Clinical Trial Protocol

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of TOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome
Protocol Number:	TOP1630-TV-04
Study Phase:	2
Product Name:	TOP1630 Ophthalmic Solution
IND Number:	[redacted]
Indication:	Dry Eye Syndrome (DES)
Investigator:	[redacted] Andover Eye Associates 138 Haverhill St, Suite 104 Andover, MA 01810
Sponsor:	TopiVert Pharma Ltd Imperial College Incubator, Level 1 Bessemer Building Prince Consort Road, London SW7 2AZ, United Kingdom
Contract Research Organization:	Ora. Inc. 300 Brickstone Square Andover, MA 01810 USA
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673 USA

NCT Number
NCT03088605

	Date
Original Protocol:	05 October 2016
Amendment 1:	20 January 2017

Confidentiality Statement

SPONSOR PERSONNEL

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MEDICAL MONITOR

Medical Monitor:	[redacted]

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Department Vice President:	[redacted]
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SYNOPSIS

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of TOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome
Protocol Number:	TOP1630-TV-04
Study Drug:	1) 0.01% TOP1630 Ophthalmic Solution 2) 0.1% TOP1630 Ophthalmic Solution 3) Placebo (Vehicle solution with no TOP1630)
Study Phase:	2
Study Objective:	In subjects with dry eye syndrome: The primary objective of this study is to compare the safety and tolerability of TOP1630 Ophthalmic Solution to placebo. The secondary objectives are to compare the efficacy of TOP1630 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye syndrome.
Overall Study Design	
Structure:	Double-masked, randomized, single-center study
Duration:	An individual subject's participation time for the Comfort Assessment is expected to be approximately 12 days. An individual subject's participation in the Safety and Efficacy Assessment is expected to be approximately 5 weeks (35 days).
Controls:	Placebo Ophthalmic Solution (Vehicle)
Dosage/Dose Regimen:	For the Comfort Assessment, 8 eligible subjects will be randomized to either active drug (TOP1630) or placebo (in the ratio of 3 active: 1 placebo) and the same subjects will be cycled through each dose cohort as described below unless a study stopping criterion is met in which case a lower dose regimen may be used for subsequent cohorts: Placebo or 0.01% TOP1630 bilaterally TID at Visit 1, followed by a rest day, followed by a day with a single dose of placebo or 0.1% TOP1630 bilaterally, followed by a rest day, and then a day of TID dosing with placebo or 0.1% TOP1630 bilaterally, followed

	by a rest day. Unless stopping criteria are implemented, subjects will proceed to receiving 4 consecutive days dosing of placebo or 0.1% TOP1630 TID (as described in Summary of Visit Schedule). For the Safety and Efficacy Assessment, eligible subjects will be randomized to one of the treatments below (in the ratio of 1 active: 1 placebo) to be administered bilaterally TID for 28 days (from Visit 2b to Visit 4b). 1) TOP1630 Ophthalmic Solution 2) Placebo (Vehicle with no TOP1630) TOP1630 dose selection will be based upon the evaluation of emergent (blinded) data from the Comfort Assessment and will not exceed the highest dose tested in that part of the study. During a 7 day study run-in period prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally at the same dosing frequency as TOP1630.
Summary of Visit Schedule:	Comfort Assessment 8 visits over the course of 12 days Visit 1a = Day 1, 0.01% TOP1630 or Placebo TID; Comfort Assessment Visit 2a = Day 2, Physician Assessment Visit 3a = Day 3, 0.1 % TOP1630 or Placebo QD, Comfort Assessment Visit 4a = Day 4, Physician Assessment Visit 5a = Day 5, 0.1 % TOP1630 or Placebo TID; Comfort Assessment Visit 6a = Day 6, Physician Assessment Visit 7a = Day 8, 0.1% TOP1630 or Placebo TID, Comfort Assessment followed by dosing daily with 0.1% TOP1630 or Placebo TID at home for Day 9 , Day 10 and Day 11 Visit 8a = Day 12, Physician Assessment Safety and Efficacy Assessment 4 visits over the course of approximately 5 weeks Visit 1b = Day -7 ± 1 day, CAE Screening Visit 2b = Day 1, CAE Confirmation / Baseline

	Visit 3b = Day 15 ± 1 day, 2-Week Follow-Up / CAE Test Visit 4b = Day 29 ± 2 days, 4-Week Follow-Up / CAE Test / Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double masked study.
Study Population Characteristics	
Number of Subjects:	Total 68 6 active and 2 placebo in the Comfort Assessment 30 active and 30 placebo in the Safety and Efficacy Assessment
Condition/Disease:	Dry Eye Syndrome
Inclusion Criteria:	Subjects must meet all of the following requirements to be eligible for enrollment into the study. Subjects who participate in the Comfort Assessment will not be permitted to participate in the Safety and Efficacy Assessment. For the Comfort Assessment: 1) Be at least 18 years of age; 2) Provide written informed consent; 3) Have a patient reported history of dry eye for at least 6 months prior to Visit 1a; 4) Have a history of use or desire to use eye drops for dry eye symptoms for at least 6 months prior to Visit 1a; For the Safety and Efficacy Assessment: All of the above criteria (at Visit 1b), and: 5) Report a score of ≥ 2 in at least one symptom of the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire at Visits 1b and 2b; 6) Report an OSDI score ≥ 18 at Visits 1b and 2b; 7) Have a conjunctival redness score of ≥ 1 according to the Ora Calibra® scale in at least one eye at Visits 1b and 2b; 8) Have a tear film break-up time (TFBUT) >1 and < 7 seconds in at least one eye at Visit 1b and 2b; 9) Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1b and 2b; 10) Have a corneal fluorescein staining score of ≥ 2

	according to the Ora Calibra® scale in at least one region (e.g. inferior, superior, or central) in at least one eye at Visits 1b and 2b; 11) Have a total lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions of the conjunctiva according to the Ora Calibra® scale in at least one eye at Visits 1b and 2b; 12) Demonstrate a response to the CAE® at Visits 1b and 2b as defined by: a. Having at least a ≥ 1 point increase in fluorescein staining in the inferior region in at least one eye following CAE exposure on the Ora Calibra® scale; and b. Reporting an Ocular Discomfort score ≥ 3 at 2 or more consecutive time points in at least one eye during CAE exposure on the Ora Calibra® scale (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, s/he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye). 13) Have at least one eye (the same eye) satisfy all criteria for 7, 8, 9, 10, 11, and 12 above; 14) At Visit 2b, subjects must have at least 5 days' worth of diary symptom data and deemed by the PI to be at least 80% compliant with vehicle eye drops.
Exclusion Criteria:	Subjects may not participate in the study (Comfort Assessment as well as the Safety and Efficacy Assessment) if any of the following criteria are met: 1) Unable or unwilling to follow instructions, including participation in all study assessments and visits; 2) Have any clinically significant slit lamp findings at Visit 1(1a or 1b) that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; 3) Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1 (1a or 1b); 4) Have any significant ocular lesion that could

	interfere with assessment of safety or efficacy or prevent study conduct in the opinion of the PI; 5) Have worn contact lenses within 14 days of Visit 1 (1a or 1b) or anticipate using contact lenses during the study; 6) Have used any eye drops within 2 hours of Visit 1 (1a or 1b); 7) Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months or any other ocular surgeries within the last 6 months; 8) Have used Restasis® or Xiidra™ within 90 days of Visit 1 (1a or 1b); 9) Have used topical ocular steroids within 30 days of Visit 1 (1a or 1b); 10) Have any planned ocular and/or lid surgeries over the study period; 11) Have temporary punctal plugs at Visit 1 that have not been stable within 45 days of Visit 1 (1a or 1b) or anticipate having temporary punctal plugs inserted during the study; 12) Have had punctal occlusion (not including punctal plugs) within 6 months of Visit 1(1a or 1b); 13) Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study) or have used any of these medications in the previous 24 hours prior to visit 1 (1a or 1b); 14) Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1 (1a or 1b); 15) Have an uncontrolled systemic disease; 16) Be a woman who is pregnant, nursing or planning a pregnancy; 17) Be unwilling to submit a urine pregnancy test at Visit 1 (1a or 1b) and Visit 8a or 4b) (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); 18) Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study; 19) Have a known allergy and/or sensitivity to the test article or its components; 20) 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; 21) Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1 (1a or 1b). Subjects that were enrolled in the Comfort Assessment will be excluded from participating in the Safety and Efficacy Assessment; 22) Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 (1a or 1b); antihistamines are not allowed at any time during the study.
Study Formulations:	• 0.01% TOP1630 Ophthalmic Solution • 0.1% TOP1630 Ophthalmic Solution • Placebo (Vehicle minus active)
Evaluation Criteria	

Safety Measures:	For the Comfort Assessment: • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • Adverse event query • Vital Signs • Drop Comfort Assessment • Intraocular pressure (non-contact) at all Visits. For the Safety and Efficacy Assessment: • Visual acuity (ETDRS) • Slit-lamp biomicroscopy • Corneal Sensitivity • Adverse event query • Undilated Fundoscopy • Vital Signs • Drop Comfort Assessment • Intraocular pressure (non-contact) Stopping criteria will be utilized in the Comfort Assessment to ensure that an appropriate dose can be carried forward into the Safety and Efficacy Assessment. This may include use of a lower dose regimen in the multiple dose assessment of comfort. Stopping criteria will also be utilized during the conduct of the Safety and Efficacy Assessment.
Exploratory Efficacy Measures:	• Corneal fluorescein staining using the Ora Calibra® Scale and NEI Scale • Conjunctival lissamine green staining using the Ora Calibra® Scale and NEI Scale • Visual Analogue Scale (VAS) for symptoms (Pre-CAE®) • Tear film break-up time (TFBUT) • Conjunctival redness the Ora Calibra® scale • Schirmer Test at Visits 2b, 3b, and 4b • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • OSDI© • Ora Calibra® Lid Margin Redness • Ora Calibra® Posterior Lid Edge Evaluation • OPI 2.0 • Ora Calibra® Ocular Discomfort Scale
Other:	Biomarker assessment by Impression Cytology (OPIA Eyeprim™)

General Statistical Methods and Types of Analyses

Analysis Populations:

- Modified Intent-to-Treat Population – The modified intent-to-treat (mITT) population includes all randomized subjects with at least one post visit 2 study assessment. Efficacy analysis will be performed on the mITT population. Subjects in the mITT population will be analyzed as randomized.

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

- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

Summaries of the comfort data from the Comfort Assessment will be performed on the safety population from that Assessment. The statistical analysis of safety data will be performed for the safety population, separately for the Comfort Assessment and the Safety and Efficacy Assessment. The analysis of baseline and all efficacy data in the Safety and Efficacy Assessment will be performed for the mITT population. The efficacy analyses may also be performed on the PP population as sensitivity analyses.

Sample Size:

The study is not powered to show statistical differences for any of the efficacy endpoints. The sample size was determined based on prior clinical trial experience in subjects with dry eye syndrome and is deemed to be sufficient to evaluate the safety and tolerability of TOP1630 Ophthalmic Solution in this population and to gather efficacy data that will aid in powering future clinical trials.

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

Multiplicity Consideration:

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

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 occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related AEs; by system organ class, preferred term for SAEs; and by system organ class, preferred term, and time of onset. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, corneal sensitivity, undilated fundoscopy, intraocular pressure (non-contact), and vital signs 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.

Safety summaries will be provided for the comfort and safety and efficacy portions of the study separately.

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
CAE®	controlled adverse environment
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
DES	Dry Eye Syndrome
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	Electrocardiograph
ERC	ethical review committee
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug application
IOP	intraocular pressure
IRB	institutional/independent review board
ITT	intent-to-treat
IUD	intra uterine device
IWRS	interactive web response system
KCS	keratoconjunctivitis sicca
Kg	Kilogram
LASIK	laser *in situ* keratomileusis
LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
Mg	Milligram
mL	Milliliter
Mm	Millimeter
NEI	National Eye Institute
µg	microgram
µL	microliter
µm	Micrometer
mmHg	millimeters of mercury
OD	right eye

OPI	ocular protection index
OS	left eye
OSDI©	ocular surface disease index
OU	both eyes
OTC	over-the-counter
PMNs	polymorphonuclear leucocytes
PP	per protocol
TID	three times a day (6 hour intervals in morning, afternoon, and evening)
SAE	serious adverse event
TFBUT/TBUT	tear film break-up time
TEAEs	treatment emergent adverse events
VA	visual acuity

1 INTRODUCTION

Dry eye syndrome (DES) is a common disorder affecting an estimated 25-30 million people in the United States, with prevalence estimates varying widely from 7.8% to almost 34%[1,2]. Dry eye incidence rises sharply with age, and women are more affected than men, purportedly due to the pathophysiological role of androgens and the complex nexus of the endocrine-immunological systems. The Dry Eye Workshop (DEWS) has redefined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface"[3].

