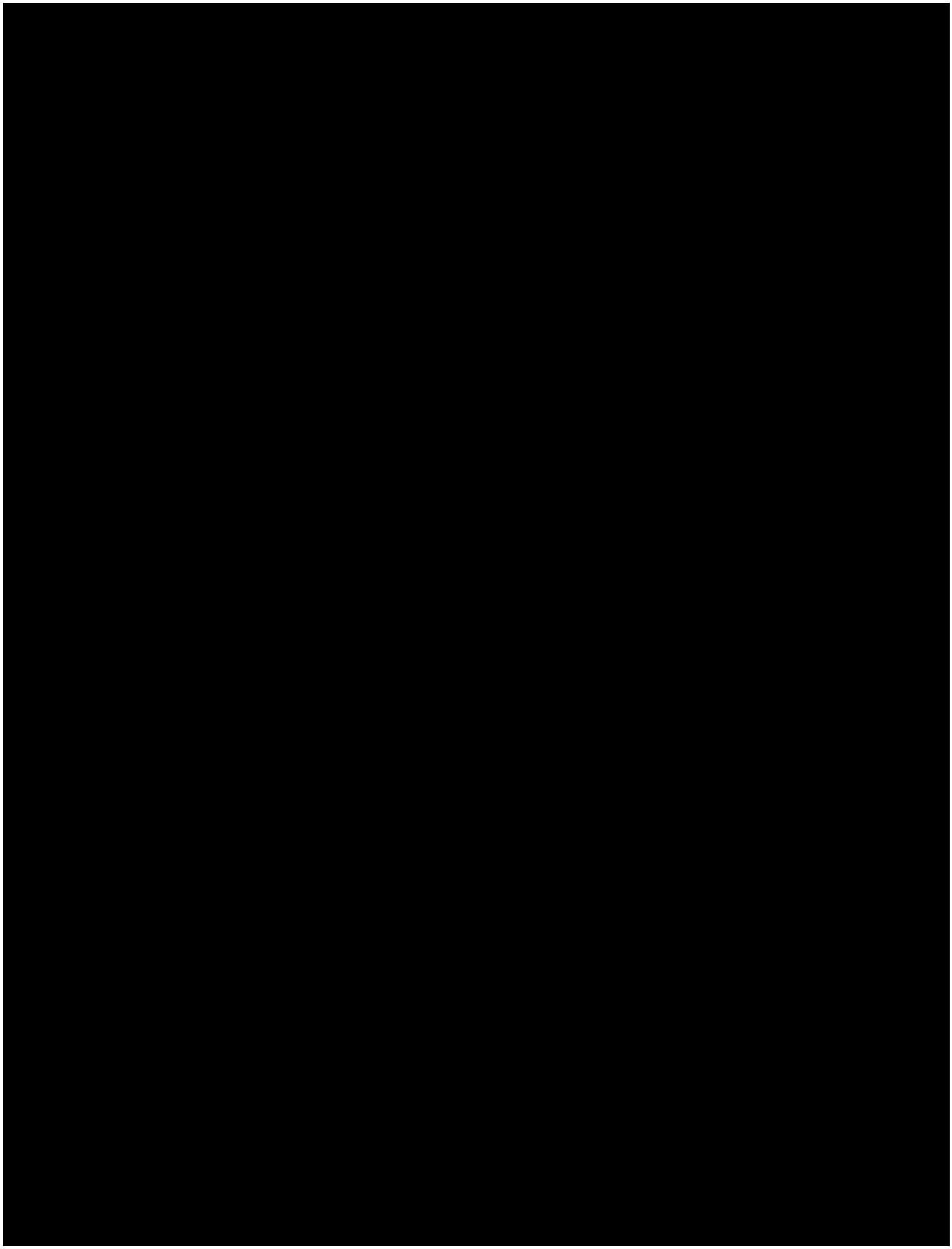
CLINICAL STUDY PROTOCOL

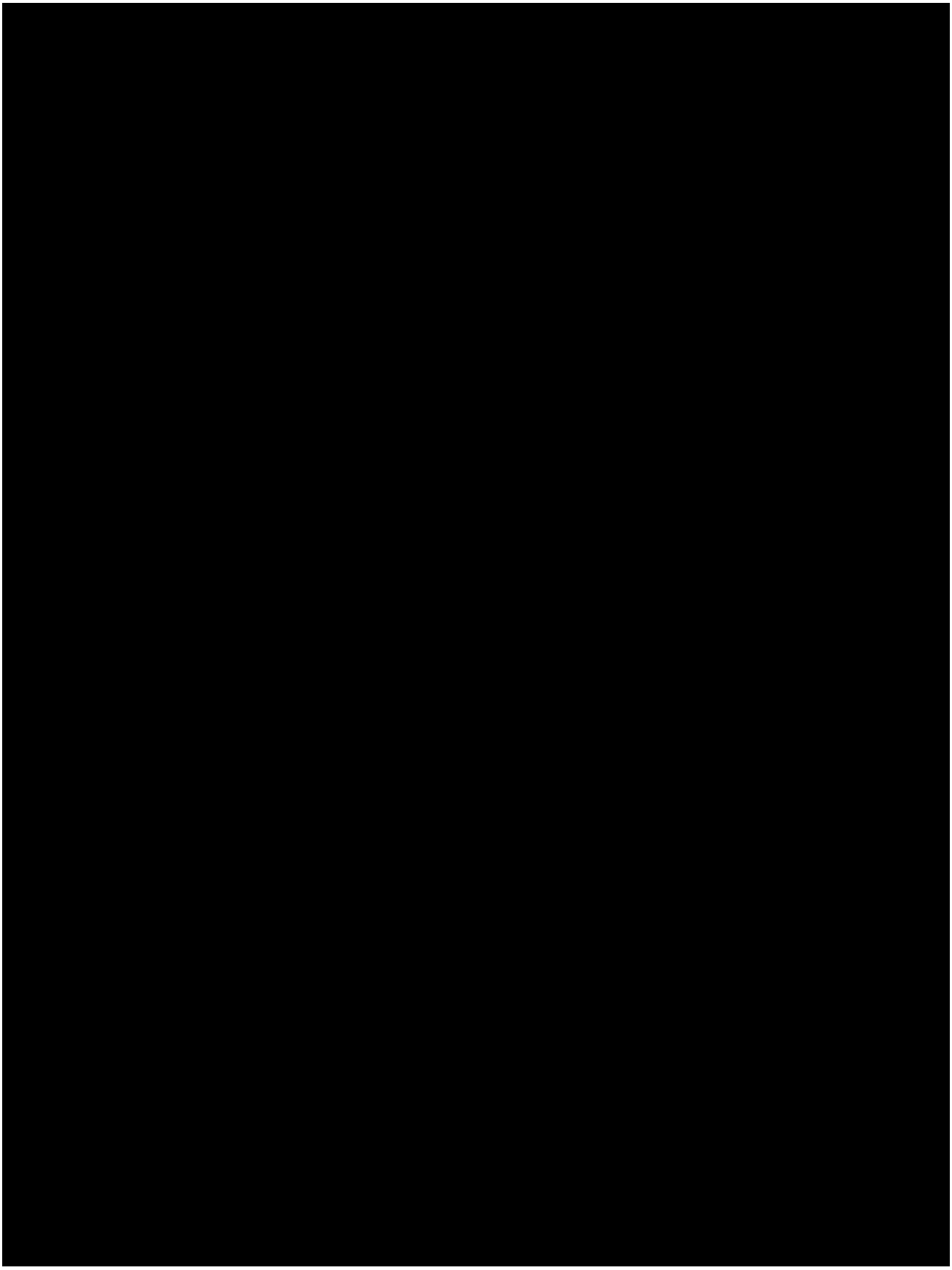
A Phase 3, Open-Label, Multi-Center Trial to Evaluate the Long-Term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-OLS)

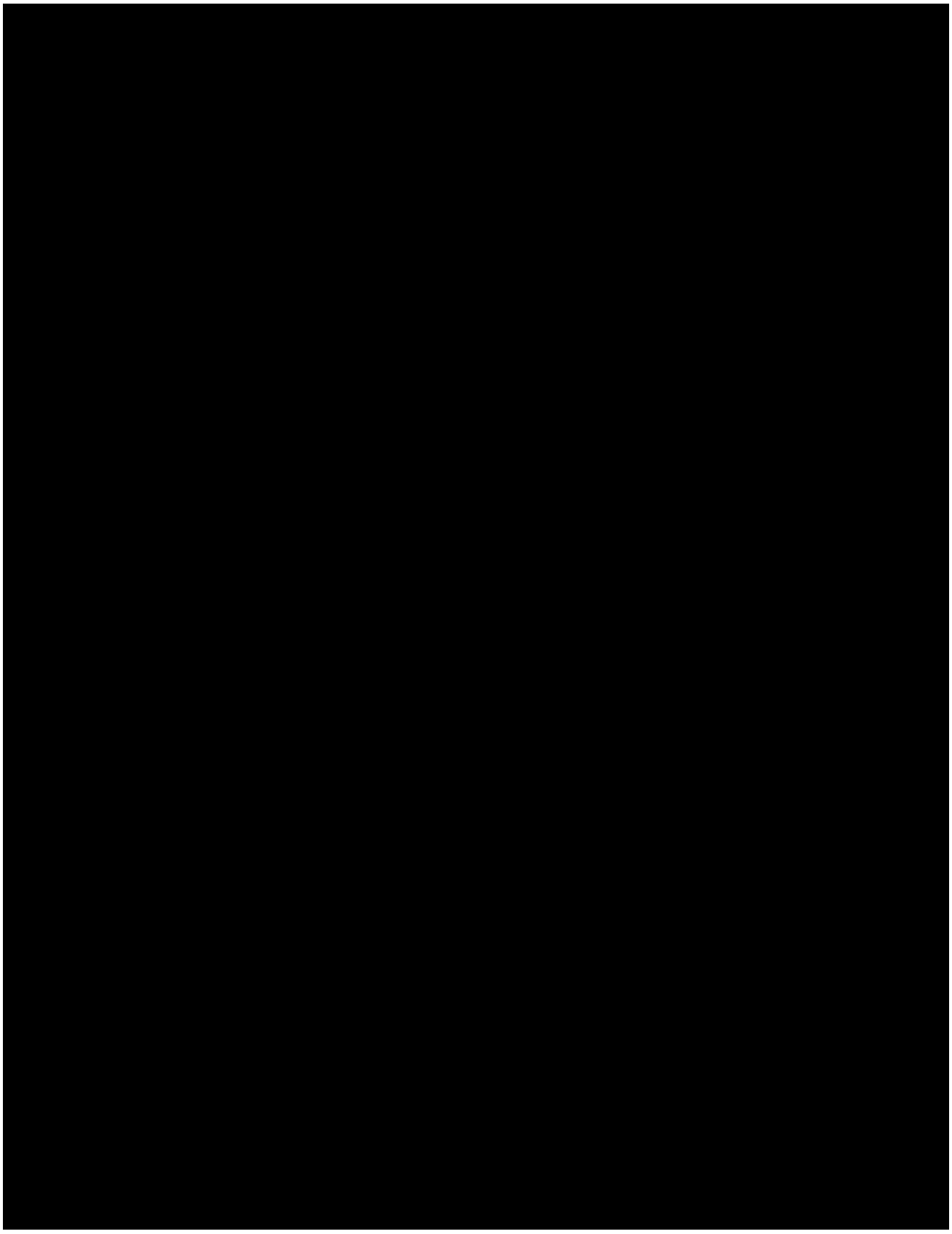
Protocol Number:	1720304
EudraCT Number:	2018-000447-11
National Clinical Trial Identified Number:	NCT03617367
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Boulevard Newark, California 94560, USA Telephone: (510) 742-3400
Protocol Version:	Amendment 5

Version History:

Version Number	**Date**
Amendment 5	10 July 2019
Amendment 4	27 June 2018
Amendment 3	04 June 2018
Amendment 2	27 March 2018
Amendment 1	02 February 2018
Original Protocol	20 September 2017







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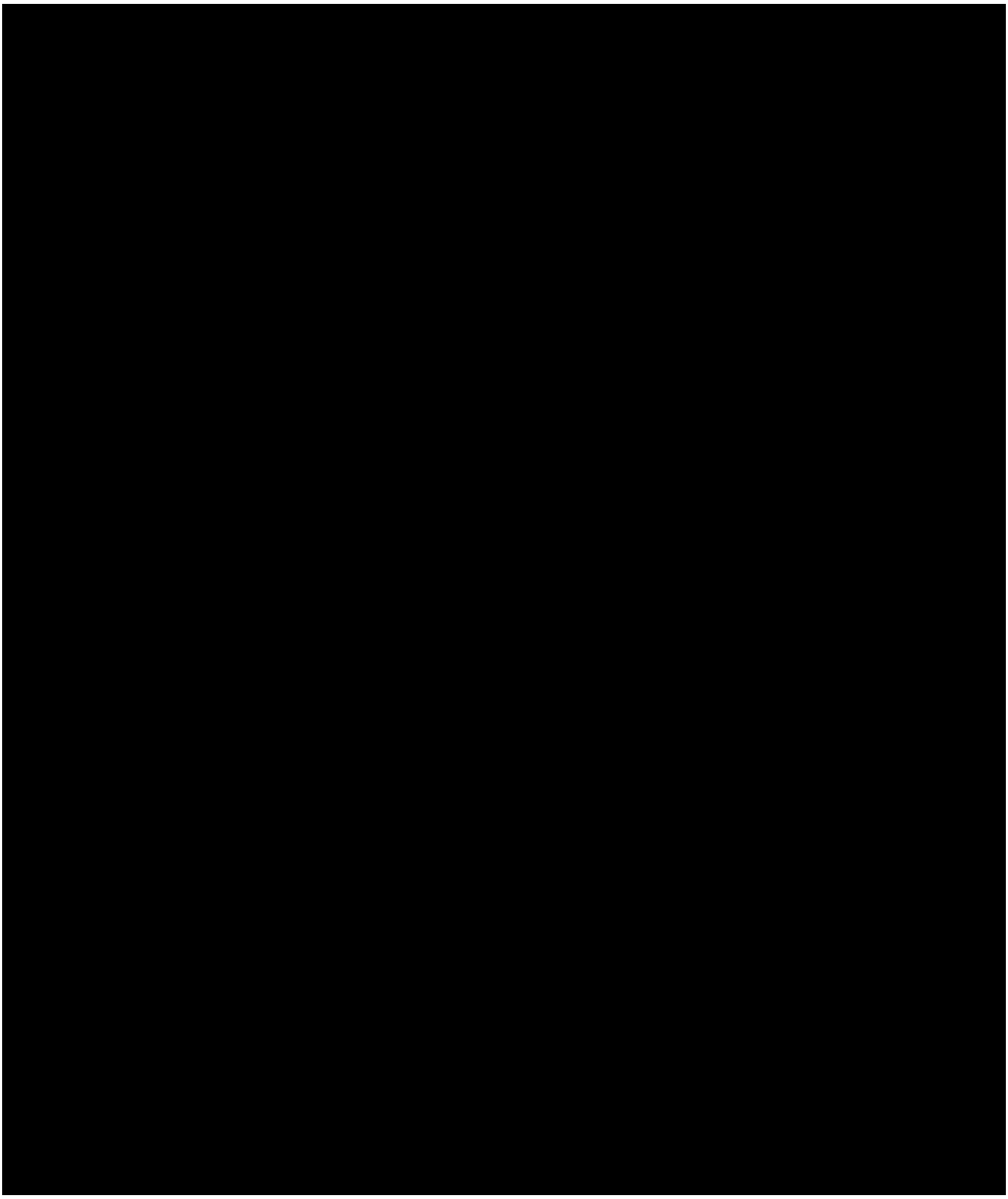


INVESTIGATOR'S AGREEMENT

I have carefully read and understand the protocol entitled: *"A Phase 3, Open-Label, Multi-Center Trial to Evaluate the Long-Term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-OLS)"* and,

I will provide copies of the protocol, including any subsequent protocol amendments, and access to all pertinent information provided by the sponsor to the trial personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug, conduct of the trial protocol, and the obligations of confidentiality.

I agree to conduct this clinical trial according to the attached protocol, in compliance with all applicable laws and regulations, and in accordance with the ethical principles stipulated in the Declaration of Helsinki.

_____ _____

Investigator Signature **Date**

_____

Printed Name

_____

Institution Name

_____

Address

_____ _____

City, State, Postal Code, Country **Phone Number**

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BoNT	botulinum toxin
BoNTA	botulinum toxin type A
BP	Blood pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CD	cervical dystonia
CDIP-58	Cervical Dystonia Impact Profile
CGIC	Clinical Global Impression of Change
CI	confidence interval
CS	clinically significant
DAXI	daxibotulinumtoxinA, RTT150
DAXI for injection	daxibotulinumtoxinA for injection, RT002
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EMG	electromyography
EOS	end-of-study
FDA	Food and Drug Administration (United States)
FEV_1	first second of exhalation
FVC	forced vital capacity
GCP	Good Clinical Practices
HD	high dose
ICH	International Council for Harmonisation
IM	Intramuscular(ly)
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Randomization System
kDa	kilodalton

Abbreviation	Definition
LD	low dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
OLS	open-label, long-term, safety (Study Protocol 1720304)
Onabot	onabotulinumtoxinA
PGIC	Patient Global Impression of Change
PI	principal investigator
PP	per protocol
PT	prothrombin time
QOL	quality of life
QT	measure of time between start of the q wave and the end of the t wave in the heart's electrical conduction
QTcF	corrected QT interval using Fridericia's correction formula
REB	Research Ethics Board
Revance	Revance Therapeutics, Inc.
RT002	previous company name for drug product daxibotulinumtoxinA for injection
RTP004	Revance novel excipient
RTT150	previous company name for drug substance, daxibotulinumtoxinA
SAE	serious adverse event
SF-36	Short Form-36 Survey
SOA	Schedule of Activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TdP	Torsade de Pointe
TEAE	treatment-emergent adverse event
TSQ	Treatment Satisfaction Questionnaire
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
U	units (botulinum toxin)
UP	unanticipated problem
US	United States
WOCBP	women of child bearing potential
WPAI	Work Productivity and Activity Impairment

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), all applicable Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, and national regulations. The principal investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB)/Research Ethics Board (REB)/ Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/Research Ethics Board (REB)/ Ethics Committee (EC) for review and approval. Approval of both the protocol and the informed consent form must be obtained before any participant is enrolled. Any amendments to the protocol, informed consent form(s), recruitment materials, and all participant materials will require review and approval by the IRB/REB/EC before the changes are implemented to the study. All changes to the informed consent form will be IRB/REB/EC approved prior to implementation; a determination will be made regarding whether a new informed consent needs to be obtained from participants who provided informed consent, using a previously approved informed consent form (ICF).

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **A Phase 3, Open-Label, Multi-Center Trial to Evaluate the Long-Term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-OLS)**

Study Description:

This is a Phase 3, open-label, multi-center trial to evaluate the long-term safety, efficacy, and immunogenicity of up to four continuous treatment cycles of daxibotulinumtoxinA (DAXI) for injection at doses of 125 U, 200 U, 250 U, and 300 U in adults with isolated cervical dystonia (CD).

Approximately 350 adult subjects will be recruited from study centers in the United States, Canada, and Europe who were enrolled in Study Protocol 1720302. These subjects from Study 1720302 include:

- Those with no reduction or increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 (i.e., no improvement or worsened disease), and the investigator agreed that there was a need for retreatment based on the subject's symptoms and neurologic exam findings
- Those who benefited from study treatment and completed follow-up study visits up to the time point of when their TWSTRS-total score reached/exceeded their target TWSTRS
- Those who benefited from study treatment but subsequently experienced significant recurrence of CD symptoms (e.g. pain) during the study before their TWSTRS-total score reached their target TWSTRS score and requested retreatment, which the investigator determined was warranted based on the subject's symptoms and neurologic exam findings
- Those who completed study visits up to Week 36 and their TWSTRS-total score never reached their target TWSTRS score. The investigator determined that these subjects can be followed in the OLS until their TWSTRS-total score is the same or higher than their target TWSTRS score or until they request retreatment, which the investigator determined was clinically indicated

All subjects will have up to 7 days from their End-of-Study (EOS) Visit in Study Protocol 1720302 to decide if they want to enroll in this study. After the 7-day decision-making period, any subjects who have not made an enrollment decision will be considered "not interested in the OLS."

After a subject has decided to enroll in the OLS, s/he will have up to 21 days to complete the screening procedures and enroll in the OLS. After 21 days, subjects who have NOT completed the screening procedures will be considered a screen failure. To be reconsidered for enrollment to the OLS, the subject will be required to repeat all screening procedures to reconfirm eligibility for enrollment in the OLS. These criteria also apply to subjects who missed the 7-day decision-making window to enroll in the OLS.

A written informed consent must be obtained from all subjects participating in the OLS before any trial-related procedures (including any screening procedures) are performed.

Eligible subjects who completed participation in Study Protocol 1720302 may be eligible for the first treatment (Baseline Treatment in Treatment Cycle 1 of OLS) during their EOS Visit window, but treatment may not be administered on the same day as the EOS Visit due to unavailability of screening safety laboratory results. In this case, the EOS Visit procedures and laboratory results from Study Protocol 1720302 will serve as the baseline data for this trial.

This study will also recruit new BoNT treatment-naïve or -experienced adult subjects, who were not enrolled in Study Protocol 1720302.

[redacted]

[redacted]

Two weeks after the Baseline/Treatment Study Visit (Day 1), study site staff will call the subject to inquire about CD symptom status and adverse events (AEs). The subject will return for protocol-specified assessments at Weeks 4, 6, 12, and every 4 weeks thereafter, up to Week 52 or EOS Visit.

Primary endpoints are safety and immunogenicity after multiple continuous treatment cycles of DAXI for injection. [redacted]

[redacted]

A subject may not be re-enrolled in the OLS after the EOS Visit (or after early discontinuation).

Study Visits and Telephone Calls:

- Screening (Days -21 to -1)
- Treatment #1, #2, #3, and #4
- Follow-up telephone calls after each Treatment:
  - Week 2 after each treatment (study site staff will call the subject)
- Follow-up visits after each Treatment:
  - Follow-up visits at Weeks 4, 6, 12, and every 4 weeks thereafter until the EOS Visit (52 weeks after Treatment #1 [Study Baseline]) (See Figure 1 Figure 1 and Table 1).

