Clinical Trial Protocol: ADX-102-AC-010

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-010
Study Phase:	1b
Investigational Product Name:	Reproxalap Ophthalmic Solutions (0.25% and 0.5%)
IND/IDE/PMA Number:	[redacted]
Indication:	Seasonal allergic conjunctivitis
Investigators:	Multi-Center
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Ave. Lexington, MA 02421 USA
Contract Research Organization:	Ora. Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810 USA
IRB/IEC:	[redacted]

	Date
Original Protocol:	15 June 2018
Version 2.0:	24 August 2018

SPONSOR (Aldeyra) PERSONNEL

Chief Medical Officer:	[redacted]

ORA PERSONNEL

Chief Medical Officer:	[redacted]
Department Vice President, Allergy:	[redacted]
Project Lead:	[redacted]

MEDICAL MONITOR

Medical Monitor:	[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-010
Investigational Product:	Reproxalap Ophthalmic Solutions (0.25% and 0.5%)
Study Phase:	Phase 1b
Exploratory Objective(s):	• Evaluate the feasibility of a novel QID and PRN dosing regimen of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design. • Evaluate the efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) on the signs and symptoms associated with seasonal allergic conjunctivitis during allergy season in an environmental clinical trial design that utilizes a diary. • Evaluate the safety of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design.
Overall Study Design:	
Structure:	*Screening Period:* At Visit 1, subjects will sign the informed consent form (ICF) [redacted] *Treatment Period:* [redacted] subjects who continue to meet eligibility criteria and have consistent and sufficient ocular itching and redness [redacted]

	[redacted] Subjects will return for a follow-up appointment [redacted] Staff will collect, review, and dispense investigational product and review diaries. Subjects will return for an exit visit [redacted] Staff will collect and review investigational product and diaries.
Duration:	This trial consists of [redacted] office visits over a period of approximately [redacted].
Control:	Vehicle Ophthalmic Solution
Dosage/ Instillation:	[redacted]

	Subjects or caregivers will be instructed on how to properly record the administration of investigational product in the provided diary.
Summary of Visit Schedule:	• Visit 1 [redacted] Screening/ Informed Consent/ Skin Test • Visit 2 [redacted] Begin GENTEAL® Tears Mild Liquid Drops run in period • Visit 3 [redacted] Enrollment, randomization, begin investigational product administration [redacted] • Visit 4 [redacted] Follow-up, collect, and dispense investigational product • Visit 5 ([redacted] Clinical Trial Exit
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to investigational product, to increase the likelihood that known and unknown subject attributes [redacted] are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. [redacted] inally, masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Approximately [redacted] will be screened in order to enroll approximately [redacted] Subjects will be randomized [redacted] of treatment with either Reproxalap Ophthalmic Solution (0.25%), Reproxolap Ophthalmic Solution (0.5%), or Vehicle Ophthalmic Solution.
Condition/Disease:	Seasonal allergic conjunctivitis
Inclusion Criteria:	*Each subject must:* 1) be at least 18 years of age of either sex and any race; 2) provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;

	3) be willing and able to follow all instructions and attend all clinical trial visits; 4) be able and willing to avoid all disallowed medication for the appropriate washout period and during the clinical trial [redacted] 5) be able and willing to discontinue wearing contact lenses [redacted] 6) have a positive history of ocular allergies and a positive skin test reaction [redacted] 7) agree to have urine pregnancy testing (for women considered capable of becoming pregnant, including all females who have experienced menarche and have not experienced menopause [as defined by amenorrhea for greater than 12 consecutive months] or have not undergone successful surgical sterilization [hysterectomy, bilateral tubal ligation, or bilateral oophorectomy]) performed at Visit 1, Visit 3, and at the exit visit; not be lactating; and agree to use a medically acceptable form of birth control throughout the clinical trial duration; 8) have a calculated visual acuity (VA) [redacted] 9) have signs and symptoms of allergic conjunctivitis [redacted] 10) have a positive bilateral CAC reaction [redacted] **OR** [redacted]

	11) be able to self-administer eye drops satisfactorily or have a caregiver routinely available. If a caregiver will be used to administer eye drops, then the caregiver must be present at Visit 2 to administer eye drops in-office; 12) have consistent [redacted]
Exclusion Criteria:	*Each subject must not:* 1. have known contraindications or sensitivities to the use of any of the investigational product medication or components; 2. have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters [redacted] 3. have had ocular surgical intervention [redacted] 4. have a known history [redacted] 5. have an active ocular infection [redacted] 6. use any of the following disallowed medications during the period indicated below [redacted] and during the trial: [redacted]

	• [redacted] 7. have any significant illness [redacted] that, at the investigators' discretion, could be expected to interfere with the subject's health or with the clinical trial parameters or put the subject at any unnecessary risk; 8. have a history [redacted] 9. have used an investigational drug or medical device [redacted] 10. be a female who is currently pregnant, planning a pregnancy, or lactating.
Study Formulations and Formulation Numbers:	• Reproxalap Ophthalmic Solution (0.25%) • Reproxalap Ophthalmic Solution (0.5%) • Vehicle Ophthalmic Solution

Evaluation Criteria:	• [redacted]
Safety Measures:	• Adverse Events (AEs; reported, elicited and observed) • VA at Distance Utilizing an ETDRS chart • Slit-lamp Biomicroscopy • IOP • Dilated Fundoscopy

General Statistical Methods and Types of Analyses

Approximately [redacted] will be screened in order to enroll approximately [redacted].

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc.

Since this is a Phase 1b exploratory clinical trial to assess the safety, tolerability, and pharmacodynamic activity of Reproxalap Ophthalmic Solution utilizing a novel dosing regimen, [redacted]

[1] [redacted]

The ocular itching efficacy variable will be assessed [redacted]

As a supportive analysis, the mean diary ocular itching scores [redacted]

The ocular itching analyses will be conducted [redacted]

The mean diary ocular redness scores [redacted]

The following analyses for the additional efficacy endpoints will be conducted using the ITT and PP populations using observed data only:

- The number of subjects responding to treatment [redacted]
- Diary score assessments [redacted]
- Ocular redness [redacted]
- The ACQLQ questionnaire will be administered [redacted]

The primary safety variable is the incidence of subjects with any adverse event during the entire trial. [redacted]

[redacted] All evaluations of safety will be described in the SAP.

Summary of Known and Potential Risks and Benefits to Human Subjects

Refer to the Investigator's Brochure and [redacted] Package insert regarding the risks and benefits to human subjects.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AC	allergic conjunctivitis
ACQLQ	Allergic Conjunctivitis Quality of Life Questionnaire
AE	adverse event
API	active pharmaceutical ingredient
ANCOVA	analysis of covariance
AUC	area under the curve
BCVA	best-corrected visual acuity
CAC	Conjunctival Allergen Challenge
CD	compact disc
CFR	Code of Federal Regulations
CPT	Current Procedural Terminology
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DHHS	Department of Health and Human Services
eCRF	electronic case report form
ERC	Ethical Review Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgE	immunoglobin-E
IEC	Independent Ethics Committee
IM	intramuscular
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intention-to-treat
LASIK	laser in situ keratomileusis
logMAR	logarithm of the minimum angle of resolution
MCMC	Markov Chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MMRM	mixed model repeated measures
NCS	not clinically significant
ND	not done
NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OD	right eye
OS	left eye
OU	both eyes
OTC	over the counter
PBS	phosphate buffered saline
PE	polyethylene
PHI	protected health information
PO	by mouth
PP	per protocol
PRN	as needed
QD	once daily
QID	Four times daily
QS	as much as will suffice
ROPI	Report of Prior Investigations
SAC	seasonal allergic conjunctivitis
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
TEAE	treatment emergent adverse event
USP	United States Pharmacopeia
VA	visual acuity
w/v	weight per unit volume

1 INTRODUCTION

Acute allergic conjunctivitis (AC), experienced by approximately 40% of the general population (Singh et al., 2010), is associated with Type I (immediate) hypersensitivity reactions. Type I reactions involve immunoglobulin E (IgE)-mediated release of histamine and other mediators from mast cells and basophils. Mast cell degranulation leads to release of inflammatory mediators and activation of enzymatic cascades generating pro-inflammatory mediators (Mishra et al, 2011). In the eye, release of a variety of mediators leads to inflammation of the conjunctival mucosa that also affects the cornea and eyelids, resulting in symptoms that include itching and burning, tearing, chemosis (conjunctival edema), conjunctival injection, hyperemia, eyelid edema, and mucus discharge. Although allergic conjunctivitis patients may also experience photophobia, allergic shiners (dark circles), and concurrent signs and symptoms of asthma or rhinitis, the absence of itching precludes a diagnosis of AC (Albrecht 2011).

Aldehydes are pro-inflammatory mediators of both allergic (TH2) and autoimmune (TH1) diseases, and elevated levels of toxic aldehydes are associated with allergic conjunctivitis and other ocular and systemic diseases (Bacsi et al 2005). Thus, aldehyde sequestering agents represent a novel and potentially broadly applicable therapeutic approach for the treatment of inflammation.

The symptoms of allergic conjunctivitis that occur within minutes of allergen exposure are likely due primarily to the release of histamine (Leonardi 2013), which peaks in tears around five minutes and significantly diminishes over 20 to 30 minutes (Ackerman et al. 2016). Immediately following, and to some degree concurrently with, the rapid rise and fall of histamine levels, the symptoms of allergic conjunctivitis are perpetuated by non-histaminic inflammatory mediators, including cellular infiltrate, cytokines, leukotrienes,

proteases, and other factors (Leonardi 2013) likely to be diminished by aldehyde sequestering agents such as reproxalap, but not antihistamines.

[redacted]

Distinct from the acute histaminic phase of allergic conjunctivitis that is partially prophylactically modulated by antihistamines, the immediate post-histaminic inflammatory phase, which occurs from 10 to 60 minutes following allergen challenge, is a condition not studied with, and likely not well addressed by, available therapy. To the Sponsor's knowledge, no allergic conjunctivitis therapy has demonstrated activity beyond 20 minutes post-challenge, and most recently approved antihistamines have demonstrated post-challenge activity of only up to 7 minutes.

[redacted]

[redacted]

2 CLINICAL STUDIES OF REPROXALAP OPHTHALMIC SOLUTION

Reproxalap topical ocular solution is being developed for ocular inflammation. The drug product, [redacted]

[redacted]

In all clinical trials, no treatment related serious adverse events (SAE) have been observed. [redacted]

[redacted]

The Phase 2 clinical trials have demonstrated [redacted]

[redacted]

2.1 Minimization of Risk

In clinical trials with Reproxalap Ophthalmic Solution in various strengths in different ocular indications, no safety signal or treatment related SAEs have been observed [redacted]

[redacted]

[redacted] Please refer to the Investigator's Brochure (IB) for additional information.

