Clinical Trial Protocol: Study ST100-001

Protocol Title:	A Phase 2 Multi-Center, Randomized, Double Masked, Placebo Controlled Study to Assess the Safety and Efficacy of ST-100 Ophthalmic Solution in Subjects Diagnosed with Dry Eye Disease
Protocol Number:	ST100-001
Study Phase:	2
Investigational Product Name:	ST-100 Ophthalmic Solution
IND Number:	143015
Indication:	Dry Eye Disease
Investigators:	Multi-Center
Sponsor:	Stuart Therapeutics, Inc. 411 SE Osceola St., Suite 203 Stuart, FL 34994 USA
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IRB/IEC:	

Original Protocol:	March 15, 2021
Protocol Amendment 1:	May 21, 2021

Confidentiality Statement

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SYNOPSIS

Protocol Title:	A Phase 2 Multi-Center, Randomized, Double Masked, Placebo Controlled Study to Assess the Safety and Efficacy of ST-100 Ophthalmic Solution in Subjects Diagnosed with Dry Eye Disease
Protocol Number:	ST100-001
Investigational Product:	1. Low dose ST-100 Ophthalmic Solution 2. High dose ST-100 Ophthalmic Solution 3. Placebo Ophthalmic Solution
Study Phase:	2
Objective(s):	The objective of this study is to compare the safety and efficacy of two different concentrations of ST-100 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.
Overall Study Design:	
Structure:	Multi-center, double-masked, randomized, placebo-controlled
Duration:	An individual subject's participation is estimated to be approximately 5 weeks (35 days)
Controls:	Placebo (vehicle minus active) Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally twice daily (BID) for 28 days (from Visit 2 to Visit 7). [redacted] During a 7-day study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID.
Summary of Visit Schedule:	6 visits over the course of approximately 5 weeks • Visit 1 = Day -7 ± 1, Controlled Adverse Environment (CAE®) Screening • Visit 2 = Day 1, CAE® Confirmation / Baseline • Visit 3 = Day 2 ± 2 hours, 24 h recovery post-CAE® • Visit 4 = Day 4 ± 2 hours, 72 h recovery post-CAE® • Visit 5 = Day 8 ± 1 day, 1-Week CAE® Follow-Up • Visit 6 = Day 15 ± 1 day, 2-Week CAE® Follow-Up • Visit 7 = Day 29 ± 1 day, 4-Week CAE® Follow-Up and Study Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double masked study
Study Population Characteristics:	
Number of Subjects:	Approximately 300 subjects will be screened to enroll 150 (50 per treatment arm) subjects

Condition/Disease:	Dry Eye Disease

Inclusion Criteria:

Subjects must:

1. Be at least 18 years of age;
2. Provide written informed consent;
3. Have a reported history of dry eye for at least 6 months prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1, except as noted in Exclusion Criterion (6) below;
5. Report a score of [redacted] on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom pre-CAE® at Visits 1 and 2;
6. Have a Schirmer's Test score of [redacted] and [redacted] at Visits 1 and 2;
7. Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye at pre-CAE® Visits 1 and 2;
8. Have a corneal fluorescein staining score of [redacted] in at least one region (e.g. inferior, superior, or central) pre-CAE® at Visits 1 and 2;
9. Have a sum corneal fluorescein staining score of [redacted] based on the sum of the inferior, superior, and central regions pre-CAE®, at Visits 1 and 2;
10. Have a total lissamine green conjunctival score of [redacted] based on the sum of the temporal and nasal regions pre-CAE® at Visits 1 and 2;
11. Demonstrate a response to the Controlled Adverse Environment (CAE®) at Visits 1 and 2 as defined by:
    a. Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure
    b. Reporting an Ora Calibra® Ocular Discomfort Score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure ([redacted];
12. Have at least one single eye satisfy all criteria for 6, 7, 8, 9, 10 and 11 above.

Exclusion Criteria:

Subjects must not:

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 used any eye drops within 2 hours of Visit 1;
5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;
6. Have used Restasis, Xiidra, or Cequa ophthalmic solutions within 45 days of Visit 1;
7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 6 months;
8. Have used, are using or anticipate using permanent or temporary punctal plugs during the study within 30 days of Visit 1;
9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, or using a moisture chamber and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);
10. Be currently taking or have taken Omega-3 supplements within the last 3 months;
11. Have corrected visual acuity greater than or equal to logarithm of the Minimum Angle of Resolution (logMAR) [redacted] as assessed by Early Treatment of Diabetic Retinopathy Study scale in both eyes at Visit 1;
12. Be a woman who is pregnant, nursing, or planning a pregnancy;

13. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
14. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – 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;
15. Have a known allergy and/or sensitivity to the test article or its components;
16. Have a condition or be in a situation that 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;
17. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
18. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;
19. Have a known history of meibomian gland procedures (e.g., LipiFlow, LPI, probing, etc.) within 6 months of study enrollment;
20. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

Evaluation Criteria:

Efficacy Measures and Endpoints:	**Primary Efficacy Measures:** The following primary endpoints will be tested: **The primary efficacy endpoint (sign) is:** • Total corneal fluorescein staining score on the Ora Calibra® scale, measured by [redacted] **The primary efficacy endpoint (symptom) is:** • Ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale, measured by [redacted] **Secondary Efficacy Measures:** • Fluorescein staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®): regions: [redacted] • Lissamine green staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®): regions: [redacted] • Tear film break-up time at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®) • Conjunctival Redness at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®) • Drop comfort assessment after randomization at Visit 2 • Ocular Surface Disease Index (OSDI) at Visits 3, 4, 5, 6, and 7 (pre-CAE®) • Four symptom questionnaire at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®) • Ocular discomfort during CAE® at Visits 4, 5, 6, and 7 • Daily diary

	• Visual Analog Scale – Burning/Stinging, Itching, Foreign Body Sensation, Blurred Vision, Eye Dryness, Photophobia, Pain at Visits 3, 4, 5, 6, and 7 (pre-CAE®) • Unanesthetized Schirmer's Test at Visit 7 (pre-CAE®) • Ocular Discomfort Scale outside of the CAE® at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®)
Safety Measures:	• Visual acuity • Slit-lamp evaluation • Adverse event query • Intraocular pressure • Undilated fundoscopy

General Statistical Methods and Types of Analyses

Analysis Populations

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

Sample Size

This study is expected to enroll [redacted] subjects in each population, for a total of [redacted] randomized subjects. Approximately [redacted] subjects will be screened. Assuming a 10% drop out rate, [redacted] subjects per group are expected to complete the study.

Multiplicity Considerations

Hierarchical fixed sequence testing will be used to maintain the type I error rate of [redacted]. The primary analysis will first evaluate the difference in the change in the total corneal fluorescein staining score from baseline (Visit 2, pre-CAE®) to Visit 7 (Day 29, pre-CAE®) between high-dose ST-100 and placebo. If the results are statistically significant in favor of high-dose ST-100 over placebo [redacted], then the study will be considered a success and high-dose ST-100 will be declared to be superior to placebo. Following the hierarchical fixed sequence testing, the following endpoints will be formally tested:

1. If the results of total corneal fluorescein staining score from baseline to Visit 7 (Day 29, pre-CAE®) between high-dose ST-100 and placebo are statistically significant in favor of high-dose ST-100 over placebo [redacted], then the difference in the change from baseline (Visit 2, pre-CAE®) of the ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale to Visit 7 (Day 29, pre-CAE®) will then be evaluated in the high-dose ST-100 vs placebo groups.

2. If the results of ocular discomfort score are statistically significant in favor of high-dose ST-100 over placebo [redacted], then the difference in the change in the total corneal fluorescein staining score from baseline (Visit 2, pre-CAE®) to Visit 7 (Day 29, pre-CAE®) between low-dose ST-100 and placebo will then be evaluated.

3. If the results of the total corneal fluorescein staining score change from baseline (Visit 2, pre-CAE®) to Visit 7 (Day 29, pre-CAE®) are statistically significant in favor of low-dose ST-100 over placebo [redacted], then the difference in the change from baseline (Visit 2, pre-CAE®) in the ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale to Visit 7 (Day 29, pre-CAE®) between low-dose ST-100 and placebo will then be evaluated.

Should any primary endpoint in the hierarchical fixed sequence fail to reject the null hypothesis, then all untested endpoints will be evaluated as exploratory endpoints as hypothesis generating comparisons. All primary endpoints will be formally tested using the ITT population with multiple imputation as specified in Estimand 1. All secondary and exploratory endpoints will not be type I error controlled and will be hypothesis generating..

Primary Endpoint Efficacy Analysis

The dependent variable for the total corneal fluorescein staining and ocular discomfort will be based on intra-subject differences [redacted] For the primary analysis of the primary endpoints, subjects without a recorded value at Visit 7 (Day 29) will have missing values multiply imputed as specified in Estimand 1.

The change from baseline at Visit 7 (Day 29) of total corneal staining will be analyzed using an analysis of covariance (ANCOVA) model with terms for change in total corneal staining from baseline and treatment group. The change from baseline at Visit 7 (Day 29) of ocular discomfort will be analyzed using an ANCOVA model with terms for baseline discomfort score and treatment group.

The least squares mean of the intra-subject differences for each treatment group will be presented for the individual analyses with two-sided p-values and 95% confidence intervals.

As a sensitivity analysis, secondary examinations of the primary endpoints will also be presented. The sensitivity analyses of the primary endpoints will use multiple imputation and Last Observation Carried Forward (LOCF) imputation, followed by an ANCOVA. Analyses will also be executed using the PP population with observed/recorded data only.

Secondary Endpoint Efficacy Analyses

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

Safety Analyses

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

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

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LIST OF ABBREVIATIONS

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

1.0 INTRODUCTION

Dry eye disease (DED) is a prevalent chronic eye condition affecting between 5% and 34% of the population worldwide. More than 16 million Americans suffer from DED, including approximately 1 million to 4 million between 65 to 84 years of age (Fiscella 2011, Messmer 2015). Furthermore, the age of onset is decreasing rapidly due to the widespread increase in electronic "screen time" such that teenagers are now more frequently showing signs and symptoms of DED. Symptoms include severe ocular burning, discomfort, pain, and in more severe cases compromised visual function, including symptomatic blurred vision. These symptoms are associated with tear film hyperosmolarity and instability, inflammation, and wounding of the corneal epithelium and the collagen substrate (Bowman's layer) that is part of the extracellular matrix (ECM) and to which the epithelium adheres and renews. As is now recognized, even the early stages of DED tissue damage penetrates well beyond the surface epithelial layer and involves the ECM, including disruption of the collagen that is contained in Bowman's layer and the underlying corneal stroma (Shetty, Deshpande et al. 2016).

Epithelial cell apoptosis incites the release of inflammatory cytokines and proteinases, most notably IL-6, IL-8 and matrix metalloproteinases (MMPs). In the eye, MMP-9 partially digests collagen via its collagenase activity leading to structural and functional disruptions in the collagen matrix underlying the corneal epithelium (Baratta et.al., *in press*). Topical anti-inflammatory therapies (e.g., Restasis®, Xiidra®, Cequa™) have been used to interrupt this process, but they act extremely slowly. Full restoration of corneal homeostasis requires a fully regenerated surface epithelium, which first requires the repair of the collagen substrate. Such repaired collagen then shows the tightly structured and organized fibrillar pattern characteristic of native type I collagen, leading to a resumption of the functional activities of collagen in modulating structural integrity of the ocular ECM and in mediating certain signal transduction activities. This restoration of collagen and ECM homeostasis in turn promotes the rapid regeneration of the corneal epithelium (*see, e.g.*, Kivanany et al., 2018; Hapach et al., 2015).

Disruptions in the epithelial basement membrane, which comprises several collagen types, are also a critical part of ocular surface pathology. Disruption in the basement membrane collagen network leads to adverse effects on the integrity of Bowman's membrane and allows inflammatory cytokines to pass through, increasing inflammatory cell infiltration in the area of the wound (Shetty, Deshpande et al. 2016). In addition to these anatomical and physiological changes, certain changes in cellular signaling activities occur as well. This is both a hallmark and a cause of DED (see, e.g., Baratta et al. (2021, in press)).

No topical therapeutic to date fully addresses the collagenase-mediated damage to the collagen-containing ocular surface tissue that is associated with DED. Topical but indirect therapies for treating tissue damage in DED are available (e.g., amniotic membrane implants, soft contact lenses, and topical anti-inflammatories such as those described above) but these indirect topical treatments and anti-inflammatories only allow the body to heal collagen secondarily, slowly and quite unpredictably. Thus, there remains an urgent and unmet medical need for a direct**,** rapidly acting and therefore more efficacious treatment option with favorable safety and comfort profiles that also will promote actual repair of the ocular tissue damage that is a hallmark of DED.

ST-100, a formulation comprising a synthetic collagen mimetic peptide, is being developed to topically treat the signs and symptoms of DED.

ST-100 is believed to rapidly repair damaged collagen via intercalation into the disrupted collagen and reformation of the native collagen I triple helix.

Currently, the most common prescription therapeutics for DED are topical anti-inflammatories such as Xiidra®, Restasis® and Cequa™. These traditional therapies, however, do not directly treat a major underlying cause and effect of DED – damage to the ocular surface tissue and specifically to the collagen in the ECM within and underlying the corneal epithelium. The Sponsor has therefore sought to identify and evaluate potential therapeutic formulations which directly repair ocular surface tissue damage which would provide a more rapid and enduring relief of symptoms compared to traditional therapeutic approaches. To date such a therapeutic has not been available. ST-100 addresses this gap as it is thought to rapidly repair damaged collagen via intercalation into damaged collagen triple helices, thereby repairing the ocular surface damage that underlies the signs and symptoms associated with DED. It is anticipated that by healing the underlying collagen matrix of corneal tissues, ST-100 will also reduce the necessity for long-term use of traditional anti-inflammatory regimens.

