CLINICAL TRIAL PROTOCOL

Protocol Title:	A Phase 2, Multi-center, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of YP-P10 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
Protocol Number:	YPP10-001
Study Phase:	2
Investigational Product Name:	YP-P10 Ophthalmic Solution
IND Number:	147759
Indication:	Dry Eye Disease
Investigators:	Gail Torkildsen, MD Andover Eye Associates 138 Haverhill Street, Suite 104 Andover, MA 01810
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Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810 USA
IRB/IEC:	Alpha IRB
Protocol:	Original Protocol: 03 March 2022 Version 2.0: 09 Jun 2022 Version 3.0: 07 October 2022 Version 4.0: 20 October 2022 Version 5.0: 03 March 2023

Confidentiality Statement

SPONSOR PERSONNEL

Senior VP, Research & Development:	[redacted]
Chief Scientific Officer:	[redacted]

ORA PERSONNEL

Department Senior Vice President:	[redacted]
Department Director:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	A Phase 2, Multi-center, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of YP-P10 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
Study Drug:	1) 0.3% YP-P10 Ophthalmic Solution 2) 1% YP-P10 Ophthalmic Solution 3) YP-P10 Placebo Ophthalmic Solution (vehicle)
Study Phase:	2
Study Objective:	The objective of this study is to compare the safety and efficacy of YP-P10 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.
Overall Study Design	
Structure:	Multi-center, randomized, double-masked, placebo-controlled, stratified study
Duration:	Approximately 13 weeks, including a 1-week run-in period and 12 weeks of treatment
Controls:	YP-P10 Placebo Ophthalmic Solution (vehicle)
Dosage/Dose Regimen:	**Screening Run-In Period:** During a [redacted] study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive YP-P10 Placebo Ophthalmic Solution (vehicle) to be administered one drop in each eye, twice daily (BID). **Treatment Period:** Subjects eligible to be randomized (Day 1) will receive one of the following (one drop each eye), BID for 12 weeks (from Visit 2 to Visit 5): [redacted]
Summary of Visit Schedule:	6 visits over the course of approximately 13 weeks • Visit 1 = Day -7 ± 1 day, Controlled Adverse Environment (CAE®) Screening • Visit 2 = Day 1, CAE® Confirmation / Baseline • Visit 3 = Day 15 ± 2 days, 2-week Follow-Up • Visit 4 = Day 29 ± 2 days, 4-week Follow-Up • Visit 5 = Day 57 ± 3 days, 8-week Follow-Up • Visit 6 = Day 85 ± 3 days, 12-week Follow-Up and Study Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, multicenter, stratified, double-masked, and vehicle-controlled study.

Study Population Characteristics	
Number of Subjects:	Approximately [redacted] ([redacted] per treatment arm) subjects will be enrolled. Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and affirmative response to a Japanese lifestyle questionnaire.
Condition/Disease:	Dry Eye Disease (DED)
Inclusion Criteria:	Individuals eligible to participate in this study must meet all of the following criteria: 1. Be at least 18 years of age; 2. Provide written informed consent; 3. Be willing and able to comply with all study procedures; 4. Have a patient-reported history of dry eye for at least 6 months prior to Visit 1; 5. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; 6. Have a best corrected visual acuity (BCVA) of [redacted] logarithm of the minimum angle of resolution (logMAR) or better (Snellen equivalent score of [redacted] or better) in each eye at Visit 1; 7. Have a score of [redacted] for both eyes according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2; 8. Have an unanesthetized Schirmer's Test score of [redacted] and [redacted] in at least one eye at Visits 1 and 2; 9. Have a corneal fluorescein staining score of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one region in one eye at Visits 1 and 2 pre-CAE® and a central score [redacted] in the same eye; 10. Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1 and 2 pre-CAE®; 11. Demonstrate in the same eye(s) a response to the CAE® at Visits 1 and 2 as defined by: a. Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;

	b. Reporting an Ocular Discomfort score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure [redacted] 12. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10 and 11 above; 13. A negative urine pregnancy test if female of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post–menopausal [12 months after last menses]) and must use adequate birth control through the study period. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.).
Exclusion Criteria:	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 1. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, lid margin inflammation, or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; 2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; 3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; 4. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months; 5. Have used Restasis®, Xiidra®, or Cequa®, Eysuvis™ and Tyrvaya™ within 60 days of Visit 1; 6. Have had any ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid surgeries over the study period; 7. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

	8. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for the following medications: a. Antihistamines (including ocular): 72 hours prior to Visit 1 b. Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose is anticipated during the study period c. Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1 d. Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study e. All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1 9. Have an uncontrolled systemic disease; 10. Be a woman who is pregnant, nursing, or planning a pregnancy; 11. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non- childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months); 12. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;

	13. Have a known allergy and/or sensitivity to the test article or its components; 14. 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; 15. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 16. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.
Study Formulations:	• 0.3% YP-P10 Ophthalmic Solution • 1% YP-P10 Ophthalmic Solution • YP-P10 Placebo Ophthalmic Solution (vehicle)
Evaluation Criteria	
Efficacy Measures:	**Primary Efficacy Measures:** The primary efficacy endpoints of the study are: • Total corneal fluorescein staining (sign) of study eye, Day 85 (Week 12) using the [redacted]. • Ocular discomfort (symptom) of both eyes, Day 85 (Week 12) as measured by the [redacted] **Secondary Efficacy Measures:** • Fluorescein staining of the cornea using the [redacted] • Lissamine green staining of the conjunctiva using the [redacted] • Conjunctival redness of each eye • Schirmer's Test of each eye • Tear film break-up time (TFBUT) of each eye • Ocular Surface Disease Index© (OSDI©) • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by visual analog scale (VAS) • Daily compliance diary • Drop comfort
Safety Measures:	• Visual acuity • Slit-lamp evaluation

	• Adverse event query • Intraocular Pressure (IOP) • Dilated fundoscopy

General Statistical Methods and Types of Analyses

Analysis Populations

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes [redacted]
- Per Protocol Population – The per protocol (PP) population includes [redacted]
- Safety Population – The safety population includes [redacted]

Sample Size

This study is expected to enroll [redacted] subjects in each group, for a total of [redacted] randomized subjects. Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and subject's affirmative response to a Japanese lifestyle questionnaire. Approximately [redacted] subjects will be screened to enroll [redacted] randomized subjects. Assuming approximately 10% drop out rate, [redacted] subjects per group are expected to complete the study. The sample size will achieve 80% power to detect a statistically significant standardized treatment effect size of [redacted] between an active dose and placebo at the 2-sided significance level of [redacted] for each primary endpoint.

Primary Efficacy Analyses for the Primary Endpoints

The primary efficacy endpoints, the changes from baseline to visit 6 in the total corneal fluorescein staining and ocular discomfort, will be analyzed with ANOVA model including the two randomization stratification factors and treatment indicator as covariates. The two stratification factors are Visit 2 pre-CAE total corneal fluorescein staining score [redacted] and Visit 2 pre-CAE ocular discomfort score [redacted]. The primary analyses of the primary efficacy endpoints will be performed on ITT population with pre-defined Estimand.

Analyses for Secondary Endpoints

For total corneal fluorescein staining score and ocular discomfort score using the VAS, a mixed-effect model with repeated measures (MMRM) may also be used to obtain the mean scores at each visit and the mean scores of the change from baseline at each post baseline visit. The ITT population with the observed data only will be used in the model. The model will include the fixed effect such as baseline, treatment, visit, interaction between treatment and visit, as well as subject as the random effect.

The secondary efficacy endpoints will be analyzed with the observed data only in the ITT population. Continuous variables will be summarized with mean and confidence intervals by treatment groups and by visits. Mean changes from baseline may also be summarized by treatment groups and visits if appropriate. ANOVA will be used to report p-values for treatment difference. For binary outcome variables, percentage difference and associated confidence intervals will be used to summarize the data. Chi-square test or logistic regression will be considered for reporting p-values.

Safety Variables

All safety analyses will be performed on the Safety Population.

Dosing information for each treatment and each subject will be listed. Discontinuation of treatment will be summarized by treatment received. The primary reason for trial drug discontinuation will also be summarized by treatment received.

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. TEAEs are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be performed for ocular and non-ocular AEs.

Concomitant medications will be coded using the most recent version of WHO-Drug Dictionary and summarized by treatment group.

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, intraocular pressure, and dilated fundoscopy will be summarized by treatment and visit using descriptive statistics. Change or shift from baseline will also be summarized where appropriate. For assessments performed by eye, both eyes will be summarized separately.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BID	Twice Daily
CAE®	Controlled Adverse Environment
CDs	Compact Discs
CFR	Code of Federal Regulations
CRF	Case Report Form
CMP	Collagen Mimetic Peptide
CRO	Contract Research Organization
DED	Dry Eye Disease
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
EDS	Eye Dryness
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCEC	Human Corneal Epithelial Cell
PBMC	Peripheral Blood Mononuclear Cells
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent To Treat
IWRS	Interactive Web Response System
LASIK	Laser In Situ Keratomileusis
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NEI	National Eye Institute
OCT	Optical Coherence Tomography
OD	Right Eye
ODS	Ocular Discomfort Scale
OP	Ocular Pain

OSDI©	Ocular Surface Disease Index
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TFBUT	Tear Film Break-Up time
TEAEs	Treatment-Emergent Adverse Events
TMF	Trial Master File
VA	Visual Acuity
VAS	Visual Analog Scale
WHO	World Health Organization

1.0 INTRODUCTION

Until recently, Dry Eye Disease (DED) has been considered a multifactorial, progressive disorder of the ocular surface resulting from insufficient tear coverage of the cornea and conjunctiva accompanied by ocular surface inflammation.

Patients with DED often experience severe burning and pain. These symptoms are associated with tear film hyperosmolarity and instability, inflammation, and wounding of the corneal epithelium and the collagen substrate (Bowman's layer) upon which it adheres and renews. While the prevalence of DED is difficult to report due to varying definitions and diagnostic criteria, the disease affects an estimated 5+% of the global population (e.g., 385,000,000 people), with some regions of the world reflecting 30+% (Gayton 2009). The incidence of DED increases with age (Bron, et al. 2017). In the United States, it is estimated that as many as 3.2 million women and 1.7 million men over the age of 50 have DED with a project ted 40% increase in number of patients affected by 2030 (Schaumberg, Dana, et al. 2009, Schaumberg, Uchino, et al. 2013). Even so, the age of onset of DED is decreasing, as incidence increases with the widespread and growing use of cell phones and handheld computers and reading devices. Side effects of topical glaucoma medications can also aggravate DED symptoms. This too represents a substantial problem, as the number of glaucoma patients soon will approach 80 million worldwide as the population ages (Quigley and Broman 2006).

