CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 3, Multicenter, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy and Safety of Tanfanercept (HL036) Ophthalmic Solution 0.25% Compared to Placebo in Subjects with Dry Eye Disease (VELOS-3)
Protocol Number:	HL036-DED-US-P302
Development Phase:	Phase 3
Investigational Product:	Tanfanercept Ophthalmic Solution 0.25%
IND Number:	135371
Indication:	Dry Eye Disease
Investigators	Multi-centered (Up to 10 sites)
Sponsor:	HanAll Pharmaceutical International Inc. 1 Church St. Suite 103 Rockville, MD 20850, USA HanAll Biopharma Co., Ltd. DaeWoong Building 3F. 12 Bongeunsa-ro 114-gil Gangnam-gu, Seoul Republic of Korea 06170
Contract Research Organization	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
HanAll Biopharma's ResponsibleMedical Officer:	[redacted] HanAll Pharmaceutical International Inc. 1 Church St. Suite 103 Rockville, MD 20850, USA
IRB:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673USA
Date of Protocol:	30 Jun 2021 (v1.0)
Amendment 1:	28 Jul 2021 (v1.1)
Amendment 2:	18 Aug 2021 (v2.0)
Amendment 3:	20 Jan 2022 (v3.0)
Amendment 4:	22 Jun 2022 (v4.0)

Statement of Compliance with Good Clinical Practice
This study will be performed in compliance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP).
Confidentiality Statement
This protocol is confidential and the information available within it may not bereproduced or otherwise disseminated.

SPONSOR PERSONNEL

[redacted] **HanAll Pharmaceutical International Inc.**	[redacted]
[redacted] **HanAll Pharmaceutical International Inc.**	[redacted]
[redacted] **HanAll Pharmaceutical International Inc.**	[redacted]
[redacted] **HanAll Pharmaceutical International Inc.**	[redacted]
[redacted] **HanAll Pharmaceutical International Inc.**	[redacted]

MEDICAL MONITOR

[redacted]	[redacted]

ORA PERSONNEL

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

SYNOPSIS

<table>
<tr><td colspan="2">NAME OF COMPANY
HanAll Pharmaceutical International Inc.
1 Church St. Suite 103
Rockville, MD 20850, USA

HanAll Biopharma, Co., Ltd.
DaeWoong Building 3F.
12 Bongeunsa-ro 114-gil
Gangnam-gu, Seoul
Republic of Korea 06170</td><td>NAME OF DRUG PRODUCT
Tanfanercept ophthalmic solution 0.25% for treatment of Dry Eye Disease</td></tr>
<tr><td colspan="3">TITLE OF STUDY:
A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety of Tanfanercept (HL036) Ophthalmic Solution 0.25% Compared to Placebo in Subjects withDry Eye Disease (VELOS-3)</td></tr>
<tr><td>PROTOCOL NUMBER:</td><td colspan="2">HL036-DED-US-P302</td></tr>
<tr><td>STUDY SITES:</td><td colspan="2">Multicenter study involving up to 10 sites located in the United States</td></tr>
<tr><td>STUDY PERIOD:
Approximately 70 days</td><td colspan="2">PHASE OF DEVELOPMENT:
Phase 3</td></tr>
<tr><td>Investigational Product:</td><td colspan="2">Tanfanercept ophthalmic solution 0.25%Placebo ophthalmic solution</td></tr>
<tr><td colspan="3">STUDY OBJECTIVES:
The objective of this study is to compare the safety and efficacy of tanfanercept ophthalmic solution0.25% to placebo for the treatment of the signs and symptoms of dry eye.</td></tr>
<tr><td colspan="3">DOSE, ROUTE AND REGIMEN:
Screening: During the 14-day (± 2 days) run-in period, open–label placebo ocular drops will be self–administered twice daily (BID) in both eyes in the morning and in the evening by all subjects.
Treatment: Sterile active drug and placebo solutions are packaged into single-use 0.6 mL low density polyethylene (LDPE) unit dose ampoules that deliver an approximate per drop volume of 30 µL. During the 8–week (57 ± 3 days) treatment period, subjects will be instructed to self–administer one drop of tanfanercept ophthalmic solution 0.25% or placebo ophthalmic solution BID in each eye in the morning and the evening during the study period.
Subjects will be randomized to one of two treatment arms (1:1) to receive study drug self-administeredby subject at Visit 2.</td></tr>
<tr><td colspan="3">DURATION OF TREATMENT:
Approximately 56 days (8 weeks)</td></tr>
<tr><td colspan="3">REFERENCE THERAPY, DOSE, ROUTE AND REGIMEN:
Open–label placebo ophthalmic solution (placebo) will be provided to subjects from Day –14 to Day -1. Placebo ocular drops will be self–administered BID in both eyes in the morning and the evening.
Following randomization, placebo will be dosed according to the same schedule as the tanfanercept ophthalmic solution 0.25%.</td></tr>
</table>

NAME OF COMPANY	**NAME OF DRUG PRODUCT**
HanAll Pharmaceutical International Inc. 1 Church St. Suite 103 Rockville, MD 20850, USA HanAll Biopharma, Co., Ltd. DaeWoong Building 3F. 12 Bongeunsa-ro 114-gil Gangnam-gu, Seoul Republic of Korea 06170	Tanfanercept ophthalmic solution 0.25% for treatment of Dry Eye Disease

NUMBER OF SUBJECTS PLANNED: Approximately 300 subjects will be enrolled in the study. Thetotal number of expected participants, including screen failures, is approximately 857 subjects.

INCLUSION CRITERIA:

1. Be at least 18 years of age
2. Provide written informed consent
3. Be willing and able to comply with all study procedures
4. Have a patient-reported history of dry eye for at least 6 months prior to Visit 1
5. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1
6. Have a best corrected visual acuity (BCVA) of [redacted] (logMAR) orbetter (Snellen equivalent score of [redacted] in each eye at Visit 1
7. Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2
8. Have a Schirmer's Test score of $\leq$ 10 mm and $\geq$ 1 mm in at least one eye at Visits 1 and 2
9. Have a corneal fluorescein staining score [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one of the cornealregions [redacted] in at least one eye at Visits 1 and 2
10. Have a central corneal staining score (CCSS) of [redacted] according to the Ora Calibra® Corneal andConjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visit 1
11. Have a CCSS of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale forGrading of Fluorescein Staining in at least one eye at Visit 2
12. Have a CCSS at Visit [redacted] to CCSS at Visit 1 in at least one eye
13. 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
14. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10, 11, 12 and 13 above
15. A negative urine pregnancy test if female is of childbearing potential (those who are not surgically sterilized [bilateral tubal ligation, hysterectomy or bilateral oophorectomy] or post–menopausal [12months after last menses]) and must use adequate birth control throughout 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:

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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 parameter
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 any cyclosporine-containing drops (e.g. Restasis®, Cequa®), or lifitegrast ophthalmic solution (Xiidra®) within 60 days of Visit 1
6. Have any previous experience using TNF inhibitor ophthalmic solutions, such as tanfanercept ophthalmic solution
7. Have had any ocular and/or lid procedures or ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid procedures or ocular and/or lid surgeries over the study period.The respective restriction periods are required for the following lid procedures:
    a) Have had any thermal pulsation treatment (e.g., LipiFlow, iLux, MiBo thermoflo, intense pulsed light) within 60 days of Visit 1
    b) Have had any intraductal meibomian gland probing within 3 months of Visit 1
8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1 or have had a permanent punctal plug or punctal occlusion procedurewithin 30 days of Visit 1
9. Be currently using any topical ophthalmic medications (including medications for glaucoma) orover-the-counter solutions, artificial tears, gels or scrubs, and not be able to 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 only if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period
    c) Corticosteroids (including EYSUVIS™) or mast cell stabilizers (including ocular): 14 days prior to Visit 1 or anticipated use during the study. Note: Use of systemic corticosteroids (including oral, nasal sprays, and inhalers) started within 45 days of Visit 1 or anticipated use during the study is exclusionary.

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d) Any other medication (ex: acetaminophen), oral or topical, not explicitly mentioned in subsections 9a-9c that is known to cause ocular drying and that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study (see Appendix 2: Prohibited Medications)

e) All other topical ophthalmic preparations (including any over-the-counter artificial tear substitutes): 72 hours prior to Visit 1

10. Have an uncontrolled systemic disease
11. Be a woman who is pregnant, nursing or planning a pregnancy
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months)
13. Be a woman of childbearing potential who is not using an acceptable means of birth control (acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner). For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if thesubject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study
14. Have a 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
17. Be in screening when enrollment is paused, completed, or discontinued.

ENDPOINTS:

The primary efficacy endpoints of the study are:

- Central corneal staining score (CCSS; sign), mean change from baseline (V2) to Day 57 ± 3(V6, Week 8)
- Eye dryness score on Visual Analog Scale (EDS; symptom), mean change from baseline (V2)to Day 57 ± 3 (V6, Week 8)

The secondary efficacy endpoints of the study are:

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

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- Conjunctival lissamine green staining by region: central, superior, inferior, temporal, nasal,corneal sum, conjunctival sum and total staining
- Conjunctival redness
- Schirmer's Test
- Tear film break-up time (TFBUT)
- Visual Analog Scale (VAS), refer to section 6.1.4
- Ocular Surface Disease Index© (OSDI©)
- Ocular Discomfort
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire for Dry Eye

The safety endpoints of the study are:

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular pressure
- Dilated fundoscopy
- Immunogenicity to tanfanercept ophthalmic solution 0.25% in serum

The other endpoints of the study are:

- Drop comfort

General Statistical Methods and Types of Analyses:

Analysis Populations:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects.The primary analysis will be performed on the ITT population with the primary estimand. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations. Protocol deviations will be assessed prior to interim database lock and unmasking.

  The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.

  Note: Protocol deviations recorded after interim database lock and unmasking will not be used for the determination of the PP population.
- Safety Population – The safety population includes all randomized subjects who have received at least one dose of the investigational product. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

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Note: Additional safety subgroup populations may be defined in the Statistical Analysis Plan (SAP).

Sample Size:

This study is expected to enroll 150 subjects in each of the two treatment arms, for a total of 300 randomized subjects. Assuming a 10% drop out rate, 135 subjects per group are expected to complete the study. This study is powered to demonstrate efficacy in the primary sign endpoint.

Assuming a common standard deviation in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS of [redacted] a sample size of 135 evaluable subjects per group will have 99.4 % power to detect a difference of [redacted] units between the active (tanfanercept ophthalmic solution 0.25%) treatment group and the placebo group at a significance level of 0.05.

Multiplicity Consideration:

Hierarchical fixed sequence testing for the primary efficacy endpoints will be used to maintain the type I error rate. The primary efficacy analysis will first test the difference in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS in the ITT population. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of tanfanercept ophthalmic solution 0.25%, then the study will be considered a success, tanfanercept ophthalmic solution 0.25% will be declared to be superior to placebo in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS, and the difference in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for EDS will then be tested at the two-sided alpha = 0.05 level in the ITT population.

If, in addition to a statistically significant test of the difference in change from baseline (V2) to Day 57 ±3 (V6, Week 8) for CCSS in favor of tanfanercept ophthalmic solution 0.25%, the test of the difference in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for EDS is also statistically significant in favor of tanfanercept ophthalmic solution 0.25%, then tanfanercept ophthalmic solution 0.25% will be declared superior to placebo in both the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS and the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for EDS.

Secondary efficacy analyses will not be type-I error controlled and will be considered exploratory and hypothesis-generating.

Primary Efficacy Analyses:

For both primary efficacy endpoints, change from baseline will be calculated as visit – (minus) baseline such that a positive difference indicates a worsening of dry eye signs or symptoms.

In addition, treatment comparisons between active and placebo will be calculated as tanfanercept – (minus) placebo,such that a negative result indicates a better score for the tanfanercept (i.e., tanfanercept demonstrated less severity in dry eye signs or symptoms than the placebo group).

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The primary analysis of the primary endpoints will use the ITT population with multiple imputation methodology as specified in Estimand 1 using Mixed Model for Repeated Measures (MMRM) if the rate of missing data for an endpoint is balanced between the two treatment groups or the rate of missing data for an endpoint is less than 10% in all subjects. If the rate of missing data for an endpoint is imbalanced between treatment groups and the rate of missing data for an endpoint is ≥ 10% in all subjects, then the primary analyses will utilize the ITT population with single imputation methodology specified in Estimand 2 using the permutation test with trimmed means methodology (Permutt et al., 2017).

The MMRM will be used to compare the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS between tanfanercept ophthalmic solution 0.25% and placebo. The initial model will include terms for baseline CCSS, site, visit (as categorical term), treatment group, and the interaction of treatment group and visit as fixed effects with correlated errors. An unstructured covariance matrix will be initially fit with the model. Should an unstructured covariance matrix fail to achieve convergence then alternate covariance structures will be attempted to be detailed in the Statistical Analysis Plan (SAP). The inclusion of site in the final model will be evaluated at an alpha level of 0.1. All post-baseline visits will be used in the model. In addition, the site by treatment interaction will be explored in a separate model to evaluate how the treatment effect may differ across sites.

Change from baseline of EDS from VAS at Day 57 ± 3 (V6, Week 8) between tanfanercept ophthalmic solution 0.25% and placebo will be analyzed as described for CFB of CCSS with adjustment for baseline EDS instead of baseline CCSS.

An alternate MMRM will be executed as supportive analysis for both primary endpoints. These additional models will include all terms in the final models of the primary analyses with [redacted]

Sensitivity analyses will include imputation by Last Observation Carried Forward (LOCF), multiple imputation by placebo group-based pattern mixture models (PMM), and analyses of observed data only using the ITT and PP populations will also be conducted.

Two-sample t-tests will also be conducted as supportive analyses of the mean change from baseline at Day 57 ± 3 (V6, Week 8).

Additional exploratory comparisons of the mean absolute scores of the primary endpoints at both Day 57 ± 3 (V6, Week 8) and baseline (V2) between the treatment groups will be conducted using two-sample t-tests and MMRM.

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Secondary Efficacy Analyses:

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max), and analyzed with two-sample t-tests and MMRM comparing each of the active treatment groups to placebo. All visit-based data will be analyzed at each visit. Changes from baseline at each post-baseline visit will be analyzed using MMRM with terms for baseline, visit (as a categorical term), treatment group and the interaction of visit and treatment group as fixed effects with correlated errors. No imputation will be performed for secondary efficacy variables. Secondary efficacy variables will be analyzed using the ITT population with observed data only unless otherwise specified in the Statistical Analysis Plan.

Safety Variables:

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

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

Other Endpoints:

Drop Comfort Scale will be summarized by treatment group using descriptive quantitative statistics bystudy eye and fellow eye.

Drop Comfort Questionnaire summarized by treatment group and visit using descriptive qualitativestatistics at the subject level.