In a non-clinical, proof-of-concept study in mice, application of ST-100 to the wounded eyes of mice was shown to induce significant recovery of the corneal epithelium, stromal matrix and Bowman's layer following lamellar keratectomy compared to phosphate-buffered saline negative controls. Together with corresponding data obtained using *in vitro* models of the corneal epithelium, these results encouraged the Sponsor to examine the potential for use of ST-100 as a topical, rapidly acting therapeutic for DED in humans.

2.0 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of two different concentrations of ST-100 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

3.0 CLINICAL HYPOTHESIS

The clinical hypotheses for this study is that low dose and high dose ST-100 Ophthalmic Solution twice daily (BID) is superior to its vehicle (BID) for the primary endpoints of signs and symptoms of dry eye, as follows:

- Sign: Pre-Controlled Adverse Environment (CAE®) total corneal fluorescein staining score on the Ora Calibra® scale, measured by [redacted]
- Symptom: Pre-CAE® ocular discomfort scale on the Ora Calibra® Ocular Discomfort scale, measured by [redacted]

4.0 OVERALL STUDY DESIGN

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

- Low dose ST-100 Ophthalmic Solution: [redacted]
- High dose ST-100 Ophthalmic Solution: [redacted]
- Placebo Ophthalmic Solution (Vehicle): [redacted]

Approximately 150 subjects will be randomly assigned to one of the three groups (1:1:1) to receive either ST-100 Ophthalmic Solution or placebo solution as topical ophthalmic drops administered bilaterally BID for 4 weeks. Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment.

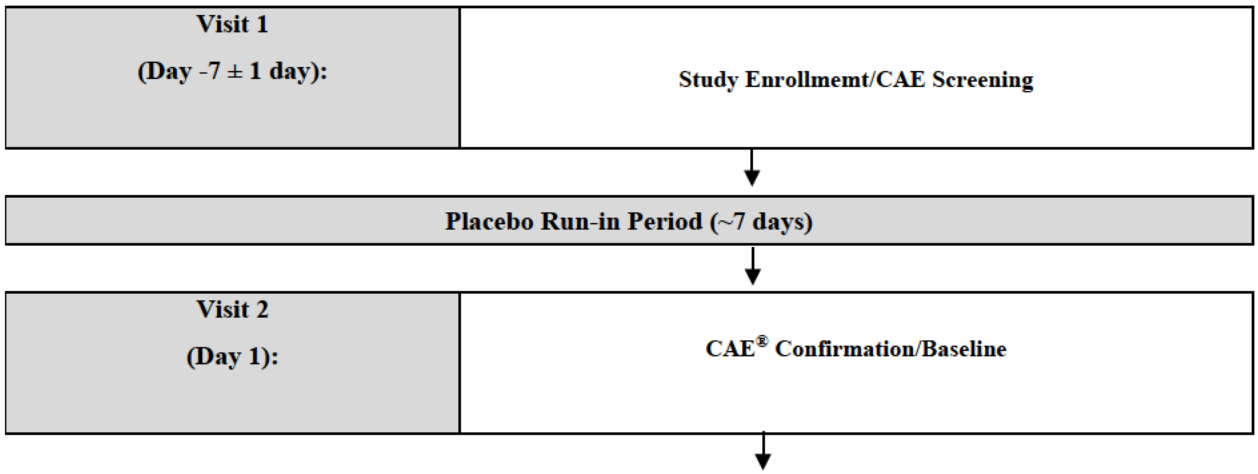
During the 7-day study run-in period prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID.

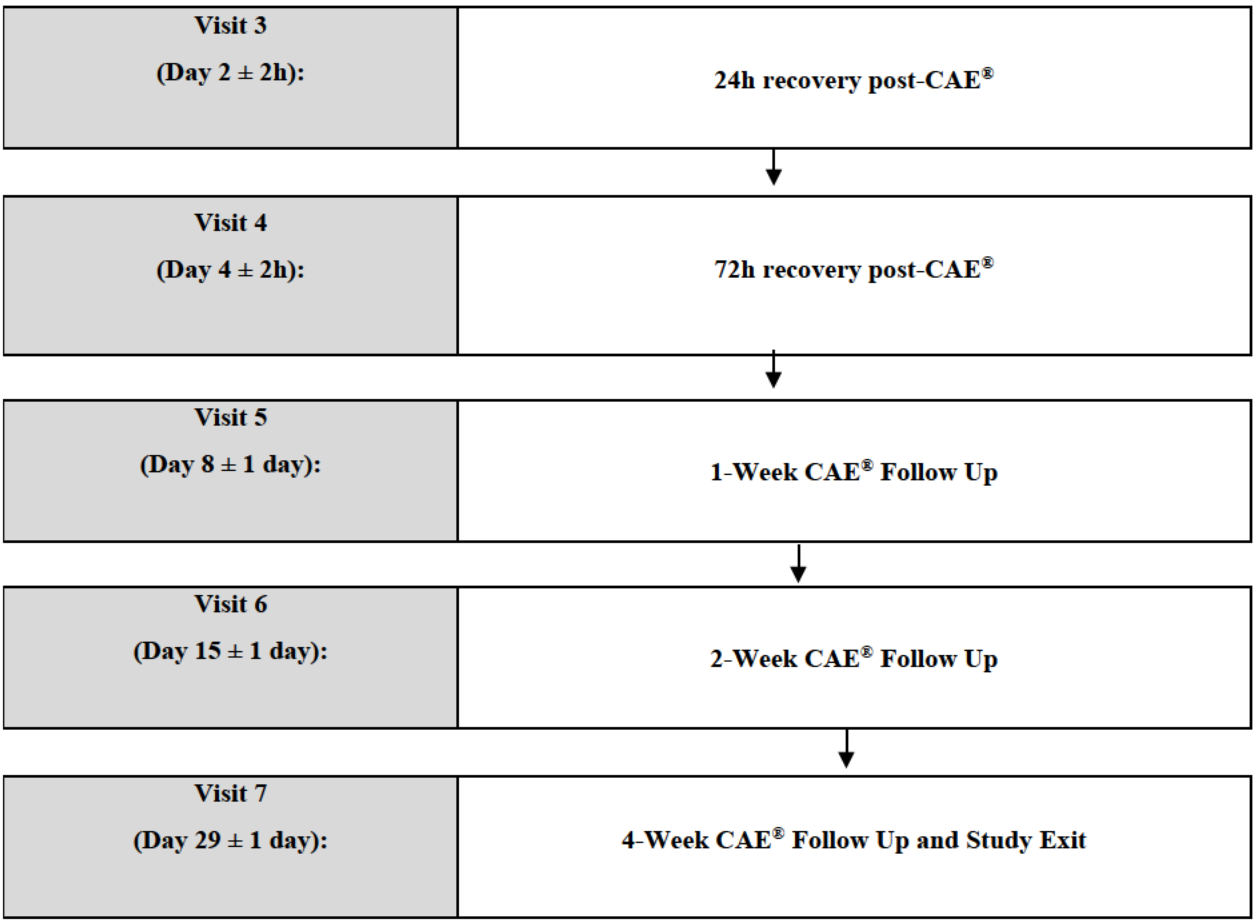
During the screening period, two 90-minute exposures to the CAE® will be conducted to ascertain eligibility to enter the study at Visit 1 (Day -7 ± 1) and Visit 2 (Day 1). Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle BID for approximately 7 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double-masked fashion for 28 days. Subjects will self-administer drops BID and will complete daily diary assessments as instructed.

The CAE® exposure will occur at Visit 1 (Day -7 ± 1), Visit 2 (Day 1), Visit 5 (Day 8 ± 1), Visit 6 (Day 15 ± 1), and Visit 7 (Day 29 ±2), with Pre-CAE®, during CAE® and Post-CAE® assessments of ocular signs and symptoms.

At Visit 3 (Day 2 ± 2h) and Visit 4 (Day 4 ± 2h), no CAE® exposure will occur but signs and symptoms will be assessed for 24h recovery post-CAE® and 72h recovery post-CAE®. Study drug will be discontinued at Visit 7. Subjects will exit from the study at this visit.

The total number of expected participants, including screen failures, is approximately 300 subjects. A study design flow chart is provided below:





5.0 STUDY POPULATION

5.1 NUMBER OF SUBJECTS (APPROXIMATE)

It is estimated that approximately [redacted] subjects will be screened to enroll approximately [redacted] randomized subjects ([redacted] in each group). Subjects will be randomized in each treatment arm. Subjects will be randomized in a 1:1:1 ratio of

- High dose ST-100 Ophthalmic Solution
- Low dose ST-100 Ophthalmic Solution
- Placebo Ophthalmic Solution (Vehicle)

5.2 STUDY POPULATION CHARACTERISTICS

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

Stuart Therapeutics
ST-100 Ophthalmic Solution

5.3 INCLUSION CRITERIA

Each subject must:

1. Be at least 18 years of age;
2. Provide written informed consent;
3. Have a reported history of dry eye for at least 6 months prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1, except as noted below in Section 5.4(6);
5. Report a score of [redacted] on the Ora Calibra® Ocular Discomfort & 4-symptom questionnaire in at least one symptom pre-CAE® at Visits 1 and 2;
6. Have a Schirmer's Test score of [redacted] at Visits 1 and 2;
7. Have a conjunctival redness score [redacted] according to the Ora Calibra® Conjunctival Redness for Dry Eye Scale in at least one eye pre-CAE® at Visits 1 and 2;
8. Have a corneal fluorescein staining score of [redacted] in at least one region (e.g. inferior, superior, or central) pre-CAE® at Visits 1 and 2;
9. Have a sum corneal fluorescein staining score of [redacted] based on the sum of the inferior, superior, and central regions, pre-CAE® at Visits 1 and 2;
10. Have a total lissamine green conjunctival score of [redacted] based on the sum of the temporal and nasal regions pre-CAE® at Visits 1 and 2;
11. Demonstrate a response to the CAE® at Visits 1 and 2 as defined by:
    a) Having at least a [redacted] point increase in fluorescein staining in the inferior region in at least one eye following CAE® exposure
    b) Reporting an Ora Calibra® Ocular Discomfort Score [redacted] at 2 or more consecutive time points in at least one eye during CAE® exposure [redacted]
12. Have at least one single eye satisfy all criteria for 6, 7, 8, 9, 10 and 11 above.

5.4 EXCLUSION CRITERIA

Each subject may not:

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 used any eye drops within 2 hours of Visit 1;
5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;
6. Have used Restasis, Xiidra, or Cequa ophthalmic solutions within 45 days of Visit 1;
7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 6 months;
8. Have used, are using or anticipate using permanent or temporary punctal plugs during the study within 30 days of Visit 1;
9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter solutions, artificial tears, gels or scrubs, or using a moisture chamber and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);
10. Be currently taking or have taken Omega-3 supplements within the last 3 months;
11. Have corrected visual acuity (VA) greater than or equal to Logarithm of the Minimum Angle of Resolution (logMAR) [redacted] as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;
12. Be a woman who is pregnant, nursing, or planning a pregnancy;
13. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
14. Be a woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – 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;
15. Have a known allergy and/or sensitivity to the test article or its components;
16. Have a condition or be in a situation that 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;
17. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
18. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;
19. Have a known history of meibomian gland procedures (e.g., LipiFlow, LPI, probing, etc.) within 6 months of study enrollment;
20. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

5.5 WITHDRAWAL CRITERIA (IF APPLICABLE)

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

Subjects may withdraw consent from the study at any time.

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

If a subject discontinues participation in the study early, every attempt will be made to complete the exit procedures required at the final study visit (Visit 7).

6.0 STUDY PARAMETERS

6.1 EFFICACY ENDPOINTS

6.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint (sign) is:

- Total corneal fluorescein staining score on the Ora Calibra® scale, measured by [redacted]

The primary efficacy endpoint (symptom) is:

- Ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale, measured by [redacted].

6.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Fluorescein staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®): regions: [redacted]
- Lissamine green staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®): regions: [redacted]
- Tear film break-up time (TFBUT) at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®)
- Conjunctival Redness at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®)
- Drop comfort assessment after randomization at Visit 2
- Ocular Surface Disease Index (OSDI) at Visits 3, 4, 5, 6, and 7 (pre-CAE®)
- Ocular discomfort Scale during CAE® at Visits 4, 5, 6, and 7
- Daily diary
- Visual Analog Scale – Burning/Stinging, Itching, Foreign Body Sensation, Blurred Vision, Eye Dryness, Photophobia, Pain at Visits 3, 4, 5, 6, and 7 (pre-CAE®)
- Unanesthetized Schirmer's Test at Visit 7 (pre-CAE®)

- Ocular Discomfort Scale outside of the CAE® at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®)
- Four symptom questionnaire at Visits 3, 4, 5, 6, and 7 (pre-CAE®, post-CAE®, and pre- to post-CAE®)

6.2 SAFETY MEASURES

The safety measures being evaluated are:

- Visual acuity
- Slit-lamp evaluation
- Adverse event query
- Intraocular pressure
- Undilated fundoscopy

7.0 STUDY MATERIALS

7.1 STUDY TREATMENTS

7.1.1 Study Drug Formulation

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

- High dose ST-100; BID
- Low dose ST-100; BID
- Placebo Ophthalmic Solution (Vehicle); BID

ST-100 Ophthalmic Solution will be formulated as a sterile solution at [redacted] for topical ophthalmic administration and is intended for clinical use. The study drug will be supplied in blow-fill seal ampoules, which allow for product administration directly to the eye. Each ampoule will contain a nominal volume of 0.25 mL.

