query Study Exit[3]

[1] To women of child-bearing potential, as defined.
[2] The Visit 2 study drug kit is redispensed at Visit 3.
[3] For subjects with negative immunogenicity results at previous visits (Visits 2, 5, or 6)

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

5 STUDY POPULATION

5.1 Number of Subjects

It is estimated that approximately 1575 subjects will be screened to enroll approximately 630 randomized subjects (315 in each arm). Subjects will be randomized in a 1:1 ratio of 0.25% HL036 Ophthalmic Solution to placebo Solution.

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

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

1. Be at least 18 years of age;
2. Provide written informed consent;
3. Be willing and able to comply with all study procedures;
4. Have a patient-reported history of dry eye for at least 6 months prior to Visit 1;
5. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1;
6. Have a best corrected visual acuity (BCVA) of [redacted] Minimum Angle of Resolution (logMAR) or better (Snellen equivalent score of [redacted]) in each eye at Visit 1;
7. Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2;
8. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm at Visits 1 and 2;
9. Have a corneal fluorescein staining score of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visits 1 and 2;
10. Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1 and 2 pre-CAE®
11. Demonstrate in the same eye(s) a response to the CAE® at Visits 1 and 2 as defined by:

[redacted]

12. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10 and 11 above.
13. A negative urine pregnancy test if female of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post–menopausal [12 months after last menses]) and must use adequate birth control through the study period. For non-sexually active females, abstinence may be regarded as an adequate method of birth control

5.4 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, lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;
4. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;
5. Have used Restasis®, Xiidra®, or Cequa® within 60 days of Visit 1;
6. Have any previous experience using HL036;
7. Have had any ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid surgeries over the study period;
8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;
9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for the following medications:
    a) Antihistamines (including ocular): 72 hours prior to Visit 1
    b) Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period
    c) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

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

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

10. Have an uncontrolled systemic disease;
11. Be a woman who is pregnant, nursing or planning a pregnancy;
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
13. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
14. Have a known allergy and/or sensitivity to the test article or its components;
15. 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;
16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
17. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria

Subjects may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and/or Sponsor and in accordance with his/her clinical judgment. However, it is encouraged that the Investigator contact the Sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a subject from the study. When possible, the tests and evaluations listed for the termination visit should be carried out.

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

Reasons for which the Investigator or HanAll Biopharma, Co., Ltd. may withdraw a subject from the study include, but are not limited to, the following:

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

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

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

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of the study are:

- Inferior corneal staining (sign), Pre- to Post-CAE® at Day 57 (Week 8)

and

- Ocular discomfort (symptom), Pre-CAE® at Day 57 (Week 8)

6.1.2 Secondary Efficacy Endpoints

- Fluorescein staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum and total staining
- Conjunctival lissamine green staining by region: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum and total staining

- Conjunctival redness
- Schirmer's Test
- Tear film break-up time (TFBUT)
- Ocular Surface Disease Index© (OSDI©)
- Visual Analog Score (VAS)
- Daily symptom diary (Ora Calibra Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score)
- Daily symptom diary by CAE® Qualification Time

6.1.3 Criteria for Effectiveness

The specific criteria for effectiveness for the endpoints derived from the measures described above are:

- Mean change from baseline to Day 57 (Week 8) in inferior corneal staining Pre- to Post-CAE® in the designated study eye as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining

and

- Mean change from baseline to Day 57 (Week 8) in ocular discomfort Pre-CAE® in the designated study eye as assessed by the Ora Calibra® Ocular Discomfort Scale

6.2 Safety Measures

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- IOP
- Dilated fundoscopy
- Immunogenicity to HL036 in Serum

7 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Study Treatments

Subjects will receive doses BID of either 0.25% HL036 Ophthalmic Solution or placebo administered to the ocular surface as an eye drop.

HL036 ophthalmic solution is a molecularly engineered TNFR1 fragment (HL036337). Molecule fragmentation and engineering techniques are applied for enhanced tissue distribution, increased stability and potency.

7.1.2 Description 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 was selected based on nonclinical studies described in Section 1.1. The proposed treatment period of 8 weeks is also based on nonclinical and clinical studies and on the anti-inflammatory mechanism of action of the drug.

7.1.3 Instructions for Use and Administration

- Study drug will be supplied as a sterile, clear, colorless liquid solution containing 0.25% Active Pharmaceutical Ingredient (API) (HL036) 5 cavity, 0.5 mL low–density polyethylene (LDPE) unit dose vials with a fill volume of approximately 0.25 mL. Each mL of the 0.25% solution contains 2.5 mg of the API. In addition to HL036, the components of the drug product solution are: sodium chloride (tonicity adjusting agent), citric acid monohydrate (buffering solution), sodium hydroxide solution and hydrochloric acid 1% (both for pH adjustments), and sterile water for injection as a solvent.
- The placebo solution consists of all components of the drug product solution with the exception of HL036.
- At the study site, all investigational product (IP) must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated qualified clinical site personnel. All IP must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Conference on Harmonization (ICH) Good Clinical Practices (GCPs) and study procedures.
- HL036 and placebo solutions should be stored refrigerated (2–8° C). Subjects will be instructed to store HL036 and placebo solutions in a refrigerator (2–8° C). It is recommended that HL036 and placebo solutions be placed at room (ambient) temperature at least 1 ± 0.5 hours prior to administration to subjects. Sterile drug product and placebo solutions are packaged into single–use 0.5 mL LDPE unit dose vials that deliver an approximate per drop volume of 50 µL. Two cavity unit dose vials are packaged in aluminum foil pouches under nitrogen. Unit dose vials are for SINGLE USE ONLY.
- At a minimum, the immediate or secondary study drug packaging will provide the following information: study sponsor identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), study identification and product retest date.