Safety Evaluations:

- Laboratory tests (hematology, prothrombin time [PT], chemistry, and urinalysis)
- [redacted]
- [redacted]
- Physical and neurological examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Dysphagia Severity Scale
- Vital signs
- Spirometry: the forced expiratory volume in the first second of exhalation (FEV_1) and forced vital capacity (FVC)
- 12-lead electrocardiograms (ECGs)
- Injection site evaluations
- Concomitant medications
- Treatment-emergent adverse events (TEAEs)
- [redacted]

Efficacy Evaluations:

- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
- Clinical Global Impression of Change (CGIC)
- Patient Global Impression of Change (PGIC)
- Cervical Dystonia Impact Profile (CDIP-58)

- Treatment Satisfaction Questionnaire (TSQ)
- Work Productivity and Activity Impairment (WPAI) Questionnaire
- Short Form-36 (SF-36) Survey

Diagnosis and Main Eligibility Criteria:

Subjects with a diagnosis of isolated CD meeting the full eligibility criteria may participate in the study. Major inclusion/exclusion criteria are presented below.

Major Inclusion Criteria:

- Adults, 18 to 80 years of age
- Meets diagnostic criteria for isolated CD (idiopathic; dystonic symptoms localized to the head, neck, shoulder areas) with at least moderate severity at Baseline (Day 1), defined as a TWSTRS-total score of at least 20, with at least 15 on the TWSTRS-Severity subscale, at least 3 on the TWSTRS-Disability subscale, and at least 1 on the TWSTRS-Pain subscale (minimum TWSTRS subscale criteria applicable only to subjects not previously enrolled in Study Protocol 1720302)
- Subjects who were previously enrolled in Study Protocol 1720302, and completed the study, including:
  - Those with no reduction or have an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 (i.e., no improvement or worsened disease status), and the investigator agreed that there was a need for retreatment based on the subject's symptoms and neurologic exam findings
  - Those who benefited from study treatment and completed follow-up study visits up to the time point of when their TWSTRS-total score reached/exceeded their target TWSTRS score
  - Those who benefited from study treatment but subsequently experienced significant recurrence of CD symptoms (e.g. pain) during the study before their TWSTRS-total score reached their target TWSTRS score and requested retreatment, which the investigator determined was warranted based on the subject's symptoms and neurologic exam findings
  - Those who completed study visits up to Week 36 and their TWSTRS-total score never reached their target TWSTRS score and they never requested another treatment. The investigator determined that these subjects can be followed in the OLS until their TWSTRS-total score is the same or higher than their target TWSTRS score or until they request retreatment, which the investigator determined is clinically indicated
- De novo subjects (not previously enrolled in Study Protocol 1720302):
  - Naïve to BoNT treatment
  - BoNT treatment-experienced; if previously treated with BoNTA, the subject must have demonstrated a clinically meaningful response to the last BoNTA treatment based on the clinical judgment of the investigator

Major Exclusion Criteria:

- Cervical dystonia attributable to an underlying etiology, (e.g., traumatic torticollis or tardive torticollis)
- Predominant retrocollis or anterocollis CD
- Significant dystonia in other body areas, or is currently being treated with botulinum toxin (BoNT) for dystonia in areas other than those associated with isolated CD
- Severe dysphagia (Grade 3 or 4 on the Dysphagia Severity Scale) at Screening or Baseline (prior to study treatment)

[redacted]

Objectives:

Primary Objectives:

- To evaluate the long-term safety of multiple continuous treatments of DAXI for injection
- To assess immunogenicity to BoNTA and RTP004 after multiple treatments of DAXI for injection

[redacted]

Endpoints:

Primary Endpoints:

- The dose- and cycle-specific incidence of drug-related AEs
- The dose- and cycle-specific incidence of study drug discontinuation due to drug-related AEs
- The dose and cycle-specific incidence of treatment-emergent immunogenicity

[redacted]

Interim Analysis:

No interim analysis is planned.

Study Population:

The study population will consist of approximately 350 adult subjects from all racial and ethnic backgrounds, males or females, between 18-80 years of age, in good general health, with a clinical diagnosis of isolated CD that is considered moderate to severe based on a TWSTRS-total score of at least 20. The subject may be naïve to BoNT injection, OR have a history of prior treatment with BoNT that was effective at controlling CD

symptoms. BoNT treatment-experienced subjects may include those who were previously enrolled in Study Protocol 1720302.

Statistical Methods:

Sample Size Justification:

The sample size for this study is based on a requirement from Regulatory Authorities to collect safety data on approximately 350 subjects treated with DAXI once and long-term safety data on at least 100 adult subjects treated with 3 or 4 continuous treatments of low-dose or high-dose DAXI for injection, with at least 50 subjects treated with the high-dose DAXI for injection for 3 or 4 continuous treatments. [redacted]

Analysis Populations:

Intent-to-Treat Population:

The intent-to-treat (ITT) population is defined as all subjects who enrolled in the OLS and received at least one dose of study drug.

The ITT population will be analyzed by specific treatment cycle and dose. The ITT analysis set will be used to conduct efficacy analyses.

[redacted]

Safety Population:

The safety analysis population consists of all randomized subjects who received at least 1 injection of study drug. Subjects will be grouped by the treatment they receive rather than their treatment assignment. The safety analysis set will be used to conduct safety analyses.

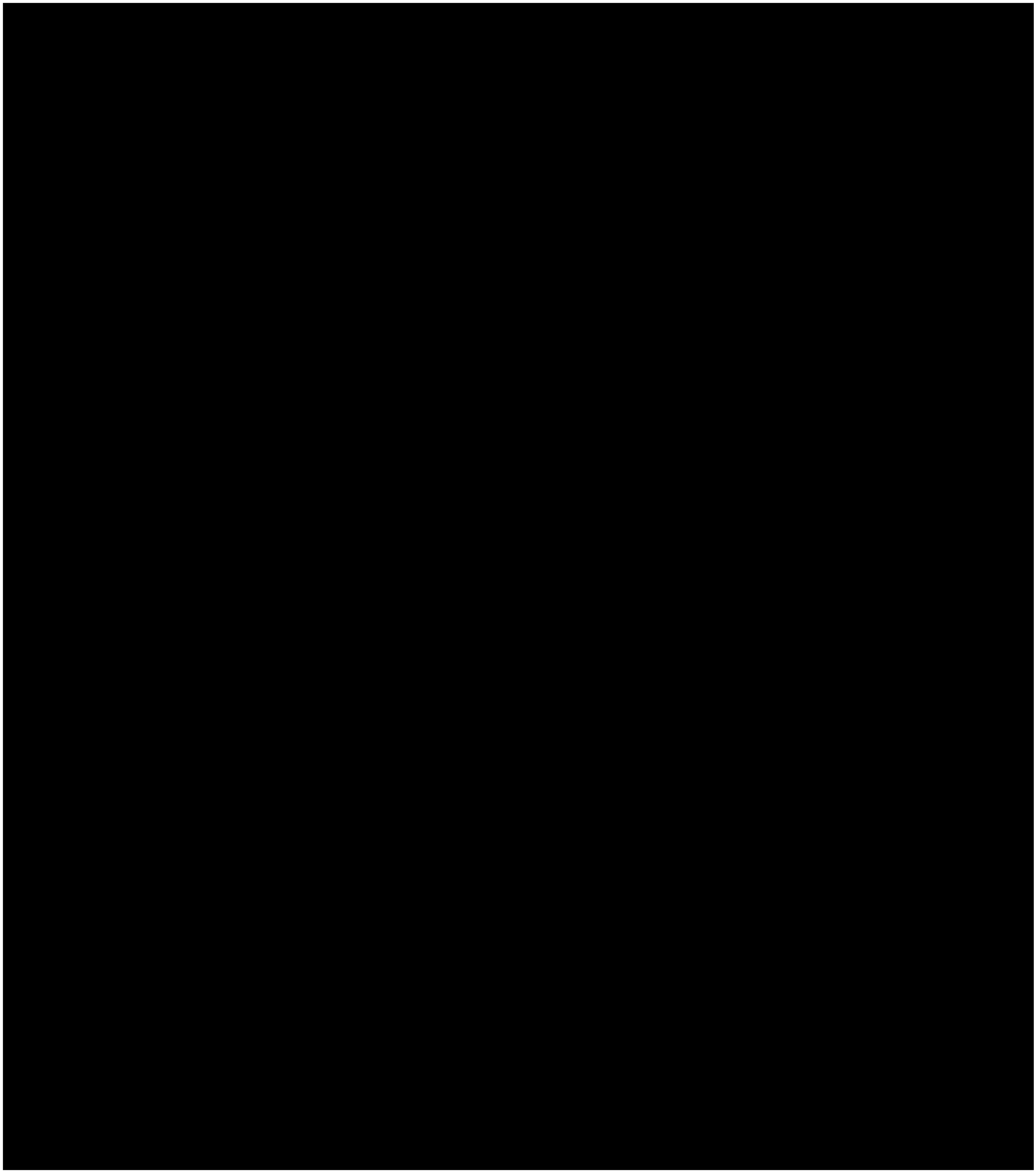
Demographic and baseline characteristics will be summarized for the ITT, PP, and safety populations.

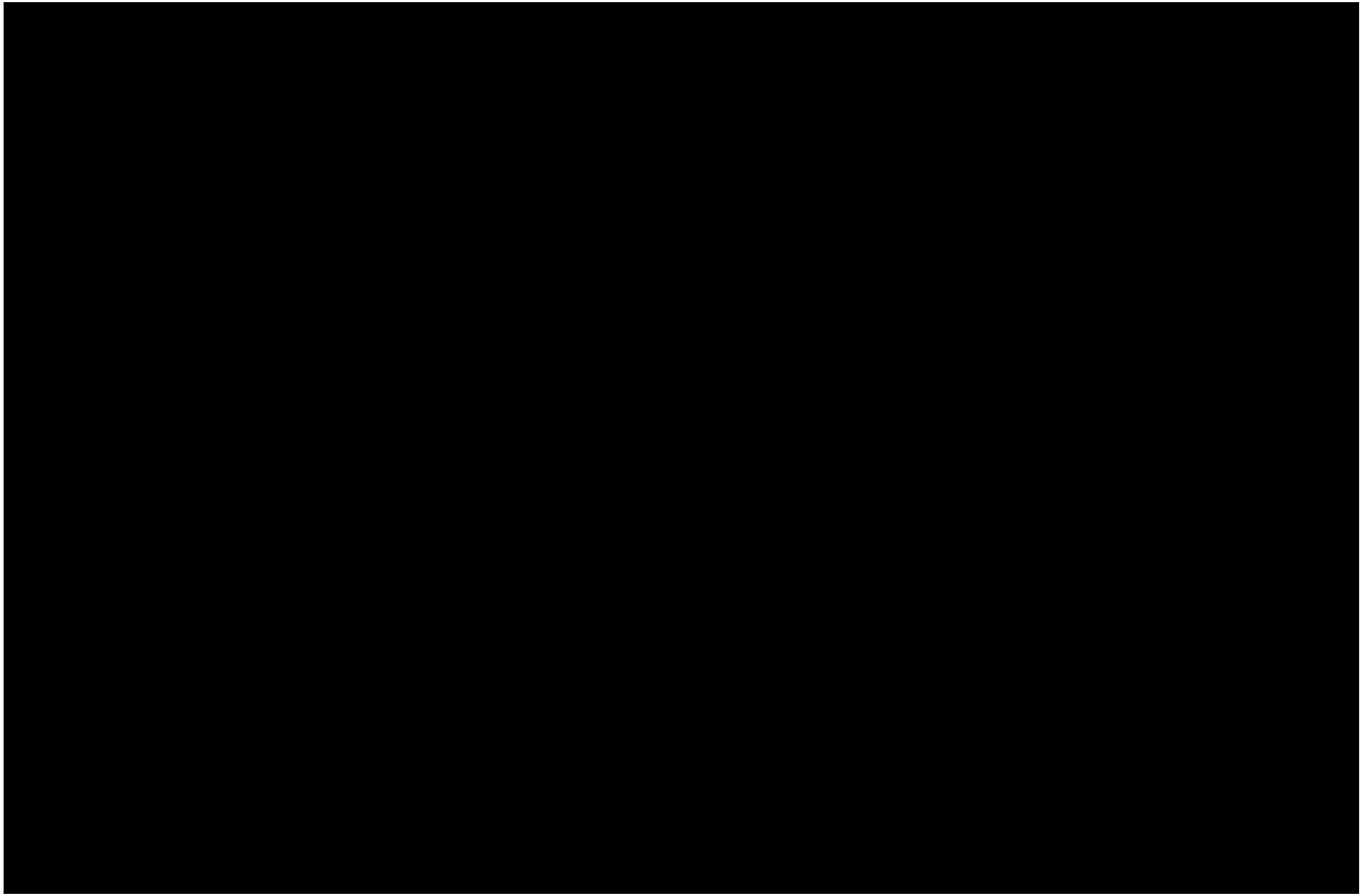
Phase: 3

Description of Sites/Facilities Enrolling Participants: Approximately 80 sites in the US, Canada, and Europe will participate in the study.

[redacted]

Participant Duration: Up to 55 weeks, including 3 weeks for screening





2 INTRODUCTION

2.1 BACKGROUND OF DISEASE

Isolated cervical dystonia (CD) is a chronic neurologic disorder characterized by involuntary patterned contractions of cervical musculature resulting in abnormal movements or postural changes of the head, neck, and shoulders. The pattern of neck muscle involvement in patients with CD is variable, leading to clinically heterogeneous directional presentations, such as rotational torticollis, laterocollis, retrocollis, or anterocollis (*Stacy 2008)*. Additional signs and symptoms may also include head oscillation due to dystonic tremor produced by uneven contractions of the cervical muscles, neck/shoulder pain, shoulder elevation, and arm tremor (*Phukan et al. 2011, Stacy 2008, and Schiebler et al. 2011*). Non-motor symptoms of CD may negatively impact mood and emotions, resulting in depression, social withdrawal, impaired sleep, poor health outcomes, and diminished quality of life (QOL) (*Ben-Shlomo et al. 2002*; *Jahanshahi, 1991*; *Lim 2007*; *Gundel et al. 2001*; *Zetterberg et al. 2012*; and *Kuyper et al. 2011*).

There is a lack of clinical diagnostic guidelines to allow easy differentiation of CD from other disorders of the neck that may simulate dystonia, and because of the wide variability in CD clinical features among individual patients, the diagnosis of CD can be open to misinterpretation and misdiagnosis. Hence, the data are limited regarding the incidence and prevalence of CD. Despite the varying prevalence estimates in the literature, an approximate 2:1 female to male ratio was consistent among many studies (*Defazio et al. 2013*).

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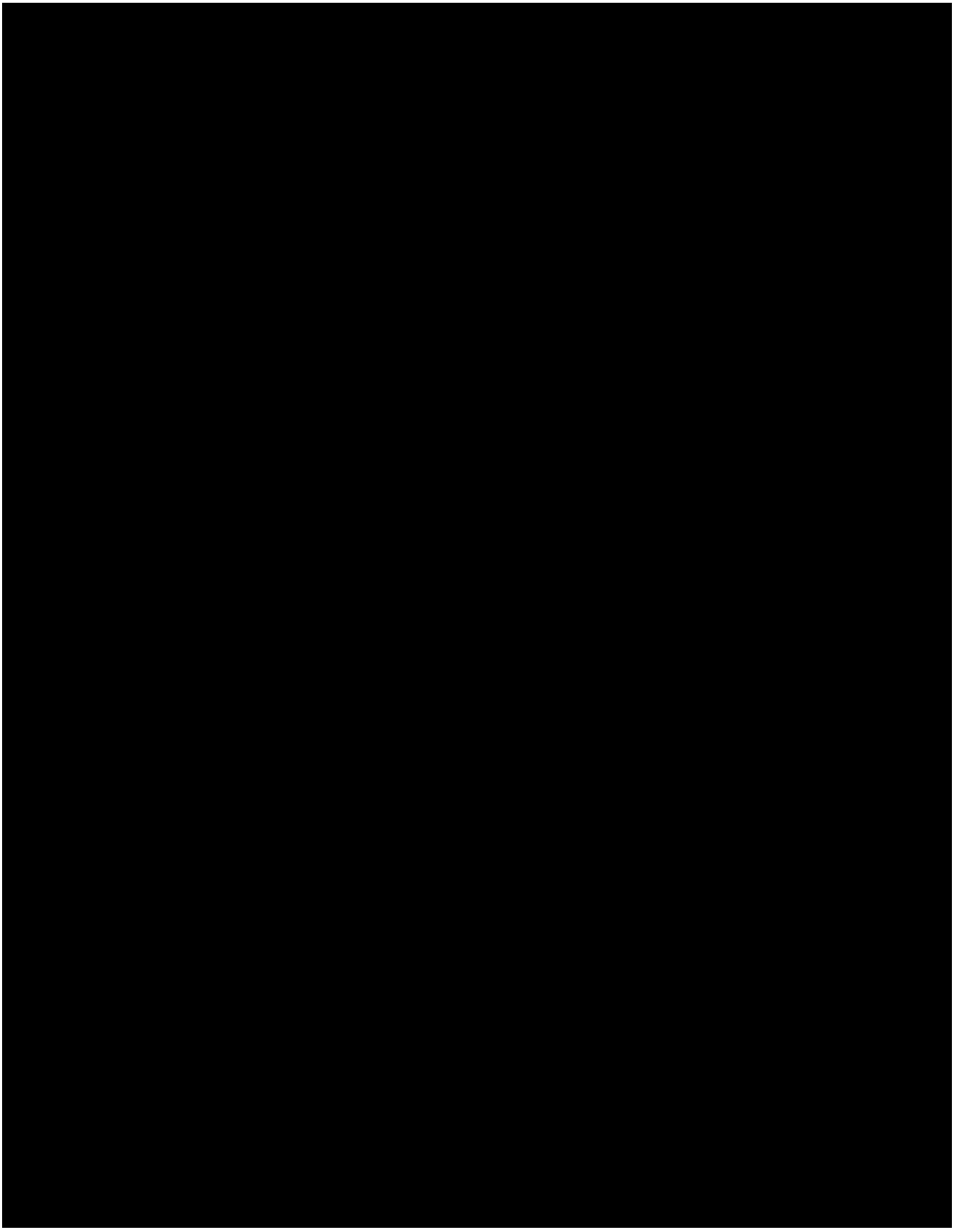