3 EXPLORATORY OBJECTIVES

The exploratory objectives are as stated below:

- Evaluate the feasibility of a novel QID and PRN dosing regimen of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design.
- Evaluate the efficacy of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) on the signs and symptoms associated with seasonal allergic conjunctivitis during allergy season in an environmental clinical trial design [redacted]
- Evaluate the safety of Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in an environmental clinical trial design.

4 CLINICAL HYPOTHESES

It is hypothesized that Reproxalap Ophthalmic Solutions (0.25% and 0.5%) will be well tolerated and more effective than the Vehicle Ophthalmic Solution for treating the signs and symptoms associated with seasonal allergic conjunctivitis [redacted]

5 OVERALL STUDY DESIGN

This is a multi-center, double-masked, randomized, parallel-group, vehicle-controlled, Phase 1b methods environmental clinical trial to evaluate Reproxalap Ophthalmic Solution (0.25%) and Reproxolap Ophthalmic Solution (0.5%) compared to Vehicle Ophthalmic Solution in subjects with seasonal allergic conjunctivitis. The trial will be comprised of [redacted].

Subjects will sign the informed consent form at [redacted] and will undergo an allergic skin test, [redacted]. At Visit 2 [redacted] each qualifying subject will undergo a bilateral conjunctival allergen challenge (CAC) [redacted]

At Visit 3 [redacted] subjects who continue to meet eligibility criteria and have consistent and sufficient ocular itching and redness [redacted] will be randomized [redacted] to receive [redacted] of treatment with either Reproxalap

Ophthalmic Solution (0.25%), Reproxolap Ophthalmic Solution (0.5%), or Vehicle Ophthalmic Solution.

Subjects or subject's caregiver will be instructed on the proper technique for instilling investigational product. [redacted] and will be instructed on how to properly record the administration of investigational product in the provided diary.

In addition [redacted], subjects or caregivers will be instructed up to four additional doses of investigational product may be administered [redacted]

Subjects will return for a follow-up appointment at Visit 4 [redacted]. Staff will collect, review, and dispense investigational product and review diaries. Subjects will return for an exit visit at Visit 5 [redacted] Staff will collect and review investigational product and diaries.

6 STUDY POPULATION

6.1 Number of Subjects (approximate)

Approximately [redacted] will be screened in order to enroll [redacted] at [redacted].

6.2 Study Population Characteristics

All subjects must meet all inclusion criteria and none of the exclusion criteria.

6.3 Inclusion Criteria

Each subject must:

1. be at least 18 years of age of either sex and any race;
2. provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form form;
3. be willing and able to follow all instructions and attend all clinical trial visits;
4. be able and willing to avoid all disallowed medication for the appropriate washout period and during the clinical trial (see exclusion 6);
5. be able and willing to discontinue wearing contact lenses [redacted];
6. have a positive history of ocular allergies and a positive skin test reaction [redacted]
7. agree to have urine pregnancy testing (for women considered capable of becoming pregnant, including all females who have experienced menarche and have not experienced menopause [as defined by amenorrhea for greater than 12 consecutive months] or have not undergone successful surgical sterilization [hysterectomy,

bilateral tubal ligation, or bilateral oophorectomy]) performed at Visit 1, Visit 3, and at the exit visit; not be lactating; and agree to use a medically acceptable form of birth control throughout the clinical trial duration;

8. have a calculated visual acuity (VA) [redacted]
9. have signs and symptoms of allergic conjunctivitis [redacted]
10. have a positive bilateral CAC reaction [redacted]
11. be able to self-administer eye drops satisfactorily [redacted]
12. have consistent [redacted] and sufficient scores [redacted] for ocular itching and redness [redacted]

6.4 Exclusion Criteria

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

1. have known contraindications or sensitivities to the use of any of the investigational product medication or components;
2. have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or trial parameters [redacted]
3. have had ocular surgical intervention within three months [redacted]
4. [redacted]
5. have an active ocular infection [redacted]
6. use any of the following disallowed medications during the period indicated below **prior to Visit 2,** and during the trial:

[redacted]

[redacted]

munotherapeutic

7. have any significant illness [redacted]
8. have a history of glaucoma, ocular hypertension or an intraocular pressure (IOP) [redacted]
9. have used an investigational drug or medical device [redacted]
10. be a female who is currently pregnant, planning a pregnancy, or lactating.

6.5 Withdrawal Criteria (if applicable)

Subjects may voluntarily withdraw from the clinical trial at any time.

Any female will be removed from the trial should she become pregnant during the course of the trial, and she will undergo a pregnancy test at her exit visit for confirmation. The pregnancy test must be confirmed by two additional tests and confirmed by the principal investigator (or sub-investigator if the principal investigator is not present). If the test result is positive a second and third time, the principal investigator (or sub-investigator if the principal investigator is not present) will inform the subject. The investigator will

document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

Additionally, subjects may be discontinued for safety or sound medical reasons, as determined by the investigator or Sponsor (see Section 9.6.2).

Reason for withdrawal will be included in the electronic case report form (eCRF), and all efforts should be made to schedule the subject for an Exit Visit to complete exit procedures. Any subject withdrawn for the trial because of an AE will be followed until AE is resolved or as clinically required, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

7 STUDY PARAMETERS

7.1 Exploratory Efficacy and Safety Measures

7.1.1 Exploratory Efficacy Measuress

- [redacted] ocular itching scores [redacted]
- [redacted] ocular redness scores [redacted].
- Responder analyses of subjects with ocular itching and redness [redacted]
- Diary score assessments [redacted].
- [redacted] ocular redness evaluated by the investigator; ocular itching evaluated by the subject; ocular redness evaluated by the subject; eyelid swelling evaluated by the subject; tearing/watery eyes evaluated by the subject.
- ACQLQ (Allergic Conjunctivitis Quality of Life Questionnaire) [redacted]

7.1.2 Safety Measures

- Adverse Events (AEs; reported, elicited, and observed)
- VA at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- IOP
- Dilated Fundoscopy

[1] Diary assessments will be performed three times daily (morning, afternoon, and evening).

7.1.3 Criteria for Effectiveness

The trial will be deemed effective if drug-treated patients evidence a trend vs. Vehicle Ophthalmic Solution in improving signs and symptoms of allergic conjunctivitis.

8 STUDY MATERIALS

8.1 Study Treatment(s)

8.1.1 Study Treatment(s)/ Formulation(s)

- Reproxalap Ophthalmic Solution (0.25%)
- Reproxalap Ophthalmic Solution (0.5%)
- Vehicle Ophthalmic Solution

8.1.2 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s).

Topical ophthalmic dosing is the optimal route of administration for ocular allergy treatments. The dosage and dosage regimen was selected based on nonclinical and clinical studies described in Section 2.

8.1.3 Instructions for Use and Administration

- Between Visits 2 and 3, all qualifying subjects will receive run-in solution [redacted] to be administered QID in both eyes for approximately [redacted]
- [redacted]
- [redacted]
- All investigational product must be stored, inventoried, and the inventories carefully and accurately documented according to applicable state, federal and local regulations, current Good Clinical Practices (GCPs), including the International Council for Harmonisation (ICH) guidelines, and clinical trial procedures.

- At a minimum, IP packaging will provide the following information: trial Sponsor identification, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), and trial identification.
- At Visit 3, a new unopened pouch of IP will be used. [redacted].
- A trained trial technician will observe the randomized subject or subject's caregiver instill one drop of assigned IP into each eye [redacted]
- During the [redacted] treatment period [redacted] Reproxalap Ophthalmic Solution (0.25%), Reproxoolap Ophthalmic Solution (0.5%), or Vehicle Ophthalmic Solution will be administered [redacted]
- A trained trial technician will instill one drop of assigned IP into each eye [redacted]

8.2 Other Clinical Trial Supplies

Other clinical trial supplies include urine pregnancy tests, Fluress (fluorescein and benoxinate), and Tropicamide, which will all be supplied by Ora, Inc.

Ragweed allergen used for skin testing and the CAC will [redacted]

Relief drops for CAC [redacted] will also be supplied by Ora, Inc.

9 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in Sections 6.2, 6.3, and 6.4 will be considered for entry into the clinical trial.

9.1.2 Informed Consent

Prior to a subject's participation in the clinical trial, the trial will be discussed with each subject, and subjects wishing to participate must give written informed consent using an informed consent form (ICF). The ICF must be the most recent version that has received favorable review by a properly constituted Institutional Review Board (IRB).

Prior to the completion of Visit 1, if it is determined a subject did not meet certain washout criteria, the subject may be brought back at a later date to re-attempt the screening process. Subjects may be re-screened a maximum of two times.

9.1.3 Washout Intervals

Prohibited medications, treatments, and activities are outlined in the exclusion criteria 6 (Section 6.4).

9.1.4 Procedures for Final Study Entry

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

9.1.5 Methods for Assignment to Treatment Groups:

All subjects screened for the clinical trial who sign an informed consent form will be assigned a 3-digit screening number that will be entered on to the Screening and Enrollment Log. Screening numbers will be assigned in a sequential order beginning with 001.

Each subject who meets all the inclusion and none of the exclusion criteria at Visit 3 [redacted] will be assigned the lowest 4-digit randomization number available at the Investigative site. [redacted]

A trained clinical trial technician will observe the subject or caregivers instill one drop of assigned investigational product into each eye [redacted] The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed investigational product kit number(s) will be recorded on the subject's source document and eCRF. The Sponsor, investigators, and clinical trial staff will be masked during the randomization process and throughout the clinical trial.

9.2 Concurrent Therapies

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

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

9.2.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the clinical trial are outlined in the Exclusion Criteria (Section 6.4).

9.2.2 Escape Medications

Subjects may receive [redacted] after the skin test has been completed [redacted]

Subjects are to be instructed not to use rescue medications [redacted] between visits. [redacted]

[redacted]

9.2.3 Special Diet or Activities

No special diets or activities are required for the clinical trial.

9.3 Examination Procedures

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

Procedures listed below should be performed in the order as listed below. See Appendix 2 for details on methodologies and grading systems.

9.3.2 Visit 1 [redacted]: Screening/ Informed Consent/ Skin Test

- *Informed Consent/HIPAA:* Prior to any changes in medical treatment or clinical trial visit procedures, the clinical trial will be discussed with each subject and subjects wishing to participate must give written informed consent and sign a HIPAA form.

  Prior to the completion of this visit, if it is determined a subject did not in fact meet certain washout criteria, the subject may be re-screened a later date. Subjects may be re-screened a maximum of two times.

- *Demographic data:* Demographic data will be recorded.

- *Urine Pregnancy Test (females of childbearing potential):* A negative urine pregnancy test is required to continue in the clinical trial, and must agree to use an adequate method of contraception for the duration of the clinical trial.

- *Allergic Skin Test (if applicable):* A diagnostic test for allergic disease [redacted] will be performed [redacted]

- *Medical/medication/ocular and non-ocular history:* All medical history, any medications, and any underlying condition(s) will be recorded. [redacted]

- *Review of Inclusion/Exclusion Criteria:* A review of protocol inclusion and exclusion criteria will be confirmed for each subject.

