Clinical Trial Protocol: ADX-102-DED-019

Protocol Title:	The TRANQUILITY Trial: A Multi-Center Randomized, Double-Masked, Parallel Design, Vehicle-Controlled Phase 2/3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-019
Study Phase:	2/3
Investigational Product Name:	0.25% Reproxalap Ophthalmic Solution
IND/IDE/PMA Number:	[redacted]
Indication:	Dry Eye Disease (DED)
Investigator:	Multi-Center
Sponsor/Contract Research Organization:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
IRB/IEC:	[redacted]

	Date
Original Protocol:	30Oct2020
Amendment #1:	23Feb2021
Amendment #2:	26Apr2021
Amendment #3:	5Nov2021

Confidentiality Statement

STUDY PERSONNEL

SPONSOR PERSONNEL

Chief Development Officer:	[redacted]

ORA PERSONNEL

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

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	The TRANQUILITY Trial: A Multi-Center Randomized, Double-Masked, Parallel Design, Vehicle-Controlled Phase 2/3 Clinical Trial to Assess the Efficacy and Safety of 0.25% -Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-019
Investigational Product:	0.25% Reproxalap Ophthalmic Solution (reproxalap)
Study Phase:	2/3
Primary Objective(s):	To evaluate the efficacy of reproxalap, as assessed by conjunctival redness, Schirmer's Test, and symptoms after dosing prior to and during exposure to the Controlled Adverse Environment® (CAE) in subjects with dry eye disease
Overall Study Design:	
Structure:	Multi-center, double-masked, randomized parallel design trial
Duration:	An individual subject's participation is estimated to be approximately 16-32 days.
Controls:	Vehicle Ophthalmic Solution (vehicle)
Dosage/Dose Regimen:	Test article (reproxalap or vehicle) will be dosed topically in both eyes. Test article will be administered QID on Day 1 (Visit 2). On Day 2 (Visit 3), test article will be administered once within 10 minutes prior to the CAE entry, once 45 minutes after initiation of the CAE, and once at CAE® exit.
Summary of Visit Schedule:	Three visits over the course of approximately 2 weeks: • Visit 1 = Day -14 -16/+2, Screening

	• Visit 2 = Day 1, Randomization/Baseline • Visit 3 = Day 2 CAE® & Study Exit Twenty subjects who meet the enrollment criteria will participate in an Initial Cohort. The Initial Cohort phase will be limited to Visit 1 (Screening), Visit 2 (Day 1), and Visit 3 (Day 2). Subjects will be randomized 1:1 to receive either reproxalap or vehicle. Results from the Initial Cohort phase will be analyzed to confirm endpoints, and statistical power for the remainder of the trial.
Measures Taken to Reduce Bias:	ADX-102-DED-019 is a randomized treatment assignment, double-masked trial.
Study Population Characteristics:	
Number of Subjects:	Twenty subjects are expected to be enrolled in the Initial Cohort of the trial. Approximately 300 subjects are expected to be enrolled in the Main Cohort of the trial.
Condition/Disease:	Dry Eye Disease (DED)
Inclusion Criteria:	Subjects must meet all of the following criteria: 1. 18 years of age (either gender and any race); 2. Ability to provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. Reported history of dry eye for at least 6 months prior to Visit 1; 4. Reported history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; 5. Corneal fluorescein staining sum [redacted] in at least one eye on the Ora Calibra Scale at Visit 1. 6. Response to the CAE at Visit 1, as defined by: a. [redacted]

	[redacted]
Exclusion Criteria:	Subjects must not meet any of the following criteria: 1. Clinically significant slit lamp findings at Visit 1 [redacted] 2. Diagnosis of an ongoing ocular infection [redacted] or active ocular inflammation at Visit 1; 3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial; 4. Artificial tear eye drop use [redacted] 5. Previous laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months; 6. [redacted] 7. Systemic corticosteroid or other immunomodulator therapy [redacted] within 14 days of Visit 1 or any planned immunomodulatory therapy throughout the study period; 8. Planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1; 9. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; 10. Use of and unwillingness to discontinue topical ophthalmic prescription (including medications

	for glaucoma) or over-the-counter (OTC) solutions (not including artificial tears), gels, or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial); 11. Corrected visual acuity [redacted] in both eyes at Visit 1; 12. Pregnancy, nursing, or planned pregnancy during the conduct of the trial; 13. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 3 (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. If of childbearing potential (female or male), unwillingness to use 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 [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial.); 15. Known allergy and/or sensitivity to the test article or its components; 16. A condition 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 trial;

	17. Current enrollment in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 18. [redacted] 19. Current use of 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; 20. Inability or unwillingness to follow instructions, including participation in all study assessments and visits.
Study Formulations and Formulation Numbers:	0.25% Reproxalap Ophthalmic Solution
Evaluation Criteria:	
Primary Endpoint	• Conjunctival redness assessed via digital photography over 90 minutes in CAE
Secondary Endpoints:	• Visual analog scale eye dryness score [redacted] in CAE • Ora Calibra® Ocular Discomfort Scale [redacted] n CAE • Schirmer's Test [redacted] on Day 1
Exploratory Endpoints:	• Visual analog scale [redacted] assessed over Days 1 and 2 [redacted] • Ora Calibra® Ocular Discomfort Scale assessed over Days 1 and 2 (excluding CAE) • Ocular Discomfort & 4-Symptom Questionnaire assessed over Days 1 and 2, and before and after CAE • Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale [redacted]

	• Change in tear RASP levels [redacted] • Conjunctival Redness [redacted] • Conjunctival redness, Ora Calibra® Ocular Discomfort Scale, and visual analog scale dryness score [redacted]
Safety Endpoints:	• Visual acuity • Slit-lamp evaluation • Adverse event query • Intraocular Pressure (IOP) • Dilated fundoscopy

General Statistical Methods and Types of Analyses:

Statistical analyses will be detailed in the statistical analysis plan (SAP), which will dominate any statistical language herein. Any changes to protocol stated analyses will also be detailed in the SAP.

Sample Size:

Assuming [redacted] overall mean change from baseline in conjunctival redness (Ora Calibra® Scale) during the CAE at Day 2 between the two groups and a common standard deviation [redacted]

Multiplicity Considerations:

[redacted]

Primary Efficacy Analyses:

Overall mean change from baseline of conjunctival redness during the [redacted] will be assessed via mixed effect model for repeated measures [redacted] of change from baseline [redacted] with baseline score [redacted]

The primary endpoint will be assessed using the ITT population [redacted]

Sensitivity analyses for the primary analyses will include the following:

- [redacted]

[redacted]

[redacted]

Secondary Efficacy Analyses:

For secondary efficacy endpoints during the [redacted] CAE, [redacted] will be assessed via [redacted] with baseline score as a covariate, nominal time, and treatment group, as fixed effects with correlated errors due to eye and nominal time point for eye level assessments. For subject level assessments [redacted], the model will have correlated errors due to nominal time point.

Overall mean change from baseline of Schirmer's Test [redacted] will be assessed [redacted] with baseline score as a covariate [redacted] time point [redacted] and treatment group as fixed effects with correlated errors due to eye and time point.

Exploratory Efficacy Analyses:

[redacted]

[redacted]

[redacted]

Primary analyses of exploratory efficacy endpoints will utilize the ITT population with observed data only.

All efficacy analyses conducted on the ITT population will be conducted using the Initial Cohort population only with observed data.

Safety Analyses: [redacted]
Summary of Known and Potential Risks and Benefits to Human Subjects: Refer to Investigator's Brochure.

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List of Abbreviations

AE	adverse event
CAE	Controlled Adverse Environment®
CFR	Code of Federal Regulations
DED	dry eye disease
DES	dry eye syndrome
DHHS	Department of Health and Human Services
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	institutional/independent review board
LogMAR	logarithm of the minimum angle of resolution
MAR	Missing at random
MNAR	Missing not at random
Ora	Ophthalmic Research Associates, Inc.
OTC	over the counter
RASP	reactive aldehyde species
SAE	serious adverse event
µL	microliter
VA	visual acuity
VAS	Visual analog scale

1 INTRODUCTION

[redacted]

2 STUDY OBJECTIVES

To evaluate the efficacy of reproxalap, as assessed by conjunctival redness, Schirmer's Test, and symptoms after dosing prior to and during exposure to the Controlled Adverse Environment® (CAE) in subjects with dry eye disease

3 CLINICAL HYPOTHESES

The clinical hypothesis is that reproxalap is more effective than vehicle in reducing the signs and symptoms of DED.

4 OVERALL STUDY DESIGN

ADX-102-DED-019 is a Phase 2/3, multi-center, randomized, double-masked, parallel design, vehicle-controlled trial designed to evaluate the efficacy and safety of 0.25% Reproxalap Ophthalmic Solution compared to vehicle in subjects with dry eye disease. Approximately twenty subjects will be enrolled in the Initial Cohort, and approximately 300 subjects will be enrolled in the Main Cohort. Male and female subjects at least 18 years of age with a subject-reported history of dry eye disease in both eyes and meeting all other eligibility criteria will be randomized to receive reproxalap or vehicle in a 1:1 ratio (approximately 150 subjects in each treatment group).

