Clinical Trial Protocol: ADX-102-DED-013

Protocol Title:	A Multi-Center, Phase 2, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-013
Study Phase:	2
Investigational Product Name:	Reproxalap Ophthalmic Solution (0.25% Novel Formulation)
IND/IDE/PMA Number:	[redacted]
Indication:	Dry Eye Disease
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
[redacted]	[redacted] [redacted] [redacted] [redacted]

	[redacted]
[redacted]	08 March 2019
Amendment 1:	17 December 2019

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

MEDICAL MONITOR

[redacted]	[redacted]

SYNOPSIS

Protocol Title:	A Multi-Center, Phase 2, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-013
Investigational Product:	1) Reproxalap Ophthalmic Solution (0.25% Novel Formulation) 2) Vehicle Ophthalmic Solution (vehicle)
Study Phase:	2
Overall Study Design:	
Structure:	Multi-center, double-masked, parallel-group, vehicle-controlled, randomized clinical trial Prior to randomization , subjects will receive 14 consecutive days [redacted] of vehicle, self–administered QID in both eyes, between Visits 1 and 2. Randomization will be 1:1 into one of two treatment arms (100 subjects per arm): 1. Reproxalap administered QID for four weeks, followed by BID administration for eight weeks 2. Vehicle administered QID for four weeks, followed by BID administration for eight weeks
Primary Objective:	Evaluation of the safety and efficacy of reproxalap compared to vehicle for the treatment of dry eye disease
Duration:	Approximately 14 weeks (98 days) including 12 weeks of treatment
Summary of Visit Schedule:	Nine visits over the course of approximately 14 weeks

	• Visit 1 = Day -14 ± 2, [redacted] Screening • Visit 2 = Day 1, [redacted] Confirmation/ Baseline • Visit 3 = Day 8 ± 2, 1-Week Follow-Up • Visit 4 = Day 15 ± 2, 2-Week Follow-Up • Visit 5 = Day 29 ± 2, 4-Week Follow-Up • Visit 6 = Day 43 ± 2, 6-Week Follow-Up • Visit 7 = Day 57 ± 3, 8-Week Follow-Up • Visit 8 = Day 71 ± 3, 10-Week Follow-Up • Visit 9 = Day 85 ± 3, 12-Week Follow-Up & Study Exit
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to test article, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Stratification will be used to balance treatment assignments within key subgroups. Masked treatment will be used to reduce the potential of bias during data collection and evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Approximately 500 subjects will be screened to enroll approximately 200 subjects (100 per treatment group).
Condition/Disease:	Dry Eye Disease (DED)

Inclusion Criteria:	Subjects must: 1. Be at least 18 years of age of either gender and any race; 2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form; 3. Have a reported history of dry eye for at least 6 months prior to Visit 1; 4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; 5. Report a score [redacted] in at least one symptom at Visit 1 and Visit 2 [redacted] 6. Have a Schirmer's Test [redacted] Visit 1 and Visit 2; 7. Have a tear film break-up time [redacted] at Visit 1 and Visit 2 [redacted]®; 8. Have a corneal fluorescein staining [redacted] in at least one region (e.g., inferior, superior, or central) at Visit 1 and Visit 2 [redacted]®; 9. Have a sum corneal fluorescein staining [redacted] at Visit 1 and Visit 2 [redacted] 10. Have a total lissamine green conjunctival [redacted] at Visit 1 and Visit 2 [redacted]®; 11. Demonstrate a response [redacted] at Visits 1 and 2 as defined by: A. Having at least [redacted] in fluorescein staining in the inferior region in at least one eye [redacted] B. [redacted]

	[redacted] 12. [redacted] 13. Have at least one of the following at Visit 2 [redacted] [redacted] B. [redacted]
Exclusion Criteria:	Subjects must not: 1. Have any clinically significant slit-lamp findings at Visit 1, [redacted] 2. [redacted] 3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study; 4. Have used any eye drops within 2 hours of Visit 1; 5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months; 6. Have used [redacted] of Visit 1;

	7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1; 8. Have used temporary or permanent punctal plugs within 30 days prior to Visit 1 or anticipate their use during the study period; 9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs that cannot be discontinued for the duration of the trial (excluding medications allowed for the conduct of the study); 10. [redacted] 11. Be a woman who is pregnant, nursing, or planning a pregnancy during the trial; 12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 9 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months); 13. Be a man or woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device (IUD); or surgical sterilization of males or 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 study; 14. Have a known allergy and/or sensitivity to reproxalap or the test article excipients; 15. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study; 16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; 17. Have previously participated in a reproxalap ophthalmic solution study; 18. Be currently using any medication known to cause ocular drying that has not been used on a stable dosing regimen for at least 30 days prior to Visit 1; 19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits;
Evaluation Criteria:	
Efficacy Measures and Endpoints:	Primary Endpoint • Subject-reported ocular dryness [redacted]

	[redacted]
Safety Measures:	• Visual acuity (VA) at distance utilizing an ETDRS chart • Slit-lamp evaluation • Adverse event (AE) query (reported, elicited, and observed) • Intraocular Pressure (IOP) • Dilated fundoscopy

General Statistical Methods and Types of Analyses

Sample Size:

Based on the results of a Phase 2b clinical trial of reproxalap in dry eye disease subjects (ADX-102-DED-009), for the outcome measurements of nasal fluorescein staining and ocular dryness VAS score, approximately 100 subjects per randomized arm will be evaluated in ADX-102-DED-013. Sample size estimates were made assuming [redacted] for the two efficacy populations, one with baseline staining severity of [redacted] and the other with dryness score severity of [redacted]. Using PASS (software version 14, NCSS,

LLC), the sample size estimated for staining was 39 per treatment arm (78 total); the sample size estimated for dryness score was 54 per treatment arm (108 total).

Primary Endpoint Efficacy Analysis:

- The primary symptom endpoint will be achieved if the change from baseline in subject-reported ocular dryness score [redacted] assessed using [redacted] from Week 2 to Week 12, in reproxalap-treated subjects is statistically significantly lower than that of vehicle-treated subjects. The population used for analysis of ocular dryness score will be subjects who have a baseline (Day 1) ocular dryness [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
ANCOVA	Analysis of covariance
BCVA	best-corrected visual acuity
BID	twice daily
CAE	controlled adverse environment
CD	compact disc
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRO	Contract research organization
DED	dry eye disease
DHHS	Department of Health and Human Services
eCRF	electronic case report form
EKG	Electrocardiogram
ERC	Ethical Review Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FSN	Fluorescein staining nasal region
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intent to treat
ITTFSN	intent to treat fluorescein nasal score
ITTOD	intent to treat ocular dryness
IUD	intrauterine device
IWRS	Interactive Web Response System
LASIK	laser in situ keratomileusis

LOCF	last observation carried forward
logMAR	logarithm of the minimum angle of resolution
LPS	lipopolysaccharide
MAR	missing at random
MDA	malonyldialdehyde
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
MMRM	Mixed Model Repeated Measures
MNAR	missing not at random
NCS	not clinically significant
ND	not done
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
OU	both eyes
OTC	over the counter
PP	per protocol
QID	Four times daily
RASP	reactive aldeyhyde species
REML	residual restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDC	Statistics and Data Corporation
SOP	standard operating procedure
TEAE	Treatment-emergent adverse event
TFBUT	tear film break-up time
VA	visual acuity
VAS	Visual Analog Scale
w/v	weight per unit volume

1 INTRODUCTION

Dry eye disease (DED) is a complex and chronic condition characterized by ocular discomfort, visual disturbance, tear film instability, increased tear osmolarity, and inflammation of the ocular surface that, in severe cases, can lead to loss of vision (Dry Eye Workshop 2007). Although estimates of the prevalence of dry eye disease vary considerably depending on the criteria used to define the disease, as many as 3.2 million women and 1.7 million men over the age of 50 are thought to have DED in the United States, and prevalence is projected to increase by 40% by 2030 as a result of population aging and increasing computer use (Schaumberg 2002, Schaumberg 2003, Schaumberg 2009, Brewitt 2001).

Reactive aldehyde species (RASP) are reactive organic molecules that bind to proteins, carbohydrates, lipids, and nucleic acids (Esterbauer 1991). RASP that are not sequestered or otherwise protected in specific metabolic processes are toxic, and aldehyde binding to cellular constituents leads to inflammation via activation of NFκB and other pro-inflammatory mediators (Yadav 2013), molecular dysfunction (O'Brien 2005), and the accumulation of indigestible metabolites, such as lipofuscin components in the retina (Boyer 2012).

In biological systems, RASP are formed by a variety of processes, including the oxidation of alcohols, polyamine and glucose metabolism, and oxidative stress. In non-disease states, levels of RASP are low due to the near ubiquitous presence of aldehyde dehydrogenases and other enzymes that catabolize aldehydes. However, in disease states, the capacity of aldehyde dehydrogenases to neutralize toxic aldehydes is exceeded, resulting in increased RASP levels. Elevation in the levels of RASP, particularly malonyldialdehyde (MDA), has been described in a variety of inflammatory ocular diseases, including pterygium, Behcet's Disease, Sjögren's Syndrome, anterior uveitis, and dry eye disease (Sandikci 2003, Cejkova 2007, Balci 2011, Turk 2014, Choi 2016, Augustin 1995).

Reproxalap is a novel small molecule, formulated for topical ophthalmic delivery, that functions as a RASP sequestering agent, or "trap," which binds rapidly and irreversibly to RASP. By irreversibly trapping RASP, reproxalap is expected to diminish inflammation thought to be caused or exacerbated by elevated RASP levels in inflammatory ocular conditions. Reproxalap has demonstrated anti-inflammatory effects in numerous ocular and non-ocular preclinical models of inflammation:

- In a rat model of lipopolysaccharide (LPS)-induced uveitis, topical ocular dosing of reproxalap significantly reduced inflammatory ocular effects and significantly reduced ocular levels of two pro-inflammatory cytokines.
- In a rabbit ocular healing study, topical ocular reproxalap significantly reduced haze intensity and reduced the rate of haze development following photorefractive keratectomy.
- In a model of LPS-induced systemic inflammation, a single intraperitoneal (IP) dose of reproxalap led to a significant reduction in levels of several pro-

inflammatory cytokines, while also increasing levels of the anti-inflammatory cytokine IL-10.

- In a phorbol 12-myristate-13-acetate-induced mouse model of contact dermatitis, IP administration of reproxalap significantly reduced edema.
- In an oxazolone-induced, delayed-type hypersensitivity mouse model, IP administration of reproxalap significantly reduced edema and resulted in statistically significant reduction of tissue cytokines at the site of inflammation.
- In a mouse model of lung inflammation, IP administration of reproxalap reduced infiltration of inflammatory cells and protein in the lung, and resulted in reductions in levels of pro-inflammatory cytokines.
- In a model of radiation-induced mucositis in hamsters, subcutaneous administration of reproxalap significantly improved healing time and reduced fibrosis (scarring).

In 1995, Augustin et al. (Augustin 1995) described elevations in tear MDA levels that correlated with severity in DED patients. Subsequently, Choi et al. (Choi 2016) reported that expression of MDA and 4-hydroxynonenal (another RASP commonly associated with inflammation) is increased in the tear film and ocular surface of patients with DED. Consistent with the literature that supports the notion that RASP mediate pro-inflammatory toxicity in DED, the anti-inflammatory effects of the RASP scavenger reproxalap have been demonstrated in Phase 2 clinical trials in DED, noninfectious anterior uveitis, and allergic conjunctivitis. In aggregate, a broad array of preclinical and clinical evidence supports the use of reproxalap for the treatment of ocular inflammation, including DED.

2 Clinical Studies of Reproxalap Ophthalmic Solution

Reproxalap ophthalmic solution is in clinical development for the treatment of ocular inflammation. The drug product, in various strengths, has completed a Phase 1 clinical trial, as well as a vehicle-controlled, double-masked Phase 2a clinical trial in allergic conjunctivitis; a vehicle-controlled, double-masked Phase 2b clinical trial in allergic conjunctivitis; a comparator-controlled, investigator-masked Phase 2 clinical trial in noninfectious anterior uveitis; a vehicle-controlled, double-masked Phase 2a clinical trial in DED; and a vehicle-controlled, double-masked Phase 2b clinical trial in DED. Phase 3 clinical trials in noninfectious anterior uveitis and allergic conjunctivitis are in progress. A total of 468 subjects have been exposed to topical ocular reproxalap in completed clinical trials.