TABLE OF CONTENTS

SYNOPSIS 4
TABLE OF CONTENTS 12
LIST OF ABBREVIATIONS 14
1 INTRODUCTION 16
2 STUDY OBJECTIVES 18
3 CLINICAL HYPOTHESES 18
4 OVERALL STUDY DESIGN 19
5 STUDY POPULATION 20
5.1 Number of Subjects 20
5.2 Study Population Characteristics 20
5.3 Inclusion Criteria 20
5.4 Exclusion Criteria 21
5.5 Withdrawal Criteria 23
6 STUDY PARAMETERS 24
6.1 Efficacy Measures 24
6.2 Safety Measures 25
7 STUDY MATERIALS 25
7.1 Study Treatments 25
7.2 Other Study Supplies 26
8 STUDY METHODS AND PROCEDURES 26
8.1 Subject Entry Procedures 26
8.2 Concurrent Therapies 27
[redacted] 27
8.4 Examination Procedures 27
8.4.1 Visit 1: Day –14 ± 2 – Screening 28
8.4.2 Visit 1a: Up to 14 days- Run-In Period (Optional) 30
8.4.3 Visit 2: Day 1 – Confirmation and Baseline 30
8.4.4 Visit 3: Day 8 ± 1 –Week 1 32
8.4.5 Visit 4: Day 15 ± 2 –Week 2 33
8.4.6 Visit 5: Day 29 ± 2 –Week 4 34
8.4.7 Visit 6: Day 57 ± 3 –Week 8 and Study Exit 35
8.5 Compliance with Protocol 37
8.6 Subject Disposition 37
8.7 Study Termination 38
8.8 Study Duration 38
8.9 Monitoring and Quality Assurance 38
9 ADVERSE EVENTS 39
9.1 Adverse Events 39
9.2 Serious Adverse Events (SAE) 41
9.3 Procedures for Reporting Adverse Events 42
9.4 Procedures for Unmasking (if applicable) 43
9.5 Type and Duration of the Follow-up of Subjects after Adverse Events 43
10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES 44
10.1 Analysis Populations 44

10.2 Statistical Hypotheses 44
10.3 Sample Size 45
10.4 Statistical Analysis 45
11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES 51
11.1 Protection of Human Subjects 51
11.2 Ethical Conduct of the Study 51
11.3 Subject Confidentiality 52
11.4 Documentation 52
11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product 52
11.6 Recording of Data on Source Documents and Case Reports Forms (CRFs) 53
11.7 Handling of Biological Specimens 53
11.8 Publications 54
12 REFERENCES 55
13 APPENDICES 56
APPENDIX 1: VELOS-3 SCHEDULE OF VISITS AND MEASUREMENTS 56
APPENDIX 2: PROHIBITED MEDICATIONS 58
APPENDIX 3: EXAM PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES 60
APPENDIX 4: PROTOCOL AMENDMENT SUMMARY 71
Appendix 5: Sponsor and Ora Approvals 87
APPENDIX 6: INVESTIGATOR'S SIGNATURE 89

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredients
BCVA	Best Corrected Visual Acuity
BID	Twice daily
CAE®	Controlled Adverse Environment®
CCSS	Central Corneal Staining Score
CFB	Change from Baseline
CFR	Code of Federal Regulations
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDS	Eye Dryness Score
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICSS	Inferior Corneal Staining Score
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirementsfor Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LASIK	Laser–assisted *in situ* keratomileusis
LDPE	Low Density Polyethylene
LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Authorities
n	Sample Size
NCS	Not Clinically Significant
NOEL	No-Observed Effect Level
OSDI©	Ocular Surface Disease Index©
OTC	Over the Counter
OU	Oculus Uterque (Both eyes)
PI	Principal Investigator
PK	Pharmacokinetic
PMM	Pattern Mixture Models
PP	Per Protocol
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TCSS	Temporal Corneal Staining Score
TEAEs	Treatment-Emergent Adverse Events
TFBUT	Tear Film Break Up Time
TNF	Tumor Necrosis Factor
TNFR	Tumor Necrosis Factor Receptor
VA	Visual Acuity
VAS	Visual Analog Scale

1 INTRODUCTION

Dry eye is a complex disease that results in eye discomfort, visual disturbance, and tear film instability. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. A recent meta-analysis of 24 large international cohort studies found the prevalence of dry eye ranged from 5% to 50% when diagnosed using symptoms regardless of the presence of signs and when diagnosed using signs regardless of symptoms, the prevalence rate was generally higher but more variable, making a true estimation of the worldwide prevalence of dry eye difficult (Stapleton, Alves et al. 2017). In the U.S., estimates range from as many as 14.7% of women, equating to roughly 76 million, and 11.7% of men, equating to roughly 52 million (Moss,Klein et al. 2008), to a more widely accepted 3.2 million women and 1.7 million men over the age of 50 have dry eye, with a projected 40% increase in the number of patients affected by 2030 (Schaumberg, Sullivan et al. 2002, Schaumberg, Sullivan et al. 2003, Schaumberg, Dana et al. 2009). Regardless of the method used to estimate prevalence, dry eye appears to be more common in women than in men (Stapleton, Alves et al. 2017).With the aging population in the United States and other countries of the developed world, and with increasing computer use, dry eye is expected to become more prevalent and finding a treatment is becoming more important (Brewitt and Sistani 2001).

Anti-tumor necrosis factor (TNF) molecules have been approved for rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, and Crohn's diseases. They are also prescribed for off-label use for uveitis, dry eye disease, macular degeneration, sciatic neuralgia, chronic obstructive pulmonary diseases and asthma. The role of TNF as a major cytokine in dry eye provides a rationale for use of TNF inhibitors in this disease.

However, the majority of TNF inhibitors are antibody-based with a large molecular size (~150 kDa) that limits tissue penetration. Considering the limited ocular distribution and excessive toxicity of TNF-inhibitor therapies administered systemically, tanfanercept ophthalmic solution 0.25% was developed as a TNF-inhibitor with increased penetration and distribution and minimal systemic side effects.

Tanfanercept is a molecularly engineered tumor necrosis factor receptor 1 (TNFR1) fragment composed of 172 amino acids. Molecule fragmentation and engineering techniques are applied for enhanced tissue distribution, increased stability, and potency. tanfanercept ophthalmic solution demonstrated potent anti-inflammatory effects in a carrageenan-induced acute *in vivo* model of inflammation, and significant efficacy in a collagen-induced arthritis model. In murine dry eye disease model and canine with dry eye disease, tanfanercept ophthalmic solution was shown to cause statistically significant clinical improvements in keratitis, goblet cell morphology, and tear cytokine levels.

In a Phase 1, first-in-human study, 20 healthy male volunteers received either 0.05% or 0.50% tanfanercept or placebo by topical ophthalmic instillation twice daily (BID). For one day, 8 subjects received tanfanercept ophthalmic solution 0.05% into the left eye while the right eye received placebo, 8 subjects received tanfanercept ophthalmic solution 0.50% in the left eye while the right eye received placebo, and 4 subjects received placebo in both eyes. Between tanfanercept ophthalmic solution-treated eyes and placebo-treated eyes, there was no significant difference in the number of subjects with adverse events (AEs) and in the frequency of AEs. A total of 27 AEs were observed in 11 subjects after the administration. Of these, 20 were mild events, and the remaining 7 events were moderate, unlikely to be related to investigational product (IP) and occurred in a single subject. No clinically significant systemic absorption of Tanfanercept was found in any subjects during the study. Assessment of safety and local tolerance showed no clinically significant observations. Therefore, tanfanercept ophthalmic solution (0.05% and 0.50%) was determined to be safe and well-tolerated.

A double-masked Phase 2 (VELOS-1) study in 150 subjects compared two concentrations of tanfanercept ophthalmic solution, 0.10% and 0.25%, to placebo in an 8-week treatment duration. Both concentrations of tanfanercept demonstrated significant clinical differences over placebo in at least one sign or symptom of dry eye disease (DED). The primary endpoints of this study were mean change in inferior corneal staining (sign) at Week 8 and mean change in ocular discomfort (symptom) at Week 8 prior to the Ora Controlled Adverse Environment® (CAE®), referred to as pre-CAE®, analyzed by an Analysis of Covariance (ANCOVA). The CAE® is an environmental chamber used to improve the accuracy for measuring signs and symptoms of dry eye by regulating indoor humidity, temperature, air flow, and visual tasks. While no significant findings favored tanfanercept ophthalmic solution treatment prior to CAE®, it was demonstrated from pre- to post-CAE® results that the Tanfanercept treatment significantly protected subjects from CAE® exposure. That is, at Week 8, subjects who had been previously treated with Tanfanercept had a significantly reduced exacerbation of ocular surface staining after the CAE®.

Further, when the primary endpoint of ocular discomfort was analyzed pre-CAE® -by a t-test, significant improvement was observed. While the results of the primary endpoints were not statistically significant, most signs and symptoms trended in favor of Tanfanercept ophthalmic solution.

A Phase 3 (VELOS-2), multi-center, randomized, double-masked, placebo-controlled, parallel-arm study in the United States compared the safety and efficacy of tanfanercept ophthalmic solution 0.25% to placebo for the treatment of the signs and symptoms of DED. Six hundred thirty-seven subjects were randomly assigned to 1 of 2 treatment groups (1:1) to receive either tanfanercept ophthalmic solution 0.25% or placebo ophthalmic solution as topical ophthalmic drops administered bilaterally BID over a period of eight weeks.

Tanfanercept ophthalmic solution 0.25% demonstrated strong efficacy to treat the signs and symptoms of DED. tanfanercept ophthalmic solution 0.25% did not improve inferior corneal staining score (ICSS) [Pre- to Post-CAE®, p=0.187] but significantly improved central corneal staining score (CCSS) [p=0.024] and temporal corneal staining score (TCSS) [p=0.045] at Week 8. Sign improvement in CCSS was observed as early as Week 1 (p=0.048) and maintained until Week 8, with stronger significance at Week 8 in subgroup of more severe baseline scores (p<0.001). tanfanercept ophthalmic solution 0.25% also significantly improved eye dryness score (EDS) at Week 8 in patients using artificial tears within 30 days of Visit 1 (p=0.033). Overall, tanfanercept ophthalmic solution 0.25% was safe and well tolerated. These data support the further development of tanfanercept ophthalmic solution 0.25% for the indication of DED.

The clinical study protocol indicated that immunogenicity testing was to be performed if there was a significant observation in safety, local tolerance, or pharmacokinetics (PK) assessments.

However, PK assessment results indicated that blood HL036 concentrations were below the lower limit of quantitation (LLOQ) in all blood samples, and no significant difference was observed between each dose group or treatment group in both safety and local tolerance assessments.

2 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of tanfanercept ophthalmic solution 0.25% to placebo for the treatment of the signs and symptoms of dry eye. A hierarchical co-primary symptom endpoint will also be evaluated.

3 CLINICAL HYPOTHESES

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

- Central corneal staining score (CCSS; sign), mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8)
- Eye dryness score on Visual Analog Scale (EDS; symptom), mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8)

4 OVERALL STUDY DESIGN

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

- Tanfanercept ophthalmic solution 0.25% (N~150)
- Placebo ophthalmic solution (N~150)

Approximately 300 subjects will be randomly assigned to one of two treatment groups (1:1) to receive either tanfanercept ophthalmic solution 0.25% or placebo ophthalmic solution as topical ophthalmic drops administered bilaterally BID.

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

The total number of expected participants, including screen failures, is approximately 857 subjects.

A study flow chart appears below:

Visit 1 (Day -14 ± 2):	**Screening**
↓	
Placebo Run-in Period (14 ± 2 day) Visit 1a (up to 14 days) Optional	
↓	
Visit 2 (Day 1):	**Confirmation/ Baseline**
↓	
Visit 3 (Day 8±1):	**1-Week Follow Up**
↓	
Visit 4 (Day 15 ± 2):	**2-Week Follow Up**
↓	
Visit 5 (Day 29 ± 2):	**4-Week Follow Up**
↓	
Visit 6 (Day 57 ± 3):	**8-Week Follow-Up and Study Exit**

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

5 STUDY POPULATION

5.1 Number of Subjects

It is estimated that approximately 857 subjects will be screened to enroll approximately 300 randomized subjects (150 in each arm). Subjects will be randomized in a 1:1 ratio of tanfanercept ophthalmic solution 0.25% to placebo ophthalmic solution.

5.2 Study Population Characteristics

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

5.3 Inclusion Criteria

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

1. Be at least 18 years of age
2. Provide written informed consent
3. Be willing and able to comply with all study procedures
4. Have a patient-reported history of dry eye for at least 6 months prior to Visit 1
5. Have a history of use or desire to use eye drops for dry eye symptoms within [redacted] of Visit 1
6. Have a best corrected visual acuity (BCVA) of [redacted] Logarithm of the Minimum Angle of Resolution (logMAR) or better (Snellen equivalent score of [redacted]) in each eye at Visit 1
7. Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2
8. Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1 and 2
9. Have a corneal fluorescein staining score [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one of the corneal regions [redacted] in at least one eye at Visits 1 and 2
10. Have a CCSS of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visit 1
11. Have a CCSS of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visit 2
12. Have a CCSS at Visit [redacted] to CCSS at Visit 1 in at least one eye
13. 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
14. Have at least one eye, the same eye, satisfy all criteria for 8, 9, 10, 11, 12 and 13 above

15. A negative urine pregnancy test if female is 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 throughout the study period. For non-sexually active females, abstinence may be regarded as an adequate method of birth control.

5.4 Exclusion Criteria

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

1. Have any clinically significant slit-lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction, lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters
2. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1
3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study
4. Have previously had laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months
5. Have used cyclosporine-containing drops (e.g. Restasis®, Cequa®), or lifitegrast ophthalmic solution (Xiidra®) within 60 days of Visit 1
6. Have any previous experience using using TNF inhibitor ophthalmic solutions, such as tanfanercept ophthalmic solution
7. Have had any ocular and/or lid procedures or ocular and/or lid surgeries in the past 6 months or have any planned ocular and/or lid procedures or ocular and/or lid surgeries over the study period. The respective restriction periods are required for the following lid procedures:
    a. Have had any thermal pulsation treatment (e.g., LipiFlow, iLux, MiBo thermoflo, intense pulsed light) within 60 days of Visit 1
    b. Have had any intraductal meibomian gland probing within 3 months of Visit 1
8. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1 or have had a permanent punctal plug or punctal occlusion procedure within 30 days of Visit 1

9. Be currently using any topical ophthalmic medication (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, and not be able to 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 only if dose has been stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study period
    c) Corticosteroids (including EYSUVIS™) or mast cell stabilizers (including ocular): 14 days prior to Visit 1 or anticipated use during the study. Note: Use of systemic corticosteroids (including oral, nasal sprays, and inhalers) started within 45 days of Visit 1 or anticipated use during the study is exclusionary
    d) Any other medication (oral or topical) not explicitly mentioned in subsections 9a-9c that is known to cause ocular drying and that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study (see Appendix 2: Prohibited Medications)
    e) All other topical ophthalmic preparations (including artificial tear substitutes): 72 hours prior to Visit 1
10. Have an uncontrolled systemic disease
11. Be a woman who is pregnant, nursing or planning a pregnancy
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 6 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months)
13. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study
14. Have a 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
17. Be in screening when enrollment is paused, completed, or discontinued.

5.5 Withdrawal Criteria

Subjects may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and/or Sponsor and in accordance with his/her clinical judgment. However, it is encouraged that the Investigator contact the Sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a subject from the study. Tests and evaluations listed for the termination visit should be carried out as outlined in Section 8.4.3.

Sponsor and Ora must be notified of all subject withdrawals as soon as possible. Sponsor also reserves the right to discontinue the study at any time for either clinical or administrative reasons.

Reasons for which a subject may be withdrawn from the study by the Investigator or the Sponsor may include, but are not limited to, the following:

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

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

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

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of the study are:

- Central corneal staining score (CCSS; sign), mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8)

and

- Eye dryness score on Visual Analog Scale (EDS; symptom), mean change frombaseline (V2) to Day 57 ± 3 (V6, Week 8)

6.1.2 Secondary Efficacy Endpoints

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

6.1.3 Other Endpoints

- Drop comfort

6.1.4 Criteria for Effectiveness

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

- Mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8) in central corneal staining in the designated study eye as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining

and

- Mean change from baseline (V2) to Day 57 ± 3 (V6, Week 8) in Eye dryness score (EDS; symptom) assessed by VAS

6.2 Safety Measures

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular Pressure (IOP)
- Dilated fundoscopy
- Immunogenicity to tanfanercept in serum

7 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Study Treatments

Subjects will receive doses BID of either tanfanercept ophthalmic solution 0.25% or placebo ophthalmic solution administered bilaterally to the ocular surface as an eye drop.

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

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen were selected based on nonclinical studies described in Section 1. The proposed treatment period of 8 weeks is also based on nonclinical and clinical studies and on the anti-inflammatory mechanism of action of the drug.

7.1.3 Instructions for Use and Administration

- Tanfanercept ophthalmic solution 0.25% will be supplied as a sterile, clear, colorless liquid solution containing 0.25% Active Pharmaceutical Ingredient (API) (tanfanercept), 0.6 mL low–density polyethylene (LDPE) unit dose ampoules with a fill volume of approximately 0.25 mL. Each mL of the 0.25% solution contains 2.5 mg of the API. In addition to tanfanercept, the components of the drug product solution are: 125 mM sodium chloride (tonicity adjusting agent), 20 mM sodium citrate (buffering solution), sodium hydroxide solution and hydrochloric acid (both for pH adjustments), and sterile water for injection as a solvent.
- The placebo ophthalmic solution consists of all components of the active drug solution with the exception of tanfanercept.
- At the study site, all IP must be stored, and temperaturemonitored under the conditions specified in the Investigator's Brochure (IB) in a secure area accessible only to the designated qualified clinical site personnel. All IP must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and study procedures.