The excipients which will be used to manufacture ST-100 Ophthalmic Solution will be standard excipients for use in ophthalmic solutions that comply with their respective USP / EP monographs.

The placebo for ST-100 Ophthalmic Solution contains all the same excipients used in the active formulation without the peptide.

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

Topical ophthalmic dosing is the optimal route of administration for dry eye treatments. The dosage and dosage regimen were selected based on positive efficacy results in the proof-of-concept nonclinical studies. The proposed treatment period is 4 weeks.

7.1.3 Instructions for Use and Administration

- Subjects will receive placebo ophthalmic solution at Visit 1, and assigned study drug kit at Visit 2, 5 and 6.
- Subjects who are randomized must administer study drug in each eye BID. At Visit 2 and 6, subjects will self-administer one dose of study drug in office. Subjects should NOT self-adminster study drug at home on the morning of their scheduled Visit 2 and Visit 6.

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

7.2.1 Labeling/Packaging

Investigational product (IP) will be packaged and labeled into clinical kits. The primary packaging of the ST-100 will be blow-fill-seal ampules with a fill volume of [redacted]. The secondary packaging is a foil pouch that contains three ampules in each pouch. Each clinical kit will contain 6 pouches, for a total of 18 ampules per kit.

Run-in Period

For the run-in period, each subject will receive 1 kit.

Treatment Period

BID Dosing: For the treatment period, each subject will receive 1 kit at Visit 2, 1 kit at Visit 5 and 2 kits at Visit 6.

7.2.2 Storage of Investigational Product

Ampoules must be stored at 2 to 8°C until the time of use. The ampoules are to be kept refrigerated at the study site and by the subject at their home. Any material remaining in the ampoule after use should be discarded. ST-100 Ophthalmic Solution should be kept out of reach of children. Drug administration instructions and discarding information will be provided with each study.

7.2.3 Accountability of Investigational Product

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

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

7.2.4 Return or Disposal of Investigational Product

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

7.3 OTHER STUDY SUPPLIES

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

8.0 STUDY METHODS AND PROCEDURES

8.1 SUBJECT ENTRY PROCEDURES

8.1.1 Overview

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

8.1.2 Informed Consent

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

8.1.3 Washout Intervals

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

8.1.4 Procedures for Final Study Entry

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

8.1.5 Methods for Assignment to Treatment Groups:

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

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

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

8.2 CONCURRENT THERAPIES

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

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

8.2.1 Prohibited Medications/Treatments

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

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 EXAMINATION PROCEDURES

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

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

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

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

All subjects will undergo the following screening assessments:

Pre–CAE®

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

- 90-minute CAE® exposure

Post–CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Intraocular Pressure (IOP)
- Undilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
- Run-in (Vehicle) and Diary Dispensation: Prior to discharge from the study site on Visit 1, subjects will be dispensed sufficient Run-in supply to last until Visit 2 and will be educated in diary recording and self–administration of vehicle run-in. Subjects will be instructed to self–administer one drop BID in each eye until Visit 2. Subjects will be instructed NOT to instill run-in on the morning of their next scheduled study visit (Visit 2).
- AE Query
- Subjects will be scheduled for Visit 2.

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

Pre–CAE®

- Study Diary/Run-in Collection
- Confirm subject has NOT administered their morning study drug dose at home
- Medical and Medication History Update
- Review of Inclusion/Exclusion Criteria
- AE query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness

- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- AE Query
- At least 15 minute wait between Schirmer's test and CAE® exposure
- 90-minute CAE® exposure;

Post–CAE®

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

8.3.4 Visit 3: Day 2 ± 2 hours, 24 h recovery post-CAE®

- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS Symptom Assessment
- OSDI Questionnaire
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- AE Query
- Subjects will be scheduled for Visit 4

8.3.5 Visit 4: Day 4 ± 2 hours, 72 h recovery post-CAE®

- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS Symptom Assessment
- OSDI Questionnaire
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Conjunctival Redness
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- AE Query
- Subjects will be scheduled for Visit 5

8.3.6 Visit 5: Day 8 ± 1, 1-Week CAE® Follow-Up

Pre–CAE®

- Study Drug Kit and Diary Collection
- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- AE Query
- 90-minute CAE® exposure
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE® and every 5 minutes thereafter

Post–CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- AE Query
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 5, subjects will be re-educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 6.

8.3.7 Visit 6: Day 15 ± 1, 2-Week CAE® Follow-Up

Pre–CAE®

- Study Drug/Study Diary Collection
- Confirm subject has NOT administered their morning study drug dose at home
- Medical and Medication History Update
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- AE Query
- 90-minute CAE® exposure;
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE® and every 5 minutes thereafter

Post–CAE®

- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- Study Drug Diary/Study Drug Dispensation: Prior to discharge from the study site on Visit 6, subjects will be re-educated in study drug diary recording and self–administration of study drug. Subjects will receive their assigned study drug kit with sufficient supply to last until Visit 7

- Study Drug Instillation at the Study Site: Subjects will self-administer their study drug dose bilaterally at the study site under supervision of a trained technician
- Ora Calibra® Drop Comfort Scale
- AE Query
- Subjects will be scheduled for Visit 7

8.3.8 Visit 7: Day 29 ± 2, 4-Week CAE® Follow-Up

Pre–CAE®

- Study Drug/Study Diary Collection
- Medical and Medication History Update
- Pregnancy Test (if applicable)
- AE Query
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- OSDI Questionnaire
- VAS Symptom Assessment
- Visual Acuity (ETDRS)
- Conjunctival Redness
- Slit Lamp Biomicroscopy
- TFBUT
- Fluorescein Staining
- Lissamine Green Staining
- At least 15-minute wait between lissamine green staining and Schirmer's test
- Schirmer's test
- AE Query
- At least 15 minute wait between Schirmer's test and CAE® exposure
- 90-minute CAE® exposure;
    - Ora Calibra® Ocular Discomfort Scale upon entering the CAE® and every 5 minutes thereafter

Post–CAE®

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

8.4 SCHEDULE OF VISITS, MEASUREMENTS AND DOSING

8.4.1 Scheduled Visits

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

8.4.2 Unscheduled Visits

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

Evaluations that may be conducted at an Unscheduled Visit include:

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

8.5 COMPLIANCE WITH PROTOCOL

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visits 1 through 6 and given written instructions. To assess dosing and symptom assessment compliance, the subject daily diaries will be collected at Visit 2, 5, 6, 7, and the subject's used and unused study drug ampules will be collected at Visit 2, 5, 6, and 7. Dosing compliance will be based on the used and unused ampule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded. Subjects will be reinstructed on dosing compliance and this will be documented in the source documents. These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

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

8.6 SUBJECT DISPOSITION

8.6.1 Completed Subjects

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

8.6.2 Discontinued Subjects

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

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

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

COVID-19 Related Discontinuations will be indicated as well with a reason for COVID-19 relatedness.

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

8.7 STUDY TERMINATION

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

8.8 STUDY DURATION

An individual subject's participation will involve 7 visits over approximately a 35-days period (7 days pre-screening, 28 days of treatment).

8.9 MONITORING AND QUALITY ASSURANCE

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

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

9.0 ADVERSE EVENTS

9.1 ADVERSE EVENT (AE)

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

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

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

9.1.1 Severity

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

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

9.1.2 Relationship to Investigational Product

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

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

9.1.3 Expectedness

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

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

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

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

9.2 SERIOUS ADVERSE EVENTS

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

- Death;
- Is life-threatening;

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

- Inpatient hospitalization or prolongation of existing hospitalization;

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

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

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

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

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

9.3 PROCEDURES FOR REPORTING SERIOUS ADVERSE EVENTS

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

9.3.1 Reporting a Serious Unexpected Suspected Adverse Reaction

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

9.3.2 Reporting a Serious Adverse Event

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

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

Contact information for reporting SAEs:

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

9.4 PROCEDURES FOR UNMASKING (IF APPLICABLE)

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

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

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

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

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

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

10.0 STATISTICAL HYPOTHESES AND METHODS OF ANALYSIS

10.1 ANALYSIS POPULATIONS

The following analysis populations will be considered:

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

- Safety Population – The safety population includes [redacted]

[redacted]

10.2 STATISTICAL HYPOTHESES

The primary endpoints will be tested for high dose and low dose ST-100 Ophthalmic Solution in a hierarchical fixed sequence. The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided.

[redacted]

10.3 SAMPLE SIZE

This study is expected to enroll [redacted] subjects in each group, for a total of [redacted] randomized subjects. Approximately [redacted] subjects will be screened. Assuming a 10% drop out rate, [redacted] subjects per group are expected to complete the study.

10.4 STATISTICAL ANALYSIS

10.4.1 General Considerations

[redacted]

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

[redacted]

10.4.2 Unit of Analysis

[redacted]

10.4.3 Missing Data

Missing data will be imputed using [redacted]

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

[redacted]

Additional sensitivity analyses will be specified and detailed in the Statistical Analysis Plan. No imputation will be used for safety endpoints.

10.4.4 Multiplicity Consideration

[redacted]

10.4.5 Efficacy Analyses

Primary Efficacy Analyses

[redacted]

[redacted]

Estimand 1:

- Population: [redacted]
- Endpoint:
  - [redacted]
  - [redacted] 29
- Inte current event:
  - [redacted]
- Population-level summary:
  - [redacted]

Additional sensitivity analyses to be specified in the SAP may utilized different assumptions in regards to intercurrent events.

Secondary Efficacy Analyses

The method of analysis for secondary endpoints will be based on the [redacted]

10.4.6 Safety Variables

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

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, undilated fundoscopy, IOP, corneal sensitivity, and clinical laboratory measurements 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. No safety endpoints will be imputed.

Safety Analyses

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

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

10.4.7 Interim Analyses

There will be no interim analyses in this study.

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

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

11.1 PROTECTION OF HUMAN SUBJECTS

11.1.1 Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

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

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

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 ETHICAL CONDUCT OF THE STUDY

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

11.3 SUBJECT CONFIDENTIALITY

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

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

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

11.4 DOCUMENTATION

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

11.4.1 Retention of Documentation

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

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

11.5 RECORDING OF DATA ON SOURCE DOCUMENTS AND CASE REPORTS FORMS (CRFS)

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will be entered in eCRF for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.6 PUBLICATIONS

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

12.0 REFERENCES

Baratta, R.O., Schlumpf, E., Del Buono, B.J., DeLorey, S.S., Calkins, D.J. (2021). Corneal collagen as a potential therapeutic target in dry eye disease. Survey of Ophthalmology (in press).

Hapach LA, VanderBurgh JA, Miller JP, Reinhart-King CA. Manipulation of in vitro collagen matrix architecture for scaffolds of improved physiological relevance. Phys Biol. 2015 Dec 21;12(6):061002

Kivanany PB, Grose KC, Yonet-Tanyeri N, Manohar S, Sunkara Y, Lam KH, Schmidtke DW, Varner VD, Petroll WM. An In Vitro Model for Assessing Corneal Keratocyte Spreading and Migration on Aligned Fibrillar Collagen. J Funct Biomater. 2018 Sep 21;9(4).