While the etiology of DED is diverse, commonality in signs and symptoms is suggestive of common underlying pathophysiological pathways. Current treatment and management of DED consists primarily of tear supplementation with lubricants (artificial tears). While artificial tears improve symptoms associated with DED, they have no effect on resolving the underlying conditions that lead to inflammation of the ocular surface. Three currently available options for treating inflammation at the ocular surface are Restasis® (cyclosporine ophthalmic emulsion), Cequa® (nanomicellar solution of cyclosporine), and Xiidra® (lifitegrast ophthalmic solution). It has been shown that only 15% of patients respond to Restasis® after 6 months of treatment, as measured by Schirmer's test, and many more report ocular side-effects such as burning and stinging (Mah, et al. 2012). Cequa® and Xiidra® have also been shown to be associated with ocular adverse events; in clinical studies of Cequa® and Xiidra® for subjects with DED, subjects reported increased ocular irritation upon instillation with Cequa® and Xiidra® compared to placebo (24.2% compared to 4.3% in the placebo group for Cequa® and 7.8% compared to 1.4% in the placebo group for Xiidra®) (Tauber, et al. 2015, Mandal, et al. 2019). Two recently approved options, EYSUVIS™ (loteprednol etabonate ophthalmic suspension) and TYRVAYA™ (varenicline solution nasal spray) have become available options for DED. As a topical steroid, EYSUVIS™ has a limited label short-term use for up to two weeks (Korenfeld, et al. 2021). TYRVAYA™ produces tear production as a result of the nasal spray triggering trigeminal nerve tear production (Wirta, et al. 2021). As such, EYSUVIS™ and TYRVAYA™ are either limited in use or do not address the inflammatory processes of dry eye disease. Thus, there remains a medical need for more efficacious treatment options with a favorable safety and comfort profile for patients with DED.

Yuyu Pharma, Inc is developing YP-P10 Peptide, a synthetic peptide with anti-inflammatory and wound healing properties, to treat the signs and symptoms of DED. In proof-of-concept preclinical efficacy studies, YP-P10 Peptide consistently and significantly improved corneal damage induced by dry eye conditions in mouse and rat models. This improvement was more efficacious and potent than approved dry eye drugs (e.g., Xiidra®, Restasis®). Findings from non-clinical studies also suggest that improvement in corneal damage in dry eye conditions is related to YP-P10 Peptide's anti-inflammatory properties due to observed reduction in cytokines and proinflammatory chemokines in tears from the dry eye rat model, Human Corneal Epithelial Cells (HCECs), and Human Peripheral Blood Mononuclear Cells (PBMCs) cellular studies.

2.0 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of YP-P10 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

3.0 CLINICAL HYPOTHESIS

The clinical hypothesis for this study is that 0.3% YP-P10 Ophthalmic Solution twice daily (BID) and 1.0% YP-P10 Ophthalmic Solution BID are superior to YP-P10 Placebo Ophthalmic Solution (vehicle) for the primary endpoints of signs and symptoms of dry eye, as follows:

- Sign: Total corneal fluorescein staining score of the study eye using the [redacted] measured by mean change from baseline (Visit 2, Pre- Controlled Adverse Environment [CAE®]) to Visit 6
- Symptom: Ocular discomfort score of both eyes using the [redacted] measured by mean change from baseline (Visit 2, Pre-CAE®) to Visit 6

4.0 OVERALL STUDY DESIGN

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

- 0.3% YP-P10 Ophthalmic Solution: 1 drop BID in each eye (N = [redacted])
- 1% YP-P10 Ophthalmic Solution: 1 drop BID in each eye (N = [redacted])
- YP-P10 Placebo Ophthalmic Solution (vehicle): 1 drop BID in each eye (N = [redacted])

Approximately [redacted] subjects will be randomly assigned to one of the three groups [redacted] to receive either YP-P10 Ophthalmic Solution or placebo solution as topical ophthalmic drops administered bilaterally BID for 12 weeks. Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and affirmative response to a Japanese lifestyle questionnaire. Inclusion of Japanese subjects will only be applicable at one site (Aesthetic Eye Care Institute, CA). Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment.

During the 7-day study run-in period prior to randomization, all subjects will receive YP-P10 Placebo Ophthalmic Solution (vehicle) in each eye BID.

During the screening period, two 90-minute exposures to the CAE® will be conducted to ascertain eligibility to enter the study at Visit 1 (Day -7 ± 1 day) and Visit 2 (Day 1). Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle BID for approximately 7 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double- masked fashion for 12 weeks. Subjects will self-administer drops BID and will complete daily diary assessments as instructed.

The CAE® exposure will occur at Visit 1 (Day -7 ± 1 day) and Visit 2 (Day 1); with Pre-CAE®, during CAE® and Post-CAE® assessments of ocular signs and symptoms.

Study drug will be discontinued at Visit 6. Subjects will exit from the study at this visit.

The total number of expected participants, including screen failures, is approximately [redacted] subjects.

A study design flow chart is provided below:

Visit 1 **(Day -7 ± 1 day):** **CAE® Screening**	**Pre-CAE®** • Informed Consent/Health Insurance Portability and Accountability Act (HIPAA) • Demographic Data and Medical/Medication/Ocular History • Review of Family Tree, Government-approved ID (e.g., Birth Certificate), and Japanese Lifestyle Questionnaire (Japanese subgroup only) • Review of Inclusion/Exclusion Criteria • Adverse Event Query • Urine Pregnancy Testing (for females of childbearing potential) • Ora Calibra® Ocular Discomfort Scale & 4 Symptom Questionnaire • Ocular Surface Disease Index (OSDI©) Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (Early Treatment Diabetic Retinopathy Study [ETDRS]) • Slit Lamp Biomicroscopy • Ora Calibra® Conjunctival Redness Scale • TFBUT • [redacted] Fluorescein Staining • Lissamine Green Staining

	• Sodium Fluorescein Staining based on Ora Calibra® Grading Scale • Schirmer's Test **Screening Challenge (CAE® #1)** • Subjects meeting all of the above evaluation (Pre–CAE® #1) criteria will undergo further screening evaluation in the CAE®. Subjects will be exposed to the CAE® for 90 minutes. Ocular Discomfort Scale (ODS) self-assessment scores will be obtained just prior to entering (at 0 min), during and just after the CAE® exposure (at 90 min). During the CAE® exposure, ODS scores will be collected at time 0 and every 5 minutes thereafter throughout the 90 minutes. **Post–CAE®** • Slit Lamp Biomicroscopy • Ora Calibra® Conjunctival Redness Scale • TFBUT • Sodium Fluorescein Staining based on Ora Calibra® Grading Scale • Intraocular Pressure (IOP) • Dilated Fundoscopy • Review of Inclusion/Exclusion Criteria • Study Drug Instillation at the Study Site • Placebo Dispensation • Monitoring and Query of AEs • Schedule Next Visit

↓

Placebo Run-in Period (~7 days)

↓

Visit 2 **(Day 1):** **CAE® Confirmation/Baseline**	**Pre-CAE®** • Study Diary/Run-in Collection • Medical and Medication History Update • Review of Inclusion/Exclusion Criteria • AE query • Ora Calibra® Ocular Discomfort Scale & 4 Symptom Questionnaire • OSDI© Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (ETDRS) • Slit Lamp Biomicroscopy

	• Ora Calibra® Conjunctival Redness Scale • TFBUT • [redacted] Fluorescein Staining • [redacted] Lissamine Green Staining • Sodium Fluorescein Staining based on Ora Calibra® Grading Scale • Schirmer's Test **<u>Confirmatory Screening Challenge (CAE® #2)</u>** • Subjects will be exposed to the CAE® for 90 minutes. Ocular discomfort self– assessment scores (ODS) will be obtained just prior to entering (at 0 min), during and just after the CAE® exposure (at 90 min). During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 minutes. **Post–CAE®** • Slit Lamp Biomicroscopy • Ora Calibra® Conjunctival Redness Scale • TFBUT • Sodium Fluorescein Staining based on Ora Calibra® Grading Scale • Review of Inclusion/Exclusion Criteria • Randomization • Study Drug Instillation at the Study Site • Drop Comfort Assessment • Monitoring and Query of AEs • Study Drug Diary/Study Drug Dispensation • Subjects will be scheduled for Visit 3
Visit 3 **(Day 15 ± 2 days):** **2-week Follow-up**	• Study Diary/Study Drug Collection • Medical / Medication History Update • Review of Inclusion/Exclusion Criteria • AE query • OSDI© Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (ETDRS) • Ora Calibra® Conjunctival Redness Scale • Slit Lamp Biomicroscopy • TFBUT • [redacted] Fluorescein Staining • [redacted] Lissamine Green Staining

	• At least 15-minute wait between lissamine green staining and Schirmer's test • Schirmer's test • Study Drug Diary/Study Drug Dispensation • Study Drug Instillation at the Study Site • Subjects will be scheduled for Visit 4
Visit 4 **(Day 29 ± 2 days):** **4-week Follow-up**	• Study Diary/Study Drug Collection • Medical and Medication History Update • Review of Inclusion/Exclusion Criteria • AE query • OSDI© Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (ETDRS) • Ora Calibra® Conjunctival Redness Scale • Slit Lamp Biomicroscopy • TFBUT • [redacted] Fluorescein Staining • [redacted] Lissamine Green Staining • At least 15-minute wait between lissamine green staining and Schirmer's test • Schirmer's test • Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 4 (Day 29 ± 2 days), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5 • Study Drug Instillation at the Study Site • Subjects will be scheduled for Visit 5
Visit 5 **(Day 57 ± 3 days):** **8-week Follow-up**	• Study Diary/Study Drug Collection • Medical and Medication History Update • Review of Inclusion/Exclusion Criteria • AE query • OSDI© Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (ETDRS)

	• Ora Calibra® Conjunctival Redness Scale • Slit Lamp Biomicroscopy • TFBUT • [redacted] Fluorescein Staining • Lissamine Green Staining • At least 15-minute wait between lissamine green staining and Schirmer's test • Schirmer's test • Study Drug Diary/Study Drug Dispensation • Study Drug Instillation at the Study Site • Subjects will be scheduled for Visit 6
Visit 6 **(Day 85 ± 3 days):** **12-Week Follow Up and Study Exit**	• Study Diary/Study Drug Collection • Medical and Medication History Update • Review of Inclusion/Exclusion Criteria • Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study • AE query • OSDI© Questionnaire • Ocular Discomfort as measured by [redacted] • Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted] • Visual Acuity (ETDRS) • Ora Calibra® Conjunctival Redness Scale • Slit Lamp Biomicroscopy • TFBUT • [redacted] Fluorescein Staining • Lissamine Green Staining • At least 15-minute wait between lissamine green staining and Schirmer's test • Schirmer's test • IOP • Dilated Fundoscopy • Study Exit

5.0 STUDY POPULATION

5.1 Number of Subjects (Approximate)

It is estimated that approximately [redacted] subjects will be screened to enroll approximately [redacted] randomized subjects ([redacted] in each group). Subjects will be randomized in each treatment arm. Subjects will be randomized in a [redacted] ratio of

- 0.3% YP-P10 Ophthalmic Solution
- 1% YP-P10 Ophthalmic Solution
- YP-P10 Placebo Ophthalmic Solution (vehicle)

Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and affirmative response to a Japanese lifestyle questionnaire.