- Tanfanercept ophthalmic solution 0.25% and placebo solutions should be stored refrigerated (2–8 °C). Subjects will be instructed to store tanfanercept ophthalmic solution 0.25% and placebo solutions in a refrigerator (2–8 °C). It is recommended that tanfanercept ophthalmic solution 0.25% and placebo solutions be placed at room (ambient) temperature at least 1 ± 0.5 hours prior to administration to subjects. Sterile active drug and placebo solutions are packaged into single-use 0.6 mL LDPE unit dose ampoules that deliver an approximate per drop volume of 50 µL. Two cavity unit dose ampoules are packaged in aluminum foil pouches under nitrogen. A unit dose ampoule is for single use only.at a minimum, the immediate or secondary study drug packaging will provide the following information: study sponsor identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), study identification and product retest date

7.2 Other Study Supplies

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

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

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

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., prior to changes in a subject's medical treatment and/or prior to study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an Informed Consent Form (ICF). The ICF must be the most recent version that has received approval/favorable review by a properly constituted 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 criteria and none of the exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups:

Prior to initiation of study run-in (at Visit 1), each subject who qualifies for entry will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion criteria and no exclusion criteria are met at Visits 1 and 2, each qualifying subject will then be assigned a randomization number at the end of Visit 2 using an interactive web response system.

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

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken. Please refer to restricted concurrent medication located in Appendix 2.

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

8.2.1 Prohibited Medications/Treatments

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

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.4 Examination Procedures

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

Procedures listed below should be performed in the given order. See Appendix 3: Examination Procedures, Tests, Equipment, and Techniques for details on methodologies and grading systems.

8.4.1 **Visit 1: Day –14 ± 2 – Screening**

All subjects will undergo the following screening assessments:

- Informed Consent/HIPAA Prior to any changes in a subject's medical treatment and/or invasive procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.
- Medical / Medication History and Demographics Collect and record all demographic data, medical history, any medications and any underlying condition(s). Significant non–ocular medical history only within the past year and medications within the past 30 days will be captured. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within 30 days prior to screening.
- Review of Inclusion and Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential) Women of childbearing potential must have a negative urine pregnancy test to continue in the study.
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- OSDI©
- BCVA Utilizing an Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart Subjects must have a score of [redacted] logMAR or better (Snellen equivalent score of [redacted]) in each eye at Visit 1.
- Slit-Lamp Biomicroscopy A slit-lamp exam will be performed at the beginning of the visit to exclude subjects with disallowed ocular conditions.
- Conjunctival Redness Score An objective measure used to score redness on the Ora Calibra® Conjuctival Redness Scale for Dry Eye. [redacted]
- Tear film break-up time (TFBUT)
- Corneal and Conjunctival Staining (fluorescein) as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining
- Corneal and Conjunctival Staining (lissamine green) as assessed by the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Lissamine Green Staining
- Schirmer's Test
- IOP

- Dilated Fundus Exam
- Review of Inclusion and Exclusion Criteria
    - Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1
    - *Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the **same eye**:*
        - Have a Schirmer's Test score of ≤ 10 mm and ≥ 1m in at least one eye at Visits 1
        - Have a corneal fluorescein staining score [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one of the corneal regions [redacted] in at least one eye at Visits 1
        - Have a CCSS of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one eye at Visit 1
        - 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
    - Following the screening procedures at this visit, all subjects who meet all eligibility criteria will self-administer their initial dose of placebo drops to both eyes (OU) (open–label, single drop), for training purposes, at the study site under supervision of trained study personnel following the last study assessment at Visit 1.
- Placebo Dispensation and Administration. Prior to discharge from the study site on Day –14, subjects will be dispensed sufficient placebo supply to last until Visit 2 and will be educated in the self–administration of placebo drops. Subjects will be instructed to self–administer one drop BID in each eye in the morning and the evening until screening Visit 2. The initial, self-administered dose taken in-office at Visit 1 will be counted as a morning dose regardless of visit time, and subjects will beinstructed to administer an evening dose that night. Subjects will be instructed NOT to instill study drug on the morning of their next scheduled study visit (Visit 2, Day 1).
- Monitoring and Query AEs Report any AEs that occur after signing the ICF.
- Schedule Next Visit Subjects will be scheduled for Visit 2.

8.4.2 Visit 1a: Up to 14 days- Run-In Period (Optional)

In the event a subject has any adverse event or concerns related to the run-in treatment phase, the site may schedule an additional visit (Visit 1a) if the PI feels one is beneficial to the subject's well-being. This optional visit may include, but is not limited to, the following:

- medical history review
- concomitant medication review
- BCVA utilizing an ETDRS chart
- slit-lamp biomicroscopy
- IOP
- adverse event review
- dosing procedures and compliance review

8.4.3 Visit 2: Day 1 – Confirmation and Baseline

- Placebo Collection: All used/unused placebo ampoules dispensed for Days –14 to 1should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning placebo dose at home. If subject dosed prior to the visit, study visit procedures should begin 4 hours after time of dosing.
- Monitoring and Query of AEs: Report any AEs that occur after signing the ICF.
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's Test

- Review of Inclusion and Exclusion Criteria
    - Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visits 1 and 2
    - *Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the **same eye**:*
        - Report a score of [redacted] according to the Ora Calibra® Ocular Discomfort& 4-Symptom Questionnaire in at least one of the dry eye symptoms at Visit 1 and 2
        - Have a Schirmer's Test score of ≤ 10 mm and ≥ 1 mm in at least one eye at Visits 1 and 2
        - Have a corneal fluorescein staining score [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining in at least one of the corneal regions [redacted] in at least one eye at Visits 1 and 2
        - Have a CCSS of [redacted] according to the Ora Calibra® Corneal and Conjunctival Staining Scale for Grading ofFluorescein Staining in at least one eye at Visit 2
        - Have a CCSS at Visit [redacted] to CCSS at Visit 1
        - Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at Visits 1and 2
        - Have at least one eye, the same eye, satisfy all inclusion criteria for 8, 9, 10, 11, 12 and 13
- Note: If only one eye qualifies then the single qualifying eye will be the study eye. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse (higher) central corneal fluorescein staining at Visit 2. If the central corneal fluorescein staining is the equivalent in both eyes, then the right eye will be selected as the study eye.
- ***Randomization*** – subjects will be randomized according to the following two strata:
    1. Visit 2 study eye CCSS [redacted] and
    2. Visit 1 CCSS minus Visit 2 CCSS (V1 CCSS - V2 CCSS); difference in study eye CCSS [redacted]
- Blood Sampling Blood samples will be collected from all subjects for immunogenicity testing [redacted]

- Study Drug Instillation at the Study Site All subjects meeting all other screening eligibility criteria after Visit 2 will be randomized to one of two treatment arms. Randomized subjects will self-administer their initial study drug dose bilaterally atthe study site.
- Ora Calibra® Drop Comfort Assessments The Ora Calibra® Drop Comfort Scale will be performed immediately after instillation and then at 1, 2, and 3 minutes following instillation.
- Monitoring and Query of AEs
- Study Drug Dispensation Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated in the self–administration of study drug. The initial, self-administered dose taken in-office at Visit 2 will be counted as a morning dose regardless of visit time, and subjects will be instructed to administer an evening dose that night. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 3, Day 8).
- Schedule Next Visit Subjects will be scheduled for Visit 3.

8.4.4 **Visit 3: Day 8 ± 1 –Week 1**

- Study Drug Collection All used/unused study drug vials dispensed for Days 1 to 8 should be collected and reviewed by a trained study technician.
- Site staff must confirm that subjects have NOT administered their morning study drug dose at home. If subject dosed prior to the visit, study visit procedures should begin 4 hours after time of dosing.
- Monitoring and Query AEs
- Recording of all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal Staining and Conjunctival (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)

- [redacted]
- Study Drug Instillation at the Study Site Subjects will self-administer their first study drug dose bilaterally for Day 8 at the study site following the last study assessment. The evening dose will be administered at home, by the subject.
- Ora Calibra® Drop Comfort Assessment The Ora Calibra® Drop Comfort Scale will be performed immediately and then at 1, and 2 minutes following initial dosing. At 3 minutes following the initial drop, the Ora Calibra® Drop Comfort Questionnaire will be performed.
- Study Drug Re-Dispensation Prior to discharge from the study site on Visit 3 (Day 8), study drug kits from Visit 2 (Day 1) will be re-dispensed to subjects with the remaining study drug to complete up to Visit 4 (Day 15). Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4, Day 15).
- Schedule Next Visit Subjects will be scheduled for Visit 4.

8.4.5 **Visit 4: Day 15 ± 2 –Week 2**

- Study Drug Collection All used/unused study drug vials dispensed for Days 8 to 15 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home. If subject dosed prior to the visit, study visit procedures should begin 4 hours after time of dosing.
- Monitor and Query AEs
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer’s Test

- [redacted]
- Study Drug Dispensation Prior to discharge from the study site on Visit 4 (Day 15), subjects will be educated on self–administration of study drug. Subjects will receive their new assigned study drug kit with sufficient supply to last until Visit 5 and will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5, Day 29). Subjects will self-administer morning dose after visit is complete, regardless of the time, and instructed to administer an evening dose that night.
- Schedule Next Visit Subjects will be scheduled for Visit 5.

8.4.6 **Visit 5: Day 29 ± 2 –Week 4**

- Study Drug Collection All used/unused study drug vials dispensed for Days 15 to 29 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home. If subject dosed prior to the visit, study visit procedures should begin 4 hours after time of dosing.
- Monitoring and Query of AEs
- Record all Changes in Concomitant Medications
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer’s Test
- [redacted]
- Monitoring and Query of AEs

- Study Drug Dispensation Prior to discharge from the study site on Visit 5 (Day 29), subjects will be educated in on self–administration of study drug. Subjects will receive two new assigned study drug kits with sufficient supply to last until Visit 6 and will be instructed to NOT self–administer study drug on the morning of their nextscheduled study visit (Visit 6, Day 57 ± 3). Subjects will self-administer morning dose after visit is complete, regardless of the time, and instructed to administer an evening dose that night.
- Schedule Next Visit Subjects will be scheduled for Visit 6.

8.4.7 **Visit 6: Day 57 ± 3 –Week 8 and Study Exit**

- Study Drug Collection All used/unused study drug vials dispensed for Days 29 to 57 should be collected and reviewed by a trained study technician.
- Site staff must confirm subjects have NOT administered their morning study drug dose at home. If subject dosed prior to the visit, study visit procedures should begin 4 hours after the time of dosing.
- Monitoring and Query of AEs
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's Test
- Intraocular Pressure
- Dilated Fundoscopy
- Blood Sampling for Immunogenicity Testing [redacted]
- Study Exit

[redacted]

8.4.9 Scheduled Visits

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

8.4.10 Unscheduled Visits

Unscheduled visits can 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. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

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

8.4.11 Early Termination Visit

In the case when a subject discontinues from the study, every effort should be made by the site to conduct an early termination visit in order to monitor subject safety. All procedures performed at an early termination visit will be recorded in the source documents and on the Early Termination Visit eCRF.

- Study Drug Collection
- Monitoring and Query of AEs
- Record all Changes in Concomitant Medications
- Urine Pregnancy Test (for females of childbearing potential)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

- VAS
- OSDI©
- BCVA Utilizing an ETDRS Chart
- Slit-Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Corneal and Conjunctival Staining (fluorescein)
- Corneal and Conjunctival Staining (lissamine green)
- Schirmer's Test
- Intraocular Pressure
- Dilated Fundoscopy
- Blood Sampling for Immunogenicity Testing
- Any other assessments needed in the judgment of the investigator
- [redacted]

8.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1, 2, 3, 4, and 5, and given written instructions. The subject's used and unused study drug vials will be collected at each visit from Visit 2 up to and including Visit 6 to assess dosing compliance. Dosing compliance will be based off the returned used and unused ampoule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of unused ampoules, then the subject will be deemed non-compliant, and a deviation should be recorded. If the subject is deemed non-compliant, the subject should be re-educated on IP compliance.

These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

8.6 Subject Disposition

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

- pregnancy
- adverse events
- lack of efficacy
- unmasking when medically necessary

- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow-up)
- sponsor termination of study
- subject choice (e.g. withdrawal of consent) and
- Any subject may be discontinued for any sound medical reason at the discretion of the investigator.

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

Discontinued subjects will not be replaced.

8.7 Study Termination

The study may be stopped at an investigative site at any time by the IRB, regulatory authorities, investigator, the sponsor, and/or Ora with appropriate notification.

8.8 Study Duration

An individual subject's participation will involve at least 6 visits over approximately a 10-week (~70 days) period (56 days of treatment and 14 days pre-screening).

8.9 Monitoring and Quality Assurance

During the course of the study, a monitor, or designee, will make routine site visits to review protocol compliance, assess study drug/device accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. 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 check. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (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) associated with medical device.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

If a female has a positive pregnancy test during the study, the investigator will notify Ora immediately (within 24 hours) via the Pregnancy Report Form and also report on the appropriate eCRF. Any subject found to be pregnant during the course of the study shall be discontinued from the study. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall follow and document medical findings throughout the pregnancy through to the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from baseline (Visit 2) will be considered an Adverse Event.

9.1.1 Reporting an Adverse Event of Special Interest

For all conjunctivitis (bacterial, viral, and hypersensitivity) AEs, the PI (or assigned study personnel) must complete a Conjunctivitis Adverse Events Reporting Instructions form. A copy of the form with a photo of the subject's eyes should be provided to Ora and the study sponsor within 72 hours of becoming aware of the event.

9.1.2 Severity

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

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

9.1.3 Relationship to Investigational Product

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

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
  - *Definite:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
  - *Probable:* Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IPis the most likely of all causes.
  - *Possible:* Relationship exists when the AE follows a reasonable sequence from the time of administration but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- ***Not Suspected*:** A reasonable possibility does not exist that the IP caused the AE. A not suspected AE can further be defined as:
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrenceof the AE are not reasonably related in time, OR exposure to IP has not occurred.

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

9.1.4 Expectedness

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

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

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

The investigator should initially classify the expectedness of an AE. The Medical Monitor will review and determine the expectedness of all AE/SAEs following the investigator's assessment. The final classification of an AE is subject to the sponsor's determination.

9.2 Serious Adverse Events (SAE)

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

- Death
- A life-threatening AE
- Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, mighthave caused death
- Inpatient hospitalization or prolongation of existing hospitalization
- Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: Emergency room visits, outpatient, same day, and ambulatory procedures, observation and short stay units, rehabilitation facilities, hospice facilities, and nursing homes.
- Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect

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

9.3 Procedures for Reporting Adverse Events

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

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

9.3.2 Reporting a Serious Adverse Event

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

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

Contact information for reporting SAEs, AESIs, and pregnancies:

Ora Safety Group: Email Address: VELOS3Safety@oraclinical.com	
Name: Title: Office Telephone: Mobile Phone: 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 arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora andSponsor should be notified before unmasking a subject's study drug treatment. The unmasked subject will be discontinued from the study.

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

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the subject is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up attempts will be recorded 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.

Any unresolved AEs or SAEs upon completion of the subject's last study visit will be followed for up to 30 calendar days by the study staff until the event or its sequelae resolve or stabilize at a level acceptable to the study physician. In addition, any newly identified AEs or SAEs determined to be potentially related to study IP or procedures after the subject's exit visit will be followed for up to 30 calendar days by the site staff until the event or its sequelae resolve or stabilizes at a level acceptable to the study physician, subject withdraws consent, or no further information can reasonably be gathered.

The investigator shall follow all pregnancies and document medical findings throughout the pregnancy through to the outcome of the pregnancy. The investigator will retain reports together with the subject's source documents and will provide a copy of all documentation to Ora.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. The primary analysis will be performed on the ITT population with the primary estimand. Subjects in the ITT population will be analyzed as randomized.
- Per Protocol Population – The per protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.
- Safety Population – The safety population includes all randomized subjects who have received at least one dose of the IP. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.

Note: Additional safety subgroup populations may be defined in the Statistical Analysis Plan (SAP).

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and efficacy data will be performed for the ITT population. The primary efficacy analysis will also be performed on the PP population as a supportive analyses.

10.2 Statistical Hypotheses

The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided at a significance level of 0.05. The primary endpoints will be tested in a hierarchical fixed sequence in the following order:

H_{01}: There is no difference in change from baseline (V2) of CCSS at Day 57 ± 3 (V6, Week 8) in the study eye between tanfanercept ophthalmic solution 0.25% and placebo ophthalmic solution in the ITT population (Ex. H_{01}: $\mu_t = \mu_p$).

H_{A1}: The change in baseline (V2) of CCSS at Day 57 ± 3 (V6, Week 8) in the study eye is less with tanfanercept ophthalmic solution 0.25% than placebo ophthalmic solution in the ITT population (Ex. H_{A1}: $\mu_t < \mu_p$).

H_{02}: There is no difference in change from baseline (V2) of EDS from VAS at Day 57 ± 3 (V6, Week 8) between tanfanercept ophthalmic solution 0.25% and placebo ophthalmic solution in the ITT population (Ex. H_{02}: $\mu_t = \mu_p$).

H_{A2}: The change in baseline (V2) of EDS from VAS at Day 57 ± 3 (V6, Week 8) is less with tanfanercept ophthalmic solution 0.25% than placebo ophthalmic solution in the ITT population (Ex. H_{A2}: $\mu_t < \mu_p$).