Visit 1 (Day -14 -16/+ 2): Screening	• Informed Consent • Demographics, Medical/Medication & Ocular History • Urine Pregnancy Testing (as needed) • Symptom Questionnaires, Ocular Dryness VAS, Visual Acuity • Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale • Slit Lamp Exam with Conjunctival Redness assessment • In-Office vehicle dose [redacted] • CAE exposure [redacted] with Ocular Dryness VAS, Ora Calibra® Ocular Discomfort Scale, and Conjunctival Redness Assessment • Slit Lamp Exam with Conjunctival Redness assessment • Ora Calibra® Corneal and Conjunctival Staining Scale • Schirmer's Test • IOP and Dilated Fundoscopy
Visit 2 (Day 1): Randomization/Baseline	• Medical/Medication Update: AE Query • Visual Acuity • Slit Lamp Exam • Symptom Questionnaires at specified time points • Conjunctival Redness at specified time points • In-Office Doses (QID) • Tear Collection & Schirmer's Test at specified time points
Visit 3 (Day 2): CAE	• Medical/Medication Update: AE Query • Urine Pregnancy Testing (as needed) • Visual Acuity, Slit Lamp Exam • Symptom Questionnaires • Conjunctival Redness at specified time points • In-Office Doses [redacted]

	• CAE exposure [redacted] with Ocular Dryness VAS, and Ora Calibra® Ocular Discomfort Scale, and Conjunctival Redness Assessments • Tear Collection at specified time points • IOP and Dilated Fundoscopy • Study Exit

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 40 subjects will be screened in the Initial Cohort to enroll 20 subjects at one site. An additional 600 subjects will be screened in the Main Cohort to enroll approximately 300 subjects across approximately 8 sites.

5.2 Study Population Characteristics

All subjects must be at least 18 years of age, be of either sex and of any race, have a subject-reported history of dry eye disease, and meet all of the inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Each subject must meet each of the following criteria:

1. 18 years of age (either gender and any race);

2. Ability to provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;

3. Reported history of dry eye for at least 6 months prior to Visit 1;

4. Reported history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;

5. Corneal fluorescein staining sum [redacted] in at least one eye on the Ora Calibra Scale at Visit 1.

6. Response to the CAE at Visit 1, as defined by:

   a. A [redacted] in the visual analog scale eye dryness score [redacted] in at least one eye during at least two consecutive time points in CAE and;

   b. A [redacted] in conjunctival redness score measured via digital photography in at least one eye during at least two consecutive time points in CAE.[1]

[1] Eye does not need to be the same eye as inclusion 5 or 6a.

5.4 Exclusion Criteria

Each subject may <u>not meet any of the following criteria</u>:

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

2. Diagnosis of an ongoing ocular infection [redacted] or active ocular inflammation at Visit 1;

3. Contact lens use within 7 days of Visit 1 or anticipate using contact lenses during the trial;

4. Artificial tear eye drop use within 2 hours of Visit 1 or within 24 hours of Visit 2 (drops cannot be used on the day of Visit 2 or Visit 3);

5. Previous laser-assisted *in situ* keratomileusis (LASIK) surgery within the last 12 months;

6. Cyclosporine 0.05% or 0.09% or lifitegrast 5.0% ophthalmic solution use within 90 days of Visit 1;

7. Systemic corticosteroid therapy or other immunomodulator (not including inhaled corticosteroids) within 14 days of Visit 1 or anticipate such therapy throughout the study period;

8. Planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1;

9. Temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

10. Use of and unwillingness to discontinue topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions (not including artificial tears), gels or scrubs for the duration of the trial (excluding medications allowed for the conduct of the trial);

11. Corrected visual acuity greater than or equal to logarithm of the minimum angle of resolution [redacted] at Visit 1;

12. Pregnancy, nursing, or planned pregnancy during the conduct of the trial;

13. Unwillingness to submit a urine pregnancy test at Visit 1 and Visit 3 (or early termination visit) if of childbearing potential. (Nonchildbearing 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. If of childbearing potential (female or male), unwillingness to use 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 [IUD]; or surgical sterilization of partner. For non-sexually active males or females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, he/she must agree to use adequate birth control as defined above for the remainder of the trial.);

15. Known allergy and/or sensitivity to the test article or its components;

16. A condition 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 trial;

17. Current enrollment in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;

18. Use of [redacted] solution in the past year;

19. Current use of 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;

20. Inability or unwillingness to follow instructions, including participation in all study assessments and visits.

5.5 Withdrawal Criteria (if applicable)

Subjects may voluntarily withdraw from the trial at any time. Additionally, subjects may be discontinued for safety reasons as determined by the investigator and/or Medical Monitor.

6 STUDY PARAMETERS

6.1 Primary Endpoint

- Conjunctival redness assessed via digital photography [redacted] in CAE

6.2 Safety Endpoints

- Visual acuity
- Slit-lamp evaluation
- Adverse event query

- Intraocular Pressure (IOP)
- Dilated fundoscopy

6.3 Secondary Endpoints

- Visual analog scale eye dryness score [redacted] in CAE
- Ora Calibra® Ocular Discomfort Scale [redacted] in CAE
- Schirmer's Test [redacted] on Day 1

6.4 Exploratory Endpoints

- Visual analog scale eye dryness score [redacted] excluding CAE)
- Ora Calibra® Ocular Discomfort Scale [redacted] excluding CAE)
- Ocular Discomfort & 4-Symptom Questionnaire [redacted] and before and after CAE
- Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale assessed [redacted]
- Change in tear RASP levels [redacted]
- Conjunctival Redness [redacted]
- Conjunctival redness, Ora Calibra® Ocular Discomfort Scale, and visual analog scale dryness score [redacted]

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Formulations

Randomized Study Treatments

- 0.25% Reproxalap Ophthalmic Solution
- Vehicle

7.1.2 Study Drug Packaging Configuration

[redacted]

7.1.3 Study Drug Storage and Accountability

[redacted]

The study drug 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 study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

7.1.4 Instructions for Dispensation, Use, and Administration

- At Visit 1, qualified subjects will be assigned a vehicle kit. Subjects will use two vials from the kit for Visit 1 in-office doses. After use, vials will be placed into a zip locked bag labeled with subject's initials and screening number for accountability.
- At Visit 2, qualified subjects will be randomized and will be assigned a single kit of 14 pouch supply of Reproxalap Ophthalmic Solution 0.25% or Vehicle. Subjects will be dosed in office four times (QID) by trained site staff.
- At Visit 3, subjects will be dosed three times in-office from the same kit by trained site staff.

[redacted]

7.2 Other Study Supplies

Tear collection supplies, Schirmer's Test strips, Scale to weigh Schirmer's strips, 2% preservative-free sodium Fluorescein Solution, Fluorescein Strips, ETDRS Series [redacted] eye occluder, alcohol swabs.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in section 5.2, 5.3, and 5.4 will be considered for entry into the trial.

8.1.2 Informed Consent

Prior to each subject's participation in the clinical trial (i.e., changes in a subject's medical treatment and/or study related procedures), the clinical trial will be discussed with the subjects, 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 Independent Review Board.

8.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria.

8.1.4 Procedures for Final Study Entry

Subjects must satisfy all of the inclusion criteria and none of the exclusion criteria in order to be entered into the study.

8.1.5 Methods for Assignment to Treatment Groups:

At Visit 1 each subject who signs the informed consent will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at each site and no numbers will be skipped or omitted.

At Visit 2, a patient who meets all the eligibility criteria will be randomized to receive treatment or vehicle in a 1:1 ratio. Patients will be assigned a randomization number and kit number via paper randomization list for the Initial Cohort and by IWRS for the Main Cohort.

The site staff will dispense to the patient the study kit labeled with the corresponding kit number. Both the randomization number and the dispensed study drug kit number will be recorded on the patient's source document and eCRF.

8.2 Concurrent Therapies

The use of any applicable concurrent medications, prescription or OTC medications is to be recorded on the subject's source document along with the reason the medication was taken.

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

8.2.1 Prohibited Medications/Treatments

Prohibited medications, treatments, and activities are outlined in the exclusion criteria.

8.2.2 Escape Medications

Not applicable.

8.2.3 Special Diet or Activities

Not applicable.

8.3 Examination Procedures

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

Visit 1 (Day -14 -16/+2, Screening)

- Informed Consent and HIPAA
- Demographics [redacted]
- Medical/Medication & Ocular History
- Urine Pregnancy Test (as needed)
- Symptom Questionnaires:
  - Ocular Discomfort & 4-Symptom Questionnaire
  - Ora Calibra® Ocular Discomfort Scale
  - Ocular Dryness Visual Analog Scale
  - Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy with Conjunctival Redness assessment
- Fluorescein Staining using the Ora Calibra® Corneal and Conjunctival Staining Scale
- Inclusion/Exclusion Criteria Review
- In-Office Vehicle Instillation by trained site staff [redacted]
- CAE Exposure [redacted] with:
  - Ocular Dryness Visual Analog Scale [redacted]
  - Ora Calibra® Ocular Discomfort Scale [redacted]
  - Conjunctival Redness Photography [redacted]
- Slit Lamp Biomicroscopy with Conjunctival Redness assessment
- Schirmer's Test
- Intraocular Pressure

- Dilated Exam
- Schedule for Visit 2

Visit 2 (Day 1, Baseline and In-Office Dosing)

- Medical/Medication Update
- Adverse Event Query
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Symptom Questionnaires
  - Ocular Discomfort & 4-Symptom Questionnaire
  - Ora Calibra® Ocular Discomfort Scale
  - Ocular Dryness Visual Analog Scale
  - Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale
- Conjunctival Redness Photography
- Inclusion/Exclusion Criteria Review
- Randomization/Enrollment
- Pre-dose #1 [redacted]
- In-Office Dose #1
- Post-dose #1 [redacted]

- Pre-dose #2 [redacted]
- In-Office Dose # 2
- Post-dose #2 [redacted]

- In-Office Dose #3
- Conjunctival Redness Photography [redacted]
- Symptom Questionnaires started within [redacted]
  - Ocular Discomfort & 4-Symptom Questionnaire
  - Ocular Discomfort
  - Ocular Dryness Visual Analog Scale
  - Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale

Wait 30 minutes between doses

- Pre-dose #4 Schirmer's Test [redacted]
  - Weigh Schirmer's Test strip before and after use
- In-Office Dose #4
- Post-dose #4 Schirmer's Test [redacted]

    - Weigh Schirmer's Test strip before and after use
- Schedule for Visit 3

Visit 3 (Day 2, CAE®)

- Medical/Medication Update
- Adverse Event Query
- Urine Pregnancy Test (as needed)
- Visual Acuity (ETDRS)
- Slit Lamp Biomicroscopy
- Conjunctival Redness Photography
- Symptom Questionnaires:
    - Ocular Discomfort & 4-Symptom Questionnaire
    - Ora Calibra® Ocular Discomfort Scale
    - Ocular Dryness Visual Analog Scale
    - Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale
- Pre-dose #1 [redacted]
- In-Office Dose #1 [redacted]
- CAE Exposure [redacted] with:
    - Ocular Dryness Visual Analog Scale [redacted]
    - Conjunctival Redness [redacted]
    - Ora Calibra® Ocular Discomfort Scale [redacted]
- In-Office [redacted]
- Post-CAE exit [redacted]
- In-Office Dose #3 [redacted]
- Symptom Questionnaires [redacted]
    - Ocular Discomfort & 4-Symptom Questionnaire
    - Ocular Discomfort
    - Ocular Dryness Visual Analog Scale
    - Ora Calibra® Conjunctival Allergen Challenge Ocular Itching Scale
- Post-dose #3 [redacted]
- Slit Lamp Biomicroscopy
- Intraocular Pressure
- Dilated Exam
- Study Exit

Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 3 , then all safety evaluations that are to be performed at Visit 3 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

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

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

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

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

8.4.2 Unscheduled Visits

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

Evaluations that may be conducted at an Unscheduled Visit include:

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

8.5 Subject Disposition

8.5.1 Completed Subjects

A completed subject is one who has not been discontinued from the study and has completed all applicable assessments.

8.5.2 Discontinued Subjects

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

- adverse events
- protocol violations
- administrative reasons (e.g., inability to continue)
- Sponsor termination of study
- other

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

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and will be clearly documented on the source document.

8.6 Study Termination

The clinical trial may be stopped at any time by the investigator, or Ora with appropriate notification.

8.7 Study Duration

An individual subject's participation is estimated to be approximately 2 – 4 weeks.

8.8 Monitoring and Quality Assurance

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

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

9 ADVERSE EVENTS

9.1 Adverse Event

For the purposes of this trial, an adverse event is defined as any untoward medical event occurring after the subject's signing of the informed consent until they are exited from the trial. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease occurring after the subject started the clinical trial, without any judgment about causality. Any pre-existing medical condition that worsens during the trial will also be considered a new adverse event. Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, relationship to study procedure, expectedness, action(s) taken, seriousness, and outcome of any sign or symptom observed by the investigator or reported by the patient upon indirect questioning.

9.1.1 Severity

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

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

9.1.2 Relationship to Study Procedures

The relationship of each AE to the study procedures should be determined by the investigator using these explanations. Decisive factors for the assessment of causal relationship of an AE to the study procedures include, but may not be limited to, temporal relationship between the AE and the procedure, known side effects of the procedure medical history, and/or concomitant medication:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between study procedure and AE;

- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable.

- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example; due to missing data or insufficient evidence.

- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.

- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data or poor documentation.

9.1.3 Expectedness

The expectedness of an adverse event should be determined based upon existing safety information about the study procedures. Therefore, the following definition will be used:

- *Unexpected*: An adverse event that is not listed in the safety information available for the study procedure at the specificity or severity that has been observed.

- *Expected*: An adverse event that is listed in the safety information available for the study procedure at the specificity and severity that has been observed.

- *Not Applicable*: Any adverse event that is unrelated to the study procedure.

9.2 Serious Adverse Events

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

- Death;

- A life-threatening adverse event;

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

- Inpatient hospitalization or prolongation of existing hospitalization;

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

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

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

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

- A congenital anomaly/birth defect.

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

9.3 Procedures for Reporting Adverse Events

All adverse events and their outcomes must be reported to Ora and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities and recorded on the appropriate source document.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All adverse events that are related (definite, probable, possible) and 'unexpected' are to be reported to Ora and the IRB as required by the IRB, federal, state, or local regulations and governing health authorities.

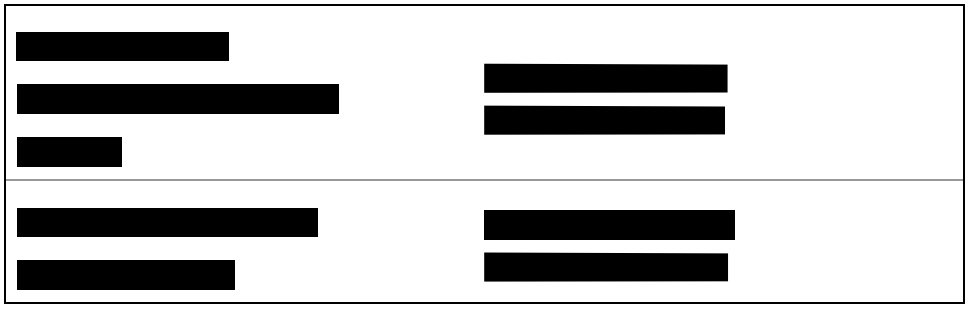
9.3.2 Reporting a Serious Adverse Event

To ensure subject safety, all serious adverse events, regardless of relationship to the investigational product, must be immediately reported. All information relevant to the serious adverse event must be recorded on the appropriate source documents. The investigator is obligated to pursue and obtain information requested by Ora in addition to that information reported on the source

document. All subjects experiencing a serious adverse event must be followed up and the outcome reported.

In the event of a serious adverse event, the investigator must notify Ora 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 with a complete case history and inform the IRB of the adverse event within their guidelines for reporting serious adverse events.

Contact information for reporting serious adverse events (SAEs):



9.4 Procedures for Unmasking Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified, when possible, before unmasking study drug as described in the following paragraph.

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 Aldeyra 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 via scratch off labels on the kits for the Initial Cohort Only. The investigator will unmask the subject using IWRS for the Main Cohort. 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.

9.5 Procedures for Reporting Adverse Events

Adverse events that are ongoing at the end of the study visit will be followed. Phone calls will be placed with any subject who experiences an adverse event until the issue is resolved or the condition is considered ongoing and stable.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

The following analysis populations will be considered:

- [redacted]

- [redacted]

All analyses will be performed for the ITT population and, in addition, on the PP population as sensitivity analyses, as needed. Descriptive statistics of safety data will be calculated for the safety population.

10.2 Statistical Hypotheses

The following hypothesis will be tested comparing reproxalap to vehicle. The null hypotheses must be rejected for the dosing regimen to claim efficacy.

[redacted]

[redacted]

10.3 Sample Size

Assuming a difference of [redacted], 149 evaluable subjects per arm will have [redacted] to detect a statistically significant difference at a two-sided alpha level [redacted]. These estimates are based on

the [redacted] from the ADX-102-DED-024 study.

10.4 Statistical Analysis

10.4.1 General Considerations

Quantitative variables will be summarized descriptively using number of subjects (n), mean, standard deviation, median, minimum, and maximum. Qualitative variables will be summarized using counts and percentages.

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

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

Baseline measures are defined [redacted]

All analyses will be [redacted] will be provided where appropriate.

The statistical analysis plan (SAP) will detail the statistical procedures, and will dominate any text herein.

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. [redacted] Assessment scales are detailed in the Appendices.

10.4.3 Missing Data

As sensitivity measures, efficacy analyses will be conducted with multiple imputation utilizing methods such as treatment-based [redacted] Per-protocol population analysis will also be conducted to assess sensitivity. Further details and changes will be described in the SAP.

10.4.4 Multiplicity Considerations

[redacted].

10.4.5 Primary Efficacy Analysis

The primary efficacy analysis of change from baseline [redacted] in conjunctival redness over all time points in the CAE will be analyzed [redacted] with baseline score as a covariate, nominal time point, and treatment group as fixed effects with correlated errors due to eye and nominal time point.

The primary analysis will utilize the [redacted]. Further details will be specified in the SAP. [redacted]

The following Estimand will be used for the primary analyses using the ITT population with observed data only:

[redacted]

[redacted] Further details will be specified in the SAP.

10.4.6 Secondary Efficacy Analyses

For secondary efficacy endpoints during the [redacted] CAE, [redacted]

The primary efficacy analysis [redacted] will be analyzed [redacted]

Primary analyses of secondary efficacy endpoints will utilize the ITT population with observed data only.

10.4.7 Exploratory Efficacy Analyses

For efficacy endpoints recorded [redacted] will be utilized.

[redacted]

[redacted]

[redacted]

All efficacy analyses conducted on the ITT population will be conducted using the Initial Cohort population only with observed data.

Additional exploratory efficacy analyses may be conducted. Further details of the exploratory analysis plan will be described in SAP.

10.4.8 Safety Variables

Adverse events will be coded using the 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. 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, 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 adverse events (including systemic).

[redacted]

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

The ADX-102-DED-019 clinical trial will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Council for Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

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

All informed consent/assent forms must be approved for use by Ora 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 sponsor 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 provided in writing by Ora prior to the consent process.

11.1.2 Institutional Review Board (IRB) Approval

The ADX-102-DED-019 clinical trial is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The investigator must obtain appropriate IRB approval before initiating the trial 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

The ADX-102-DED-019 clinical trial 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 trial 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 IRB approving this trial, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

11.4 Documentation

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

11.4.1 Retention of Documentation

All trial related correspondence, patient records, consent forms, and copies of source documents should be maintained on file for at least two years. 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. Ora must be notified in writing of the name and address of the new custodian.