5.2 Study Population Characteristics

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

5.3 Inclusion Criteria

Each subject must:

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

a. Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure;

b. Reporting an Ocular Discomfort score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure ([redacted]

12. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10 and 11 above;

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

5.4 Exclusion Criteria

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

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

2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;

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

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

5. Have used Restasis®, Xiidra®, or Cequa®, Eysuvis™ and Tyrvaya™ within 60 days of Visit 1;

6. Have had any ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid surgeries over the study period;

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

8. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); the respective wash-out periods are required for the following medications:

    a. Antihistamines (including ocular): 72 hours prior to Visit 1

b. Oral aspirin or aspirin–containing products allowed if dose has been stable over past 30 days prior to Visit 1 and no change in dose is anticipated during the study period

c. Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1

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

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

9. Have an uncontrolled systemic disease;

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

11. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);

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

13. Have a known allergy and/or sensitivity to the test article or its components;

14. 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;

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

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

5.5 Withdrawal Criteria (If Applicable)

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

Subjects may withdraw consent from the study at any time.

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

If a subject discontinues participation in the study early, every attempt will be made to complete the exit procedures required at the final study visit (Visit 6).

6.0 STUDY PARAMETERS

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint (sign) is:

- Total corneal fluorescein staining score of the study eye using the [redacted], measured by mean change from baseline (Visit 2 pre-CAE®) to Day 85 (Visit 6).

The primary efficacy endpoint (symptom) is:

- Ocular discomfort score of both eyes using the [redacted], measured by mean change from baseline (Visit 2 pre-CAE®) to Day 85 (Visit 6).

6.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Fluorescein staining of the cornea using the modified NEI scale by region: central, superior, inferior, temporal, nasal, and corneal sum of each eye
- Lissamine green staining of the conjunctiva using the modified NEI scale by region: inferior temporal, superior temporal, temporal, inferior nasal, superior nasal, nasal, and conjunctival sum of each eye
- Conjunctival redness of each eye
- Schirmer's Test of each eye
- TFBUT of each eye
- OSDI©
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Daily compliance diary
- Drop comfort

6.1.3 Exploratory Efficacy Endpoints

There are no exploratory efficacy endpoints planned.

6.2 Safety Endpoints

The safety endpoints being evaluated are:

- Visual acuity
- Slit-lamp evaluation
- Adverse event
- Intraocular Pressure
- Dilated fundoscopy

7.0 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Study Drug Formulation

All arms will be double-masked. Subjects will be randomized [redacted] into:

- 0.3% YP-P10 Ophthalmic Solution; BID
- 1% YP-P10 Ophthalmic Solution; BID
- YP-P10 Placebo Ophthalmic Solution (Vehicle); BID

YP-P10 Ophthalmic Solution will be formulated as a sterile solution at [redacted] for topical ophthalmic administration and is intended for clinical use. The study drug will be supplied in blow-fill seal ampoules, which allow for product administration directly to the eye. Each ampoule will contain a nominal volume of [redacted].

The excipients which will be used to manufacture YP-P10 Ophthalmic Solution will be standard excipients for use in ophthalmic solutions that comply with their respective USP / EP monographs.

The placebo for YP-P10 Ophthalmic Solution contains all the same excipients used in the active formulation without the peptide.

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

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

7.1.3 Instructions for Use and Administration

- Subjects will receive YP-P10 Placebo Ophthalmic Solution (vehicle) at Visit 1, and assigned study drug kit at Visits 2, 3, 4, and 5.
- Subjects who are randomized must administer study drug in each eye BID. At Visits 2, 3, 4, and 5, subjects will self-administer one dose of study drug in office.
- Subjects should withhold their study drug dose on the morning of all study visits. The subject will take the study drug dose in clinic on the day of their visit.

7.2 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

7.2.1 Labeling/Packaging

Investigational product (IP) will be packaged and labeled into clinical kits. The primary packaging of the YP-P10 Ophthalmic Solution will be blow-fill-seal ampules with a fill volume of [redacted]. The secondary packaging is a foil pouch that contains three ampules in each pouch.

<u>Screening Run-in Period</u>

For the run-in period, 6 pouches of 3 ampoules will be packaged in a 1-week clinical kit. Each subject will receive 1 kit.

Treatment Period

BID Dosing: For the treatment period, 12 pouches of 3 ampoules will be packaged in a 2-week clinical kit. Each subject will receive 6 kits total, with each subject receiving 1 kit per visit on Visit 2 (Day 1) and Visit 3 (Day 15) and 2 kits per visit at Visit 4 (Visit 29) and Visit 5 (Day 57).

7.2.2 Storage of Investigational Product

Ampoules must be stored at 15 - 25°C until the day of use. Any material remaining in the ampoule after use should be discarded. YP-P10 Ophthalmic Solution should be kept out of reach of children. Drug administration instructions and discarding information will be provided with each study.

7.2.3 Accountability of Investigational Product

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

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

7.2.4 Return or Disposal of Investigational Product

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

7.3 Other Study Supplies

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

8.0 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

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

8.1.2 Informed Consent

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

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria (Section 5.4)

8.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion and none of the exclusion criteria (Section 5.3 and 5.4).

8.1.5 Methods for Assignment to Treatment Groups:

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

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS. Subjects will be stratified by the following sign and symptom:

- Total corneal fluorescein staining score of the study eye ([redacted]) at Visit 2, pre-CAE [redacted]
- Ocular discomfort score using the [redacted] at Visit 2, pre-CAE [redacted]

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

8.2 Concurrent Therapies

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

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

8.2.1 Prohibited Medications/Treatments

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

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

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

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

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

8.3.2 Visit 1: Day –7 ± 1 – CAE® Screening

All subjects will undergo the following screening assessments:

Pre–CAE®

- Informed Consent/HIPAA
- Demographic Data and Medical/Medication/Ocular History
- Review of Family Tree, Government-approved ID (e.g., Birth Certificate), and Japanese Lifestyle Questionnaire (Japanese subgroup only)
- Review of Inclusion/Exclusion Criteria
- Adverse Event Query
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study. Females of childbearing potential include all females who have experienced menarche and have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
- Ora Calibra® Ocular Discomfort Scale & 4 Symptom Questionnaire
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness Scale
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- Sodium Fluorescein Staining based on Ora Calibra® Grading Scale
- Schirmer's Test

Screening Challenge (CAE® #1)

Subjects meeting all of the above evaluation (Pre–CAE® #1) criteria will undergo further screening evaluation in the CAE®. Subjects will be exposed to the CAE® for 90 minutes. Ocular Discomfort Scale (ODS) self-assessment scores will be obtained just prior to entering (at 0 min), during and just after the CAE® exposure (at 90 min). During the CAE® exposure, ODS scores will be collected at time 0 and every 5 minutes thereafter throughout the 90 minutes.

Post–CAE®

- Slit Lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness Scale
- TFBUT
- Sodium Fluorescein Staining based on Ora Calibra® Grading Scale
- IOP
- Dilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
- Study Drug Instillation at the Study Site: All subjects meeting all screening eligibility criteria after Visit 1 will be dispensed Placebo Run-in. Subjects will self- administer their initial study drug dose bilaterally at the study site.
- Placebo Dispensation. Prior to discharge from the study site on Day –7, subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated in self– administration of placebo. Subjects will be instructed to self–administer one drop BID in each eye until screening Visit 2. Subjects will be instructed NOT to instill study drug on the morning of their next scheduled study visit (Visit 2, Day 1).
- Monitoring and Query of AEs
- Schedule Next Visit: Subjects will be scheduled for Visit 2.

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

Pre–CAE®

- Study Diary/Run-in Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- AE query
- Ora Calibra® Ocular Discomfort Scale & 4 Symptom Questionnaire
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness Scale
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- Sodium Fluorescein Staining based on Ora Calibra® Grading Scale

- Schirmer's Test

Confirmatory Screening Challenge (CAE® #2)

Subjects will be exposed to the CAE® for 90 minutes. Ocular discomfort self–assessment scores (ODS) will be obtained just prior to entering (at 0 min), during and just after the CAE® exposure (at 90 min). During the CAE® exposure, ODS will be collected at time 0 and every 5 minutes thereafter throughout the 90 minutes.