10.3 Sample Size

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

This study is expected to enroll 150 subjects in each of the two treatment arms, for a total of 300 randomized subjects. Assuming a 10% drop out rate, 135 subjects per group are expected to complete the study.

Assuming a common standard deviation in the change from baseline (V2) to Day 57 ± 3 (V6, Week 8) for CCSS of [redacted]units, a sample size of 135 evaluable subjects per group will have 99.4 % power to detect a difference of [redacted]units between the active treatment group and the placebo group at a significance level of 0.05.

10.4 Statistical Analysis

10.4.1 General Considerations

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

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

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

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

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

10.4.2 Unit of Analysis

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

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria. If only one eye qualifies then the single qualifying eye will be the study eye. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse (higher) central corneal fluorescein staining at Visit 2. If the central corneal fluorescein staining is the equivalent in both eyes, then the right eye will be selected as the study eye.

10.4.3 Missing Data

The primary efficacy analyses will be performed using the multiple imputation methodology specified in Estimand 1. Additional sensitivity analyses will be executed including:

- Multiple imputation via placebo group-based pattern mixture models (PMM) imputation with the ITT population under the assumption of missing not at random for all missing data.

- Last Observation Carried Forward (LOCF) imputation methodology using the ITT population
- Observed data only using ITT and PP populations.

No secondary efficacy endpoints or safety endpoints will be imputed.

10.4.4 Multiplicity Consideration

Hierarchical fixed sequence testing will be used to maintain the type I error rate. The primary analysis will first test the difference in the change from baseline (V2) of central corneal fluorescein staining in the study eye at Day 57 ± 3 (V6, Week 8) in the ITT population. If the test of the difference is statistically significant at the two-sided alpha = 0.05 level in favor of tanfanercept, then the study will be considered a success, tanfanercept will be declared to be superior to placebo in the change from baseline (V2) of central corneal fluorescein staining at Day 57 ± 3 (V6, Week 8), and the difference in the change from baseline (V2) of eye dryness score at Day 57 ± 3 (V6, Week 8) will then be tested at the two-sided alpha = 0.05 level in the ITT population.

If, in addition to a statistically significant test of the difference in change from baseline (V2) of central corneal fluorescein staining in the study at Day 57 ± 3 (V6, Week 8) in favor of tanfanercept, the test of the difference in the change from baseline (V2) of eye dryness score at Day 57 ± 3 (V6, Week 8) in the ITT population is also statistically significant in favor of tanfanercept, then tanfanercept will be declared superior to placebo in both the change from baseline (V2) of central corneal fluorescein staining andthe change from baseline (V2) of eye dryness score at Day 57 ± 3 (V6, Week 8).

Secondary efficacy analyses will not be type-I error controlled and will be considered exploratory and hypothesis-generating.

10.4.5 Primary Efficacy Analyses

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

The primary analysis of the primary endpoints will use the ITT population for the primary endpoints of Change from Baseline (CFB) of CCSS at Day 57 ± 3 and CFB of EDS at Day 57 ± 3. If the rate of missing data for a primary endpoint is balanced between the two treatment groups (demonstrated by Fisher's exact test with a p-value ≥ 0.05) or the rate of missing data for an endpoint is less than 10% in all subjects, then primary analysis will be executed using MMRM with multiple imputation methodology using the following estimand:

Estimand 1:

- Population:
  - ITT population
- Endpoint:
  - CFB in CCSS in the study eye at Day 57 ± 3 in the ITT population
  - CFB in EDS from VAS at Day 57 ± 3 in the ITT population
- Intercurrent event:
  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed. [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance. [treatment policy strategy]
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed. [treatment policy strategy]
  - Withdrawal due to lack of efficacy or adverse events. Missing values assumed to be missing not at random will be multiply imputed using placebo group-based PMM imputation. [hypothetical strategy]
  - Missing data with withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events. Missing values assumed to be missing at random will be multiply imputed using randomized treatment group-based Markov Chain Monte Carlo (MCMC) imputation. [hypothetical strategy].
- Population-level summary:
  - Difference in the mean CFB in CCSS in the study eye at Day 57 ± 3 between tanfanercept and placebo in the ITT population.
  - Difference in the mean CFB in EDS (VAS) at Day 57 ± 3 between tanfanercept and placebo in the ITT population.

If the rate of missing data for an endpoint is imbalanced between treatment groups (demonstrated by Fisher's exact test with a p-value of <0.05) and the rate of missing data for an endpoint is ≥ 10% in all subjects, then the primary analyses will utilize the ITT population with single imputation methodology specified in Estimand 2 using the permutation test with trimmed means methodology.

Estimand 2:

- Population:
  - ITT population

- Endpoint:
  - CFB in CCSS in the study eye at Day 57 ± 3 in the ITT population
  - CFB in EDS from VAS at Day 57 ± 3 in the ITT population
- Intercurrent event:
  - Discontinuation of study medications is ignored. Measures obtained after discontinuation of study medication will be analyzed [treatment policy strategy]
  - Non-optimal compliance is ignored. Measures will be analyzed regardless of treatment compliance [treatment policy strategy]
  - Use of prohibited concomitant medications is ignored. Measures obtained after use of prohibited concomitant medications will be analyzed [treatment policy strategy]
  - Withdrawal or missed assessments for any reason. Missing values will be singly imputed using randomized treatment group-based worst observed value imputation [hypothetical strategy]. Note: imputed values will ultimately be trimmed from analyses per trimmed means methodology.
- Population-level summary:
  - Difference in the mean CFB in CCSS in the study eye at Day 57 ± 3 between tanfanercept and placebo in the ITT population

The proportion of data trimmed in the permutation test with trimmed means analysis will be dependent on the maximum rate of missing data in any treatment group using the following:

Maximum Rate of Missing Data (%)	Data Trimmed (%)
10% to <20%	20%
20% to <30%	30%

MMRM will be used to compare the change from basline in CCSS at Day 57 ± 3 (V6, Week 8), as measured on the Ora Calibra® scale, between Tanfanercept Ophthalmic Solution 0.25% and Placebo. The MMRM will include terms for baseline in CCSS, site, visit, treatment group, and the interaction of visit and treatment group as fixed effects with correlated errors. An unstructured covariance matrix will be initially fit with the model. Should an unstructured covariance matrix fail to achieve convergence then alternate covariance structures will be attempted to be detailed in the Statistical Analysis Plan (SAP). The inclusion of site in the final model will be evaluated at an alpha level of 0.1.

If site is retained in the final primary analyses, the site by treatment interaction will be explored in a separate analysis to evaluate how the treatment effect may differ across sites. All post-baseline visits will be used in the model. Two-sample t-tests will also be conducted as supportive analyses.

Change from baseline of EDS from VAS at Day 57 ± 3 (V6, Week 8) between tanfanercept ophthalmic solution 0.25% and placebo will be analyzed as described for CFB of CCSS with adjustment for baseline EDS instead of baseline CCSS.

Example SAS code for the MMRM of the primary analyses is as follows:

```
PROC MIXED DATA = INDATA METHOD = REML;
  CLASS SUBJID TREATMENT VISIT SITE;
  MODEL CHG = BASELINE SITE VISIT|TREATMENT / DDFM = KR SOLUTION COVB;
  REPEATED VISIT/SUBJECT = SUBJID TYPE = UN R RCORR;
  LSMEANS TREATMENT TREATMENT*VISIT / CL PDIFF;
RUN;
```

where

- *SUBJID* is the subject ID
- *TREATMENT* is the name of the treatment group variable
- *VISIT* is the visit
- *SITE* is the site id
- *CHG* is the change from baseline
- *BASELINE* is the baseline value

An alternate MMRM will be executed as a sensitivity analyses for both primary endpoints. These additional models will include all terms in the final models of the primary analyses [redacted]

Additional exploratory comparisons of the mean absolute scores of the primary endpoints at both Day 57 ± 3 (V6, Week 8) and baseline (V2) between the treatment groups will be conducted using two-sample t-tests and MMRM.

Least squares means and standard errors for each treatment group and for the difference between treatment groups will be presented from the MMRM together with two-sided p-values and 95% confidence intervals. Two-sided exact p-values and 95% confidence intervals will be presented from the permutation test with trimmed means.

10.4.6 Secondary Efficacy Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max). CFB at visit will be summarized descriptively as well. No imputation will be performed for secondary efficacy variables. All analyses of secondary efficacy variables will use the ITT population with observed data only.

Corneal fluorescein staining by region and total, conjunctival lissamine green staining by region and total, TFBUT, conjunctival redness, unanesthetized Schirmer's test, symptoms from VAS, OSDI©, Ocular Discomfort Scale, and Ocular Discomfort & 4-Symptom Questionnaire will be analyzed by visit using two-sample t-tests and MMRM. All visit-based data will be analyzed at each visit. Changes from baseline at each post-baseline visit will be analyzed using MMRM with terms for baseline, visit (as a categorical term), treatment group and the interaction of visit and treatment group as fixed effects with correlated errors. No imputation will be performed for secondary efficacy variables. Secondary efficacy variables will be analyzed using the ITT population with observed data only unless otherwise specified in the Statistical Analysis Plan.

10.4.7 Safety Variables

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

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

10.4.8 Other Variables

Drop comfort Scale will be summarized by treatment group using descriptive quantitative statistics. Study eye and fellow eye will be summarized separately. Drop Comfort Questionnaire will be summarized by treatment group and visit using descriptive statistics. Other endpoints will be assessed using the Safety population.

10.4.9 Interim Analyses

No interim analyses are planned in this study.

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

This study will be conducted in compliance with the protocol, current GCPs, including the ICH Guidelines, and in general, consistent with principles that have their origin with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IPs in the countries involved will be adhered to. Any deviations to the protocol, GCPs, and ICH Guidelines will be documented and submitted to the IRB per IRB Guidelines.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject.

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

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

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 Ethical Conduct of the Study

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

11.3 Subject Confidentiality

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

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

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

11.4 Documentation

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

11.4.1 Retention of Documentation

All study related correspondence, subject records, ICFs, record of the distribution and use of all IPs and copies of eCRFs should be maintained on file for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

11.5.1 Labeling/Packaging

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

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

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

11.5.2 Storage of Investigational Product

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

11.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s) and is to only be used in accordance with this protocol. The 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.

11.5.4 Return or Disposal of Investigational Product

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

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

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff who have been trained on the system and have access to the system. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the last subject randomized completes Visit 6, the data from Visits 1- 6 will be locked. After final database lock, electronic copies of all applicable Subjects eCRF will be provided to each Investigator'Site to be maintained on file by the Investigator.

11.7 Handling of Biological Specimens

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

11.8 Publications

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

12 REFERENCES

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Schaumberg DA, Sullivan DA, Dana MR. Epidemiology of dry eye syndrome.Advances in experimental medicine and biology 2002;**506**: 989-98.

Stapleton, F., M. Alves, V. Y. Bunya, I. Jalbert, K. Lekhanont, F. Malet, K. S. Na, D. Schaumberg, M. Uchino, J. Vehof, E. Viso, S. Vitale and L. Jones (2017). "TFOS DEWS II Epidemiology Report." Ocul Surf **15**(3): 334-365

13 APPENDICES

APPENDIX 1: VELOS-3 SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Screening Visit 1 Day -14±2	Run-In Period (Up to 14 days) *Optional* Visit 1a	Baseline Visit 2 Day 1	Week 1 Visit 3 Day 8 ±1	Week 2 Visit 4 Day 15 ± 2	Week 4 Visit 5 Day 29 ± 2	Week 8 Visit 6 Day 57 ± 3 or Early Termination	Optional Blood Sample Collection Visit
Informed Consent / HIPAA	X							
Medical / Medication History and Demographics	X	X						
Placebo Run-in Collection			X					
Study Drug Collection				X	X	X	X	
Medical / Medication Update			X	X	X	X	X	
Pregnancy Test	X[2]						X[2]	
Ocular Discomfort Scale	X		X	X	X	X	X	
Ocular Discomfort & 4-Symptom Questionnaire	X		X	X	X	X	X	
VAS	X		X	X	X	X	X	
OSDI© Questionnaire	X		X	X	X	X	X	
Visual Acuity (ETDRS)	X	X	X	X	X	X	X	
Slit-lamp Biomicroscopy	X	X	X	X	X	X	X	
Conjunctival Redness	X		X	X	X	X	X	
TFBUT	X		X	X	X	X	X	
Fluorescein Staining	X		X	X	X	X	X	
Lissamine Green Staining	X		X	X	X	X	X	
Schirmer's Test	X		X		X	X	X	
Intraocular Pressure	X	X					X	

Procedure	Screening Visit 1 Day -14±2	Run-In Period (Up to 14 days) *Optional* Visit 1a	Baseline Visit 2 Day 1	Week 1 Visit 3 Day 8 ±1	Week 2 Visit 4 Day 15 ± 2	Week 4 Visit 5 Day 29 ± 2	Week 8 Visit 6 Day 57 ± 3 or Early Termination	Optional Blood Sample Collection Visit
Dilated Fundus Exam	X						X	
Review of Qualification Criteria	X		X					
Placebo Run-In Dispensation and Instillation	X							
Blood Sampling for Immunogenicity			X			X	X	
[redacted]								
Randomization			X					
Study Drug Instillation			X	X				
Drop Comfort Scale			X	X				
Drop Comfort Questionnaire			X	X				
Adverse Event Query	X	X	X	X	X	X	X	
Study Drug Dispensation			X	X[1]	X	X		
Confirm Dosing Compliance		X	X	X	X	X	X	
Exit Subject from Study							X	

[1] The Visit 2 study drug kit is re-dispensed at Visit 3 (as each kit includes 2-week supply of study drug).
[2] To women of child-bearing potential.

[redacted]

APPENDIX 2: PROHIBITED MEDICATIONS

Washout Period	**Prohibited Medication/Procedure/Surgery**	**Examples** *Examples listed **DO NOT** include all exclusionary medications/procedure/surgery within each category*
72 Hours (prior to V1)	Antihistamines (including ocular)	Zyrtec, Allegra, Claritin, Benadryl, Sudafed
	All other topical ophthalmic preparations	Includes any OTC artificial tear substitutes
7 days (prior to V1)	Contact Lenses	
14 days (prior to V1)	Corticosteroids	Hydrocortisone, Advair, Flonase, including EYSUVIS™
	Mast cell stabilizers (Including ocular)	Lodoxamide, Nedocromil, Pemirolast, Ketotifen
30 Days (prior to V1)	Oral aspirin or aspirin-containing products that have been taken on **UNSTABLE** dose. *If the subject is taking aspirin or aspirin-containing products, it must be taken on a STABLE dose and the dose cannot change during the study period.*	*Stable dose is defined as unchanged for at least 1 month prior to the start of Visit 1 and expected to remain unchanged throughout the study*
	Unstable** medications known to cause ocular drying.	The following medication classes: Antidepressants, Anticholinergics, Diuretics, Beta-Blockers
	Punctal Plugs (temporary or permanent)	
	Other Investigational Product or Device	

Washout Period	**Prohibited Medication/Procedure/Surgery**	**Examples** *Examples listed **DO NOT** include all exclusionary medications/procedure/surgery within each category*
45 days (prior to V1)	Systemic corticosteroids (include oral, nasal sprays, and inhalers)	
60 Days (prior to V1)	Cyclosporine-containing drops or lifitegrast ophthalmic solution	Restasis®, Cequa®, Xiidra®
	Any thermal pulsation treatment	LipiFlow, iLux, MiBo thermoflo, intense pulsed light
3 months (prior to V1)	Intraductal meibomian gland probing	
12months (prior to V1)	laser-assisted in situ keratomileusis	LASIK

Abbreviation: OTC = over the counter; V1 = Visit 1

APPENDIX 3: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

Visual Acuity Procedures (ETDRS Chart)

LogMAR visual acuity (VA) must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. VA testing should be done with the subject wearing their most recent correction. If at any visit after Visit 1, more than 10 letters in BCVA are lost compared to screening visit record, then refraction should be performed.

Equipment

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

Measurement Technique

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

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

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as 1 of 2 letters, he or she should be asked to choose 1 letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR VA for that eye.

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

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

Repeat the procedure for the left eye.

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

Slit-Lamp Biomicroscopy Procedures

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

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

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

Dilated Fundoscopy

Dilated fundoscopy will be performed using indirect ophthalmoscopy. The investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

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

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

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

Intraocular Pressure

Intraocular pressure will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. A single measurement is made to obtain a determination of IOP. The same tonometer employing the Investigator's standard technique will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale for Dry Eye

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

[redacted]

Visual Analogue Scale (VAS)

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

The subject will be asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on the horizontal line to indicate the current level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort." Subjects are to evaluate their current ocular discomfort symptoms as experienced while completing the questionnaire.