Approaches to treatment vary; however, disease modification usually has targeted the inflammatory aspects of the disease. The only currently approved therapies for dry eye are cyclosporine ophthalmic emulsion (Restasis®) and lifitigrast ophthalmic solution (Xiidra™). Despite a commonly reported side effect of burning/stinging while using these drops, Restasis® is widely prescribed and used for the treatment of DES[4]. Xiidra™ has recently been approved and is also associated with burning and stinging following application[5]. A well-tolerated drug that reduces the inflammatory response in DES would be a major step forward from current treatment options.

TopiVert's narrow spectrum kinase inhibitors (NSKIs) promise to deliver long-term efficacy, improving both signs and symptoms of dry eye syndrome by effectively treating the underlying inflammation. Specifically, they target several important kinases (p38-alpha, syk and src family kinases src and lck) involved in the inflammatory cascade. TopiVert has demonstrated these kinases are up regulated in dry eye syndrome and inhibition leads to synergistic anti-inflammatory effects on key cell signaling pathways involved in inflammation. TOP1630 has been specifically designed to act locally at surface of the eye, with little or no systemic absorption, minimizing any untoward effects of the drug in the rest of the body. Thus TOP1630 has the potential to deliver a very favorable efficacy and safety profile for the sustained treatment of DES.

This study is the first in man for administration with TOP1630. Please refer to the Investigator's Brochure for further information on TOP1630.

2 STUDY OBJECTIVES

In subjects with dry eye syndrome:

The primary objective of this study is to compare the safety and tolerability of TOP1630 Ophthalmic Solution to placebo.

The secondary objectives are to compare the efficacy of TOP1630 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye syndrome.

3 CLINICAL HYPOTHESES

The clinical hypotheses for this study are that TOP1630 Ophthalmic Solution has an acceptable safety and toleration profile compared to placebo and demonstrates clinically meaningful differences on signs and symptoms in subjects with dry eye syndrome.

4 OVERALL STUDY DESIGN

This is a Phase 2, single-center, randomized, double-masked study designed to evaluate the safety, tolerability and efficacy of TOP1630 Ophthalmic Solution compared to placebo in subjects with dry eye syndrome.

For the Comfort Assessment, 8 subjects at least 18 years of age with a subject reported history of dry eye syndrome in both eyes and meeting all other study eligibility criteria will be randomized to receive 0.01% to 0.1% TOP1630 or placebo in a 3:1 ratio (6 subjects in the TOP1630 arm, 2 subjects in the placebo arm). The study will consist of two periods: the 1st period will consist of single or TID dosing over 24 hours (on up to three separate dosing occasions) with safety assessments during the subsequent 24 hours. The 2nd period will consist of TID dosing over days 8 to 11, followed by safety assessments over the subsequent 24 hours. The same subjects will proceed through both periods unless a study stopping criteria is met in which case a lower dose regime may be used for subsequent cohorts. A study flow chart appears below:

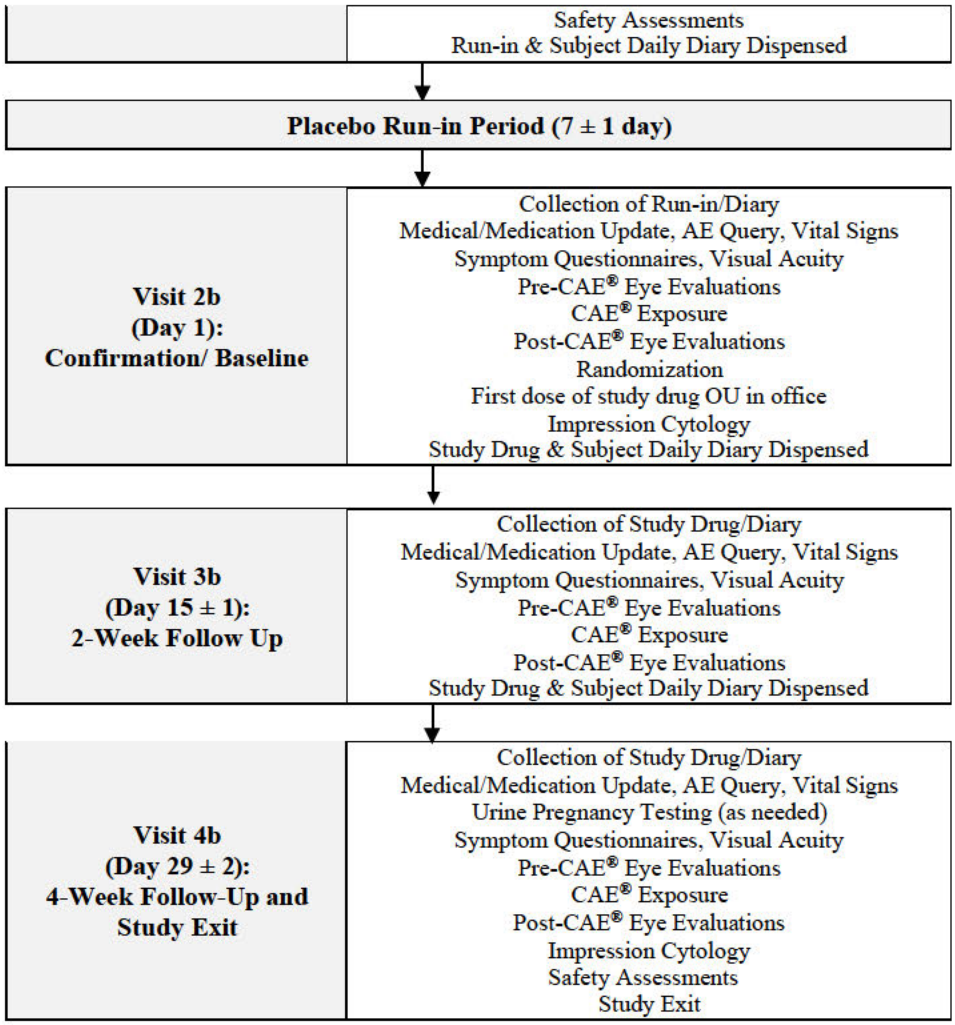
Visit 1a (Day 1): 0.01% or Placebo TID	Informed Consent Demographics, Medical/Medication & Ocular History Vital Signed Urine Pregnancy Testing (as needed) Visual Acuity, Baseline Slit Lamp Biomicroscopy, IOP and Comfort Assessment Morning 0.01% TOP1630 or Placebo Dose Slit Lamp Biomicroscopy, Comfort Assessment Afternoon 0.01% TOP1630 or Placebo Dose Comfort Assessment Evening 0.01% TOP1630 or Placebo Dose Visual Acuity, Slit Lamp Biomicroscopy, IOP, and Comfort Assessment Subject leaves clinic at completion of Visit.
Visit 2a (Day 2: 24 +/- 3 hrs after first dose): Physician Assessment	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP
Visit 3a (Day 3) TOP1630 0.1% or Placebo QD	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP 0.1 % TOP1630 or Placebo Dose (QD) Comfort Assessment Visual Acuity, Slit Lamp Biomicroscopy, IOP Subject leaves clinic at end of visit
Visit 4a (Day 4: 24 +/- 3 hrs after Day 3 dose): Physician Assessment	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP
Visit 5a (Day 5):	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP, and

TOP1630 0.1% or Placebo TID	Comfort Assessment Morning 0.1% TOP1630 or Placebo Dose Slit Lamp Biomicroscopy, Comfort Assessment Afternoon 0.1 % TOP1630 or Placebo Dose Comfort Assessment Evening 0.1% TOP1630 or Placebo Dose Visual Acuity, Slit Lamp Biomicroscopy, IOP, and Comfort Assessment Subject leaves clinic at completion of Visit
Visit 6a (Day 6: 24 +/- 3 hrs after Day 5 dose): Physician Assessment	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP
Visit 7a (Day 8): Multi-Dose Phase Start	Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP 0.1 % TOP1630 or Placebo TID (at home) Comfort Assessment (at home) Study Drug for at-home dosing and Comfort Questionnaire dispensed
Subject will dose 0.1% TOP1630 or Placebo TID at home on Days 8-11. No site Visits.	
Visit 8a (Day 12: 24 +/- 3 hrs after first dose on Day 11): Study Exit	Collection of Study Drug/Comfort Questionnaire Medical/Medication Update, AE Query, Vital Signs Visual Acuity, Slit Lamp Biomicroscopy, IOP Urine Pregnancy Testing (as needed) Study Exit

Analysis of the Comfort Assessment will be conducted in a blinded manner to ensure study stopping criteria have not been met and to confirm the dose for the 4 week Safety and Efficacy Assessment. If study stopping criteria have been met, unmasking may be needed to fully assess the data prior to dose selection. A separate study plan will be created to outline the process for evaluation of stopping criteria and dose selection for the Safety and Efficacy Assessment.

For the Safety and Efficacy Assessment, 60 subjects at least 18 years of age with a subject-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized to receive treatment with TOP1630 Ophthalmic Solution (dose determined by outcome of Comfort Assessment) or placebo in a 1:1 ratio (approximately 30 subjects in each treatment group). This study will consist of two periods: a 7-day run-in period and a 28-day treatment period. A study flow chart appears below:

Visit 1b (Day -7 ± 1): Screening	Informed Consent Demographics, Medical/Medication & Ocular History Vital Signs Urine Pregnancy Testing (as needed) Symptom Questionnaires, Visual Acuity Pre-CAE® Eye Evaluations CAE® Exposure Post-CAE® Eye Evaluations



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

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

For the Comfort Assessment, it is estimated that, assuming a 60% screen failure rate, approximately 20 subjects will be screened to enroll 8 randomized subjects in a 3:1 ratio (6 in the TOP1630 arm and 2 in the placebo arm).

For the Safety and Efficacy Assessment, it is estimated that, assuming a 60% screen failure rate, approximately 150 subjects will be screened to enroll approximately 60

randomized subjects. Subjects will be randomized in a 1:1 ratio (30 subjects in the TOP1630 arm and 30 in the placebo arm).

5.2 Study population characteristics

Inclusion Criteria

Subjects must meet all of the following requirements to be eligible for enrollment into the study:

For the Comfort Assessment:

1. Be at least 18 years of age;
2. Provide written informed consent;
3. Have a patient reported history of dry eye for at least 6 months prior to Visit 1a;
4. Have a history of use or desire to use eye drops for dry eye symptoms for at least 6 months prior to Visit 1a;

For the Safety and Efficacy Assessment:

All of the above criteria (at Visit 1b), and:

5. Report a score of ≥ 2 in at least one symptom of the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire at Visits 1b and 2b;
6. Report an OSDI© score ≥ 18 at Visits 1b and 2b;
7. Have a conjunctival redness score of ≥ 1 according to the Ora Calibra® scale in at least one eye at Visits 1b and 2b;
8. Have a tear film break-up time (TFBUT) >1 and < 7 seconds in at least one eye at Visit 1b and 2b;
9. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1b and 2b;
10. Have a corneal fluorescein staining score of ≥ 2 according to the Ora Calibra® scale in at least one region (e.g. inferior, superior, or central) in at least one eye at Visits 1b and 2b;
11. Have a total lissamine green conjunctival score of ≥ 2, based on the sum of the temporal and nasal regions of the conjunctiva according to the Ora Calibra® scale in at least one eye at Visits 1b and 2b;
12. Demonstrate a response to the CAE® at Visits 1b and 2b as defined by:
    a. Having at least a ≥ 1 point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure on the Ora Calibra® scale; and
    b. Reporting an Ocular Discomfort score ≥ 3 at 2 or more consecutive time points in at least one eye during CAE® exposure on the Ora Calibra® scale (if a subject has an Ocular Discomfort rating of 3 at time = 0 for an eye, s/he must report an Ocular Discomfort rating of 4 for two consecutive measurements for that eye).

13. Have at least one eye (the same eye) satisfy all criteria for 7, 8, 9, 10, 11, and 12 above;
14. At Visit 2b, subjects must have at least 5 days' worth of diary symptom data and deemed by the PI to be 80% compliant with vehicle eye drops.