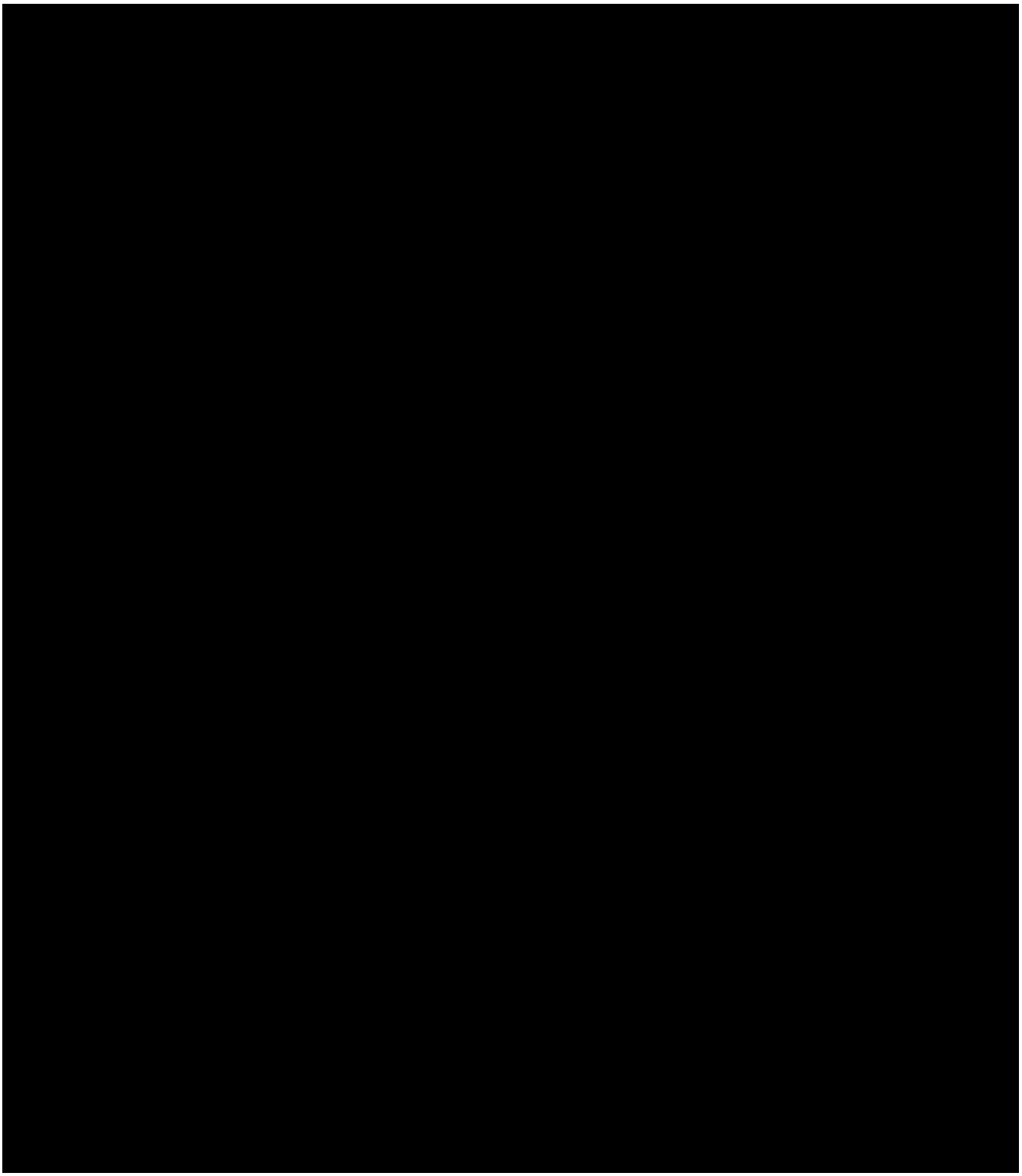

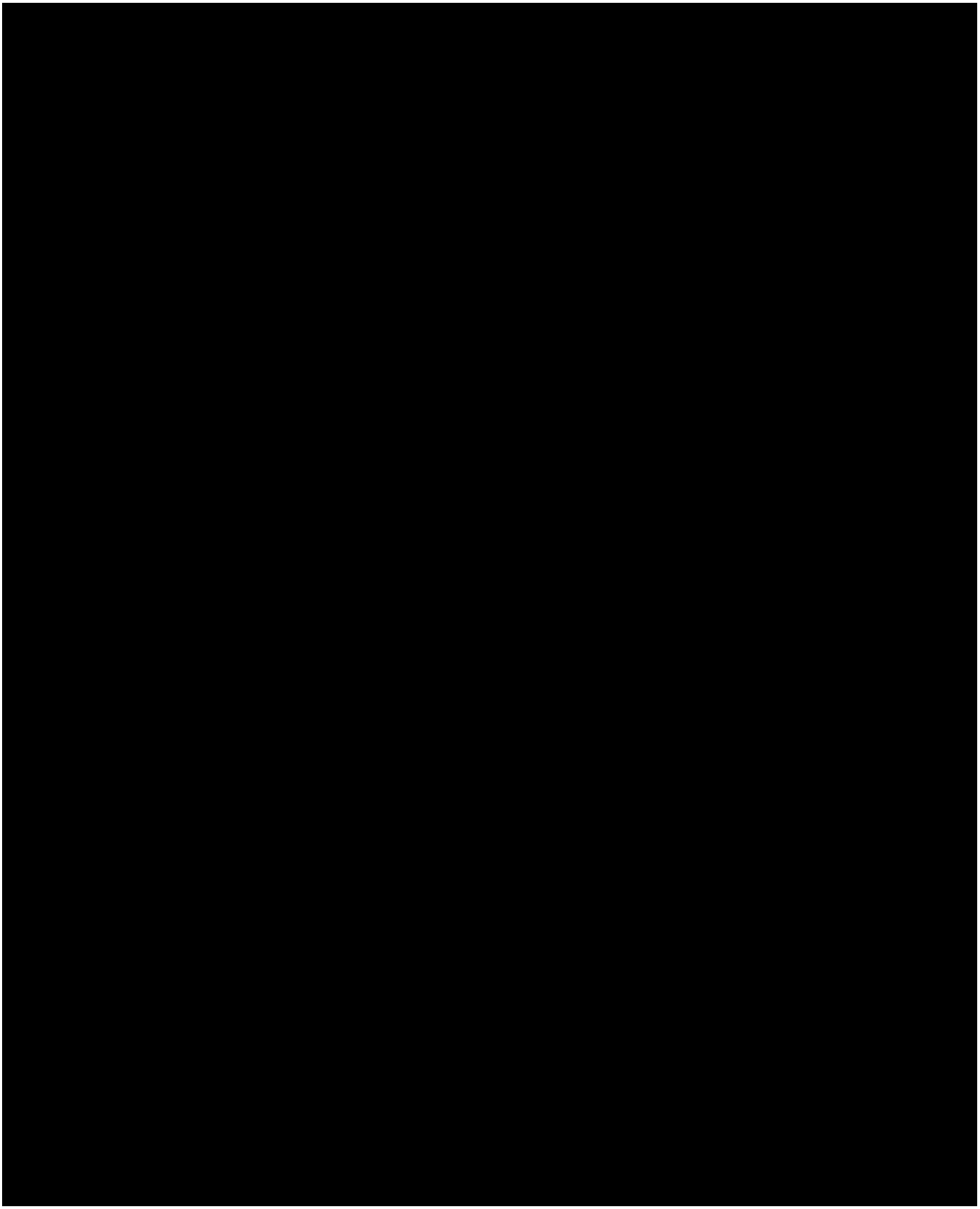

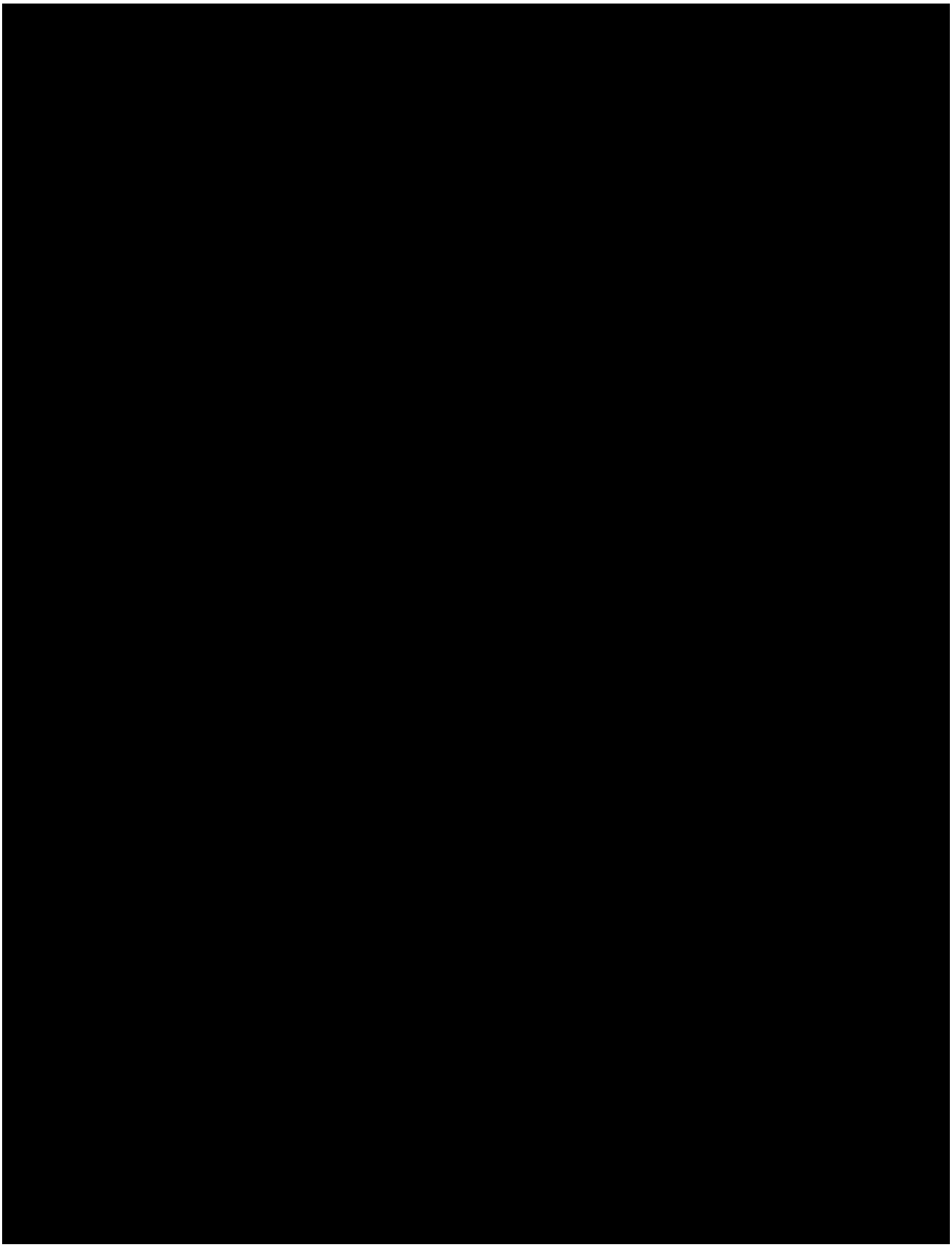

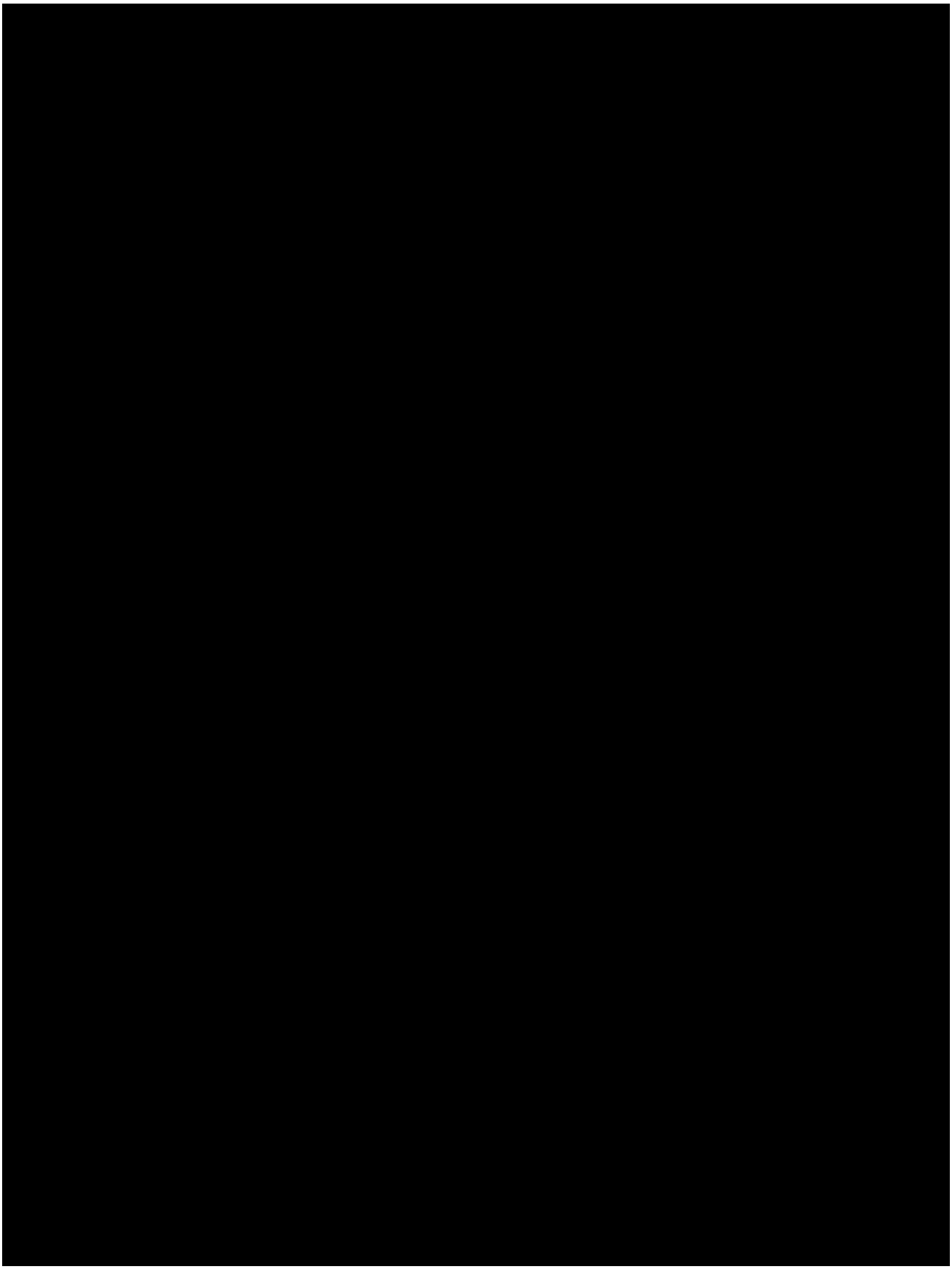

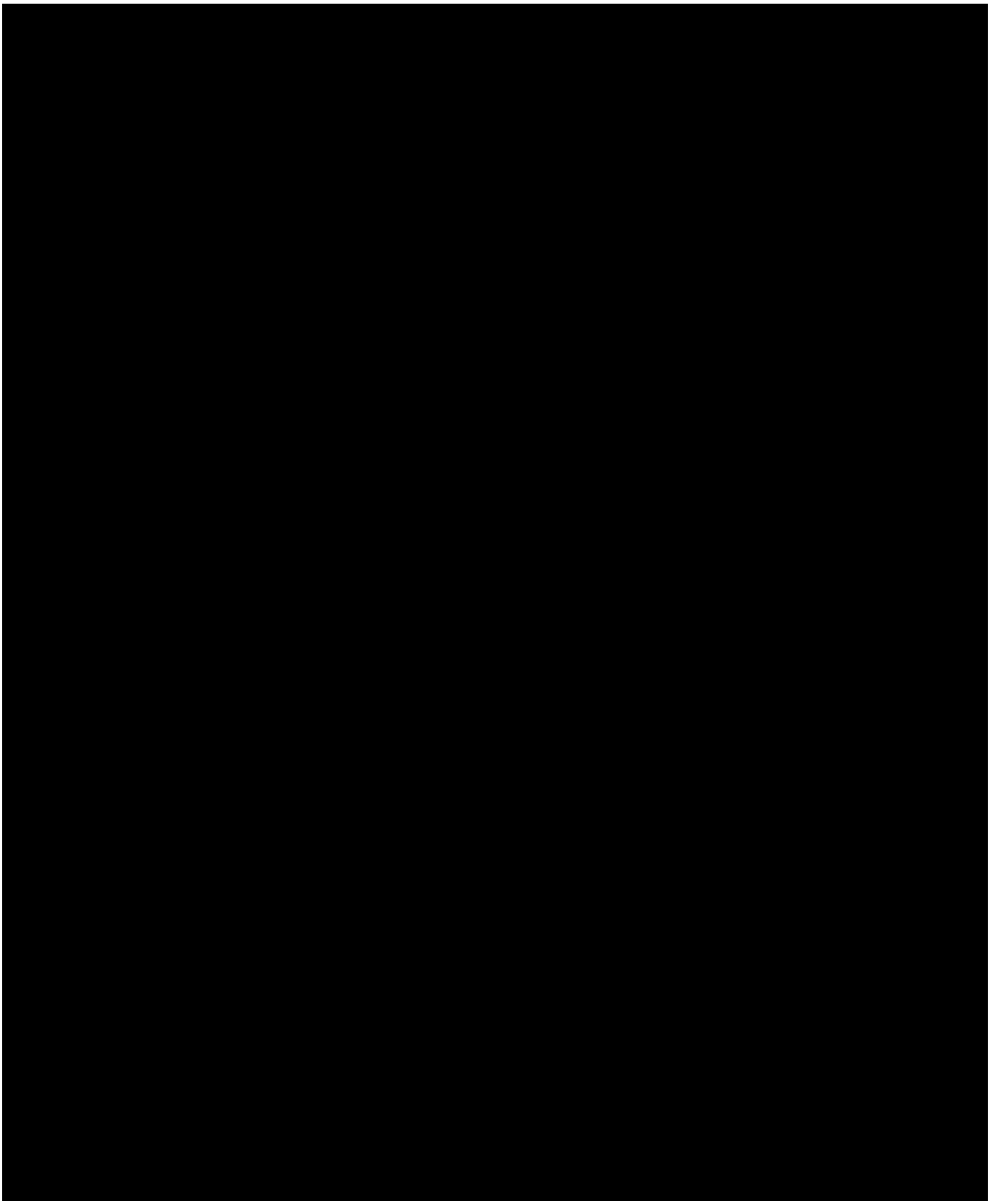

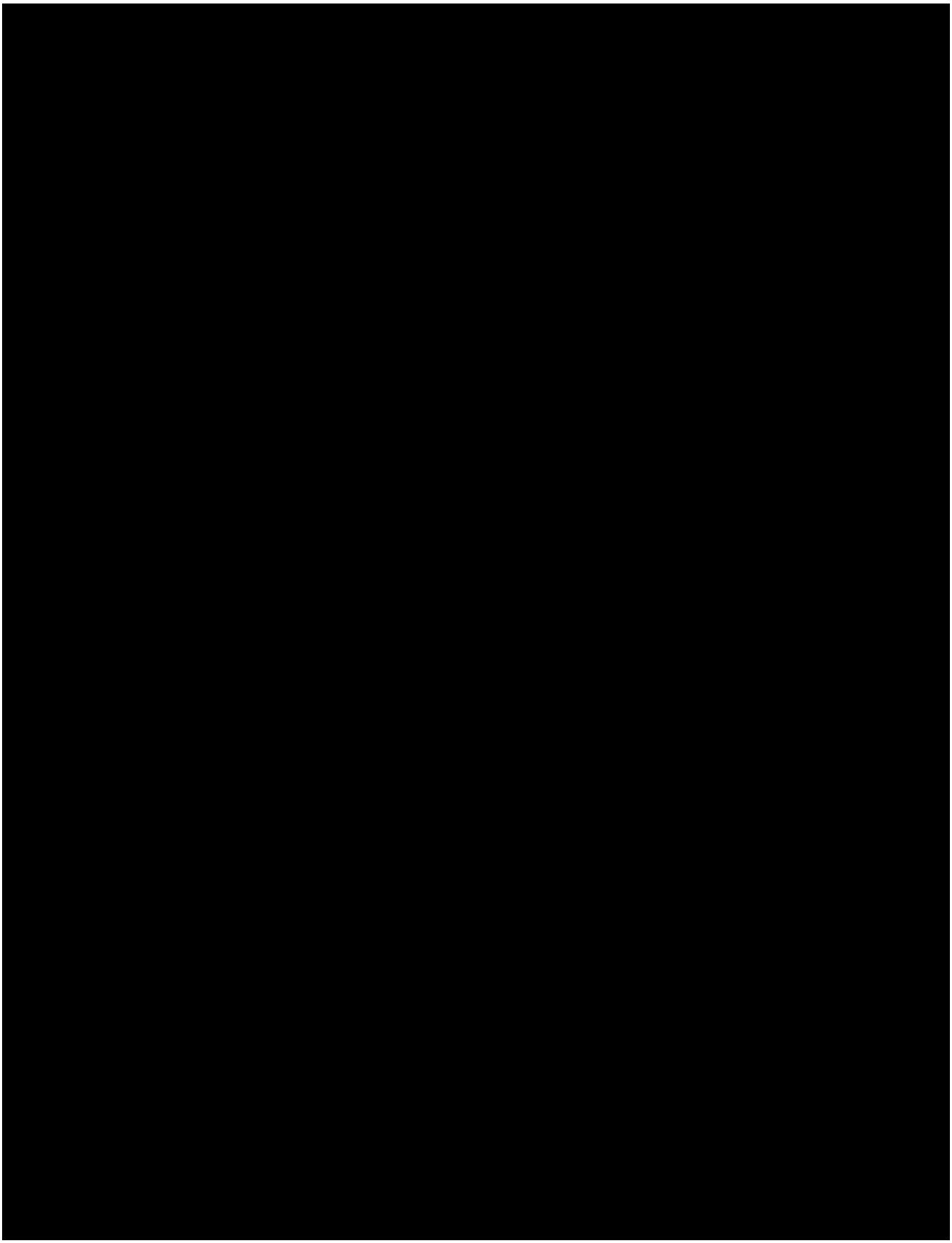

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3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary:		
• To evaluate the long-term safety of multiple continuous treatments of DAXI for injection • To assess immunogenicity of BoNTA and RTP004 after multiple treatments of DAXI for injection	• The dose- and cycle-specific incidence of drug-related AEs • The dose- and cycle-specific incidence of study drug discontinuation due to drug-related AEs • The dose and cycle-specific incidence of treatment-emergent immunogenicity	Clinically relevant outcome measures for this indication

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, open-label, multi-center trial to evaluate the long-term safety, efficacy, and immunogenicity of up to four continuous treatments of multi-dose DAXI for injection (125 U, 200 U, 250 U, and 300 U) in adults with isolated CD.

Approximately 350 adult subjects will be recruited from study centers in the US, Canada, and Europe who were enrolled in Study Protocol 1720302. These subjects from 1720302 include:

- Those with no reduction or have an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 (i.e., no improvement or worsened disease status), and the investigator agreed that there was a need for retreatment based on the subject's symptoms and neurologic exam findings
- Those who benefited from study treatment and completed follow up study visits up to the time point of when their TWSTRS-total score reached/exceeded their target TWSTRS score
- Those who benefited from study treatment but subsequently experienced significant recurrence of CD symptoms (e.g. pain) during the study before their TWSTRS-total score reached their target TWSTRS score and requested retreatment, which the investigator determined was warranted based on the subject's symptoms and neurologic exam findings
- Those who completed study visits up to Week 36 and their TWSTRS-total score never reached their target TWSTRS score and they never requested another treatment. The investigator determined that these subjects can be followed in the OLS until their TWSTRS-total score is the same or higher than their target TWSTRS score or until they request retreatment, which the investigator determined is clinically indicated

All subjects will have up to 7 days from their End-of-Study (EOS) Visit in Study Protocol 1720302 to decide if they want to enroll in the OLS. After the 7-day decision-making period, any subjects who have not made an enrollment decision will be considered "not interested in the OLS."

After a subject has decided to enroll in the OLS, s/he will have up to 21 days to complete the screening procedures and enroll in the OLS. After 21 days, subjects who have NOT completed the screening procedures will be considered a screen failure. To be reconsidered for enrollment to the OLS, the subject

will be required to repeat all screening procedures to reconfirm eligibility for enrollment in the OLS. These criteria also apply to subjects who missed the 7-day decision-making window to enroll in the OLS.

A written informed consent must be obtained from all subjects participating in the OLS before any trial-related procedures (including any screening procedures) are performed.

Eligible subjects who completed participation in Study Protocol 1720302 may be eligible for the first treatment (Baseline Treatment in Treatment Cycle 1 of OLS) during their EOS Visit window, but treatment may not be administered on the same day as the EOS Visit due to unavailability of screening safety laboratory results. In this case, the EOS Visit procedures and laboratory results from Study Protocol 1720302 will serve as the baseline data for this trial.

This study will also recruit new BoNT treatment-naïve or -experienced adult subjects, who were not enrolled in Study Protocol 1720302.