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

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

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

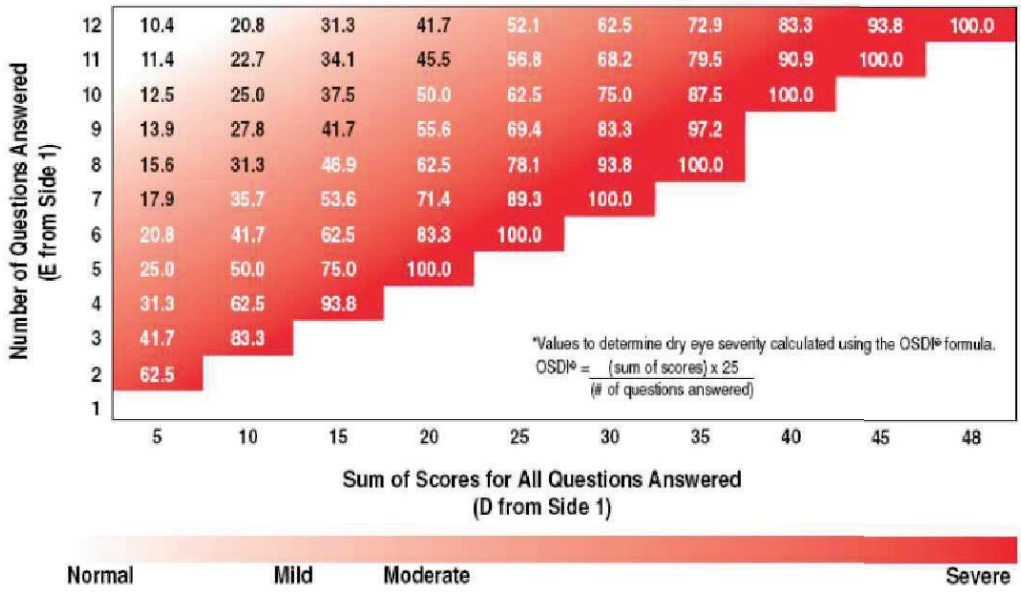
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1,2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



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

Ora Calibra® Conjunctival Redness Scale for Dry Eye

[redacted]

Tear Film Break-Up Time (TFBUT)

The examiner will instill [redacted] solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the subject will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT.

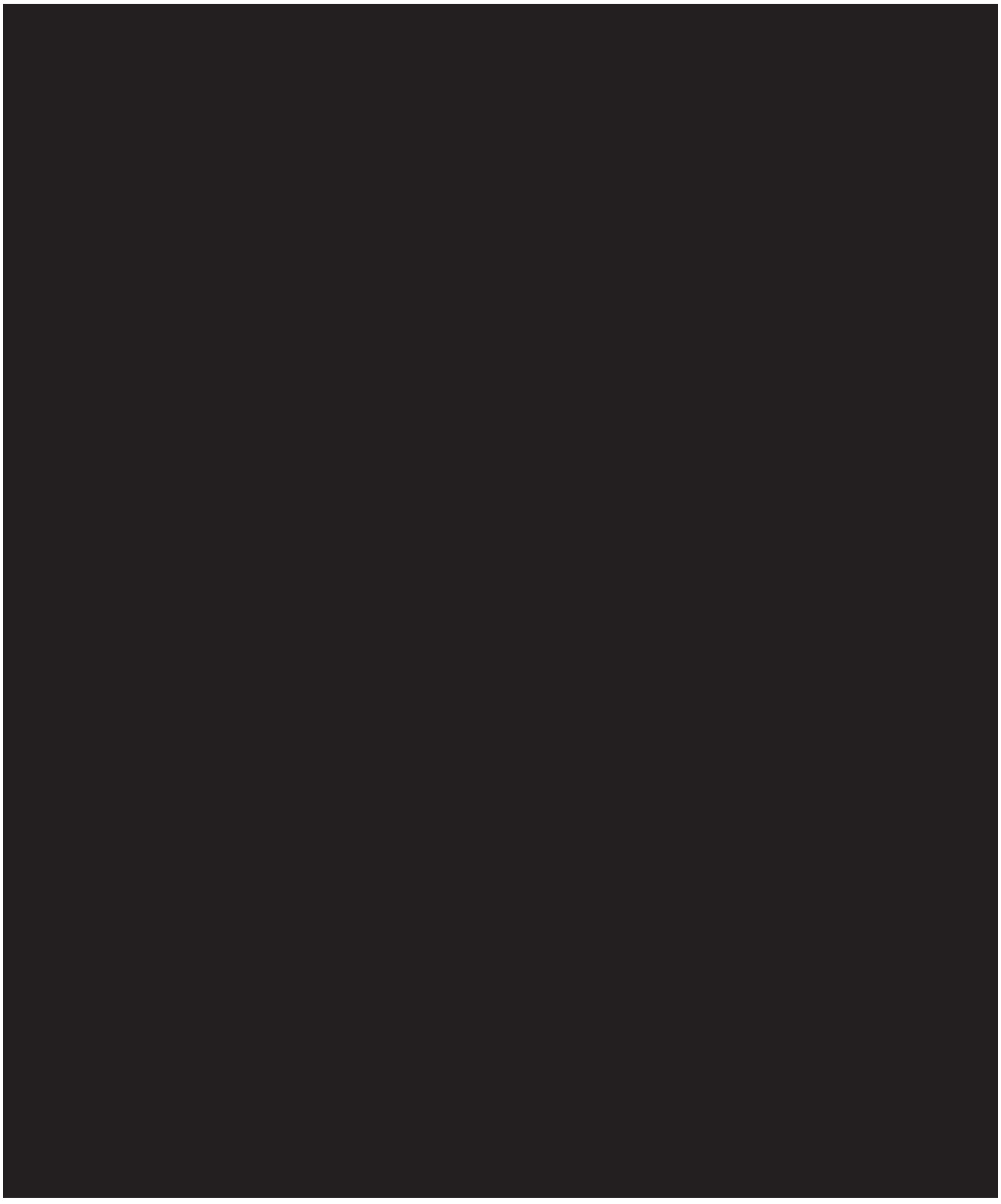
With the aid of a slit-lamp, the examiner will monitor the integrity of the tear film, noting the time it takes to form micelles from the time that the eye is opened. TFBUT will be measured in seconds using a stopwatch and a digital image recording system for the right eye followed by the left eye. A Wratten #12 yellow filter will be used to enhance the ability to grade TFBUT.

For each eye, 2 measurements will be taken and averaged unless the 2 measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement wouldbe taken and the 2 closest of the 3 would be averaged.

Fluorescein Staining

The examiner will instill [redacted] solution into the inferior conjunctival cul-de-sac of each eye (fluorescein strips are not allowed). In order to achieve maximum fluorescence, the examiner should wait approximately 3-5 minutes after instillation before evaluating fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will begraded with the Ora Calibra® Corneal and Conjunctival Staining Scale.

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



Lissamine Green Staining

The Investigator will instill [redacted] into the inferior conjunctival cul-de-sac and wait approximately 30 seconds before evaluating staining. The subject will be instructed to blink several times to distribute the lissamine green. The staining will be graded with the Ora Calibra® Corneal and Conjunctival Staining Scale.

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

[redacted]

Unanesthetized Schirmer's Test

Schirmer Tear Test will be performed at least 15 minutes after lissamine green, according to the following procedure:

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

Drop Comfort Assessments

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

Subject-Reported Drop Comfort Scale

[redacted]

Ora Calibra® Drop Comfort Scale

[redacted]

Subject-Reported Drop Comfort Questionnaire

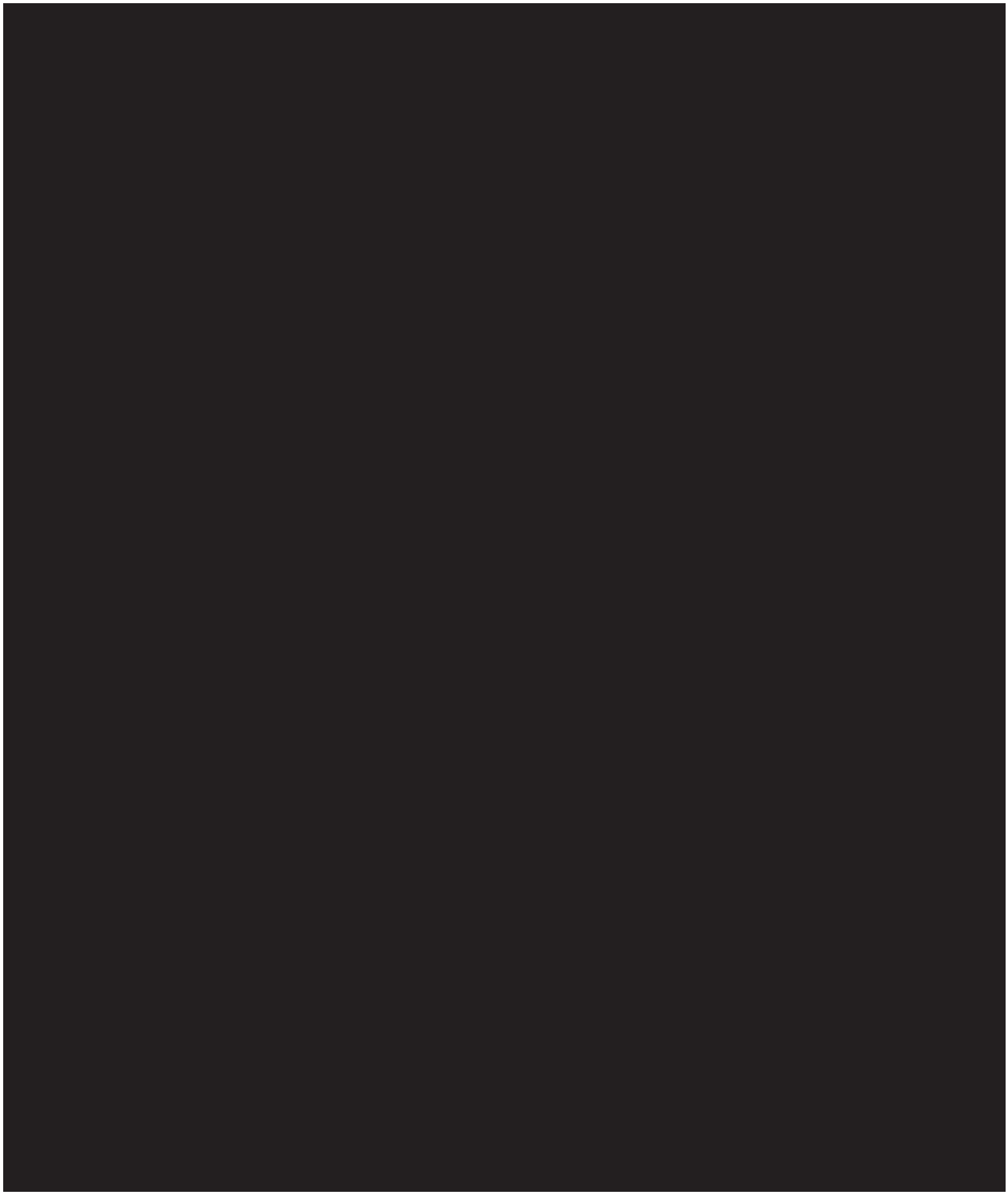
[redacted]