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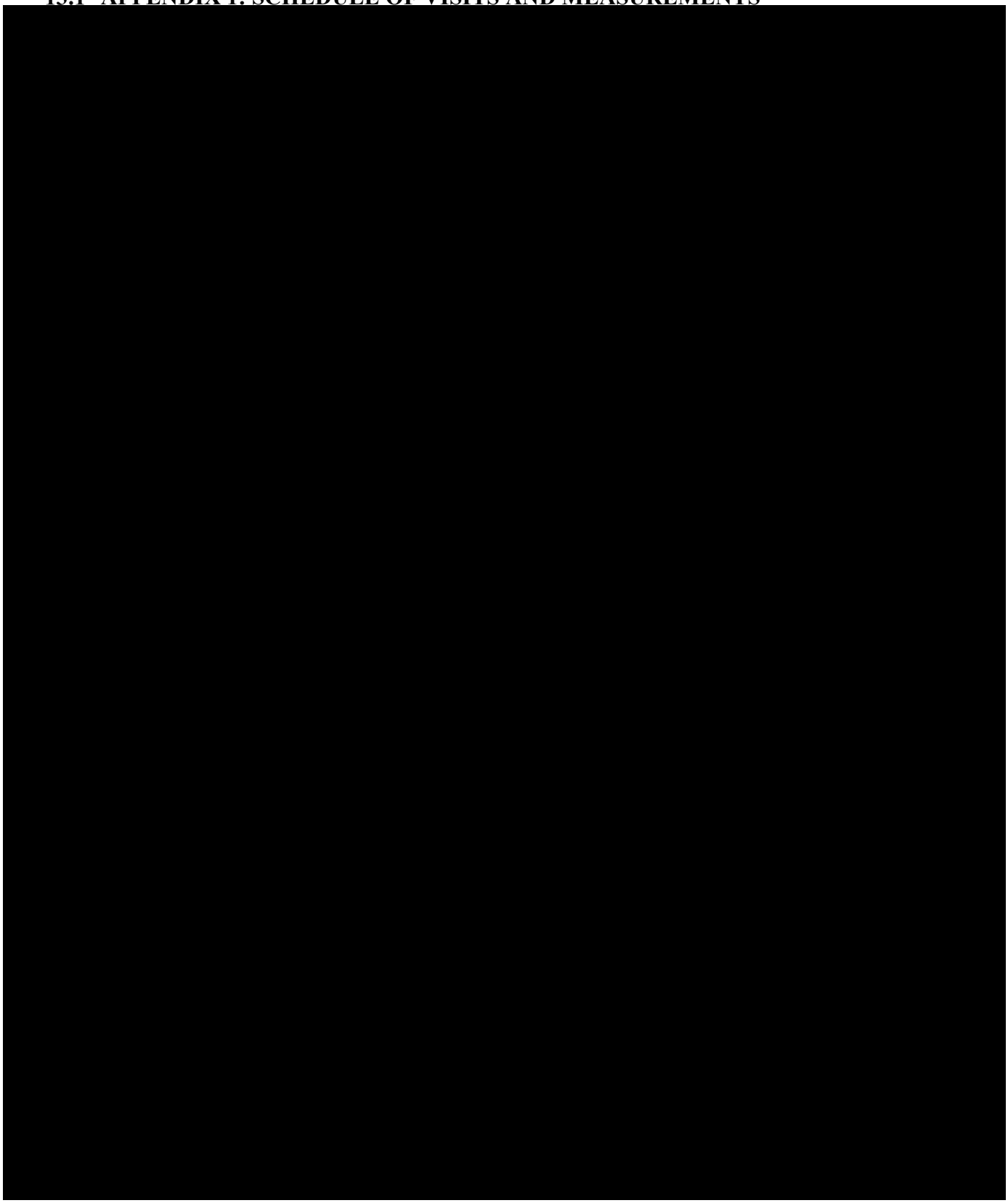
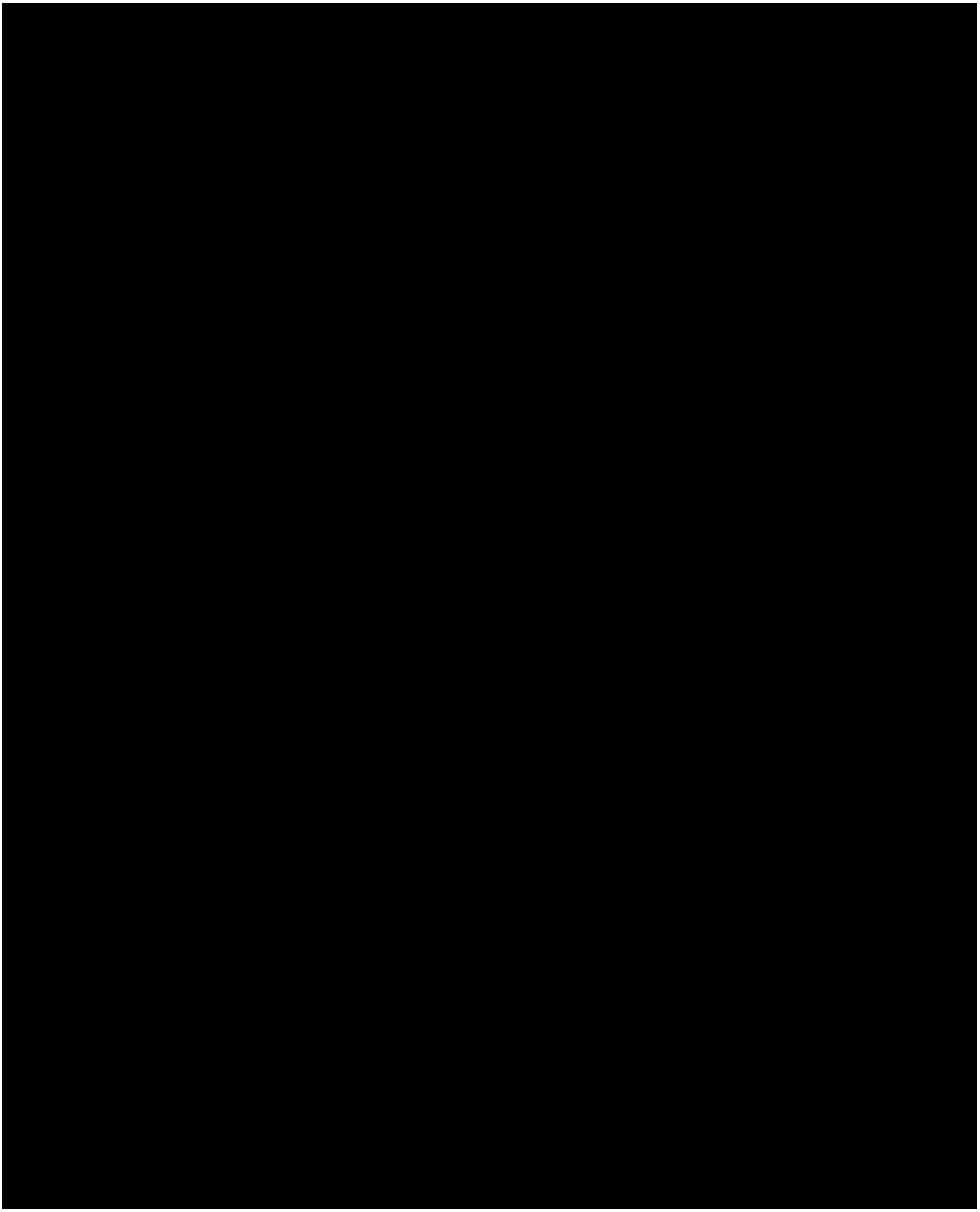
Messmer, E. M. (2015). "The pathophysiology, diagnosis, and treatment of dry eye disease." Dtsch Arztebl Int **112**(5): 71-81; quiz 82.

Shetty, R., K. Deshpande, R. Deshmukh, C. Jayadev and R. Shroff (2016). "Bowman Break and Subbasal Nerve Plexus Changes in a Patient With Dry Eye Presenting With Chronic Ocular Pain and Vitamin D Deficiency." Cornea **35**(5): 688-691.

13.0 APPENDICES

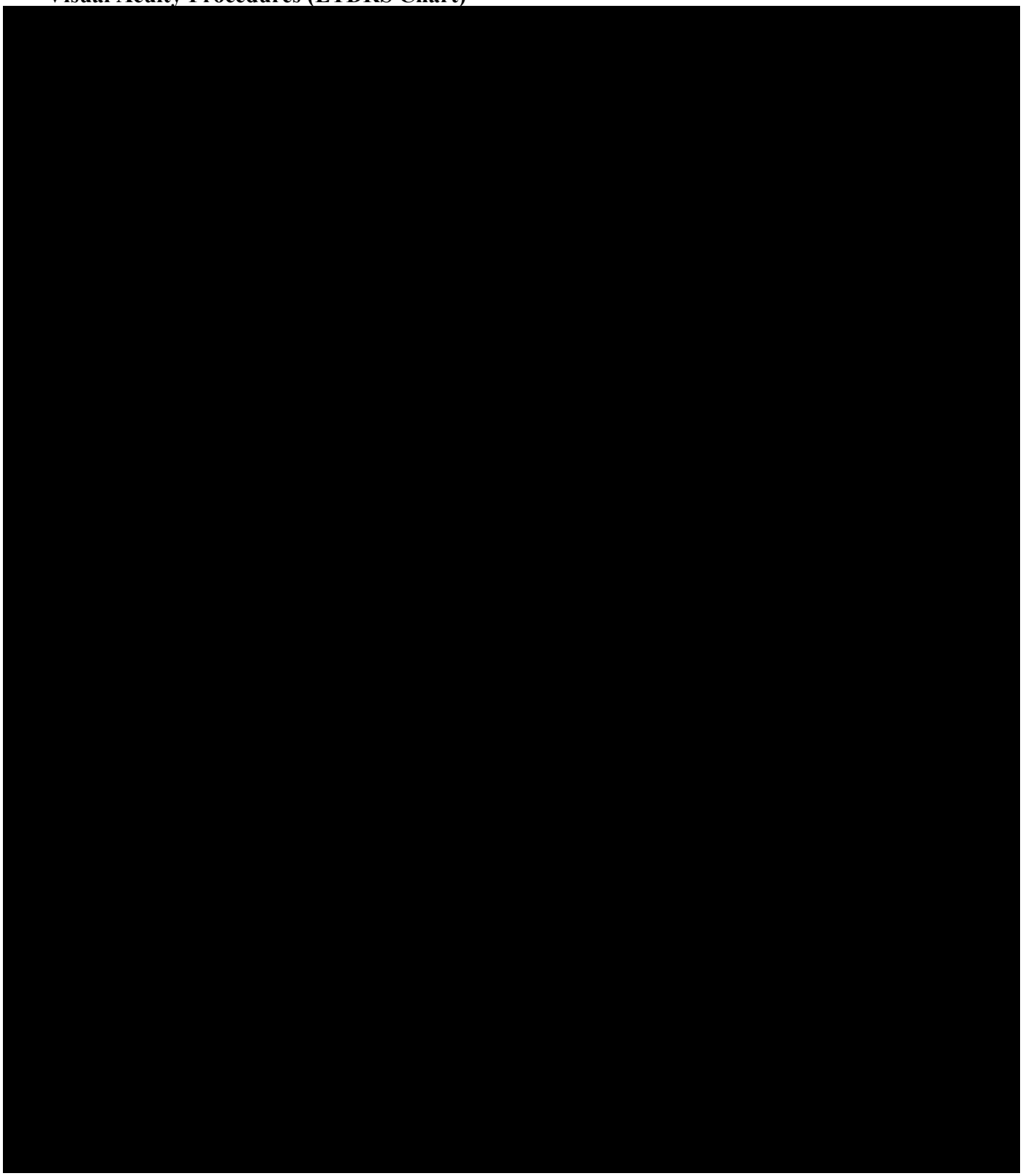
13.1 APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS





13.2 APPENDIX 2: EXAMINATION PROCEDURES, TESTS, & EVALUATIONS

Visual Acuity Procedures (ETDRS Chart)



[redacted]

Slit Lamp Biomicroscopy Procedures

[redacted]

Undilated Fundoscopy

[redacted]

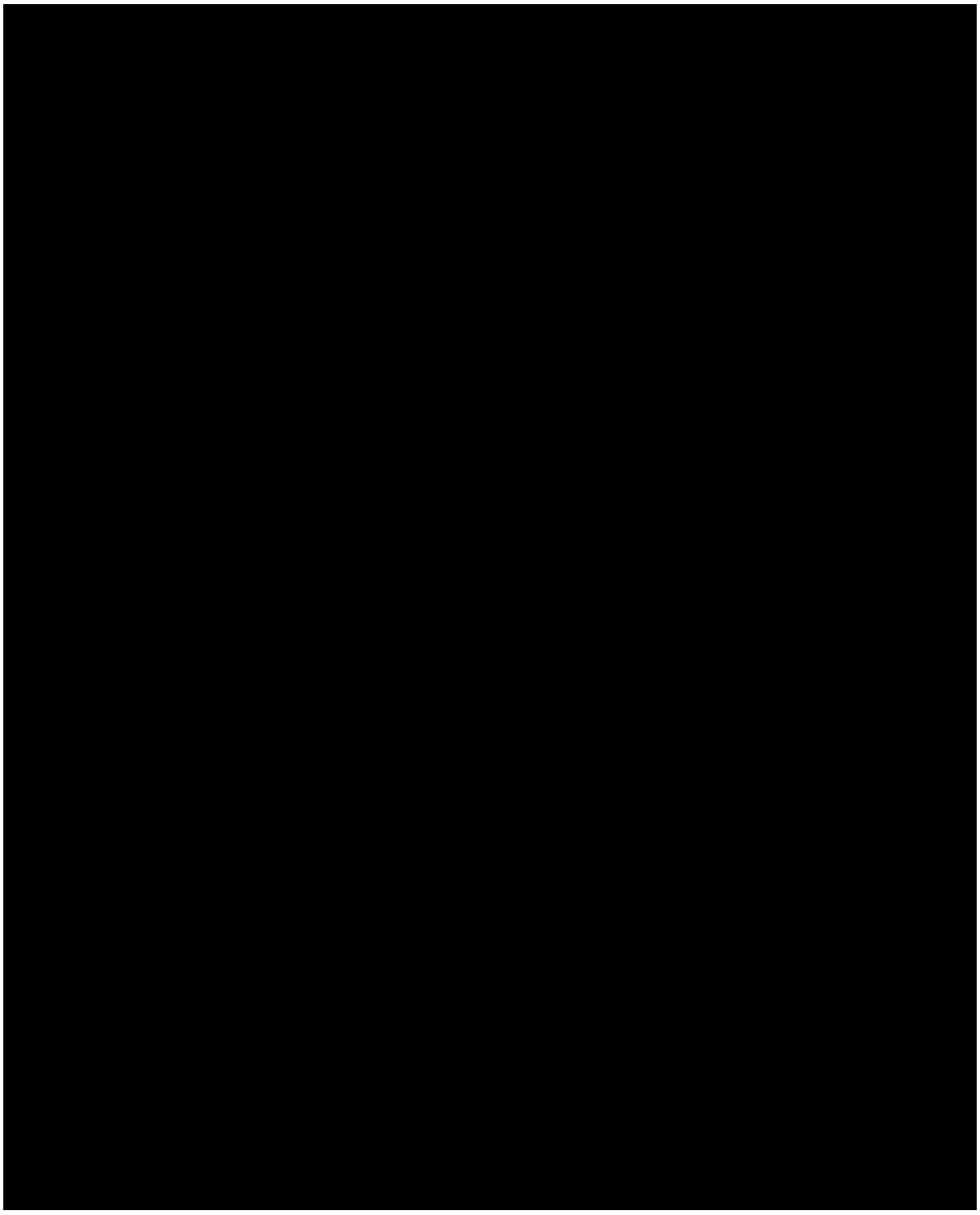
Intraocular Pressure (IOP)