In all clinical trials, no treatment-related serious adverse events (SAE) have been observed. Generally mild to moderate transient ocular stinging, lasting only up to a few minutes, was reported in most subjects treated in the Phase 1 and the allergic conjunctivitis and dry eye disease Phase 2 clinical trials, and in a small proportion of

subjects in the noninfectious anterior uveitis Phase 2 and the allergic conjunctivitis Phase 2b clinical trials. Table 1 summarizes the clinical exposure to topical ocular reproxalap for completed clinical trials.

[redacted]

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

[redacted]

[redacted]

[redacted]

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

The ADX-102-DES-007 clinical trial was a single-center, Phase 2a, randomized, double-masked, parallel-group design to assess the safety, tolerability, and pharmacodynamic activity of 28 days of QID dosing with three different formulations of reproxalap ophthalmic solutions (0.1%, 0.5%, and 0.5% lipid formulation) in subjects with DED.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.1 Minimization of Risk

In clinical trials with reproxalap topical ocular solution in various strengths in different ocular indications, no safety signal or treatment-related SAE's have been observed (Section 2). Generally mild to moderate transient ocular discomfort and ocular stinging, lasting only up to a few minutes, was the most frequently reported AE.

In addition, extensive in vitro and in vivo studies conducted to assess the safety, efficacy, and pharmacokinetics of reproxalap have shown that reproxalap is effective in animal models of inflammation, is not toxic to the eye, and can achieve therapeutically relevant concentrations in the eye. Nonclinical safety and toxicology studies of reproxalap administration by several routes of administration have consistently demonstrated reproxalap to be well tolerated, with no significant adverse findings at significant dose multiples of those expected in planned clinical trials. In aggregate, the nonclinical studies completed to date provide compelling evidence that reproxalap has the potential to ameliorate pathologic ocular inflammation without off-target pharmacological or toxic effects. The excipients in the novel formulation are similar to those that have been used in the non-clinical safety and previous clinical studies. The concentrations of the excipients in the novel formulation are varied in degree but well within the allowable limits for topical ophthalmic delivery. Please refer to the Investigator's Brochure for additional information.

3 STUDY OBJECTIVES

The overall objective of this study is to evaluate the safety and efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) compared to Vehicle Ophthalmic Solution for the treatment of dry eye disease.

4 CLINICAL HYPOTHESES

The clinical hypotheses is that Reproxalap Ophthalmic Solution (0.25% Novel Formulation) is more effective than vehicle in reducing the signs and symptoms of DED.

5 OVERALL STUDY DESIGN

The clinical trial is a Phase 2, multicenter, randomized, double–masked, parallel-group, vehicle-controlled design with block enrollment. Subjects will be randomized to one of the following treatment groups at Visit 2 and will be instructed to follow a dosing regimen QID dosing for four weeks followed by BID dosing for weeks 5-12:

- Reproxalap Ophthalmic Solution (0.25% Novel Formulation)
- Vehicle Ophthalmic Solution (vehicle)

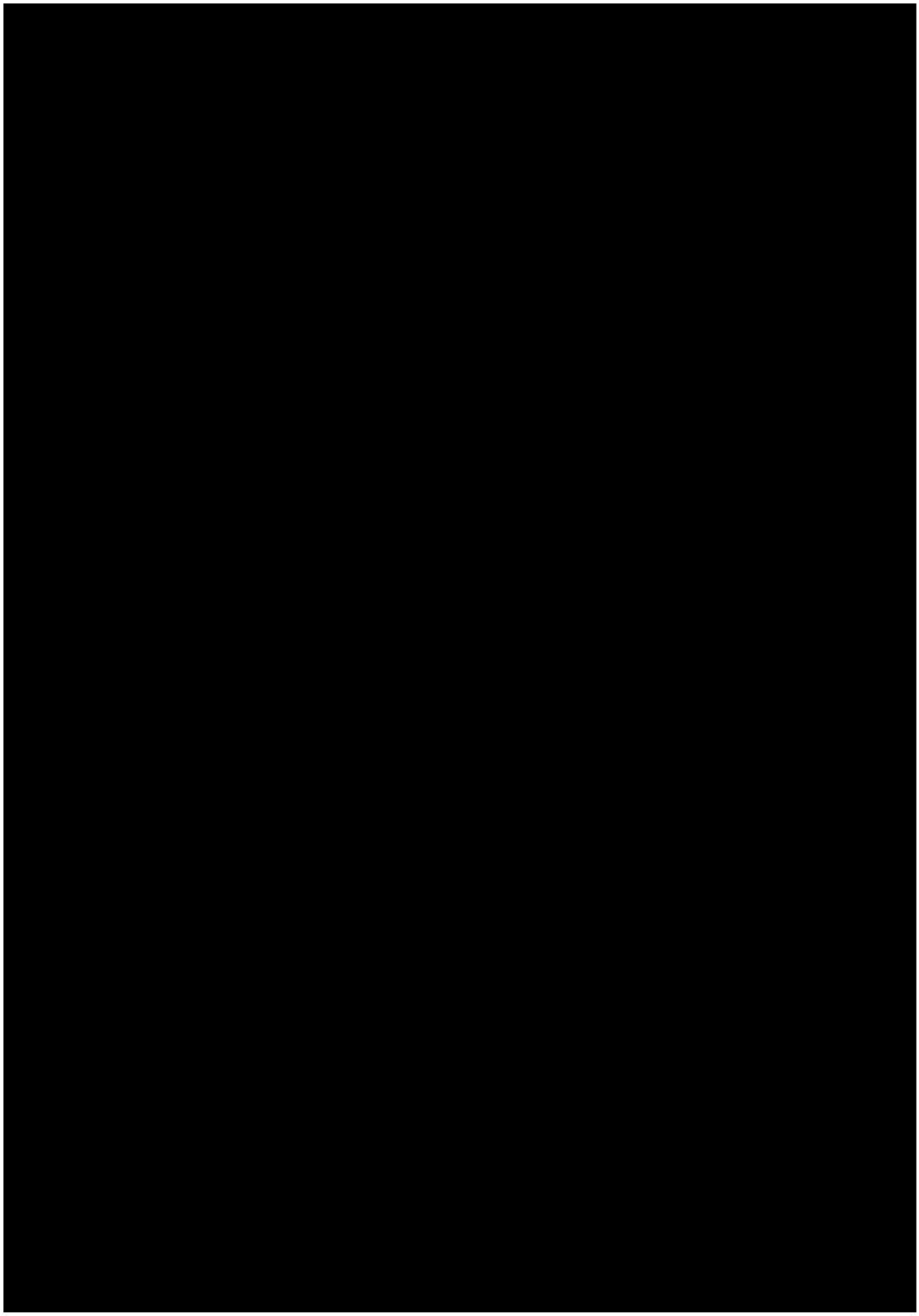
Approximately 200 subjects will be randomly assigned to one of the two treatment groups (1:1) to receive either Reproxalap Ophthalmic Solution (0.25% Novel Formulation) or vehicle solution as topical ophthalmic drops administered bilaterally QID for four weeks followed by BID dosing for weeks 5-12. Subjects, Sponsor, CRO and site personnel will be masked to treatment assignment.

During the screening period, two 90-minute exposures to the CAE® will be conducted to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 84 days. Subjects will self-administer drops daily as instructed.

At Visits 3 - 9, no CAE® exposure will occur but signs and symptoms will be assessed.

All subjects will dose with randomized treatment QID between Visit 2 and Visit 5 and switch to BID dosing between Visit 5 and Visit 9.

The total number of expected participants, including screen failures, is approximately 500 subjects.



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

6 STUDY POPULATION

6.1 Number of Subjects (approximate)

It is estimated that approximately 500 subjects will be screened to enroll approximately 200 randomized subjects (100 in each group). Subjects will be randomized in a 1:1 ratio of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) to Vehicle Ophthalmic Solution.

6.2 Study Population Characteristics

All subjects must be at least 18 years of age, and 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 gender and any race;
2. Provide written informed consent and sign the Health Information Portability and Accountability Act (HIPAA) form;
3. Have a reported history of dry eye for at least 6 months prior to Visit 1;
4. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;
5. Report a score of [redacted] Questionnaire in at least one symptom at Visit 1 and Visit 2 Pre-CAE®;
6. Have a Schirmer's Test [redacted] Visit 1 and Visit 2;
7. Have a tear film break-up time (TFBUT) [redacted] Visit 1 and Visit 2 [redacted]
8. Have a corneal fluorescein staining [redacted] in at least one region (e.g., inferior, superior, or central) at Visit 1 and Visit 2 [redacted]
9. Have a sum corneal fluorescein staining score [redacted] based on the sum of the inferior, superior, and central regions, at Visit 1 and Visit 2 [redacted];
10. Have a total lissamine green conjunctival score [redacted] based on the sum of the temporal and nasal regions at Visit 1 and Visit 2 [redacted]
11. Demonstrate a response [redacted] at Visits 1 and 2 as defined by:

A. Having [redacted] in fluorescein staining in the inferior region in at least one eye [redacted];

B. Reporting an [redacted]

13. Have at least one of the following at Visit 2 [redacted]

A. [redacted]

B. Have a fluorescein staining [redacted] in the nasal region in at least one qualifying eye.

6.4 Exclusion Criteria

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

1. Have any clinically significant slit-lamp findings at Visit 1, including active blepharitis; meibomian gland dysfunction (MGD); lid margin inflammation; or active ocular allergies that require therapeutic treatment, or, in the opinion of the investigator may interfere with the assessment of the safety or efficacy of reproxalap or vehicle;
2. Have or be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal) or active ocular inflammation at Visit 1;
3. Have worn contact lenses within 7 days of Visit 1 or anticipate using contact lenses during the study;
4. Have used any eye drops within 2 hours of Visit 1;
5. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 12 months;
6. Have used ophthalmic cyclosporine or lifitigrast 5.0% ophthalmic solution within 90 days of Visit 1;
7. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within 6 months of Visit 1;
8. Have used temporary or permanent punctal plugs within 30 days prior to Visit 1 or anticipate their use during the study period;

9. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, that cannot be discontinued for the duration of the trial (excluding medications allowed for the conduct of the study);
10. Have corrected visual acuity (VA) [redacted]
11. Be a woman who is pregnant, nursing, or planning a pregnancy during the trial;
12. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 9 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g., has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
13. Be a man or woman of childbearing potential who is not using an acceptable means of birth control; acceptable methods of contraception include: hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom; intrauterine device (IUD); or surgical sterilization of males or 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 study;
14. Have a known allergy and/or sensitivity to reproxalap or the test article excipients;
15. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;
16. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
17. Have previously participated in a reproxalap ophthalmic solution study;
18. Be currently using any medication known to cause ocular drying that has not been used on a stable dosing regimen for at least 30 days prior to Visit 1;
19. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.

6.5 Withdrawal Criteria (if applicable)

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

Subjects may withdraw consent from the study at any time.

The Sponsor and investigators may discontinue any subject for non-compliance, or for any medical reason.

7 STUDY PARAMETERS

7.1 Efficacy Measures and Endpoints

7.1.1 Primary Efficacy Measure(s)

- Subject-reported ocular dryness [redacted]

7.1.2 Primary Efficacy Endpoint

- The primary endpoint is the overall mean change from baseline in subject-reported ocular dryness score [redacted] assessed using MMRM from Week 2 to Week 12. The population used for analysis of ocular dryness score will be subjects who have a baseline ocular dryness score [redacted]

7.1.3 [redacted]

[redacted]

7.1.6 [redacted]

[redacted]

7.1.7 [redacted]

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

7.1.8 Criteria for Effectiveness

The primary endpoint will be achieved if the overall mean change from baseline in subject-reported ocular dryness score [redacted] assessed [redacted] from Week 2 to Week 12, in reproxalap-treated subjects is statistically significantly lower than that of vehicle-treated subjects. The population used for analysis of ocular dryness score will be subjects who have a baseline (Visit 2) ocular dryness score of [redacted]

7.2 Safety Measures

- Visual acuity at distance utilizing an ETDRS chart
- Slit-lamp evaluation
- Adverse event query (reported, elicited and observed)
- IOP
- Dilated fundoscopy

8 STUDY MATERIALS

8.1 Study Treatment(s)

8.1.1 Study Treatment(s)/ Formulation(s):

- Reproxalap Ophthalmic Solution (0.25% Novel Formulation)
- Vehicle Ophthalmic Solution (vehicle)

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 DED treatment. The dosage and dosage regimen were selected based on nonclinical and clinical studies described in Section 2. The proposed treatment period of 12 weeks is based on the Phase 2 clinical trials and on the anti-inflammatory mechanism of action of reproxalap.