7.2 Other Study Supplies

Urine pregnancy tests, Schirmer's test strips, sodium fluorescein, lissamine green, Fluress, blood draw supplies.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Sections 5.3, 5.4, and 5.5 will be considered for entry into this study.

8.1.2 Informed Consent

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

8.1.3 Washout Intervals

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

8.1.4 Procedures for Final Study Entry

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

8.1.5 Methods for Assignment to Treatment Groups:

Prior to initiation of study run-in (at Visit 1), each subject who qualifies for entry 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. If all inclusion and exclusion criteria are met at Visits 1 and 2, each qualifying subject will then be assigned a randomization number at the end of Visit 2 using an interactive web response system.

The randomization number will be recorded on the patient's source document and electronic case report form (eCRF). A new kit will be dispensed at Visits 2, 4, and 5 based on the subject's randomization. The visit 2 kit will be re-dispensed at Visit 3. The Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the study.

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

Procedures listed below should be performed in the given order. See Appendix 2: Examination Procedures, Tests, Equipment, and Techniques for details on methodologies and grading systems.

8.3.1 Visit 1: Day –14 ± 1 – CAE® Screening

All subjects will undergo the following screening assessments:

Pre–CAE®

- Informed Consent/HIPAA Prior to any changes in a subject's medical treatment and/or invasive procedures (e.g., CAE®), the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.
- Demographic Data and Medical/Medication/Ocular History Collect and record all demographic data, medical history, any medications and any underlying condition(s). Significant non–ocular medical history only within the past year and medications within the past 30 days will be captured. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 30 days prior to screening.
- 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.
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- Ocular discomfort using a VAS
- OSDI©
- BCVA Utilizing an Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart Subjects must have a score of [redacted] logMAR or better (Snellen equivalent score of [redacted]) in each eye at Visit 1.
- Slit Lamp Biomicroscopy A slit lamp exam will be performed at the beginning of the visit and again Post–CAE® to exclude subjects with disallowed ocular conditions.

- Conjunctival Redness Score. An objective measure used to score redness on the Ora Calibra® Conjunctival Redness Scale for Dry Eye. Half point increments (0.5) may be used.
- TFBUT
- Corneal and Conjunctival Staining (fluorescein) as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining
- Corneal and Conjunctival Staining (lissamine green) as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Lissamine Green Staining
- Monitoring and Query AEs Report any AEs that occur after signing the ICF.

Screening Challenge (CAE® #1)

Subjects meeting all of the above evaluation (Pre–CAE® #1) criteria will undergo further screening evaluation in the CAE®. Subjects will be exposed to the CAE® for [redacted]. Ocular discomfort self-assessment scores (ODS) will be obtained just prior to entering, during and just after the CAE® exposure. During the CAE® exposure, ODS will be collected at [redacted].

Post–CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's test
- IOP
- Dilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
    - Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the *same eye*:
        - Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;

- Reporting an Ocular Discomfort score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure [redacted]
- If both eyes are equal, the right eye (OD) will be designated as the study eye.

o Following the screening procedures at this visit, all subjects who meet all eligibility criteria and have a positive response (as defined above) will self-administer their initial dose of placebo drops to both eyes (OU) (open–label, single drop), for training purposes, at the study site under supervision of trained study personnel following the last Post– CAE® #1 study assessment. Only a single dose of placebo drops will be administered OU on Day –14.

- Placebo and Diary Dispensation and Administration. Prior to discharge from the study site on Day –14, subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated in study drug diary recording and self–administration of placebo. Subjects will be instructed to self–administer one drop BID in each eye in the morning and the evening until screening Visit 2. The initial, self-administered dose taken in-office at Visit 1 will be counted as a morning dose regardless of visit time, and subjects will be instructed to administer an evening dose that night. Subjects will be instructed NOT to instill study drug on the morning of their next scheduled study visit (Visit 2, Day 1).
- Monitoring and Query of AEs Report any AEs that occur after signing the ICF.

- Schedule Next Visit Subjects will be scheduled for Visit 2.