Post–CAE®

- Slit Lamp Biomicroscopy
- Ora Calibra® Conjunctival Redness Scale
- TFBUT
- Sodium Fluorescein Staining based on Ora Calibra® Grading Scale
- Review of Inclusion/Exclusion Criteria
- Randomization
- Study Drug Instillation at the Study Site: All subjects having a positive response and meeting all other screening eligibility criteria at the end of Visit 2 will be randomized to one of the three treatment groups utilizing the IWRS system. Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician
- Drop Comfort Assessment: A drop comfort evaluation will be performed immediately upon administration of study drug and then at 1, 2, and 3 minutes following initial dosing using the Ora Calibra Drop Comfort Scale.
- Monitoring and Query of AEs
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3
- Subjects will be scheduled for Visit 3

8.3.4 Visit 3: Day 15 ± 2 days, 2-week Follow-up

- Study Diary/Study Drug Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- AE query
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)

- Ora Calibra® Conjunctival Redness Scale
- Slit Lamp Biomicroscopy
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 3 (Day 15 ± 2 days), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 4
- Study Drug Instillation at the Study Site
- Subjects will be scheduled for Visit 4

8.3.5 Visit 4: Day 29 ± 2 days, 4-week Follow-up

- Study Diary/Study Drug Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- AE query
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)
- Ora Calibra® Conjunctival Redness Scale
- Slit Lamp Biomicroscopy
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 4 (Day 29 ± 2 days), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 5

- Study Drug Instillation at the Study Site
- Subjects will be scheduled for Visit 5

8.3.6 Visit 5: Day 57 ± 3 days, 8-week Follow-up

- Study Diary/Study Drug Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- AE query
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)
- Ora Calibra® Conjunctival Redness Scale
- Slit Lamp Biomicroscopy
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 5 (Day 57 ± 3 days), randomized subjects will be educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 6
- Study Drug Instillation at the Study Site
- Subjects will be scheduled for Visit 6

8.3.7 Visit 6: Day 85 ± 3 days, 12-week Follow-up and Study Exit

- Study Diary/Study Drug Collection
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study
- AE query
- OSDI© Questionnaire
- Ocular Discomfort as measured by [redacted]

- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by [redacted]
- Visual Acuity (ETDRS)
- Ora Calibra® Conjunctival Redness Scale
- Slit Lamp Biomicroscopy
- TFBUT
- [redacted] Scale Fluorescein Staining
- [redacted] Scale Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- IOP
- Dilated Fundoscopy
- Study Exit

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 1: Schedule of Visits and Measurements for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

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

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit-lamp Biomicroscopy
- Visual Acuity
- IOP
- Urine Pregnancy Test
- Dilated Fundoscopy
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator

8.5 Compliance with Protocol

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visits 1 through 6 and given written instructions. To assess dosing and symptom assessment compliance, the subject daily diaries will be collected at Visits 1 through 6, and the subject's used and unused study drug ampules will be collected at Visit 3 through 6. Dosing compliance will be based on the used and unused ampule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded.

Subjects will be reinstructed on dosing compliance and this will be documented in the source documents. These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

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

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

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

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

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

All subjects will be encouraged to remain in the study and provide safety and efficacy outcomes after the advent of intercurrent events including treatment discontinuation and receipt of additional prohibited medications. Any subject who discontinues due to an intercurrent event may remain enrolled in the study if agreed by the subject and principal investigator, and continue to participate in all subsequent visits for safety and efficacy assessments.

8.7 Study Termination

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

8.8 Study Duration

An individual subject's participation will involve 6 visits over approximately a 92-day period (7 days pre-screening, 85 days of treatment).

8.9 Monitoring and Quality Assurance

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

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

9.0 ADVERSE EVENTS

9.1 Adverse Event (AE)

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

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the case report form (CRF). Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Treatment emergent adverse events (TEAE) are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

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

9.1.1 Severity

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

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

9.1.2 Relationship to Investigational Product

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

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

9.1.3 Expectedness

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

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

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

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

9.2 Serious Adverse Events

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

- Death;
- Is life-threatening;

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

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

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

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

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

9.3 Procedures for Reporting Serious Adverse Events

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

9.3.1 Reporting a Serious Unexpected Suspected Adverse Reaction

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

9.3.2 Reporting a Serious Adverse Event

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

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

Contact information for reporting SAEs:

Name:	[redacted]
Title:	[redacted]
Office Telephone:	[redacted]
Office Facsimile:	[redacted]

9.4 Procedures for Unmasking (If Applicable)

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment group has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and the study Sponsor should be notified before unmasking study drug. Ora and the study Sponsor must be informed immediately about any unmasking event.

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

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

9.5 Type and Duration of the Follow-Up of Subjects After Adverse Events

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

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

10.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSIS

10.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes [redacted]
- Per Protocol Population – The per protocol (PP) population includes [redacted]

- Safety Population – The safety population includes [redacted]

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

10.2 The Primary Endpoints

The primary efficacy endpoint (sign) is:

- Total corneal fluorescein staining score of the study eye using the [redacted], measured by mean change from baseline (Visit 2 pre-CAE®) to Day 85 (Visit 6).

The primary efficacy endpoint (symptom) is:

- Ocular discomfort score of both eyes using the [redacted], measured by mean change from baseline (Visit 2 pre-CAE®) to Day 85 (Visit 6).

10.3 Estimand Definition for the Primary Endpoints

Estimand 1 describes strategies of handling intercurrent events that potentially occur during the trial conduct for the primary analyses of the primary endpoints. The proposed strategies will potentially provide relatively conservative treatment effect based on the assumptions associated with each intercurrent event.

- [redacted]

Estimand 2 for sensitivity analyses:

- [redacted]

- [redacted]
- [redacted]
- [redacted]

10.4 Statistical Hypotheses for the Primary Endpoints

The null and alternative hypotheses for the two primary endpoints and two doses of YP-P10 Ophthalmic Solution are:

[redacted]

10.5 Secondary Endpoints

The definition of the secondary endpoints can be found in Section 6.1.2.

10.6 Sample Size

This study is expected to enroll [redacted] subjects in each group, for a total of [redacted] randomized subjects. Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and subject's affirmative response to a Japanese lifestyle questionnaire. Approximately [redacted] subjects will be screened to enroll [redacted] randomized subjects. Assuming approximately 10% drop out rate, [redacted] subjects per group are expected to complete the study. The sample size will achieve 80% power to detect a statistically significant standardized treatment effect size of [redacted] between an active dose and placebo at the 2-sided significance level of [redacted] for each primary endpoint.

10.7 Statistical Analysis

10.7.1 General Considerations

Quantitative variables will be summarized descriptively using [redacted] Qualitative variables will be summarized using [redacted]

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

For the purpose of summarization, medical history and AEs will be coded to Medical Dictionary for Regulatory Authorities (MedDRA), as appropriate.

Baseline measures are defined as [redacted] Change from baseline will be calculated as [redacted] Treatment comparisons between active and vehicle will be calculated as [redacted]

10.7.2 Unit of Analysis

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

- Study Eye: [redacted]

10.7.3 Missing Data

Effort will be made to minimize the missing data when possible, for all endpoints.

For the primary endpoints, missing patterns and reasons will be examined. If the missing is considered missing-at-random, the data will be imputed by treatment group based on Markov Chain Monte Carlo (MCMC) in the ITT population. If the missing is missing-not-at-random due to intercurrent events, the imputation methods are defined in the estimands Section 10.3. In addition, tipping approach will be used to evaluate the impact of the missing values on the treatment effect.

For the secondary endpoints, missing data will not be imputed.

10.8 Multiplicity Consideration

Hierarchical fixed sequence testing procedure will be used to maintain the study-wise 2-sided type I error rate of [redacted] for testing multiple primary endpoints and multiple doses. The hierarchical order is specified as the following (Figure 1):

Figure 1 Testing Sequence of the Primary Endpoints:

Any test in the hierarch order fails to show statistical significance, the test results below the hierarchical order will not be claimed in this study. The claim of indication will be based on the totality evidence across all doses and from all studies.

The tests for the secondary endpoints are considered exploratory in this study. The totality of evidence across doses and from future studies will be considered for any future claim of the secondary endpoints.

10.9 Efficacy Analyses

10.9.1 Primary Analyses of the Primary Efficacy Endpoints

The primary efficacy endpoints, the changes from baseline to Day 85 (Visit 6) in the total corneal fluorescein staining and ocular discomfort, will be analyzed with ANOVA model including the two randomization stratification factors and treatment indicator as covariates. The two stratification factors are Visit 2 pre-CAE total corneal fluorescein staining score [redacted] and Visit 2 pre-CAE ocular discomfort score [redacted].

The least squares means and their respective standard errors (SEs) of the change from baseline for each treatment group and the treatment differences between each dose level and placebo will be presented for the individual endpoints with 2-sided p-values and 2-sided 95% confidence intervals. The missing data of the primary efficacy endpoints will be imputed as specified in Section 10.7.3. The strategies of handling the intercurrent events in the primary analysis are described in Estimand 1 in Section 10.3.

The primary analyses of the primary efficacy endpoints will be performed on ITT population with Estimand 1.

10.9.2 Sensitivity Analyses for the Primary Efficacy Endpoints

The primary efficacy endpoints will be analyzed in the ITT population with Estimand 1 using ANCOVA model controlling the baseline value and treatment indicator as well as with Estimand 2 using the same ANOVA model specified in the primary analyses. The primary endpoints will also be analyzed with the ITT and PP populations using the observed data only using the same ANOVA model. Wilcoxon rank sum tests will be performed as additional sensitivity analyses with the ITT and PP populations using the observed data only.

Missing data imputation will also be implemented using a tipping point analysis for the primary endpoints in the ITT population.

10.9.3 Analyses of the Secondary Efficacy Endpoints

For total corneal fluorescein staining score and ocular discomfort score using the [redacted], a [redacted] may also be used to obtain the mean scores at each visit and the mean scores of the change from baseline at each post baseline visit. The ITT population with the observed data only will be used in the model. The model will include the fixed effect such as baseline, treatment, visit, interaction between treatment and visit, as well as subject as the random effect.

The secondary endpoints will be analyzed with the observed data only in the ITT population. Continuous variables will be summarized with mean and confidence intervals by treatment groups and by visits. Mean changes from baseline may also be summarized by treatment groups and visits if appropriate. ANOVA will be used to report p-values for treatment difference. For binary outcome variables, percentage difference and associated confidence intervals will be used to summarize the data. Chi-square test or logistic regression will be considered for reporting p-values.

10.10 Safety Variables

All safety analyses will be performed on the Safety Population.

Dosing information for each treatment and each subject will be listed. Discontinuation of treatment will be summarized by treatment received. The primary reason for trial drug discontinuation will also be summarized by treatment received.

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. TEAEs are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. Furthermore, frequencies will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be performed for ocular and non-ocular AEs.

Concomitant medications will be coded using the most recent version of WHO-Drug Dictionary and summarized by treatment group.

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, intraocular pressure, and dilated fundoscopy will be summarized by treatment and visit using descriptive statistics. Change or shift from baseline will also be summarized where appropriate. For assessments performed by eye, both eyes will be summarized separately.

10.11 Subgroup Analyses for the Primary Efficacy Endpoints

The subgroup analyses will be performed based on various demographic characteristics using the ITT population, such as age groups, gender, race, and ethnicity.