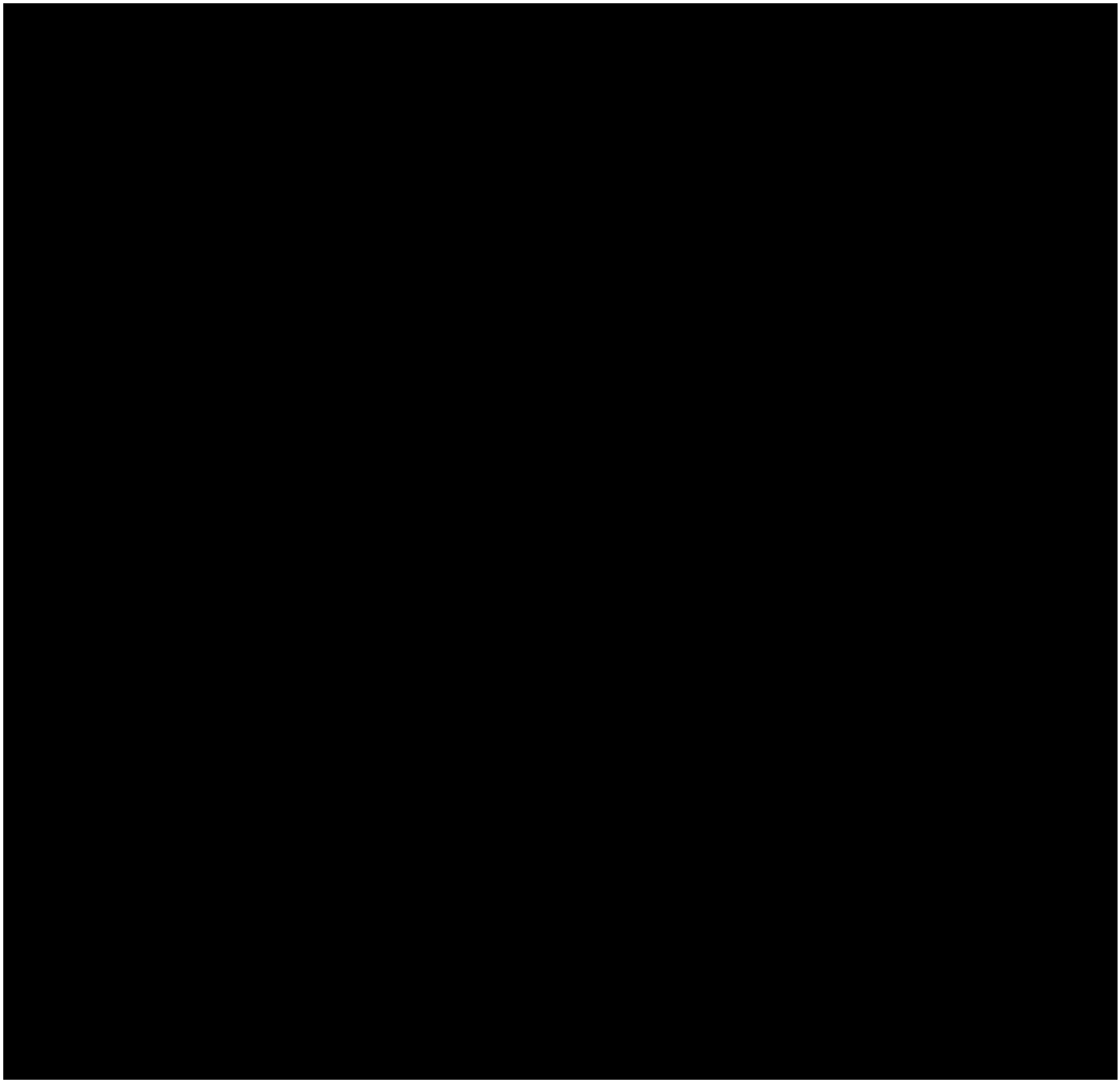
[redacted]

Unanesthetized Schirmer's Test

[redacted]

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





Visual Analog Scale (VAS)

Tear Film Break-Up Time (TFBUT)

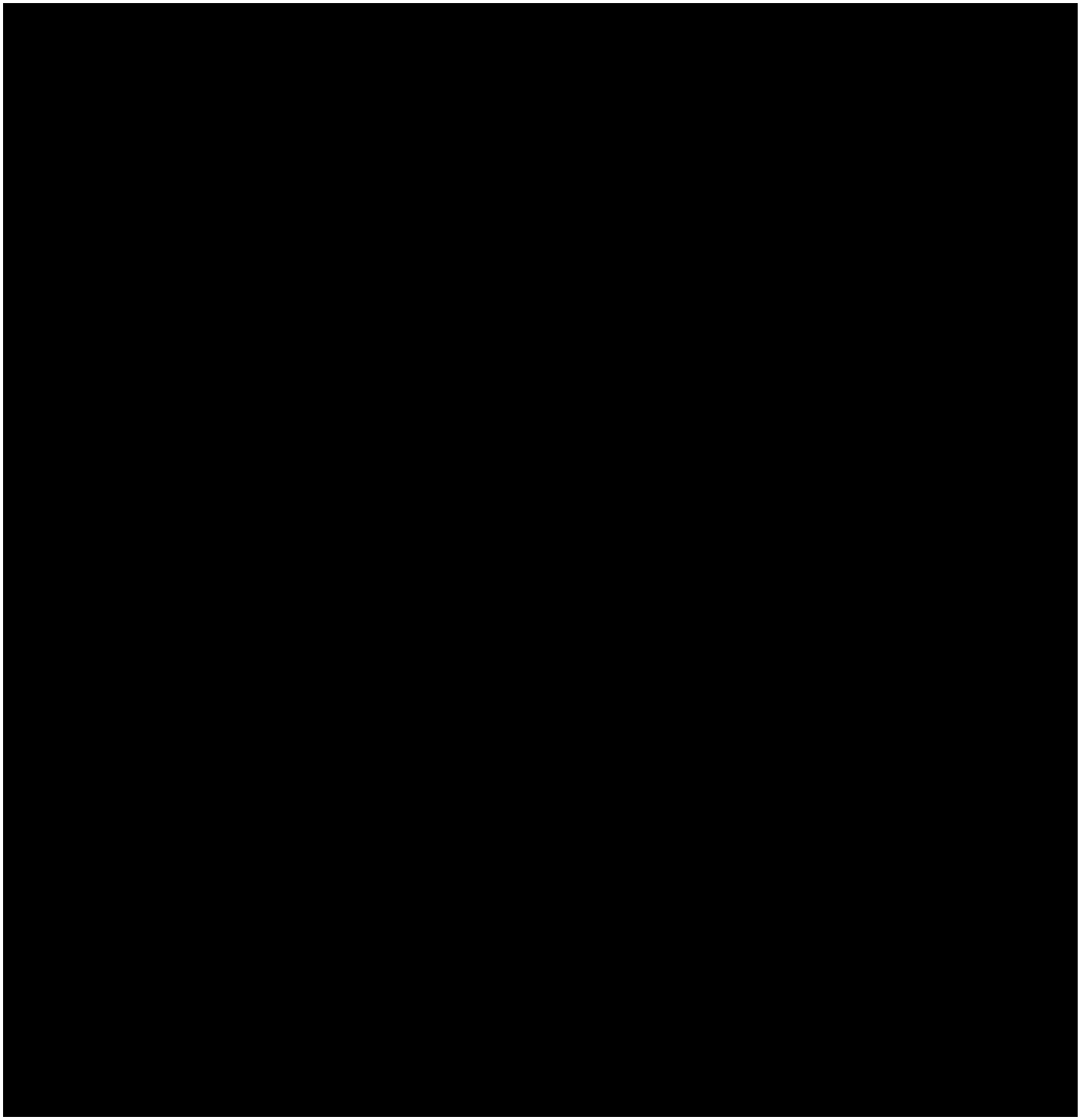
Ora proprietary scales – Not for distribution without permission

Ora Calibra® Ocular Discomfort Scale for Dry Eye

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

Fluorescein Staining

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



Lissamine Green Staining

[redacted]

Ora Calibra® Conjunctival Redness Scale for Dry Eye

[redacted]

Drop Comfort Assessments

[redacted]

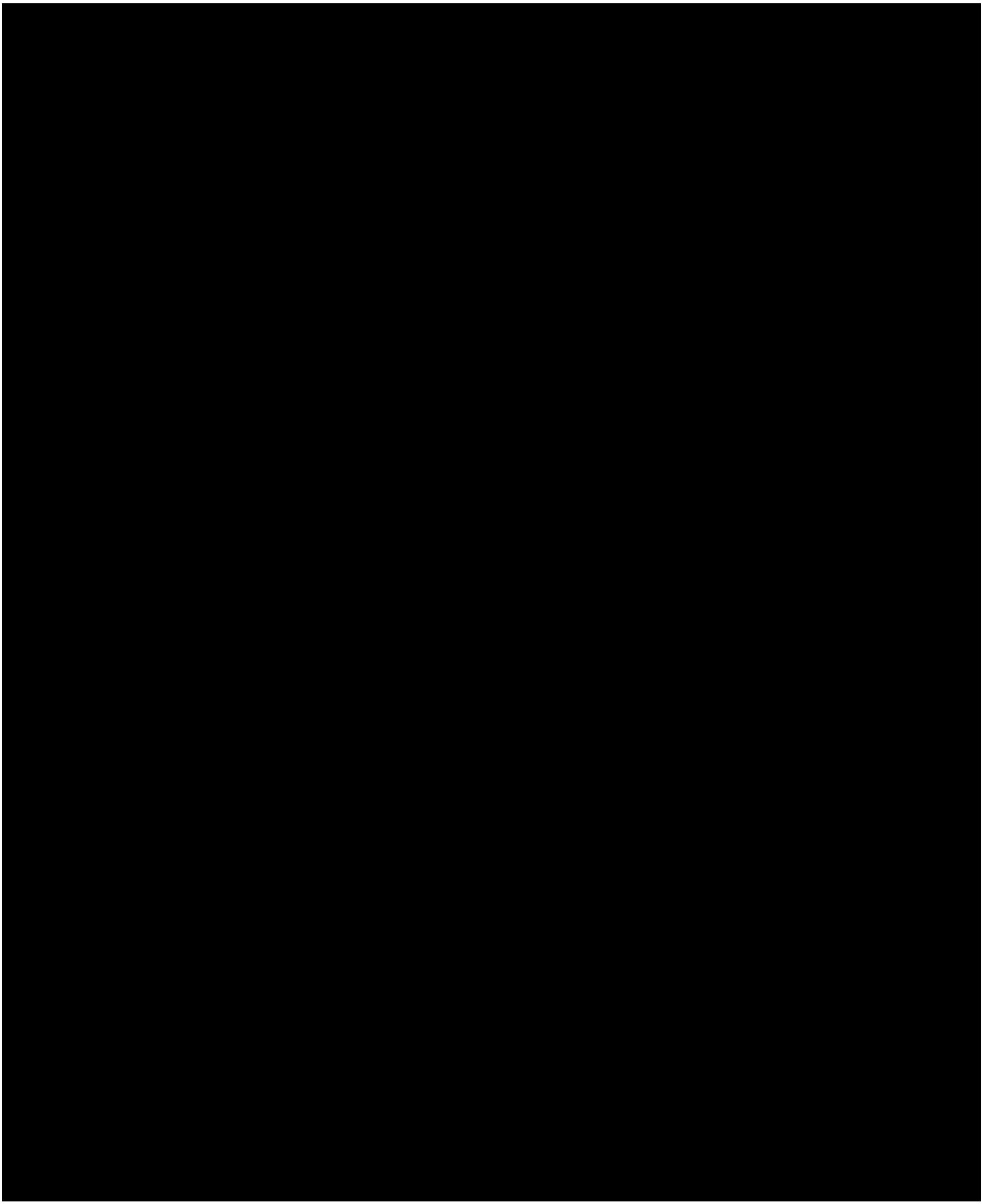
Subject-Reported Drop Comfort Scale

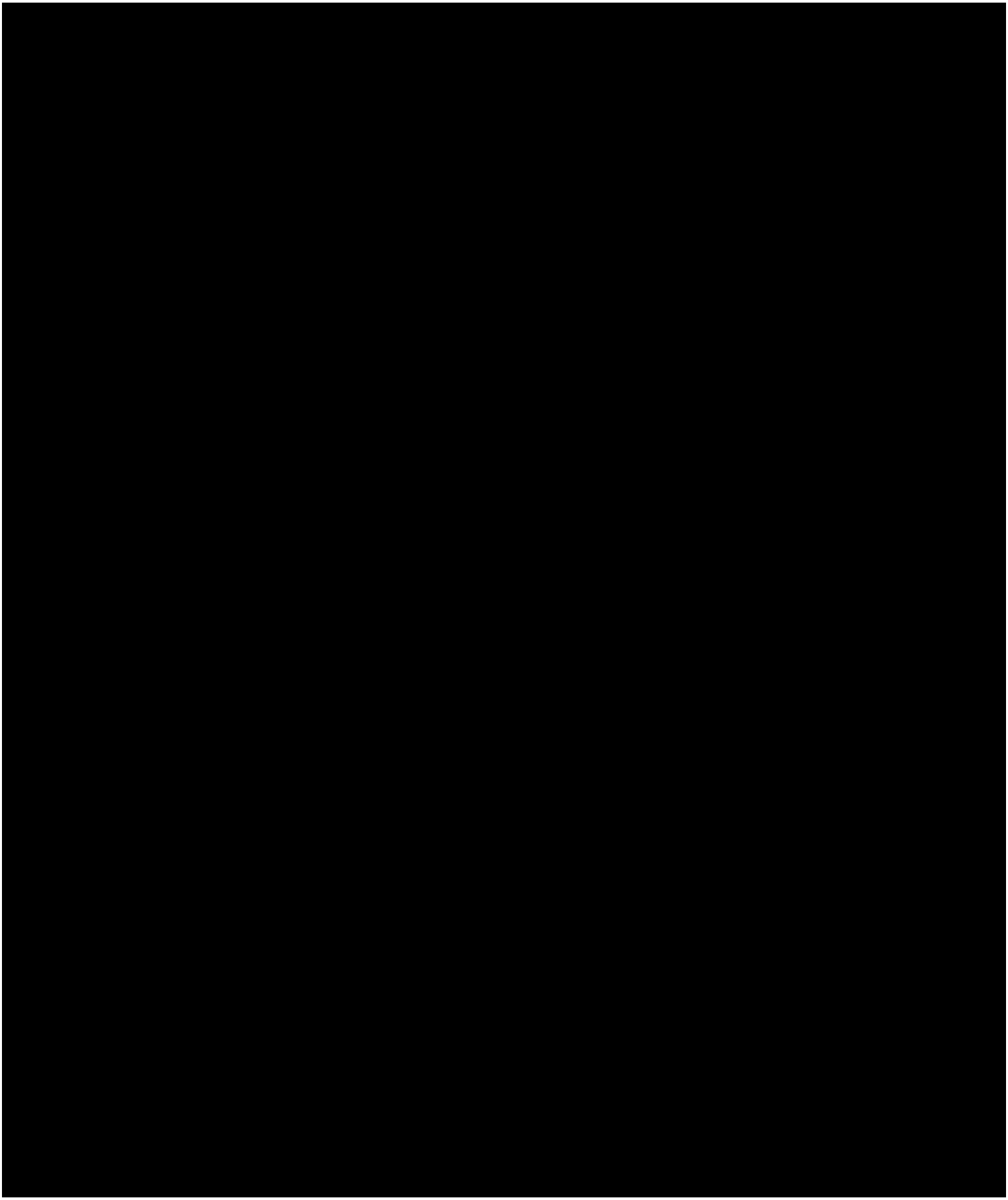
[redacted]