Exclusion Criteria

Subjects may not participate in the study (Comfort Assessment as well as the Safety and Efficacy Assessment) if any of the following criteria are met:

1. Unable or unwilling to follow instructions, including participation in all study assessments and visits;
2. Have any clinically significant slit lamp findings at Visit 1 (1a or 1b) that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
3. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1 (1a or 1b);
4. Have any significant ocular lesion that could interfere with assessment of safety or efficacy or prevent study conduct in the opinion of the PI;
5. Have worn contact lenses within 14 days of Visit 1 (1a or 1b) or anticipate using contact lenses during the study;
6. Have used any eye drops within 2 hours of Visit 1 (1a or 1b);
7. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months or any other ocular surgeries within the last 6 months;
8. Have used Restasis® or Xiidra™ within 90 days of Visit 1 (1a or 1b);
9. Have used topical ocular steroids within 30 days of Visit 1 (1a or 1b);
10. Have any planned ocular and/or lid surgeries over the study period;
11. Have temporary punctal plugs at Visit 1 that have not been stable within 45 days of Visit 1 (1a or 1b) or anticipate having temporary punctal plugs inserted during the study;
12. Have had punctal occlusion (not including punctal plugs) within 6 months of Visit 1(1a or 1b);
13. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study) or have used any of these medications in the previous 24 hours prior to visit 1 (1a or 1b);
14. Have corrected visual acuity greater than or equal to logMAR+0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1 (1a or 1b);
15. Have an uncontrolled systemic disease;
16. Be a woman who is pregnant, nursing or planning a pregnancy;
17. Be unwilling to submit a urine pregnancy test at Visit 1 (1a or 1b) and Visit 8a or 4b (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);

18. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; IUD; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
19. Have a known allergy and/or sensitivity to the test article or its components;
20. 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;
21. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1 (1a or 1b). Subjects that were enrolled in the Comfort Assessment will be excluded from participating in the Safety and Efficacy Assessment;
22. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1 (1a or 1b); antihistamines are not allowed at any time during the study.

5.3 Withdrawal Criteria and Study Stopping Criteria

Subjects may withdraw consent from study participation at any time.

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

Subjects may be discontinued prior to their completion of the study due to the following safety stopping criteria being met for any subject:

- Persistent loss of 3 or more lines of visual acuity not explained by the condition under investigation and confirmed upon repeat testing
- Development of persistent corneal opacities or severe keratitis
- Persistent ocular irritation or redness not explained by condition
- IOP increase of 12 or more confirmed upon repeat testing
- Sight threatening adverse events such as corneal melting or corneal ulceration;
- Any other possibly related adverse events

Other reasons for discontinuation:

- Protocol violations

- Administrative reasons (e.g., inability to continue, lost to follow up)
- Subject choice (e.g. withdrawal of consent)
- Non compliance
- Any valid medical reason at discretion of investigator (see section 8.6.2)
- Other

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

Discontinued subjects will not be replaced.

Study Stopping Criteria

Comfort Assessment

The Comfort Assessment will be considered for stopping should 3 or more subjects experience any of the following:

- discontinue dosing due to persistent irritation deemed not to be due to underlying disease activity
- suffer persistent loss of 3 or more lines of visual acuity not explained by the condition under investigation and confirmed upon repeat testing
- develop persistent corneal opacities or severe keratitis
- suffer an IOP increase of 12 or more confirmed upon repeat testing
- subjects undergo sight threatening adverse events such as corneal melting or corneal ulceration

If the study is stopped for any of the above reasons, a lower dose may be considered for completion of the remainder of the study if deemed appropriate by the Sponsor and PI.

Safety and Efficacy Assessment

The Safety and Efficacy Assessment will be considered for stopping should more than 10 subjects discontinue dosing due to any of the following:

- persistent irritation deemed not to be due to underlying disease activity
- persistent loss of 3 or more lines of visual acuity not explained by the condition under investigation and confirmed upon repeat testing
- persistent corneal opacities or severe keratitis
- an IOP increase of 12 or more confirmed upon repeat testing

- other sight threatening adverse events such as corneal melting or corneal ulceration

6 STUDY PARAMETERS

6.1 Safety Measures

- Visual acuity (ETDRS)
- Slit-lamp biomicroscopy
- Corneal sensitivity (Pre-CAE®)
- Adverse event query
- Undilated fundoscopy
- Vital signs at all visits
- Drop comfort assessment
- Intraocular pressure (non-contact)

6.2 Exploratory Efficacy Measures

- Corneal fluorescein staining on the Ora Calibra® and NEI scales
- Conjunctival lissamine green staining on the Ora Calibra® and NEI scales
- Visual Analogue Scale (VAS) (Pre-CAE®)
- Tear film break-up time
- Conjunctival redness the Ora Calibra® scale
- Schirmer Test at Visits 2b, 3b, and 4b
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- Ora Calibra® Lid Margin Redness
- Ora Calibra® Posterior Lid Edge Evaluation
- OPI 2.0
- Ora Calibra® Ocular Discomfort Scale

6.3 Biomarkers

- Impression Cytology (OPIA Eyeprim™).

7 STUDY MATERIALS

7.1 Study Drug(s)

7.1.1 Formulations

Comfort Assessment

- 0.01% TOP1630 Ophthalmic Solution

- 0.1% TOP1630 Ophthalmic Solution
- Placebo Ophthalmic Solution (Vehicle with no TOP1630)

Run-In

- Placebo Ophthalmic Solution (Vehicle with no TOP1630)

Safety and Efficacy Assessment

- TOP1630 Ophthalmic Solution (dose determined by outcome of Comfort Assessment)
- Placebo Ophthalmic Solution (Vehicle with no TOP1630)

7.1.2 Dispensation Schedule

Comfort Assessment

- At Visit 1a, qualified subjects will be randomized and receive their assigned study drug Comfort Kit. They will administer the first three doses of placebo or 0.01% TOP1630 in office.
- At Visit 3a, subjects will administer a single dose of placebo or 0.1% TOP1630 from their assigned study drug Comfort Kit. Unless stopping criteria (as outlined in Section 5.3) are met, the remaining doses for each subject for the remainder of the Comfort Assessment will be at the 0.1% concentration of TOP1630 or placebo. If stopping criteria are met after the introduction of the 0.1% TOP1630, the Comfort Assessment study may proceed with the subjects' dosing with the lower concentration 0.01% TOP1630 (or placebo).
- At Visit 5a, subjects will dose TID in office with placebo or 0.1% TOP1630 from their assigned study drug Comfort Kit.
- At Visit 7a, a Take Home Kit from their assigned study drug Comfort Kit will be dispensed to subjects for at-home dosing TID with placebo or 0.1% TOP1630 from days 8 through 11 (4 days TID).
- At Visit 8a all study drug will be collected.

Safety and Efficacy Assessment

- At the end of Visit 1b, qualified subjects will receive a kit of run-in (Placebo) for one week, dosing TID until Visit 2b. Subject will be instructed to dose in 6-hour intervals in the morning, afternoon, and in the evening before bed.
- The run-in kit will be collected at the beginning of Visit 2b and accountability will be performed by a study technician.
- At the end of Visit 2b, qualified subjects will be randomized and the first dose of study drug will be administered in office, and subjects will take remaining doses at home.

- At the end of Visit 2b, subjects will be given two kits of 24 bottles each of TOP1630 Ophthalmic Solution or placebo for TID dosing.
- At Visit 3b, subjects will receive two new kits of the same test article they were previously randomized to (at Visit 2b) for TID dosing.
- At Visits 3b and 4b, remaining/unused study drug will be collected from subjects for drug accountability.
- Subjects will be instructed to not use run-in (at Visit 2b) or study drug on the day of visits (Visit 3b and 4b) prior to the visit.

7.1.3 Instructions for Use

Subjects will be instructed to dose by instilling 1 drop in each eye TID in approximately 6 hour intervals (morning, afternoon, and in the evening before bed). Subjects will be instructed to use a second drop only if the first drop does not fully coat the eye. Subjects will be given detailed instructions on study drug administration, accountability, and storage at each visit.

7.2 Other Study Supplies

Urine pregnancy tests, Schirmer's test strips, sodium fluorescein, lissamine green/strips, Fluress, Eyeprim™ (impression cytology).

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Informed Consent

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

8.1.2 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.2).

8.1.3 Procedures for Final Study Entry

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

8.1.4 Methods for Assignment to Treatment Groups:

For the Comfort Assessment, prior to initiation of the study (at Visit 1a), 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, each qualifying subject will then be assigned a randomization number at Visit 1a.

For the Safety and Efficacy Assessment, prior to initiation of study run-in (at Visit 1b), 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 1b and 2b, each qualifying subject will then be assigned a randomization number at the end of Visit 2b.

The Sponsor, Investigator, study staff and subject will be masked to the subject's treatment arm 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 electronic case report form (eCRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted. Subjects who were enrolled in the Comfort Assessment portion of the study will not be permitted to participate in the Safety and Efficacy Assessment.

8.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 5.2).

8.2.2 Escape Medications

No escape medications are allowed for this study.

8.2.3 Special Diet or Activities

Subjects will only be permitted to leave the clinic space under supervision by a staff member during Visits 1a and 5a.

Subjects will be instructed not to smoke (cigarettes, e-cigarettes, etc) for the duration of each of their clinic visits.

8.3 Examination Procedures

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

The following procedures will be performed (see Appendix 2 for description):

For the Comfort Assessment:

Visit 1a (Day 1): 0.01% TOP1630

- Informed consent / HIPAA
- Demographic data and medical / medication history
- Urine pregnancy test (for females of childbearing potential)
- Baseline visual acuity
- Vital Signs (Pulse, Blood Pressure, and O_2 Saturation)
- Baseline slit lamp biomicroscopy
- Baseline intraocular pressure (non-contact)
- Review of Qualification Criteria
- Adverse Event Query
- Randomization & Assignment of study drug kit according to randomization
- 0.01% TOP1630 or Placebo Morning Dose
- Comfort assessment
- 0.01% TOP1630 or Placebo Afternoon Dose
- Comfort assessment
- 0.01% TOP1630 or Placebo Evening Dose
- Comfort assessment
- Visual acuity
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- Adverse Event Query

Visit 2a (Day 2 [24 +/- 3 hrs from Visit 1a first dose]): Physician Assessment

- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)

Visit 3a (Day 3): 0.1% TOP1630, QD

- Medical/Medication History Update
- Adverse Event Query

- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- 0.1% TOP1630 or Placebo Dose
- Comfort Assessment

Visit 4a (Day 4) [24 +/- 3 hrs from Visit 3a dose]): Physician Assessment

- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact).

Visit 5a (Day 5): 0.1% TOP1630, TID

- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- 0.1% TOP1630 or Placebo Morning Dose
- Comfort assessment
- 0.1% TOP1630 or Placebo Afternoon Dose
- Comfort assessment
- 0.1% TOP1630 or Placebo Evening Dose
- Comfort assessment
- Visual acuity
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- Adverse Event Query

Visit 6a (Day 6 [24 +/- 3 hrs Visit 5a first dose]): Physician Assessment

- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact).

Visit 7a (Day 8): 0.1% TOP1630, TID

- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- Subject doses TOP1630 or Placebo at home TID
- Comfort assessment at Home
- Dispensation of study drug kit according to randomization for TID dosing until Visit 8a
- Dispensation of comfort assessment questionnaire

At home dosing of TOP1630 TID on days 9, 10, and 11. No site Visits.

Visit 8a (Day 12): Assessment and Exit

- Return study drug kit and comfort assessment questionnaires
- Medical/Medication History Update
- Adverse Event Query
- Visual acuity
- Vital Signs
- Slit lamp biomicroscopy
- Intraocular pressure (non-contact)
- Urine pregnancy test (for females of childbearing potential)
- Study exit

For the Safety and Efficacy Assessment:

Visit 1b (Day -7 ±1): Screening

Pre-CAE® Procedures

- Informed consent / HIPAA
- Demographic data and medical / medication history
- Urine pregnancy test (for females of childbearing potential)
- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Ocular Surface Disease Index© (OSDI©)
- 7 question Visual Analogue Scale (VAS) for symptoms of DES
- Visual acuity
- Vital Signs

- Review of qualification criteria
- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- Ora Calibra® Lid Margin Redness
- Ora Calibra® Posterior Lid Edge Evaluation
- Tear Film Break-up Time (TFBUT)
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale
- Corneal sensitivity
- Unanesthetized Schirmer's Test, to be performed at least 15 minutes after Lissamine Green staining
- Adverse Event Query
- 90-minute CAE® exposure
    - Ora Calibra® Ocular Discomfort upon entering the CAE® and every 5 minutes thereafter

Post- CAE® Procedures

- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- TFBUT
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale
- Intraocular pressure (non-contact)
- Undilated fundoscopy
- Review of qualification criteria
- Adverse event query
- Dispensation of run-in (RUN-IN) for TID dosing until Visit 2b;
    - Subjects will be instructed to dose in each eye three times daily (morning, afternoon, and in the evening before bed);
- Dispensation of diaries and subject instructions;

- Subjects will be instructed to complete their diary and dose in each eye in the afternoon and before bed on the evening of Visit 1b
- Subjects will be instructed to complete diary symptoms TID prior to drop instillation in the morning, afternoon, and evening before bed until Visit 2b
- Subjects will be instructed to complete their diary on the morning of their next visit (Visit 2b)
- Subjects will be instructed to not dose with run-in placebo on the morning of their next visit (Visit 2b)

- Qualified subjects will be scheduled for Visit 2b.