- *AE Query*

- *Scheduling of Next Visit:* Qualifying subjects will be scheduled [redacted]

9.3.3 Visit 2 [redacted] Titration CAC [redacted]

- *Update of Medical/Medication History*

- *AE Query*

- *ACQLQ:* Qualifying subjects will be asked to complete the ACQLQ.
- *Visual Acuity Utilizing an ETDRS Chart:* Subjects must have a score [redacted] in each eye in order to qualify.
- *Initial Ocular Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess initial ocular allergic signs and symptoms. [redacted]

- *Slit-lamp Biomicroscopy:* A slit-lamp examination will be performed [redacted]

- *Review of Inclusion/Exclusion Criteria*

- *Titration CAC:* A CAC will be performed [redacted]
  - [redacted]
  - [redacted]
    - [redacted]
- *Post-CAC Ocular Allergic Signs and Symptoms Assessment:* [redacted], subjects will receive an ocular examination by the investigator [redacted]
- *IOP Measurement:* [redacted], intraocular pressure (IOP) will be measured [redacted].
- *Dilated Fundoscopy:* [redacted] a dilated fundoscopy will be performed [redacted]
- *Review of Inclusion/Exclusion Criteria*
- [redacted]*:* A trained clinical trial technician will instruct the subject or subject's caregiver on the proper technique for instillation [redacted]
- *Dispensation of* [redacted] */Dosing and Allergic Assessment Diary:* Subjects or caregivers will be instructed to instill one drop of [redacted] at home [redacted]. I [redacted]

Subjects or caregivers will be instructed on how to properly record the administration [redacted]

- *AE Query*
- *Scheduling of Next Visit:* Subjects will be scheduled to return to the office [redacted]

9.3.4 Visit 3 [redacted] Enrollment, randomization, begin [redacted] for 28 day period ending at Visit 5.

- *Update of Medical/Medication History*
- *AE Query*
- [redacted] *Dosing Diary Review and Collection*: The diary will be collected and reviewed for compliance. A [redacted]
- *Urine Pregnancy Test (females of childbearing potential)*
- *Visual Acuity Utilizing an ETDRS Chart:* The investigator should be notified if there is a clinically significant visual acuity decrease [redacted]
- *Slit Lamp Biomicroscopy*

- *Ocular Allergic Signs and Symptoms Assessment:* The investigator and the subject will assess ocular allergic signs [redacted]
- *Review of Inclusion/Exclusion Criteria*
- *Randomization:* Subjects who meet all of the inclusion criteria and none of the exclusion criteria, and who otherwise qualify to continue in the clinical trial, will be randomly assigned to masked investigational product treatment [redacted]
- *ACQLQ:* Randomized subjects will be asked to complete the ACQLQ.
- *Investigational Product Instillation:* A trained clinical trial technician will instruct the subject or caregivers on the proper technique for instillation [redacted]
- *Dispensation of Investigational Product, Dosing and Allergic Assessment Diary:* Subjects or caregivers will be instructed to instill one drop in each eye [redacted] uring the clinical trial period. [redacted]

  Subjects or caregivers will be instructed on how to properly record the administration of investigational product, discard used investigational product,as well as how to properly record allergic signs and symptoms of the worst eye [redacted].
- *AE Query*

- *Scheduling of Next Visit:* Subjects will be scheduled to return to the office [redacted]

9.3.5 Visit 4 [redacted] Follow-up, collect, and dispense investigational product

- *Update of Medical/Medication History*
- *AE Query*
- *Investigational Product and Dosing Diary Review and Collection*: The diary will be collected and reviewed for compliance. [redacted]
- *Visual Acuity Utilizing an ETDRS Chart:* The investigator should be notified if there is a clinically significant visual acuity decrease [redacted]
- *Slit Lamp Biomicroscopy*
- *Ocular Allergic Signs and Symptoms Assessment*
- *Investigational product Instillation:* A trained clinical trial technician will instill investigational product [redacted]
- *Dispensation of Investigational Product/Dosing and Allergic Assessment Diary:* Subjects or caregivers will be instructed to continue to instill one drop in each eye [redacted]

Subjects or caregivers will be instructed to stop dosing the evening prior [redacted]

- *AE Query*
- *Scheduling of Next Visit:* Subjects will be scheduled to return to the office [redacted]

9.3.6 Visit 5 [redacted] Exit

- *Update of Medical/Medication History*
- *AE Query*
- *Investigational Product and Dosing Diary Review and Collection*: The diary will be collected and reviewed for compliance. [redacted]
- *ACQLQ:* Subjects will be asked to complete the ACQLQ.
- *Urine Pregnancy Test (for females of childbearing potential)*
- *Visual Acuity Utilizing an ETDRS Chart:* The investigator should be notified if there is a clinically significant visual acuity decrease [redacted]
- *Slit Lamp Biomicroscopy*
- *Ocular Allergic Signs and Symptoms Assessment*
- *Intraocular Pressure Measurement:* IOP will be measured in each eye [redacted]
- *Dilated Fundoscopy*
- *Adverse Event Query*
- *Clinical Trial Exit*

9.4 Schedule of Visits, Measurements, and Dosing

9.4.1 Scheduled Visits

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

If a subject is discontinued at a scheduled trial visit, the remaining assessments should be captured on the Unscheduled Visit/Early Exit Visit pages of the source document and corresponding eCRF.

9.4.2 Unscheduled Visits

For Unscheduled Visits, the reason for the visit should be clearly documented on the appropriate eCRF, including findings from all evaluations that are completed.

Unscheduled visits may be performed to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit/Early Exit Visit pages of the source document and corresponding eCRF.

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit), include:

- Update of Medical/Medication History
- Collect Returned Investigational Product and Diary
- Urine Pregnancy Test
- VA at Distance Utilizing an ETDRS chart
- Slit-lamp Biomicroscopy
- IOP
- Dilated Fundoscopy
- Assessment of AEs

9.5 Compliance with Protocol

Subjects will be instructed and provided written instructions on proper use of the dosing diary as well as the instillation and storage of [redacted] The diaries and unused investigational product ampules will be collected at each visit [redacted] to assess dosing and symptom assessment compliance. [redacted]

Site staff will review concomitant medication and record any dosing regimen changes [redacted]

Subjects who are inappropriately enrolled or no longer fulfill the clinical trial eligibility criteria will be discontinued from the clinical trial. The reason for discontinuation will be recorded as "protocol violation" in the source document and in the eCRF.

All protocol violations, regardless of causation, will be recorded in the subject's source document as well as the eCRF [redacted]

9.6 Subject Disposition

9.6.1 Completed Subjects

A completed subject [redacted]

9.6.2 Discontinued Subjects

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

- subject request/withdrawal;
- AEs;
- protocol violations;
- administrative reasons [redacted]
- Sponsor termination of the clinical trial
- any sound medical reason, as determined by the investigator; or
- other.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora, Inc. and/or Sponsor and will be clearly documented on the eCRF. Subjects who are discontinued from the clinical trial will not be replaced.

9.7 Study Termination

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

9.8 Study Duration

Subjects will participate [redacted]

9.9 Monitoring and Quality Assurance

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

Regulatory authorities of domestic and foreign agencies, quality assurance, or 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.

10 ADVERSE EVENTS

10.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of 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, in response to an open question from clinical trial personnel, or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any pre-existing medical condition that worsens after administration of study medication will also be considered a new adverse event. Study medication includes the drug under evaluation or any other medications required by the protocol given during any stage of the clinical trial.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

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.

10.1.1 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 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:

- [redacted]

10.1.2 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 administration. The following characterizations will be used:

- ***Definitely Related***
- ***Probably Related***
- ***Possibly Related***
- ***Unlikely to be related***
- ***Not Related***

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

AE events 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 determination of the Sponsor's Medical Monitor.

10.2 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or Sponsor/designee, the AE results in any of the following outcomes:

- death;
- a life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor/designee, the subject at immediate risk of death as a result of the AE. "Life threatening" 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). 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; or admission to 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; and

  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, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, Inc., the Sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF. Collection of AEs/SAEs will begin at the time of informed consent and may be recorded up until 30 days post-instillation of IP.

10.3.1 Reporting a Suspected Unexpected Adverse Reaction

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

10.3.2 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 eCRF. The investigator is obligated to pursue and obtain information requested by Ora, Inc. and/or the Sponsor/designee in addition to that information reported on the eCRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the investigator must notify the appropriate contact in the Safety Management Plan immediately; obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide Ora, Inc. and the Sponsor/designee 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 in a manner according to the IRB guidelines for reporting SAEs.

10.4 Procedures for Unmasking (if applicable)

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. The investigator should make every effort to contact Ora, Inc. to discuss the subject's emergency situation and the need to unmask a clinical trial subject prior to unmasking IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's clinical trial drug kit, which contains a scratch-off laminate under which the treatment is identified along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject. The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with

breaking the mask must be recorded and reported as specified in this protocol. The investigator has the responsibility to contact Ora, Inc. within 24 hours of breaking the blind.

If treatment assignment is unmasked, the IP treatment will be discontinued immediately, and the subject will be discontinued from the clinical trial.

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

AEs will be followed until:

- resolution (return to baseline status or to 'normal'),
- stabilization of the event has occurred (no improvement or worsening expected by the Investigator), or
    - Note: The principal investigator determines whether the condition is to be chronic. Alternatively, the event may be determined to be resolved or resolved with sequelae.
- the event is otherwise explained, regardless of whether the subject is still participating in the clinical trial.

The investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise explained. If the subject is lost to follow-up, the investigator should make three reasonable attempts to contact the subject via telephone 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. The status of the AE must be noted and followed as aforementioned.

If the investigator becomes aware of any new information regarding a SAE (e.g., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora, Inc. within 24 hours. 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.

11 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 Study Populations

11.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population [redacted]

11.1.2 Per-Protocol Population

The Per-Protocol (PP) population [redacted]

11.1.3 Safety Population

The Safety population [redacted].

11.2 Exploratory Efficacy Measures

- [redacted]
- Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ) at Visits 2, 3, and 5.