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

Pre–CAE®

- Study Diary/Placebo Collection Subject study diaries and all used/unused placebo vials dispensed for Days –14 to 1 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning placebo dose at home.
- Review of Inclusion/Exclusion Criteria
- Monitoring and Query of AEs Report any AEs that occur after signing the ICF.
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale

- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)

Confirmatory Screening Challenge (CAE® #2)

Subjects will be exposed to the CAE® for [redacted]. Ocular discomfort self–assessment scores (ODS) will be obtained just prior to entering, during and just after the CAE® exposure. During the CAE® exposure, ODS will be collected at [redacted].

Post–CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's test
- Review of Inclusion/Exclusion Criteria
    - Eligible subjects must replicate a positive response at this visit in the same eye as was elicited in Visit 1. A positive response is defined as meeting ALL of the following criteria in the same eye:
        - Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;
        - Reporting an Ocular Discomfort score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure [redacted]

- If both eyes are equal, the right eye (OD) will be designated as the study eye.

Randomization

- Blood Sampling for Immunogenicity Testing Blood samples will be collected from all subjects for immunogenicity testing prior to study drug instillation.
- Study Drug Instillation at the Study Site All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria after Visit 2 will be randomized to one of two treatment arms. Randomized subjects will self-administer their initial study drug dose bilaterally at the study site.
- Drop Comfort Assessment A drop comfort evaluation will be performed immediately and then at 1, 2, and 3 minutes following initial dosing.
- Monitoring and Query of AEs
- 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. The initial, self-administered dose taken in-office at Visit 2 will be counted as a morning dose regardless of visit time, and subjects will be instructed to administer an evening dose that night. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 3, Day 8).
- Schedule Next Visit Subjects will be scheduled for Visit 3.

8.3.3 Visit 3 (Day 8)

There is no CAE® evaluation at Day 8, Visit 3.

- Study Drug Diary/Study Drug Collection. Site staff must confirm that subjects have NOT administered their morning study drug dose at home. Subjects will undergo repeat assessments as follows.
- Monitoring and Query AEs
- Recording of all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT

- Corneal Staining and Conjunctival (fluorescein)
- Corneal and and Conjunctival Staining (lissamine green)
- Study Drug Instillation at the Study Site Subjects will self-administer their first study drug dose bilaterally for Day 8 at the study site following the last study assessment. The evening dose will be administered at home, by the subject.
- Monitoring and Query AEs
- Study Drug Re-Dispensation. Prior to discharge from the study site on Visit 3 (Day 8), study drug kits from Day 1 will be re-dispensed to subjects with the remaining study drug to complete up to Day 15. Subjects will again be educated in study drug diary recording and self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4, Day 15).
- Schedule Next Visit Subjects will be scheduled for Visit 4.

8.3.4 Visit 4: Day 15 ± 2

Pre-CAE®

- Study Drug Diary/Study Drug Collection Subject study drug diaries and all used/unused study drug vials dispensed for Days 8 to 15 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home
- Monitor and Query AEs
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)

CAE®

During the CAE® exposure, ODS will be collected at [redacted].

Post-CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's test
- Study Drug Diary/Study Drug Dispensation Prior to discharge from the study site on Visit 4 (Day 15), 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 5 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5, Day 29).
- Schedule Next Visit Subjects will be scheduled for Visit 5.

8.3.5 Visit 5: Day 29 ± 2

Pre-CAE®

- Study Drug Diary/Study Drug Collection Subject study drug diaries and all used/unused study drug vials dispensed for Days 15 to 29 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home
- Monitoring and Query of AEs
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI©

- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)

CAE®

During the CAE® exposure, ODS will be collected at [redacted].

Post-CAE®

- Blood Sampling for Immunogenicity Testing
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's test
- Monitoring and Query of AEs
- Study Drug Diary/Study Drug Dispensation Prior to discharge from the study site on Visit 5 (Day 29), 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 6 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 6, Day 57).
- Schedule Next Visit Subjects will be scheduled for Visit 6.

8.3.6 Visit 6: Day 57 ± 3

Pre-CAE®

- Study Drug Diary/Study Drug Collection Subject study drug diaries and all used/unused study drug vials dispensed for Days 29 to 57 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home
- Monitoring and Query of AEs
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS discomfort scale
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)

CAE®

During the CAE® exposure, ODS will be collected at [redacted].

Post-CAE®

- Blood Sampling for Immunogenicity Testing
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire Ocular Discomfort Score
- VAS discomfort scale
- Slit lamp biomicroscopy
- Conjunctival redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)

- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's test
- Intraocular Pressure
- Dilated fundoscopy
- Monitoring and Query of AEs
- Study Exit for subjects with negative immunogenicity results at previous visits (Visits 2, 5, or 6)

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

Subjects may be asked to return for Blood Sampling for Immunogenicity Testing if they tested positive immunogenicity results at previous visits (Visits 2, 5, or 6). This visit will occur 1-9 months after Visit 6.