Visit 2b (Day 1): Confirmation/Baseline

Pre-CAE® Procedures

- Collection and review of run-in (RUN-IN) and subject diaries
- Subject will be asked if he/she dosed with run-in on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Medical/medication history update
- Adverse event query
- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- 7 question Visual Analogue Scale (VAS) for symptoms of DES
- Visual Acuity
- Vital Signs
- Review of qualification criteria
- Slit-lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness
- Ora Calibra® Lid Margin Redness
- Ora Calibra® Posterior Lid Edge Evaluation
- Ora Calibra® OPI 2.0
- TFBUT

- Fluorescein staining – Ora Calibra® and NEI Scale
- Lissamine Green staining – Ora Calibra® and NEI Scale
- Unanesthetized Schirmer's Test - to be performed at least 15 minutes after Lissamine Green staining
- 90-minute CAE® exposure;
    - Ora Calibra™ Ocular Discomfort upon entering the CAE® and every 5 minutes thereafter;

Post- CAE® Procedures

- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom questionnaire
- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- TFBUT
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale
- Adverse Event Query
- Review of qualification criteria
- Randomization & Dispensation of study drug kit according to randomization for TID dosing until Visit 3b
- Subject self-administers first dose of study drug, OU
- Ora Calibra® Drop Comfort and Questionnaire
- Wait at least 15 minutes from in office dose to Impression Cytology
- Impression cytology (OPIA Eyeprim™) – to be performed on the "worst eye" as defined in Section 10.4.2. Anesthetic may be used at the discretion of the Investigator
- Subjects will be instructed to dose in each eye three times daily (morning, afternoon, and in the evening before bed)
- Dispensation of diaries:
    - Subjects will be instructed to complete diary symptoms TID prior to drop instillation in the morning, afternoon, and in the evening before bed until Visit 3b;
    - Subjects will be instructed to complete their diary TID to account for each dose of study drug taken;

  - Subjects will be instructed to complete their diary and dose in each eye in the afternoon and before bed on the evening of Visit 2b;
  - Subjects will be instructed to complete their diary on the morning of their next visit (Visit 3b);
  - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 3b);
- Subject will remain at the site for at least 30 minutes after instillation of study drug
- Qualified subjects will be scheduled for Visit 3b.

Visit 3b (Day 15 ± 1): 2-Week Follow-Up

Pre-CAE® Procedures

- Collection and review of study drug and subject diaries
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Medical / medication history update
- Adverse event query
- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- 7 question Visual Analogue Scale (VAS) for symptoms of DES
- Visual Acuity
- Vital Signs
- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- Ora Calibra® Lid Margin Redness;
- Ora Calibra® Posterior Lid Edge Evaluation;
- TFBUT
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale

- Unanesthetized Schirmer's Test - to be performed at least 15 minutes after Lissamine Green staining
- 90-minute CAE® exposure;
    - Ora Calibra® Ocular Discomfort upon entering the CAE® and every 5 minutes thereafter;

Post-CAE® Procedures

- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom questionnaire
- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- TFBUT
- Fluorescein staining – Ora Calibra®; and NEI Scale
- Lissamine Green staining – Ora Calibra®; and NEI Scale
- Adverse Event Query
- Dispensation of study drug kit according to randomization for TID dosing until Visit 4b
- Subject self-administers dose of study drug, OU
- Ora Calibra® Drop Comfort and Questionnaire
- Subjects will be instructed to dose in each eye three times daily (morning, afternoon, and in the evening before bed)
- Dispensation of diaries:
    - Subjects will be instructed to complete diary symptoms TID in the morning, afternoon, and the evening before bed prior to drop instillation until Visit 4b;
    - Subjects will be instructed to complete their diary TID to account for each dose of study drug taken;
    - Subjects will be instructed to complete their diary and dose in each eye in the afternoon and before bed on the evening of Visit 3b;
    - Subjects will be instructed to complete their diary on the morning of their next visit (Visit 4b);
    - Subjects will be instructed to not dose with study drug on the morning of their next visit (Visit 4b);
- Subjects will be scheduled for Visit 4b.

Visit 4b (Day 29 ± 2): 4-Week Follow-Up and Study Exit

Pre-CAE® Procedures

- Collection and review of study drug and subject diaries
- Subject will be asked if he/she dosed with study drug on the morning of the visit; if the subject indicates he/she dosed that morning, he/she should wait at least 4 hours from the time of dosing before efficacy assessments are performed
- Medical / medication history update
- Adverse event query
- Ora Calibra® Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI©
- 7 question Visual Analogue Scale (VAS) for symptoms of DES
- Visual Acuity
- Vital Signs
- Urine pregnancy test (for females of childbearing potential)
- Slit-lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness
- Ora Calibra® Lid Margin Redness
- Ora Calibra® Posterior Lid Edge Evaluation
- Ora Calibra® OPI 2.0
- TFBUT
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale
- Corneal Sensitivity
- Unanesthetized Schirmer's Test, to be performed at least 15 minutes after Lissamine Green staining
- 90-minute CAE® exposure;
    - Ora Calibra® Ocular Discomfort upon entering the CAE® and every 5 minutes thereafter;

Post-CAE® Procedures

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

- Slit-lamp biomicroscopy
- Ora Calibra® Conjunctival Redness
- TFBUT
- Fluorescein staining – Ora Calibra® and NEI scale
- Lissamine Green staining – Ora Calibra® and NEI scale
- Impression cytology (OPIA Eyeprim™) to be performed on the "worst eye" as defined in Section 10.4.2. Anesthetic may be used at the discretion of the Investigator
- Intraocular pressure (non-contact)
- Undilated Fundoscopy
- Adverse event query
- Study exit.

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 8a or 4b, then all safety evaluations that were to be performed at the Visit should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

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

If a female reports a pregnancy or has a positive pregnancy test during the study 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.

8.4 Schedule of Visits and Measurements

8.4.1 Scheduled Visits

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

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the

source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Visual Acuity;
- Slit-lamp Biomicroscopy;
- Intraocular pressure (non-contact);
- Pregnancy Test;
- Undilated Fundoscopy;
- Assessment of Adverse Events;
- Assessment of concomitant medications and/or treatments; and
- Any other assessments needed in the judgment of the investigator.

8.5 Compliance with Protocol

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visit 1a and 7a (in the Comfort Assessment) and Visits 1b, 2b, and 3b (in the Safety and Efficacy Assessment) and given written instructions. In the Comfort Assessment, used and unused study drug bottles will be collected at Visit 8a. In the Safety and Efficacy Assessment, the subject daily diaries and used and unused study drug bottles will be collected at each visit from Visit 2b up to and including Visit 4b to assess dosing and symptom assessment compliance. Dosing compliance will be based on the used and unused bottle count. If the subject is less than 80% or more than 114% compliant with dosing based on the expected number of used bottles, then the subject will be deemed non-compliant and a deviation should be recorded.

In the Safety and Efficacy study, subjects must have at least 5 days' worth of diary symptom data and deemed by the Investigator to be at least 80% compliant with dosing during the placebo run-in to be able to continue in the study. In the subject daily diary, if more than 20% of applicable 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 and has undertaken all study assessments applicable for study completion.

8.6.2 Discontinuation and Stopping Criteria

Refer to Section 5.3 for withdrawal and stopping criteria.

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 time for the Comfort Assessment is expected to be approximately 12 days.

An individual subject's participation in the Safety and Efficacy Assessment is expected to be approximately 5 weeks (35 days).

8.9 Monitoring and Quality Assurance

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

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

9 ADVERSE EVENTS

9.1 Adverse Event

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

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

Collection of Adverse Events will begin at the time of informed consent.

If there is a worsening of a medical condition that was present prior to the administration of the informed consent, this should also be considered a new adverse event and reported. Any medical condition present prior to the administration of the study drug that remains unchanged or improved should not be recorded as an adverse event at subsequent visits.

Study drug includes the investigational drug under evaluation, placebo, or any other medications required by the protocol given during any stage of the study.

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

9.1.1 Severity

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

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

9.1.2 Relationship to Study Drug

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

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE;
- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.

- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

9.1.3 Expectedness

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

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

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

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

9.2 Serious Adverse Events

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

- Death;
- A life-threatening adverse event;

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

- Inpatient hospitalization or prolongation of existing hospitalization;

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

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

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

  Note: A serious adverse event specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

- A congenital anomaly/birth defect.

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

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to Ora, the study sponsor, and the IRB/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 adverse events 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.

9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the study drug, must be reported to the medical monitor within 24 hours of becoming aware of the event. All information relevant to the serious adverse event 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 a serious adverse event must be followed up and the outcome reported.

In the event of a serious adverse event, the investigator must notify Ora and the sponsor within 24 hours; obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora and the study sponsor with a complete case history, which includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; Site should inform the IRB of the adverse event according to the IRB guidelines for reporting serious 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 (ongoing and stable). If the subject is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the subject via telephone, and then a letter via certified mail.

Contact information for reporting Serious Adverse Events:

Name:	
Title:	Project Manager, Dry Eye
Company:	Ora, Inc.
Office Telephone:	978-685-8900 x 9568
Alternative Telephone:	978-482-6817
Office Facsimile:	978-689-0020
Name:	
Title:	Medical Monitor
Office Telephone:	617-573-5575
Mobile Phone:	401-935-9662
Office Facsimile:	617-573- 4324

9.4 Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergency situations), Ora and/or the study

sponsor should be notified before unmasking study drug. Subjects will also be unmasked for treatment-related SAEs or pregnancies in a similar manner.
The Investigator should complete the appropriate forms (per the Safety Plan) and, when possible, discuss with Ora, the Medical Monitor, and TopiVert Pharma, Ltd whether unmasking is required. The Investigator can unmask study drug assigned to a subject using the black blinding laminate label that was placed in the Source Document from the subject's study drug kit by removing the protective plastic over it and then scratching it off. Documentation must be completed by the unmasking Investigator and filed in the subject's study file. The subject's study file must include documentation for the unmasking reason and date along with the signature and name of the person who unmasked the subject. A copy of the appropriate forms must be provided to Ora for the Trial Master File. Unmasked subjects 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 subject is lost to follow-up, the Investigator should make reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

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

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- Modified Intent-to-Treat Population – The modified intent-to-treat (mITT) population includes all randomized subjects with one post baseline efficacy assessment. Efficacy analysis will be performed on the mITT population. Subjects in the mITT population will be analyzed as randomized.

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

- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

Summaries of the comfort data from the Comfort Assessment portion of the study will be performed on the safety population from that Assessment. The statistical analysis of safety data will be performed for the safety population, separately for the Comfort Assessment and the Safety and Efficacy Assessment of the study. The analysis of baseline and all efficacy data in the Safety and Efficacy Assessment of the study will be performed for the mITT population. The efficacy analyses may also be performed on the PP population as sensitivity analyses.

10.2 Statistical Hypotheses

Although the primary objectives of the study are to evaluate safety and tolerability, exploratory hypothesis testing will be performed for efficacy endpoints. For each efficacy endpoint and time point, the statistical hypotheses are as follows:

H_0: There is no difference between the TOP1630 Ophthalmic Solution treatment group and placebo for the respective endpoint.

H_1: There is a difference between the TOP1630 Ophthalmic Solution treatment group and placebo for the respective endpoint. A difference in favor of TOP1630 Ophthalmic Solutions will be considered a success for that endpoint.

10.3 Sample Size

The study is not powered to show statistical differences for any of the efficacy endpoints. The sample size was determined based on prior clinical trial experience in subjects with dry eye syndrome and is deemed to be robust sufficient to evaluate the safety and tolerability of TOP1630 Ophthalmic Solution in this population and to gather efficacy data that will aid in powering future clinical trials.

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

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 of data from the Comfort Assessment and Safety and Efficacy Assessment of the study will be summarized separately. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

[redacted]

All efficacy analyses will be 2-sided at a significance level of 0.10.

10.4.2 Unit of Analysis

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

[redacted]

10.4.3 Missing Data

The efficacy analyses will be performed using observed data. In addition, for key endpoints of corneal staining and ocular discomfort, missing data will be imputed using the following methods:

- Using the last observation carried forward (LOCF) imputation method for missing values
- Using multiple imputation methods to account for missing data

10.4.4 Multiplicity Consideration

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

10.4.5 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 occurs or worsens after the first dose of study treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related AEs; by system organ class, preferred term for SAEs; and by system organ class, preferred term, and time of onset. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, corneal sensitivity, undilated fundoscopy, intraocular pressure (non-contact), and vital signs will be summarized by treatment group, visit, and time point (where relevant) 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.

10.4.6 Tolerability Analyses

Drop Comfort Assessment results, completed by the subject, and physician assessment results will be summarized descriptively using counts and percentages with each response. In addition, scores will be summarized continuously using number of subjects (n), mean, median, standard deviation, minimum and maximum. Tolerability endpoints will be summarized for the Comfort Assessment and Safety and Efficacy

Assessment separately, as well as combining the like treatment arms from both study Assessments.