11.3 Statistical Hypotheses

This is a Phase 1b exploratory clinical trial to assess the safety, tolerability, and pharmacodynamic activity of Reproxalap Ophthalmic Solution utilizing a novel dosing regimen in subjects with allergic conjunctivitis in an environmental design. [redacted]

11.4 Adjustment for Multiplicity

[redacted]

[redacted]

11.5 General Imputation Methods

Missing data for the ocular itching and redness variables [redacted]

Missing data for efficacy variables [redacted]

11.6 Sample Size

Approximately [redacted] will be screened in order to enroll [redacted]

11.7 Demographic and Baseline Medical History

The demographic and baseline medical history data will be summarized [redacted]

11.8 Exploratory Efficacy Analysis

The ocular itching efficacy variable will be assessed [redacted]

[redacted]

The ocular itching analyses will be conducted [redacted]

The mean diary ocular redness scores [redacted]

The following analyses for the additional efficacy endpoints will be conducted [redacted]

- The number of subjects responding to treatment [redacted]
- Diary score assessments [redacted]
- Ocular redness [redacted]
- The ACQLQ questionnaire [redacted]

11.9 Safety Analysis

[redacted]

The secondary safety variables of visual acuity, slit-lamp biomicroscopy, IOP, and dilated fundoscopy will be summarized [redacted]

11.10 Statistical Analysis Plan

Prior to database lock, the Sponsor will finalize a statistical analysis plan (SAP) that will detail all planned analyses. Any analyses conducted in addition to those specified in the SAP will be clearly documented as post hoc.

11.11 Interim Analysis

No interim analyses are planned.

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

This clinical trial will be conducted in compliance with the protocol, current GCPs, including the International Council 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 adhered to.

12.1 Protection of Human Subjects

12.1.1 Subject Informed Consent

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

All ICFs must be approved for use by the Sponsor and receive approval 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, Inc. prior to submission to the governing IRB and that it is read, signed and dated by all subjects, subsequently enrolled in the clinical trial, as well as those currently enrolled in the clinical trial.

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

12.1.2 Institutional Review Board Approval

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

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

12.2 Ethical Conduct of the Study

The clinical trial will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

12.3 Subject Confidentiality

All personal clinical trial subject data collected and processed for the purposes of the clinical trial should be maintained by the investigator and site 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, Inc., the Sponsor, the IRB/IEC approving this clinical trial, the Food and Drug Administration (FDA), the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the subject's original medical and clinical trial 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.

A report of the results of this clinical trial 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.

12.4 Documentation

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

12.4.1 Retention of Documentation

All clinical trial related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of eCRFs 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 and 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 clinical trial records, custody must be transferred to a person who will accept the aforementioned responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

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

12.5.1 Labeling/Packaging

Investigational drug will be packaged and labeled into clinical kits.

[redacted]

The subject kit will be labeled with the following:

- clinical trial protocol number,
- contents,
- randomization number,
- lot number,
- subject number and initials (manually recorded),
- storage conditions,
- Investigational New Drug statement, and
- Sponsor's name, address, and phone number.

The foil pouch label will be labeled with the following:

- clinical trial protocol number,
- contents,
- randomization number,
- storage conditions,
- Investigational New Drug statement,
- manufacturer name and address, and
- Sponsor name, address, and phone number

12.5.2 Storage of Investigational Product

Investigational product must be stored in a secure area accessible only to the investigator and site designees. [redacted]

Investigational product will be administered only to subjects entered into the clinical trial, in accordance with the conditions specified herein.

12.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or the 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 clinical trial. A detailed inventory must be completed for the IP.

12.5.4 Return or Disposal of Investigational Product

At the conclusion of the clinical trial, IP reconciliation will be performed and all remaining IP will be destructed and disposed of according to clinical site's SOP. Sponsor will be provided with a final accounting of IP for approval prior to destruction.

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

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements, and will be performed only by staff who have been trained on the system and have access to the system. Data will not be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the clinical trial 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.

12.7 Publications

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

13 REFERENCES

Ackerman, S., Smith, L.M., and Gomes, P.J. (2016). Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. *Ther. Adv, Chronic Dis. 7*(1), 52-67.

Albrecht S. Conjunctivitis. *US Pharm*. 2011;36(4):29-34.

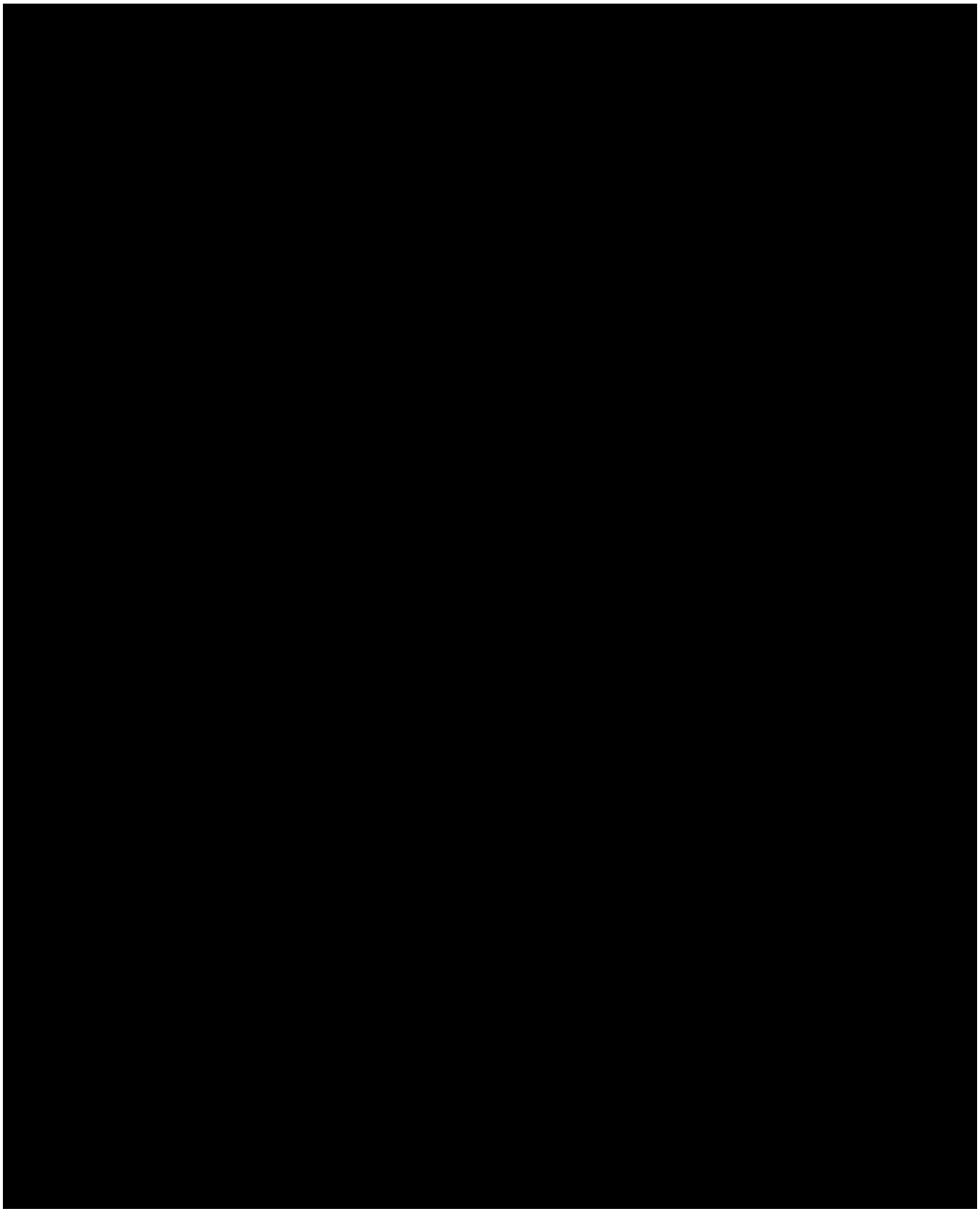
Bacsi A, Dharajiya N, Choudhury BK, Sur S, Boldogh I. Effect of pollen-mediated oxidative stress on immediate hypersensitivity reactions and late-phase inflammation in allergic conjunctivitis. *J Allergy Clin Immunol*. 2005;116(4):836-843.

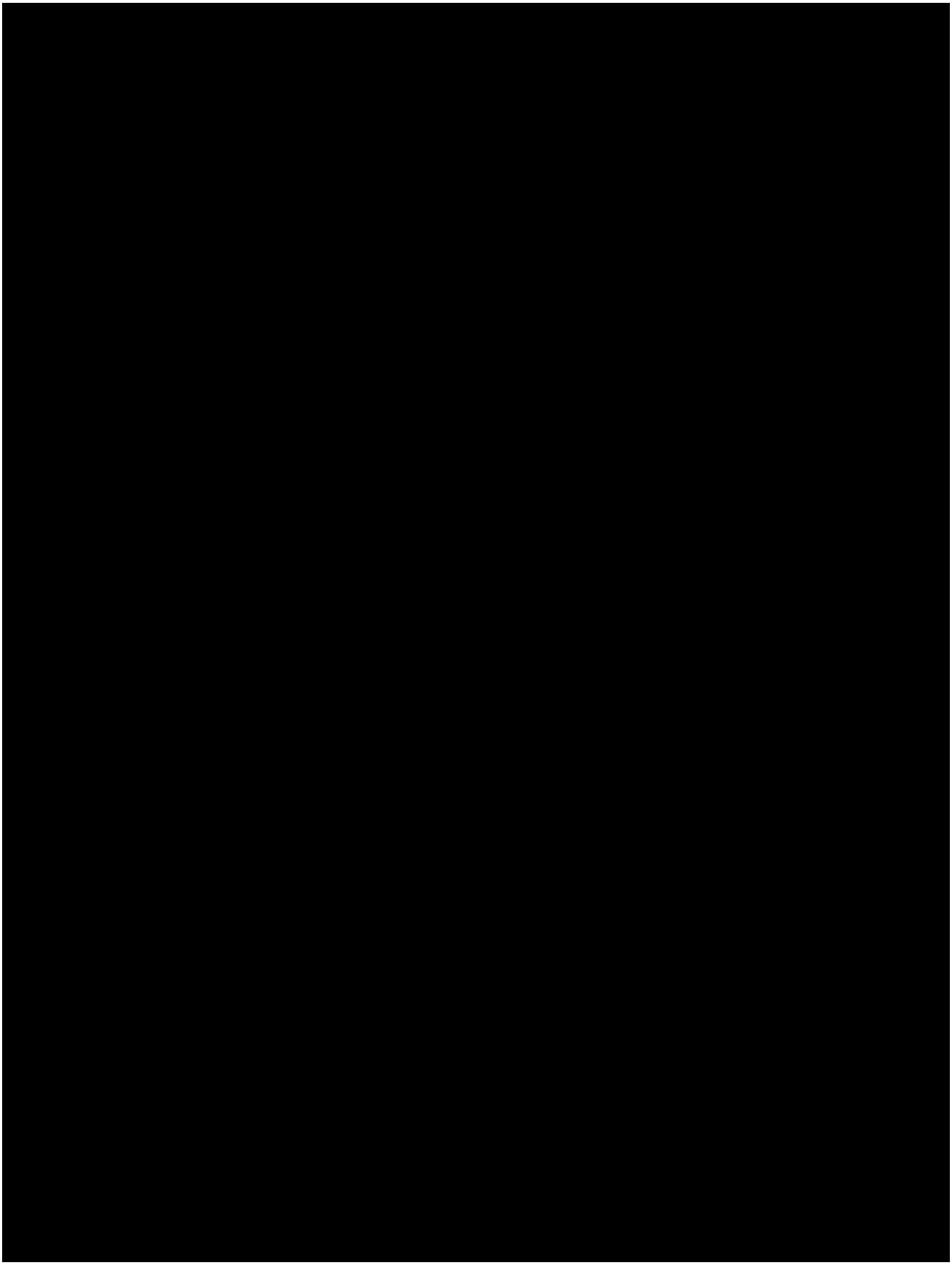
Leonardi, A. (2013). Allergy and allergic mediators in tears. *Exp. Eye Res. 117*, 106-117.