In particular, subgroups for the Japanese participants enrolled in this study will be analyzed to fulfill the requirement of regional health authorities.

The subgroup analyses based on the two stratification factors, Visit 2 pre-CAE total corneal fluorescein staining score [redacted] and ocular discomfort score [redacted], will also be performed.

10.12 Interim Analyses

There will be no interim analyses in this study.

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

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

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent/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.

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

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

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

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

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

11.4 Documentation

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

11.4.1 Retention of Documentation

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

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

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

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system.

Data will be entered in eCRF for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.6 Publications

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

12.0 REFERENCES

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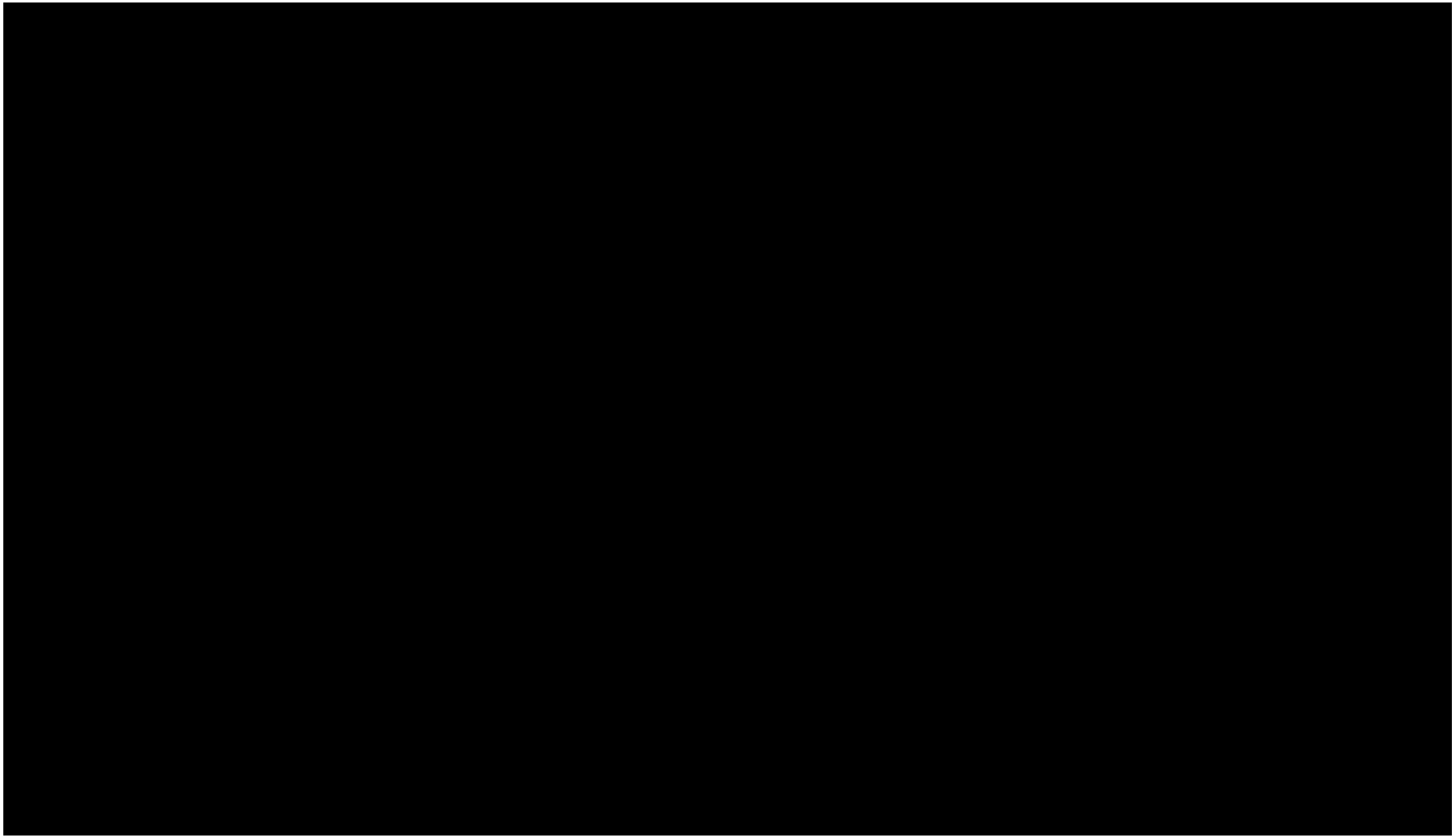
13.0 APPENDICES

13.1 Appendix 1: Schedule of Visits and Measurements



13.2 Appendix 2: Examination Procedures, Tests, & Evaluations

Visual Acuity Procedures (ETDRS Chart)

[redacted]

Equipment

[redacted]

Measurement Technique

[redacted]

[redacted]

[redacted]

LogMAR Visual Acuity Calculations

[redacted]

[redacted]

[redacted]

Slit Lamp Biomicroscopy Procedures

[redacted]

Dilated Fundoscopy

[redacted]

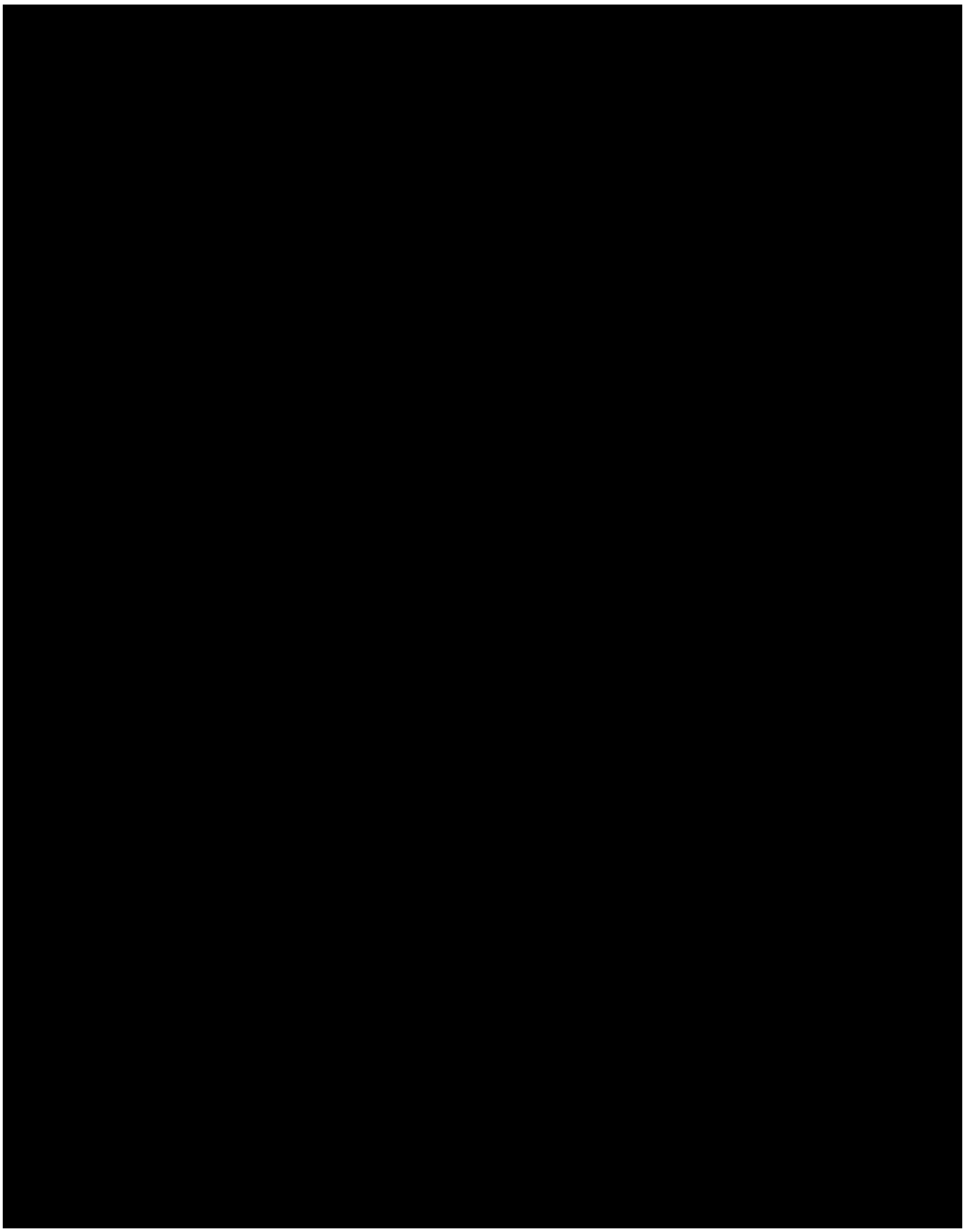
Intraocular Pressure (IOP)