Unscheduled visits may also 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:

- Blood Sampling for Immunogenicity Testing;
- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Intraocular Pressure;
- Urine Pregnancy Test;
- Dilated Fundoscopy;
- Assessment of Adverse Events;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.4.3 Early Termination Visit

- Collection of study drug/dosing diary
- Medication/medical history update;
- Assessment of AE's
- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Urine Pregnancy Test (if applicable);
- Blood sampling for immunogenicity testing (if applicable)
- 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 symptom diary and proper instillation and storage of study drug at the end of Visits 1, 2, 3, 4 and 5, and given written instructions. The subject daily diaries and unused study drug vials will be collected at each visit from Visit 2 up to and including Visit 6 to assess dosing and symptom assessment compliance. Dosing compliance will be based off of the unused vial count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of unused vials, then the subject will be deemed non-compliant and a deviation should be recorded.

In the subject daily symptom diary, if more than 20% of Dose Taken boxes are checked "no", left blank, or missing for a diary period, a subject will be deemed non-compliant and a diary deviation will be recorded. If more than 20% of the total diary symptom assessments for that dosing period are missed, these subjects will be deemed non-compliant and a diary symptom assessment deviation will be recorded. These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

- adverse events (AEs);
- unmasking when medically necessary;
- protocol violations;
- administrative reasons (e.g., inability to continue, lost to follow up);

- sponsor termination of study;
- subject choice (e.g. withdrawal of consent); and
- other

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

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

Discontinued subjects will not be replaced.

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 6 visits over approximately a 10-week (~70 days) period (56 days of treatment and 14 days pre-screening).

8.9 Monitoring and Quality Assurance

During the course of the study a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug/device 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 ADVERSE EVENTS

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 (eg, 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 (eg, 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 (eg, anatomical limitations), and therapeutic parameters (eg, energy applied, sizing, dose release) associated with medical device.

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 eCRF. 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 1 comprehensive event.

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

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

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

9.1.1 Reporting an Adverse Event of Special Interest

For all conjunctivitis and allergic conjunctivitis AEs, the PI (or assigned study personnel) must complete a copy of the Conjunctivitis AEs Report Form provided by the sponsor (Appendix 3: Conjunctivitis Adverse Events Report Form). A copy of the form with a photo of the subject's eyes should be emailed to Ora, and the study sponsor within 72 hours of AE report by the subject.

9.1.2 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.

9.1.3 Relationship to Investigational Product

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

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite:* 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.
  - *Probable:* 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.
  - *Possible:* Relationship exists when the AE follows a reasonable sequence from the time of administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- ***Not Suspected*:** A reasonable possibility does not exist that the IP caused the AE. A not suspected AE can further be defined as:
  - *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.

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

9.1.4 Expectedness

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

- *Unexpected*: an AE 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 AE that is listed in the IB at the specificity and severity that has been observed.
- *Not applicable:* an AE unrelated to the IP.

AEs 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.

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

9.2 Serious Adverse Events

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

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the 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.

- Inpatient hospitalization or prolongation of existing hospitalization;

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

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

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

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

- A congenital anomaly/birth defect.

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

9.3 Procedures for Reporting Adverse Events

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

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

For all conjunctivitis and allergic conjunctivitis AEs, the PI (or assigned study personnel) must complete a copy of the Conjunctivitis AEs Report Form provided by the sponsor. A copy of the form with a photo of the subject's eyes should be emailed to Ora, and the study sponsor within 72 hours of AE report by the subject.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate case report forms. The investigator is obligated to pursue and obtain information requested by Ora and/or the sponsor in addition to that information reported on the case report form. All subjects experiencing an SAE must be followed up and the outcome reported.

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

Contact information for reporting SAEs:

Name:	[redacted]
Title:	Clinical Project Manager, Dry Eye
Company:	Ora, Inc.
Office Telephone:	[redacted]
Alternative Telephone:	
Office Facsimile:	
Name:	[redacted]
Title:	Medical Monitor
Office Telephone:	[redacted]
Mobile Phone:	
Office Facsimile:	

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 arm 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. The unmasked subject will be discontinued from the study.

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

The investigator will follow unresolved AEs to resolution 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 patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient 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 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

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. The primary analysis will be performed on the ITT population with the Markov Chain Monte Carlo (MCMC) imputation method for missing values. The ITT population may also be analyzed with Last Observation Carried Forward (LOCF) imputation, imputation via pattern mixture models, and with observed data only 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 IP. 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 baseline and efficacy data will be performed for the ITT population. The primary efficacy analysis will also be performed on the PP population as sensitivity analyses.

10.2 Statistical Hypotheses

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

H_{01}: There is no difference between 0.25% HL036 Ophthalmic Solution) and placebo in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 (Visit 6), using the Ora Calibra® scale.

H_{11}: The change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 (Visit 6) using the Ora Calibra® scale is less with 0.25% HL036 Ophthalmic Solution than with placebo.

H_{02}: There is no difference between 0.25% HL036 Ophthalmic Solution and placebo in the change from baseline of the pre-CAE® ocular discomfort evaluated at Visit 6, using the Ora Calibra® Ocular Discomfort Scale.

H_{12}: The change from baseline of the pre-CAE® ocular discomfort at Visit 6 using the Ora Calibra® Ocular Discomfort Scale is less with 0.25% HL036 Ophthalmic Solution than with placebo.