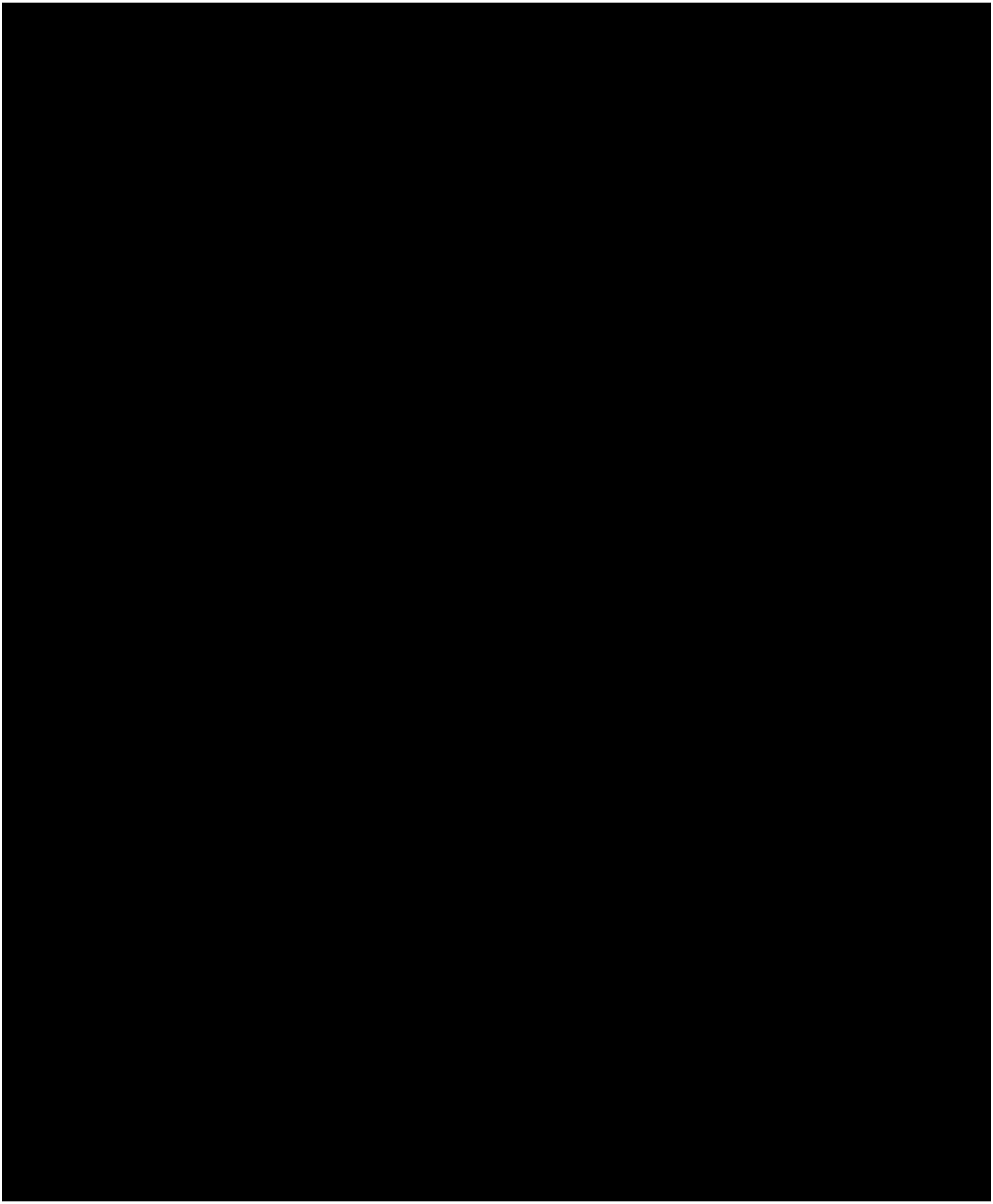
Ora Calibra® Drop Comfort Scale

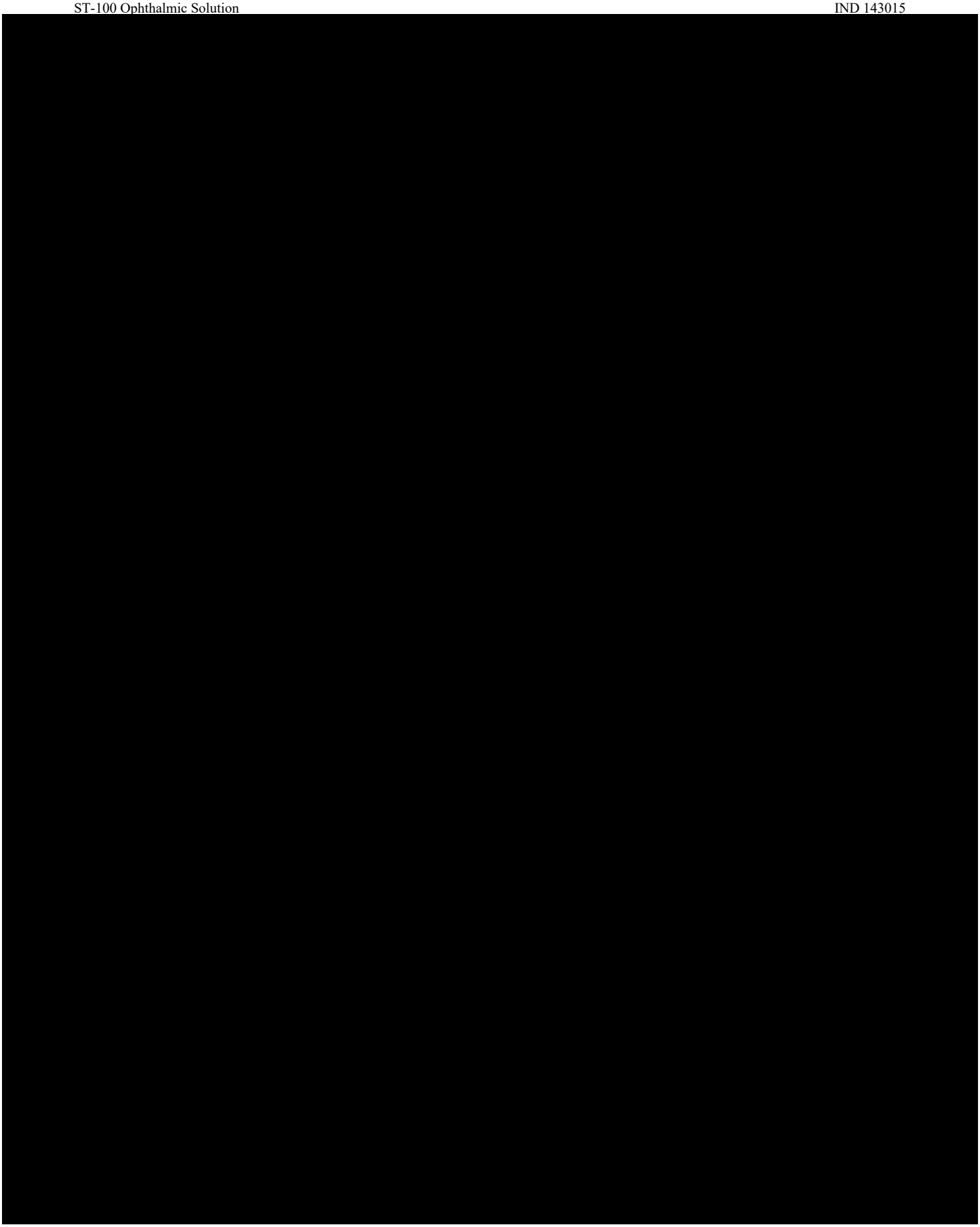
[redacted]