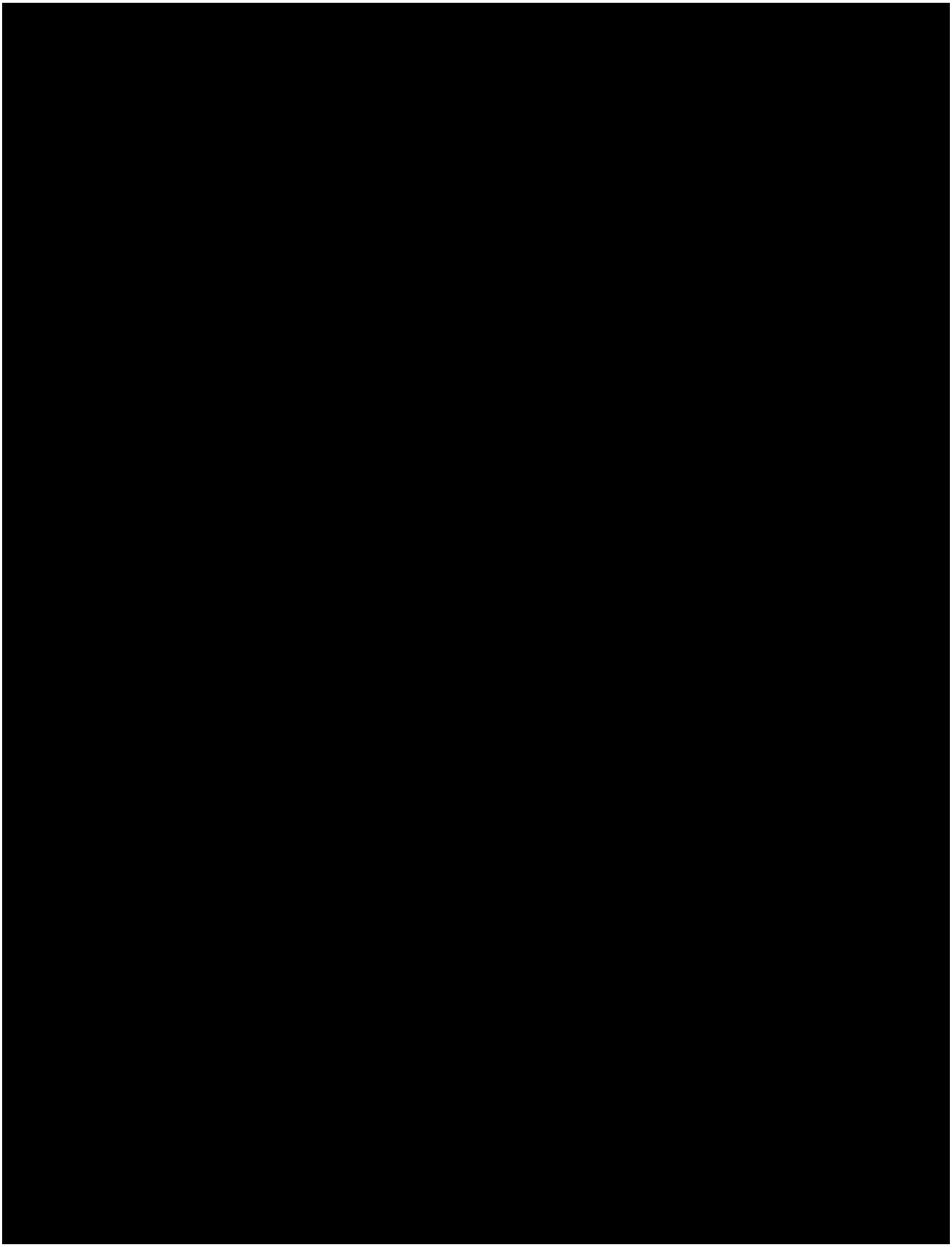
Mishra G, Tamboli V, Jwala J, Mitra A. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. *Inflamm Allergy Drug Discov*. 2011;5(1):26-36.

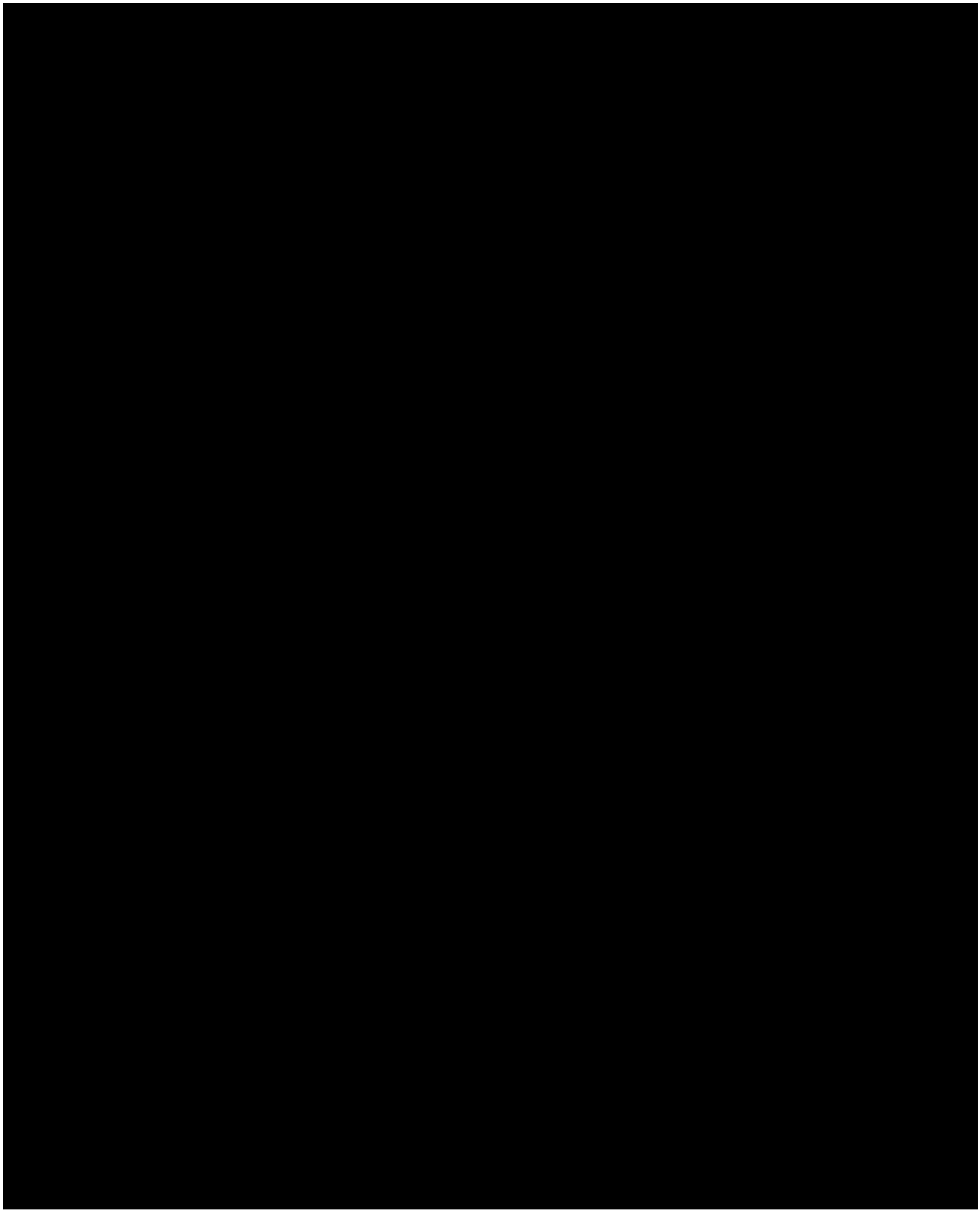
Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. 2010;126(4):778-783.