8.1.3 Instructions for Use and Administration

- Reproxalap and vehicle are supplied as patient kits, with each kit containing 15 foil pouches, and each foil pouch containing five single-dose units.
- The vehicle solution consists of all components of the drug product solution with the exception of reproxalap.
- At the study site, all Investigational Product (IP) must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated qualified clinical site personnel. All IP must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Council on Harmonisation (ICH) Good Clinical Practices (GCPs) and study procedures.
- Reproxalap and vehicle should be stored refrigerated (2–8° C). Subjects will be instructed to store reproxalap and vehicle in a refrigerator (2–8° C). Five cavity unit dose ampules are packaged in aluminum foil pouches under nitrogen. Unit dose ampules are for SINGLE USE ONLY.
- Subjects will receive four treatment kits. After Visit 5 all subjects will change their dosing regimen from QID to BID for the remainder of the treatment period.
- At a minimum, the immediate or secondary study drug packaging will provide the following information: study Sponsor identification, directions for use, required storage conditions, caution statements (including "New Drug–Limited by Federal Law to Investigational Use" language), and study identification.

8.2 Other Study Supplies

Other study supplies include urine pregnancy tests, Schirmer's test strips, sodium fluorescein, lissamine green, Fluress, Tropicamide, VAS rulers, and Tear Osmolarity cards.

9 STUDY METHODS AND PROCEDURES

9.1 Subject Entry Procedures

9.1.1 Overview

Subjects as defined by the criteria in sections 6.3, 6.4, and 6.5 will be considered for entry into this study.

9.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form. The informed consent form must be the most recent version

that has received approval/favorable review by a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

9.1.3 Washout Intervals

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

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

Subjects are to be stratified by Visit 2 (Baseline) [redacted] and Visit 2 (Baseline) Pre-CAE fluorescein nasal staining score in the study (worst) eye using the following strata:

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

[redacted] will continue until the sample size for the co-primary analysis described in Section 11.3 has been achieved.

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

The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). The Sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

9.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding case report form (CRF) along with the reason the medication was taken.

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

9.2.1 Prohibited Medications/Treatments

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

9.2.2 Escape Medications

No escape medications are required for this study.

9.2.3 Special Diet or Activities

No special diets or activities are required for this study.

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 given order. See Appendix 2 on methodologies and grading systems.

9.3.2 Visit 1: Day -14 ± 2 – [redacted]

All subjects will undergo the following screening assessments:

[redacted]

- [redacted] Consent/HIPAA
- Demographic Data and Medical/Medication/Ocular History
- Review of Inclusion/Exclusion Criteria
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- Fluorescein Staining (corneal and conjunctival)
- Lissamine Green Staining (corneal and conjunctival)

[redacted]

[redacted]

- [redacted]

[redacted]

- Slit Lamp Biomicroscopy

[redacted]

- IOP
- Dilated Fundoscopy
- Review of Inclusion/Exclusion Criteria
- Run-in Instillation at the Study Site: All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria at the end of Visit 1 will receive run-in drops for dosing. Qualified subjects will self-administer their initial run-in dose bilaterally at the study site under the supervision of a trained technician.
- Run-in Dispensation: Prior to discharge from the study site on Day -14, subjects will be dispensed sufficient Run-in supply to last until Visit 2 and will be educated on self–administration of vehicle run-in. Subjects will be instructed to self–administer one drop QID in each eye until Visit 2. Subjects will be instructed NOT to instill run-in on the morning of their next scheduled study visit (Visit 2).
- AE Query
- Subjects will be scheduled for Visit 2.

9.3.3 Visit 2: Day 1 – [redacted] Confirmation and Baseline

[redacted]

- Study Run-in Collection
- Review of Inclusion/Exclusion Criteria
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]

- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- At least 15-minute wait between lissamine green staining and Schirmer's test

[redacted]

- [redacted]
  - [redacted] every 5 minutes thereafter;

[redacted]

- Slit Lamp Biomicroscopy

[redacted]

- Review of Inclusion/Exclusion Criteria
- Randomization
- Study Drug Instillation at the Study Site: All subjects having a positive response (as defined above) and meeting all other screening eligibility criteria at the end of Visit 2 will be randomized to one of two treatment groups utilizing the IWRS system. Randomized subjects will self-administer their initial study drug dose bilaterally at the study site under supervision of a trained technician. Subjects will be instructed to dose four times a day (QID) in both eyes until their next visit.
- Study Drug Dispensation: Prior to discharge from the study site on Visit 2 (Day 1), randomized subjects will be educated on self–administration of study drug. Subjects

will receive their assigned study drug kit with sufficient supply to last until Visit 3 and will be instructed NOT to self–administer study drug on the morning of their next scheduled study visit (Visit 3).

- AE Query
- Subjects will be scheduled for Visit 3.

9.3.4 Visit 3 (Day 8 ± 2)

- Study Drug Collection
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy
- [redacted]
- Study Drug Dispensation: Prior to discharge from the study site on Visit 3, subjects will be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 4. Subjects will be reinstructed to dose four times a day (QID) in both eyes until their next visit.
- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 4)
- AE Query
- Subjects will be scheduled for Visit 4.

9.3.5 Visit 4 (Day 15 ± 2)

- Study Drug Collection

- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- Study Drug Dispensation: Prior to discharge from the study site on Visit 4, subjects will be assigned a new study drug kit via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 5. Subjects will be reinstructed to dose four times a day (QID) in both eyes until their next visit.
- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 5)
- AE Query
- Subjects will be scheduled for Visit 5.

9.3.6 Visit 5 (Day 29 ± 2)

- Study Drug Collection
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]

- [redacted]
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- Study Drug Dispensation: Prior to discharge from the study site on Visit 5, subjects will be assigned a new study drug kit via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 6.
- Subjects will now switch to the BID treatment regimen. Subjects will be instructed to dose twice a day (BID) in each eye through the end of the treatment period.
- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 6)
- AE Query
- Subjects will be scheduled for Visit 6.

9.3.7 Visit 6 (Day 43 ± 2)

- Study Drug Collection
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- BCVA Utilizing an ETDRS Chart

- Slit Lamp Biomicroscopy

- Study Drug Dispensation: Prior to discharge from the study site on Visit 6, subjects will be re-dispensed the remaining unused ampules from their previous kits for at-home dosing up to Visit 7. Subjects will be reinstructed to dose BID in both eyes until their next visit.
- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 7)
- AE Query
- Subjects will be scheduled for Visit 7.

9.3.8 Visit 7 (Day 57 ± 3)

- Study Drug Collection
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

- Study Drug Dispensation: Prior to discharge from the study site on Visit 7, subjects will be assigned a new study drug kit via the IWRS and will also be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 8. Subjects will be reinstructed to dose BID both eyes until their next visit.

- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 8)
- AE Query
- Subjects will be scheduled for Visit 8.

9.3.9 Visit 8 (Day 71 ± 3)

- Study Drug Collection
- Medical/medication history update
- AE query
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- Study Drug Dispensation: Prior to discharge from the study site on Visit 8, subjects will be re-dispensed the remaining unused ampules from their previous kit for at-home dosing up to Visit 9. Subjects will be reinstructed to dose BID in both eyes until their next visit.
- Subjects will again be educated on self–administration of study drug. Subjects will be instructed to NOT self–administer study drug on the morning of their next scheduled study visit (Visit 9)
- AE Query
- Subjects will be scheduled for Visit 9.

9.3.10 Visit 9 (Day 85 ± 3)

- Study Drug Collection

- Medical/medication history update
- AE query
- Urine Pregnancy Test (for females of childbearing potential): Women of childbearing potential must have a negative urine pregnancy test to continue in the study
- Multi-symptom Visual Analogue Scale (VAS)
- [redacted]
- BCVA Utilizing an ETDRS Chart
- Slit Lamp Biomicroscopy

[redacted]

- IOP
- Dilated Fundoscopy
- AE Query
- Study Exit

9.3.11 Early Termination/Discontinuation

If a subject is discontinued from the study prior to Visit 9 (Day 85 ± 3), then all safety evaluations that are to be performed at Visit 9 should be performed on the day of discontinuation (early termination) or at the discretion of the investigator.

9.3.12 General Safety Measures

As specified in each visit procedure, adverse events (AEs) (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be

promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate eCRF.

If a female has a positive pregnancy test during the study, then 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.

9.4 Schedule of Visits, Measurements and Dosing

9.4.1 Scheduled Visits

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

9.4.2 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 concomitant medications and/or treatments
- Any other assessments needed in the judgment of the investigator.

9.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1 through 8 and given written instructions. The subject's used and unused study drug ampules will be collected at each visit from Visit 2 up to and including Visit 9 to assess dosing compliance. Dosing compliance will be based on the unused ampule count.

[redacted]

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

9.6 Subject Disposition

9.6.1 Completed Subjects

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

9.6.2 Discontinued Subjects

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

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- Sponsor termination of study
- 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/or Sponsor and will be clearly documented on the eCRF.

9.7 Study Termination

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

9.8 Study Duration

An individual subject's participation will involve nine visits over approximately a 14-week (~98 days) period (84 days of treatment and 14 days pre-screening).

9.9 Monitoring and Quality Assurance

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

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

10 ADVERSE EVENTS

10.1 Adverse Event

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

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

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

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 to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

[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 definitions 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 Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- ***Expected:*** An AE that is listed in the 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 Medical Monitor's determination.

10.2 Serious Adverse Events

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

- Death;
- A life-threatening AE;

Note: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, 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 (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

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

10.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, 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 CRF. Adverse Events will be collected after the signing of the Informed Consent.

10.3.1 Reporting a Suspected Unexpected Adverse Reaction

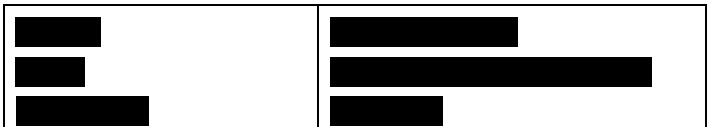
All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

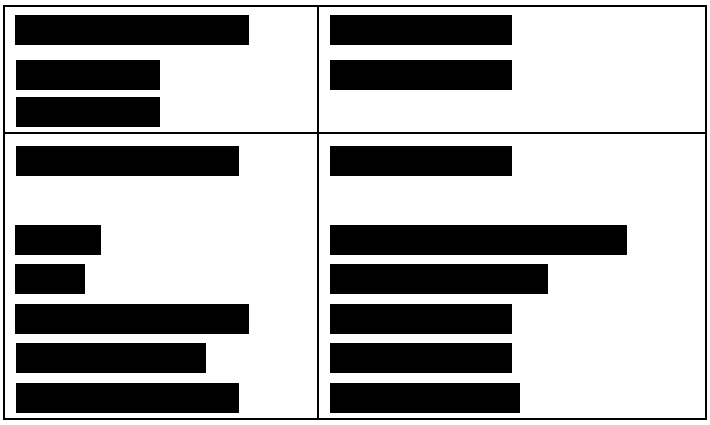
10.3.2 Reporting a Serious Adverse Event

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

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

Contact information for reporting SAEs:





10.4 Procedures for Unmasking (if applicable)

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

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify 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 using IWRS. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the TMF. For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study.

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

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

serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

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

11 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

11.1 Analysis Populations

The following analysis populations will be considered:

- Intent-to-Treat Population – The intent-to-treat (ITT) population includes all randomized subjects. Subjects in the ITT population will be analyzed as randomized.

- Per-Protocol Population – The per-protocol (PP) population includes subjects in the ITT population who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. Subjects in the PP population will be analyzed as treated.

- Safety Population – The safety population includes all randomized subjects who have received at least one dose of the investigational product. Subjects in the safety population will be analyzed as treated.

[redacted]

The primary analysis of ocular dryness score [redacted] will be performed on [redacted] The population used for analysis of fluorescein nasal region score will be performed on ITTFSN. The population used for analysis [redacted] will be performed on ITTOD. The analysis of other secondary efficacy endpoints (except ocular dryness and fluorescein nasal) will be performed for the ITT population and on the PP population as sensitivity analyses. The statistical analysis of safety data will be performed for the safety population.

11.2 Statistical Hypotheses

The following hypothesis will be tested comparing reproxalap to vehicle at 12 weeks. The null hypotheses must be rejected for the dosing regimen to claim efficacy.