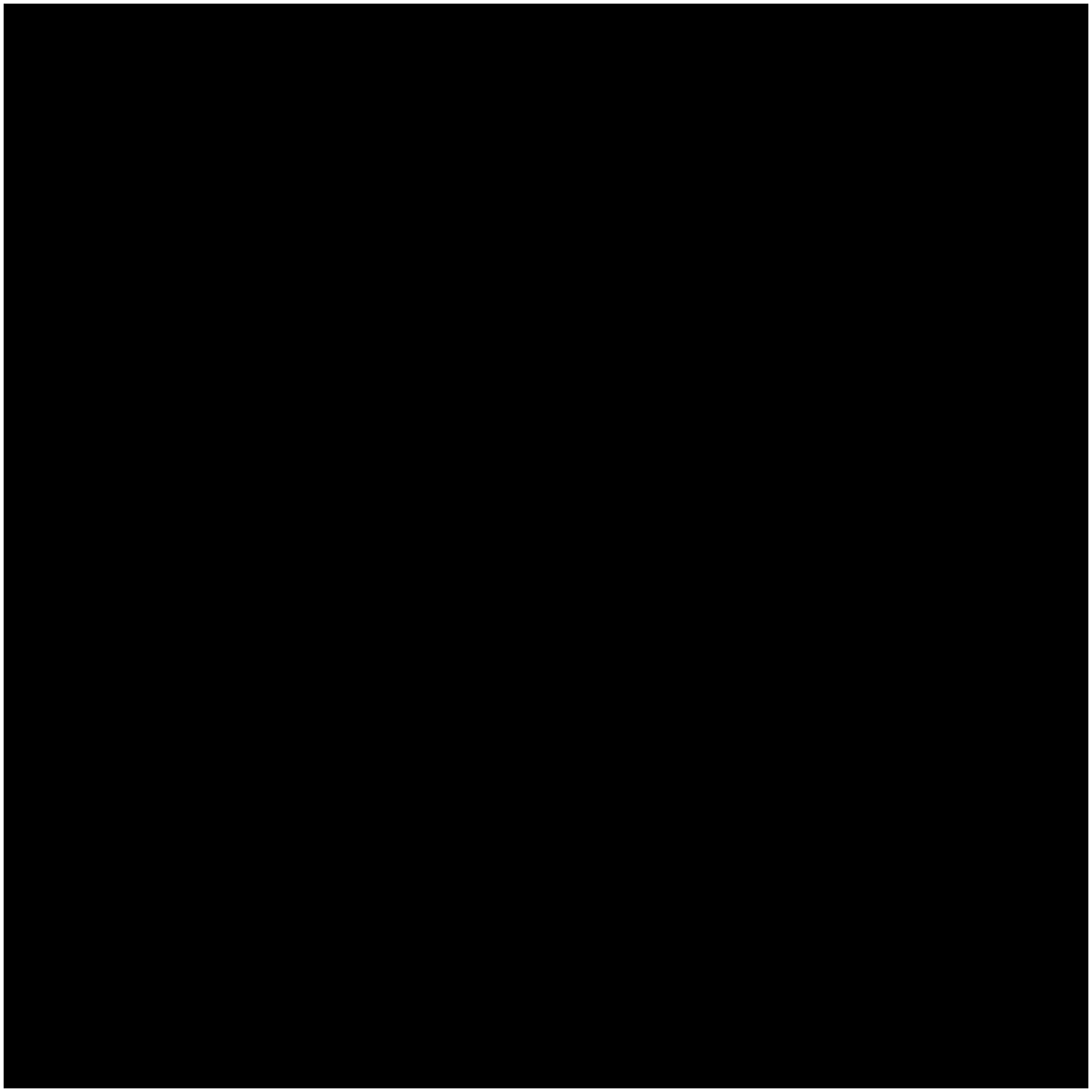
[redacted]

Unanesthetized Schirmer's Test

[redacted]

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





Tear Film Break-Up Time (TFBUT)

[redacted]

Visual Analog Scale (VAS)

[redacted]

Figure 2 Visual Analog Scale

[redacted]

Figure 3 Ocular Discomfort: Visual Analog Scale

Sodium Fluorescein Staining of the Cornea Based on the Modified National Eye Institute (NEI) Grading Scheme

Figure 4 Modified NEI Corneal Staining Grading Scheme

[redacted]

Lissamine Green Staining of the Conjunctiva Based on the Modified National Eye Institute (NEI) Grading Scheme

[redacted]

Figure 5 Modified NEI Conjunctival Staining Grading Scheme

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale

[redacted]

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

[redacted]

Ora proprietary scales – Not for distribution without permission

[redacted]

Figure 6 Ora Calibra® Grading Scale: Cornea

Staining Areas:

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Conjunctival Redness Scale for Dry Eye

[redacted]

Ora proprietary scales – Not for distribution without permission

Drop Comfort Assessments

[redacted]

Subject-Reported Drop Comfort Scale

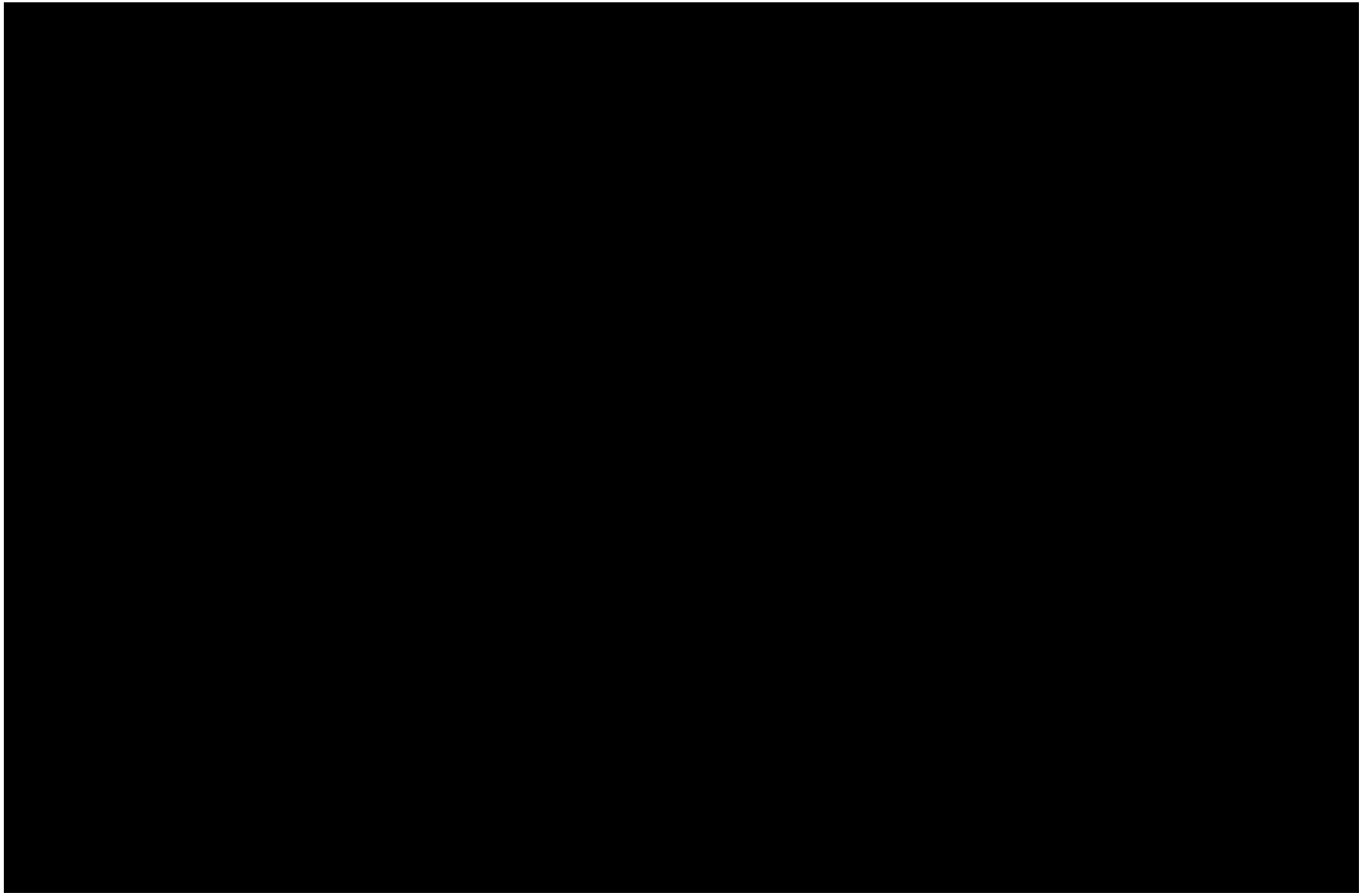
[redacted]