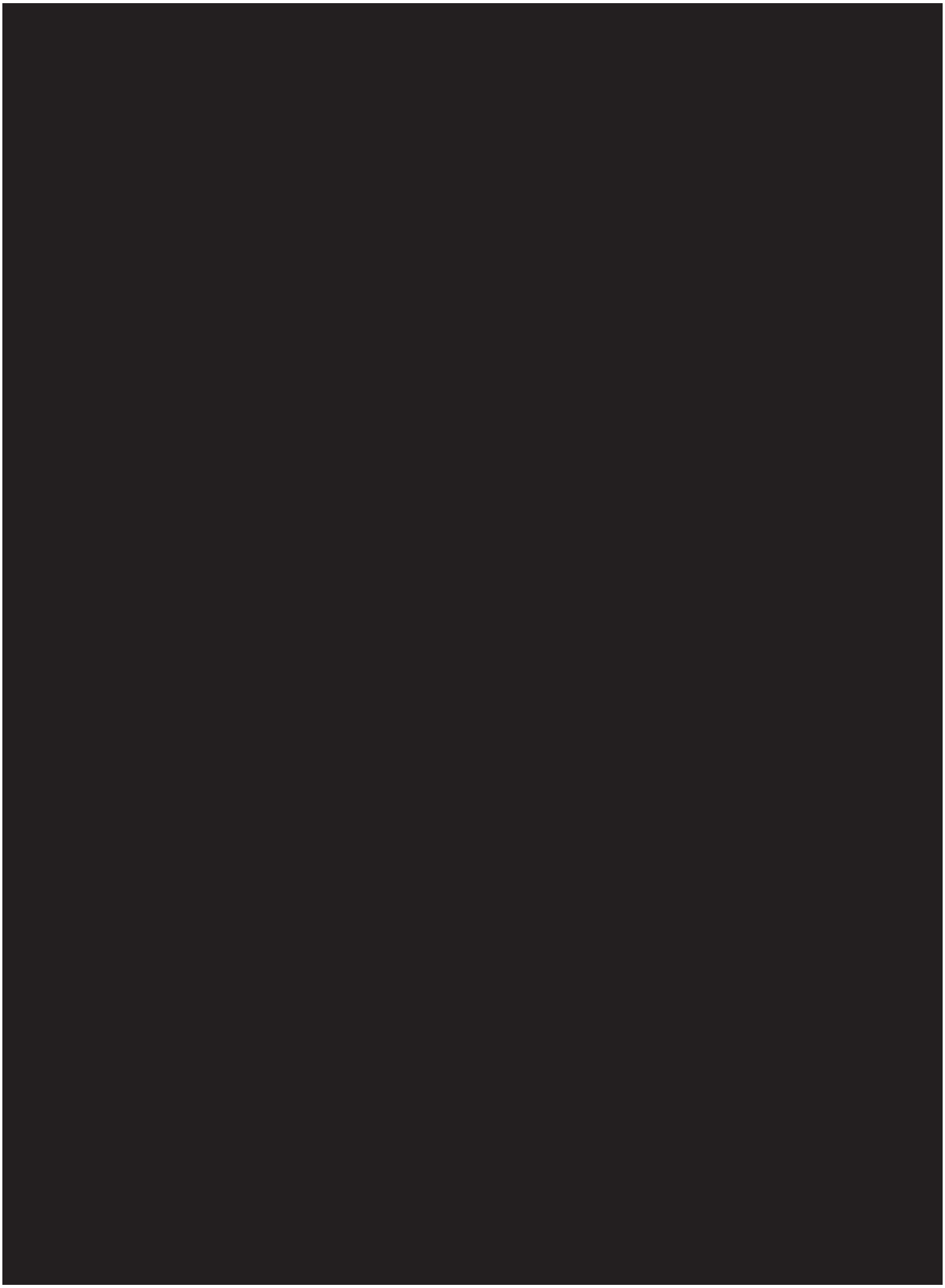
Ora Calibra® Drop Comfort Questionnaire

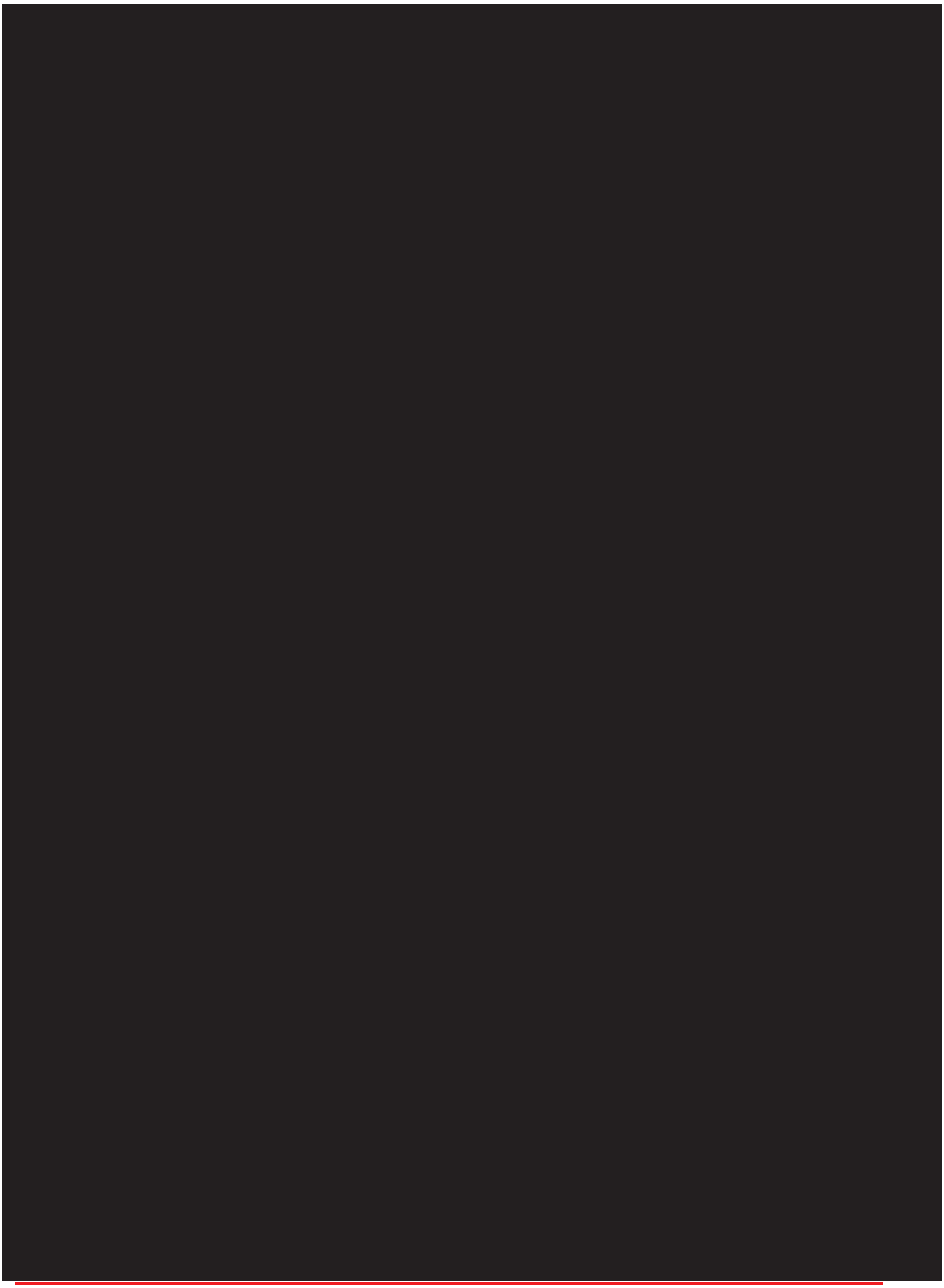
[redacted]

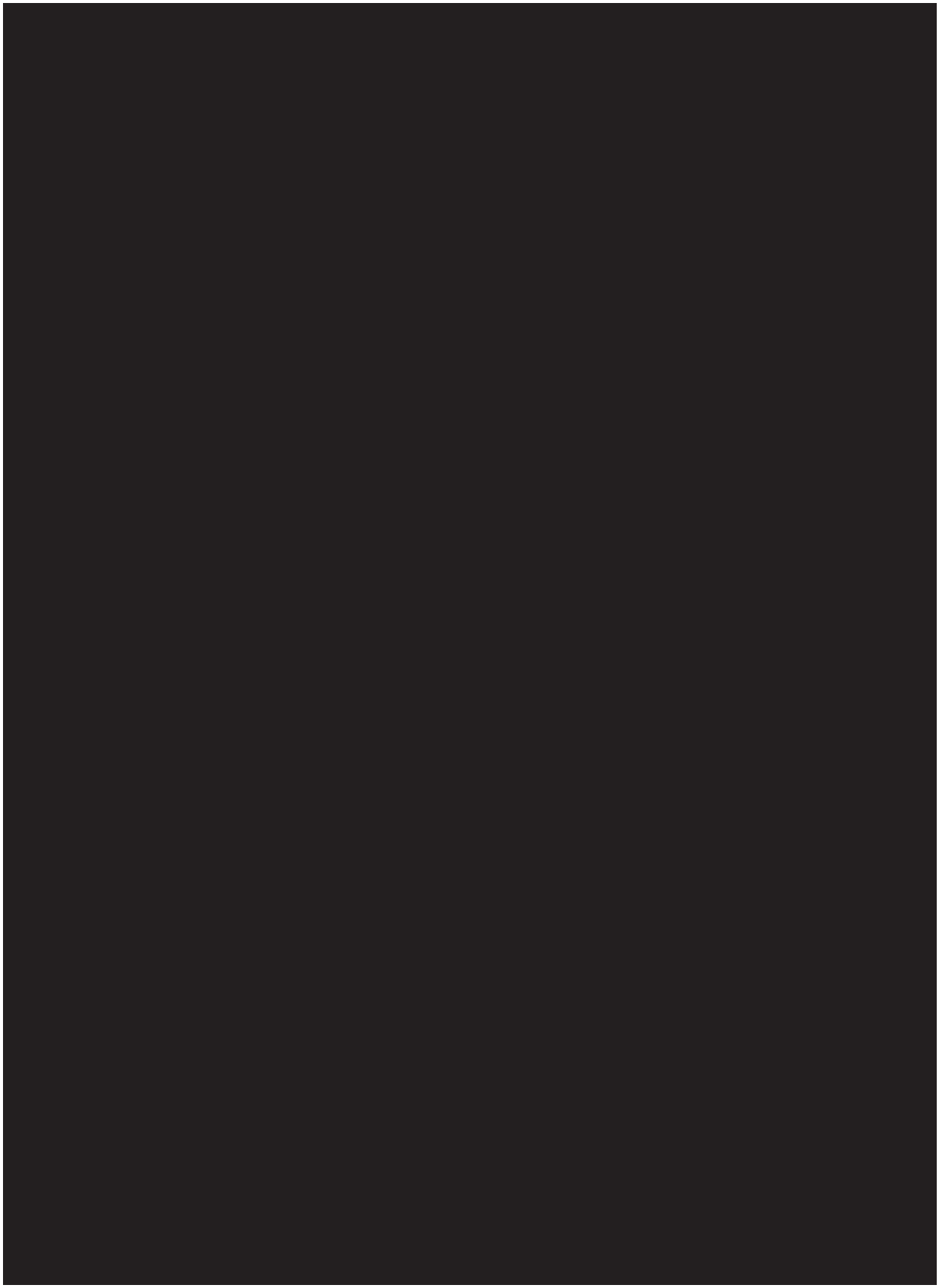
Blood Sampling for Immunogenicity Testing

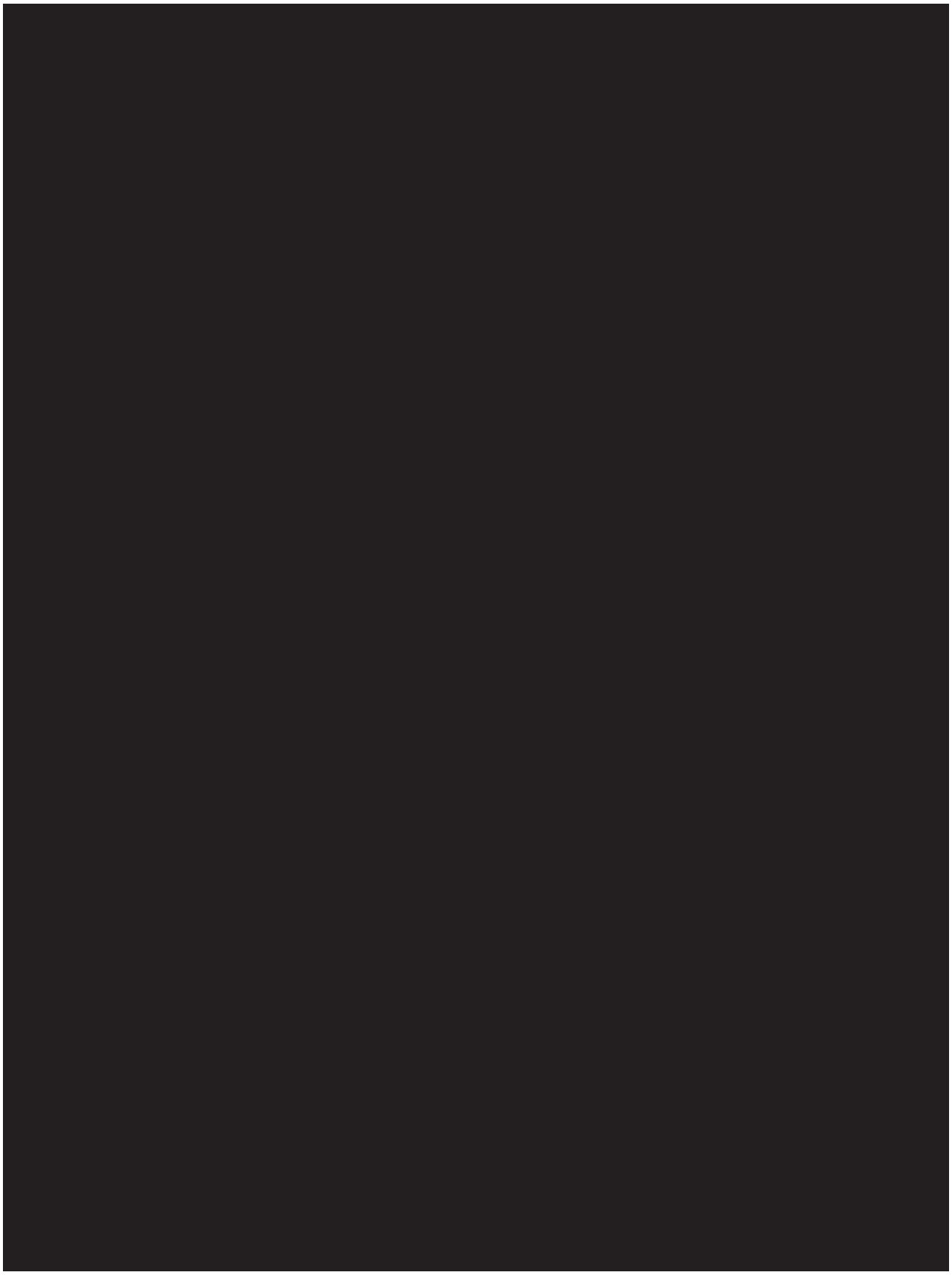
Serum blood draws will be collected at Visits 2, 5, and 6 for immunogenicity testing. Instructions for the collection, handling, and shipping of blood for immunogenicity testing are given in a separate laboratory manual.