[redacted]

11.3 Sample Size

Based on the results of a Phase 2b clinical trial of reproxalap in dry eye disease subjects (ADX-102-DED-009), for the outcome measurements of ocular dryness VAS score and nasal fluorescein staining, approximately 100 subjects per randomized arm will be evaluated in ADX-102-DED-013. Sample size estimates were made assuming an alpha of 0.05 and power of 90% for the two efficacy populations, one with baseline staining severity of 2 units or more and the other with dryness score severity of 3 units or more. Using PASS (software version 14, NCSS, LLC), the sample size estimated for staining was 39 per treatment arm (78 total); the sample size estimated for dryness score was 54 per treatment arm (108 total).

11.4 Statistical Analysis

11.4.1 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 WHO Drug dictionaries, as appropriate.

Baseline measures are defined as the last non-missing measure prior to the initiation of randomized study treatment at Day 1. Change from baseline will be calculated as follow-up visit value minus baseline value. Treatment comparisons between active and vehicle will be matched by dosing regimen and calculated as active minus vehicle.

All analyses will be 2-sided at a significance level of 0.05. 95% confidence intervals will be provided where appropriate.

The statistical analysis plan (SAP) will serve as the final determinant of the statistical procedures, notwithstanding anything herein.

11.4.2 Unit of Analysis

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

[redacted]

11.4.3 Missing Data

The primary analyses using MMRM method will be performed on the ITTOD and ITTFSN population with observed data only. Efficacy analyses may also be conducted using the ITT, ITTOD, and ITTFSN populations with multiple imputation under missing at random (MAR) and missing not at random (MNAR) assumptions. Per-protocol population analysis may also be conducted to assess sensitivity. Further detail will be described in the SAP.

11.4.4 Multiplicity Considerations

A sequential (closed) testing procedure will be used to control the overall Type I error rate due to multiple comparisons for the primary, key secondary and secondary endpoint of fluorescein nasal staining score. The order of treatment comparisons is as follows:

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

11.4.5 Primary Efficacy Analysis

The overall mean change from baseline in [redacted] from Week 2 to Week 12 will be analyzed using [redacted] in subjects in the ITTOD population.

The [redacted] will be fit with baseline value, treatment and visit, as well as the two-way interaction between treatment and visit. Change from baseline of the variable of interest (either ocular dryness or fluorescein nasal staining) will be the dependent variable.

An unstructured covariance structure will be used to model the within-patient correlation over time. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. If the unstructured covariance structure matrix results in a lack of convergence under the default fitting algorithm used by PROC MIXED, the model will be fit using covariance matrices of the following order until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

All the data from the two treatment groups will be included in the models. Comparisons between two treatment groups (for example, between reproxalap and vehicle) at a given visit or for combined visits will be obtained by comparing the corresponding least squares means via customized SAS statements in the model.

Change from baseline will also be analyzed using ANCOVA models with terms for baseline value and treatment group, two-sample t-tests, and Wilcoxon rank sum tests as sensitivity analyses.

[redacted]

[redacted]

- [redacted]
- [redacted]

Further details of the analysis plan will be described in statistical analysis plan document (SAP).

[redacted]

11.4.9 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).

Other safety endpoints including visual acuity, slit lamp biomicroscopy, intraocular pressure (IOP), tear osmolarity and dilated fundoscopy will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, worst eye (study eye) and fellow eye will be summarized separately.

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

This study will be conducted in compliance with the protocol, current GCPs, 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/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. 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 informed consent/assent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC

and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

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

12.1.2 Institutional Review Board (IRB) Approval

This study 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 study 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

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

12.3 Subject Confidentiality

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

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

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

12.4 Documentation

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

12.4.1 Retention of Documentation

All study-related correspondence, subject records, consent forms, record of the distribution and use of all IP, and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until

there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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.

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12.5.3 Accountability of Investigational Product

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

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

12.5.4 Return or Disposal of Investigational Product

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

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

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

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff who have been trained on the system and have access to the system. Data will 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 study and database lock, compact discs (CDs) containing copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