[redacted]

4.3 STUDY VISITS AND TELEPHONE CALLS

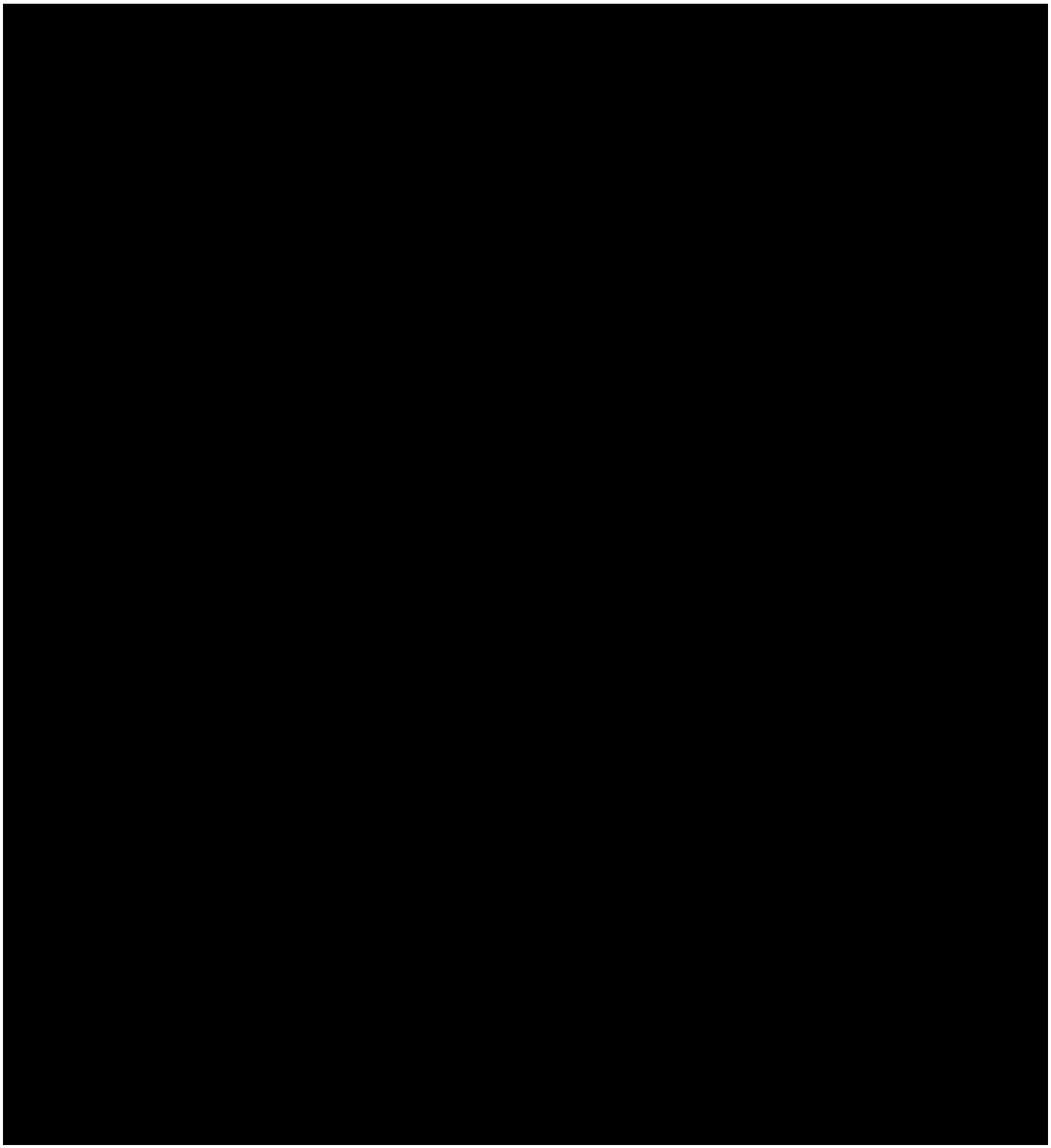
Figure 3 summarizes the schedule of telephone calls and assessments by treatment cycle.

- Screening (Days -21 to -1)
- Baseline Treatment #1, Treatment #2, #3, #4
- Follow-up telephone call after each Treatment:
  - Week 2 after each treatment (study site staff will call the subject)
- Follow-up visits after each Treatment:
  - Weeks 4, 6, 12, and every 4 weeks thereafter until Week 52/End-of-Study Visit (See Figure 1 and Table 1)

Safety assessments include laboratory tests (hematology, PT, chemistry, and urinalysis), [redacted], physical and neurological examinations, the C-SSRS, Dysphagia Severity Scale, vital signs, pulmonary function by spirometry, 12-lead ECGs, injection site evaluations, concomitant medications, AE monitoring at protocol-specified timepoints, [redacted]

Efficacy assessments, including the TWSTRS (total score and subscale scores), CDIP-58, CGIC, PGIC, TSQ, WPAI, and SF-36 Survey, will be performed at protocol-specified timepoints as outlined in the SOA (Table 1).

No interim analysis is planned for this study.



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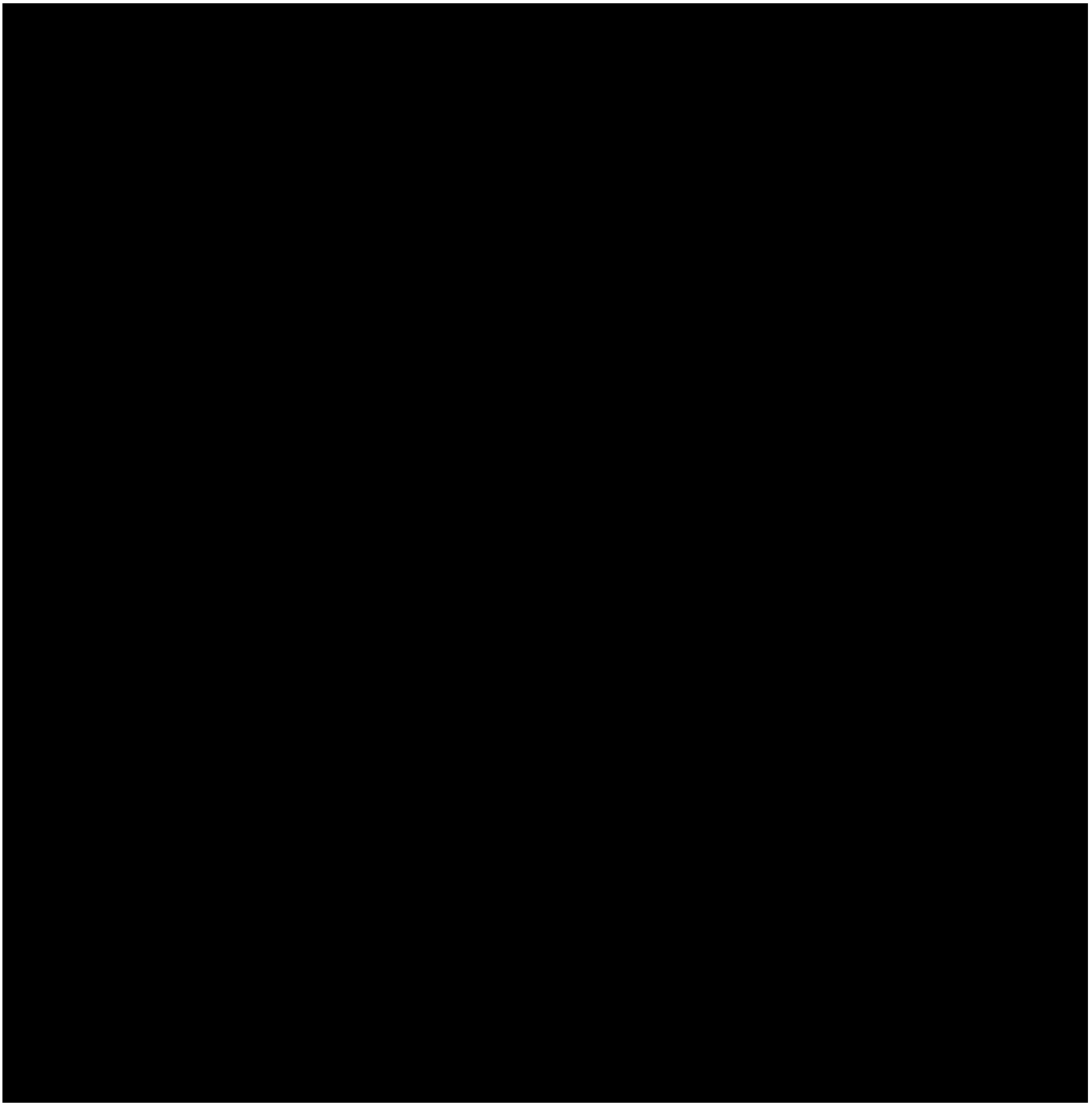


5 STUDY POPULATION

5.1 INCLUSION CRITERIA

All participants must meet the following inclusion criteria:

1. Adults, 18 to 80 years of age

2. Meets diagnostic criteria for isolated CD (idiopathic; dystonic symptoms localized to the head, neck, shoulder areas) with at least moderate severity at Baseline (Day 1), defined as a TWSTRS-total score of at least 20, with at least 15 on the TWSTRS-Severity subscale, at least 3 on the TWSTRS-Disability subscale, and at least 1 on the TWSTRS-Pain subscale (minimum TWSTRS subscale criteria applicable only to subjects not previously enrolled in Study Protocol 1720302)

3. Subjects who were previously enrolled in Study Protocol 1720302, who completed the study, including:

    a) Those with no reduction or have an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 (i.e., no improvement or worsened disease status), and the investigator agreed that there was a need for retreatment based on the subject's symptoms and neurologic examination findings
    b) Those who benefited from study treatment and complete follow-up study visits up to the time point of when their TWSTRS-total score reached/exceeded their target TWSTRS score
    c) Those who benefit from study treatment but subsequently experienced significant recurrence of CD symptoms (e.g., pain) during the study before their TWSTRS-total score reached their target TWSTRS score and requested retreatment, which the investigator determined was warranted due based on the subject's symptoms and neurologic examination findings
    d) Those who completed study visits up to Week 36 and their TWSTRS-total score never reached their target TWSTRS score and they never requested another treatment. The investigator determined that these subjects can be followed in the OLS until their TWSTRS-total score is the same or higher than their target TWSTRS score or until they request retreatment, which the investigator determined is clinically indicated

4. De novo subjects (not previously enrolled in Study Protocol 1720302):

    a) Naïve to BoNT treatment
    b) BoNT treatment-experienced; if previously treated with BoNTA, the subject must have demonstrated a clinically meaningful response to the last BoNTA treatment based on the clinical judgment of the investigator

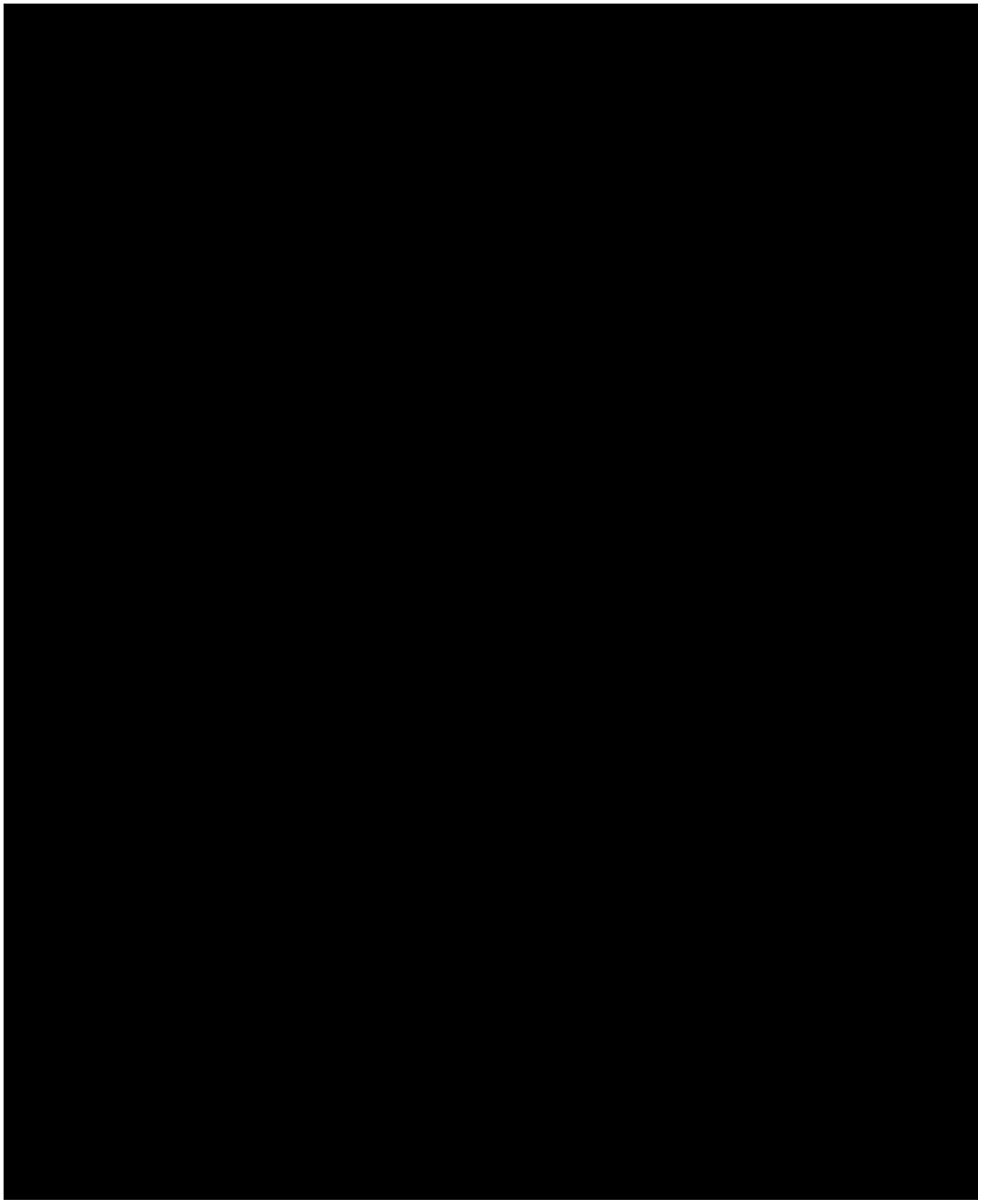
5. Written informed consent including authorization to release health information

5.2 EXCLUSION CRITERIA

Subjects will not be enrolled if they meet any of the following exclusion criteria:

1. Cervical dystonia attributable to an underlying etiology, (e.g., traumatic torticollis or tardive torticollis)
2. Predominant retrocollis or anterocollis CD
3. Significant dystonia in other body areas, or is currently being treated with BoNT for dystonia in areas other than those associated with isolated CD

4. Severe dysphagia (Grade 3 or 4 on the Dysphagia Severity Scale) at Screening or Baseline (prior to study treatment)



No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

Deviation from any entry criterion excludes a subject from enrollment into the study.

[redacted]

5.4 LIFESTYLE CONSIDERATIONS

5.4.1 THERAPIES AND MEDICATIONS

5.4.1.1 CONCOMITANT MEDICATIONS

Concomitant medications are any prescription or over-the-counter medication, including herbs, vitamins, or other nutritional supplements, used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications electronic case report form (eCRF) from Screening through end of study.

[redacted]

[redacted]

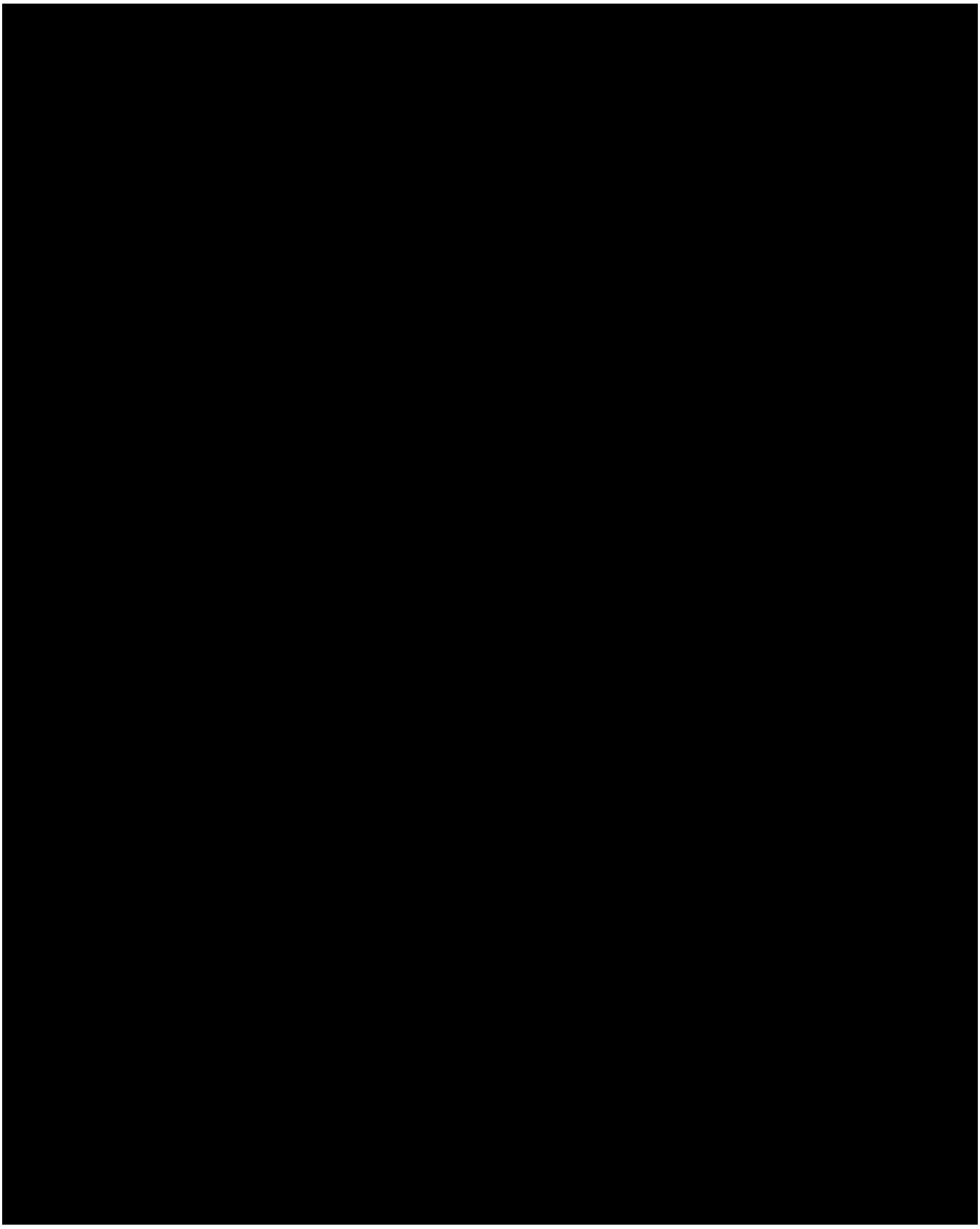
5.5 SCREEN FAILURES

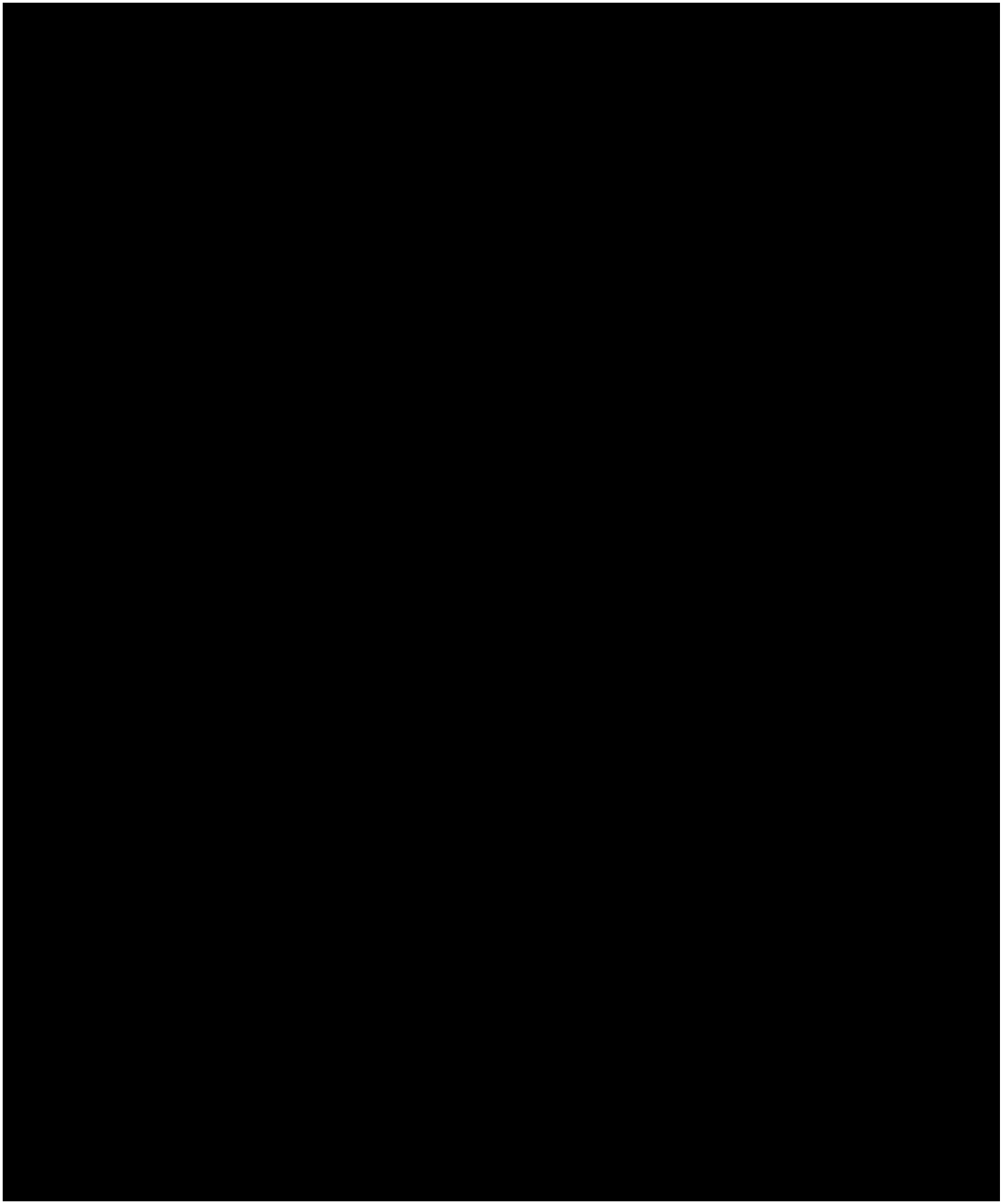
A screen failure subject will be an individual from whom informed consent is obtained and is documented in writing (i.e., subject signs an informed consent form) but who does not meet the study eligibility requirements.

[redacted]

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Sponsor will actively monitor recruitment and retention in accordance with ICH guidelines and support sites and subjects appropriately.





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6.4 STUDY INTERVENTION COMPLIANCE

Due to the fact that these treatment interventions are administered IM by investigators at the study site, study intervention compliance is not applicable.

6.5 CONCOMITANT MEDICATION

Concomitant medications are any prescription or over-the-counter preparations, including herbs, vitamins, or other nutritional supplements, used by subjects during participation in the study. Use of concomitant medications will be recorded on the Concomitant Medications eCRF from Screening through end of study.

Subjects are allowed to be on a stable dose of medications (if any) used for focal dystonia treatment (e.g., anticholinergics, muscle relaxants, benzodiazepines) for at least 4 weeks prior to Baseline (Day 1) and continuing through end of study.

6.5.1 RESCUE MEDICINE

Rescue medication for CD is not allowed in this trial. Subject(s) may withdraw from the study at any time if rescue medication for CD is required.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Subjects may receive one or multiple treatments of DAXI for injection. After the first treatment, subsequent treatment(s) is(are) based on the subject's response to prior treatment. A subject may not receive subsequent treatments due to significant adverse effects or lack of treatment benefit.