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

11.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits.

[redacted]

Each pouch will contain five ampules to provide a sufficient supply of randomized study drug.

11.5.2 Storage of Study Drug

The study drug must be stored in a secure area accessible only to the investigator and his/her designees. The study drug will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. [redacted]

11.5.3 Accountability of Study Drug

The study drug 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 study drug must only be distributed to subjects properly qualified under this protocol to receive study drug. The investigator must keep an accurate accounting of the study drug by maintaining a detailed inventory. This includes the amount of study drug received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the sponsor or their designee or destroyed on behalf of the Sponsor following local regulations.

11.6 Recording of Data on Source Documents and electronic Case Report Forms (eCRFs)

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF 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.

11.7 Handling of Biological Specimens

See Appendix 2 "Examination Procedures, Tests, Equipment, and Techniques" for tear collection procedures. Processing, shipping, and handling procedures will be done by following the Laboratory Manual.

11.8 Publications

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

12 REFERENCES

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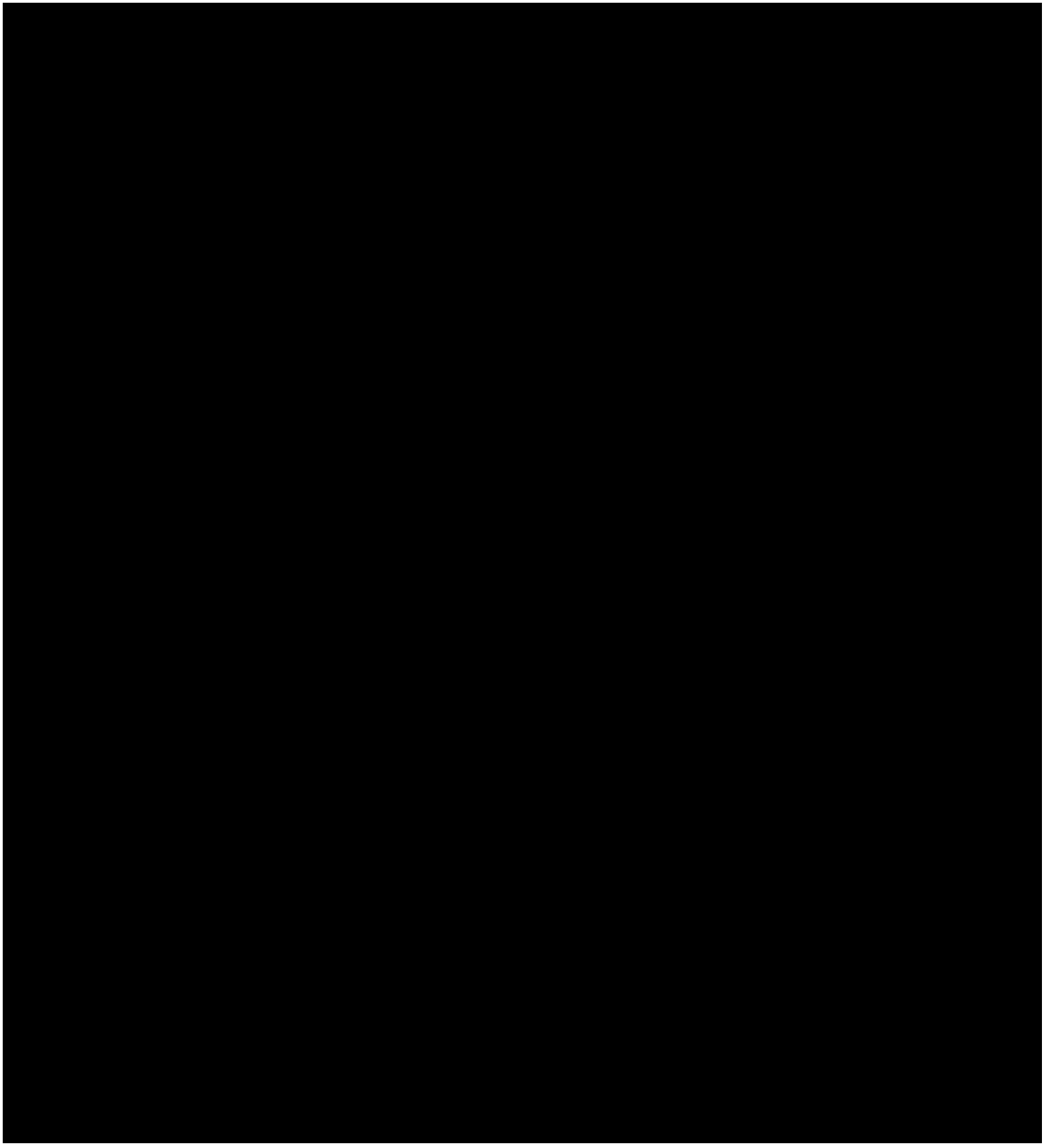
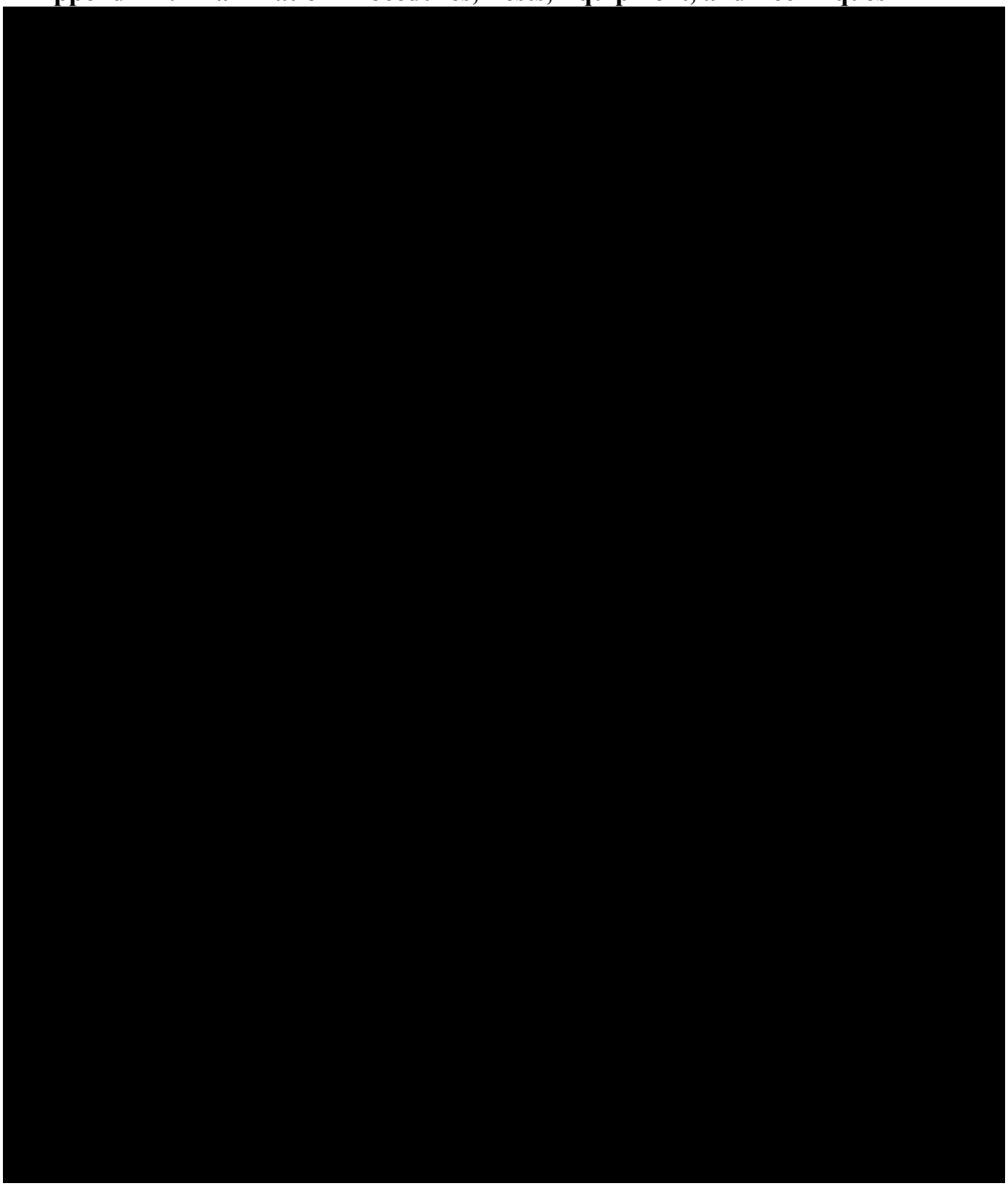
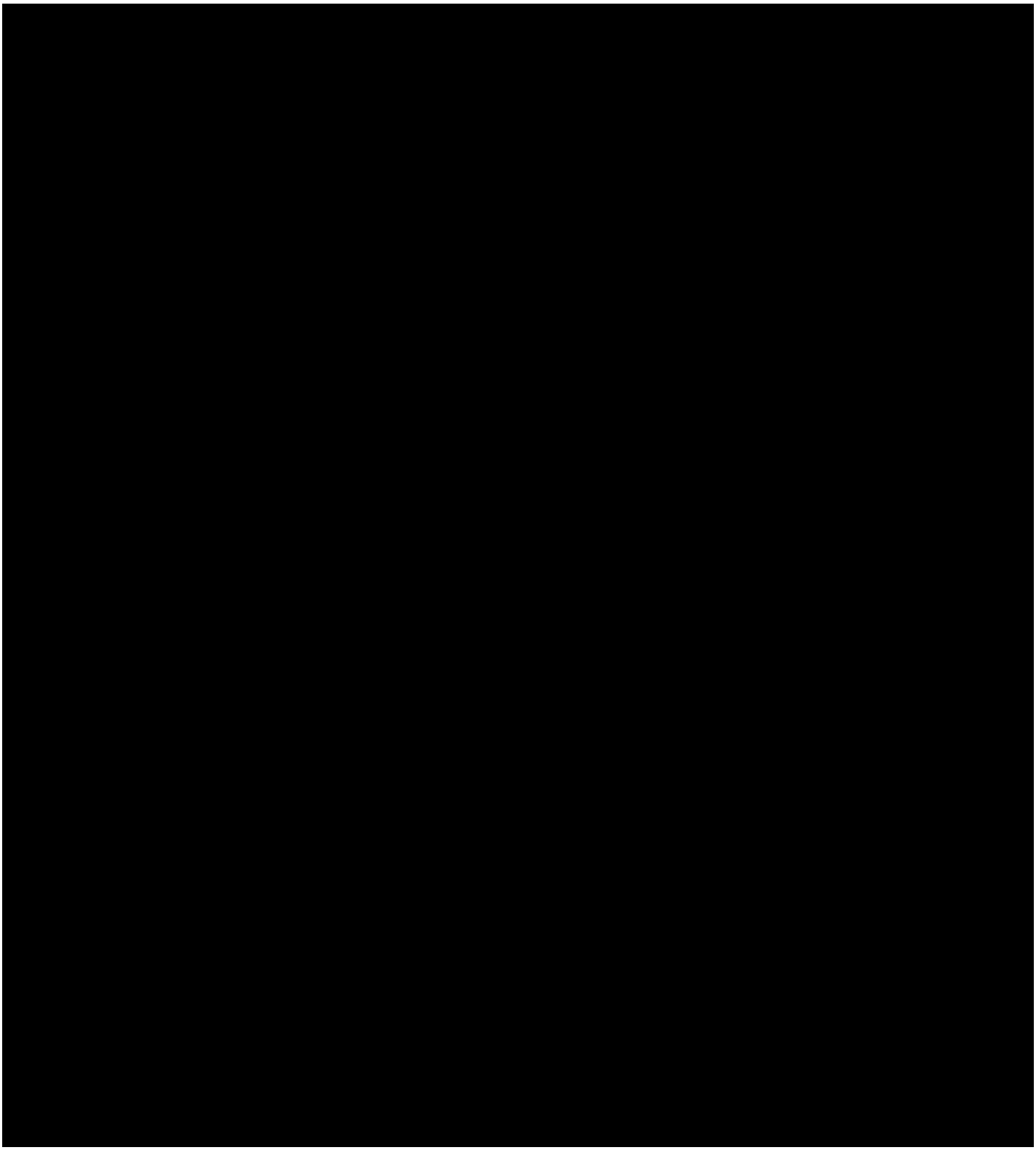
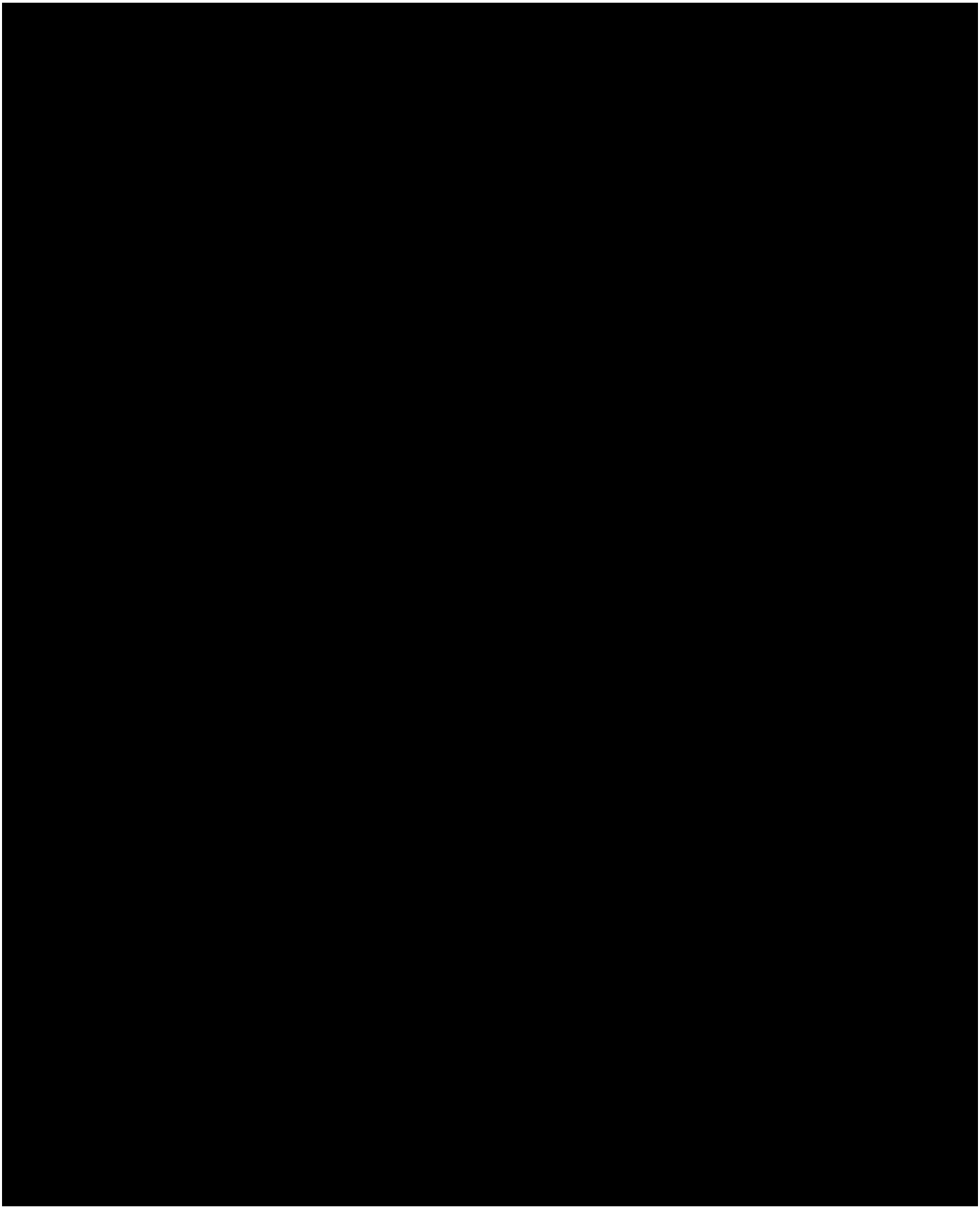
Appendix 1: Schedule of Visits and Measurements