12.7 Publications

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

13 REFERENCES

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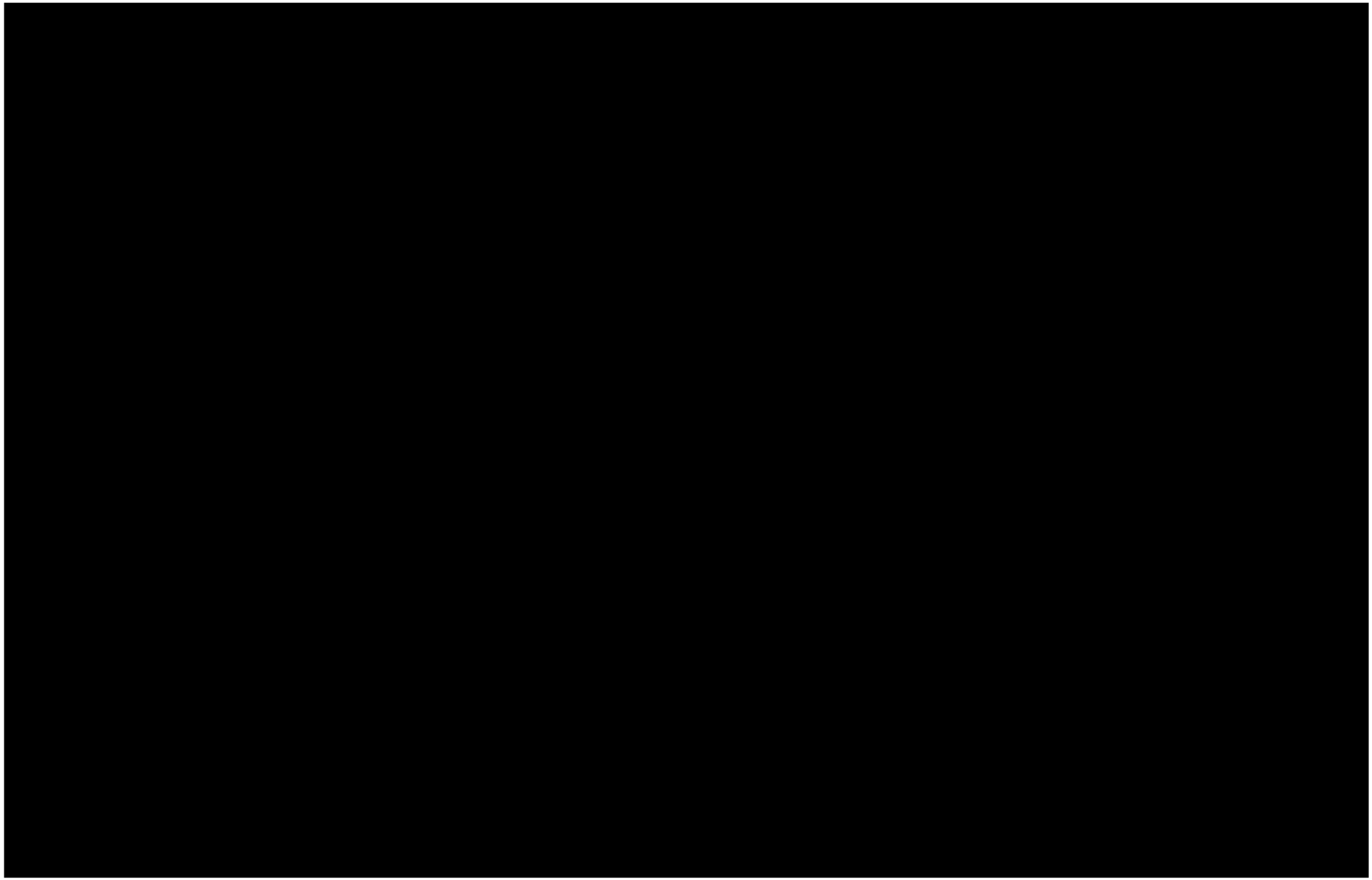
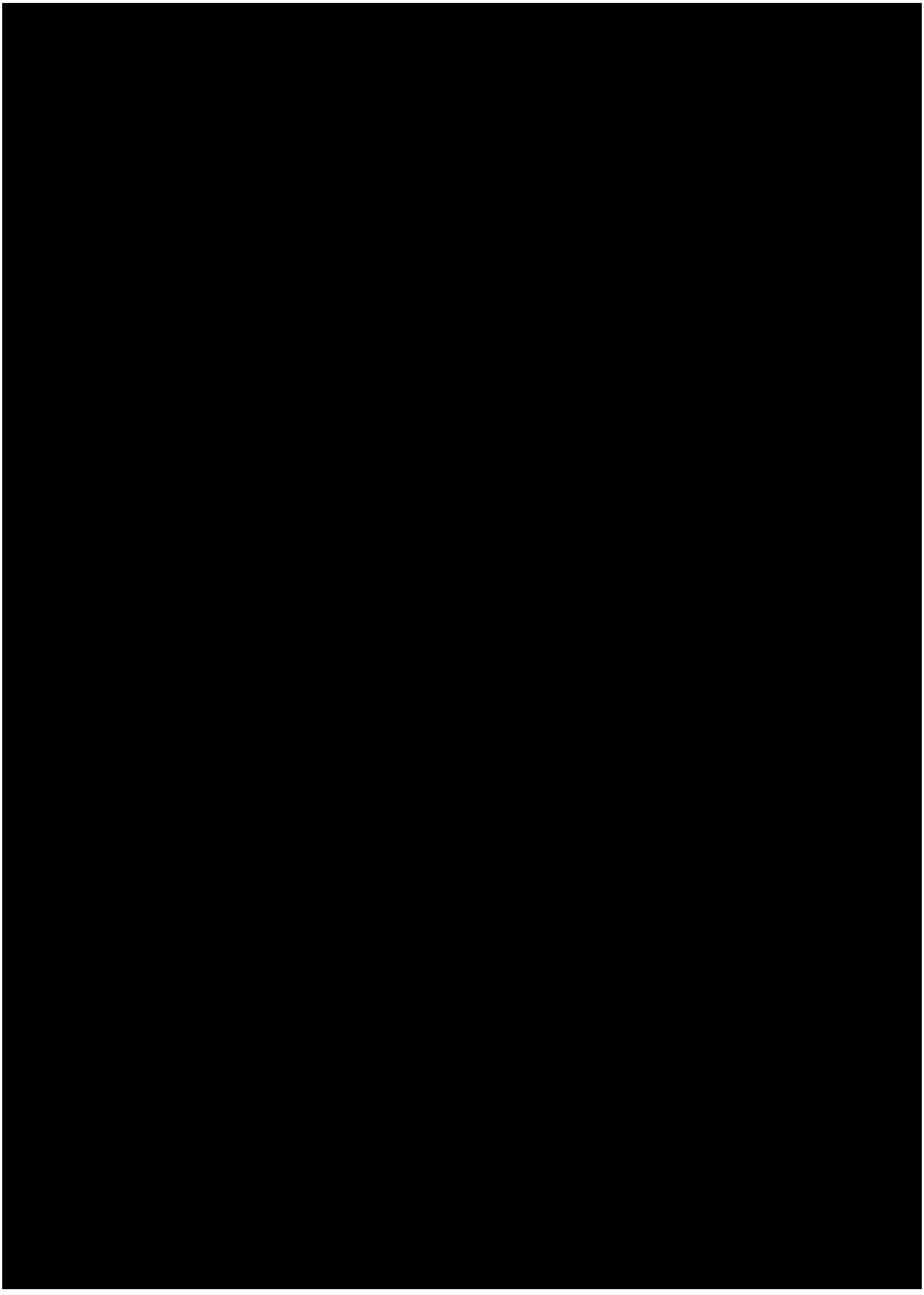
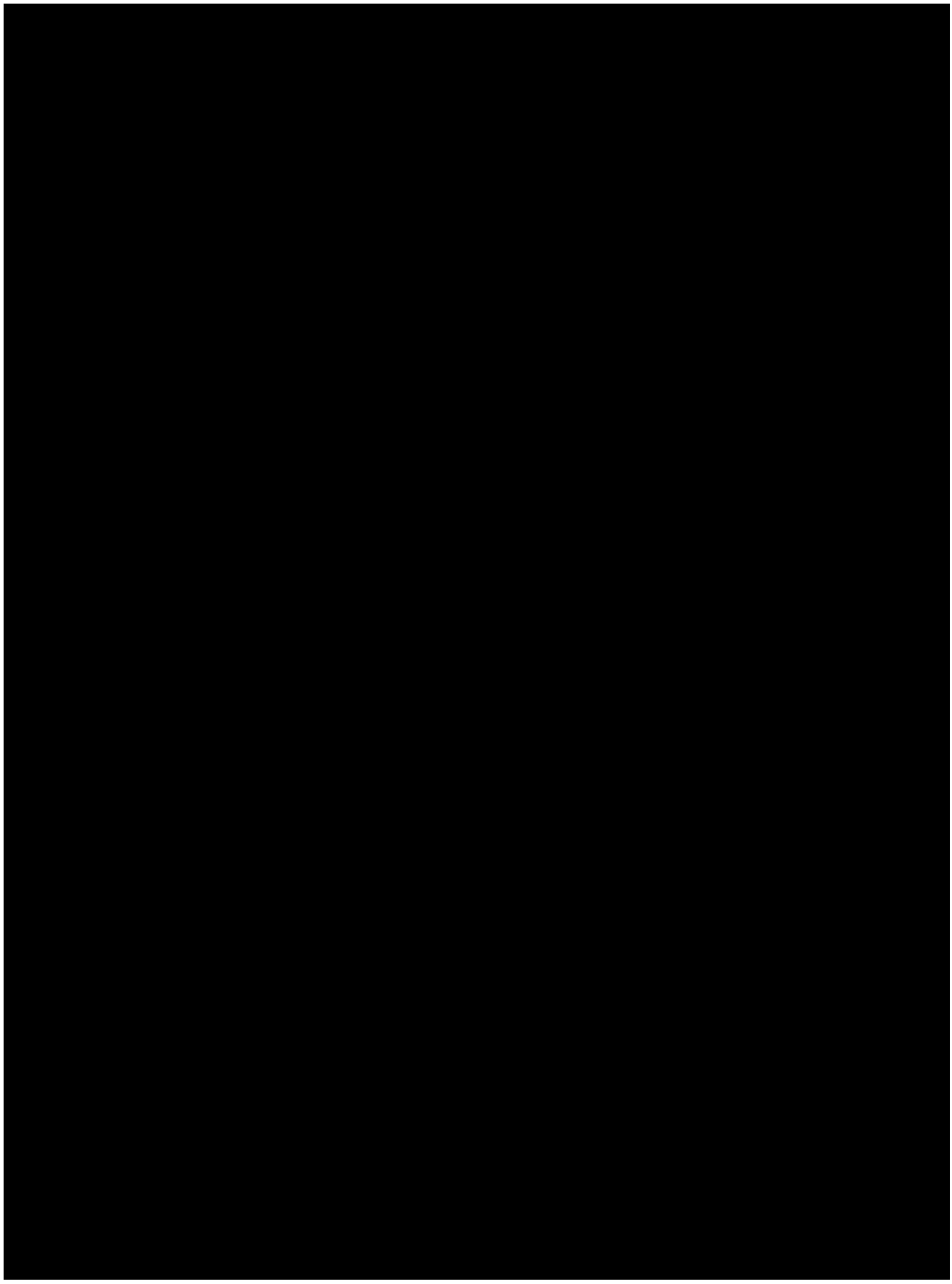
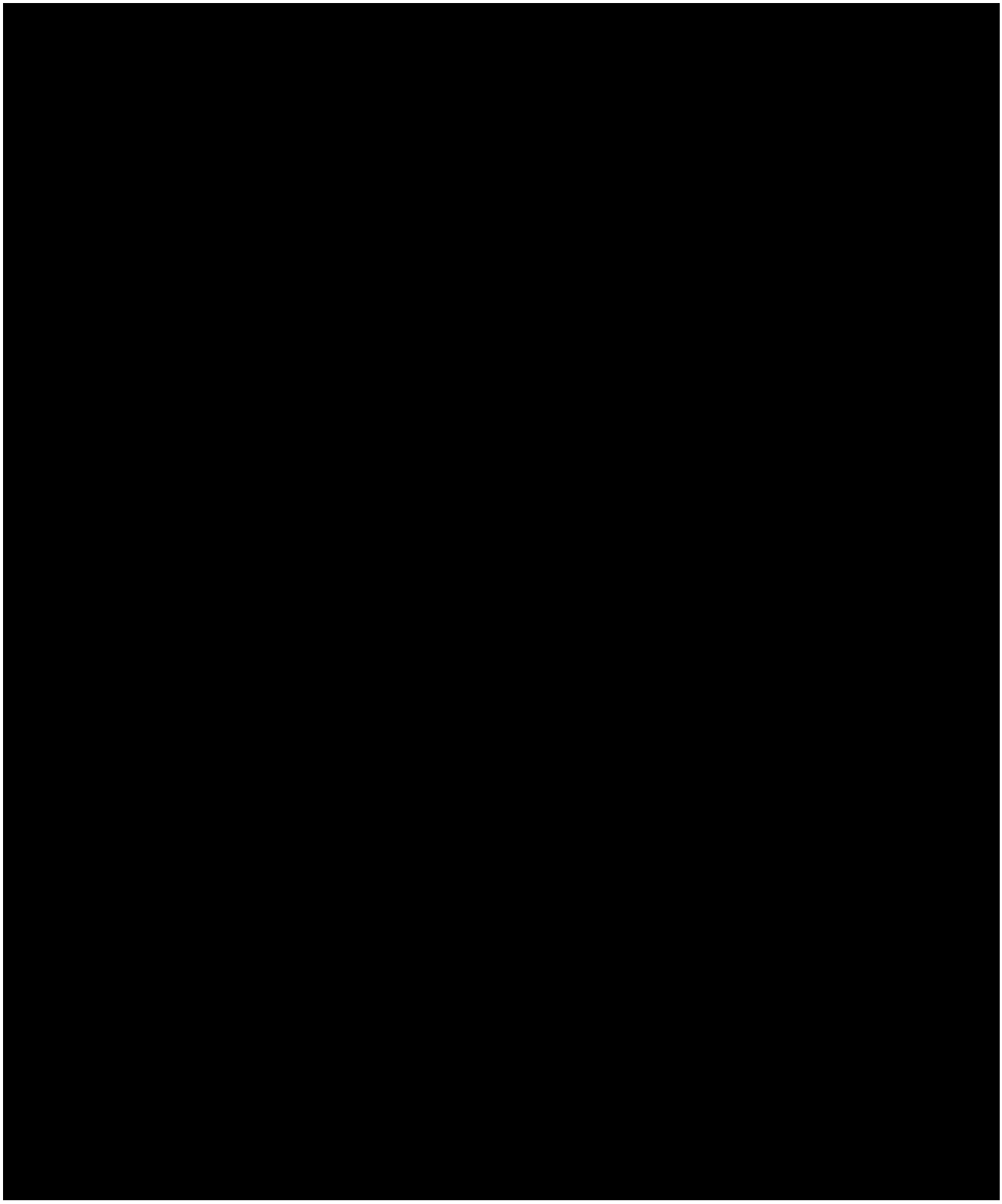
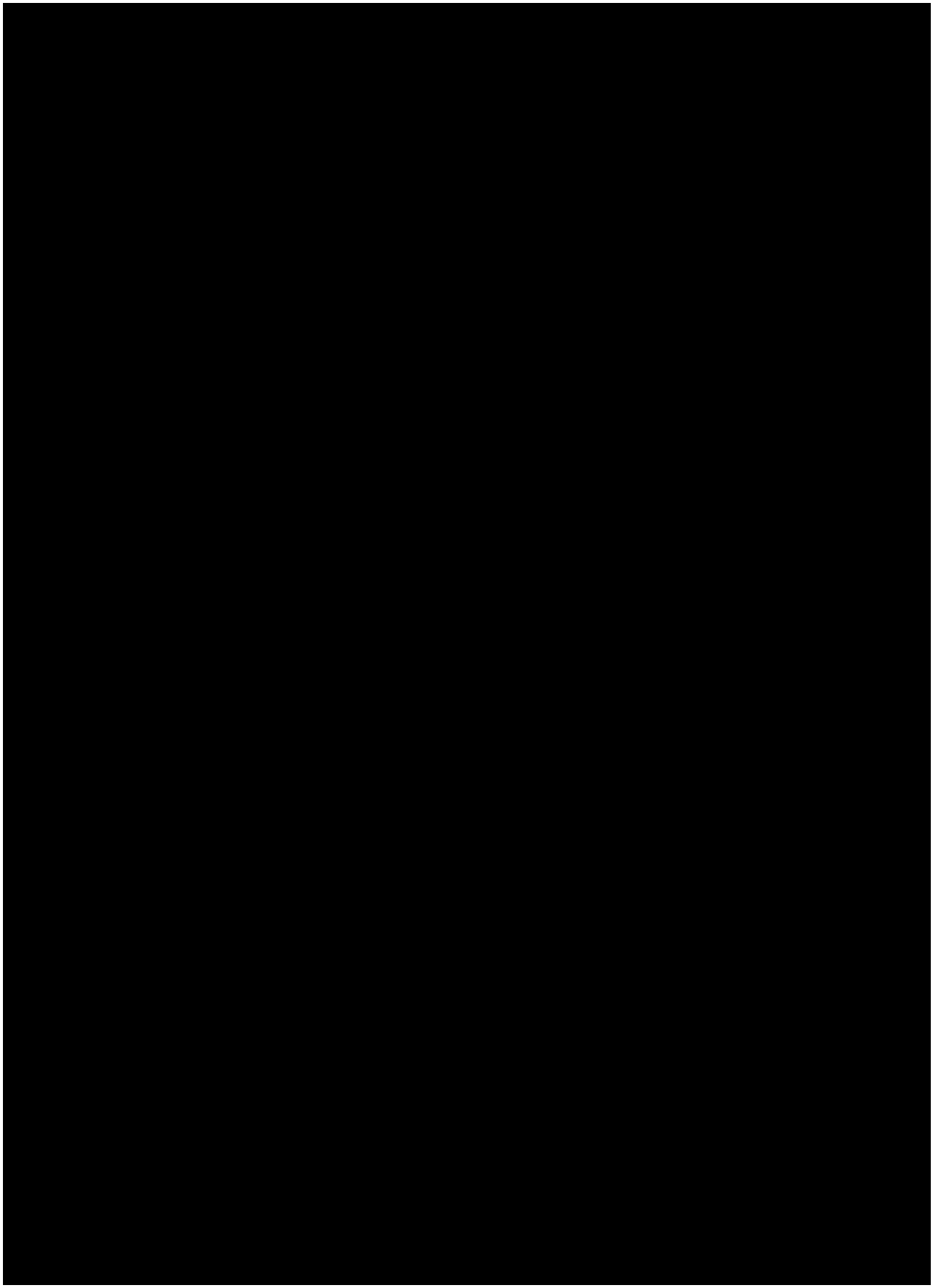
14 Appendices