10.3 Sample Size

The primary objective of the study is to demonstrate a statistically significant difference between the active treatment and placebo.

This study is expected to enroll 315 subjects in each of the two treatment arms, for a total of 630 randomized subjects. Assuming a 10% drop out rate, 283 subjects per group are expected to complete the study.

Assuming a common standard deviation in the change from baseline for the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining of 0.74 units, a sample size of 283 subjects per group will have 99% power to detect a difference of 0.3 units between the active treatment group and the placebo group at a significance level of 0.05. A sample size of 283 subjects per treatment arm will have 93% power to detect a mean difference of 0.3 units in the change from baseline for the pre-CAE® ocular discomfort as assessed by the Ora Calibra® Ocular Discomfort Scale, assuming a standard deviation of 1.03 units. The power for both the sign and symptom endpoints is 93%, assuming independence between the endpoints.

10.4 Statistical Analysis

10.4.1 General Considerations

The quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative 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) and World Health Organization Drug dictionaries, as appropriate.

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2. If a measure is taken both pre-CAE® and post-CAE®, the baseline will be the time point matched value at Visit 2. For measures from daily subject diaries, baseline is defined as the average of all days during the run-in period. For changes from pre-CAE® to post-CAE® post first treatment, the change from pre-CAE® to post-CAE® at Visit 2 will be considered the baseline value.

All primary and secondary analyses will be 2-sided at a significance level of 0.05.

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 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 worse (higher) inferior corneal staining pre-CAE® at Visit 2. If the inferior corneal staining is the same in both eyes, then the study eye will be the eye with the highest ocular discomfort pre-CAE® at Visit 2. If the ocular discomfort is the same in both eyes, then the right eye will be selected as the study eye.

10.4.3 Missing Data

The primary efficacy analyses will be performed using the MCMC multiple imputation method for missing values. Additionally, LOCF imputation methodology and imputation via pattern mixture models will also be used to impute missing data for the analyses of the primary efficacy variables. For LOCF, the last value from the previous visits will be carried forward, matching pre-CAE® or post-CAE® time points. A pre-CAE® time point will never be imputed for a post-CAE® value, and vice versa. An analysis using observed data only will also be performed for the primary efficacy variables.

No secondary efficacy endpoints or safety endpoints will be imputed.

10.4.4 Multiplicity Consideration

Hierarchical fixed sequence testing will be used to maintain the type I error rate. The primary analysis will first test the difference in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of HL036, then the study will be considered a success, HL036 will be declared to be superior to placebo in the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57, and the difference in the change from baseline of the pre-CAE® ocular discomfort at Day 57 will be tested at the two-sided alpha = 0.05 level.

If, in addition to a statistically significant test of the difference in change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 in favor of HL036, the test of the difference in the change from baseline of the pre-CAE®

ocular discomfort at Day 57 is also statistically significant in favor of HL036, then HL036 will be declared superior to placebo in both the change from baseline of the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining and the change from baseline of the pre-CAE® ocular discomfort at Day 57.

10.4.5 Primary Efficacy Analyses

For both endpoints, change from baseline will be calculated as visit – baseline such that a positive difference indicates a worsening of dry eye signs or symptoms. In addition, treatment comparisons between active and placebo will be calculated as active – placebo, such that a negative result indicates a better score for the active treatment (i.e., the active treatment had a smaller increase in dry eye signs or symptoms than the placebo group).

ANCOVA models will be used to compare the change from baseline in the pre-CAE® to post-CAE® change in inferior corneal fluorescein staining at Day 57 (Visit 6), as measured on the Ora Calibra® scale, between 0.25% HL036 Ophthalmic Solution and Placebo. The ANCOVA models will include terms for baseline pre-CAE® to post-CAE® change in inferior corneal fluorescein staining and study site. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across study sites. The primary analysis will use MCMC imputation to have a full accounting of the ITT population at the Day 57 visit, as described in Section 10.4.3. As supportive analyses, imputation by LOCF, multiple imputation by pattern mixture models and analyses of observed data only will also be conducted. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted as supportive analyses.

Ocular discomfort will be analyzed similarly. ANCOVA models will be used to compare the change from baseline in the pre-CAE® ocular discomfort score at Day 57 (Visit 6), as measured on the Ora Calibra® Ocular Discomfort Scale, between 0.25% HL036 Ophthalmic Solution and Placebo. The ANCOVA models will include terms for baseline (Visit 2) ocular discomfort and study site. In addition, the study site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across sites.

10.4.6 Secondary Efficacy Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max), and analyzed with two-sample t-tests comparing each of the active treatment groups to placebo. All visit-based data will be analyzed at each visit and change from baseline. Change scores from pre- to post-CAE® will be calculated as Post-CAE® score – Pre-CAE® score. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline and site will also be assessed where appropriate. No imputation will be performed for secondary efficacy variables.