10.4.7 Exploratory Efficacy Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, minimum and maximum), and analyzed with two-sample t-tests comparing the active treatment groups to placebo. All visit-based data will be analyzed at each visit as well as change from baseline. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline will also be assessed where appropriate. Corneal fluorescein staining by region and total (Ora and NEI scales), lissamine green staining by region, tear film break-up time, conjunctival redness, unanesthetized Schirmer's test, ocular symptoms (Ora Calibra® scales and VAS), OSDI©, ocular discomfort and changes from baseline in these measures will be analyzed by visit and time point, where applicable (i.e., pre- and post-CAE®), using two-sample t-tests and Wilcoxon rank sum tests. Changes from baseline will also be analyzed using ANCOVA models adjusting for baseline values. For the measures of symptoms during CAE®, the ANCOVA models will also include the pre-CAE® measure as a covariate. Drop comfort will be summarized descriptively. Symptoms recorded on the daily diary will be analyzed using repeated measure ANCOVA models, where baseline scores are calculated as the average scores in the run-in period and post-baseline scores are calculated as weekly morning, afternoon, evening, and daily averages.

A full statistical analysis plan (SAP) will be finalized before database lock and unmasking.

10.4.8 Interim Analyses

No interim analyses are planned; however, assessments from the Comfort Assessment will be analyzed in a blinded manner to ensure study stopping criteria have not been met and to confirm the dose for the 4 week Safety and Efficacy Assessment. If study stopping criteria have been met, unblinding may be needed to fully assess the data prior to dose selection.

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

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local,

state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

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 (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/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.

11.1.2 Institutional Review Board (IRB) Approval

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

Only an IRB/ERC approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

Monitors, auditors and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the

study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

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

11.4 Documentation

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

11.4.1 Retention of Documentation

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

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

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

11.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits.

For the Comfort Assessment, subjects will receive one Subject Comfort Kit containing all of the drug needed for dosing. Within the kit will be 3 bottles labeled "Visit 1a", one bottle labeled "Visit 3a", and 3 bottles labeled "Visit 5a". In addition, there will be a Take-Home kit which will contain 15 bottles, enough for 4 days of dosing plus 3 reserve bottles.

For the Safety and Efficacy Assessment, 24 bottles will be packaged in one week clinical kits. One bottle contains enough supply for one dose. The extra bottles in the kit will not be used and will be returned to the clinical site at the next visit. Subjects will receive 2 kits at each visit 2b and 3b.

Further information on the labeling and packaging of study drug can be found in the study Dispensation and Collection Plan.

11.5.2 Storage of Study Drug

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

11.5.3 Accountability of Study Drug

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 Study Drug

All study drugs will be returned to the sponsor or their designee for destruction.

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

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 is 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 (CDs) 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

Impression cytology samples will be collected from the worst eye at Visits 2b and 4b. Samples will be stored at the site and then submitted to the sponsor upon request for processing, storage and analysis. Details of sample collection, handling, storage, and shipping procedures are found in a study procedure manual.

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. The study sponsor and Ora will have the final decision regarding the manuscript and publication.

12 REFERENCES

1. Panel. AAoOCED. Preferred Practice Pattern (R) Guidelines. Dry Eye Syndrome2013.
2. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). The ocular surface 2007;5:93-107.
3. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). The ocular surface 2007;5:75-92.
4. Mah F, Milner M, Yiu S, Donnenfeld E, Conway TM, Hollander DA. PERSIST: Physician's Evaluation of Restasis((R)) Satisfaction in Second Trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review. Clinical ophthalmology 2012;6:1971-6.
5. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease: Results of the Randomized Phase III OPUS-2 Study. Ophthalmology 2015;122:2423-31.

13 APPENDICES

Appendix 1: Schedule of Visits and Measurements

Table 1 Schedule of Visits and Measurements (Comfort Assessment)

Procedure	Visit 1a (Day 1)	Visit 2a (Day 2)	Visit 3a (Day 3)	Visit 4a (Day 4)	Visit 5a (Day 5)	Visit 6a (Day 6)	Visit 7a (Day 8)	Visit 8a (Day 12)
HIPAA/Informed Consent	X							
Medical / Medication History and Demographic	X							
Medical History Update and Adverse Event Query	X	X	X	X	X	X	X	X
Urine Pregnancy Test[1]	X							X
Randomization	X							
Visual Acuity Assessment	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X	X	X
Intraocular pressure (non-contact) Assessment	X	X	X	X	X	X	X	X
Study Drug Dosing or Dispensation/Collection[2]	X		X		X		X[3]	X[3]
On Site Comfort Assessment	X		X		X		X[4]	
Study Exit								X

[1]For females of childbearing potential.

[2]Study drug dosing at 0.01% to 0.1% TOP1630 or Placebo, QD or TID.

[3]Study drug Take Home kit dispensed for at-home dosing on Days 8-11. Take Home kit collected at Visit 8a.

[4]Comfort Assessment to be done at home on Day 8-11.

Table 2 Schedule of Visits and Measurements (Safety and Efficacy Assessment)

Procedure	Visit 1b Day -7 ± 1		Visit 2b Day 1		Visit 3b Day15 ± 1		Visit 4b Day 29 ±2	
	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®	Pre CAE®	Post CAE®
Informed Consent / HIPAA	X							
Medical / Medication History and Demographic	X							
Run-in Placebo Collection			X					
Study Drug Collection					X		X	
Diary Collection			X		X		X	
Medical / Medication History Update			X		X		X	
Adverse Event Query	X	X	X	X	X	X	X	X
Pregnancy Test	X[1]						X[1]	
Ocular Discomfort – Ora, Calibra® / Dry Eye Symptoms	X	X	X	X	X	X	X	X
OSDI© Questionnaire	X		X		X		X	
Visual Acuity (ETDRS)	X		X		X		X	
Vital Signs	X		X		X		X	
Review of Qualification Criteria	X	X	X	X				
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	X
VAS Symptom Assessment	X		X		X		X	
Impression Cytology (EyePrim)				X				X
Conjunctival Redness, Ora Calibra® Scale	X	X	X	X	X	X	X	X
Lid Margin Redness, Ora Calibra® Scale	X		X		X		X	
Posterior Lid Edge Evaluation, Ora Calibra® Scale	X		X		X		X	
TFBUT	X	X	X	X	X	X	X	X

Fluorescein Staining-Ora Calibra® and NEI Scale	X	X	X	X	X	X	X	X
Lissamine Green Staining-Ora Calibra® and NEI Scale	X	X	X	X	X	X	X	X
Corneal Sensitivity (Cochet-Bonnet)	X						X	
OPI 2.0			X				X	
Unanesthetized Schirmer's Test	X		X		X		X	
CAE® Exposure	X		X		X		X	
CAE® Discomfort – Ora Calibra® Ocular Discomfort Scale	X		X		X		X	
Intraocular pressure (non-contact)		X						X
Undilated Fundus Exam		X						X
Run-in Placebo & Diary Dispensation		X						
Randomization				X				
Subject self-instillation of study drug				X		X		
Ora Calibra® Drop Comfort Assessment				X		X		
Study Drug Dispensation				X		X		
Diary Dispensation		X		X		X		
Exit Subject from Study								X
[1]For females of childbearing potential.								

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

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

Visual Acuity Procedures

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

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

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only ETDRS Series 2000 Chart 1 & 2, and the right eye (OD) 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/she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

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

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

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number

of letters missed up to and including in the last line read. This total sum represents the logMAR visual acuity for that eye.

For Example: 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 (OS).

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

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

Collection of Vital Signs

Each subject will have vital signs assessments (resting blood pressure, pulse and Oxygen saturation (SpO_2)) conducted at each study visit for both the Comfort and Safety and Efficacy Assessment. Vital signs are to be conducted by qualified site staff member delegated by the Principal Investigator.

Systolic/ Diastolic Blood Pressure (mmHg)

Systolic and diastolic blood pressure should be measured in the same arm, when possible, each time using a sphygmomanometer for subjects who have been in a resting state (seated upright) at least 5 minutes. Blood pressure will be recorded in mm Hg.

Pulse (bpm)

Pulse will be measured for subjects who have been in a resting state (seated) for at least 5 minutes. Pulse will be measured using the Pulse Oximeter, and recorded in beats per minute.

Oxygen Saturation (Sp O_2 %)

SpO_2 will be measured for subjects who have been in a resting state (seated) for at least 5 minutes using the Pulse Oximeter and recorded as a percentage.

Slit-lamp Biomicroscopy

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

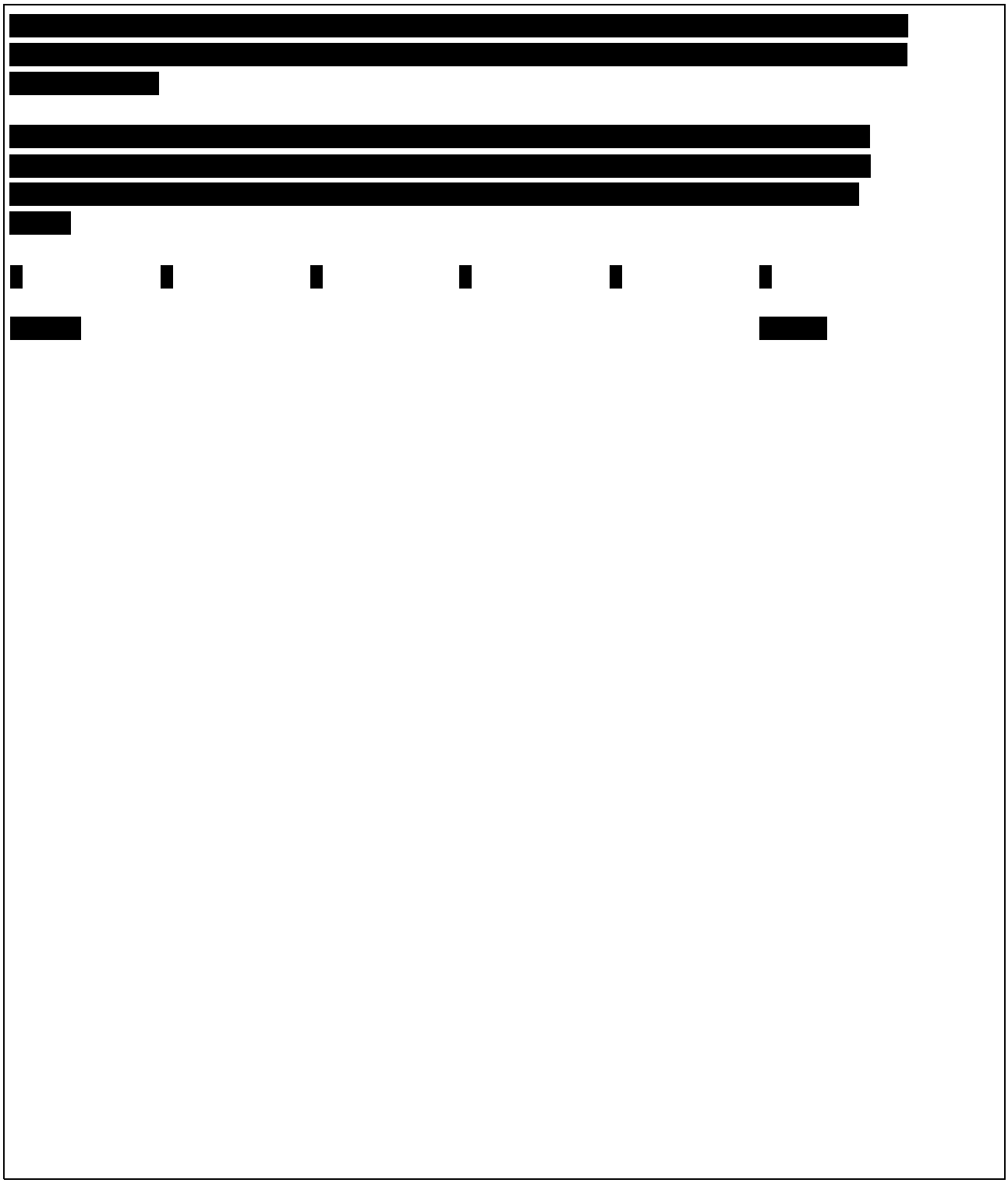
- **Cornea**
- **Conjunctiva**
- **Anterior Chamber**
- **Iris**
- **Lens**
- **Lid**