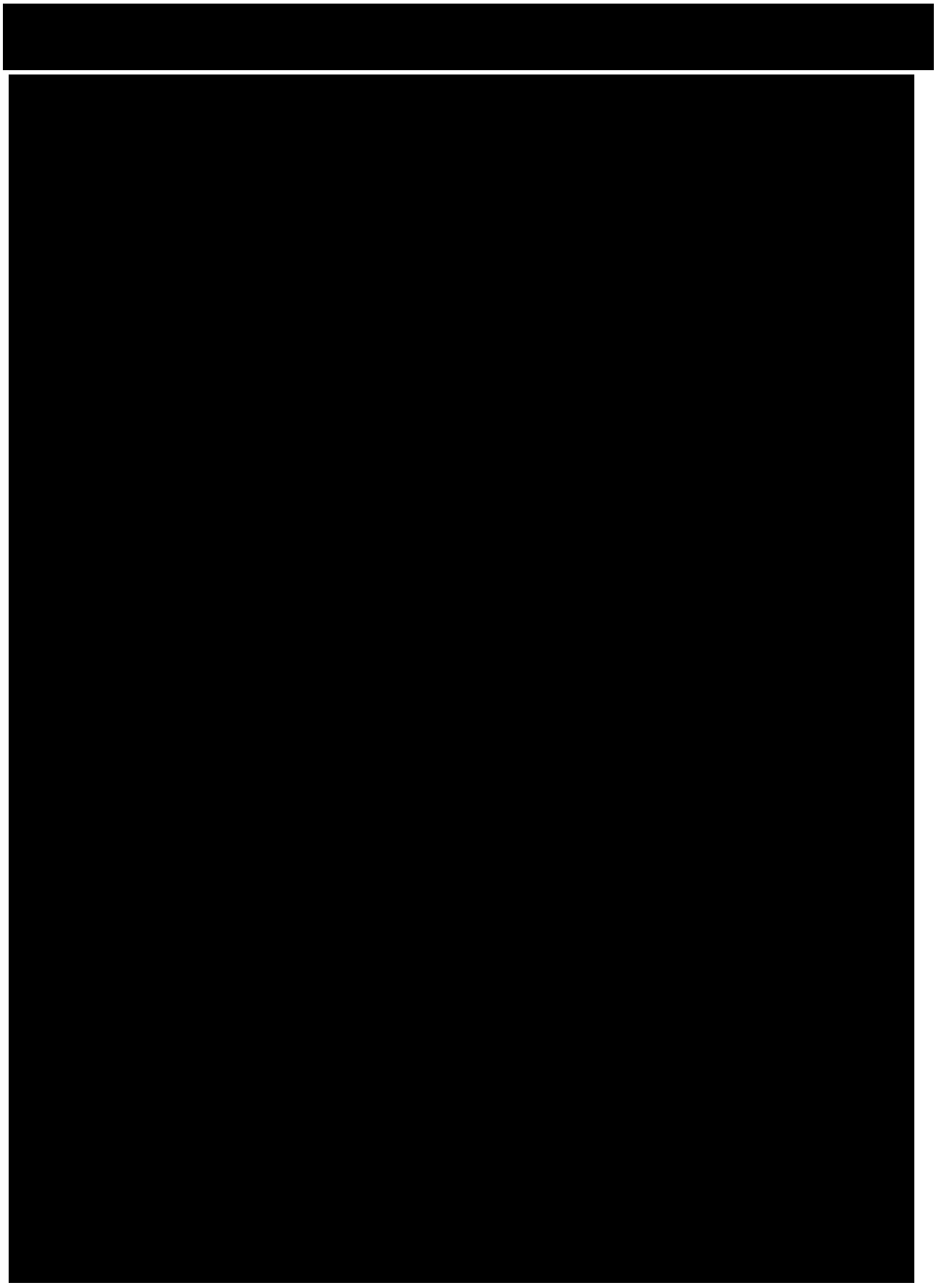


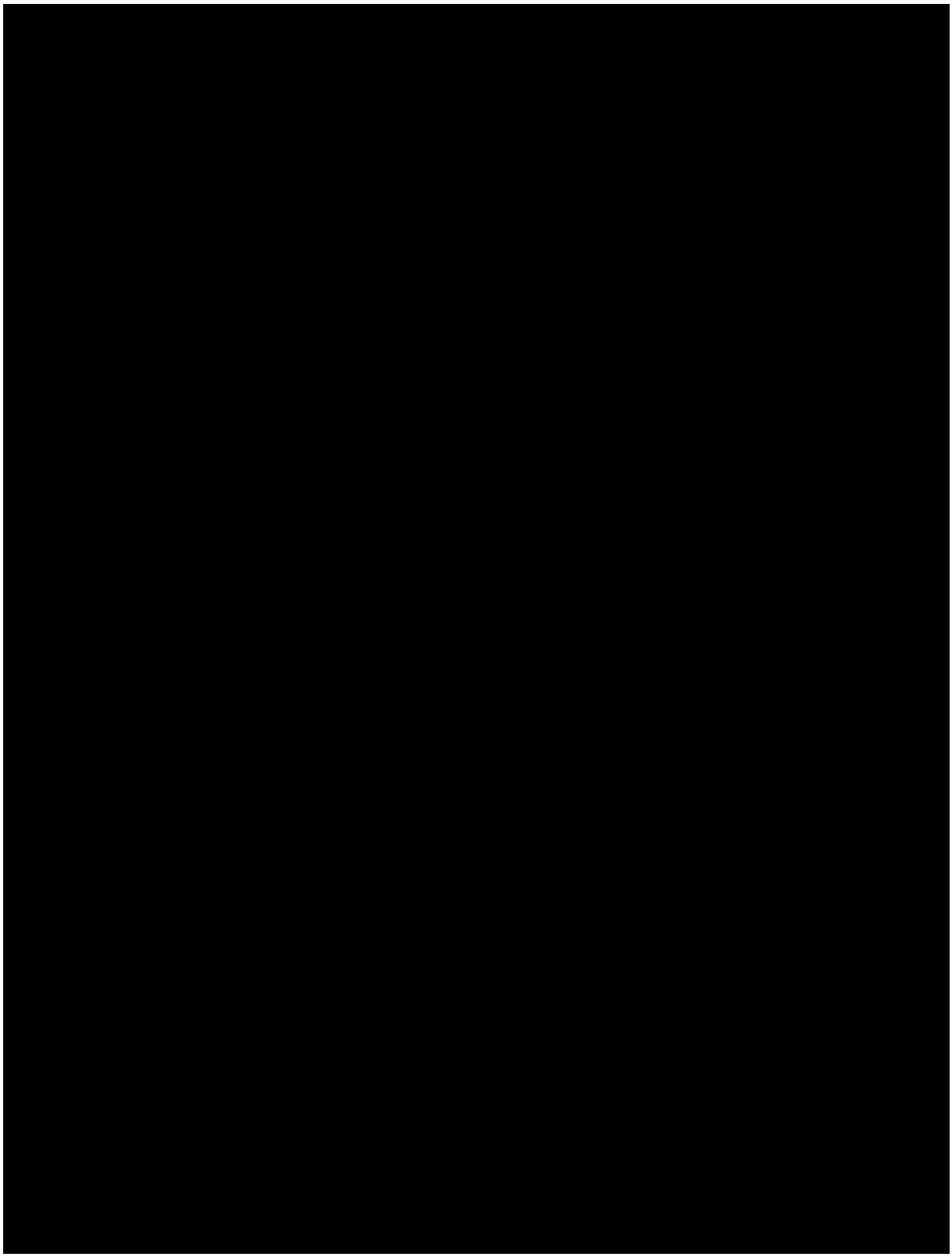


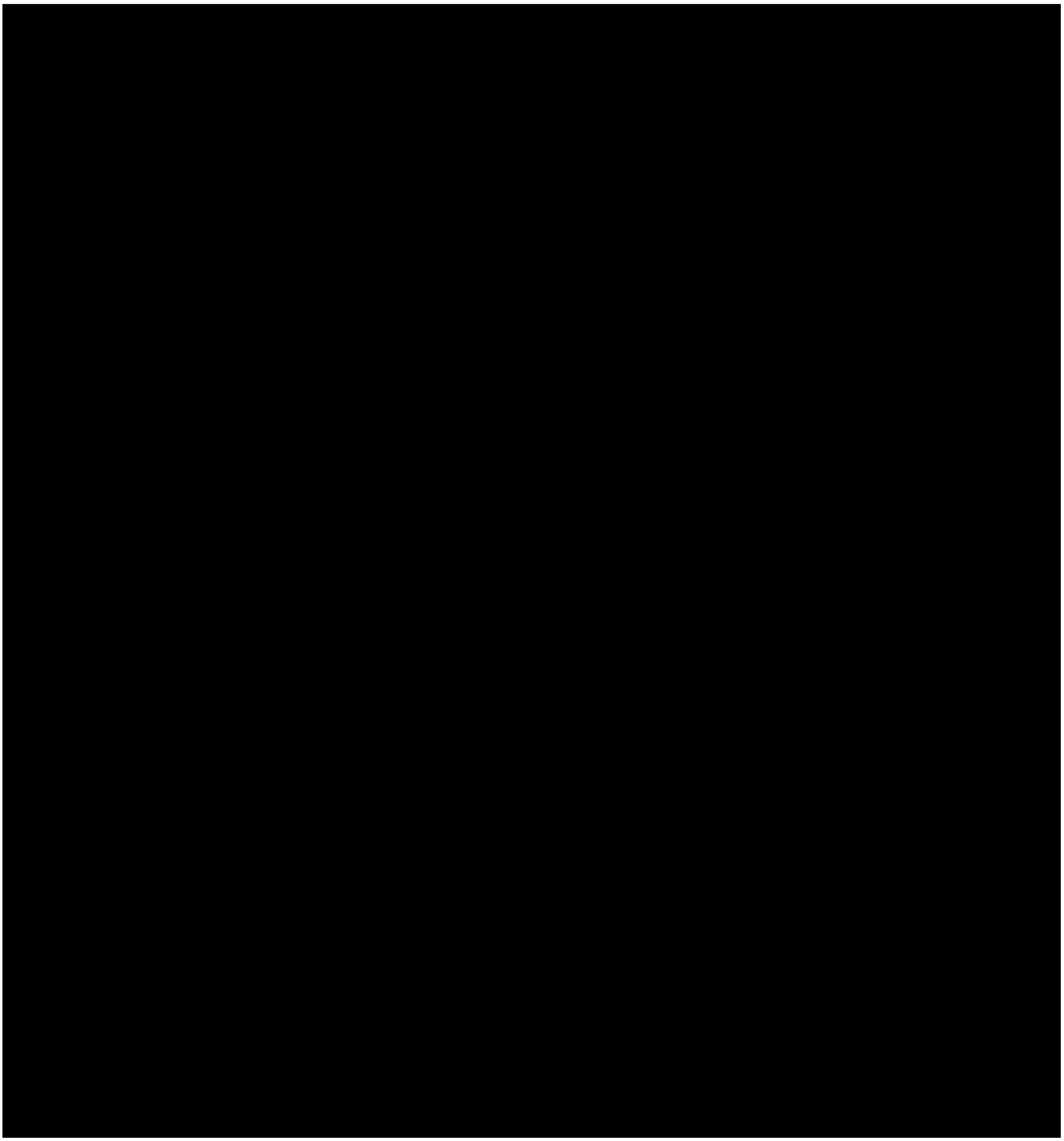












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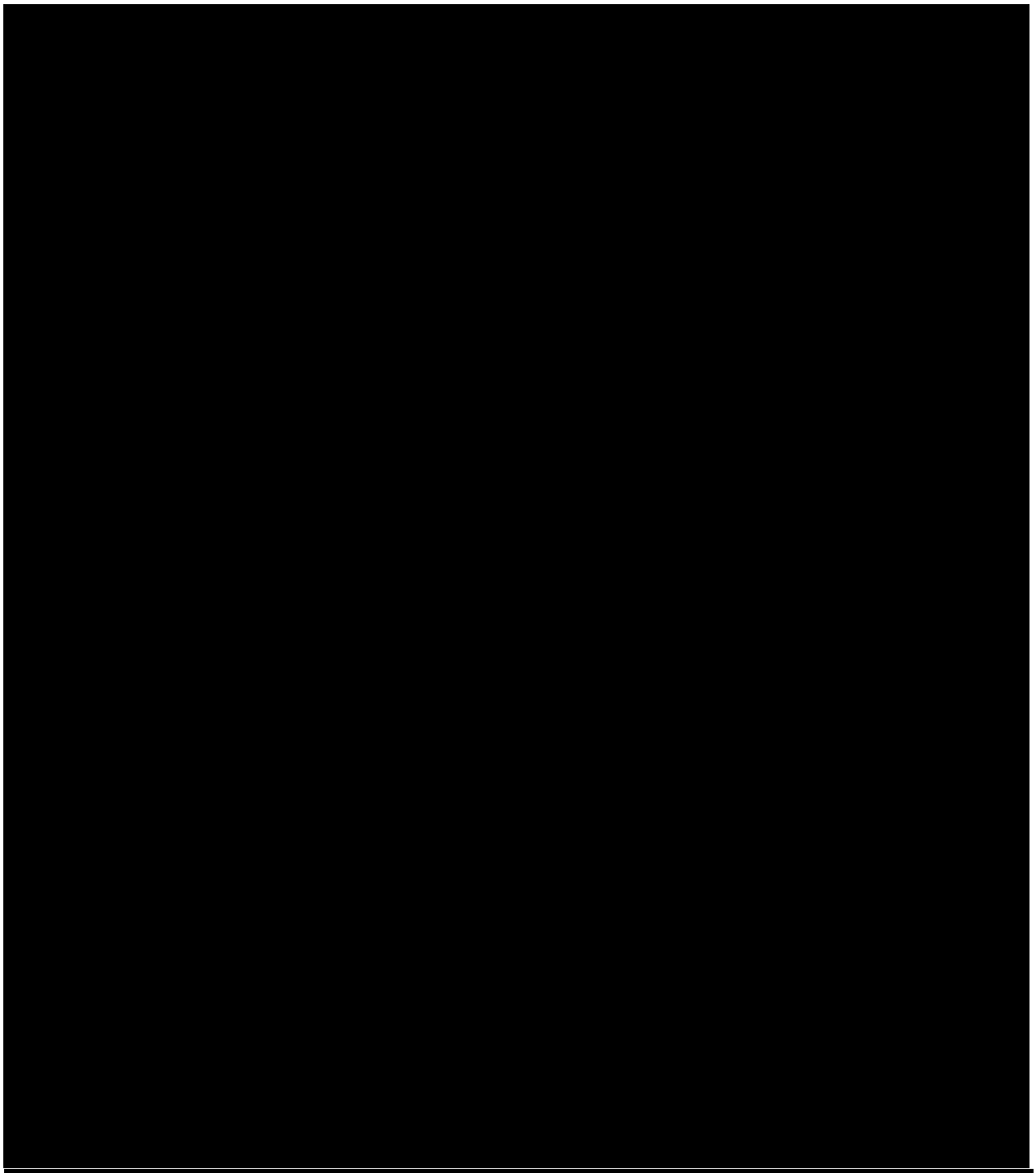