7.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time with notification.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance (e.g., failure to follow study procedures or to keep follow-up appointments)
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- The subject experiences no reduction or have an increase in the average TWSTRS-total score at Weeks 4 and 6 post-injection relative to the pre-injection TWSTRS-Total score at the beginning of the treatment cycle (i.e., **lack of efficacy**: no improvement or worsened disease status)
- If the investigator determines that another BoNT treatment is needed to control the CD symptoms and less than 12 weeks have elapsed since the last study treatment administration
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

If the subject withdraws consent and discontinues from the study, the investigator will record the reason for consent withdrawal, if one is provided by the subject, in the subject's study records and on the eCRF. If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, the subject should be asked to return to the study center to complete the assessments specified in the EOS Visit.

If at any time during the study, the investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The investigator can discontinue a subject at any time if medically necessary. Appropriate documentation in the subject's study record and eCRF

regarding the reason for discontinuation must be completed. Prior to discontinuing a subject from study participation, the investigator will discuss his/her intentions with the medical monitor or designee.

All subjects who fail to return to the study center for the required follow-up visits will be contacted by phone to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that contact be made with the investigator.

The sponsor has the right to terminate or to stop the study at any time. Should this be necessary, both the sponsor and the investigator will ensure that proper study discontinuation procedures are completed.

Subjects who sign the informed consent form and are enrolled but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are enrolled and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, if it does not fall within the next visit's window, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. If the re-scheduled visit would fall within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 PROCEDURES AND METHODS

8.1.1 SUBJECT ENTRY PROCEDURES

Subject informed consent must be obtained prior to conducting screening procedures.

At screening, visit procedures include collection of samples for serum chemistry, hematology, PT, [redacted], urinalysis, [redacted], collection of concomitant medication and medical history information. Results from clinical laboratory tests and centrally-read ECGs must be obtained and reviewed by the investigator. Any WOCBP having a positive pregnancy test pre-treatment will not be treated.

After the required screening procedures are completed and study eligibility is confirmed, as defined by the eligibility criteria in **Sections 5.1** and **5.2** a subject will be enrolled in the study and the selected dose of DAXI for injection will be prepared by a trained, dose preparer and administered by the treating investigator.

8.1.1.1 PREGNANCY

A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for 12 consecutive months) or without a uterus and/or both ovaries.

WOCBP and male subjects must, accordingly, use an effective method of birth control such as oral contraceptive, injection, implant, patch, vaginal ring, intrauterine coil or device, tubal ligation, and female/male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). True abstinence (i.e., no heterosexual intercourse), or having a vasectomized partner is considered acceptable methods of contraception. Effective methods of contraception must be used from the start of study, Baseline visit, to 30 days after the end of study participation.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about study participation for WOCBP. The topics should generally include:

- Informed consent document
- Pregnancy prevention information
- Risks to unborn children
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, WOCBP and male subjects must be advised of the importance of avoiding pregnancy during participation in this clinical study from the Baseline visit to 30 days after the end of study participation, and the potential risk factors for an unintentional pregnancy. The subject must sign the informed consent document stating that the above-mentioned risks/consequences were discussed with her/him.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The investigator must immediately notify the sponsor or the authorized representative of any female subject who becomes pregnant any time during study participation. The site will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Given that this is a single treatment

administration study, subjects who become pregnant after receiving their study treatment will not be automatically discontinued from the study, but will NOT receive additional study treatment for the duration of the study.

8.1.2 STUDY VISITS AND PROCEDURES

[redacted]

8.1.2.1 SCREENING VISIT

Subjects will be screened within 3 weeks prior to investigational product administration (Treatment Visit). Screening procedures may be performed over more than one visit within this time period, as necessary.

Specific indication medical history/prior treatment will be captured, including date of CD diagnosis and prior treatment for CD within the past year.

Subjects may be taking prohibited medications that require a washout period that extends beyond the screening period duration. These subjects are to return for a subsequent Screening Visit within 3 weeks prior to the Baseline/Treatment Visit, at which time all screening procedures should be performed as in the SOA (Table 1).

8.1.2.2 BASELINE/TREATMENT/RETREATMENT VISIT

The Baseline Treatment must be performed within 3 weeks of the Screening Visit. Subsequent to qualifying for the study, additional baseline assessments will be obtained (refer to the SOA, Table 1).

[redacted]

[redacted]

8.1.2.4 END-OF-STUDY VISIT

The EOS Visit for each subject in the OLS may occur when the subject:

- Prematurely withdraws from the study for specific reasons (e.g., AEs, pregnancy, or withdraws consent)
- Has no improvement or worsened disease status (i.e., lack of efficacy) after a treatment (consistent with no change or increase from baseline in the average of the TWSTRS-total score at Weeks 4 and 6 post-treatment)
- Requires another treatment less than 12 weeks from the last injection
- Reaches Week 52

Refer to the SOA (Table 1) for EOS activities.

8.1.3 VARIATION FROM SCHEDULED VISIT DAYS

To allow for scheduling flexibility, limited variation will be permitted from the specified time of each visit (Table 3).

Table 3. Allowed Variation from Scheduled Visit Days

Scheduled Visit After Each Treatment	Allowed Variation (calendar days)
Weeks 4 and 6	± 3 days
Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/EOS	± 6 days
Treatment #2, #3, and #4	± 14 days

Note: Two weeks after each Treatment (at Week 2 [allowed variation: ± 3 days]), the subject will be contacted by telephone to follow up on clinical effect, any AEs or changes in concomitant medications.

A subject who experiences significant recurrence of CD symptoms (e.g. pain) during the study before his/her TWSTRS-total score reaches the target TWSTRS score may request another treatment before the next scheduled visit. In this case, the subject may have an unscheduled visit for the investigator to assess whether another treatment is warranted based on the subject's symptoms and neurologic exam findings. If the investigator confirms that retreatment is clinically indicated, the subject may receive another treatment at this visit, unless less than 12 weeks have passed since the last injection or the injection will occur after Week 40 (i.e., there is less than 12 weeks of follow up left in the 52-week study period).

Note: After each Treatment, study visits are reset to begin from that Treatment to Week 4, Week 6, Week 12, and every 4 weeks thereafter.

8.2 SAFETY AND OTHER ASSESSMENTS

Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

8.2.1 PHYSICAL EXAMINATION

A complete physical examination will include examination of the following parameters and body systems: skin, neck (including thyroid), head, eyes, ears, nose, throat, heart, lungs, abdomen, back, lymph nodes, extremities, vascular and neurological (see **Section 8.2.2** for details). If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

At Screening and Baseline Treatment visits, a complete physical examination will be performed. At visits post-treatment, the physical examination may be abbreviated, as deemed medically appropriate at the discretion of the investigator.

Significant physical examination findings which meet the definition of an AE will be recorded on the AE page post-treatment; significant findings that are present prior to investigational product administration are included on the Medical History page.

8.2.2 NEUROLOGICAL EXAMINATION

A standard neurological examination will include assessment of mental status, cranial nerves, motor and sensory function, reflexes, muscle strength, coordination, station and gait.

Significant neurological examination findings which meet the definition of an AE will be recorded on the AE page post-treatment; significant findings that are present prior to investigational product administration are included on the Medical History page.

8.2.3 VITAL SIGNS

Vital signs captured include height (screening only), weight, body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures.

8.2.4 PULMONARY FUNCTION TEST

Pulmonary function will be recorded using spirometry as requested by Regulatory Authorities. Parameters that will be measured are forced vital capacity (FVC), which is the total volume of air exhaled during the forced expiratory volume test, and the forced expiratory volume in the first second of exhalation (FEV_1).

8.2.5 12-LEAD ECG

A single standard supine 12-lead ECG will be obtained after a subject has rested quietly for at least 10 minutes, using equipment provided from the central reader. The ECG is to be repeated up to 2 times if the result is abnormal, as clinically appropriate. ECG data will be submitted to a central reader for measurement.

8.2.6 PREGNANCY TESTING

All WOCBP will have a serum pregnancy test at screening and urine pregnancy test at all designated post-screening timepoints as indicated in the SOA (Table 1). If the urine pregnancy test is positive, a serum pregnancy test will be performed to confirm. If any result is positive prior to investigational product administration, the subject will not be allowed to participate. Refer to **Section 8.1.1.1** for further information.

8.2.7 CLINICAL LABORATORY DATA

As outlined in Table 4, non-fasting samples for serum chemistry, hematology, PT, serum antibodies and urinalysis will be collected at designated study timepoints (refer to Table 1). Blood and urine specimens will be collected using applicable safety precautions and processed according to clinical laboratory instructions.

Table 4. Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Additional Tests
• Hemoglobin • Hematocrit • Leukocyte count (total) • Leukocyte count (differential) • Red blood cell count • Platelet count	• Glucose • Total bilirubin • Alanine aminotransferase • Aspartate aminotransferase • Alkaline phosphatase • Blood urea nitrogen • Pregnancy (WOCBP at Screening) • Potassium • Sodium • Calcium • Carbon Dioxide (Bicarbonate) • Chloride • Creatinine • Total Protein	• Specific gravity • pH • Glucose • Protein • Blood • Bilirubin • Ketones	• Prothrombin time (PT) • Urine Pregnancy (WOCBP only)* • Serum pregnancy test at end of study if urine pregnancy test is positive [redacted]

* If positive at post-treatment timepoints, confirm by serum pregnancy test

It is the investigator's responsibility to review the results of all laboratory tests as they become available. For each laboratory test result outside the reference range, the investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. Likewise, if laboratory tests are taken at follow-up visits, the investigator must ascertain if this is an abnormal and clinically significant change pretreatment for that individual subject. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. The investigator must sign and date all written laboratory results (chemistry, hematology plus PT, and urinalysis) and note Not Clinically Significant (NCS) or Clinically Significant (CS) for each out of range laboratory value. If a laboratory value is determined to be a clinically significant result for that subject, this may be considered an AE. Refer to **Section 8.2** for further information.

[redacted]

8.2.8 INJECTION SITE EVALUATION

Injection sites will be evaluated to determine if there are any injection site reactions to the investigational product. Any injection-related pain, redness, bruising or swelling, etc., will be reported as AEs.

8.2.9 COLUMBIA-SUICIDE SEVERITY RATING SCALE

The C-SSRS is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe subject responses (Appendix H). The C-SSRS is to be administered at each visit, including unscheduled ones. Both the Lifetime/Recent and Since Last Visit versions will be utilized. All assessors will receive formal training in the use of this tool.

A subject who endorses "suicidal ideation" must be referred to a mental health professional for further assessment and/or treatment.

8.2.10 DYSPHAGIA SEVERITY SCORE

The investigator will assess subjects for the presence of dysphagia at Screening, and if present, determine the severity of dysphagia. Subjects who have severe or very severe (Grade 3 or 4) dysphagia at Screening are not eligible to enroll in this study.

Investigator will re-assess the presence of dysphagia and the severity, if present, at the Baseline Treatment Visit prior to study drug administration. If severe or very severe (Grade 3 or 4) dysphagia is present at Baseline, the subject is not eligible to enroll in the study.

When subjects report dysphagia at any post-baseline visits, the investigator will determine the status (ongoing or new) and severity of dysphagia (Grade 1, 2, 3, or 4) using the dysphagia severity scale provided in Appendix I**.** Any post-baseline dysphagia determined by the investigator to be new or ongoing with an increase in severity (grade) relative to Baseline, will be considered an AE and will be recorded on the eCRF. When dysphagia is an adverse event, the dysphagia severity assessment should be performed at every subsequent study visits until the dysphagia has resolved or return to the pre-treatment status.

8.2.11 ADVERSE EVENTS

Adverse Events (AEs) will be graded as mild, moderate, or severe as defined in **Section 8.3.3.1** of this protocol.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

For this protocol, an **AE** is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) that emerges or worsens following administration of the study drug and until the end of study participation. The untoward medical occurrence may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory result), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A TEAE is one that occurs after any exposure to treatment.

A pre-existing condition is one that is present prior to the start of the study and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

Any clinically significant change in the study safety evaluations, (e.g., vital signs, physical/neurological examinations, etc.) post-injection must be reported as an AE.

For each laboratory test result outside the reference range, the investigator must ascertain if the abnormal lab result is a clinically significant result for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed; the investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test. If a laboratory value is determined to be a clinically significant result for a subject, this may be considered an AE.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An **SAE** includes any event that results in any of the following outcomes:

- Death
- Life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe.)
- Persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions
- Requires in-patient hospitalization or prolongs hospitalization (i.e., a prolonged hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or investigational product before conception or during pregnancy)
- Does not meet any of the above serious criteria but based upon investigator's clinical judgment put the subject at significant risk of morbidity or death or may require medical or surgical intervention to prevent one of the outcomes listed above (i.e., is a significant or important medical event)

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The investigator is responsible for evaluating all AEs and determining the severity of the event. Severity will be categorized as mild, moderate, or severe according to the following definition:

- **Mild:** Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- **Moderate:** Event may be of sufficient severity to make a subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- **Severe:** Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Relationship of an AE to investigational product will be assessed as follows:

- **Definite:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; when the event responds to withdrawal of investigational product and recurs with re-administration of investigational product
- **Probable:** There is a clinically plausible time sequence between the onset of the AE and the administration of investigational product; the AE is unlikely to be caused by the concurrent/underlying illness, other drugs or procedures
- **Possible:** There may or may not be a clinically plausible time sequence between the onset of the AE and the administration of investigational product and a cause cannot be ruled out
- **Unrelated:** There is not a temporal or causal relationship to investigational product administration

8.3.3.3 EXPECTEDNESS

The Sponsor medical monitor will be responsible for determining whether an AE is expected or unexpected. An unexpected AE is one not identified in nature, severity, or frequency in the current protocol or Investigator's Brochure.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

8.3.4.1 FOLLOW-UP OF NON-SERIOUS ADVERSE EVENTS

Non-serious AEs that are identified during the last scheduled study visit must be recorded on the AE eCRF as ongoing. If the non-serious AE is dysphagia or the non-serious AE is determined to be related to study treatment by the investigator, the subject should be followed until the dysphagia or drug-related AE resolves, returns to the pre-treatment status, or determines by the investigator to be stable.

Any clinically significant abnormal test results (e.g., laboratory findings, ECG findings) at the final assessment should be followed to resolution or until determined by the investigator to be stabilized. Repeat tests may be indicated to establish this.

If a subject has any clinically significant lab abnormalities at the end of the study, the medical monitor should be notified, and every effort made by the investigator to arrange follow up evaluations at appropriate intervals to document the course of the lab abnormalities.

8.3.4.2 FOLLOW-UP OF POST STUDY SERIOUS ADVERSE EVENTS

SAEs that are identified on the last scheduled contact must be recorded on the AE eCRF page and reported to the sponsor or the authorized representative according to the reporting procedures outlined in **Section 8.3.6**. This may include unresolved previously reported SAEs, or new SAEs. The investigator should follow the SAE until it resolves or is determined by the investigator to be stable, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor or the authorized representative, and the IRB/REB/EC, up to the point the event has resolved or is determined to be stable. Resolution means the subject has returned to the baseline state of health, and stable means the investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the administration of investigational product should be reported to the sponsor or the authorized representative, and the IRB/REB/EC, as required.

8.3.5 ADVERSE EVENT REPORTING

The investigator will assess subject post-treatment and at each subsequent study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and eCRFs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

An investigator must report an SAE to the sponsor or the authorized representative within **24 hours** of their awareness of the event:

1. Complete and return an SAE Form with all information known to date; including the investigator's assessment of causality.

2. If the event is fatal or life-threatening, telephone the sponsor or the authorized representative as soon as the investigator learns of the event.

3. Obtain and maintain all pertinent medical records (discharge summary, autopsy report, etc.) and clinical judgments of medical personnel who assisted in subject's treatment and follow-up.

4. Provide follow-up information to the sponsor or the authorized representative.

Regulatory authorities, IRBs/REBs/ECs, and investigators will be notified of SAEs in accordance with applicable regulations and requirements (e.g., GCPs, ICH Guidelines, national regulations and local requirements).

The investigator will collect information on SAEs until subject's health has returned to baseline, the SAE has stabilized, or remaining health issues have otherwise been explained.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The sponsor will disclose clinical trial data to individuals, to investigators at clinical sites, and publicly as aggregate summaries, in accordance with applicable regulations and requirements.

8.3.8 EVENTS OF SPECIAL INTEREST

8.3.8.1 CLINICAL DIAGNOSTIC CRITERIA FOR ANAPHYLAXIS QUERY

Anaphylaxis is highly likely when any *one (1)* of the following three (3) criteria are fulfilled:
(*Sampson et al., 2006*)

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   And at least *one (1)* of the following

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two (2) or more of the following that occur rapidly after exposure *to a likely allergen for that subject* (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

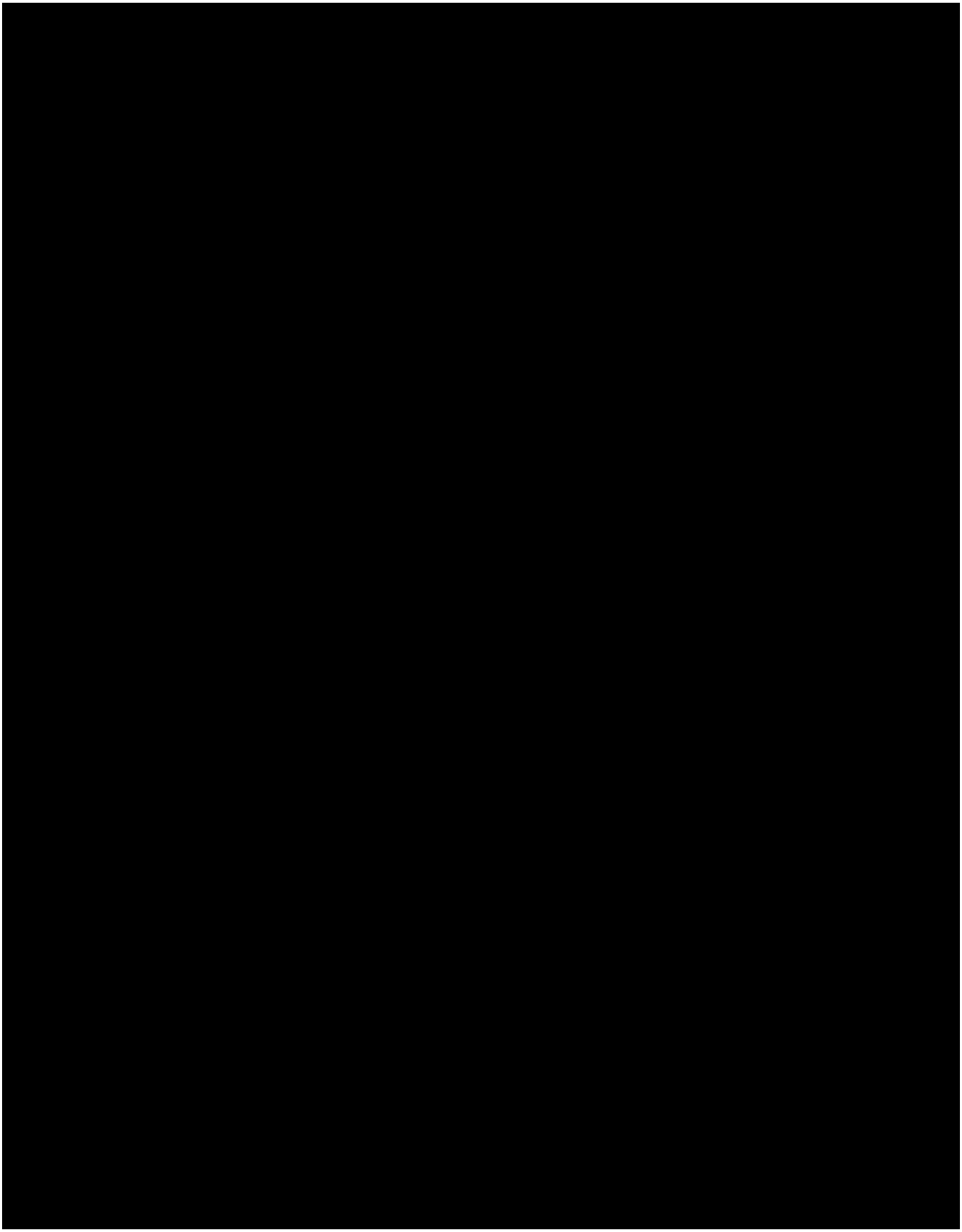
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that subject* (minutes to several hours):

   a. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

[redacted]



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8.3.9 REPORTING OF PREGNANCY

During the trial, all WOCBP should be instructed to contact the investigator immediately (within 24 hours) if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The investigator must immediately notify the sponsor or the authorized representative of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and send the form to the authorized representative. The site will be asked to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Subjects who become pregnant during the study will not be discontinued from the study, but will NOT receive additional treatment in the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

In accordance with the Office for Human Research Protections (OHRP), FDA final rule and the European Union Directive 2001/20/EC, unanticipated problems (UPs) will be defined as follows:

- Untoward and unintended responses to an investigational medicinal product related to any dose administered
- Unexpected in terms of the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)
- Serious in that it results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect
- A reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP). This means that there are facts (evidence) or arguments to suggest a causal relationship

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report UPs to the reviewing IRB/REB/EC and sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB/REB/EC project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the Regulatory Authorities and IRB/REB/EC, in accordance with applicable regulations and requirements, within **7 days** and to the sponsor within **24 hours** of the investigator becoming aware of the event.
- Any other UP will be reported to the Regulatory Authorities and IRB/REB/EC, in accordance with applicable regulations and requirements, within **14 days** and to the sponsor within **14 days** of the investigator becoming aware of the problem.

All suspected unexpected serious adverse reactions (SUSARs) will be reported in compliance with the requirements of the respective Regulatory Authority.