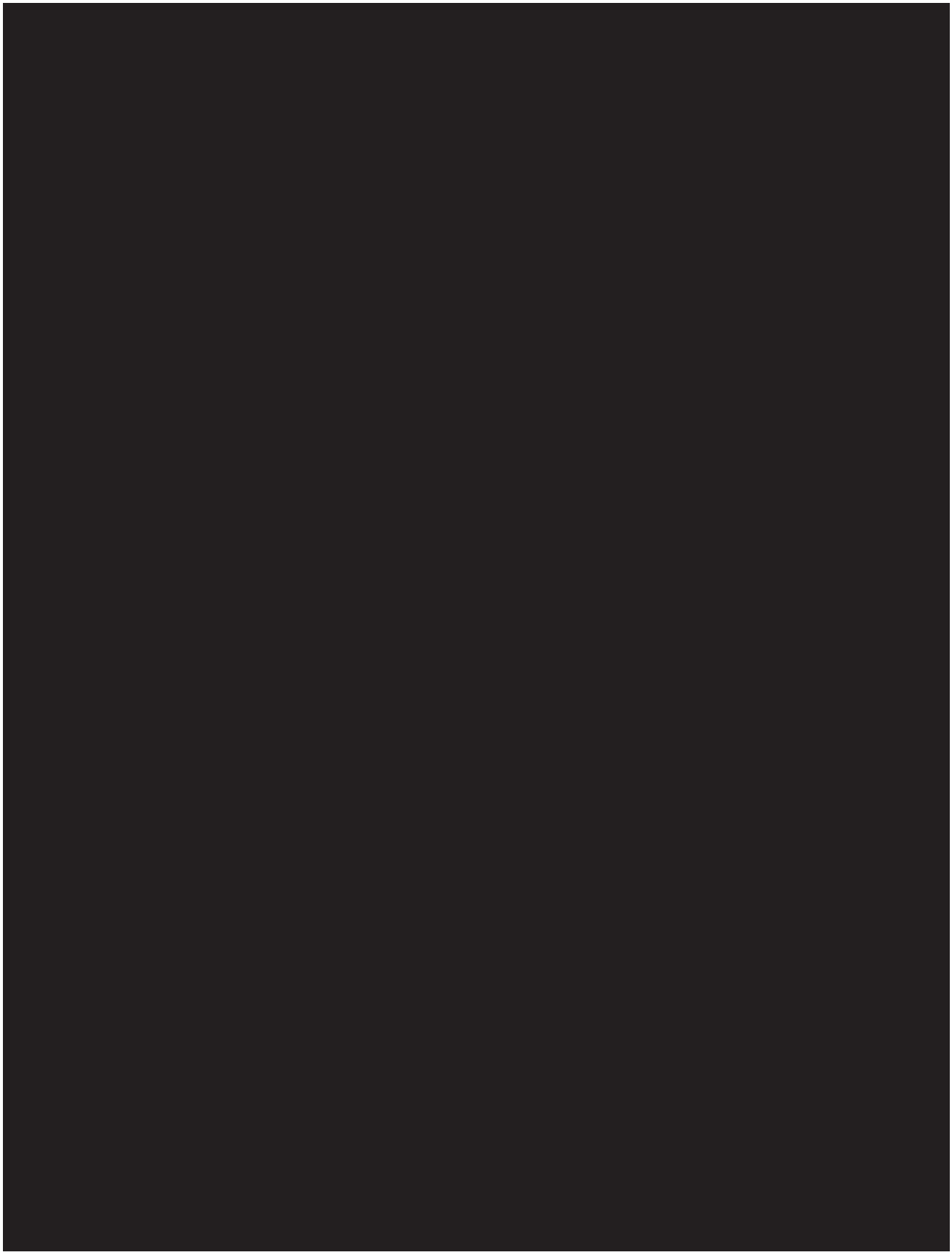


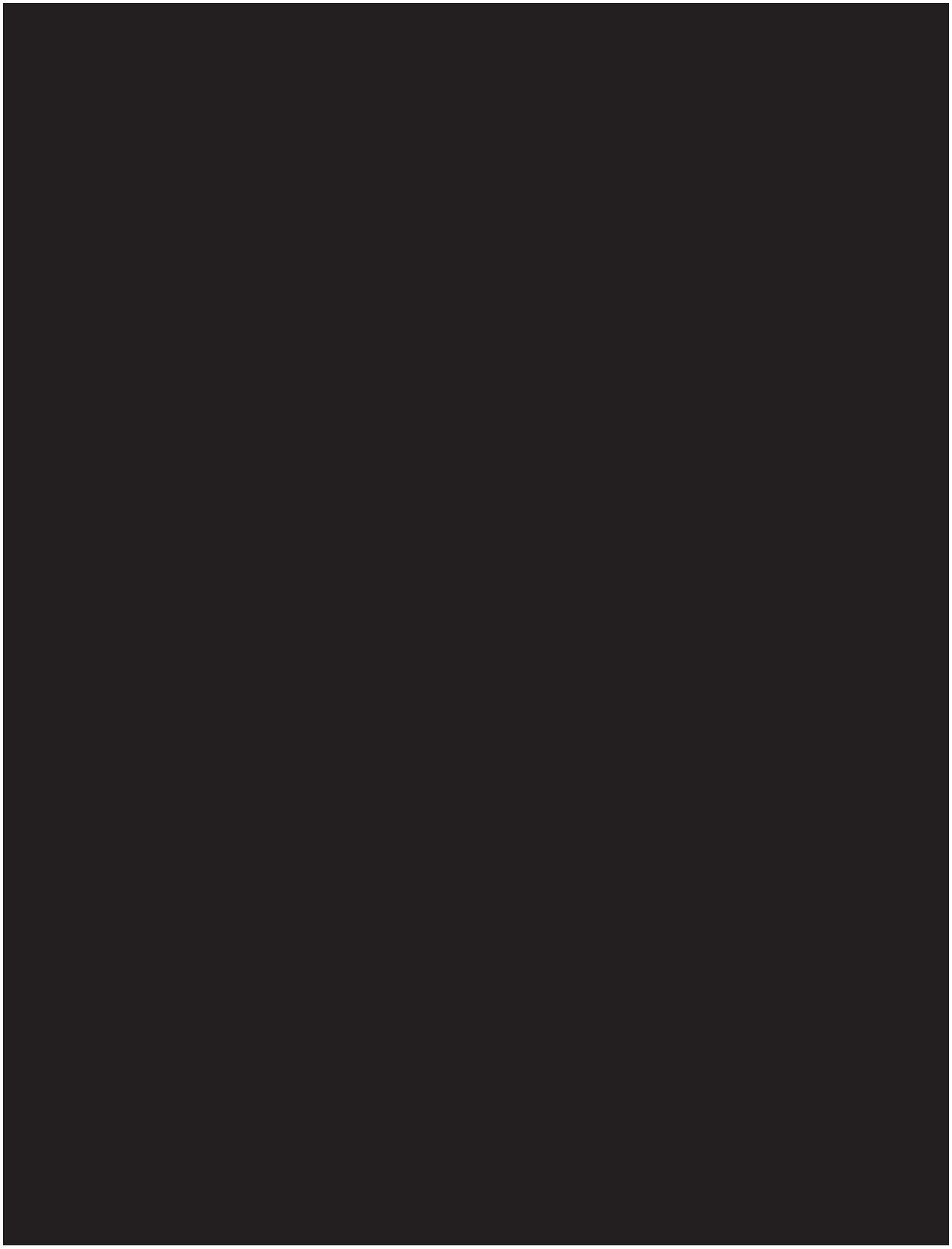


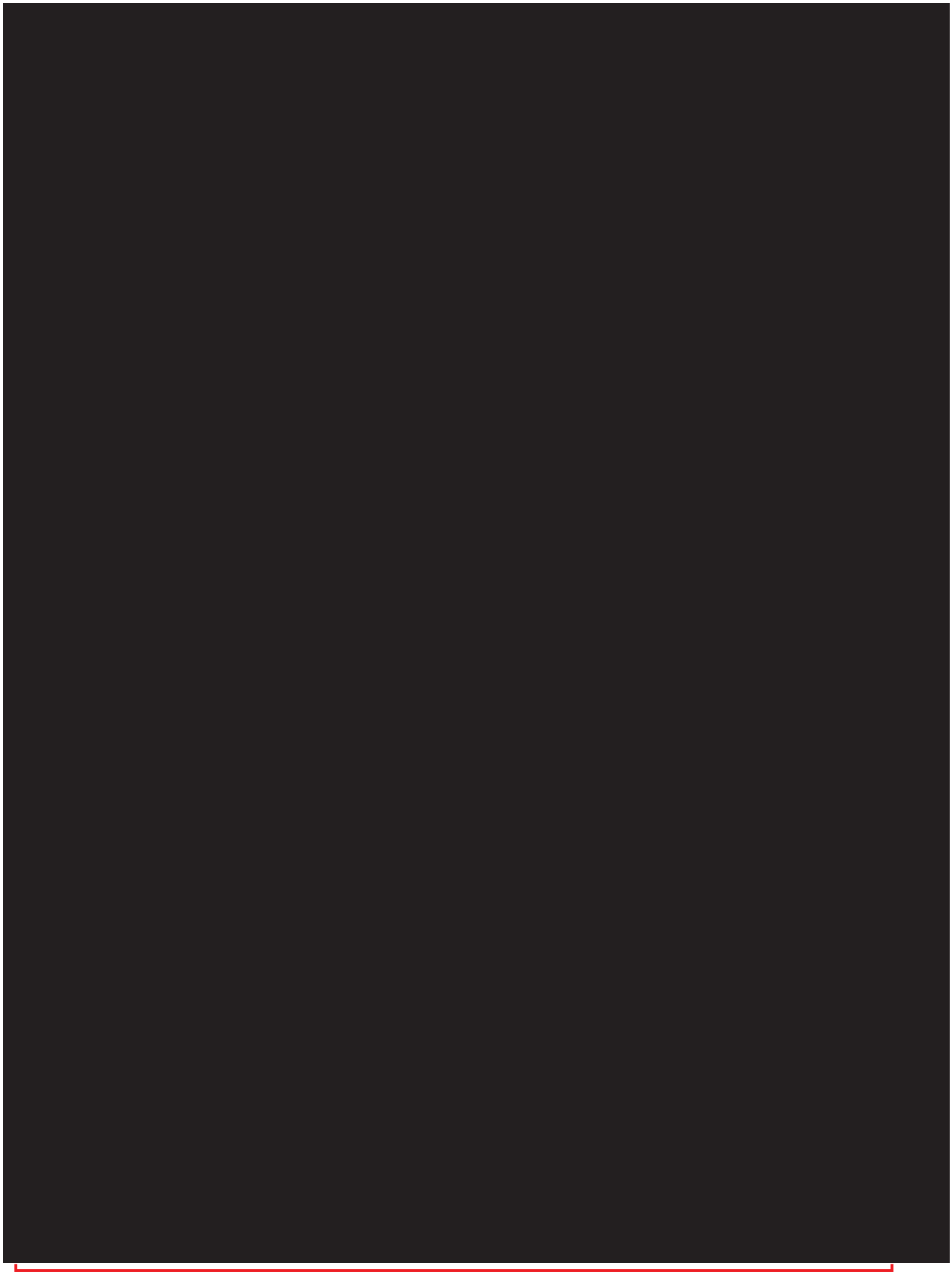


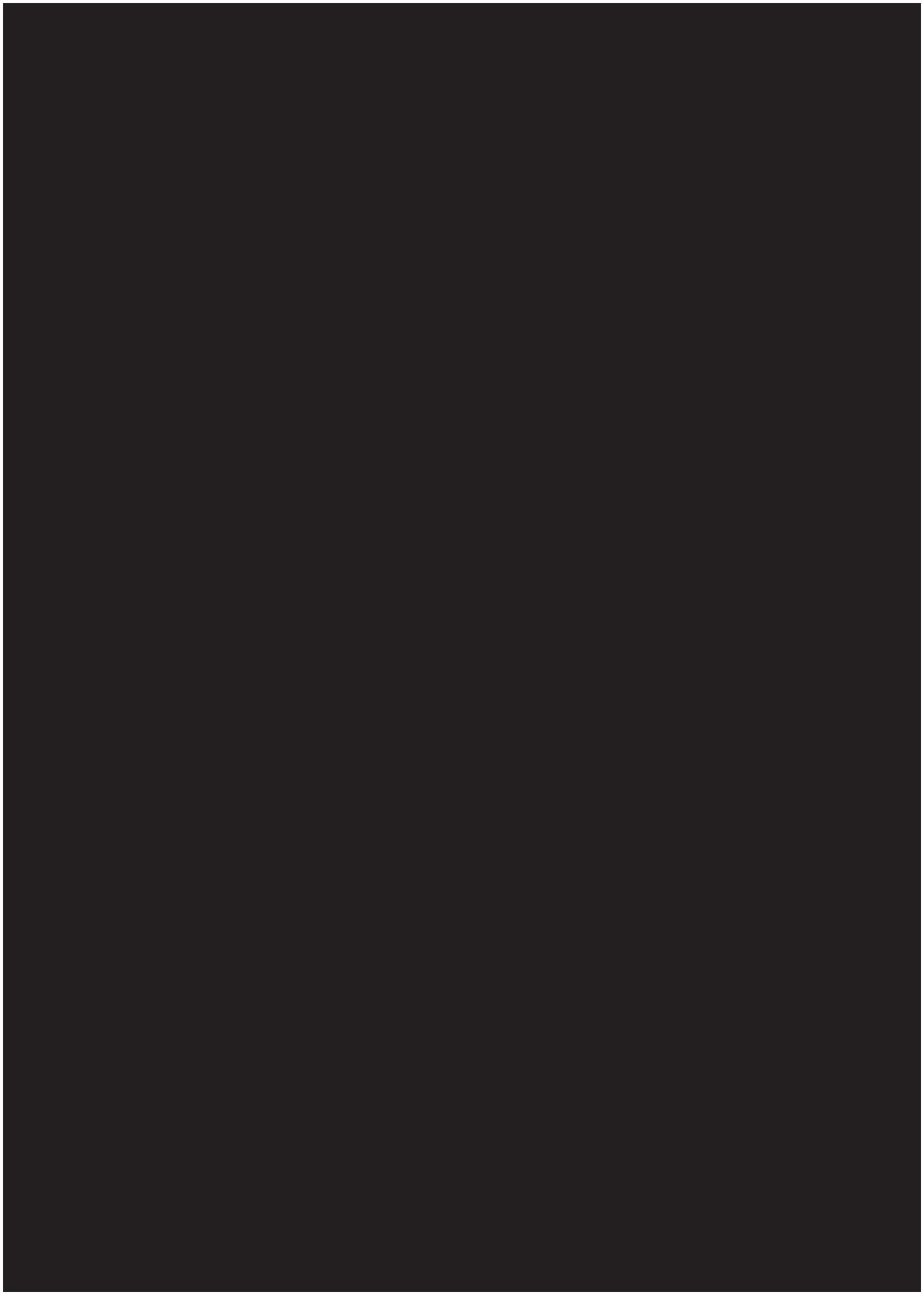


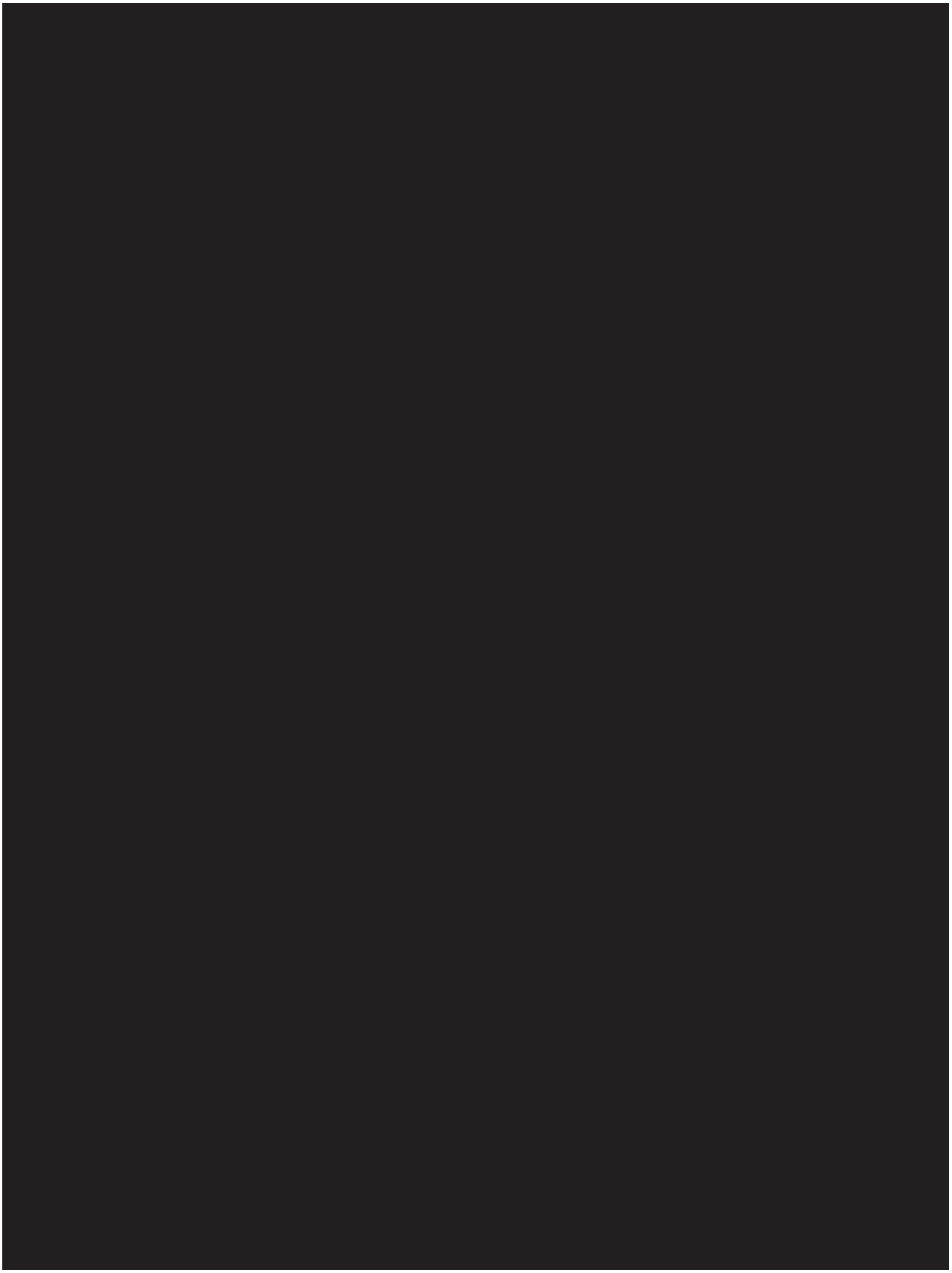


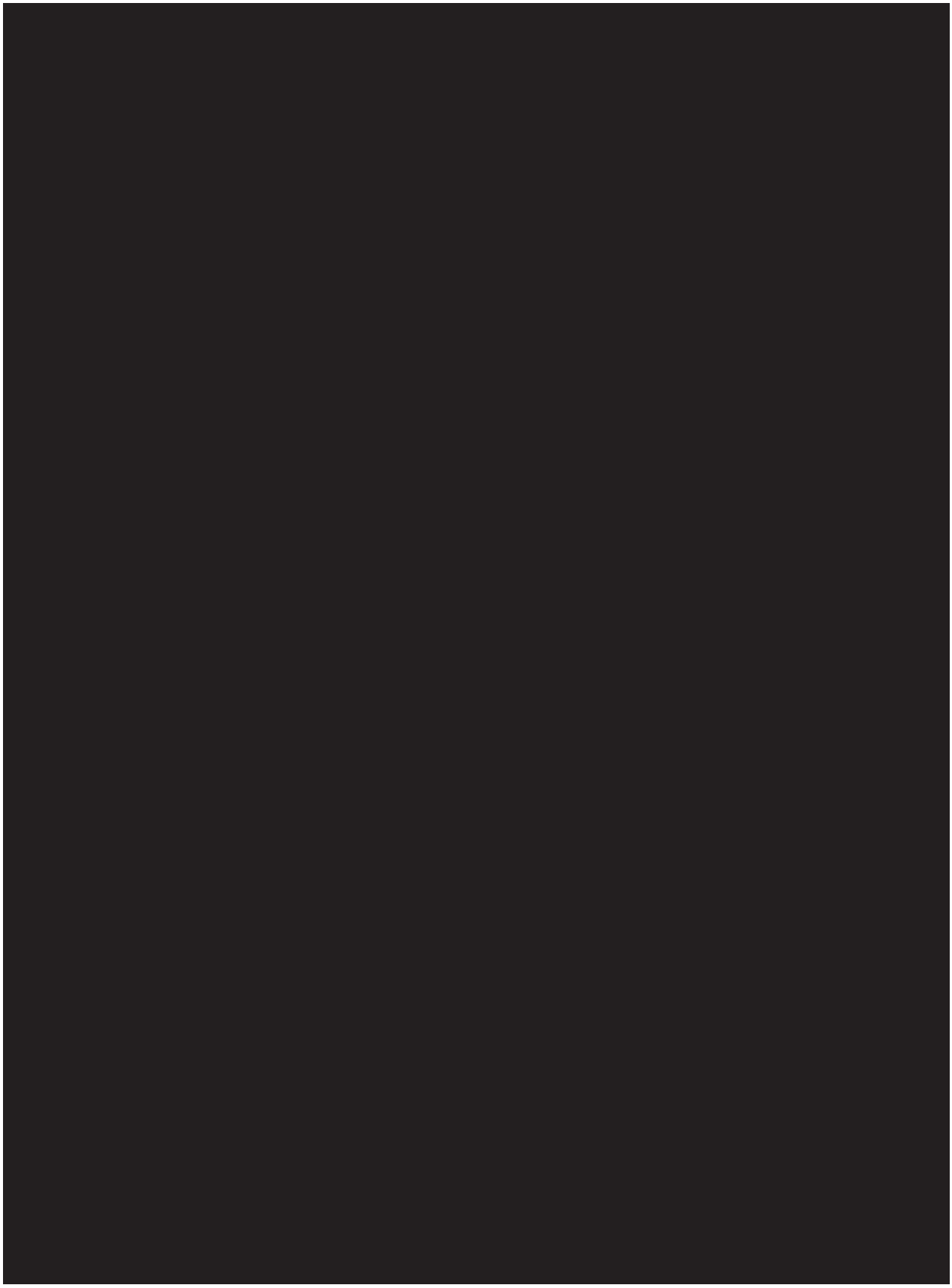


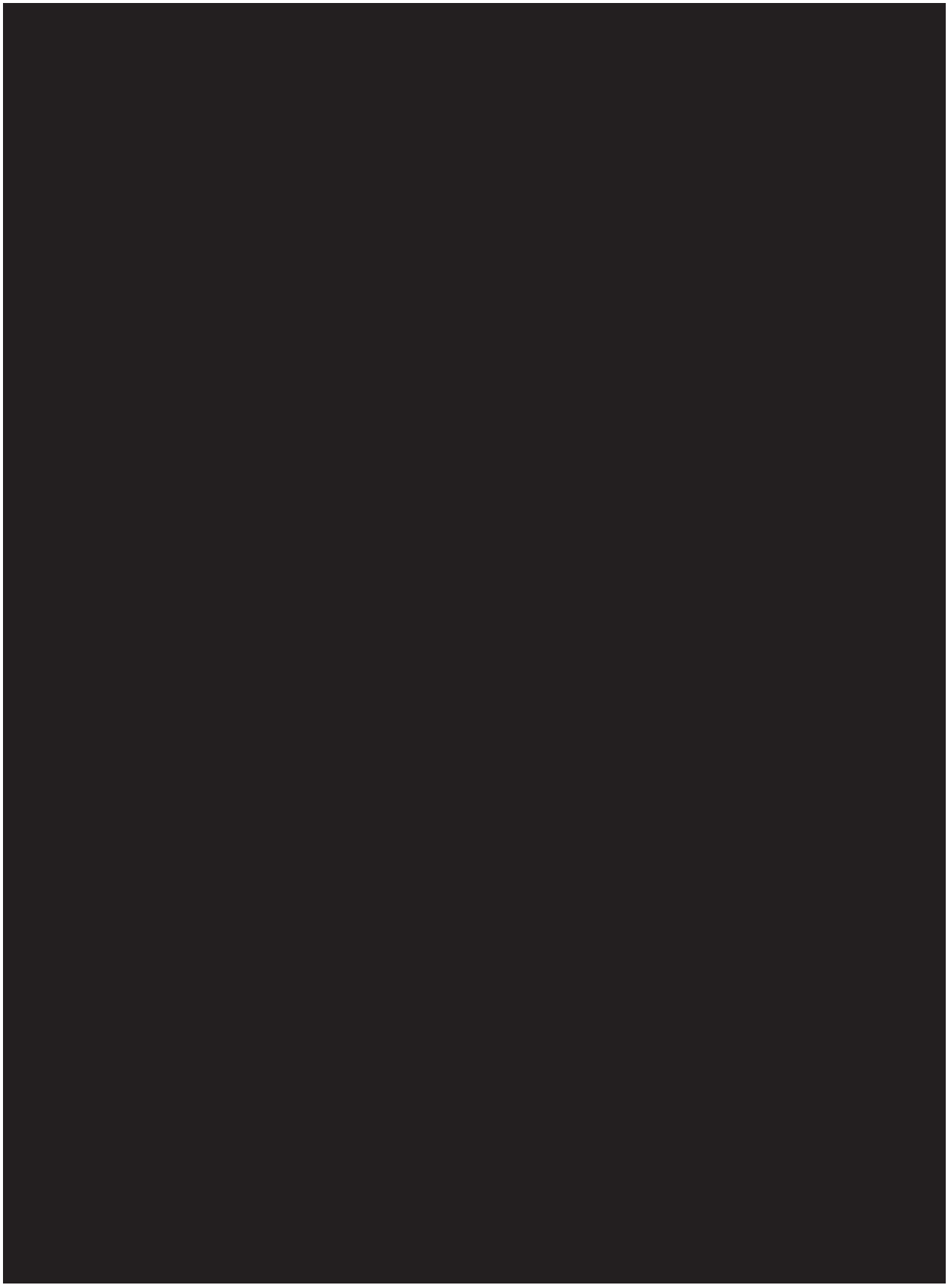


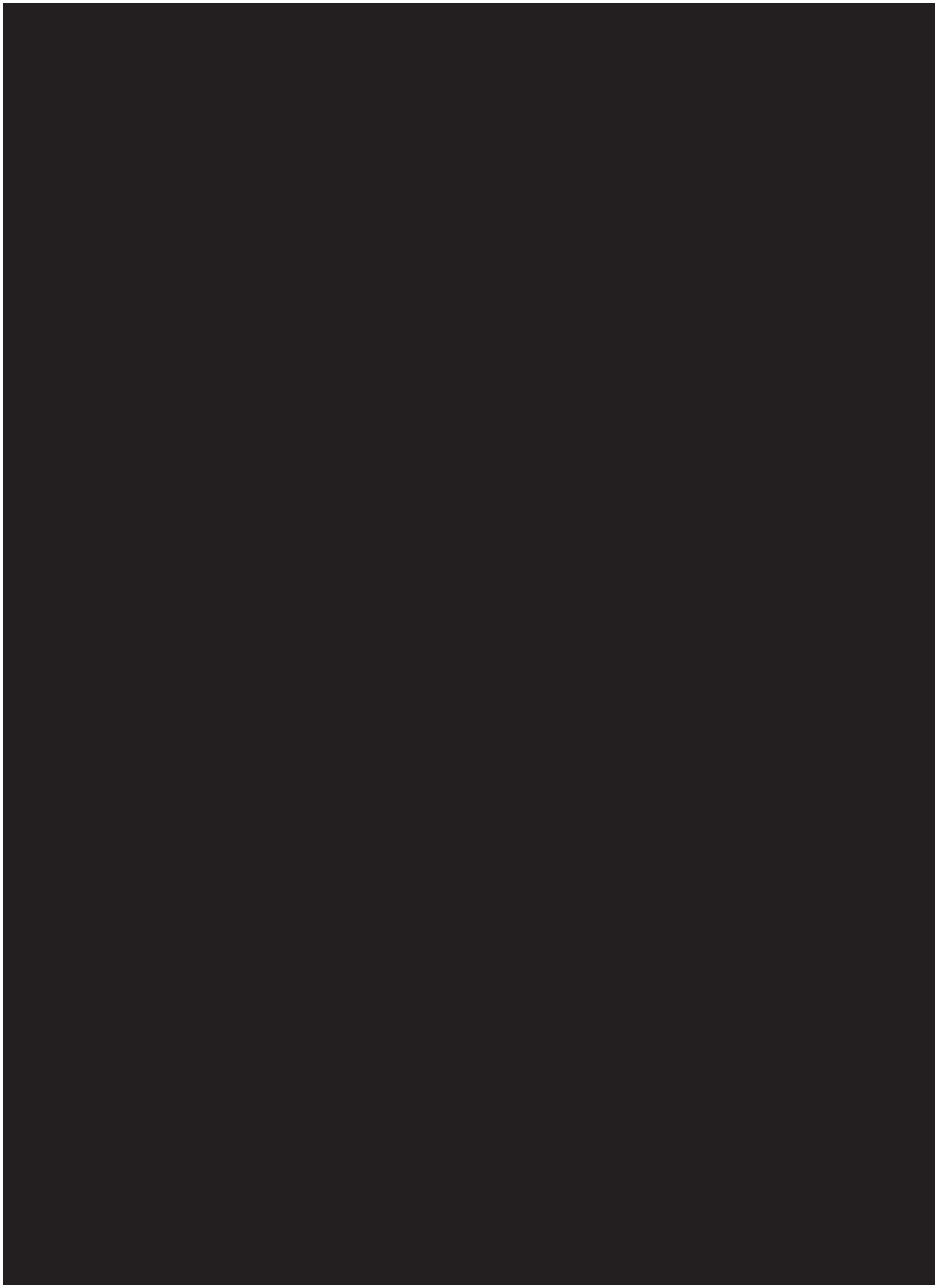


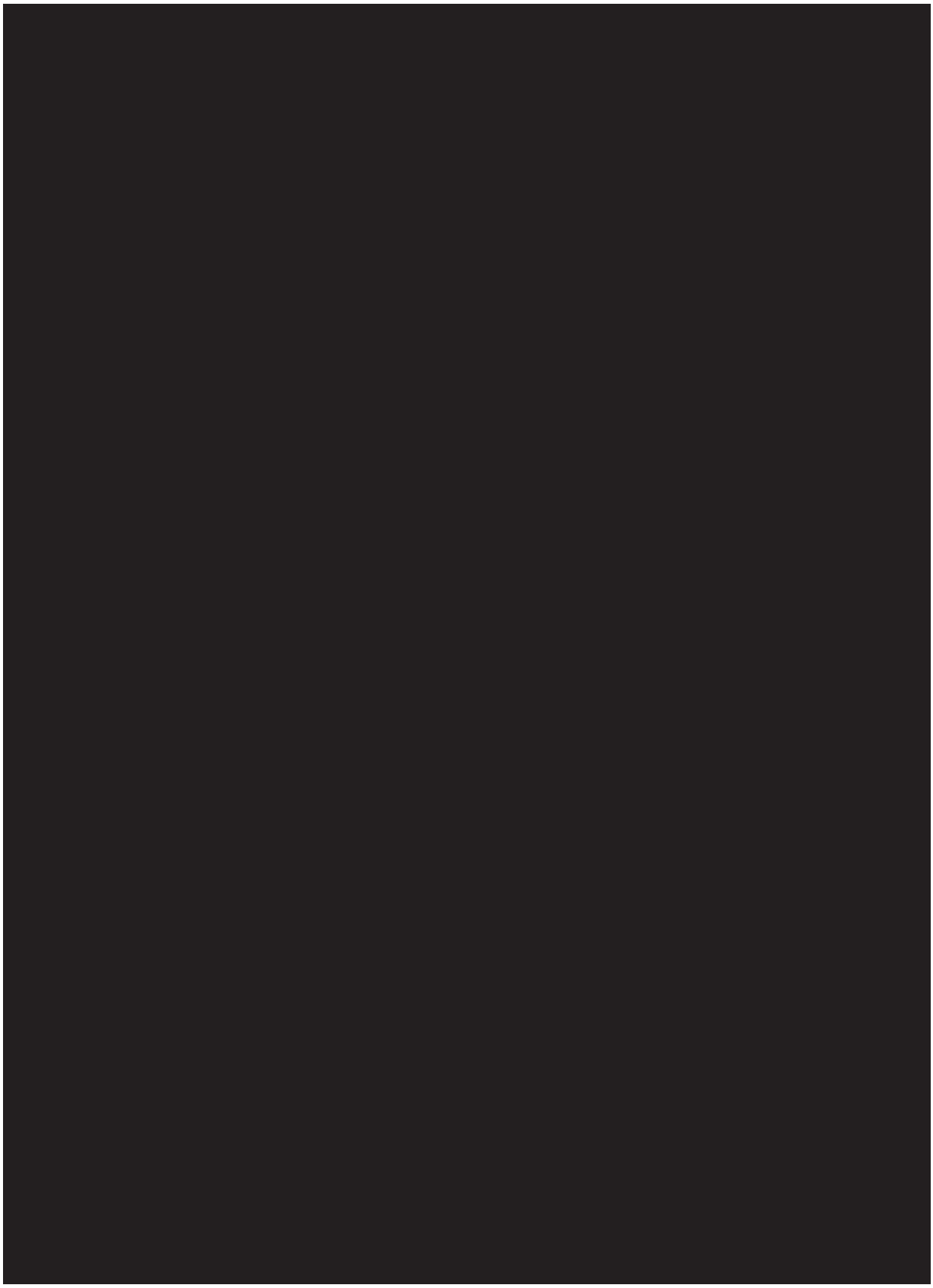


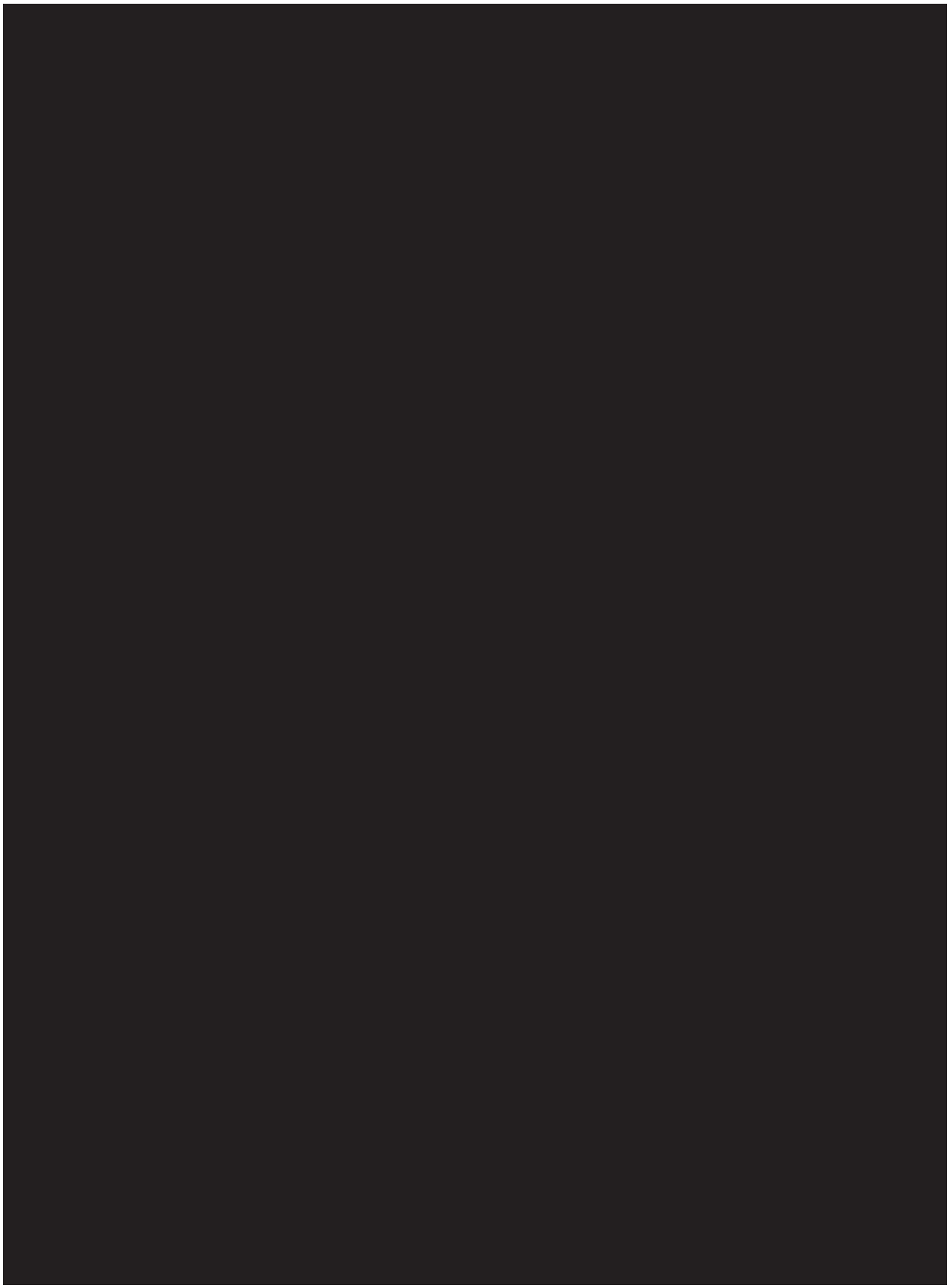












Appendix 5: Sponsor and Ora Approvals

Protocol Title:	A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safety ofTanfanercept Ophthalmic Solution 0.25% Compared to Placeboin Subjects with Dry Eye (VELOS-3)
Protocol Number:	HL036-DED-US-P302
Version:	4.0
Final Date:	22 June 2022

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

Signed: [redacted] Date: 06/23/2022

Chief Medical Officer, Chief Development Officer
HanAll Pharmaceutical International, Inc,

Sig[redacted] Date: 06/23/2022

VP, Head of Clinical Development Operations
HanAll Pharmaceutical International, Inc .

Sig[redacted] Date: 06/23/2022

Sr. Director, Clinical Operations,
HanAll Pharmaceutical International, Inc

Signed: [redacted] Date: 06/23/2022

HanAll Pharmaceutical International, Inc

Signed [redacted] Date: 06/23/2022

[redacted]ment
HanAll Pharmaceutical International, Inc

Signed [redacted] Date: 06/24/2022

Signed [redacted] Date: 06/23/2022

[redacted]

Signed [redacted] Date: 06/23/2022

Signed [redacted] Date: 06/23/2022

APPENDIX 6: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy and Safetyof Tanfanercept Ophthalmic Solution 0.25% Compared to Placebo in Subjects with Dry EyeHL036 (VELOS-3)
Protocol Number:	HL036-DED-US-P302
Version:	4.0
Final Date:	22 June 2022

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:_____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____