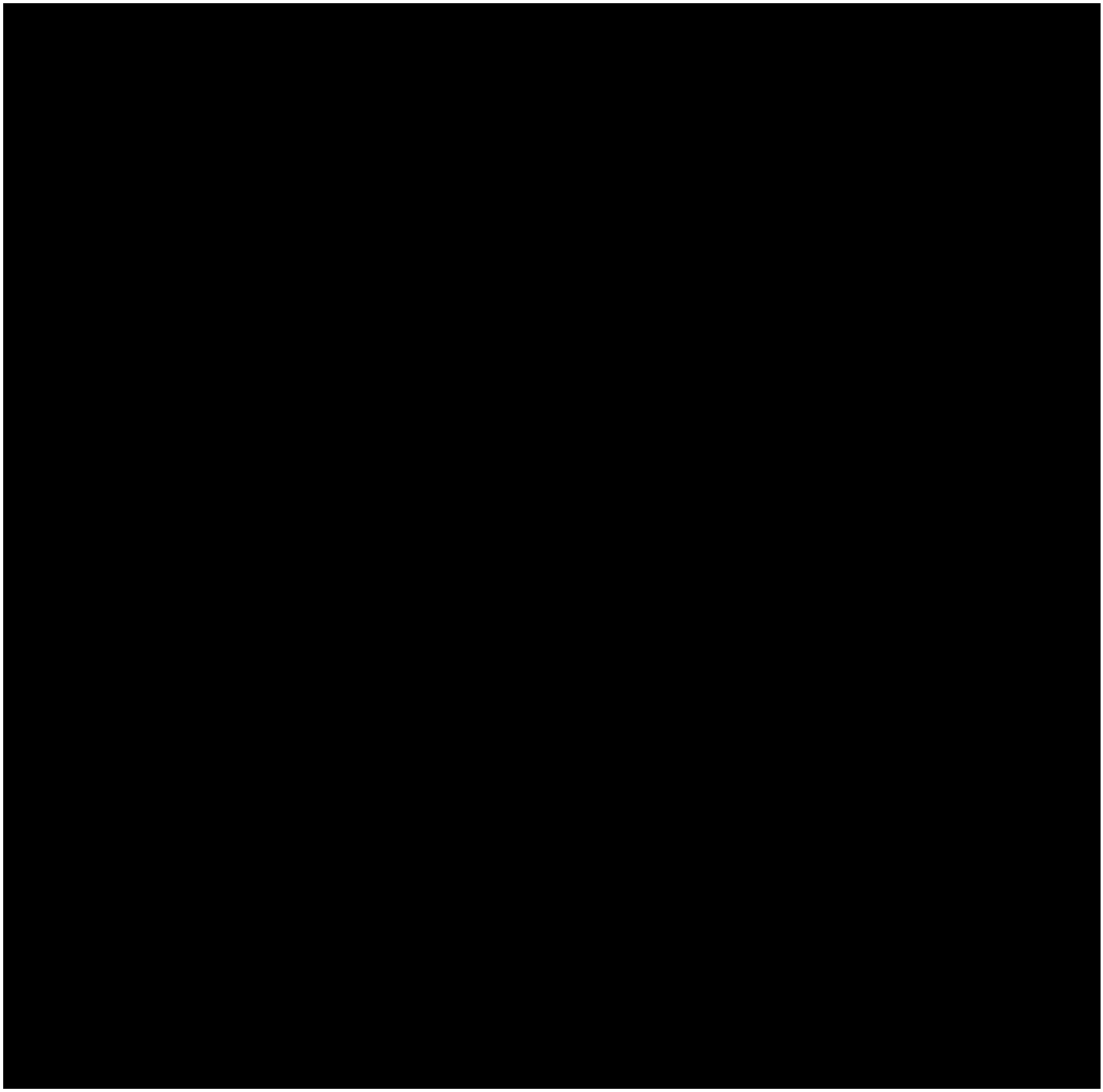


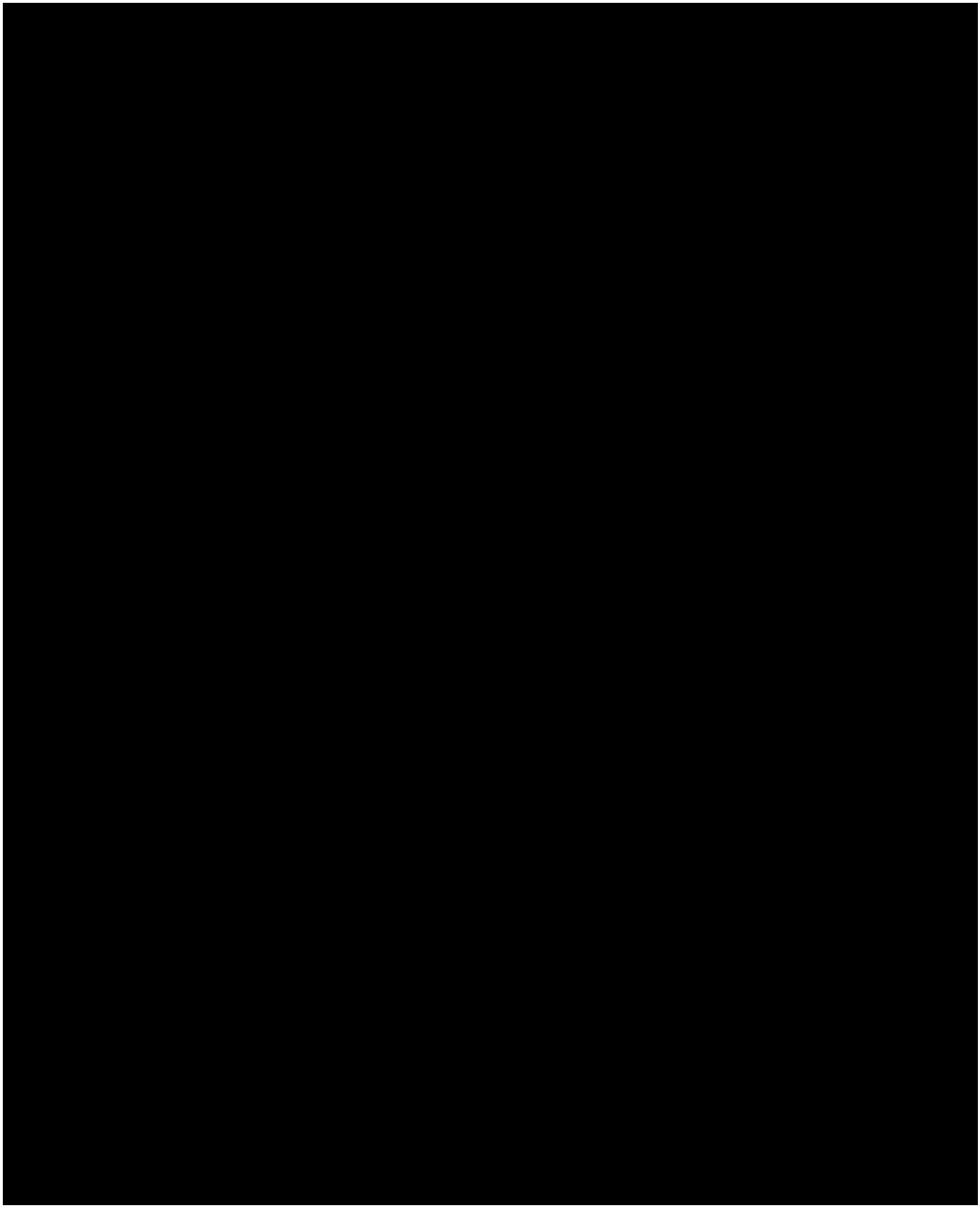
Appendix 2: Examination Procedures, Tests, Equipment, and Techniques

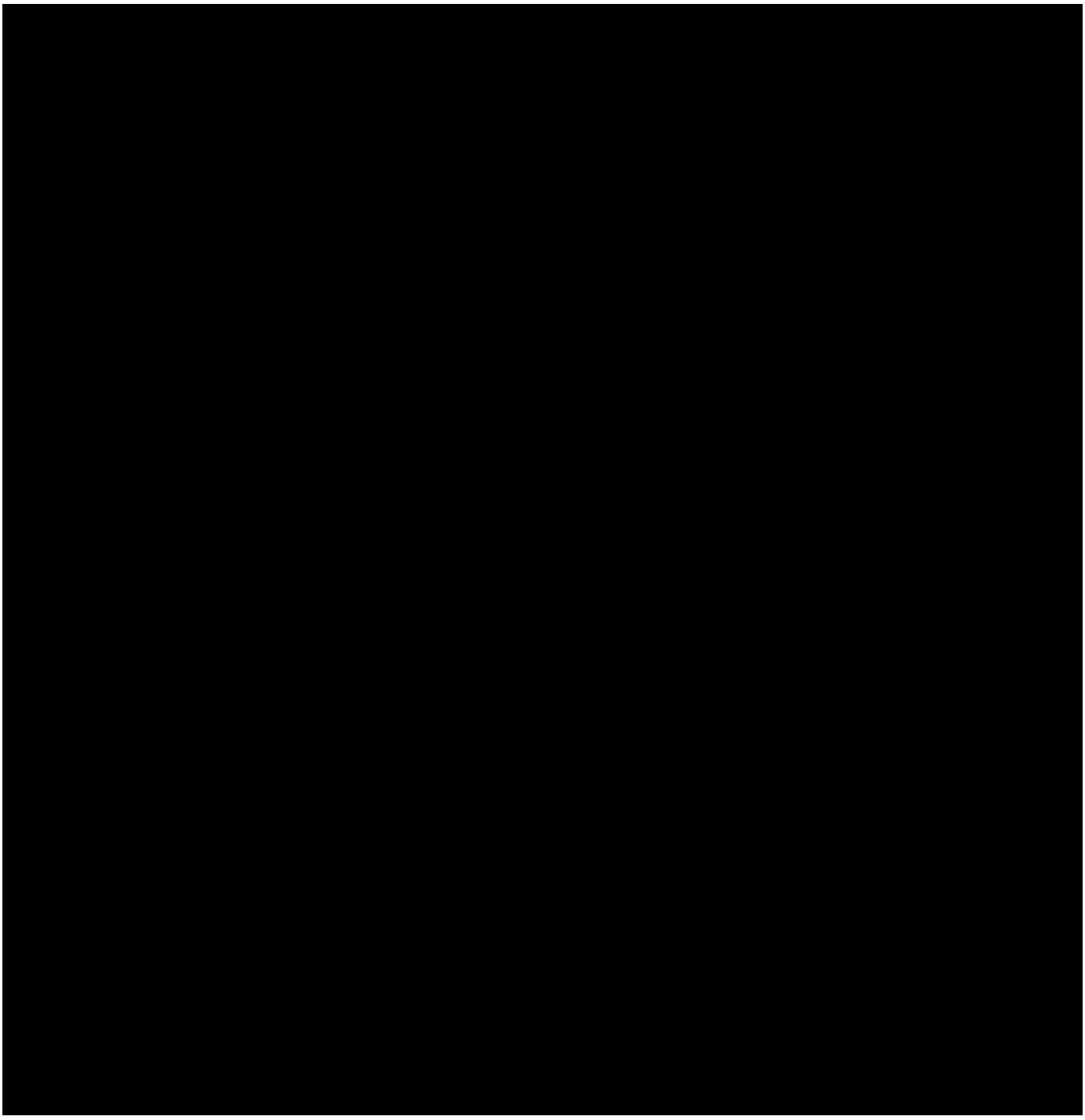












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Appendix 3: Amendment Summary of Changes Table