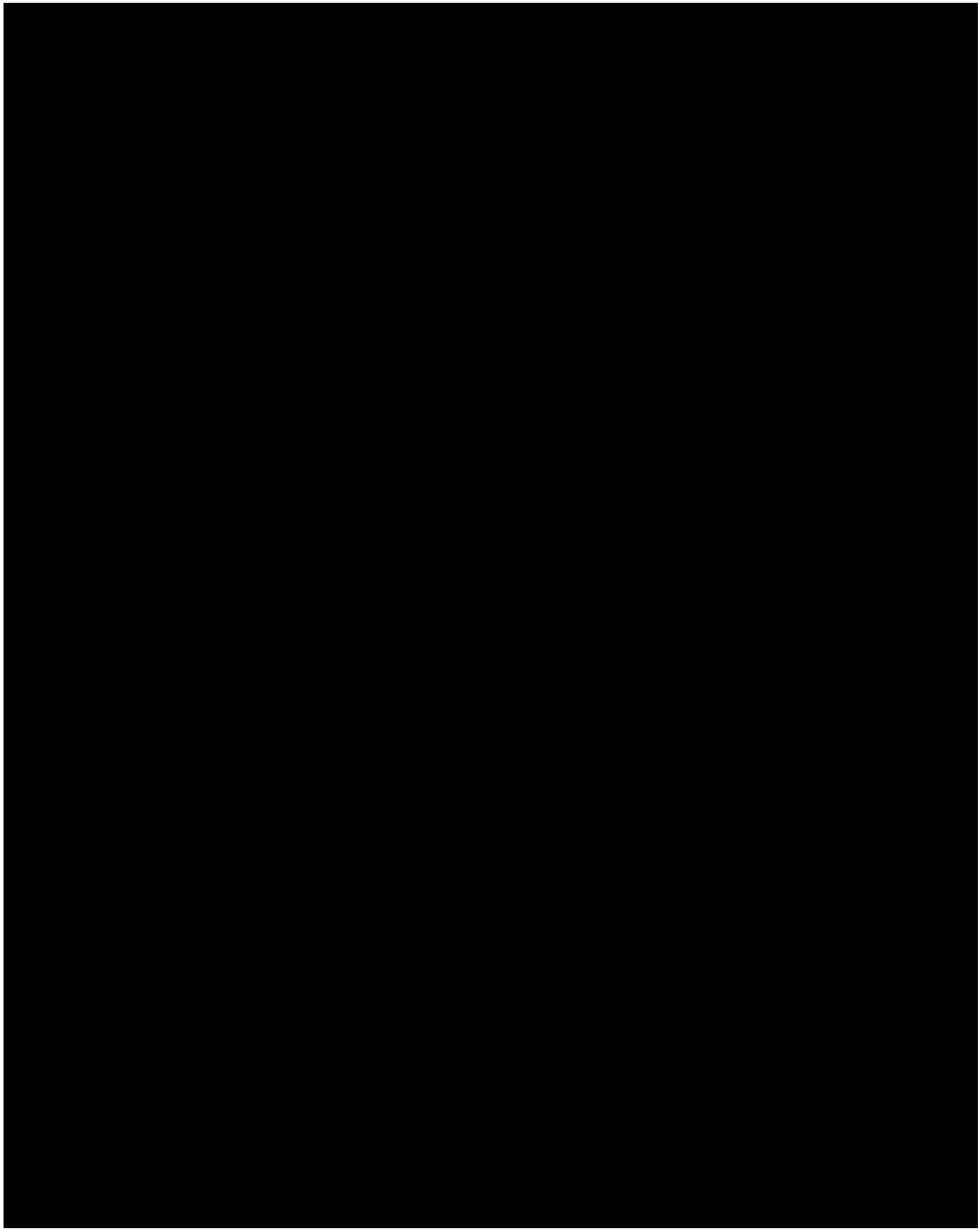
8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The sponsor will disclose clinical trial data to individuals, to investigators at clinical sites, and publicly as aggregate summaries, in accordance with applicable regulations and requirements.

8.5 EFFICACY ASSESSMENTS

As part of study preparations, investigators will receive standardized training on the efficacy assessments in this study. It is recommended that the same investigator perform all efficacy assessments for a given subject from Baseline to end of study.

[redacted]



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9 STATISTICAL ANALYSIS

All statistical analyses will be performed using Statistical Analysis Software (SAS®) version 9.3 or higher. A statistical analysis plan (SAP) will be created during the study conduct.

Efficacy and safety data will be summarized with descriptive statistics. Multiple imputation with MMRM will be used to impute the missing TWSTRS-total scores up to subject discontinuation or completion. In the case a subject is lost to follow-up, no imputation will be done beyond their last date of contact. No imputations will be made for safety or efficacy data other than the TWSTRS-total score.

Efficacy endpoint based on the Total TWSTRS will be summarized for the ITT (multiple imputation) and for and PP populations. All other efficacy endpoints will be summarized for the ITT (observed cases) and for PP populations.

Safety data will be summarized for the safety population.

9.1 SAMPLE SIZE JUSTIFICATION

The sample size for this study is based on a requirement from Regulatory Authorities to collect safety data on approximately 350 subjects treated once and long-term safety data on at least 100 adult subjects with isolated cervical dystonia treated with 3 or 4 continuous treatment cycles of low-dose or high-dose DAXI for injection, with at least 50 subjects treated with the high-dose DAXI for injection for 3 or 4 continuous treatment cycles. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3 PRIMARY STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives:

- To evaluate the long-term safety of multiple continuous treatments of DAXI for injection
- To assess immunogenicity to BoNTA and RTP004 after multiple treatments of DAXI for injection

Primary Endpoints:

- Dose- and cycle-specific incidence of drug-related adverse events
- Dose- and cycle-specific incidence of drug discontinuation due to drug-related AEs
- Dose- and cycle-specific incidence of immunogenicity

[redacted]

[redacted]

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

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9.6 PLANNED ANALYSES

All efficacy endpoints, including responder rates, will be summarized with descriptive statistics by dose and/or treatment cycle, unless otherwise specified.

Discontinuation rate will be summarized by dose and cycle as well as overall. Additionally, the number of weeks on study will be summarized with descriptive statistics.

Duration of effect after each treatment, defined as time (number of weeks) from treatment until loss of 80% of the peak treatment effect (i.e., the average of the change from baseline in the TWSTRS-total score at Weeks 4 and 6)

- If a subject has no reduction in the TWSTRS-total score at Week 4 and Week 6, his/her duration of effect will be set to 0. If a subject discontinues or withdraws from the study prior or at Week 6, his/her duration of effect will be set to 0.
- If a subject discontinues or withdraws from the study prior to reaching his/her target TWSTRS score at any visit after Week 6, his/her duration of effect will be censored at the last visit. If a subject rolled over from Study Protocol 1720302 at Week 36 prior to reaching his/her target TWSTRS score, his/her duration will be calculated from the injection date in Study Protocol 1720302 to the time his/her TWSTRS-total score reaches/exceeds the target TWSTRS score.

Kaplan-Meier survival curves will be plotted for each dose level for the time-to-event endpoints. Point estimate of median duration and 2-sided, 95% confidence intervals (CIs), will be generated using the log-rank test. A subject might be counted more than once or in multiple groups due to multiple injections cycle. Exploratory statistical comparisons between subgroups and duration of response evaluation may be performed.

[redacted]

No interim analysis is planned.

9.7 POPULATIONS

9.7.1 INTENT-TO-TREAT

The Intent-to-Treat (ITT) population is defined as all subjects who enrolled and were treated with at least one dose of study drug.

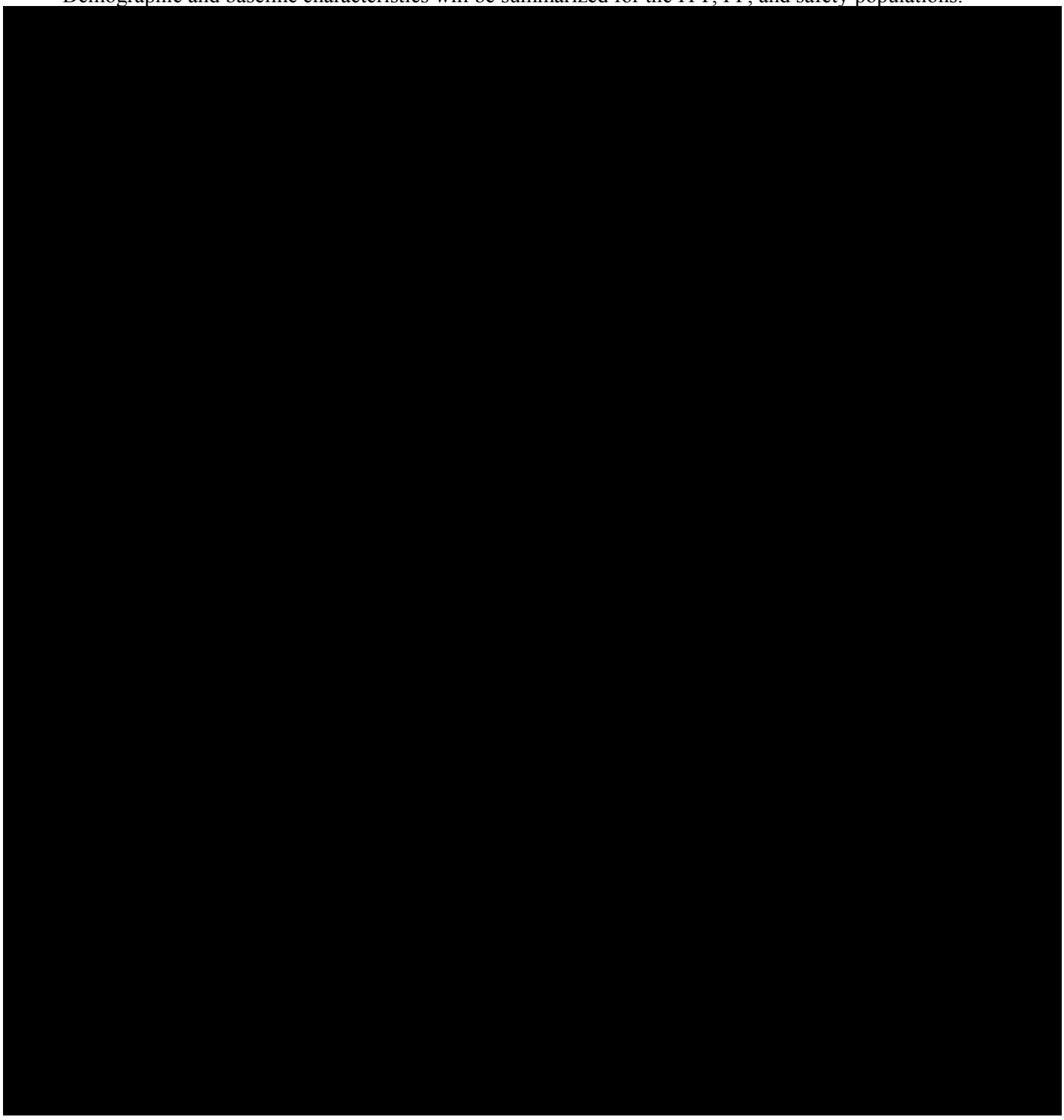
The ITT population will be analyzed by treatment dose.

[redacted]

9.7.3 SAFETY

The safety population is defined as all subjects who enrolled and received at least 1 dose of study drug. The safety population will be analyzed by treatment dose the subject received rather than the treatment dose selected for the subject by the Investigator. The safety analysis set will be used to conduct safety analyses.

Demographic and baseline characteristics will be summarized for the ITT, PP, and safety populations.



9.13 PROTOCOL DEVIATIONS

Subjects with major protocol deviations will be excluded from the PP population. Protocol deviations will be summarized for all enrolled subjects. A data listing will be provided by subject.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Written informed consent will be obtained from all subjects before any study-related procedures (including any pre-treatment screening procedures) are performed. The investigator may discuss the study and the possibility for entry with a potential subject without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, and including withdrawal from current medication (if required prior to study entry). The investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this study has been given a full explanation of the procedures and expectations for study participation.

When applicable, the site-specific informed consent must be forwarded to the sponsor for approval prior to submission to an IRB/REB/EC that is registered with appropriate local or federal agencies as required. Each subject will sign the consent form that has been approved by the same IRB/REB/EC that was responsible for protocol approval. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, Health Canada's Food and Drug Regulations, Division 5, European Medicines Agency (EMA), as well as the elements required by the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guideline, and applicable national and local regulatory requirements. The consent form must also include a statement that the sponsor, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

Once the appropriate essential information has been provided to the subject and fully explained by the investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the study, the IRB/REB/EC approved consent document shall be signed and dated by both the subject and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/REB/EC or other Regulatory Authorities. The subject will be given a copy of the

signed informed consent document with the original kept on file by the investigator. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND)/Clinical Trial Application (CTA) sponsor and Regulatory Authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB/REB/EC, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, REB, EC and/or FDA, EMA and Health Canada.

[redacted]

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an independent Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB) composed of individuals with the appropriate expertise, including indication and/or neuromodulators and/or data management. The DMC/DSMB will be appointed to review safety data during the study and will monitor quality and completeness of the safety data, as well as signals and outcomes (SAEs, AEs, laboratories, and other outcome data). Data will be reviewed unblinded, as this is an open label study.

The DMC/DSMB will consist of 5 members, including a chair, a biostatistician, two neurologists, and a pulmonologist. Details of the composition, identity of members, and scope of the committee's mandate will be presented in a DMC/DSMB charter document.

10.1.7 CLINICAL MONITORING

All aspects of the study will be monitored by the sponsor or authorized representatives of the sponsor according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]). [redacted]

[redacted]

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

For this study, all protocol-specified data will be recorded in the source documents, and data will be entered on the eCRFs from the source documents. In addition to signature confirmation that a subject meets the study eligibility criteria, upon each subject's completion of the study, the investigator will sign a statement indicating that all pages of the subject's case report have been reviewed. Signature stamps and "per signatures" are not acceptable.

It is sponsor's policy that the study data be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to Screening.

Checks will be performed to ensure the quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the investigator or study coordinator. Data queries, documented on data query forms, will be sent to the research facility. Site personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate. All unused sponsor source documents and binders must be returned to the sponsor upon completion of the study.

The investigator must keep written or electronic source documents for every subject participating in the clinical study. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name

- Contact information
- Age
- Sex
- Medical history
- Concomitant diseases
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (e.g., laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to the sponsor. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study. The investigator will ensure that the study documents forwarded to the sponsor, and any other documents, contain no mention of subject names.

Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate) and countersigned by the investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Regulatory authorities, the IRB/REB/EC and/or the sponsor's Quality Assurance group (or designee) may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. The investigator must guarantee direct access to these documents. Electronic CRFs (eCRFs) will be kept by the sponsor or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by the sponsor after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

10.1.9.2 STUDY RECORDS RETENTION

It is a sponsor requirement that all investigators participating in clinical studies maintain detailed clinical data for one of the following periods:

- Country-specific requirements, or
- A period of at least two years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or
- A period of two years after the sponsor notifies the investigator that the data will not be submitted for review by any Regulatory Authority

The investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor and relevant regulatory agencies. If the investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to sponsor in writing.

10.1.9.3 TREATMENT OF MISSING DATA

Some data elements will be missing in this study due to subjects who withdraw from the study, subjects who are lost to follow-up, or subjects who do not complete all study visits. The completion status of each subject will be documented (e.g., completed protocol, withdrew from study, lost to follow-up, etc.). All reasonable efforts will be made by the study staff to maintain contact with the study participants during their participation in the study. The study coordinator will attempt to contact any subjects who are lost to follow-up. For subjects who are unwilling to return to clinic for follow-up, the study coordinator will attempt to contact them and to collect study data from them during a telephone call or by forms sent to them through the mail.

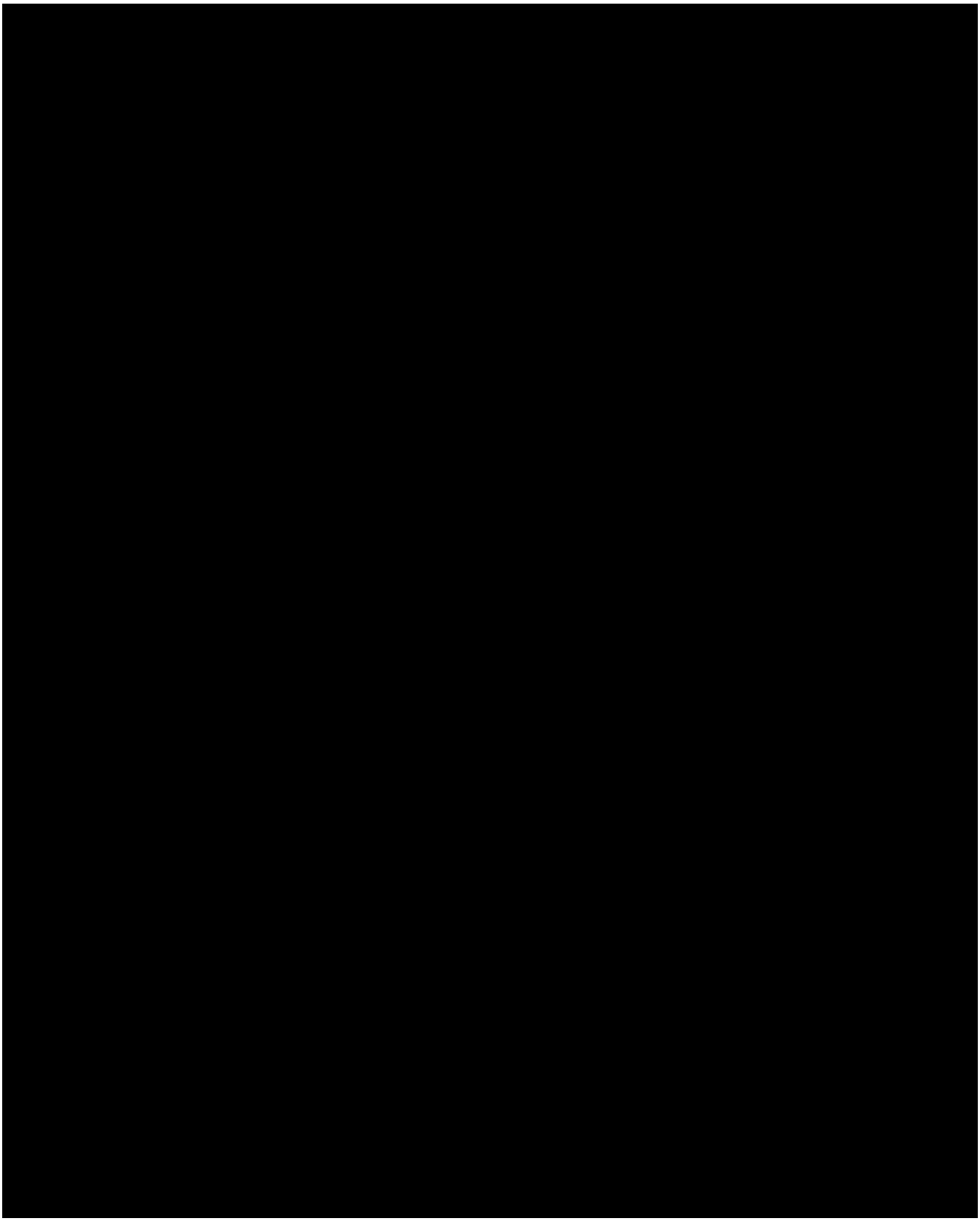
10.1.9.4 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and must be sent to the reviewing IRB/REB/EC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/REB/EC requirements.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the medical monitor and the sponsor at the earliest possible time by

telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the medical monitor.



10.2 ADDITIONAL CONSIDERATIONS

10.2.1 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, the Declaration of Helsinki, IRB, REB, or EC requirements and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and informed consent form by an HHS-registered IRB/REB/EC) to the sponsor before investigational product will be shipped to the study site.