Corneal fluorescein staining by region and total, conjunctival lissamine green staining by region, TFBUT, conjunctival redness, unanesthetized Schirmer's test, drop comfort assessment, OSDI©, ocular discomfort and dry eye symptoms, ocular discomfort during CAE®, pre- to post-CAE® changes, and changes from baseline in these measures will be analyzed by visit using two-sample t-tests and Wilcoxon rank sum tests, as appropriate.

The worst symptom for each subject will be identified as the symptom with the highest average score during the run-in period (Days -14 to -1) as recorded in the subject diary. For morning, evening and daily average assessments, the weekly averages of the worst symptom and each individual symptom will be analyzed using two-sample t-tests and Wilcoxon rank sum tests.

10.4.7 Safety Variables

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it 1) occurs after the first dose of randomized study treatment or 2) if it is present prior to receipt of randomized study treatment but worsens in severity or increases in frequency 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 AEs; by system organ class and preferred term for SAEs; and by system organ class, preferred term, and day of onset. Separate analyses will be performed for ocular specific and all AEs (including systemic).

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

10.4.8 Interim Analyses

No interim analyses are planned for this study.

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

This study will be conducted in compliance with the protocol, current GCPs, including the 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 IPs in the countries involved will be adhered to.

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.

All informed consent/assent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (eg, due to a protocol amendment or significant new safety information), it is the investigator’s responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC 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 study sponsor and provided in writing by Ora and/or study sponsor prior to the consent process.

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

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

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the 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 eCRFs 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, ICFs, record of the distribution and use of all IPs and copies of eCRFs should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the 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 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

11.5.1 Labeling/Packaging

Run-in and Investigational drug will be packaged and labeled into clinical kits.

For the run-in period, 17 pouches will be packaged in a 2-week clinical kit. Each pouch will contain 2 single-use vials to provide a sufficient medication supply for one day.

For the treatment period, 17 pouches will be packaged in a 2-week clinical kit. Each patient will receive 4 kits. Each pouch will contain 2 vials to provide a sufficient supply of randomized study drug for one day.

11.5.2 Storage of Investigational Product

The study drugs must be stored in a secure area accessible only to the investigator and his/her designees. Study drug(s) must be refrigerated (2-8°C, Do Not Freeze), protected from light, and secured at the investigational site in a locked container.

11.5.3 Accountability of Investigational Product

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

11.5.4 Return or Disposal of Investigational Product

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

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

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The investigator is responsible for ensuring that study data are completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (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 not be entered 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 containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7 Handling of Biological Specimens

Blood samples will be submitted to one or more central laboratories and / or analytical laboratories for processing, storage and analysis. All laboratories meet Good Laboratory Practice requirements.

11.8 Publications

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

12 REFERENCES

1. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Archives of ophthalmology 2009;127:763-8.
2. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. American journal of ophthalmology 2003;136:318-26.
3. Schaumberg DA, Sullivan DA, Dana MR. Epidemiology of dry eye syndrome. Advances in experimental medicine and biology 2002;506:989-98.
4. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. Survey of ophthalmology 2001;45 Suppl 2:S199-202.

13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Visit 1 Day -14±1		Visit 2 Day 1		Visit 3 Day 8±1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Visit 6 Day 57 ± 3	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Non CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Informed Consent / HIPAA	X										
Medical / Medication History and Demographics	X										
Medical / Medication Update			X		X	X		X		X	
Placebo Run-In Dispensation		X									
Placebo Run-in Collection			X								
Randomization				X							
Run-in Instillation		X									
Study Drug Dispensation				X	X[1]		X		X		
Study Drug Instillation				X	X						
Study Drug Collection					X	X		X		X	
Diary Dispensation		X		X	X		X		X		
Diary Collection			X		X	X		X		X	
Review of Qualification Criteria	X	X	X	X							
Adverse Event Query	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X[2]									X[2]	

Procedure	Visit 1 Day -14±1		Visit 2 Day 1		Visit 3 Day 8±1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Visit 6 Day 57 ± 3	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Non CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Drop Comfort Assessment				X							
Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X	X	X	X	X	X	X
Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire	X	X	X	X	X	X	X	X	X	X	X
VAS Discomfort Scale	X	X	X	X	X	X	X	X	X	X	X
OSDI© Questionnaire	X		X		X	X		X		X	
Visual Acuity (ETDRS)	X		X		X	X		X		X	
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X
Conjunctival Redness	X	X	X	X	X	X	X	X	X	X	X
TFBUT	X	X	X	X	X	X	X	X	X	X	X
Fluorescein Staining	X	X	X	X	X	X	X	X	X	X	X
Lissamine Green Staining	X	X	X	X	X	X	X	X	X	X	X
CAE® Exposure	X		X			X		X		X	
Discomfort Grading during CAE® Exposure	X		X			X		X		X	
Schirmer's Test		X		X			X		X		X
Intraocular Pressure		X									X
Dilated Fundus Exam		X									X

Procedure	Visit 1 Day -14±1		Visit 2 Day 1		Visit 3 Day 8±1	Visit 4 Day 15 ± 2		Visit 5 Day 29 ± 2		Visit 6 Day 57 ± 3	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Non CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Blood sampling for Immunogenicity testing				X					X		X
Exit Subject from Study											X[3]

[1] The Visit 2 study drug kit is redispensed at Visit 3.
[2] To women of child-bearing potential, as defined.
[3] For subjects with negative immunogenicity results at previous visits (Visits 2, 5, or 6)

APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

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 (ie, 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", eg, 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 (eg, '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 (ie, 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.