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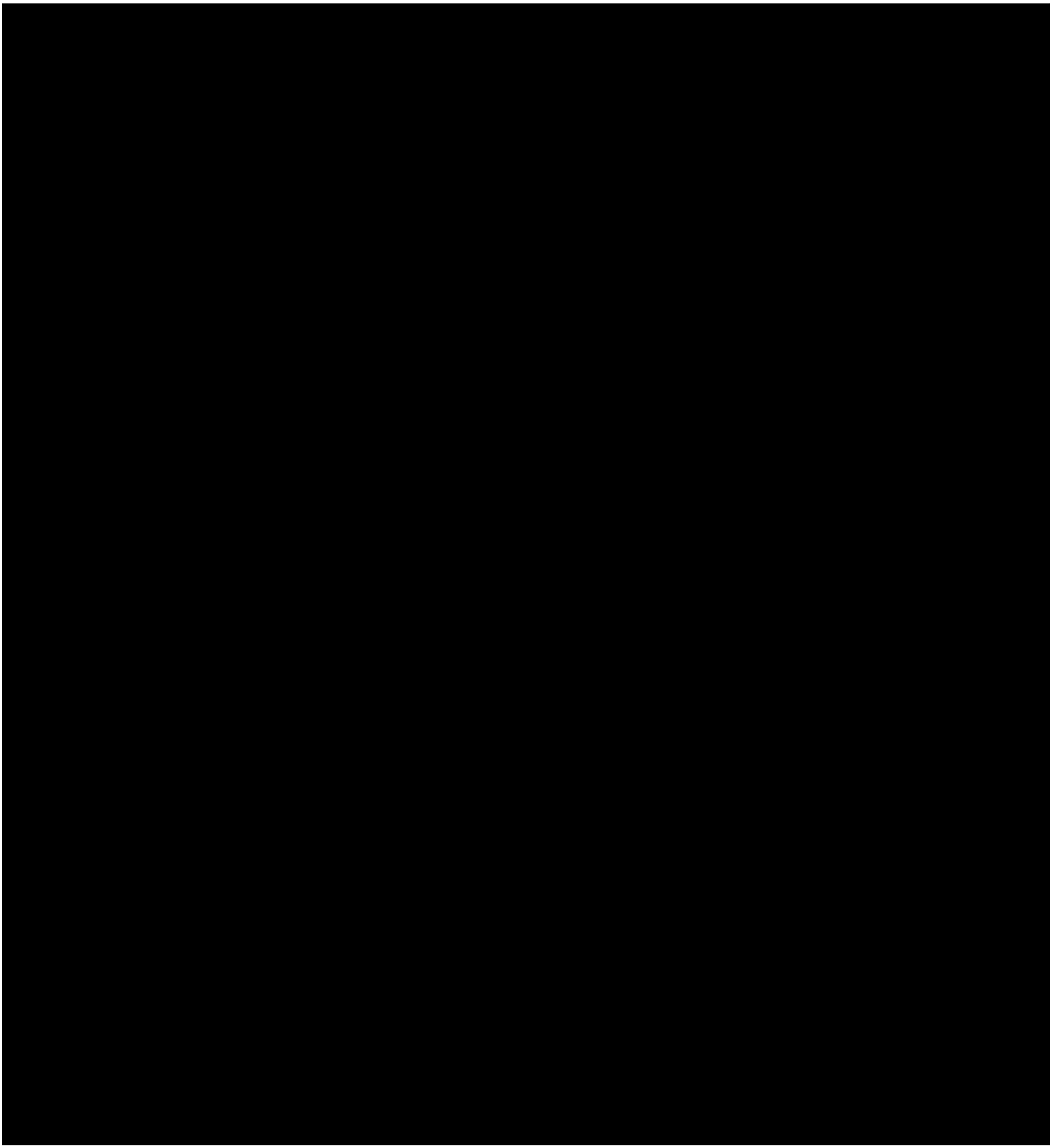