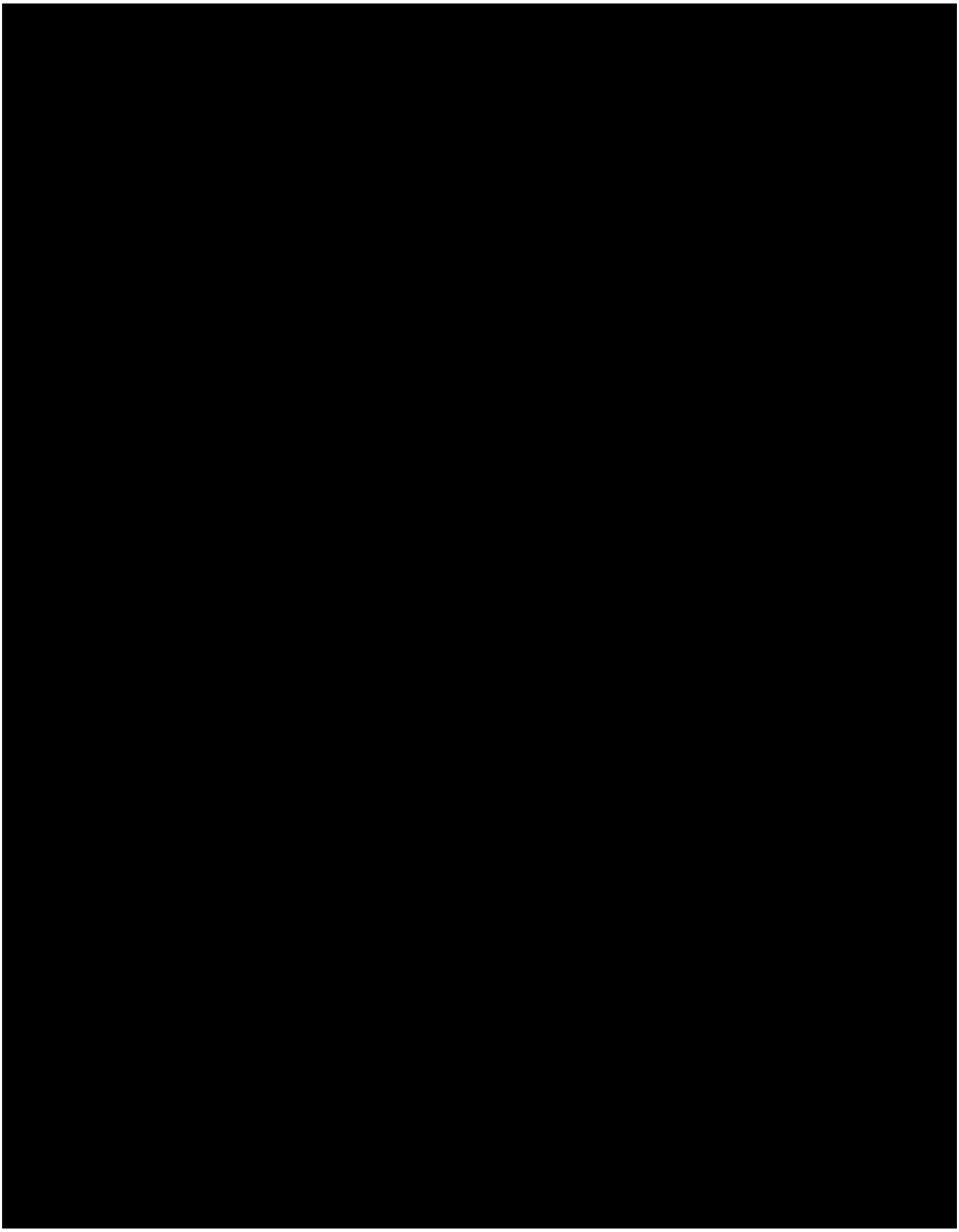
14 APPENDICES

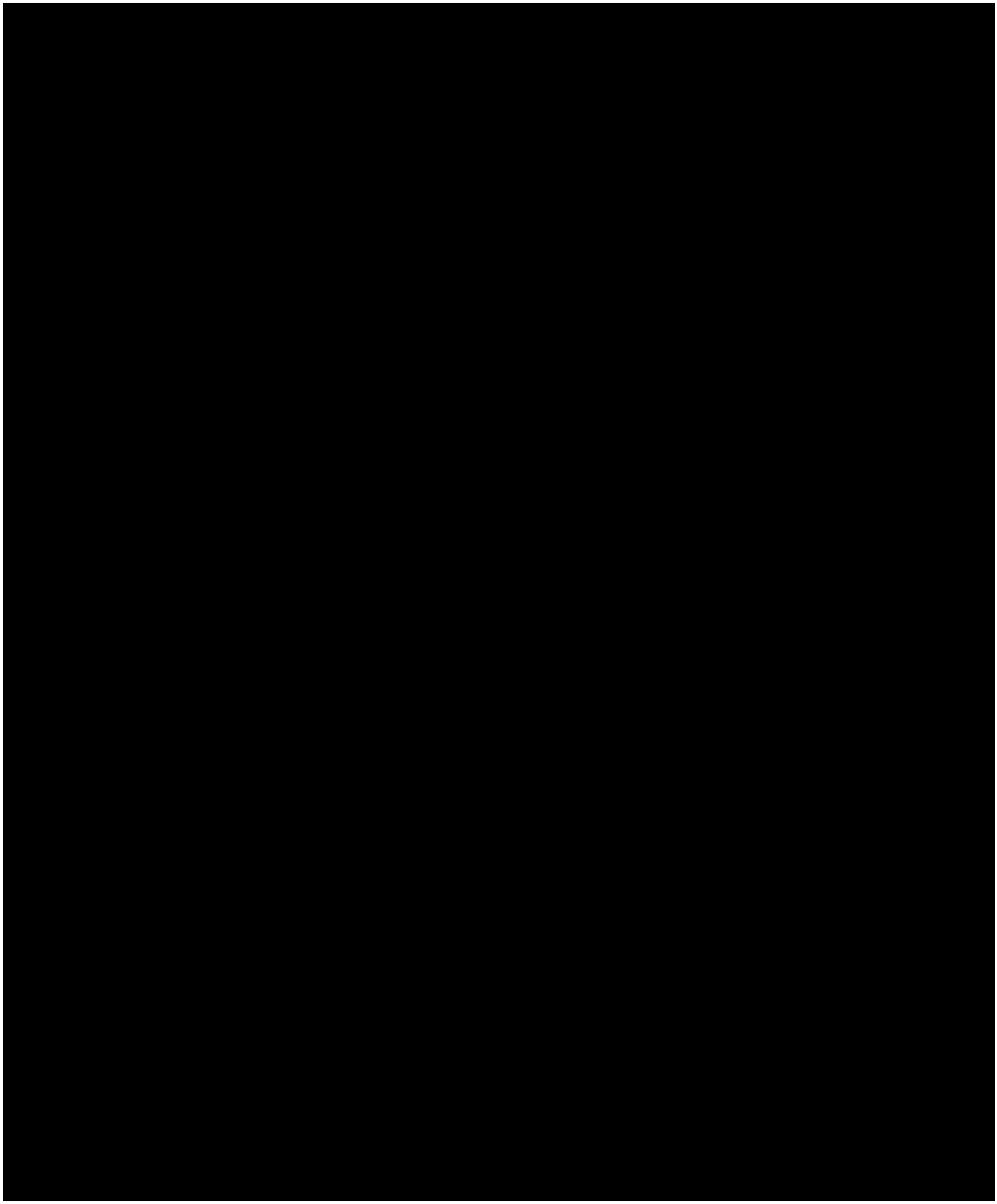


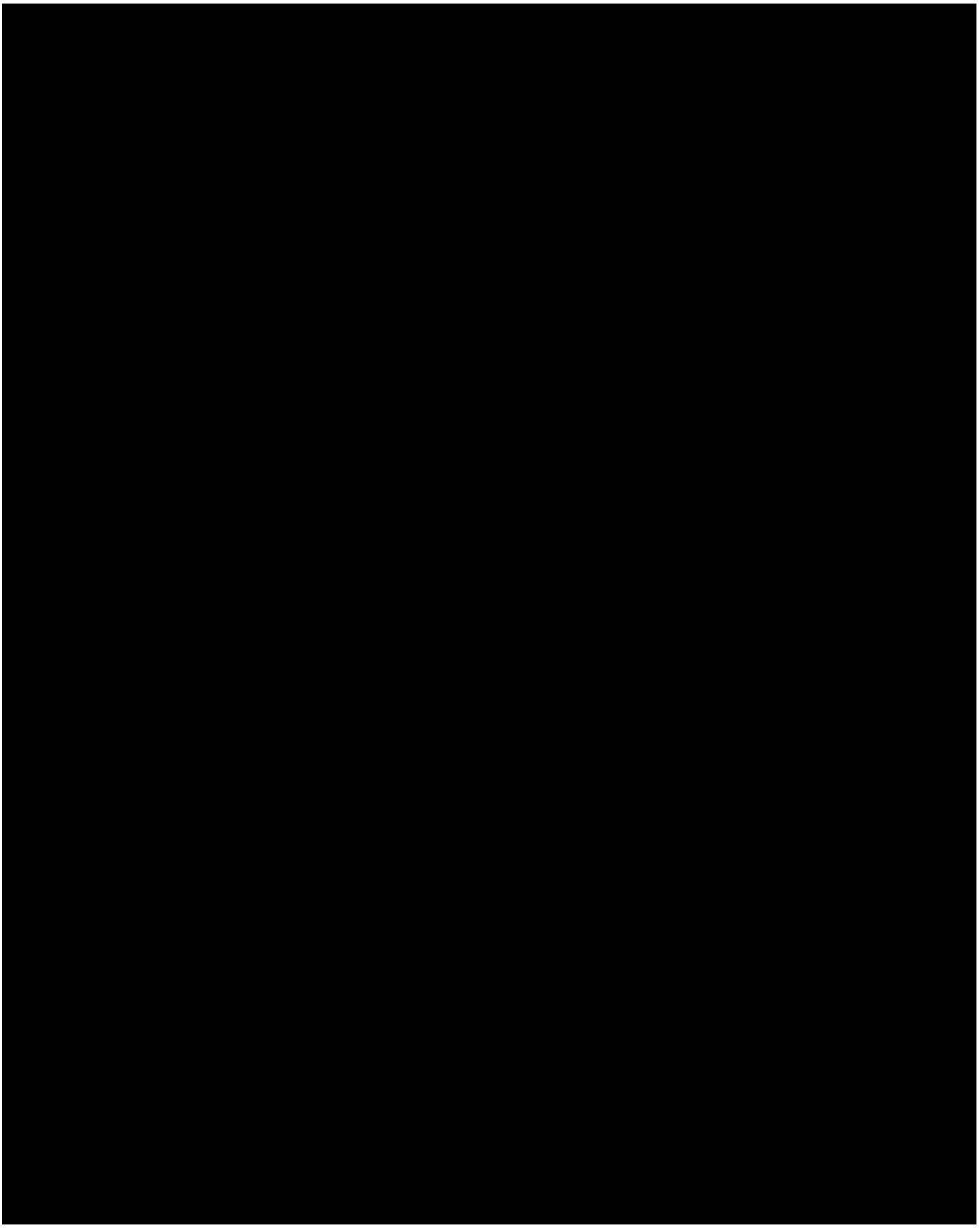


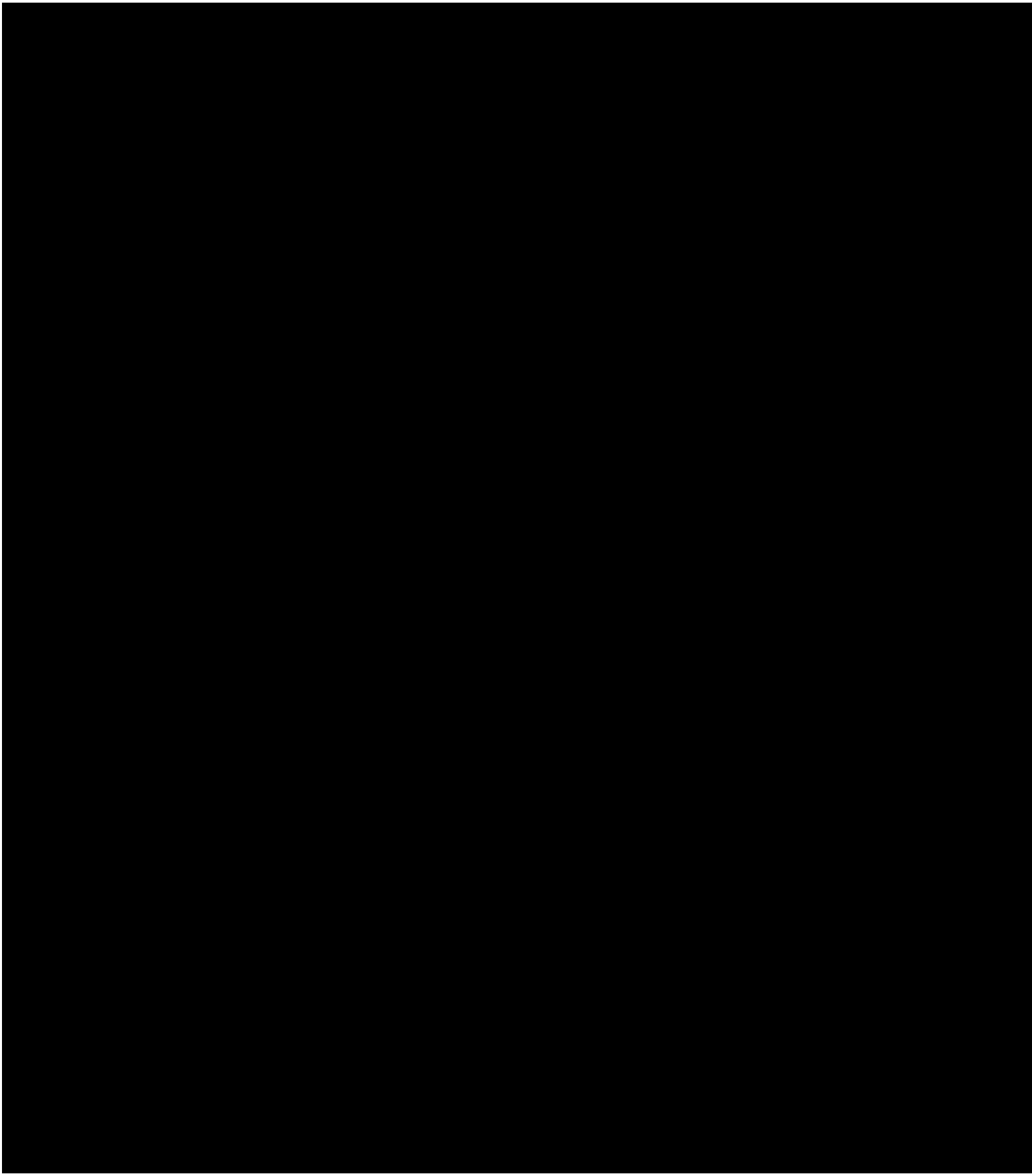




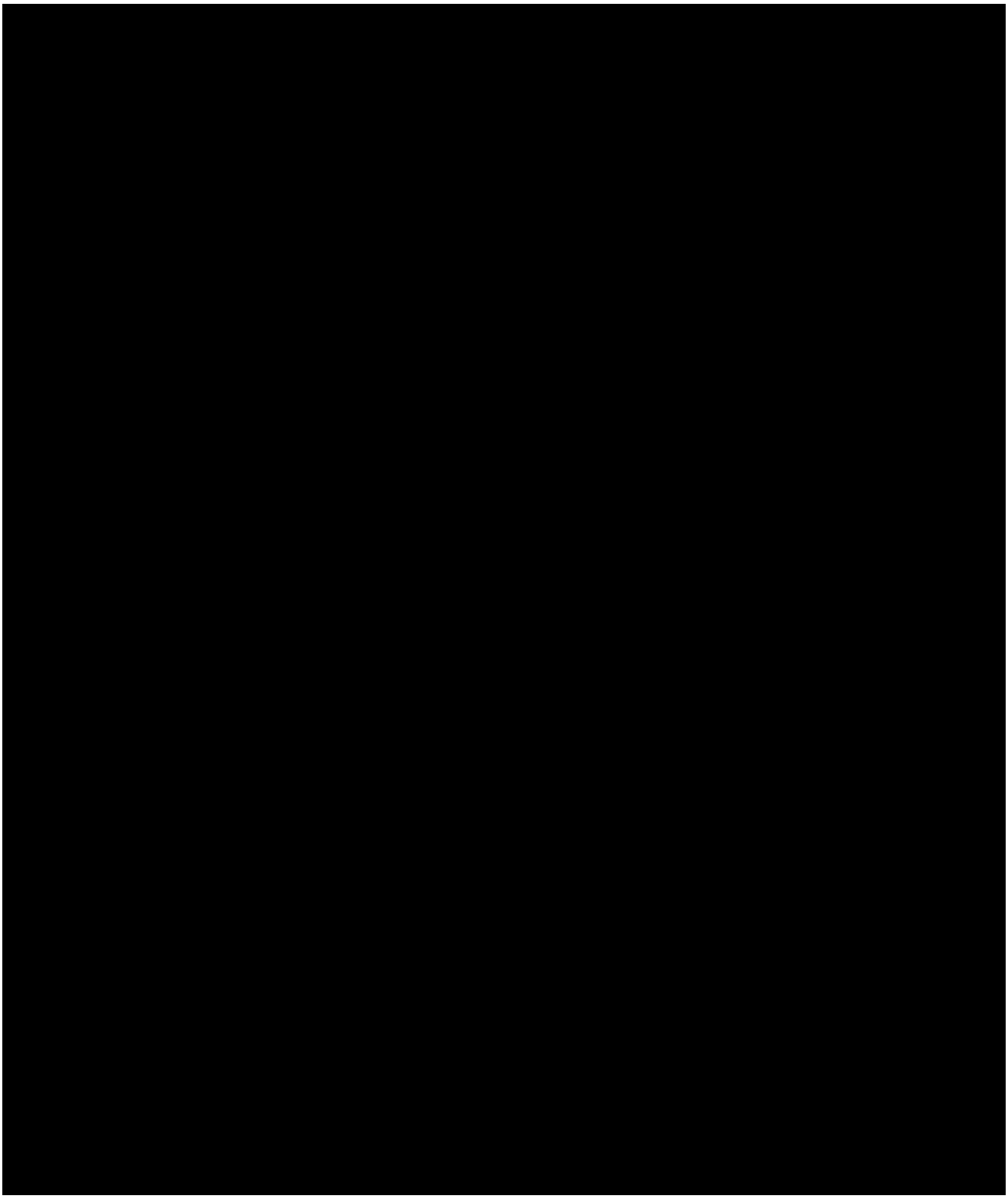


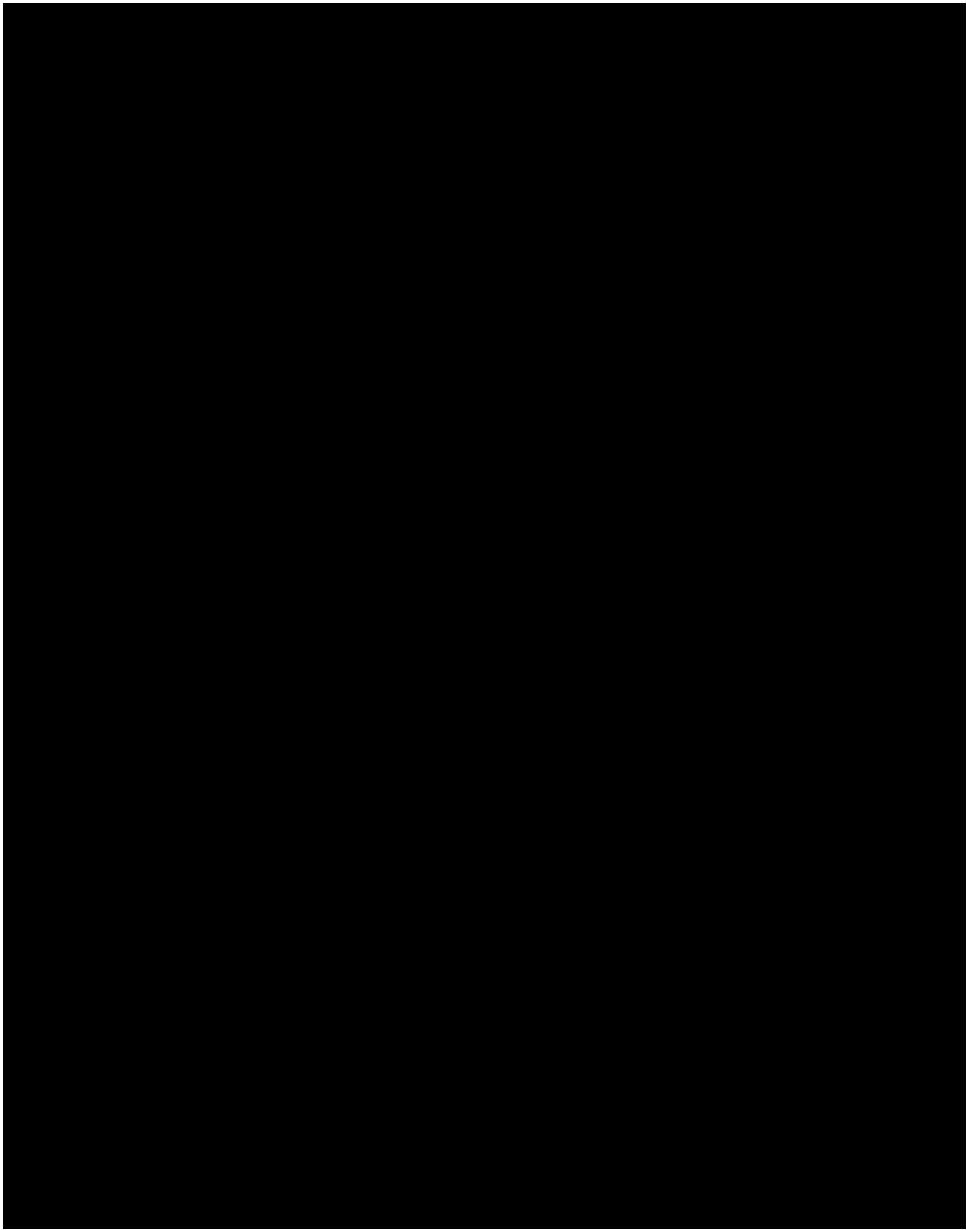


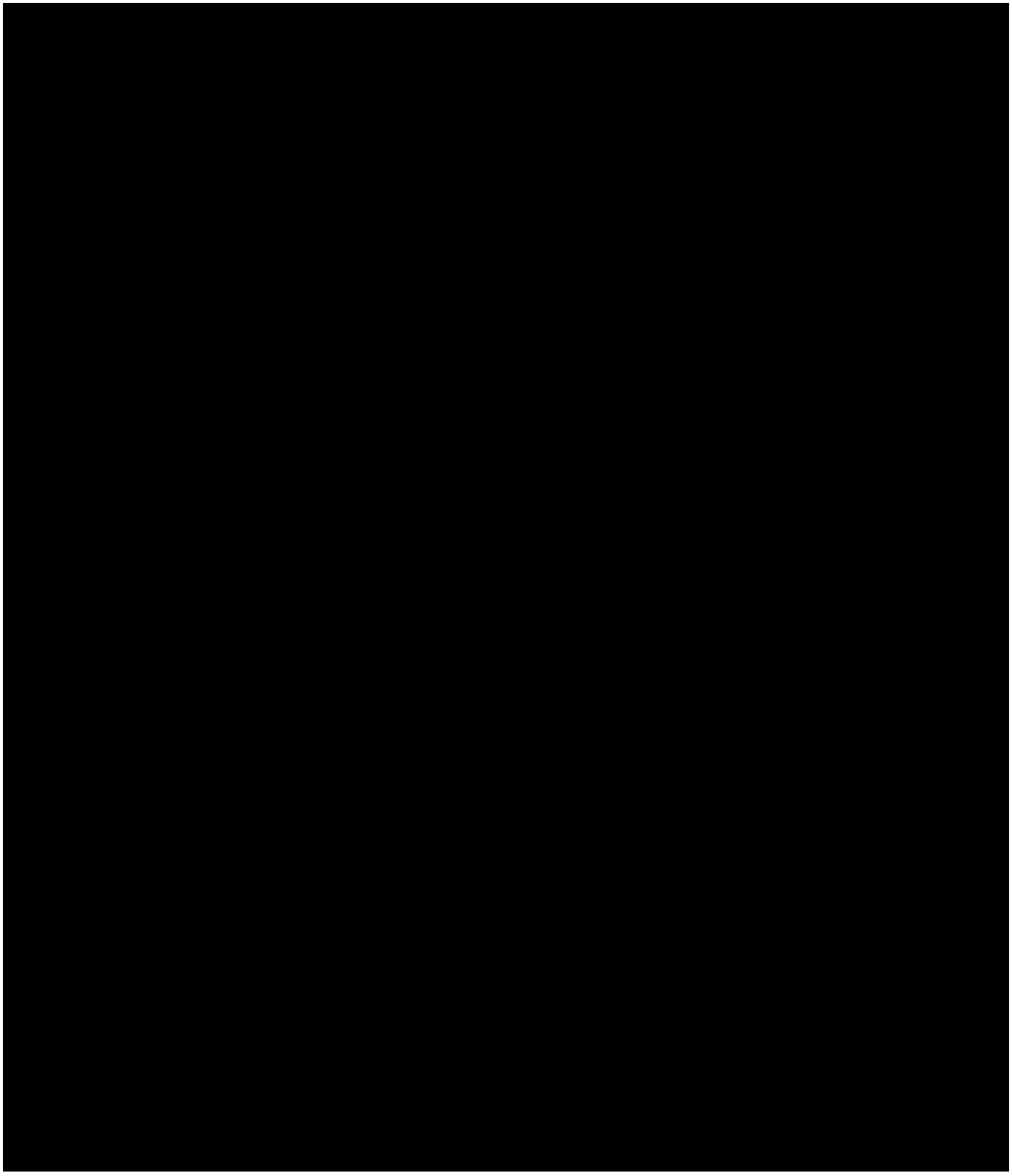


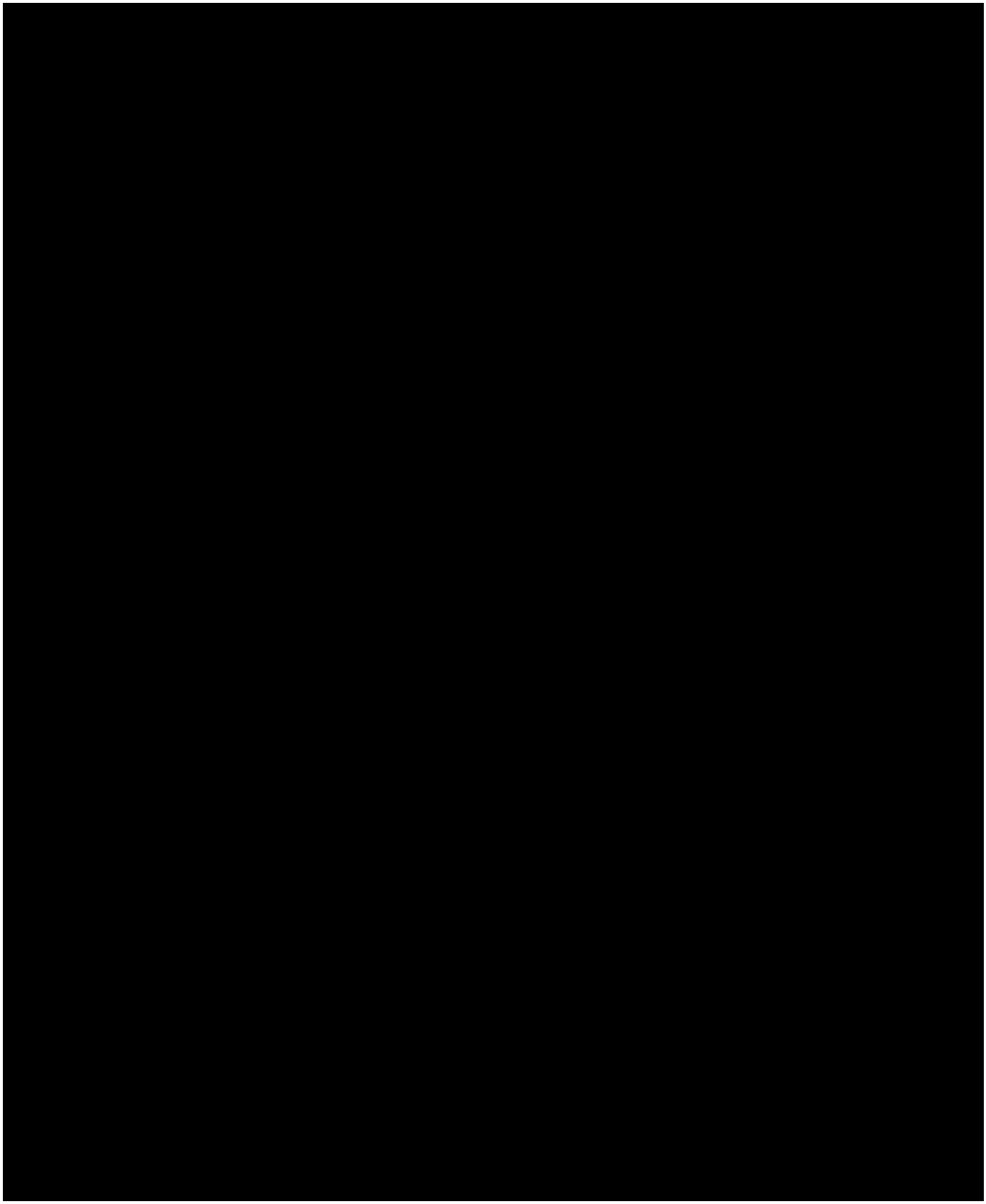


[redacted]

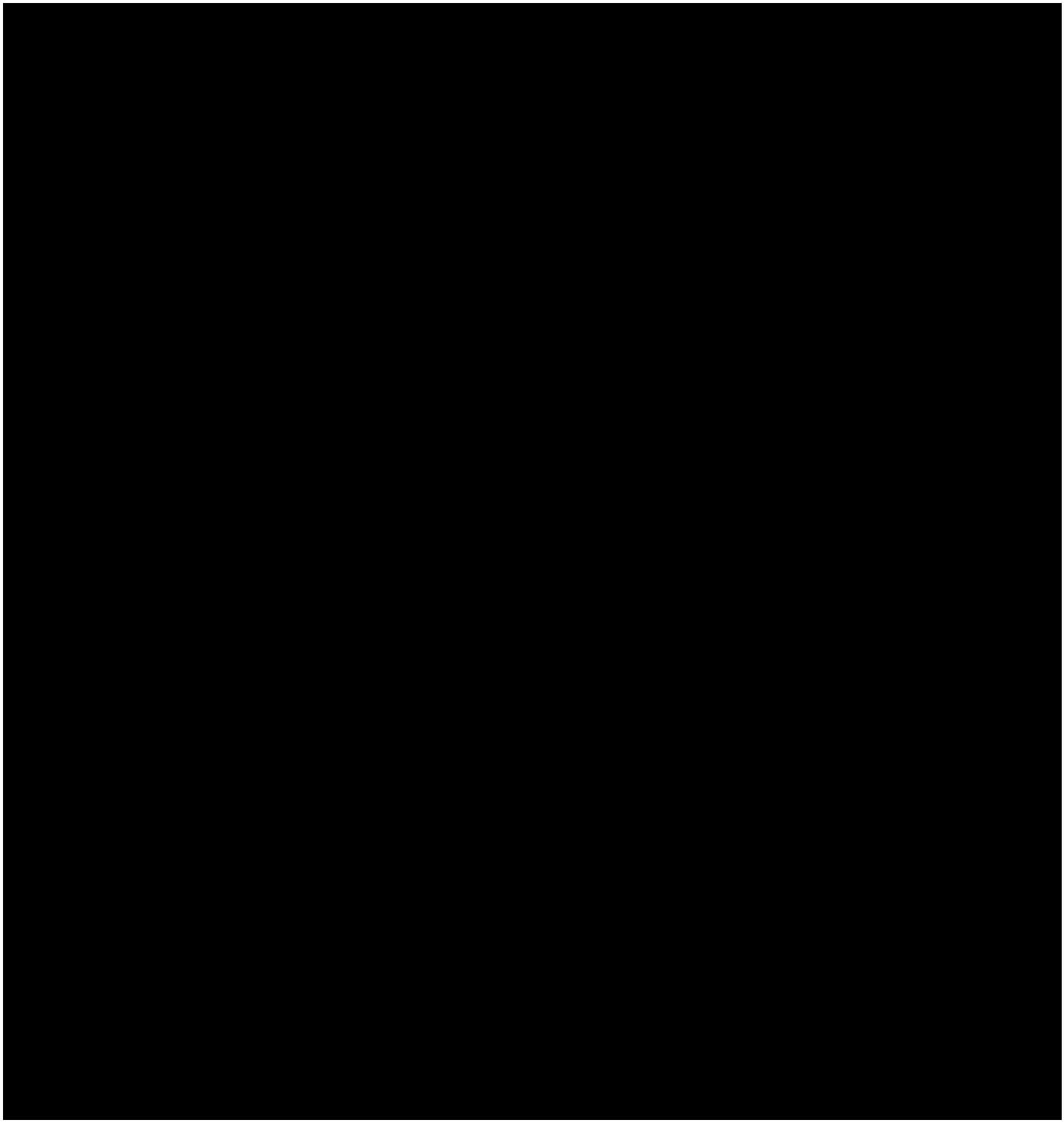








APPENDIX 5: PROTOCOL AMENDMENT



APPENDIX 6: ORA APPROVALS

Protocol Title: A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis

Protocol Number: ADX-102-AC-010

Final Date: 24 August 2018

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

APPENDIX 7: SPONSOR (ALDEYRA) APPROVALS

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-010
Final Date:	24 August 2018

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 8: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Multi-Center, Double-Masked, Randomized, Parallel-Group, Vehicle-Controlled, Environmental Clinical Trial with Reproxalap Ophthalmic Solutions (0.25% and 0.5%) in Subjects with Seasonal Allergic Conjunctivitis
Protocol Number:	ADX-102-AC-010
Final Date:	24 August 2018

I agree to implement and conduct the trial 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, Inc. 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.