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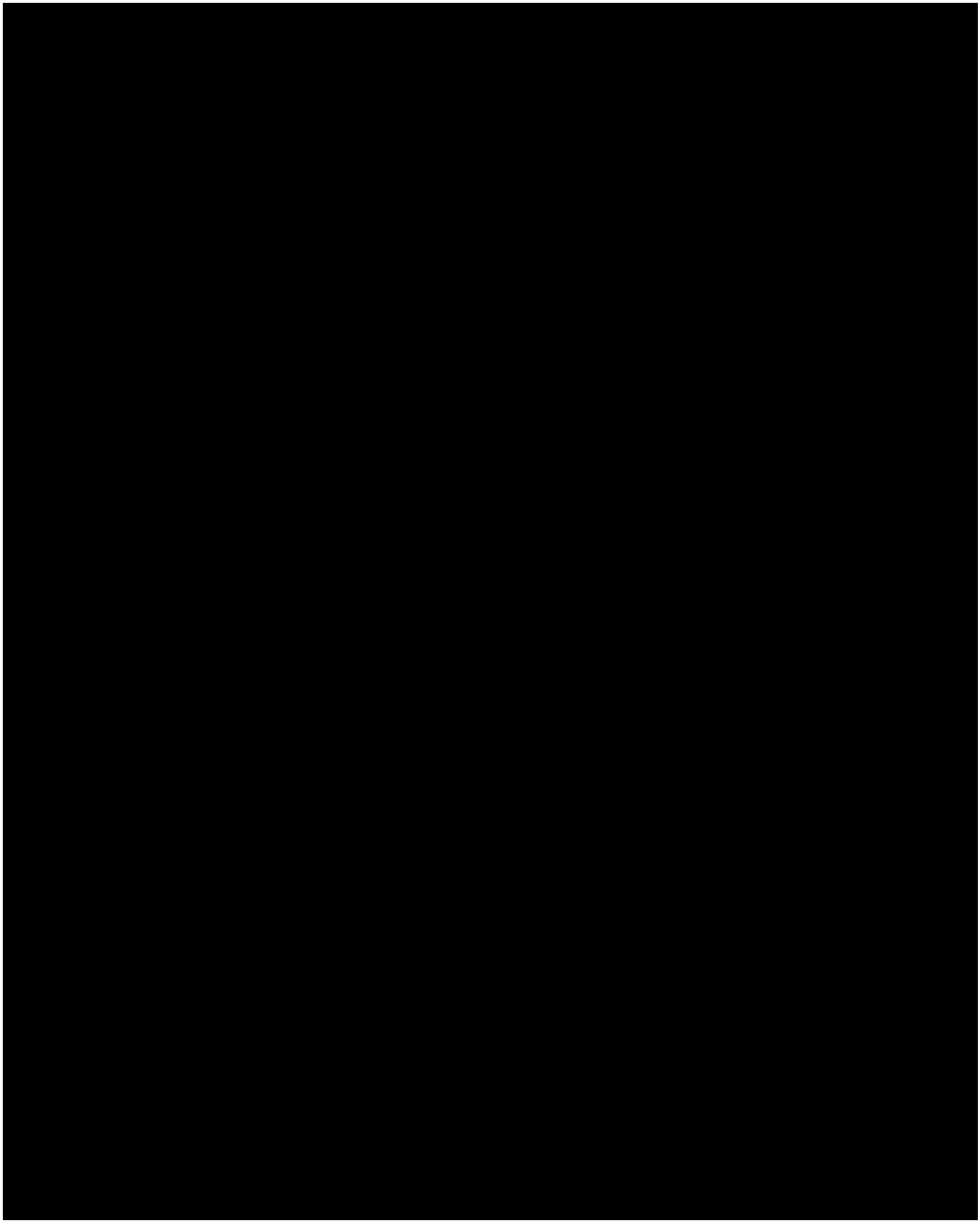
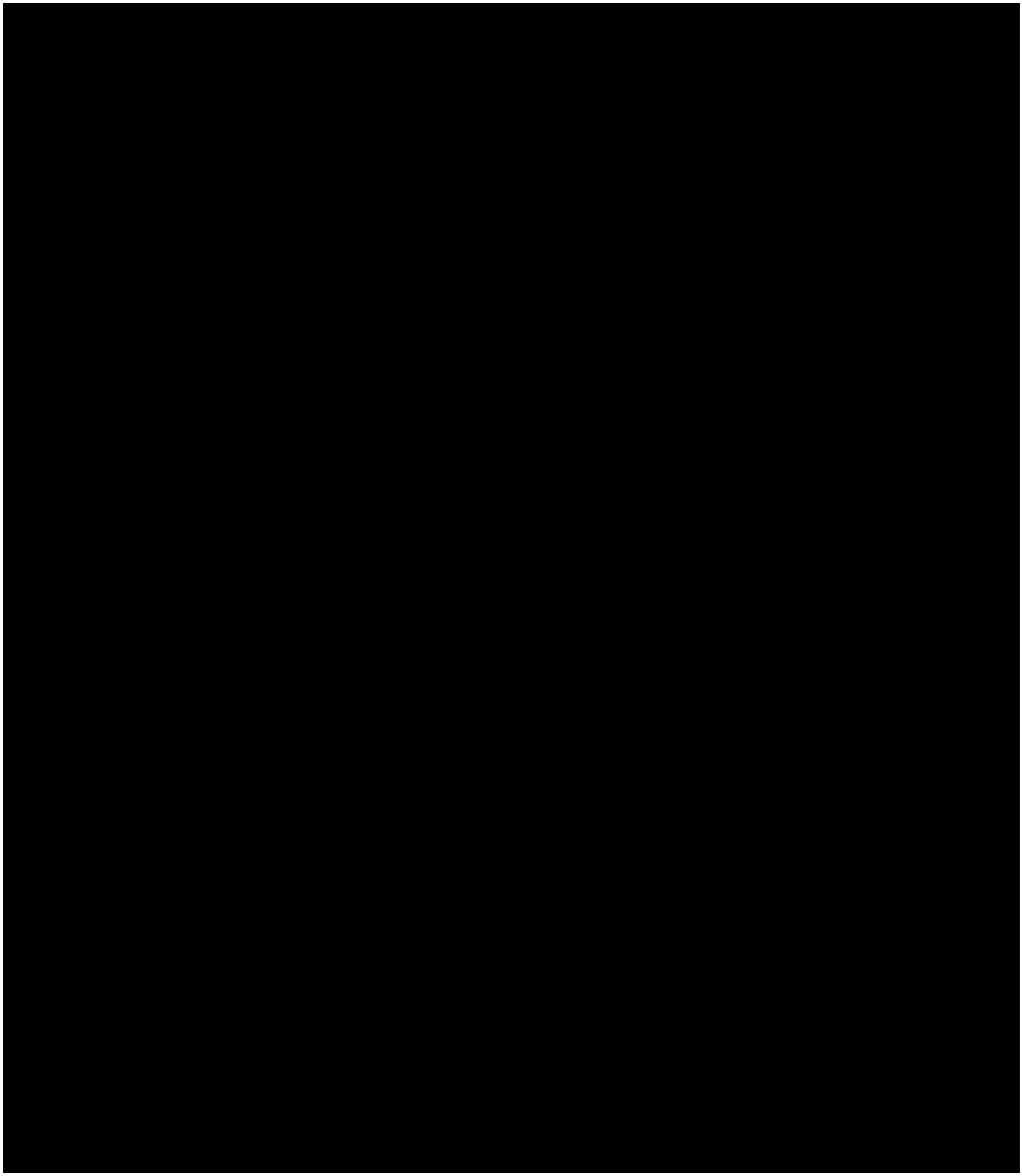
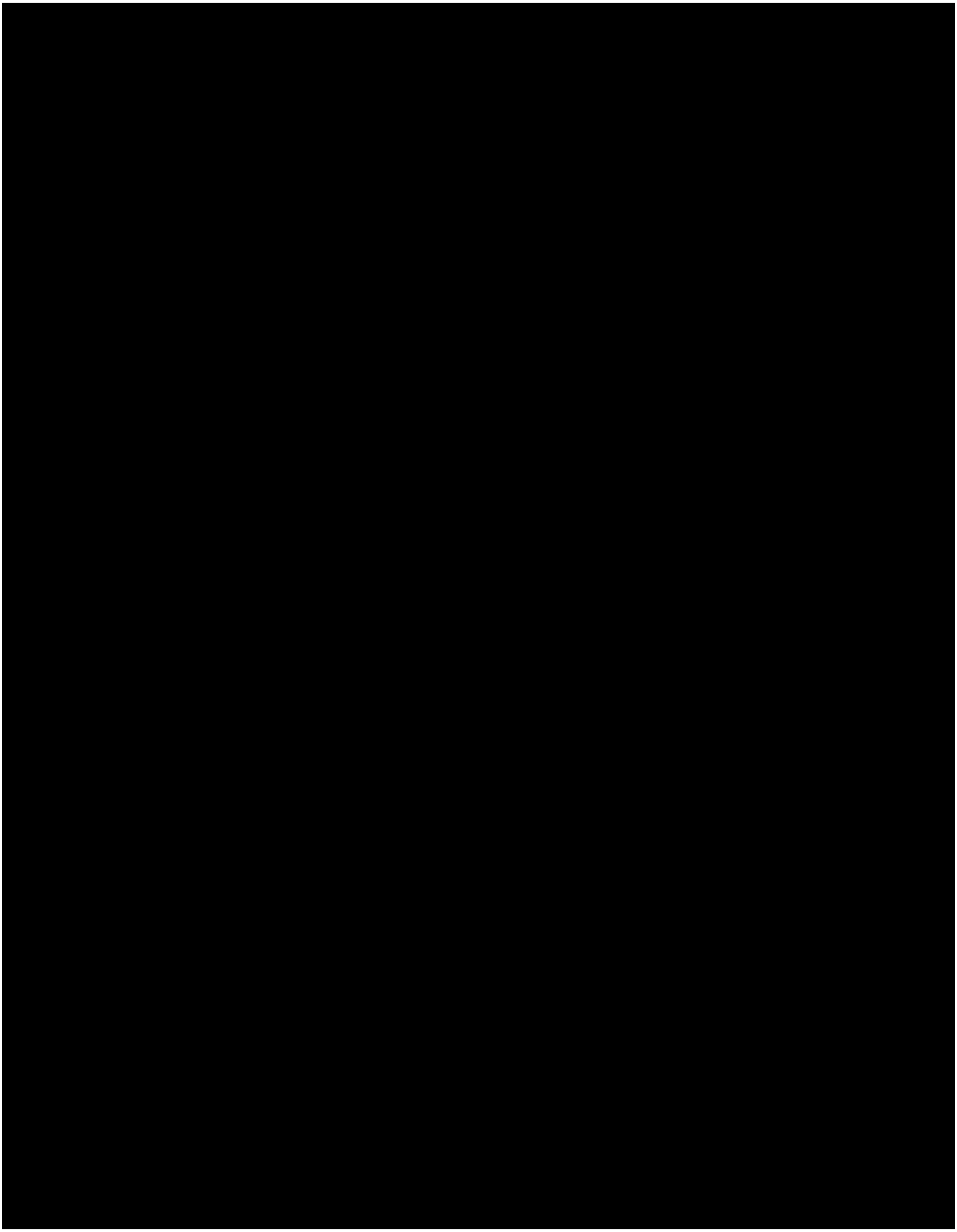
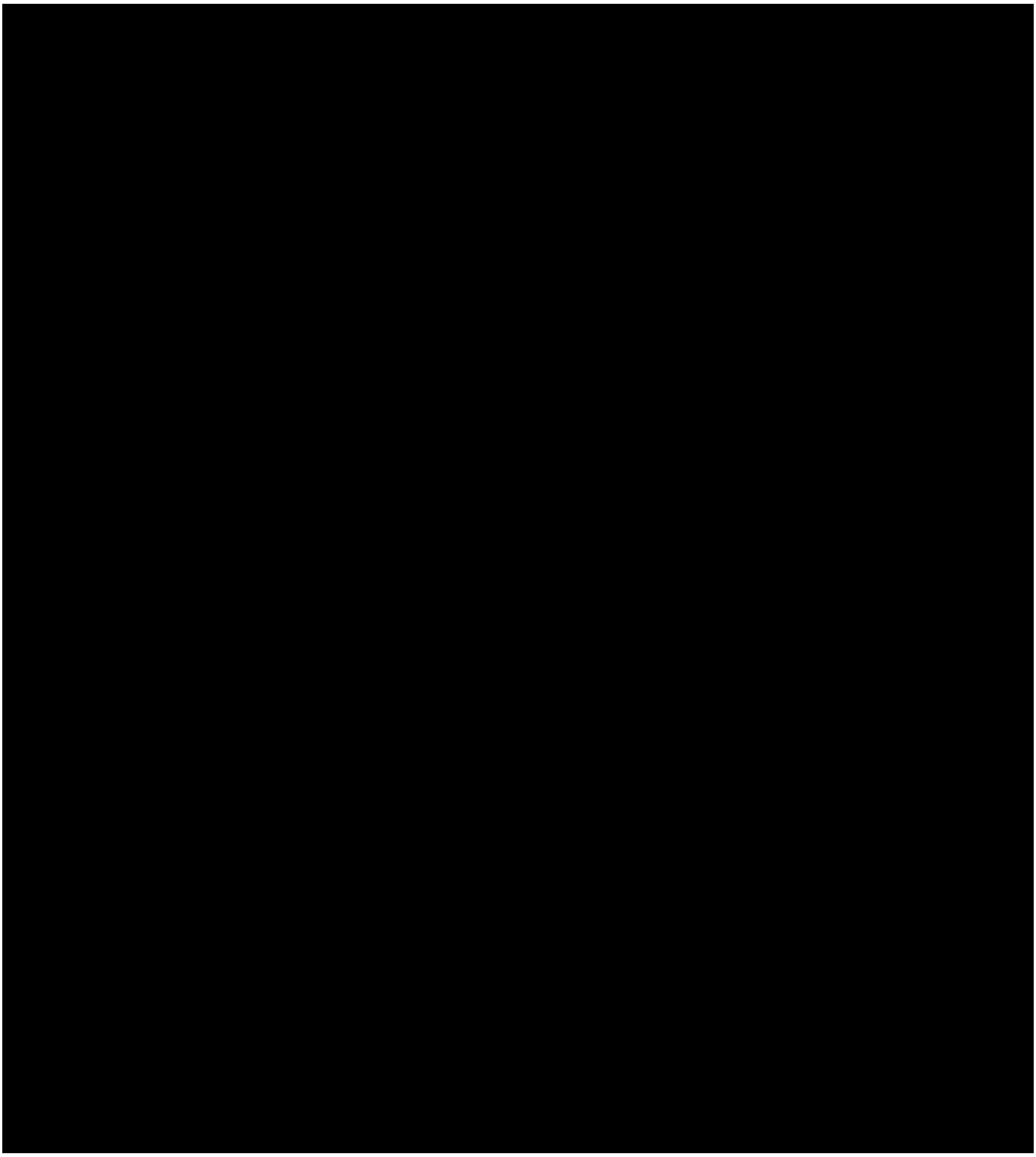
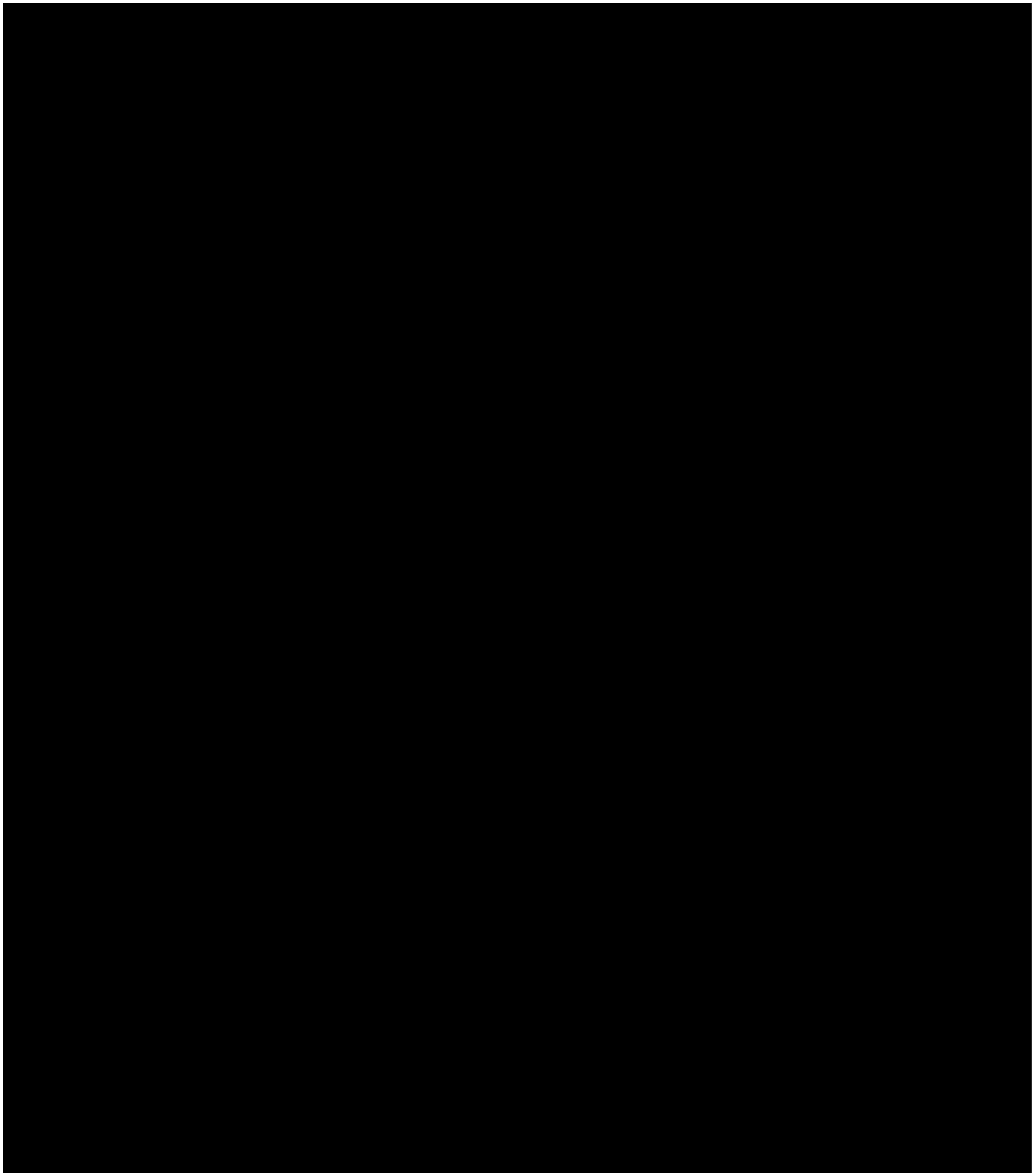