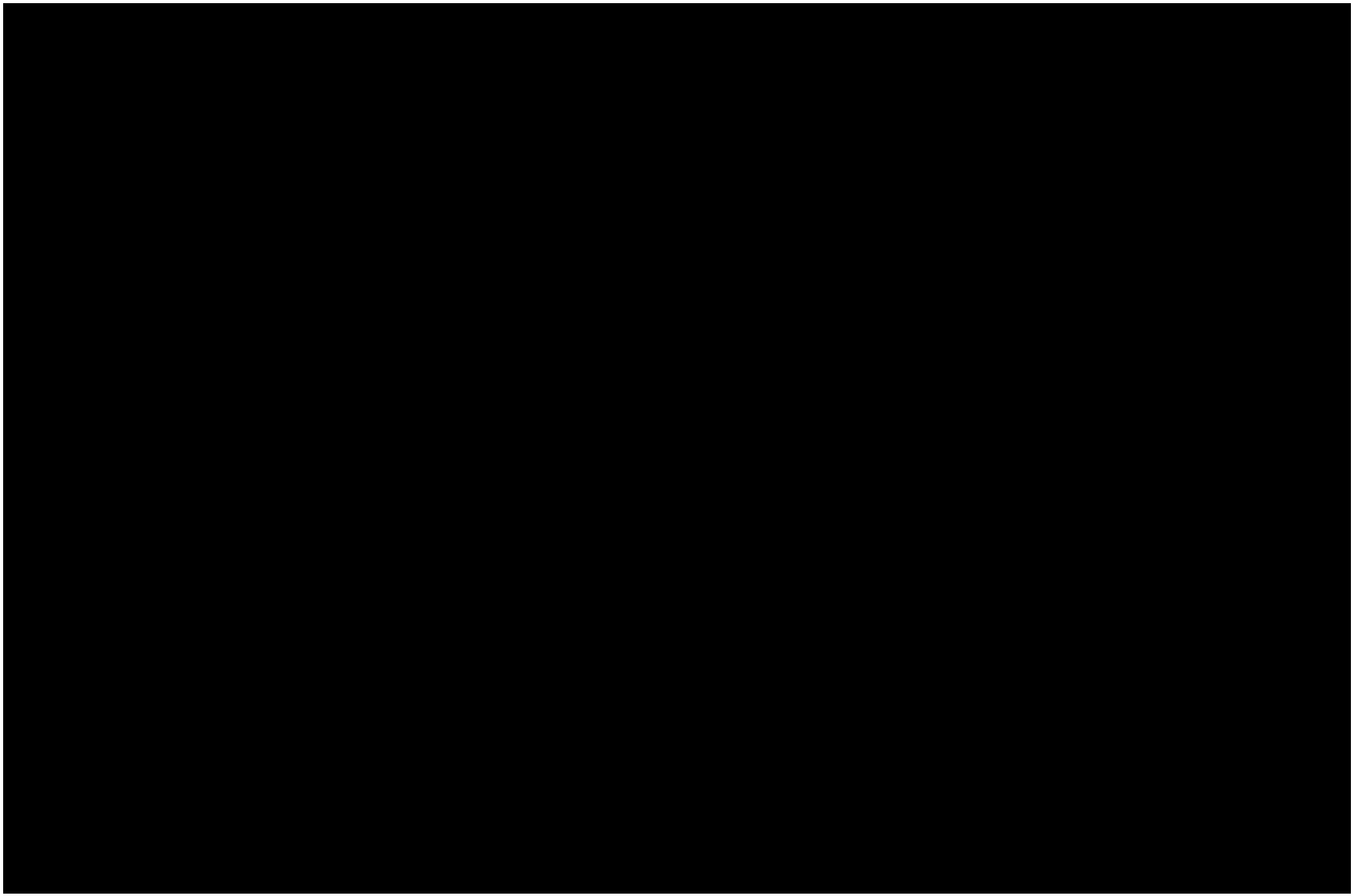
Ora Calibra® Drop Comfort Scale

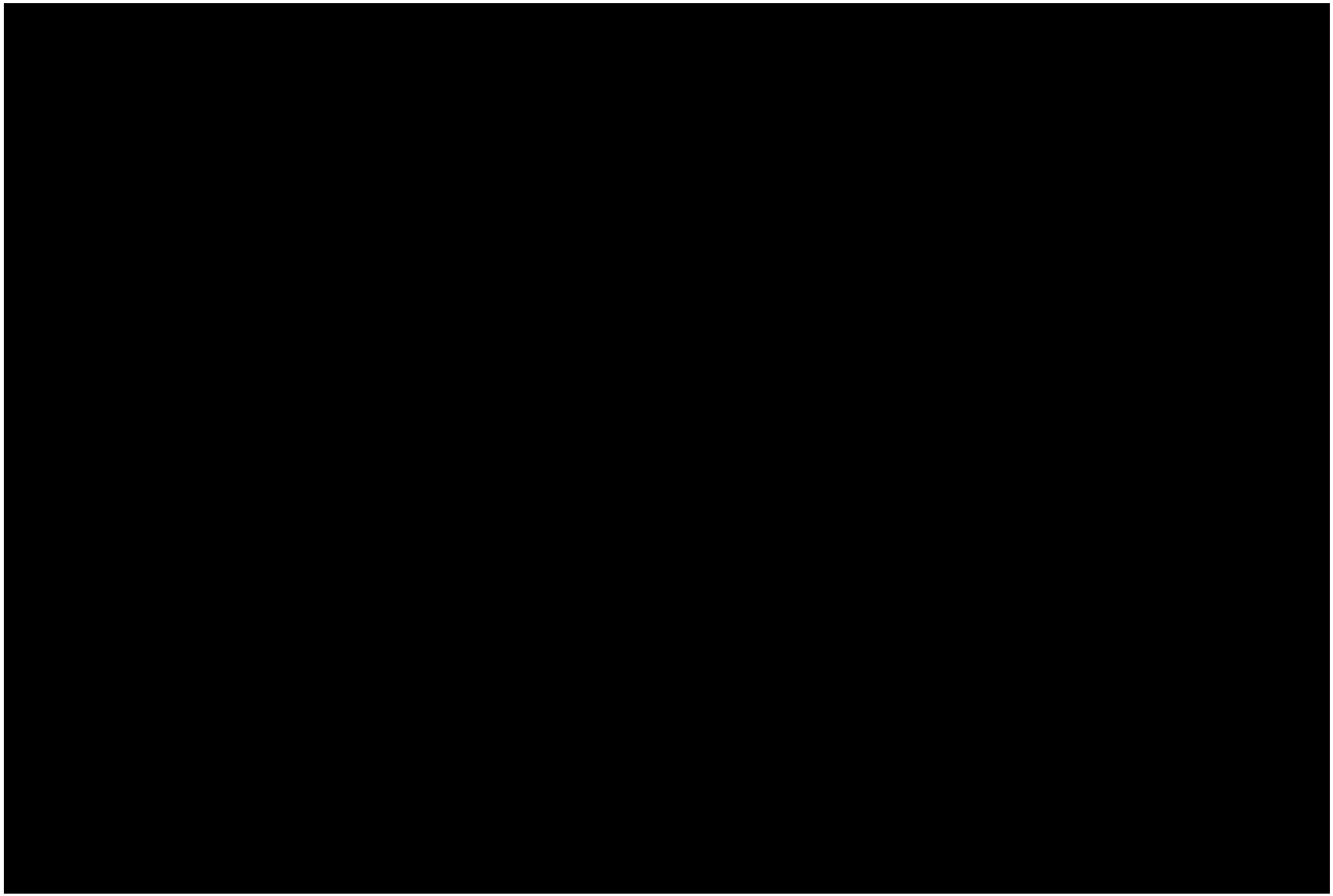
[redacted]