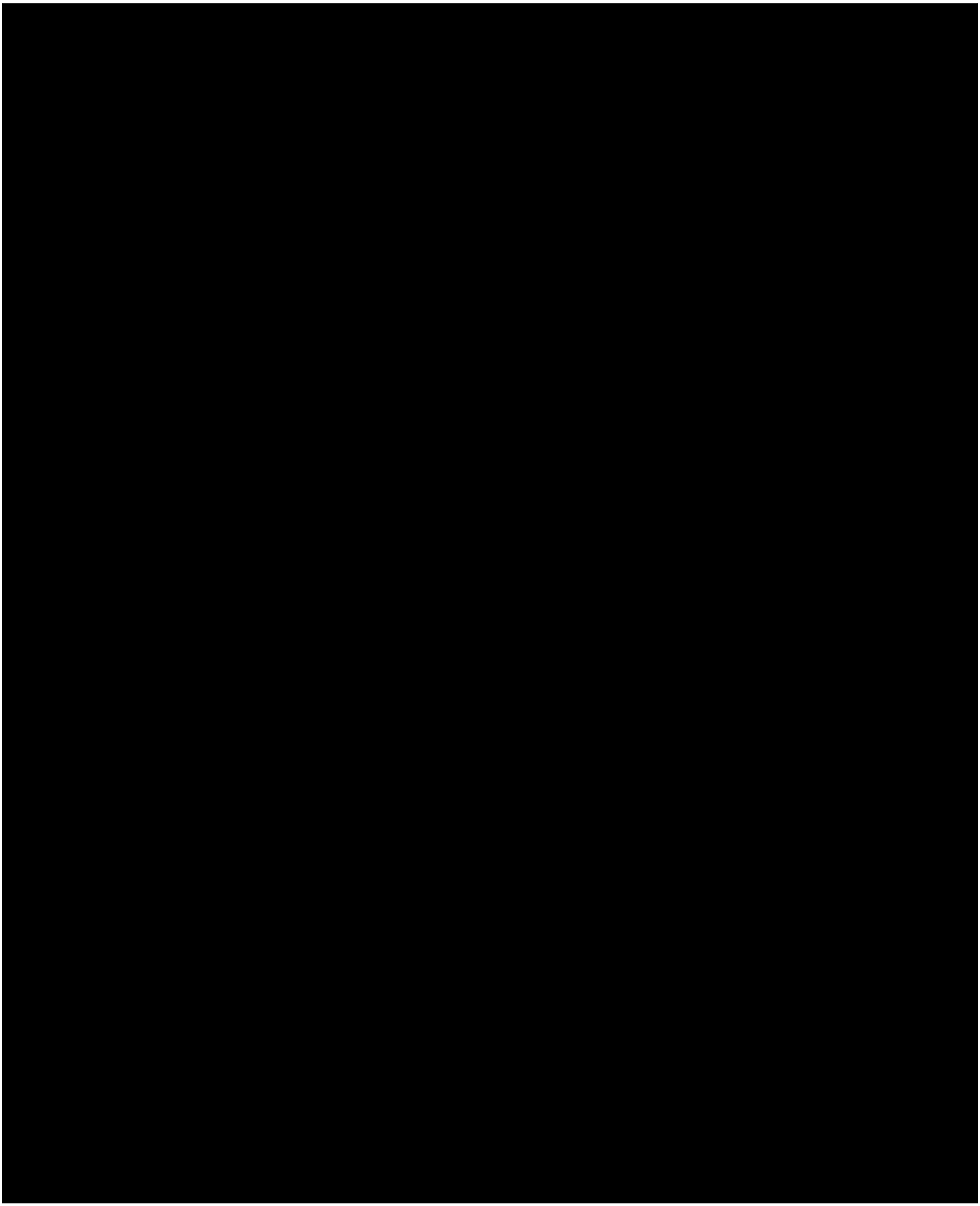
Subject Diary

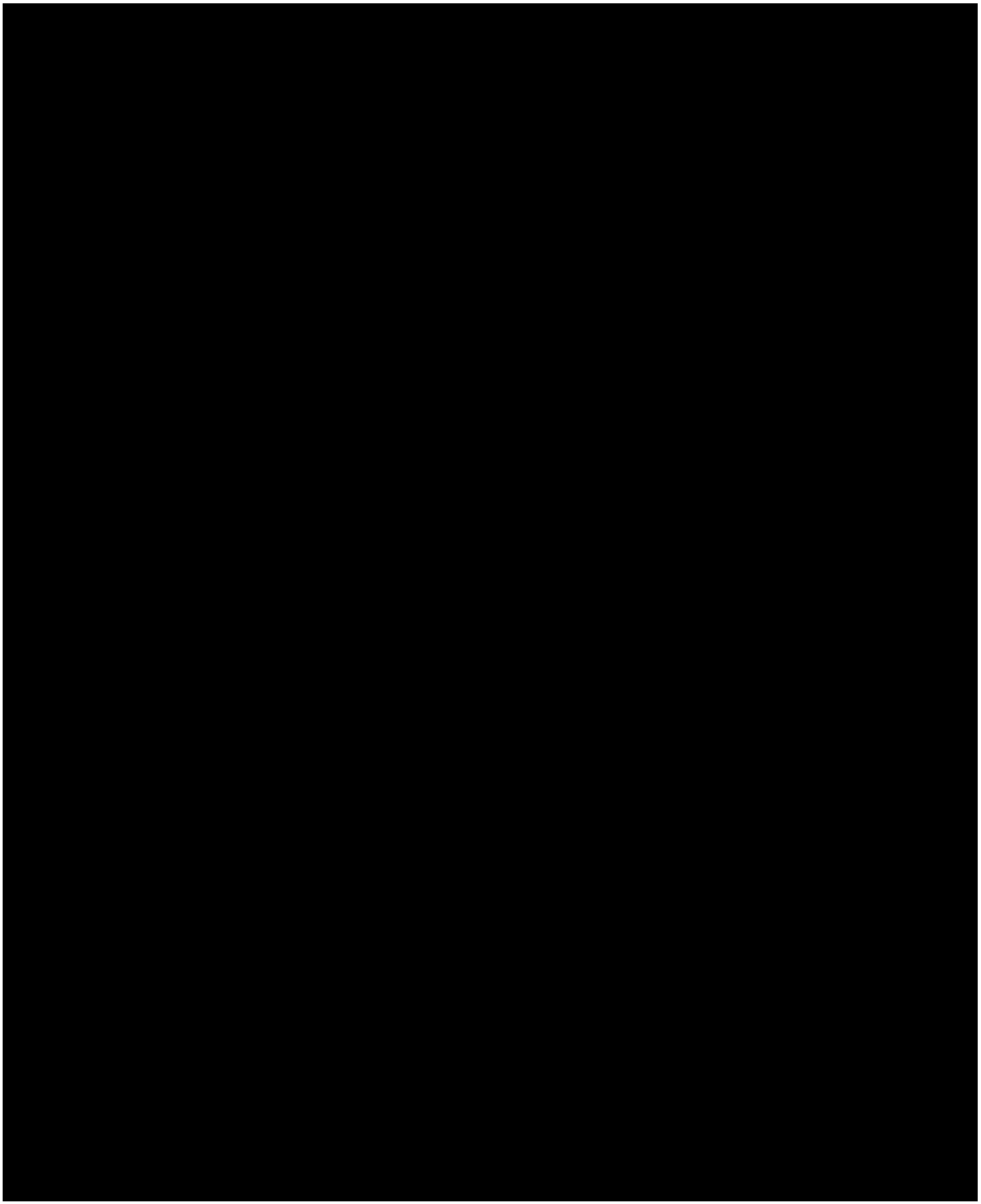




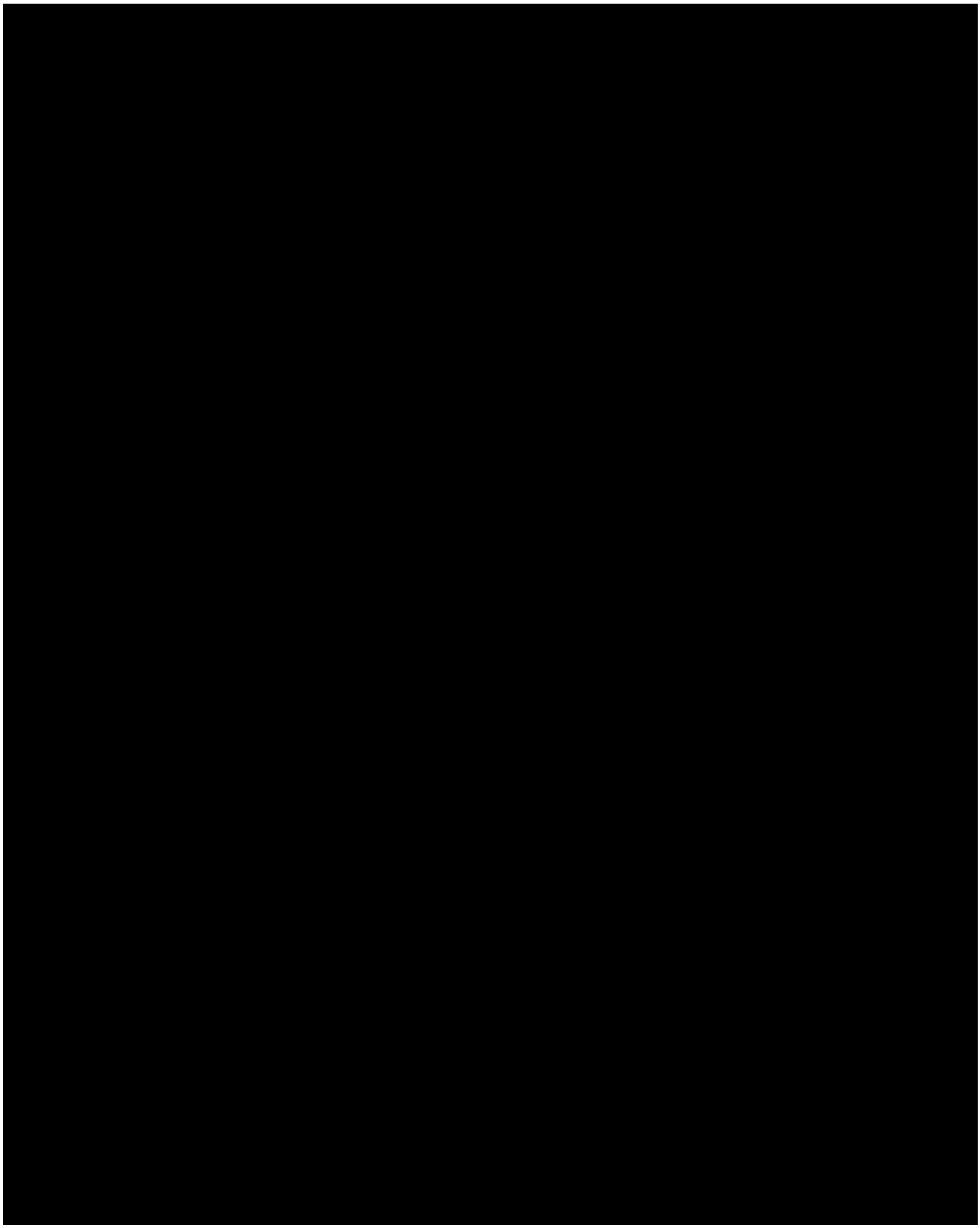


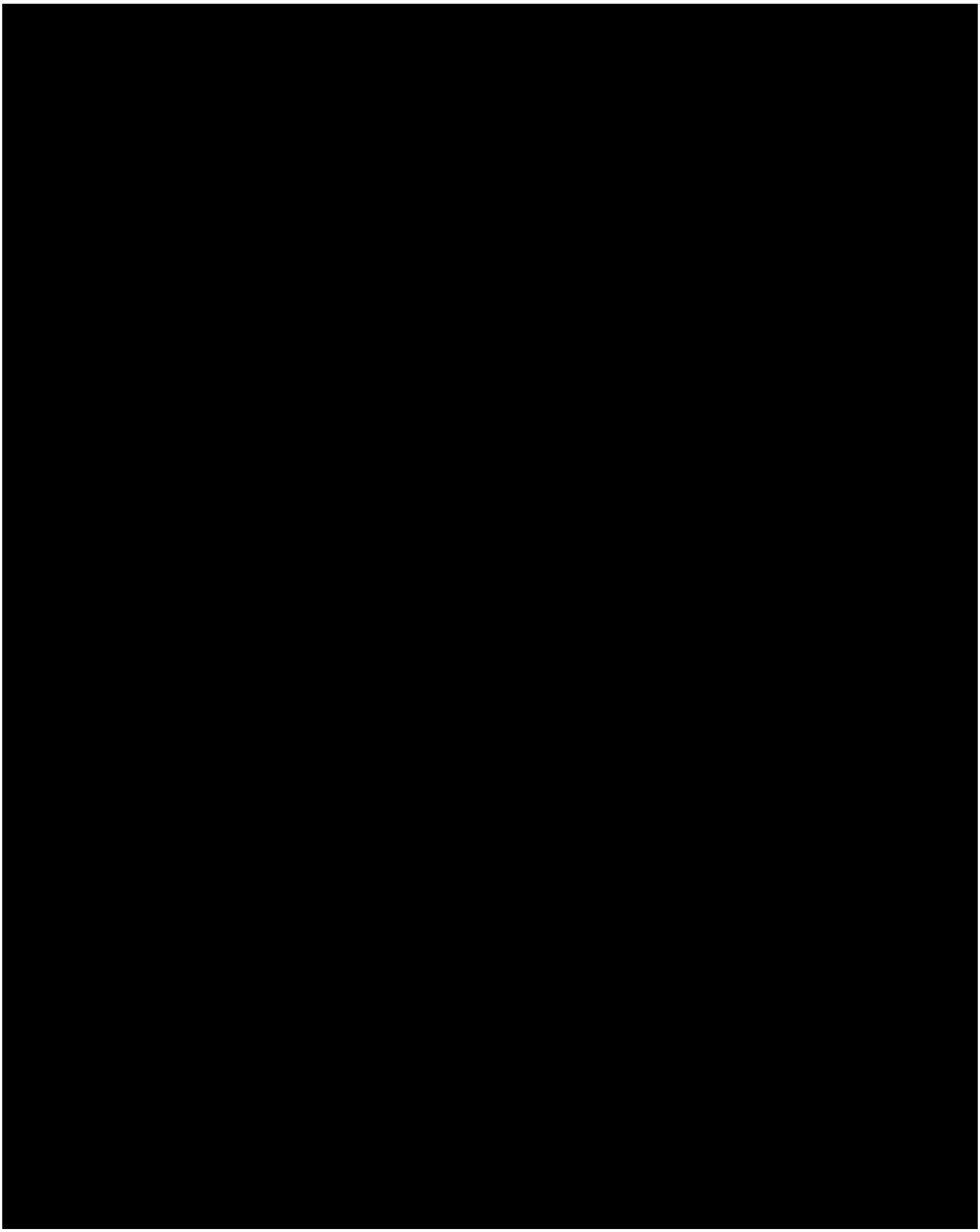


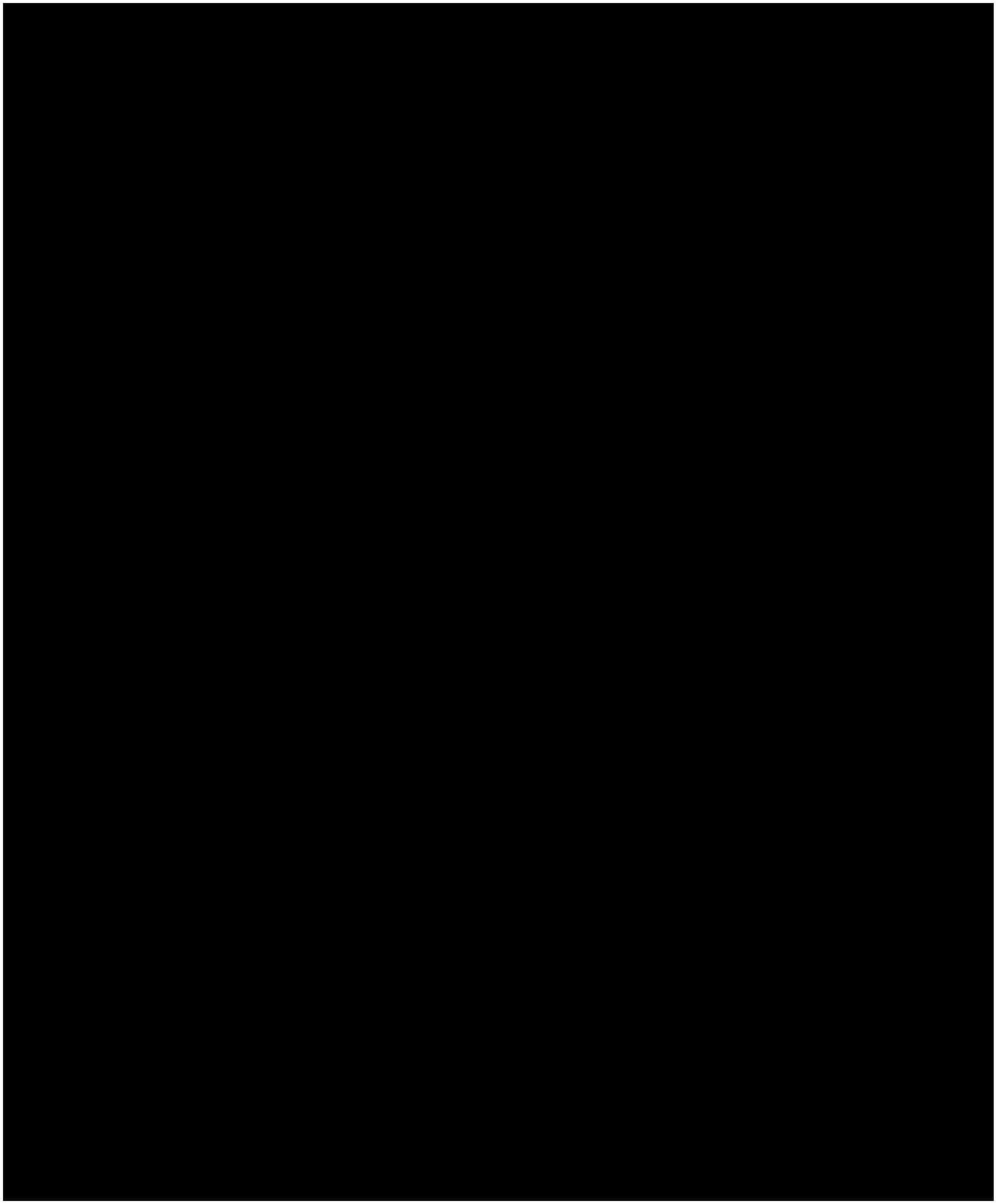


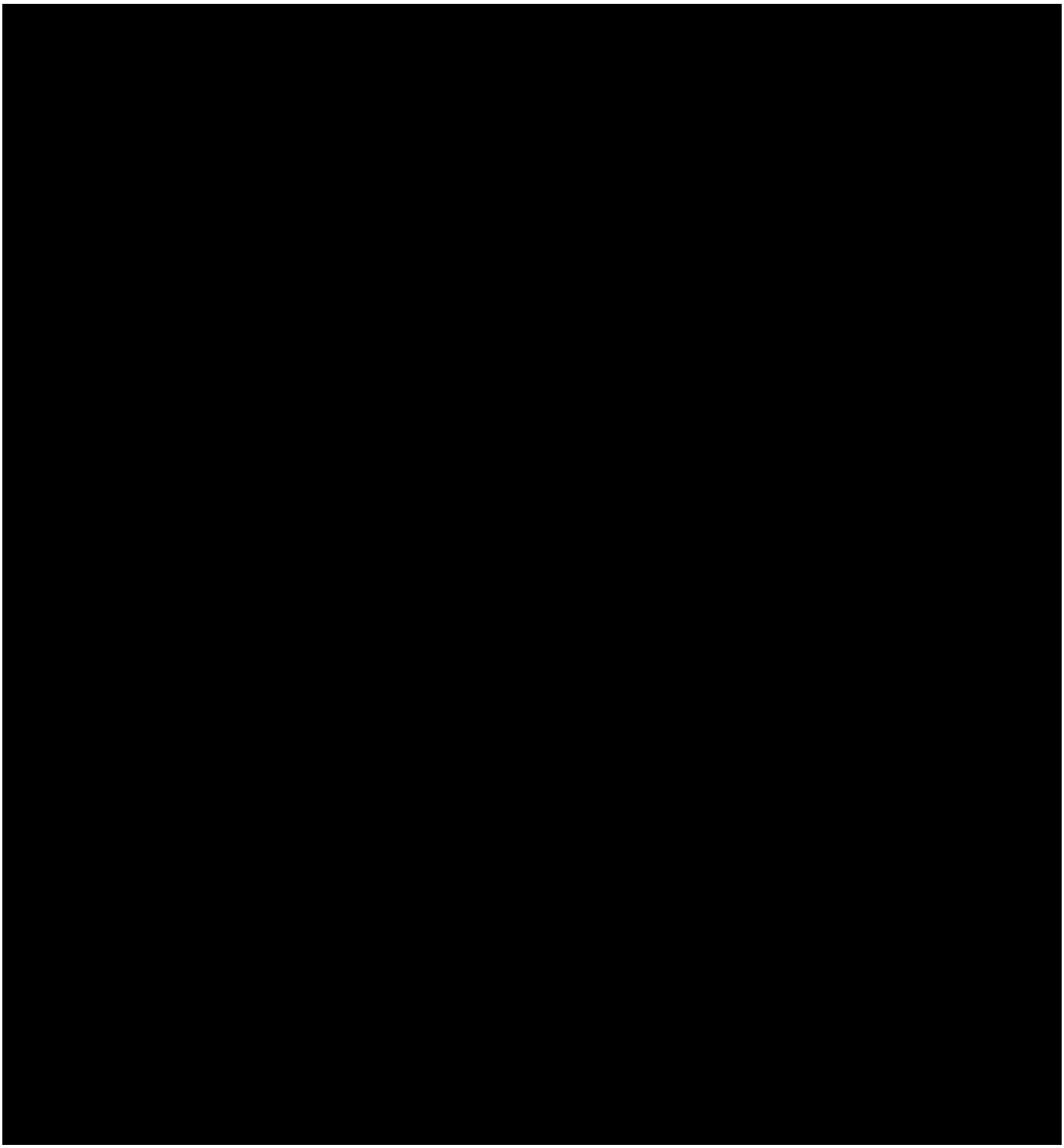


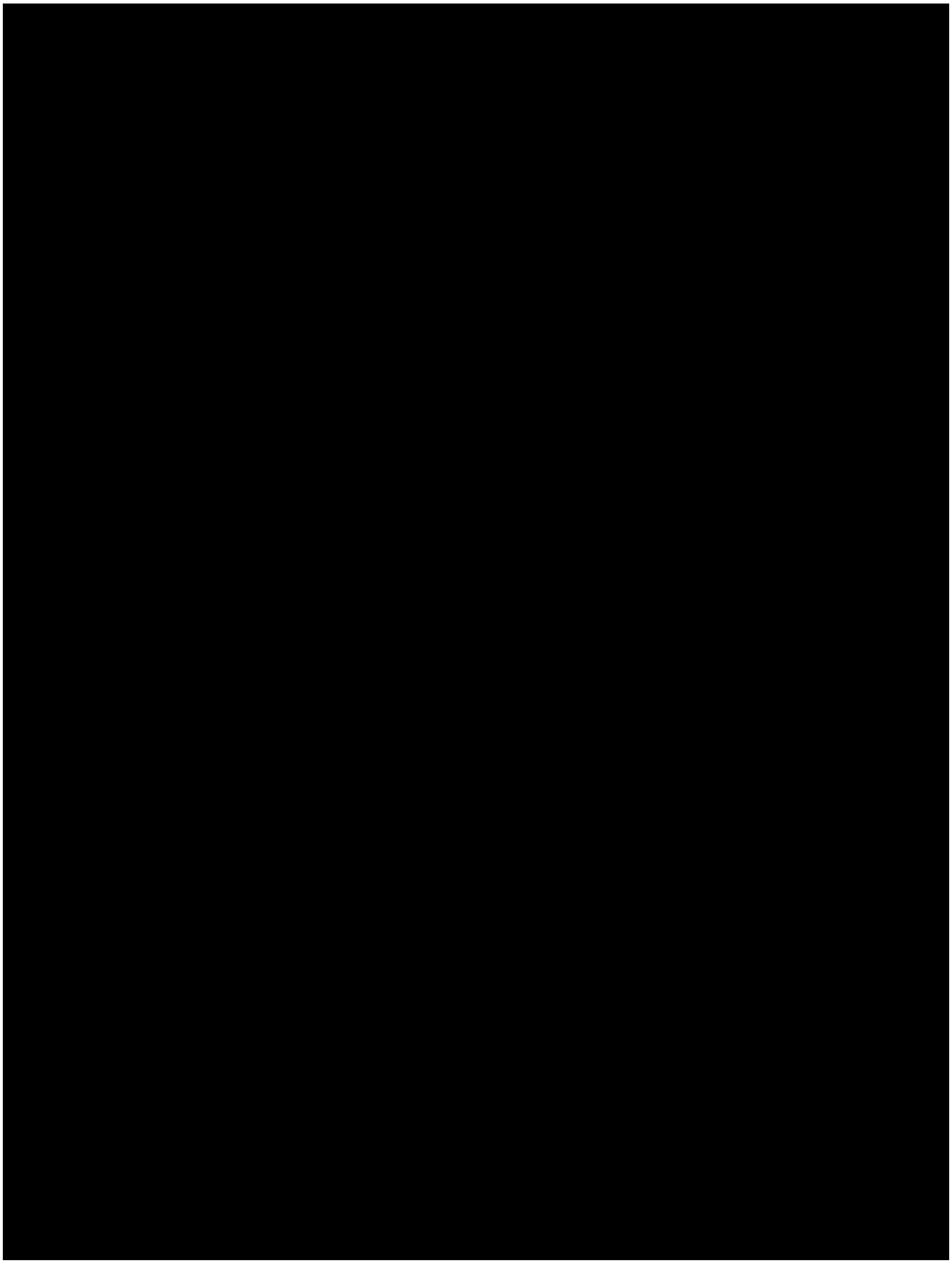
13.3 APPENDIX 3: PROTOCOL AMENDMENT SUMMARY







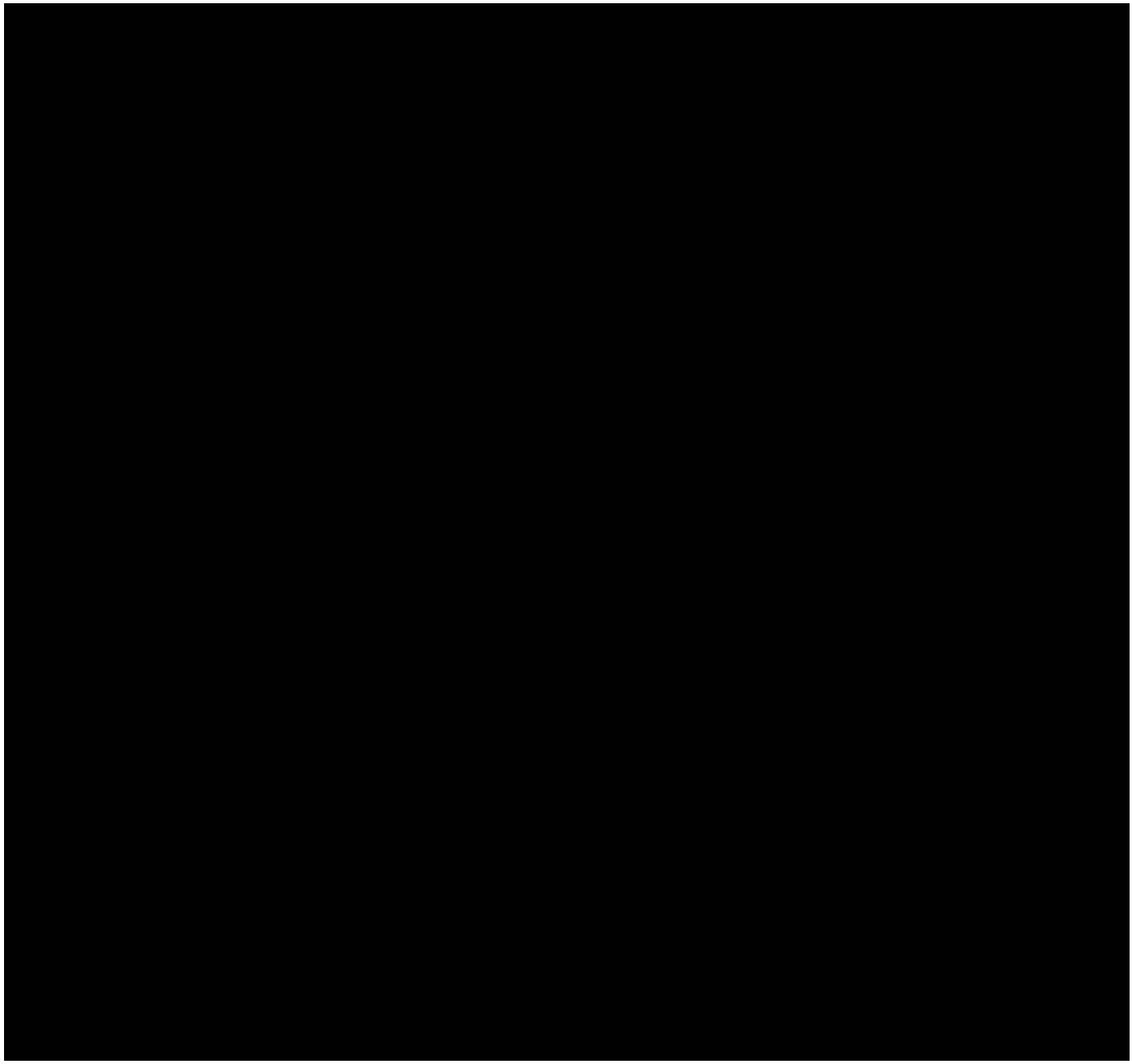




13.4 APPENDIX 4: SPONSOR AND ORA APPROVALS

Protocol Title:	A Phase 2 Multi-Center, Randomized, Double Masked, Placebo Controlled Study to Assess the Safety and Efficacy of ST-100 Ophthalmic Solution in Subjects Diagnosed with Dry Eye Disease
IND Number	143015
Final Date:	May 21, 2021

This clinical study protocol was subject to critical review and has been approved by the sponsor. The



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IND Number	143015
Final Date:	May 21, 2021

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13.5 APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 2 Multi-Center, Randomized, Double Masked, Placebo Controlled Study to Assess the Safety and Efficacy of ST-100 Ophthalmic Solution in Subjects Diagnosed with Dry Eye Disease
IND Number	143015
Final Date:	May 21, 2021

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.

Document History

SignNow E-Signature Audit Log

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

Document name:	ST100-001 Protocol Amdendment 1 21May2021 Published-Unsigned
Document created:	05/24/2021 14:00:06
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Document Sent:	05/24/2021 14:07:47 UTC
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	05/24/2021 14:08:06UTC