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

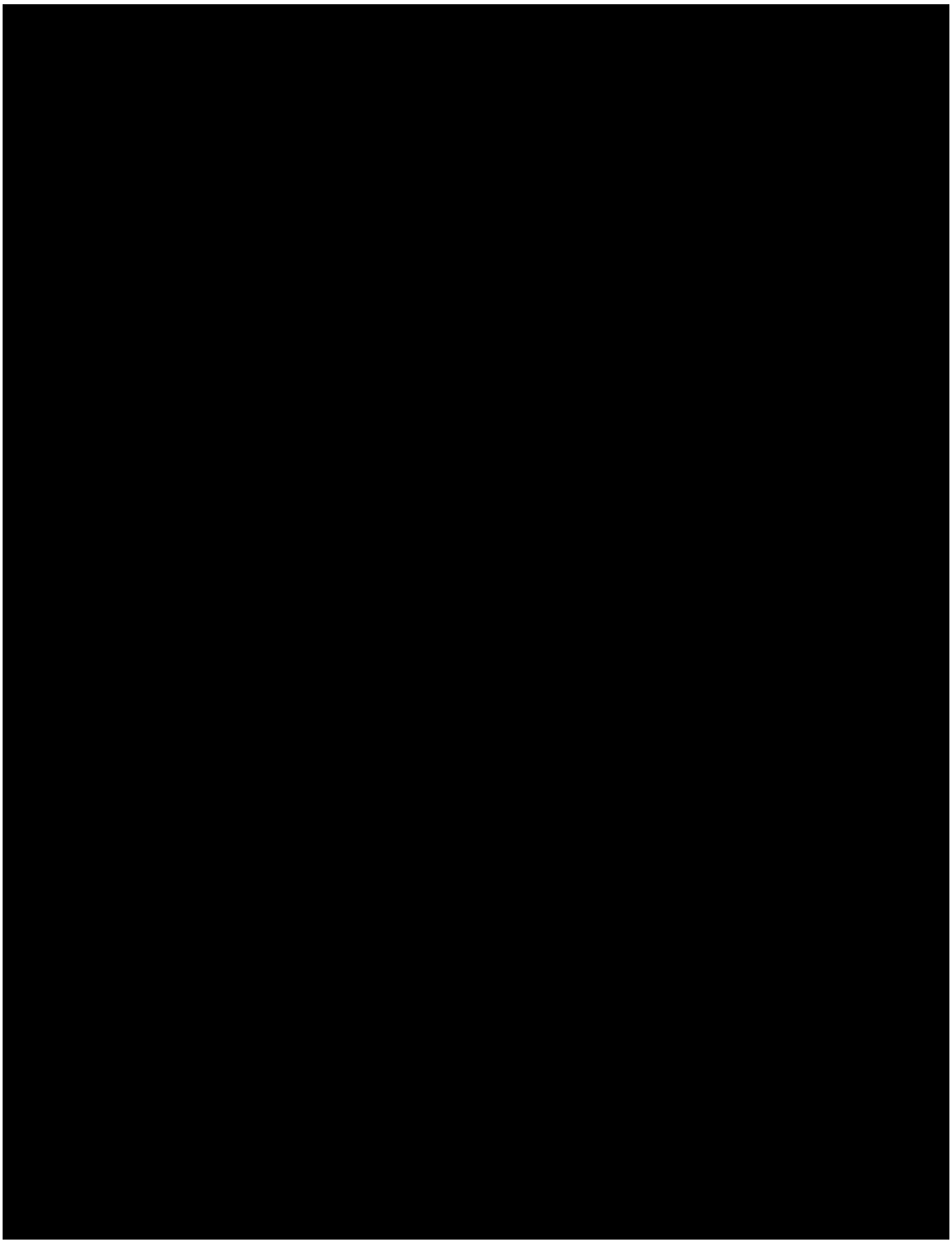
Ora Calibra® Ocular Discomfort Scale

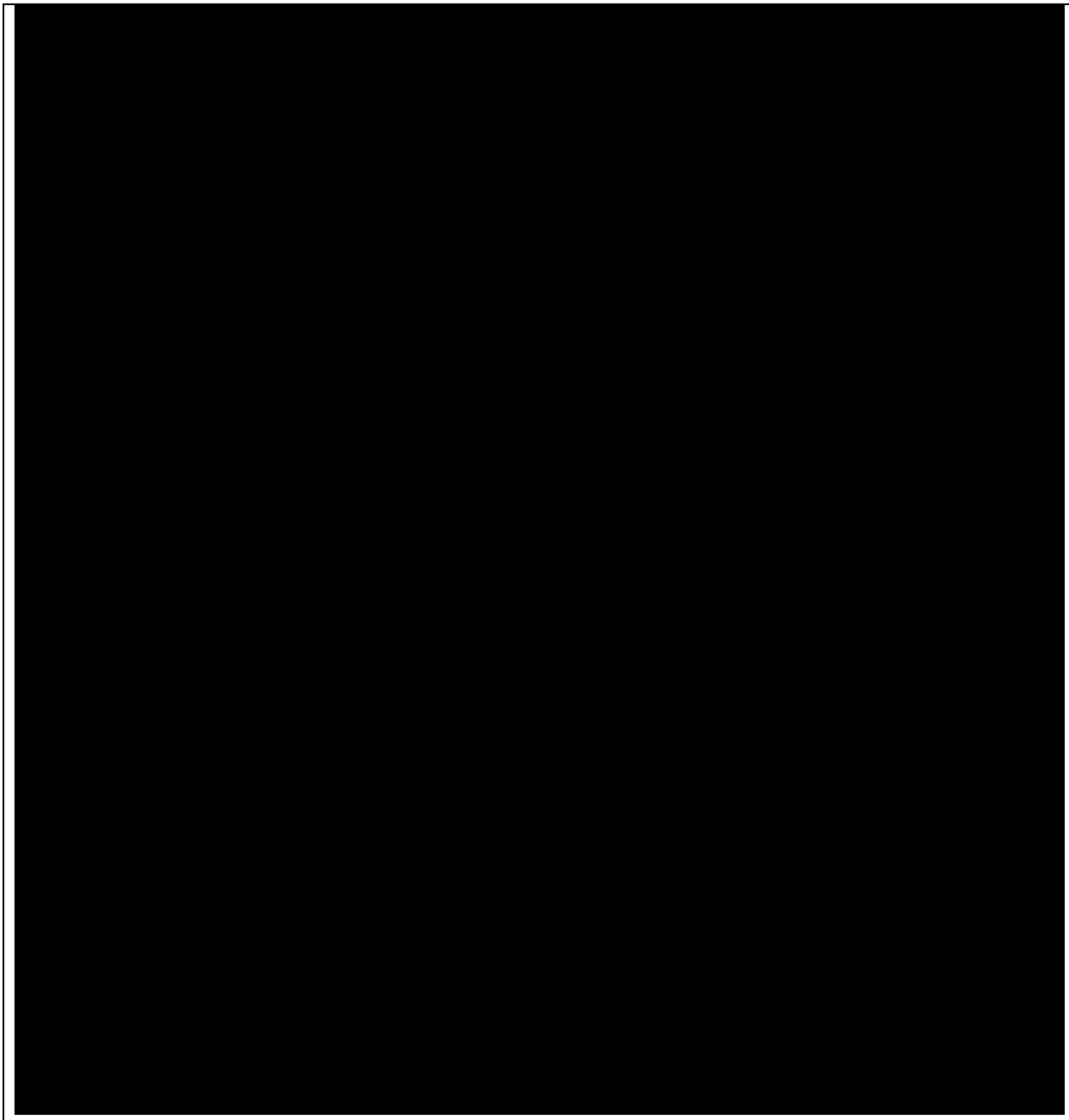
[redacted]

Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

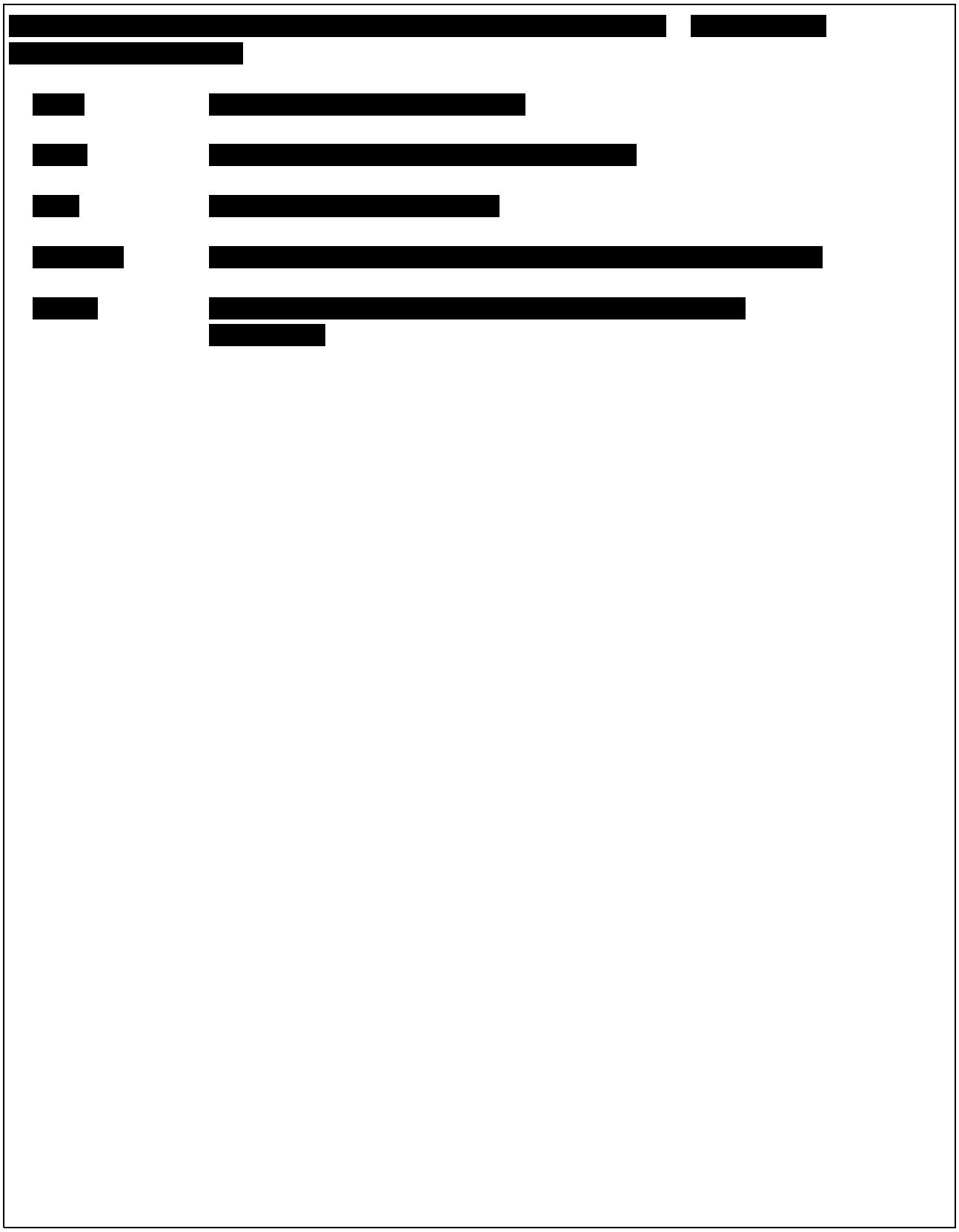


Ocular Surface and Disease Index (OSDI) ©





Ora Calibra® Conjunctival Redness Scale



Ora Calibra® Lid Margin Redness

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

[redacted]

Ora Calibra® Posterior Lid Edge Evaluation:

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

[redacted]

Tear Film Break-Up Time (TFBUT)

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the 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.

[redacted]

Fluorescein Staining

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

Ora Calibra® Corneal and Conjunctival Staining Scale

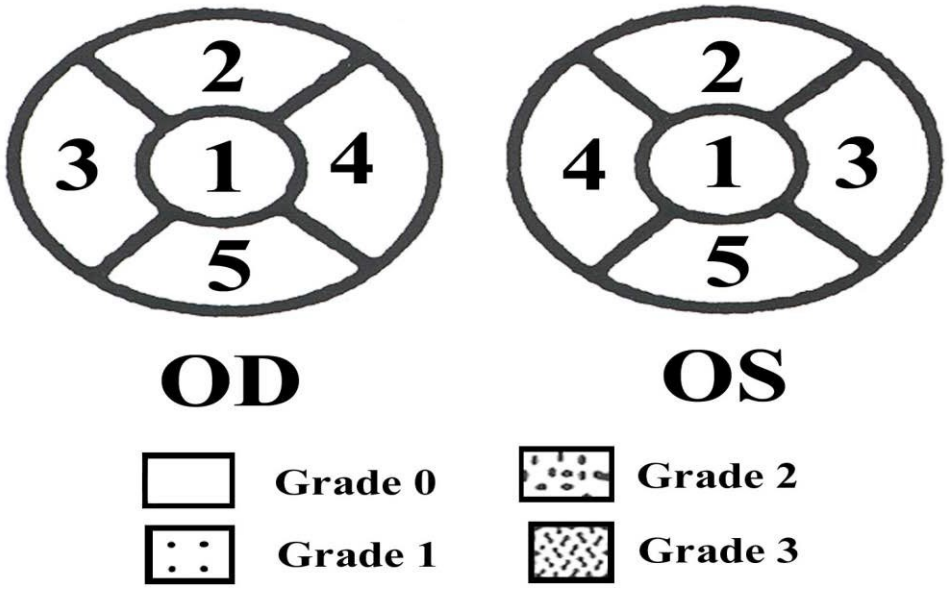
This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

[redacted]

Fluorescein Staining – NEI/Industry Workshop Scale

Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the five areas on each cornea. Grade 0 will be specified when no staining is present. The maximum score is 15.