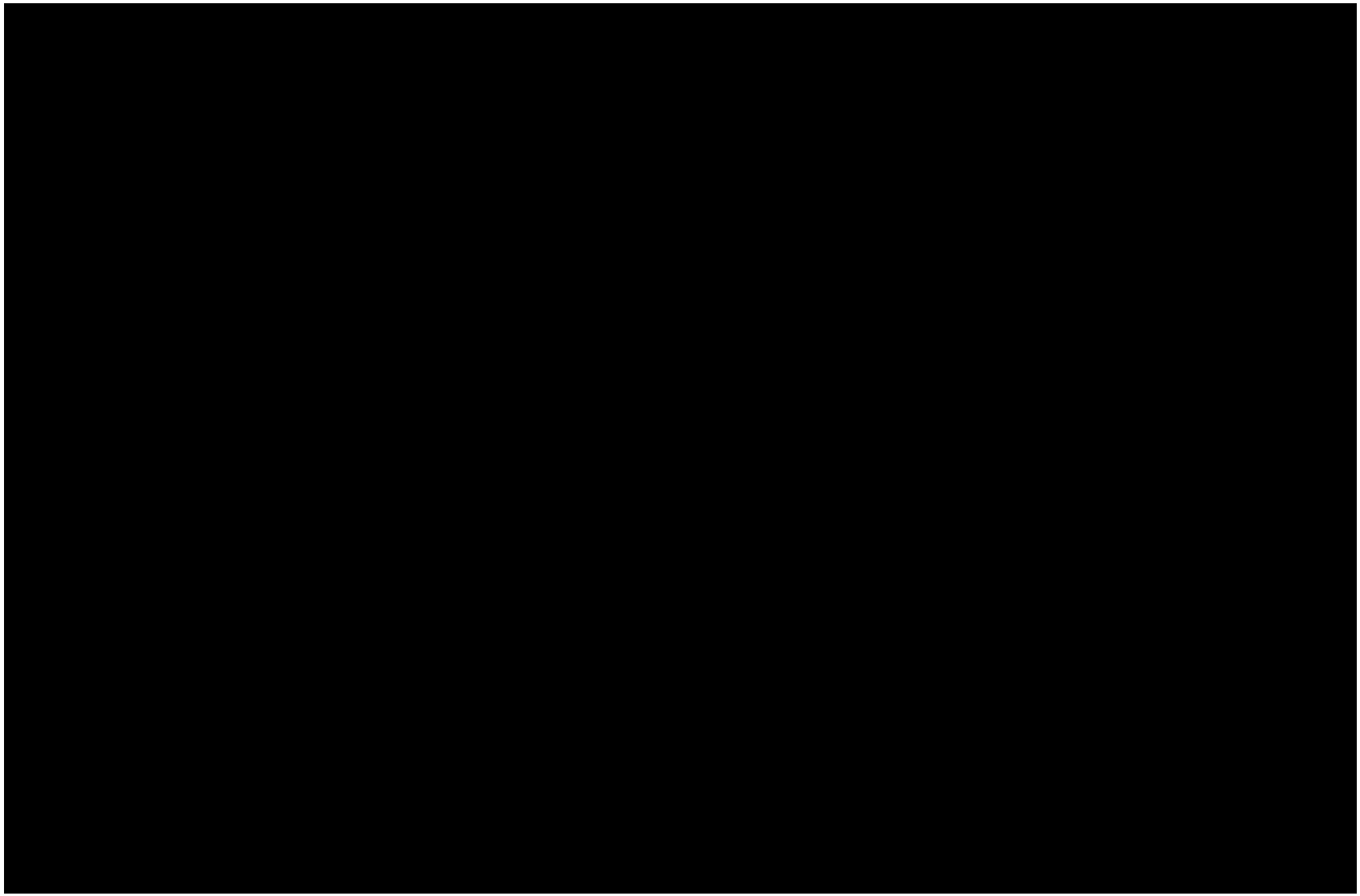
Subject Compliance Daily Diary

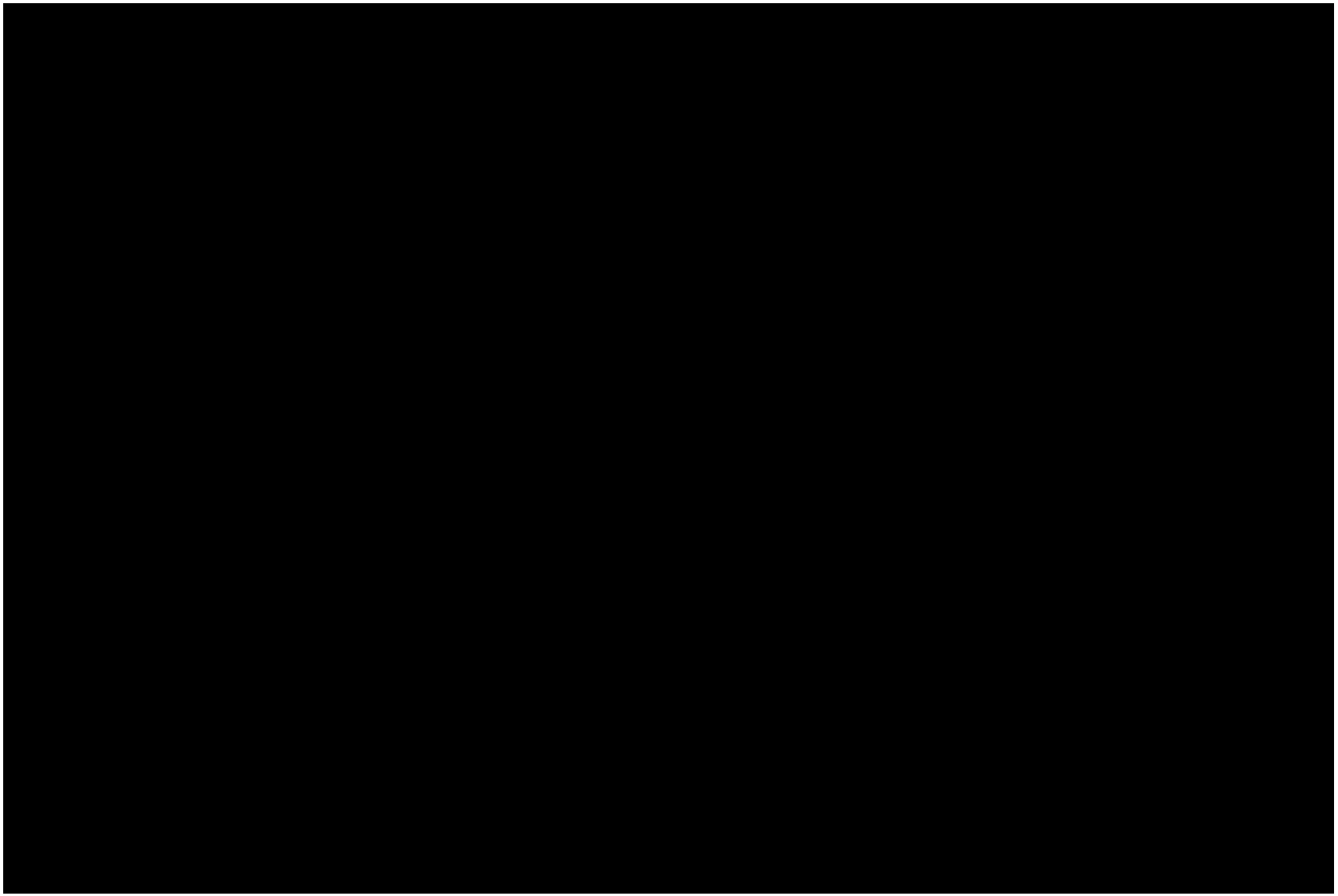
[redacted]

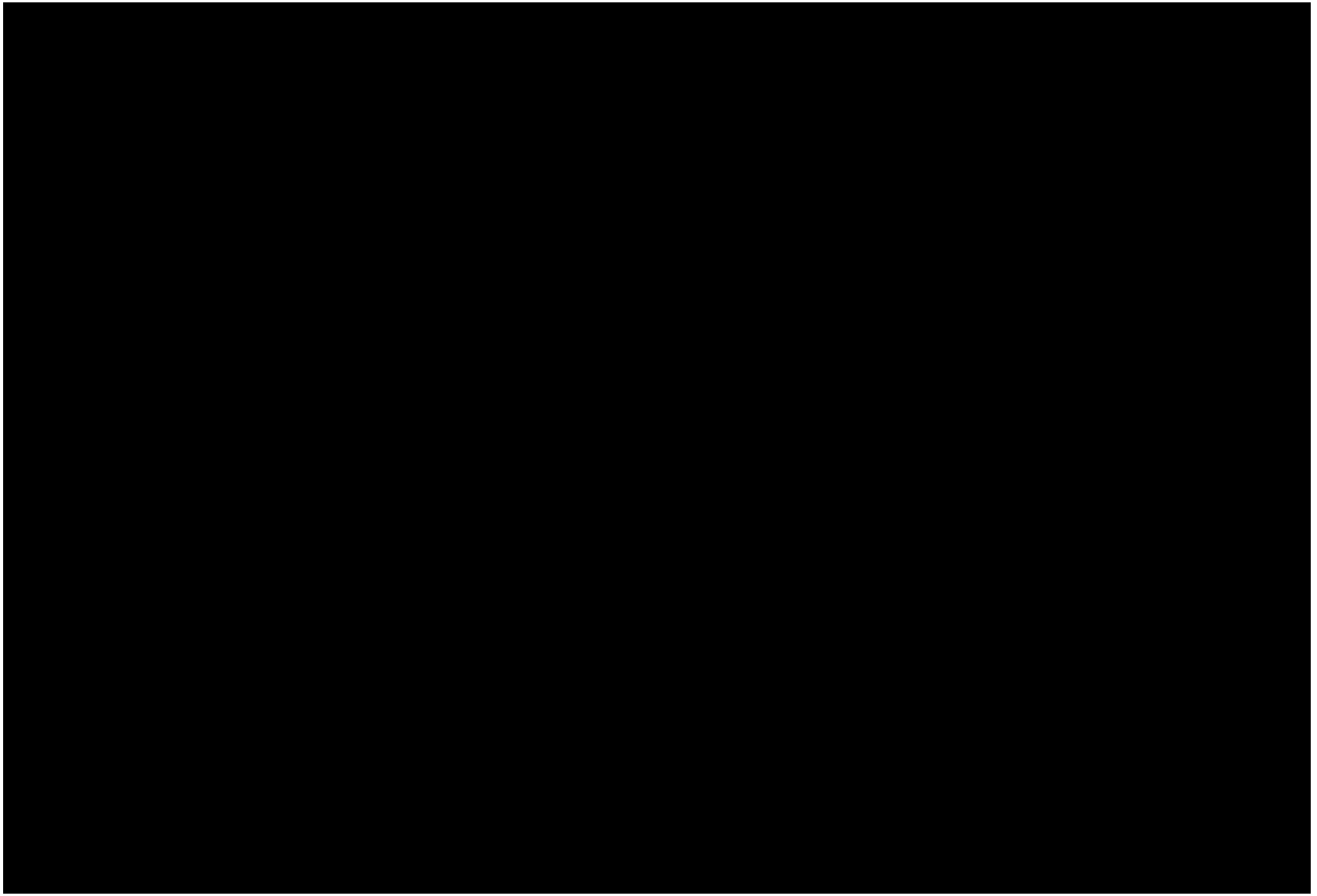












Family Tree Verification Form

[redacted]

Figure 7 Family Tree Verification Form

[redacted]

Yuyu Pharma, Inc.
YP-P10 Ophthalmic Solution

13.3 Appendix 3: Protocol Amendment Summary

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

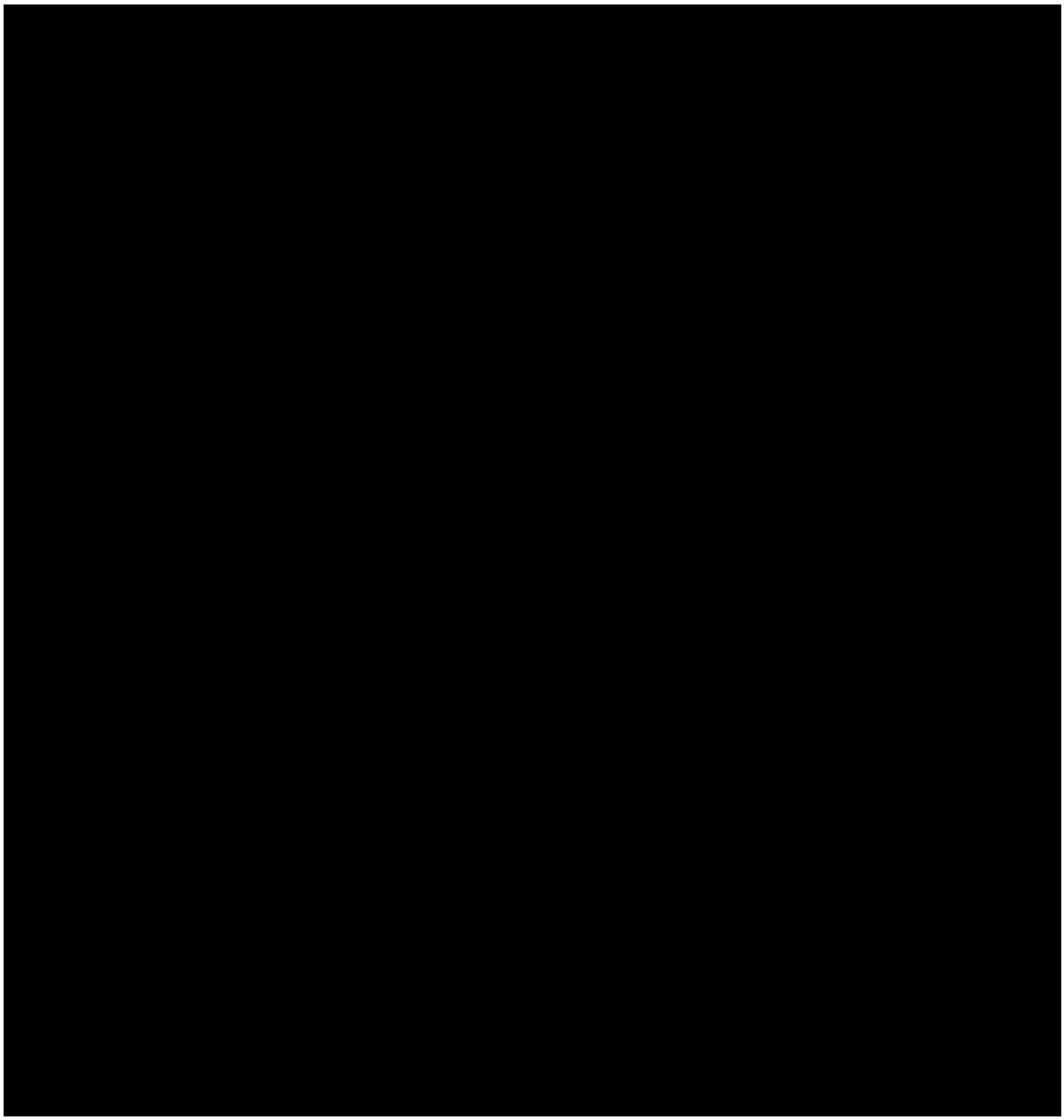
[redacted]

[redacted]

13.4 Appendix 4: Sponsor and Ora Approvals

Protocol Title:	A Phase 2, Multi-center, Randomized, Double– Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of YP-P10 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
IND Number	147759
Final Date:	TBD

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.



13.5 Appendix 5: Investigator's Signature

Protocol Title:	A Phase 2, Multi-center, Randomized, Double– Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of YP-P10 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye
IND Number	147759
Final Date:	TBD

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

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

Signed: _____ Date: _____

Document History

SignNow E-Signature Audit Log

All dates expressed in MM/DD/YYYY (US)

[redacted]