Dilated Fundoscopy

Dilated fundoscopy 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. A dilated 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.

It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects. The use of cyclopentolate 1% ophthalmic solution is recommended as secondary dilating medication, should the need arise.

Intraocular Pressure

Intraocular pressure 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.

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale for Dry Eye

[redacted]

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

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

[redacted]

Visual Analogue 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 current 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%

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)

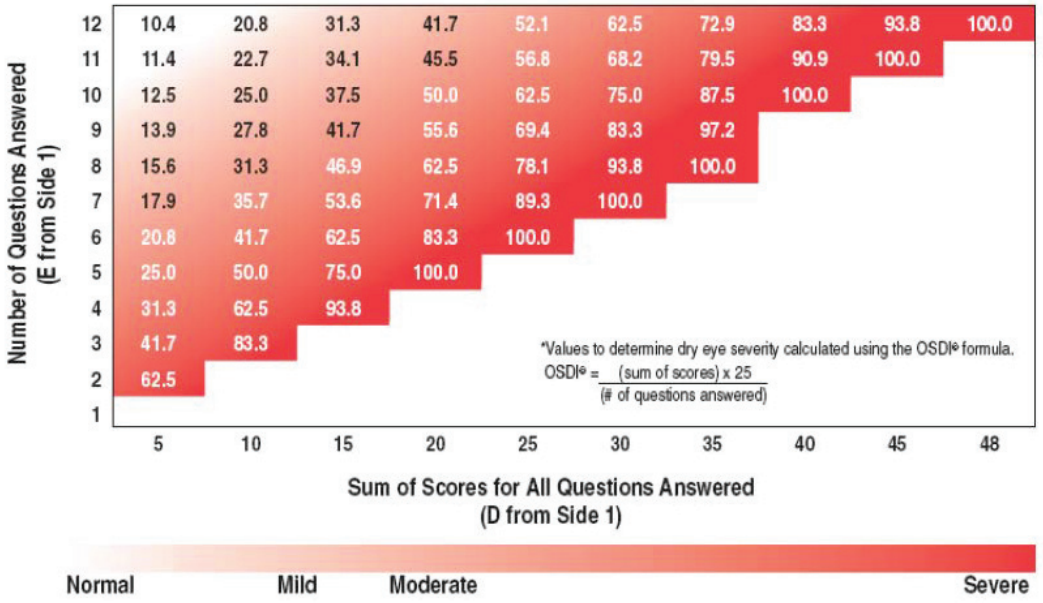
Please turn over the questionnaire to calculate the patient's final OSDI© score.

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

Ora Calibra® Conjunctival Redness Scale for Dry Eye

[redacted]

Tear Film Break-Up Time (TFBUT)©

The examiner will instill [redacted] 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 the2 closest of the 3 would be averaged.

Fluorescein Staining

The examiner will instill [redacted] 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 and NEI scale.

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

[redacted]

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

Staining areas:

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

Lissamine Green Staining

The Investigator will instill [redacted] 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 as well as the NEI scale.

Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Lissamine Green Staining

[redacted]

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

Staining areas:

[redacted]

Unanesthetized Schirmer's Test

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

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

Drop Comfort Assessments

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

Subject-Reported Drop Comfort Scale

Ora Calibra® Drop Comfort Scale

[redacted]

Subject-Reported Drop Comfort Questionnaire

[redacted]

Ora Calibra® Drop Comfort Questionnaire

[redacted]

Blood Sampling for Immunogenicity Testing

Serum blood draws will be collected at Visits 2, 5, and 6 (limited to subjects with positive results from previous visits 2, 5, or 6) for immunogenicity testing. Based on immunogenicity results from visits 2, 5, and 6, subjects may be asked to participate in follow-up visit(s) 1-9 months after Visit 6. Instructions for the collection, handling, and shipping of blood for immunogenicity testing are given in a separate laboratory manual.

APPENDIX 3: CONJUNCTIVITIS ADVERSE EVENTS REPORT FORM

Conjunctivitis AEs Report Form

A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

Date of Report (dd/mm/yyyy)**:**

Subject's ID #:

Subject History

• Past Medical History: ☐ Conjunctivitis ☐ Pollen allergy ☐ Seasonal allergic rhinoconjunctivitis
If yes, indicate the last occurrence of each of the above (mm/yyyy):

Event Information

• Adverse Event: ☐ Conjunctivitis ☐ Allergic Conjunctivitis
• Start Date of Event (dd-mm-yyyy):
• Which eye(s) is/are affected? ☐ Left ☐ Right ☐ Both
• Check symptoms which patient complained of or physician noted:
☐ Injected sclera ☐ Redness ☐ Burning ☐ Unusual crusting on eye when awakening
☐ Ocular itchiness ☐ Nasal itchiness ☐ Sneezing ☐ Excessive tearing
☐ Other signs or symptoms:

Did any unusual activity or exposure precede the start of this conjunctivitis? ☐ Yes ☐ No
If so, what?