Score each of 5 areas on the cornea of each eye.



Lissamine Green Staining

The Investigator will instill 10 μL of lissamine green solution into the inferior conjunctival cul-de-sac and wait approximately 30 seconds before evaluating staining. Lissamine may also be applied using lissamine strips. 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. Digital images of lissamine green staining may be taken for digital analysis.

Lissamine Green Staining – NEI/Industry Workshop Scale

The nasal and temporal conjunctivae are divided into three segments as diagrammed. Score each of the six areas of the conjunctiva of each eye.

1 – Temporal

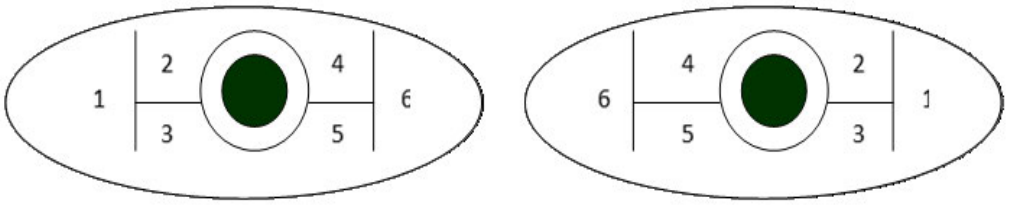
2 – Superior Temporal

3 – Inferior Temporal

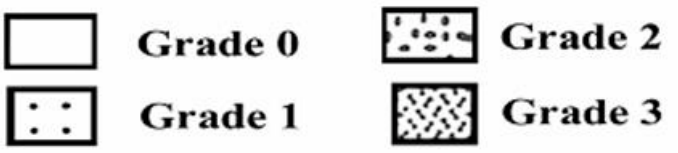
4 – Superior Nasal

5 – Inferior Nasal

6 – Nasal



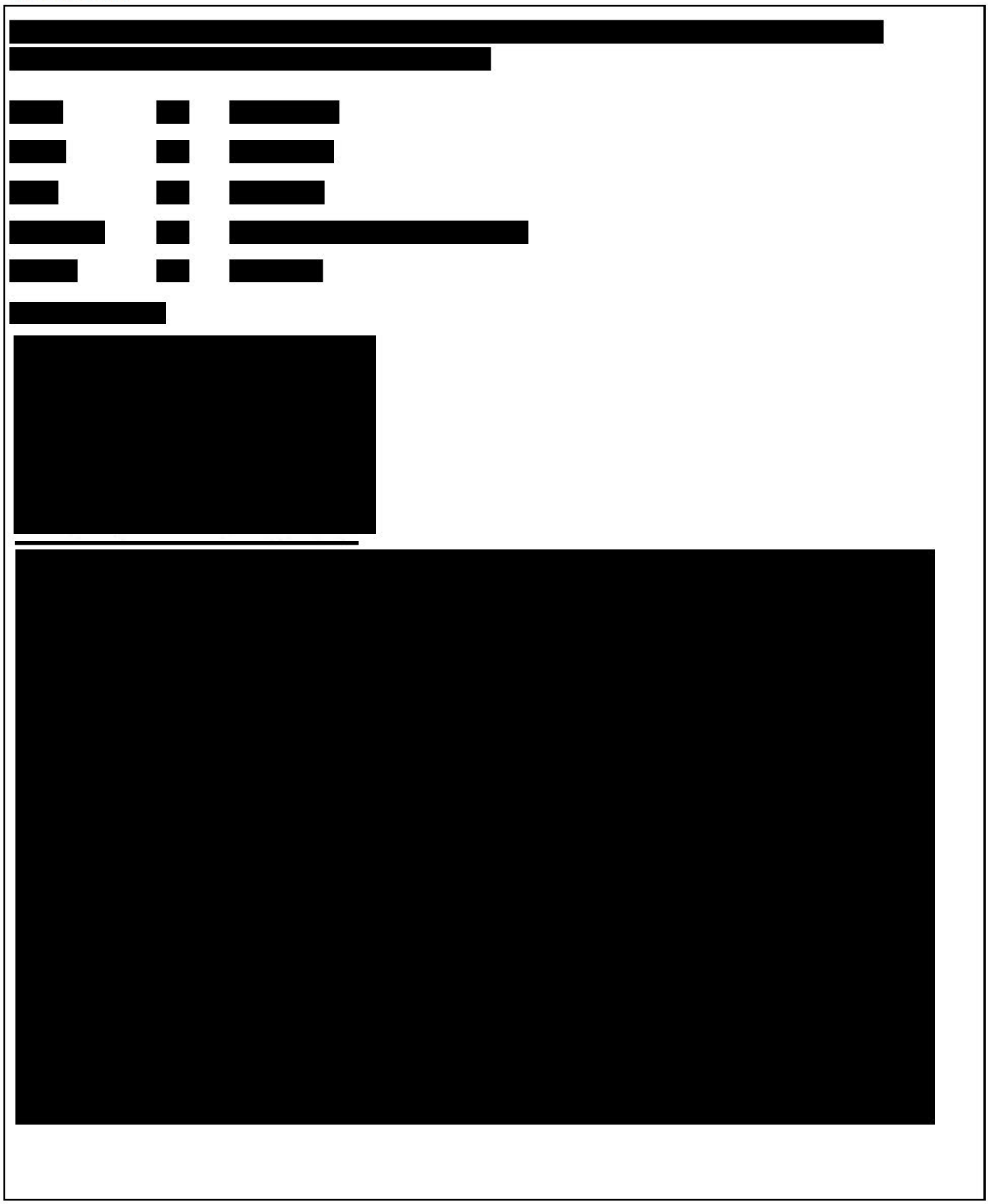
Right Eye **Left Eye**



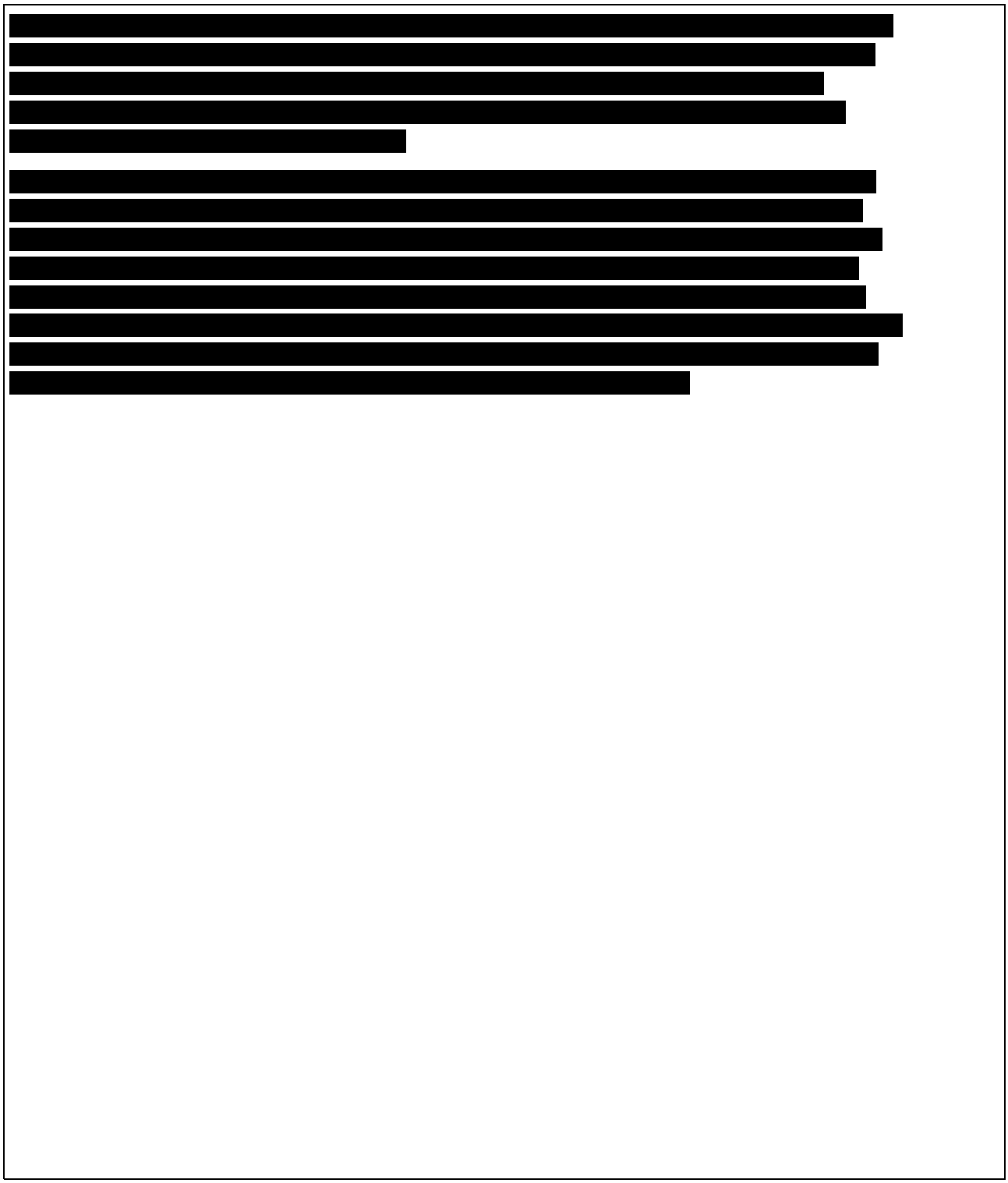
A standardized grading system of 0 - 3 is used for each of the six areas on each conjunctiva. Grade 0 will be specified when no staining is present. The maximum score is 18.

Ora Calibra® Corneal and Conjunctival Staining Scale

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



Ora Calibra® Ocular Protection Index (OPI) 2.0 System



Visual Analogue Scale

Subjects will be asked the following questions regarding ocular discomfort (unrelated to study drug instillation) at all visits. The assessment period will include the previous week as well.

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

Burning/Stinging	0% 50% 100%
Itching	0% 50% 100%
Foreign body sensation	0% 50% 100%
Blurred Vision	0% 50% 100%
Eye Dryness	0% 50% 100%
Photophobia	0% 50% 100%
Pain	0% 50% 100%

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

Procedure for Evaluating Intraocular Pressure

IOP will be measured in each eye by non-contact tonometry by the investigator or qualified technician and the results will be recorded in mmHg.