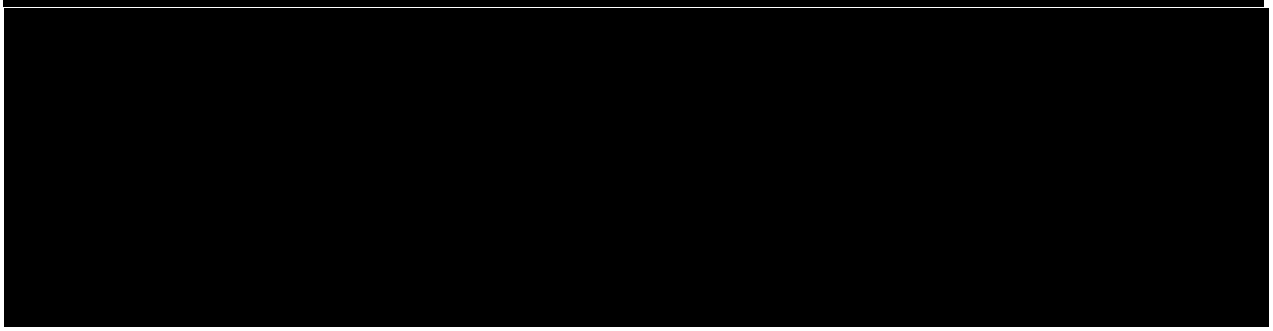
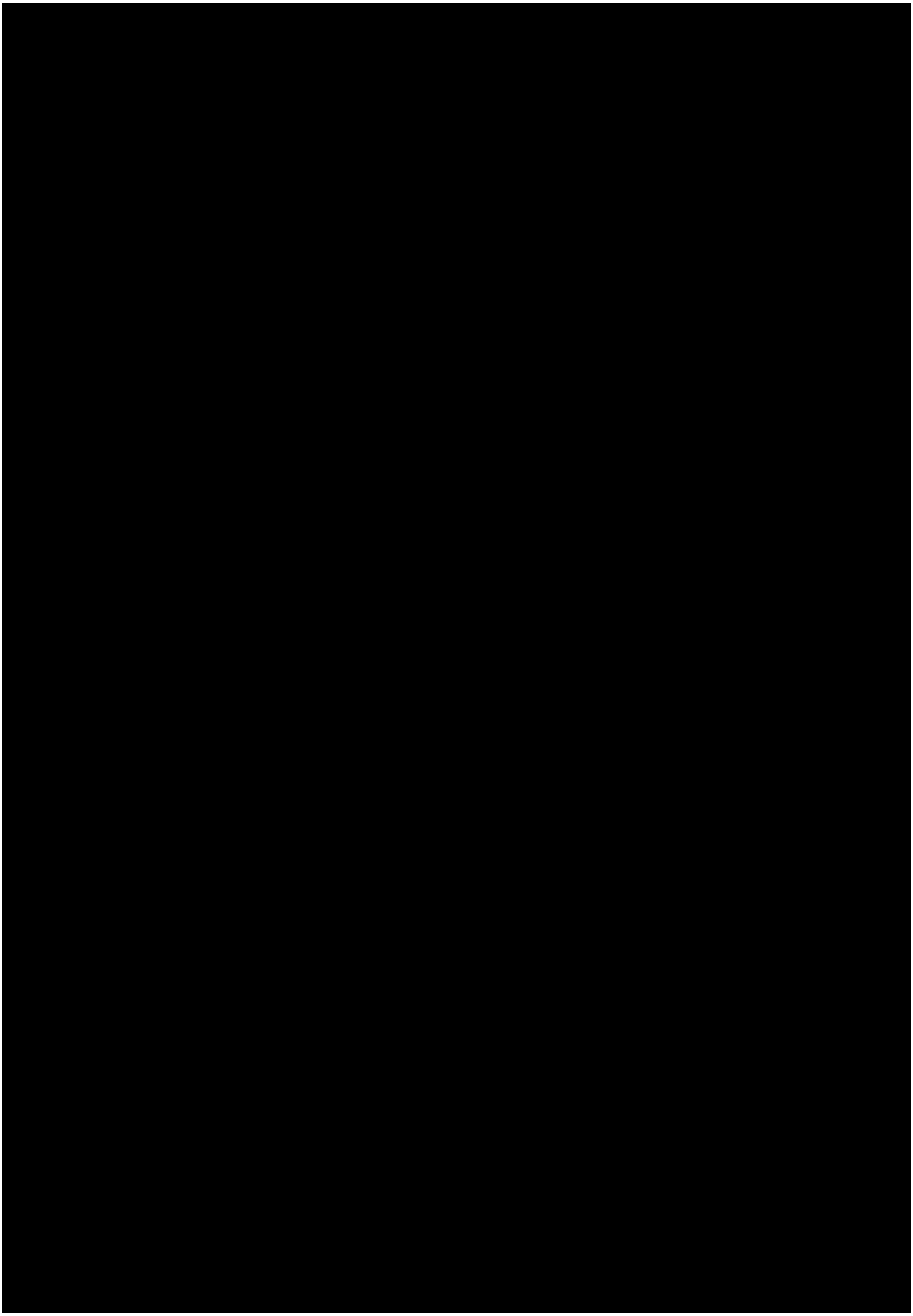
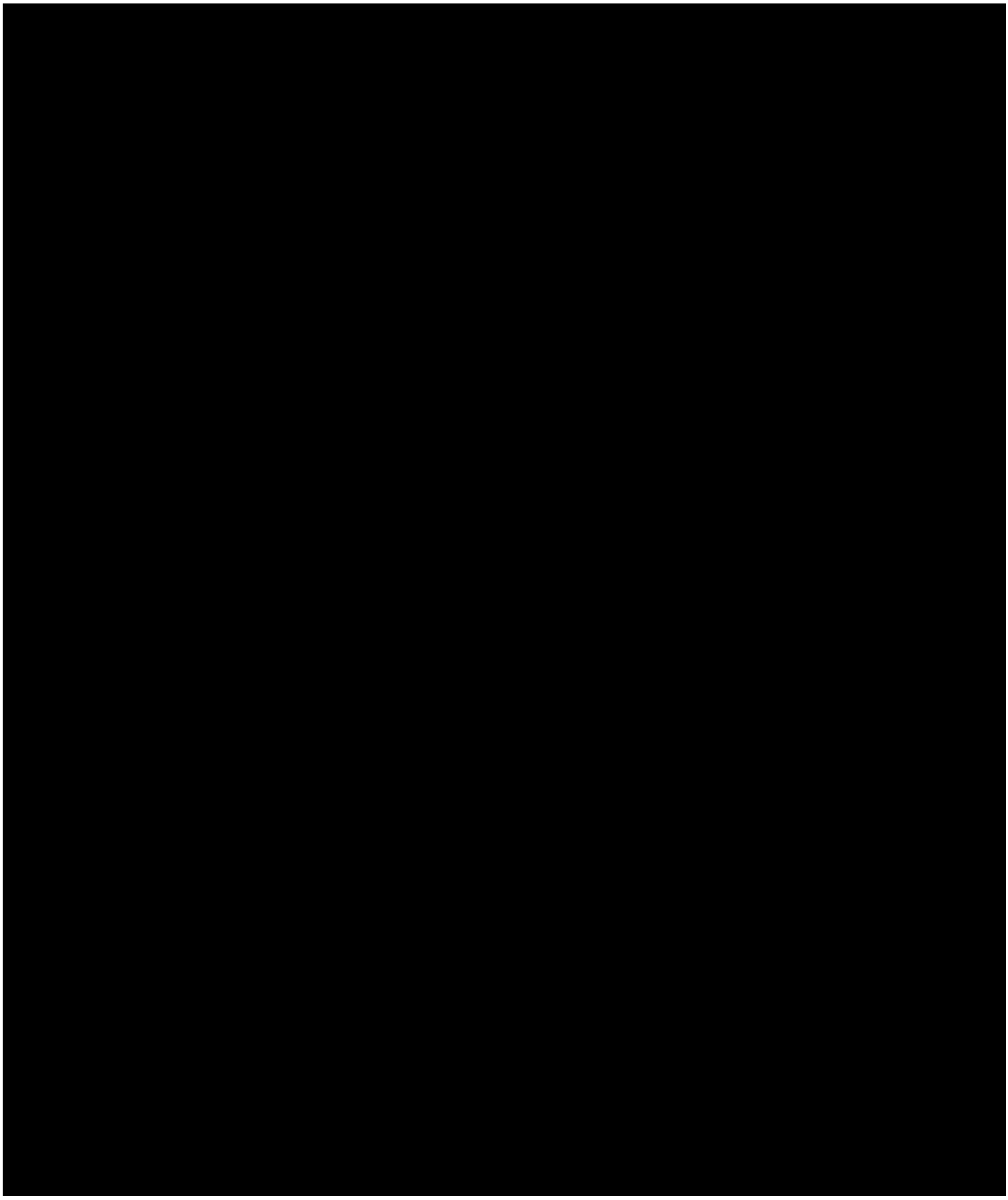
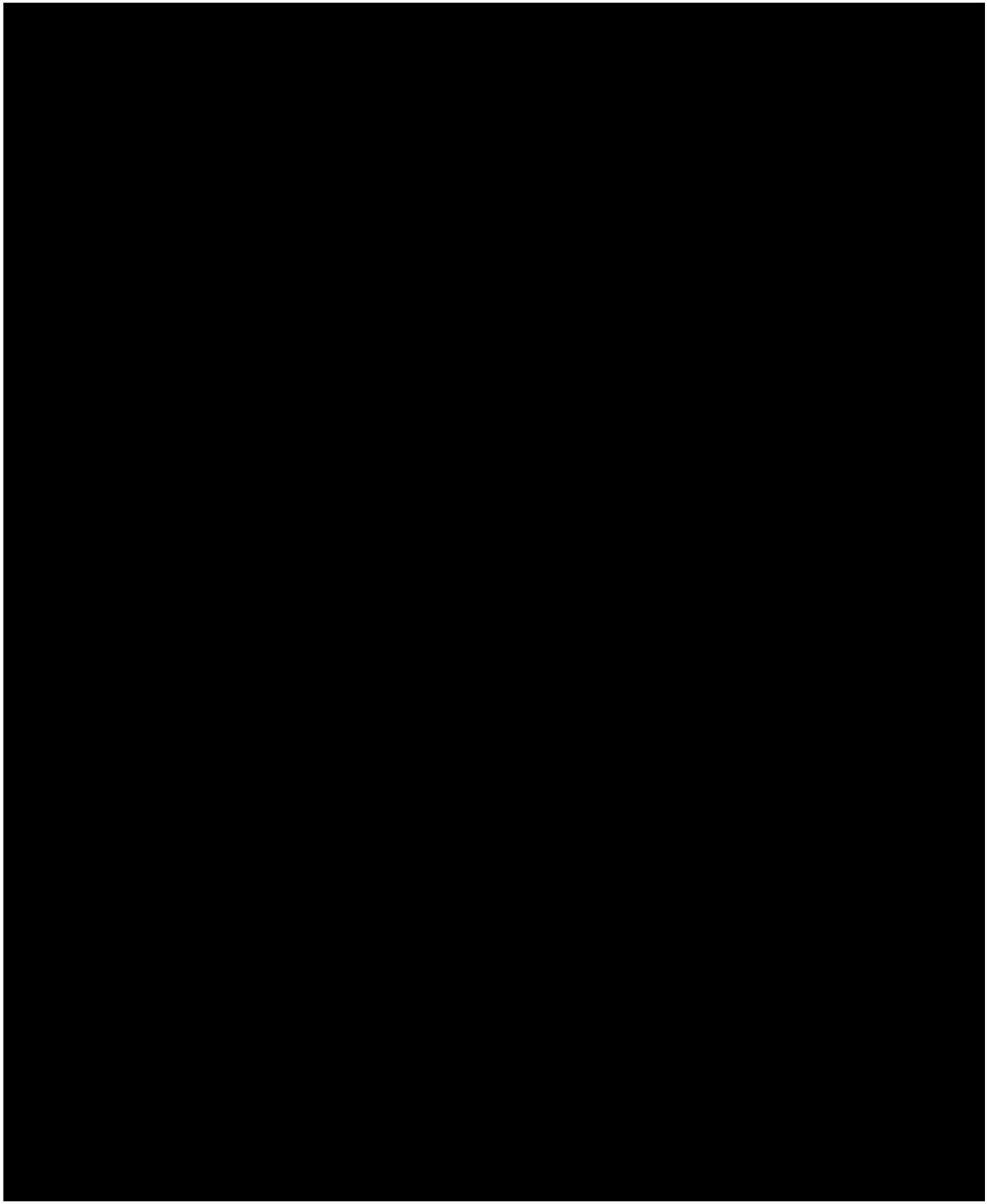
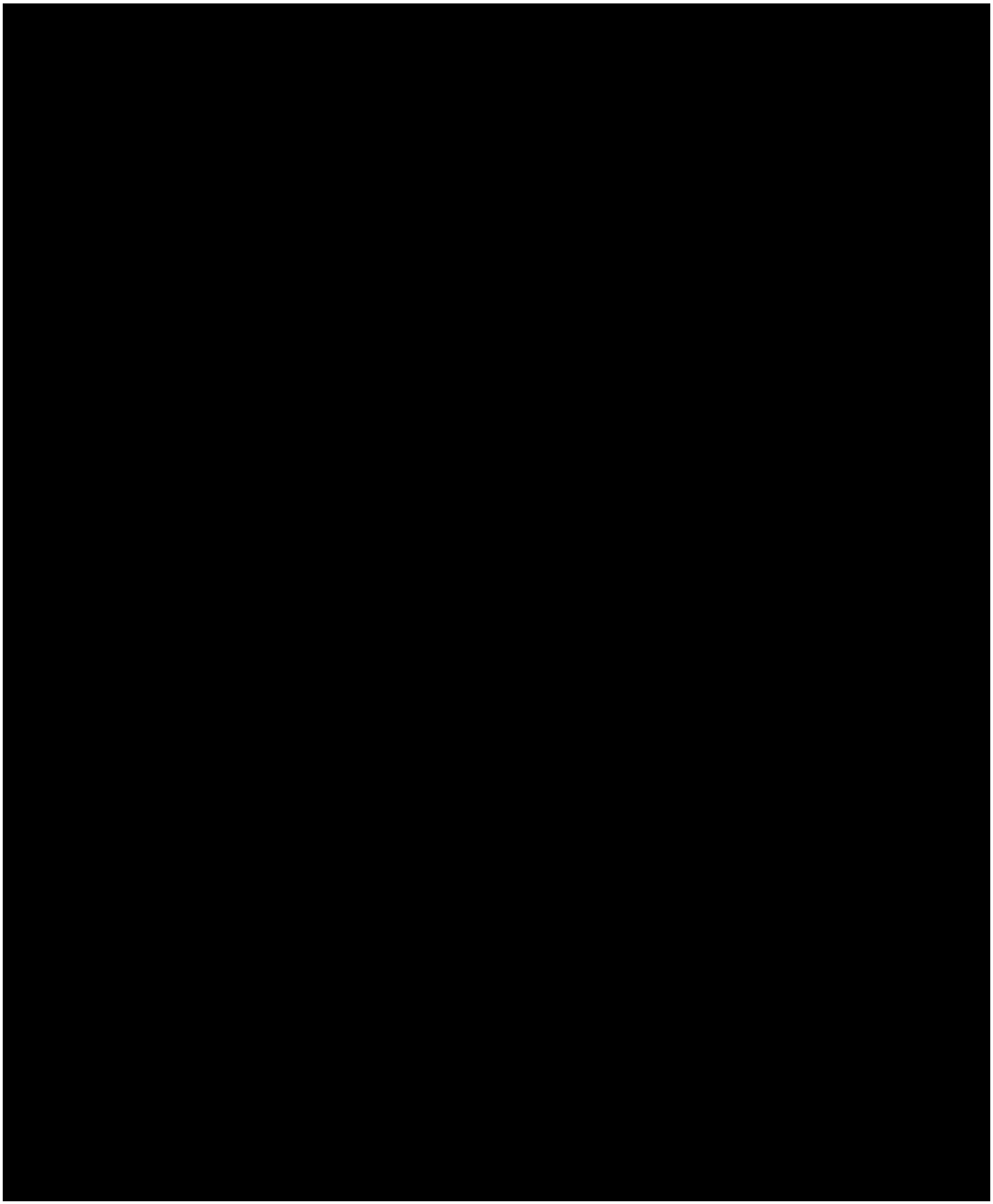