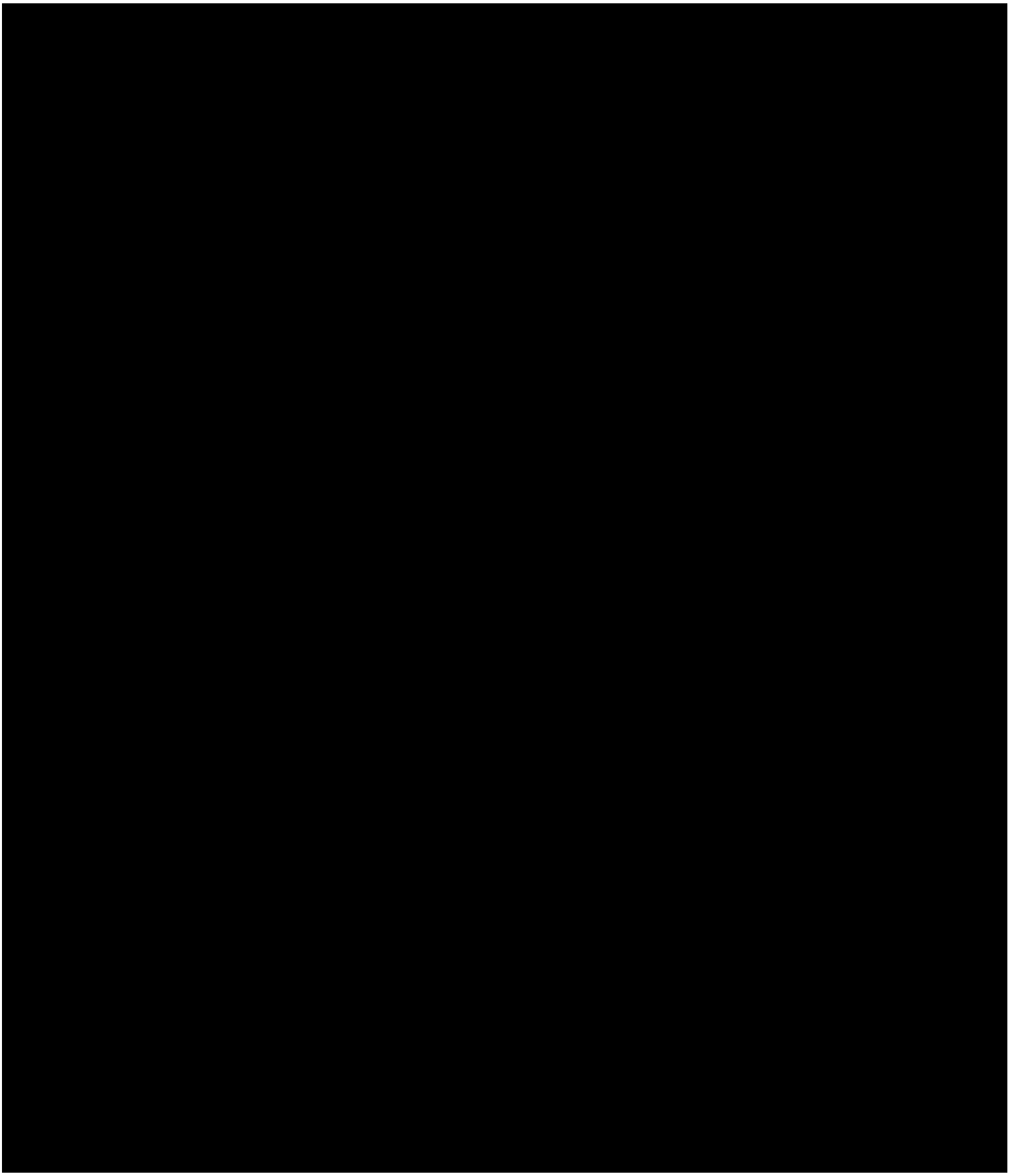

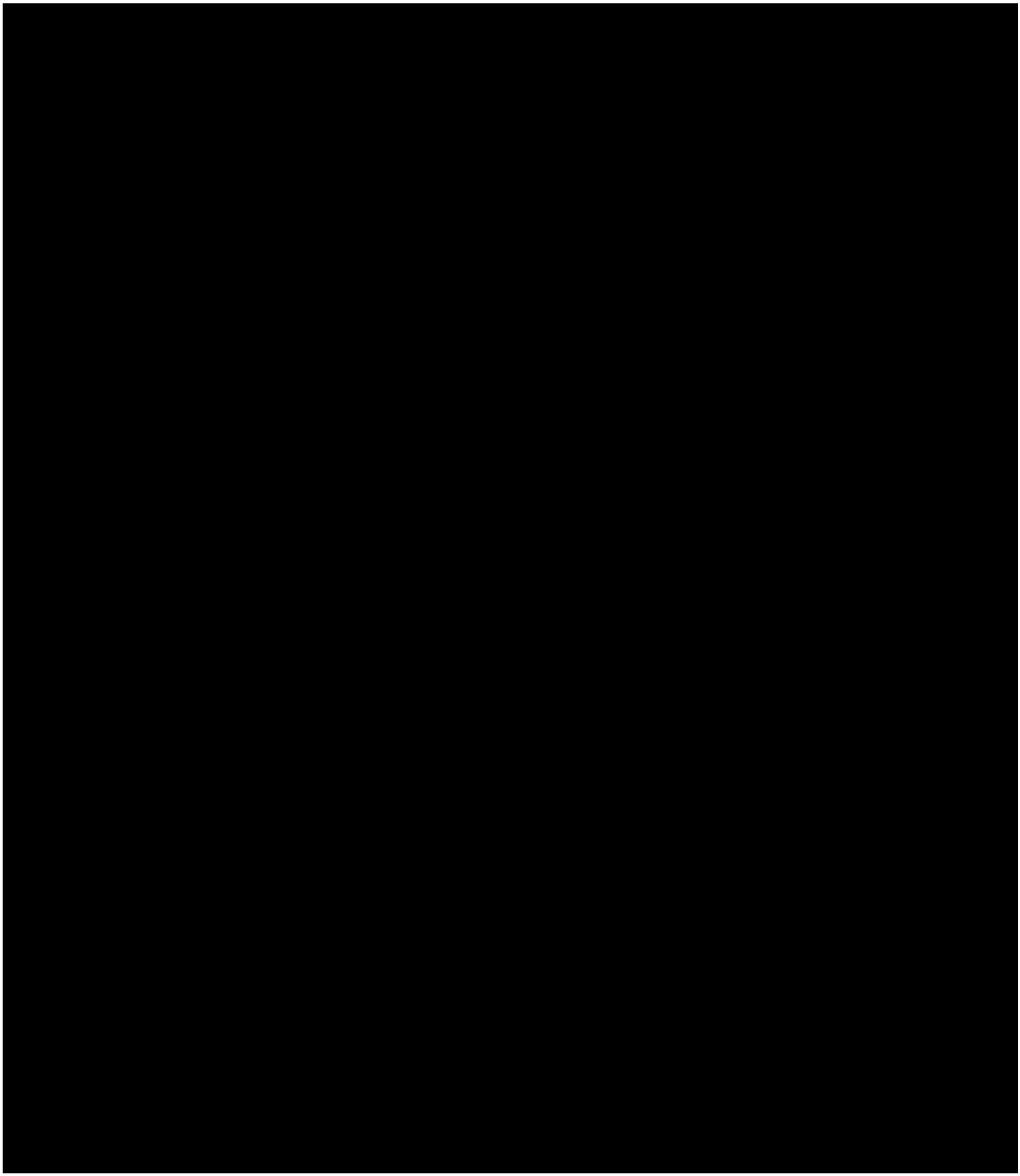

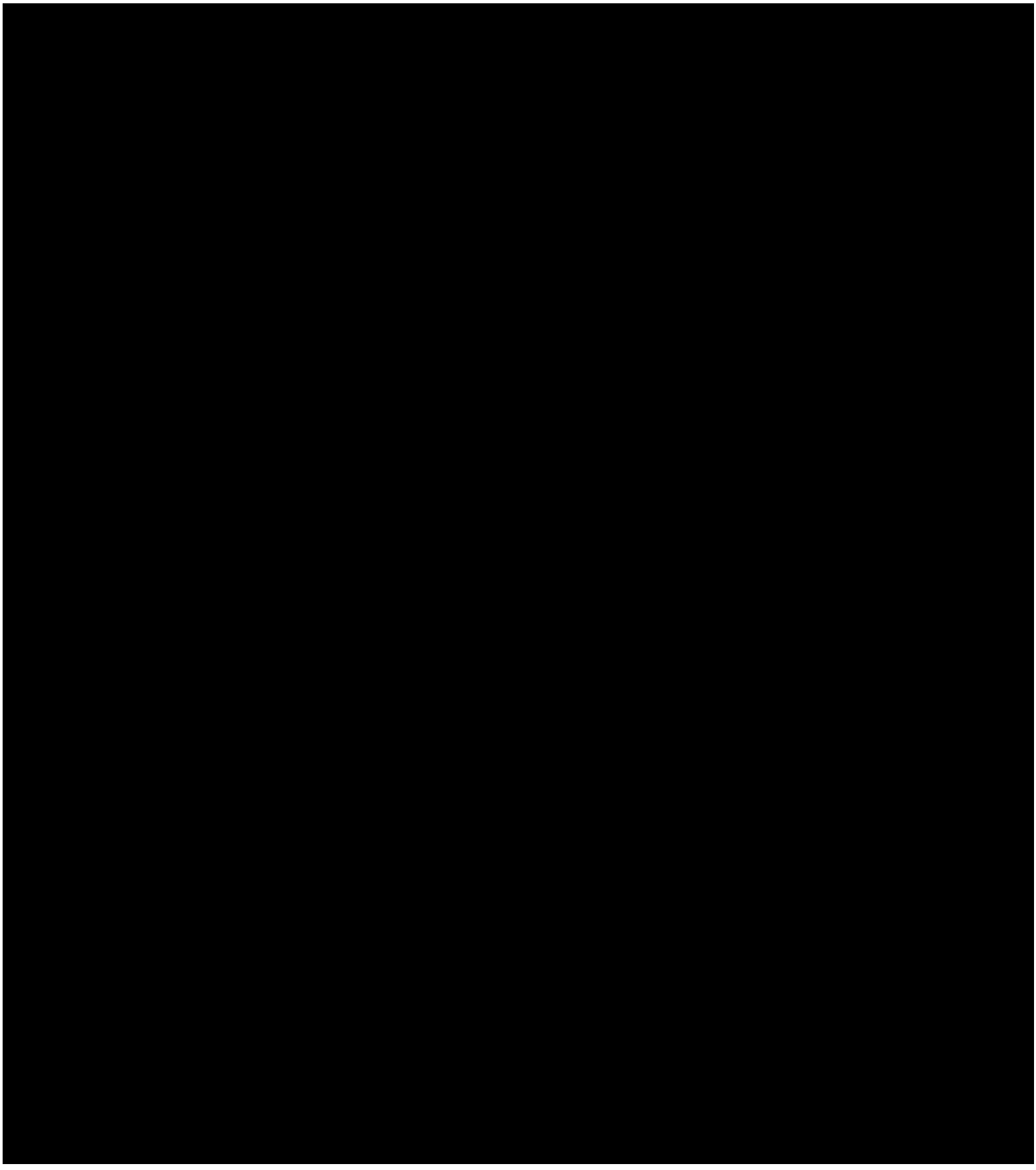

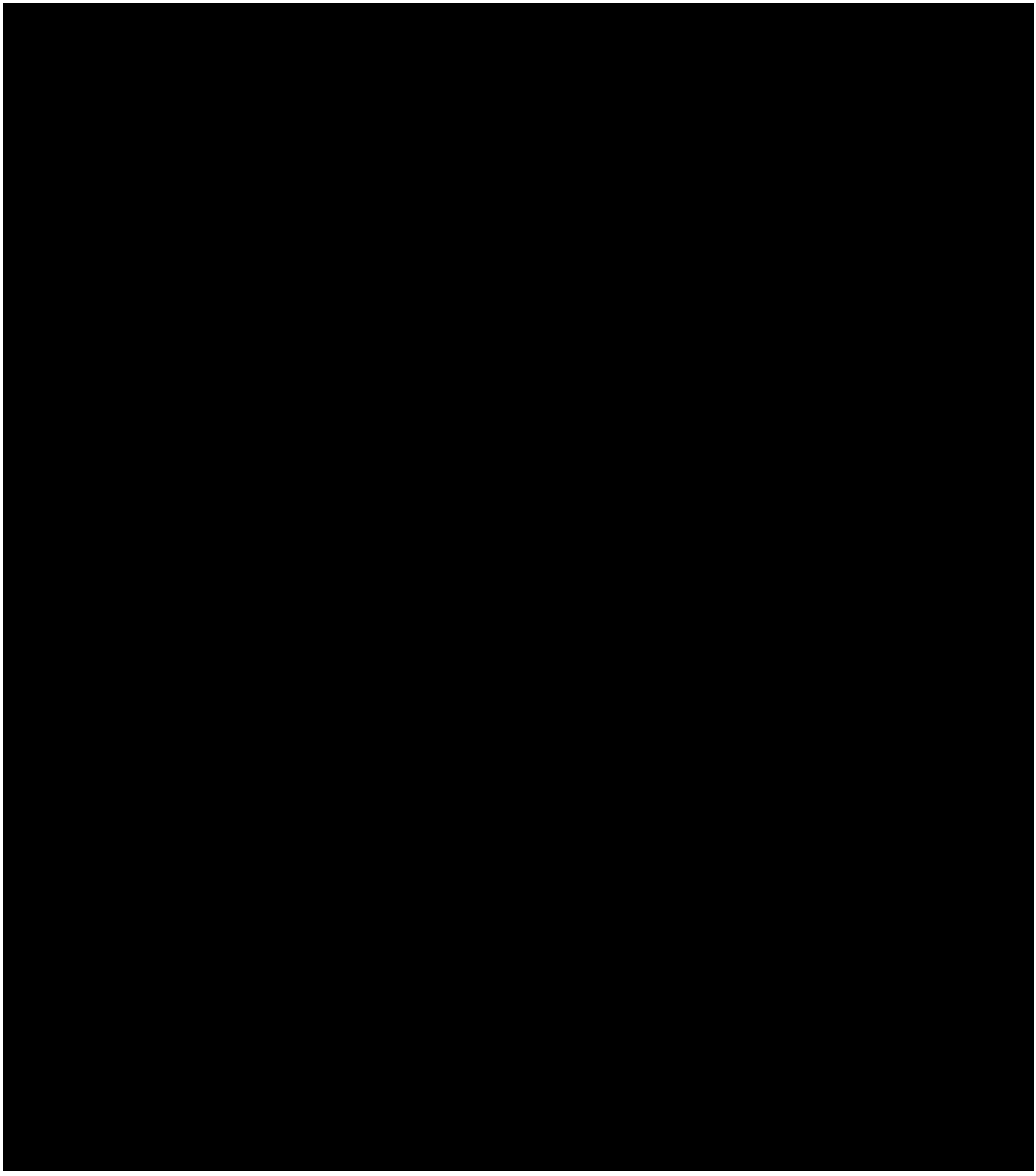

Appendix 4: Sponsor and Ora Approvals

Protocol Title: The TRANQUILITY Trial: A Multi-Center Randomized, Double-Masked, Parallel Design, Vehicle-Controlled Phase 2/3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease

Protocol Number: ADX-102-DED-019

Protocol Date: 5 November 2021

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

[redacted]

Appendix 5: Investigator's Signature

Protocol Title:	The TRANQUILITY Trial: A Multi-Center Randomized, Double-Masked, Parallel Design, Vehicle-Controlled Phase 2/3 Clinical Trial to Assess the Efficacy and Safety of 0.25% Reproxalap Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-019
Protocol Date:	5 November 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 in confidence and, when this information is submitted to an Institutional Review Board (IRB) 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:	Signature Page
Document created:	11/05/2021 16:27:06
Document pages:	1
Document ID:	6b9c6d672c14474e8623b17fb5d4d355c0b6be7b
Document Sent:	11/05/2021 16:28:14 UTC
Document Status:	Signed
	11/05/2021 16:28:39UTC