Investigator assessment of severity?
☐ Unknown ☐ Mild ☐ Moderate ☐ Severe

Relatedness

☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Reason why you consider event to be IP related *(if applicable)*:

Action Taken

☐ Drug Continued ☐ Drug Withdrawn ☐ Not Applicable

A Digital Picture of Both Eyes

☐ Attached to the report form

Site Investigator Comments: ☐ N/A

Printed Name of Site Investigator	**Signature**	**Date**

APPENDIX 4: PROTOCOL AMENDMENT SUMMARY

Not applicable.

APPENDIX 5: SPONSOR AND ORA APPROVALS

Protocol Title: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

Protocol Number: HL0363-DED-US-P301

Final Date: 24 Jan 2019

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: [redacted] Date: 07Feb2019
Product and Business Development, HanAll

Signed: _____ Date: _____
[redacted]
V.P. Dry Eye, Ora Inc.

Signed: _____ Date: _____
[redacted], Ora Inc.

Signed [redacted] Date: 07Feb2019
Product and Business Development, HanAll

Signed: _____ Date: _____
[redacted]
Clinical Project Manager, Ora Inc.

Signed: _____ Date: _____
[redacted]
Principal Research Biostatistician, SDC

Signed: _____ Date: _____
[redacted]
Medical Monitor

APPENDIX 5: SPONSOR AND ORA APPROVALS

Protocol Title: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

Protocol Number: HL0363-DED-US-P301

Final Date: 24 Jan 2019

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 [redacted] Date: 07Feb2019
Product and Business Development, HanAll

Signed: _____ Date: _____
[redacted]
V.P. Dry Eye, Ora Inc.

Signed: _____ Date: _____
[redacted]
Director, Dry Eye, Ora Inc.

Signed: [redacted] Date: 07Feb2019
Product and Business Development, HanAll

Signed: _____ Date: _____
[redacted]
Clinical Project Manager, Ora Inc.

Signed: _____ Date: _____
[redacted]
Principal Research Biostatistician, SDC

Signed: _____ Date: _____
[redacted]
Medical Monitor

APPENDIX 5: SPONSOR AND ORA APPROVALS

Protocol Title:	A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
Protocol Number:	HL0363-DED-US-P301
Final Date:	24 Jan 2019

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

Signed: _____ Date: _____
[redacted]
Product and Business Development, HanAll

Signed: _____ Date: 06 Feb 2019
[redacted]
V.P. Dry Eye, Ora Inc.

Signed _____ Date: 06Feb2019
[redacted]
Director, Dry Eye, Ora Inc.

Signed: _____ Date: _____
[redacted]
Product and Business Development, HanAll

Signed: _____ Date: 6 Feb 2019
[redacted]
Clinical Project Manager, Ora Inc.

Signed: _____ Date: _____
[redacted]
Principal Research Biostatistician, SDC

Signed: _____ Date: _____
[redacted]
Medical Monitor

APPENDIX 5: SPONSOR AND ORA APPROVALS

Protocol Title:	A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
Protocol Number:	HL0363-DED-US-P301
Final Date:	24 Jan 2019

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: [redacted] Date: _____

[redacted]
Product and Business Development, HanAll

Signed [redacted] Date: 06 Feb 2019

[redacted]
V.P. Dry Eye, Ora Inc.

Signed: [redacted] Date: 06Feb2019

[redacted]
Director, Dry Eye, Ora Inc.

Signed: [redacted] Date: _____

[redacted]
Product and Business Development, HanAll

Signed: [redacted] Date: 6 Feb 2019

[redacted]
Clinical Project Manager, Ora Inc.

Signed: [redacted] Date: 11 Feb 2019

[redacted]
Principal Research Biostatistician, SDC

Signed: [redacted] Date: _____

[redacted]
Medical Monitor

1.0 APPROVALS

[redacted]
Product and Business Development, HanAll

Date

[redacted]
Director, Product and Business Development, HanAll

Date

[redacted]
Vice President, Dry Eye, Ora

Date

[redacted]
Clinical Project Manager, Dry Eye, Ora

Date

[redacted]
Director, Dry Eye, Ora

Date

[redacted]
Director, Monitoring Services, Ora

Date

[redacted]
Clinical Data Manager, SDC

Date

[redacted]
Sr. Principal Biostatistician, SDC

Date

[redacted]
[redacted]edical Monitor

06 FEB 2019
Date

APPENDIX 6: INVESTIGATOR'S SIGNATURE

Protocol Title: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of 0.25% HL036 Ophthalmic Solution Compared to Placebo in Subjects with Dry EyeHL036

Protocol Number: HL036-DED-US-P301

Final Date: 24 Jan 2019

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:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>