Investigator's standard technique will be used throughout the study Procedure for Evaluating Corneal Sensitivity

The aesthesiometer (Cochet–Bonnet) is a nylon thread contained in a pen–like case that can be extended specific distances from the tip of the case. The following steps will be followed by the examiner for evaluating corneal sensitivity:

1. Remove Cochet–Bonnet from box
2. Extend the filament to 60 mm (the filament should not have bends in it – if it does, the readings will be incorrect and the filament should not be used)
3. The examiner will inform the subject that a thin delicate plastic filament will be used to test their corneal sensitivity and that they will feel the sensation similar to a strand of hair on their eye. (If the subject is hesitant, a spot on the subject's hand will be cleaned with an alcohol pad and the filament touched to the hand to demonstrate the painless contact)
4. The examiner will instruct the subject to say "Yes" when they feel sensation on their eyeball
5. The examiner will place their free hand on the cheek below the eye being measured to stabilize subject's head position
6. The examiner will position their hand with the device such that the filament is normal (90 degree angle with corneal surface). The device should be between the examiner's index, middle finger, and thumb.
7. The examiner will extend fingers such that the filament applies gentle pressure on the central corneal surface. The examiner will then ask subject if they can perceive the filament touching the central corneal surface.
    a. If the subject responds "Yes", the examiner will ensure the response is valid by performing a sham (not touching the cornea) application and also confirm that response was not due to eyelids touching the filament.
    b. If the subject responds "No", then the filament is shortened the length by 5mm and reapplied to the cornea
    c. If the subject responds "Yes", record length; if the subject responds "No", go to step b.
8. Step 7 is repeated three times.
9. The filament is retracted such that only 10 mm are exposed
10. The tip is wiped with an alcohol pad gently ENSURING that it does NOT bend the filament
11. The alcohol is allowed to dry before reusing device (alcohol can cause corneal abrasions)

Impression Cytology Sampling (OPIA Eyeprim™ Device)

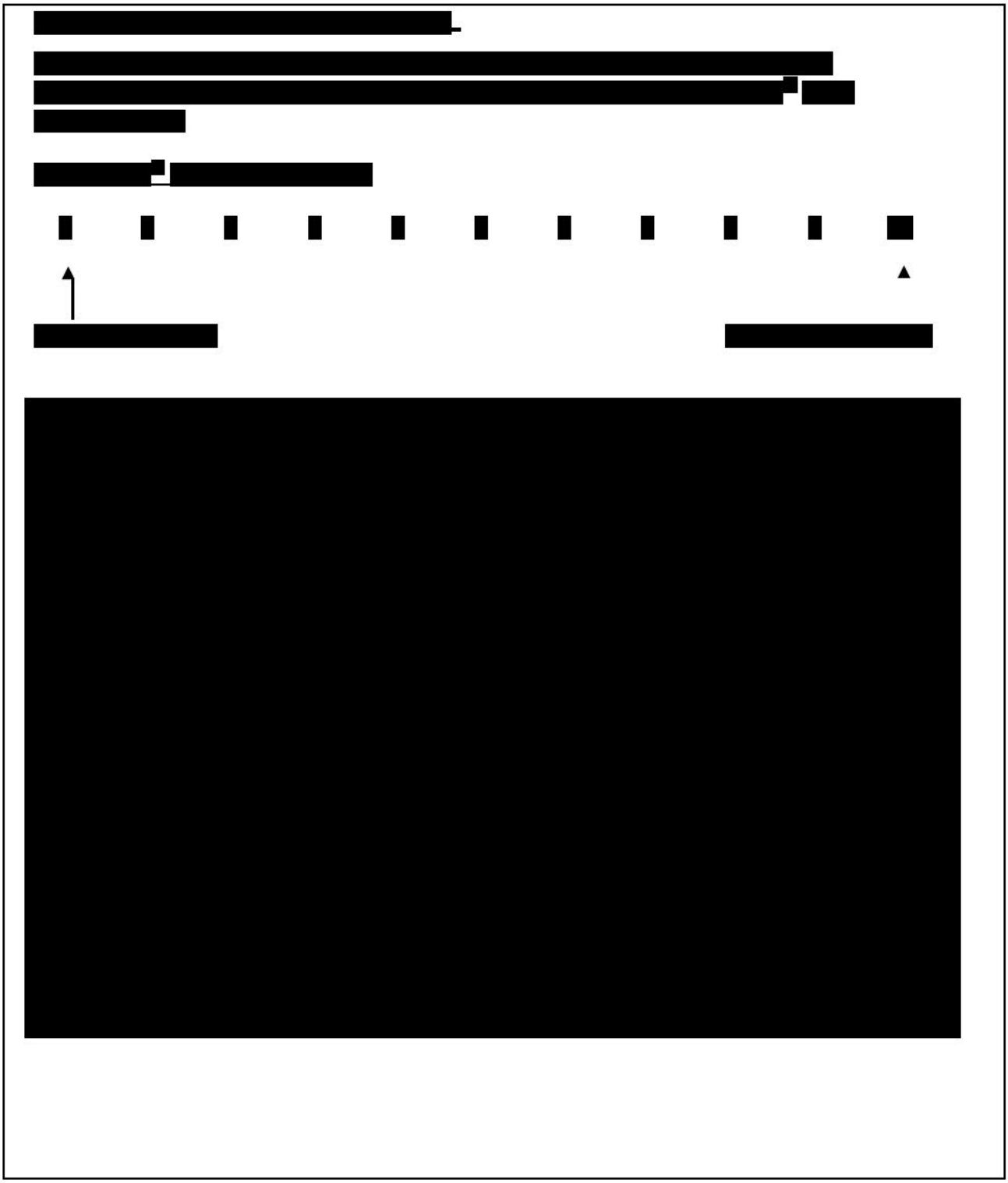
Procedure for Conducting Undilated Fundoscopy

A non-contact undilated fundoscopy exam will be performed. Observations will be graded as Normal or Abnormal. Abnormal findings will be described. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

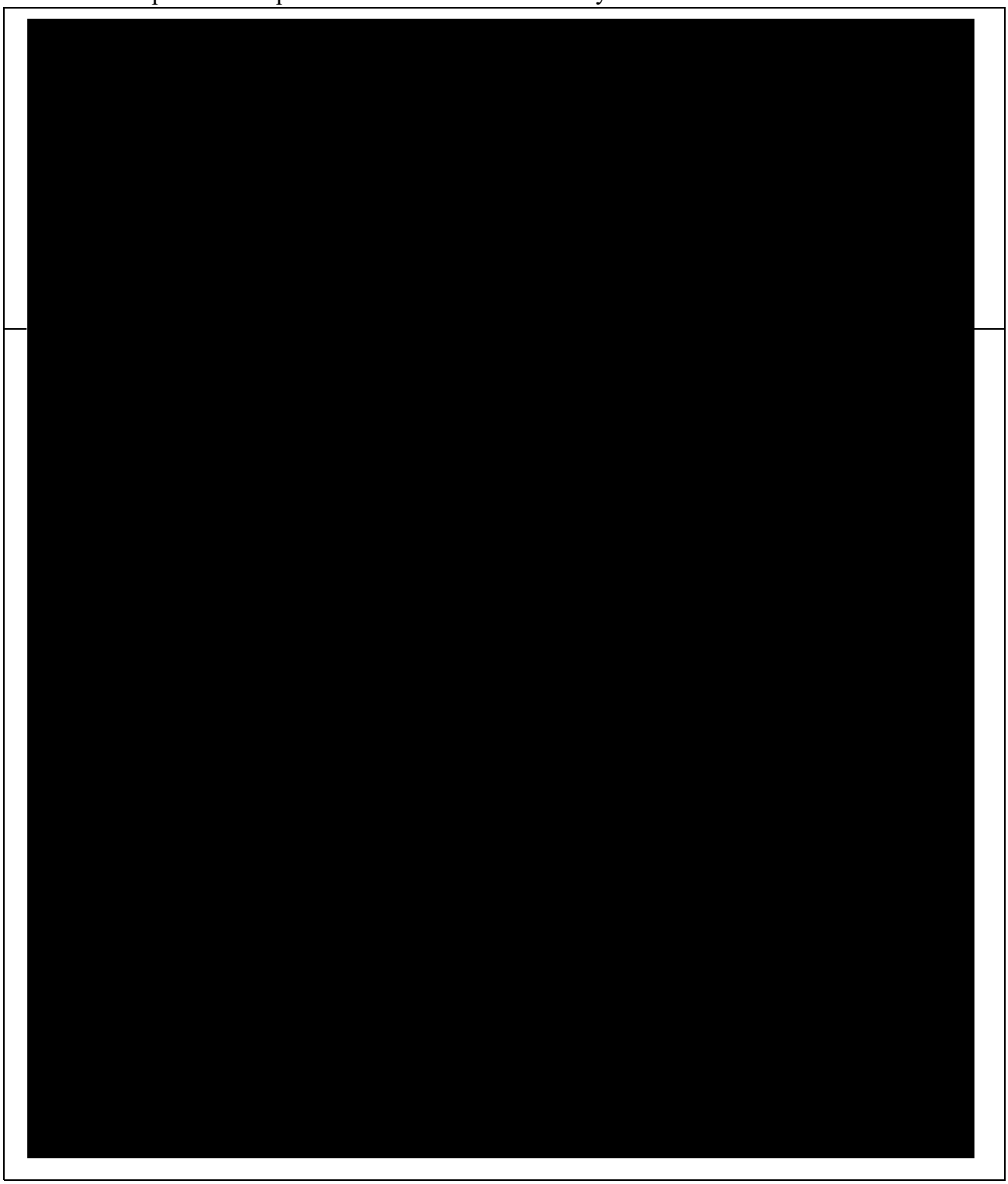
Drop Comfort Assessments

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



At Home Ora Calibra® Drop Comfort Assessment

Subjects will be instructed to dose with study drug TID at home between Visits 7a – 8a and complete the drop comfort assessment for each eye after each dose



Subject Diary

Subjects will be instructed to complete diary TID prior to each dose. Subjects will also indicate if their dose was taken.

Appendix 3: Amendment Summary of Changes

[redacted]

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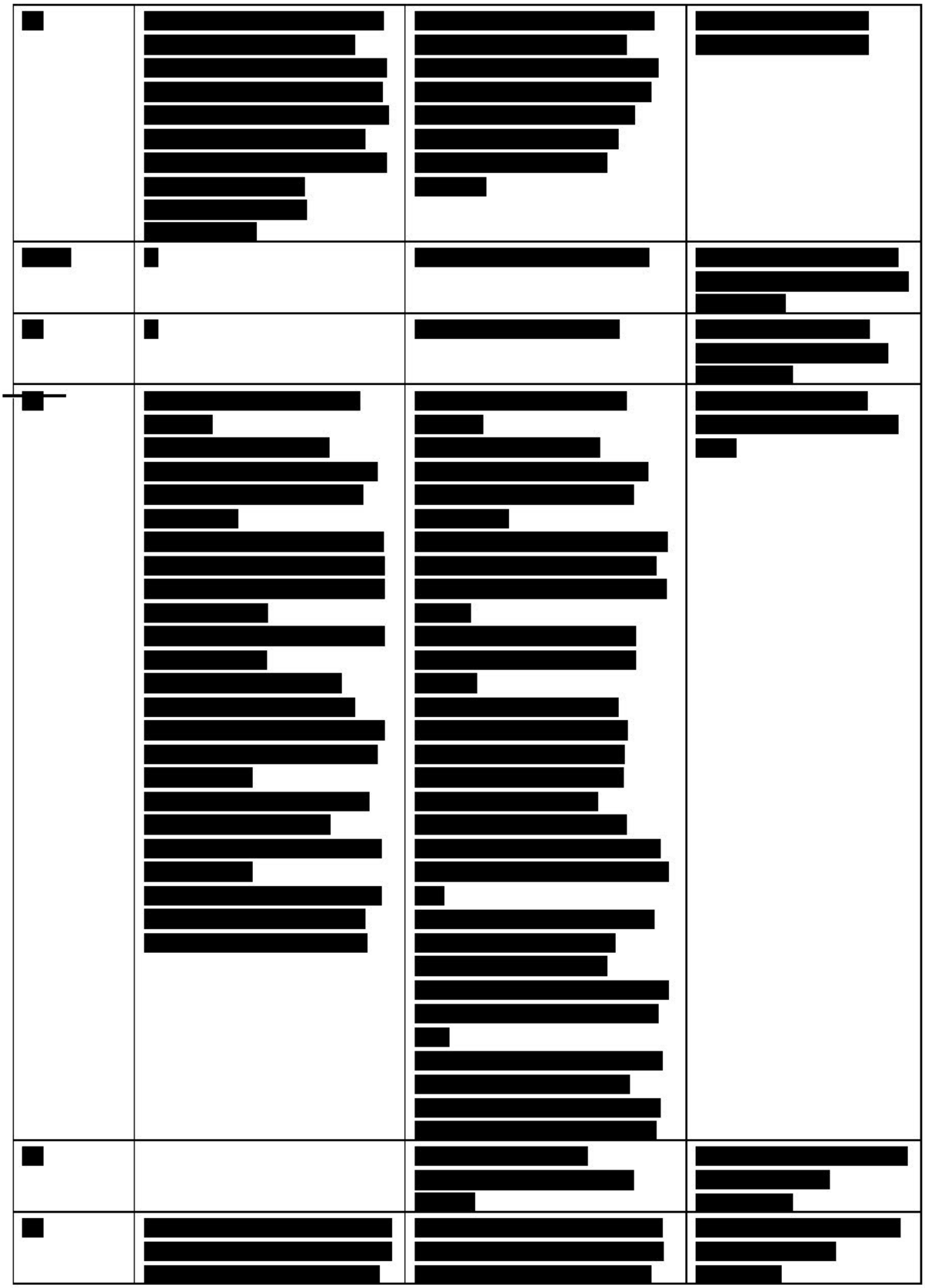

	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	

Appendix 4: Sponsor and Ora Approvals

Protocol Title: A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy ofTOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome

Protocol Number: TOP1630-TV-04

Amendment 1 Date: 20 JAN 2017

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.

Appendix 4: Sponsor and Ora Approvals

Protocol Title: A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy ofTOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome

Protocol Number: TOP1630-TV-04

Amendment 1 Date: 20 JAN 2017

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Appendix 4: Sponsor and Ora Approvals

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Protocol Number: TOP1630-TV-04

Amendment 1 Date: 20 JAN 2017

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.

[redacted]

Appendix 5: Investigator's Signature

Protocol Title: A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of TOP1630 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Syndrome

Protocol Number: TOP1630-TV-04

Amendment 1 Date: 20 JAN 2017

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.