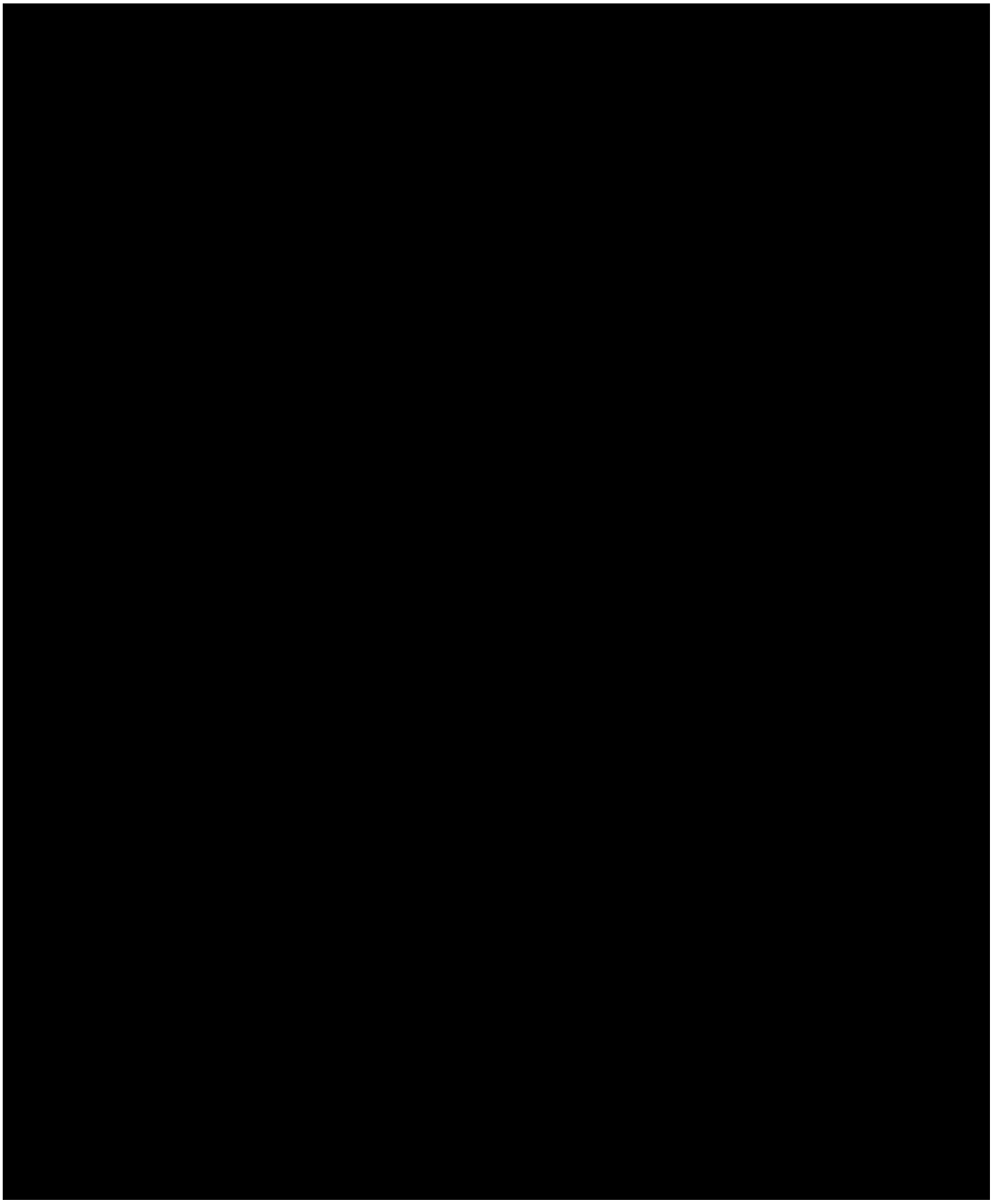






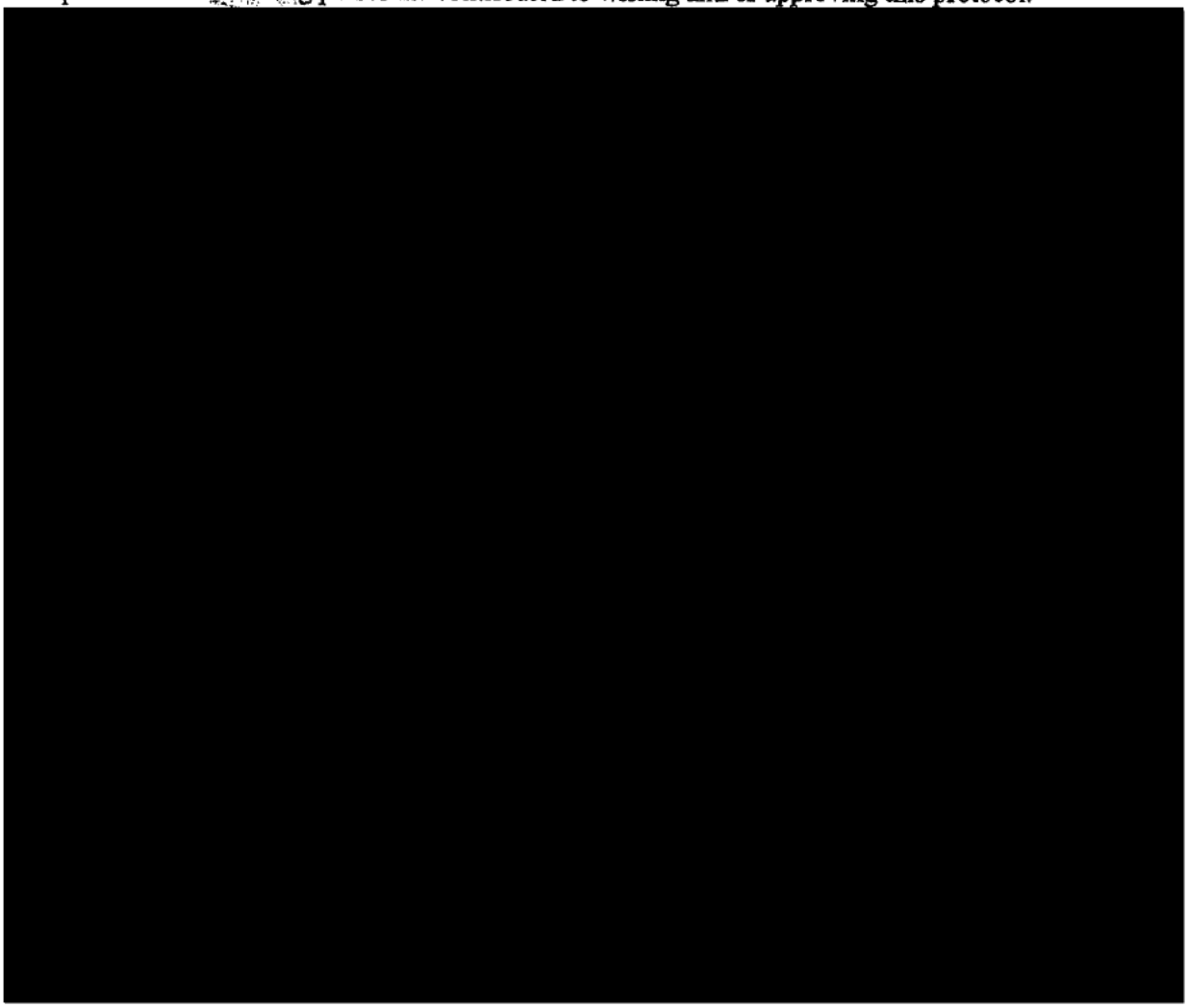






Protocol Title:	A Multi-Center, Phase 2, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-013
Final Date:	17 December 2019

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



APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Multi-Center, Phase 2, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) Compared to Vehicle in Subjects with Dry Eye Disease
Protocol Number:	ADX-102-DED-013
Final Date:	17 December 2019

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

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