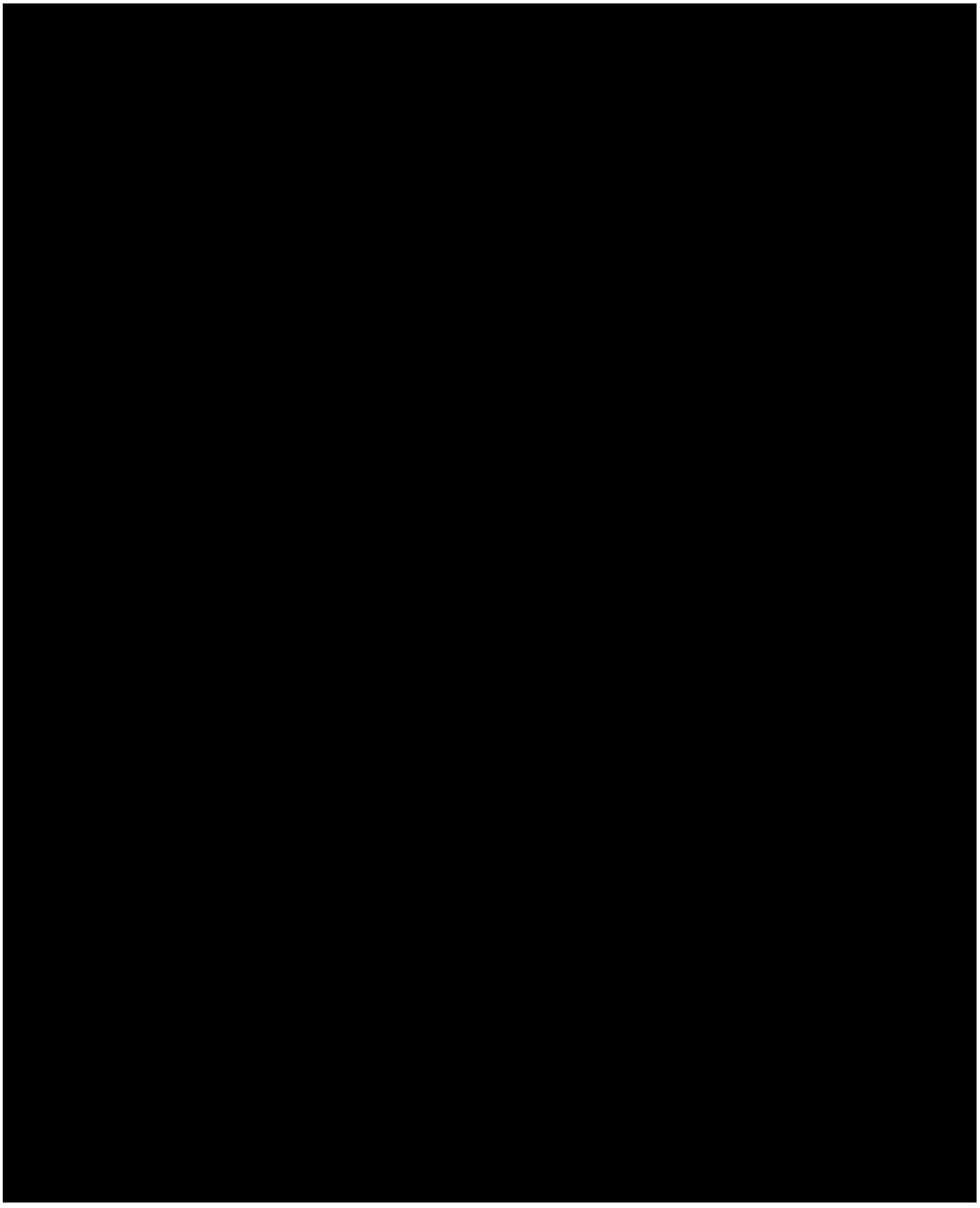


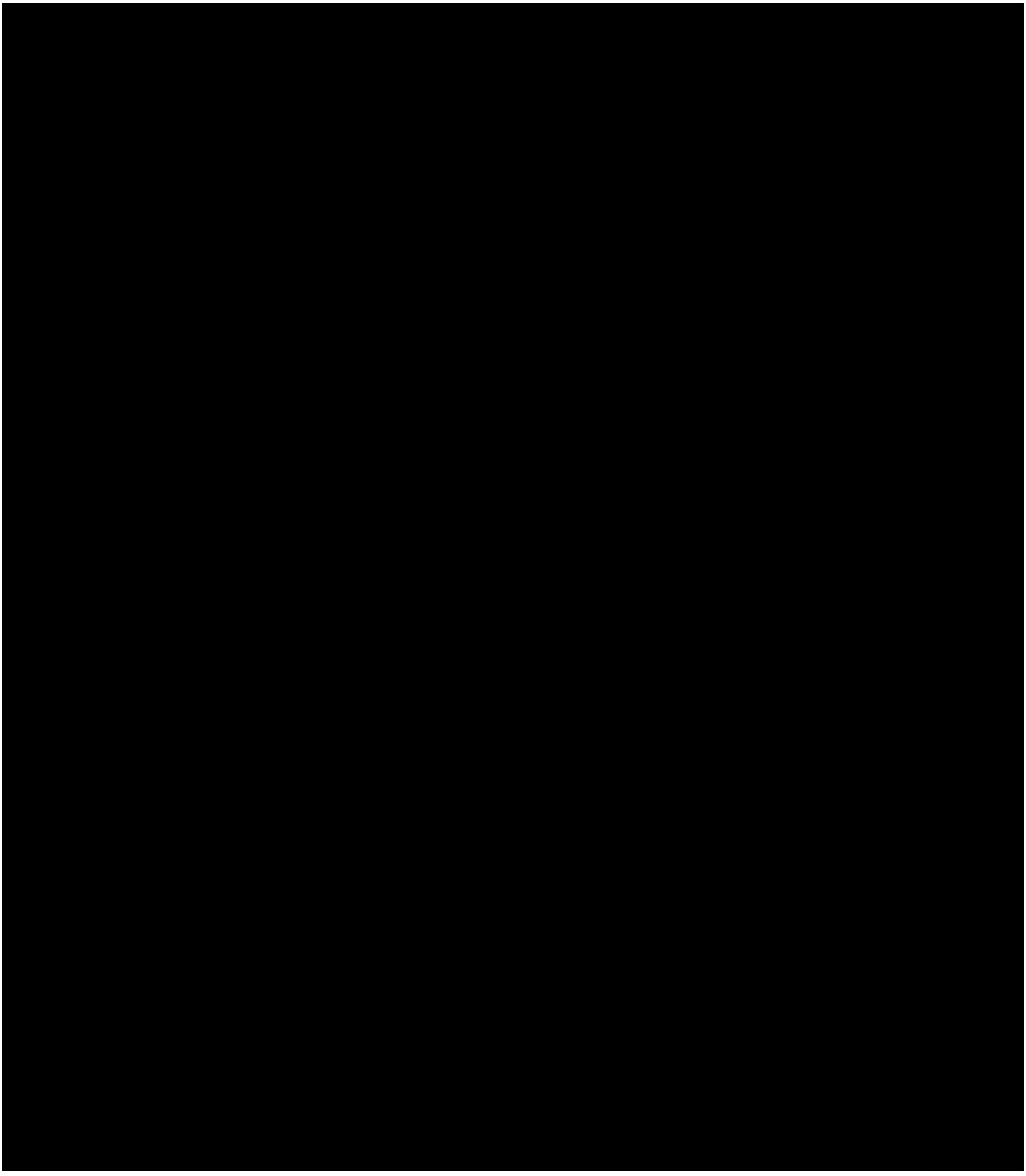
*UNILATERAL injection only

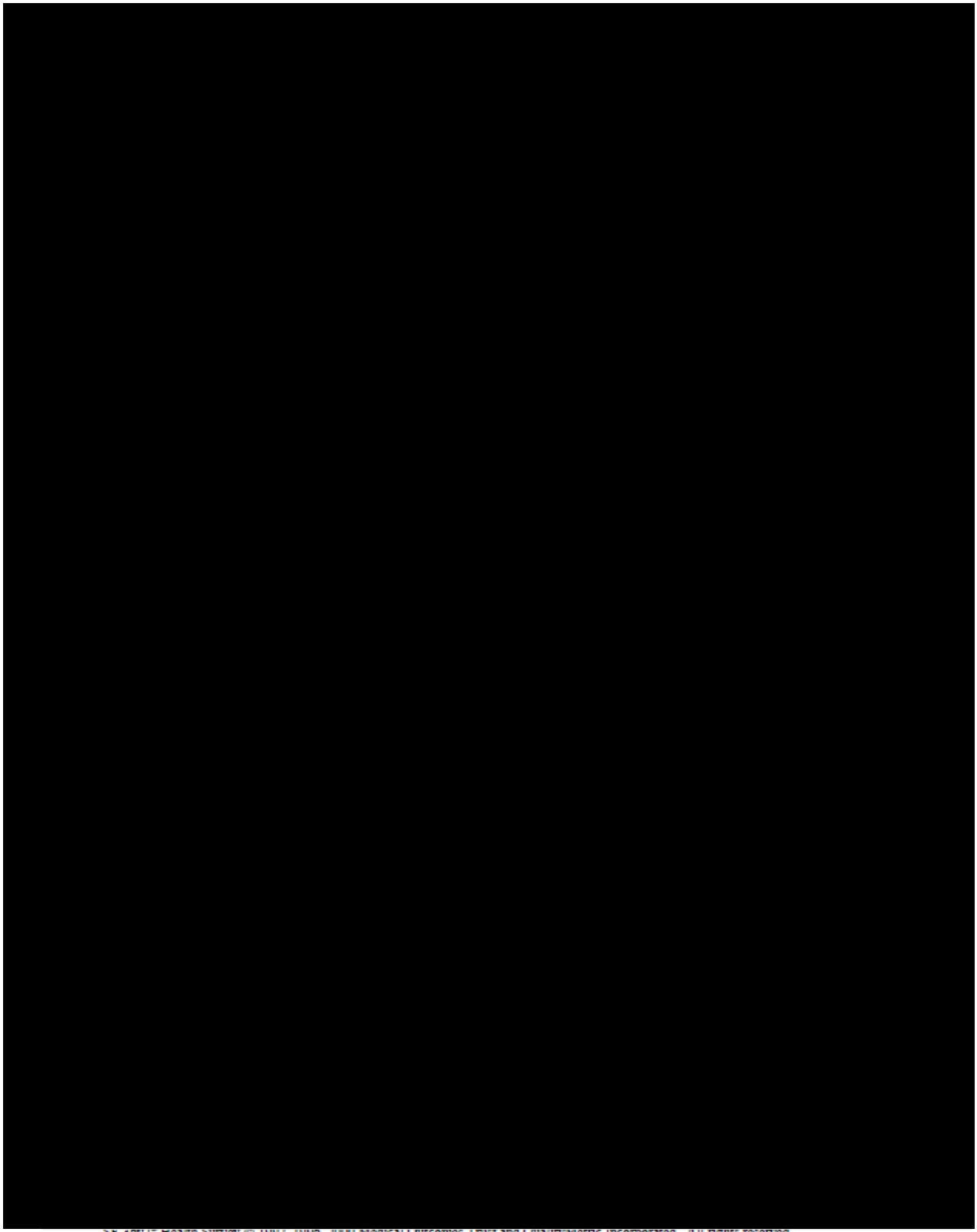


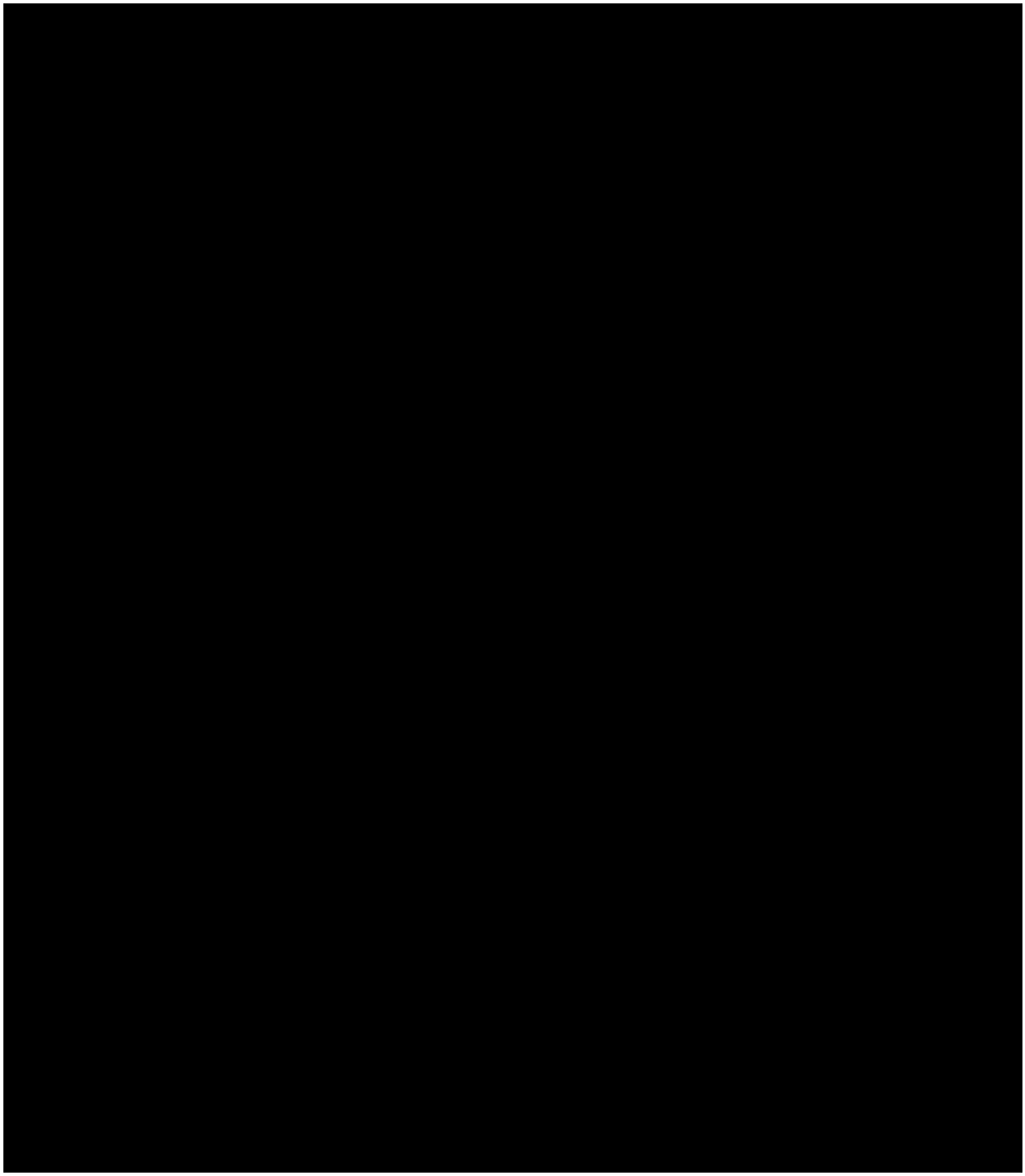


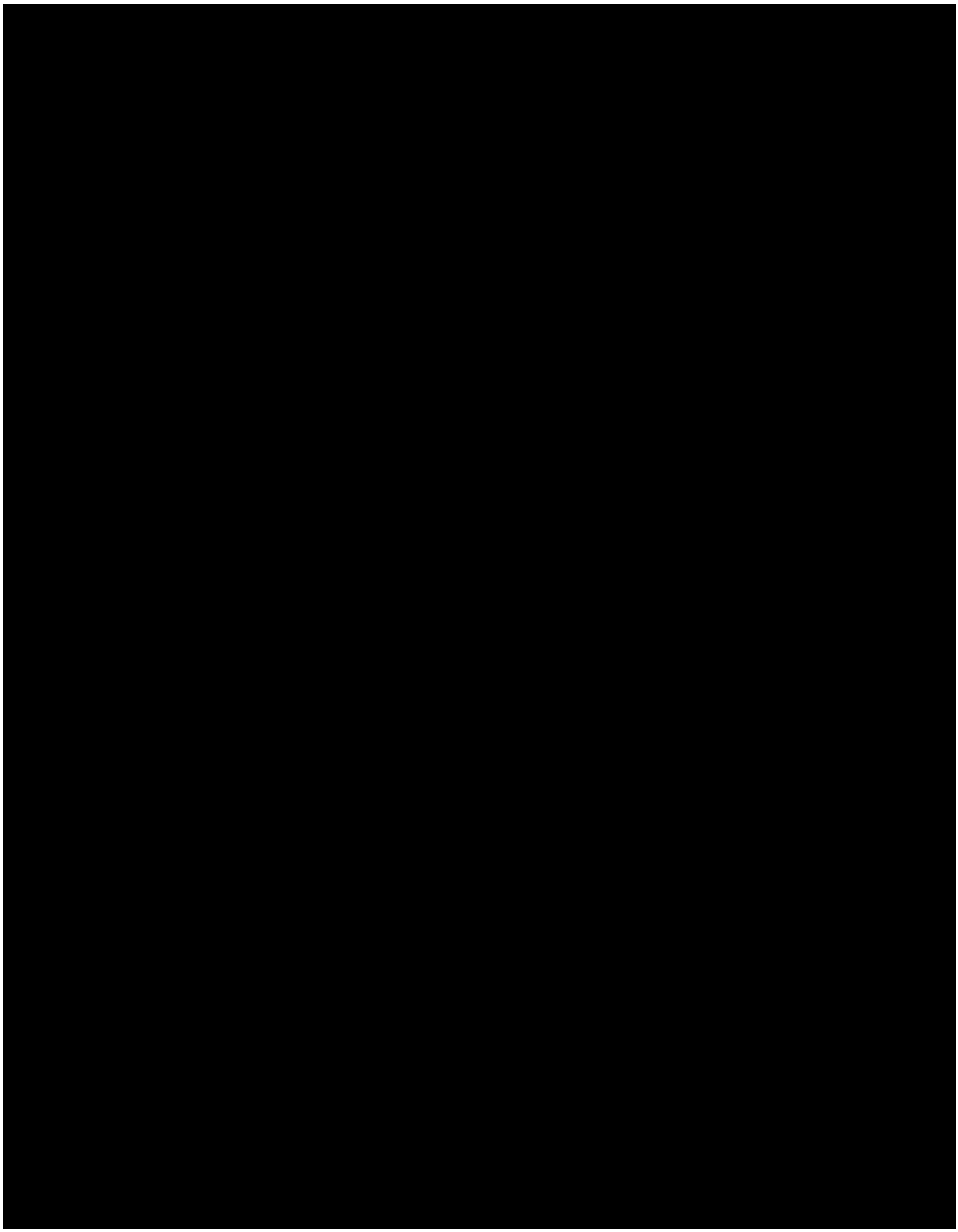


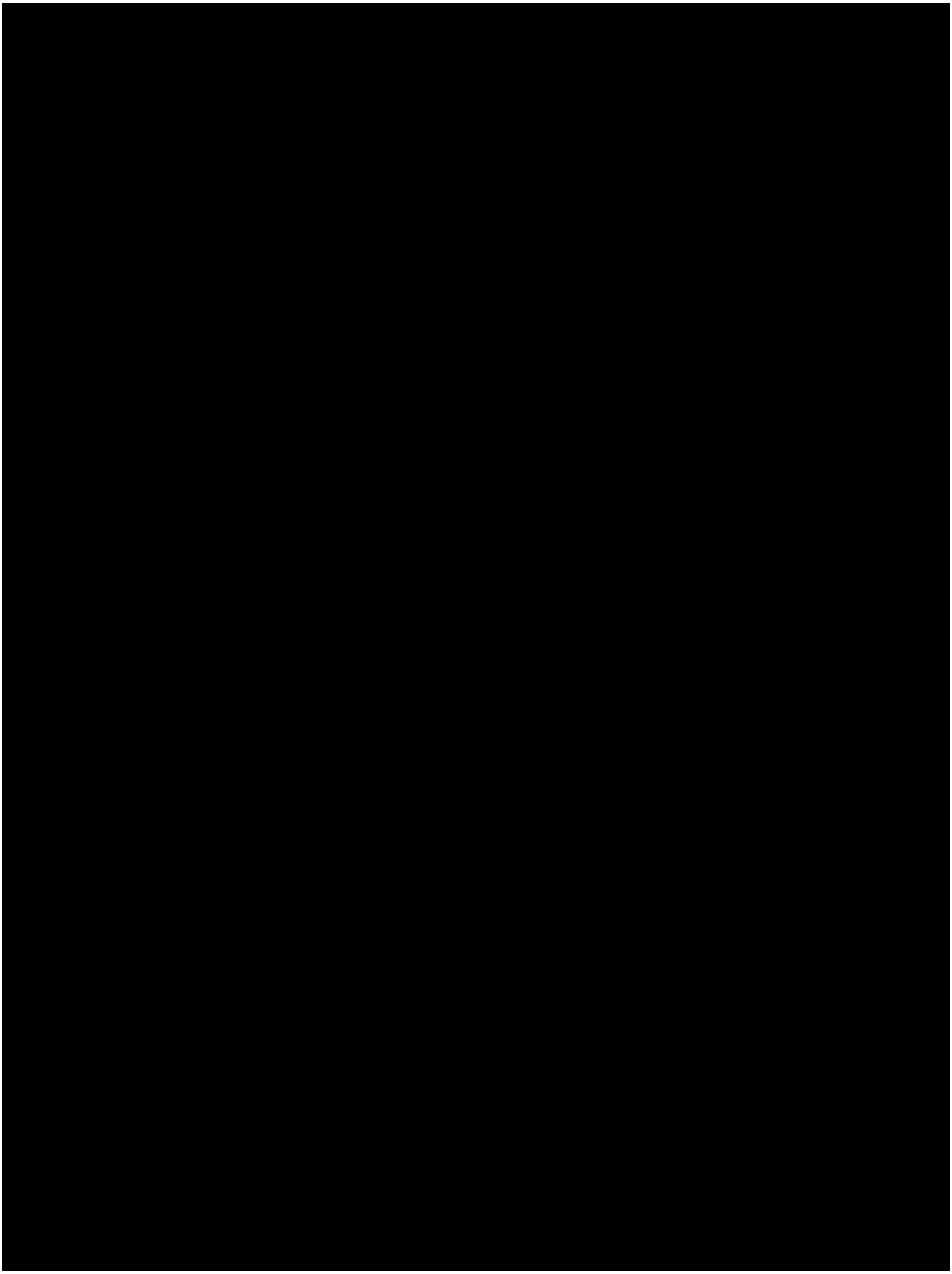


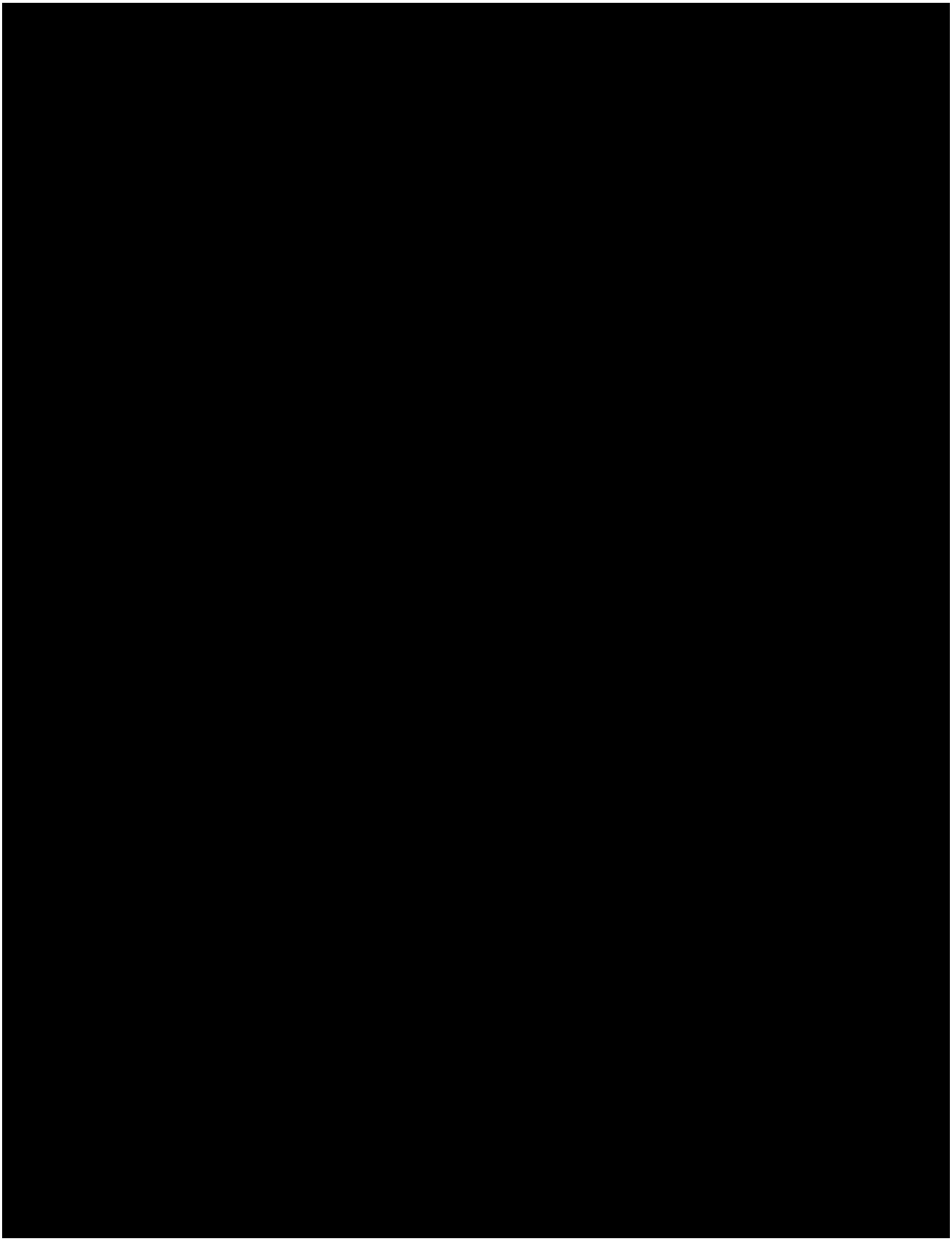


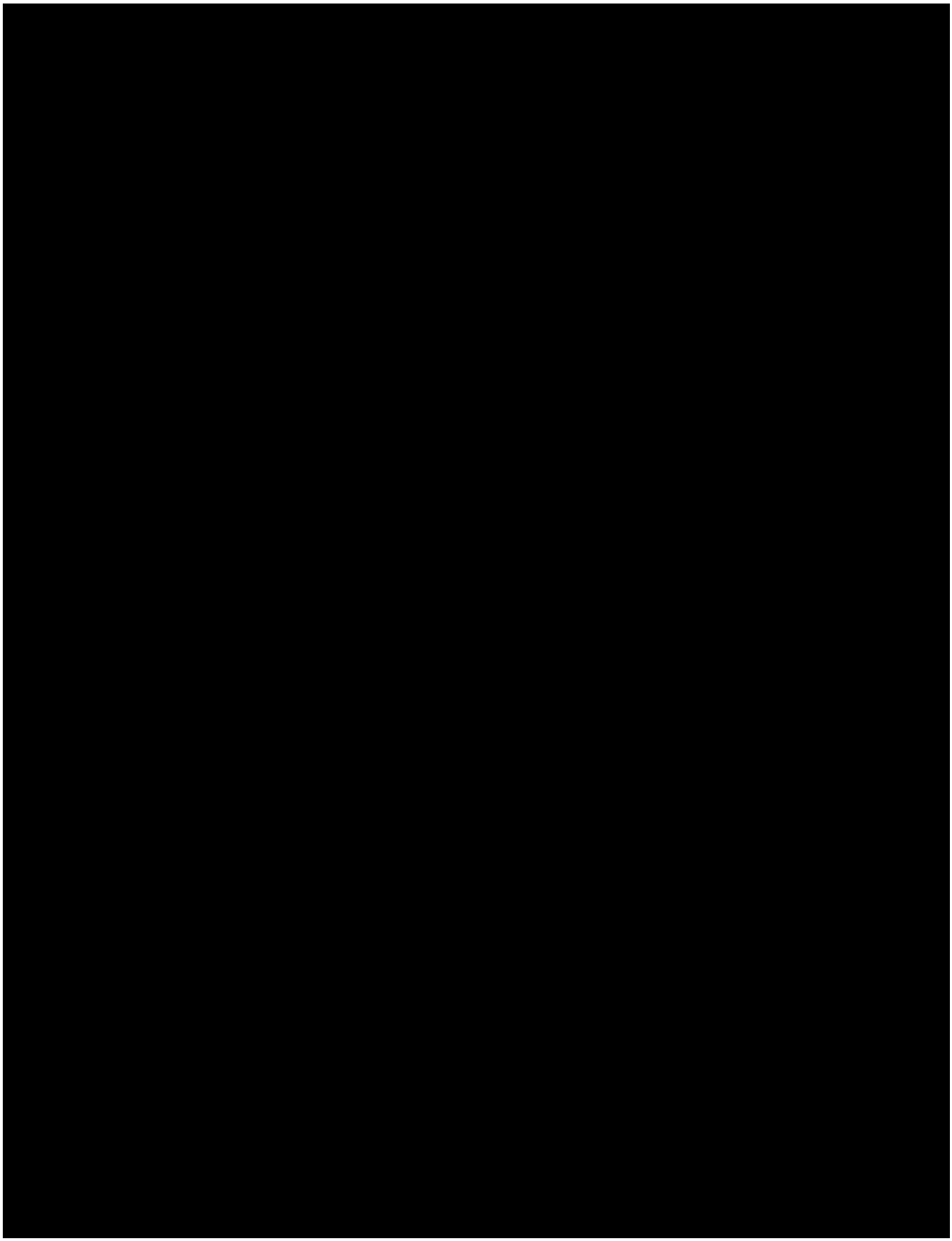


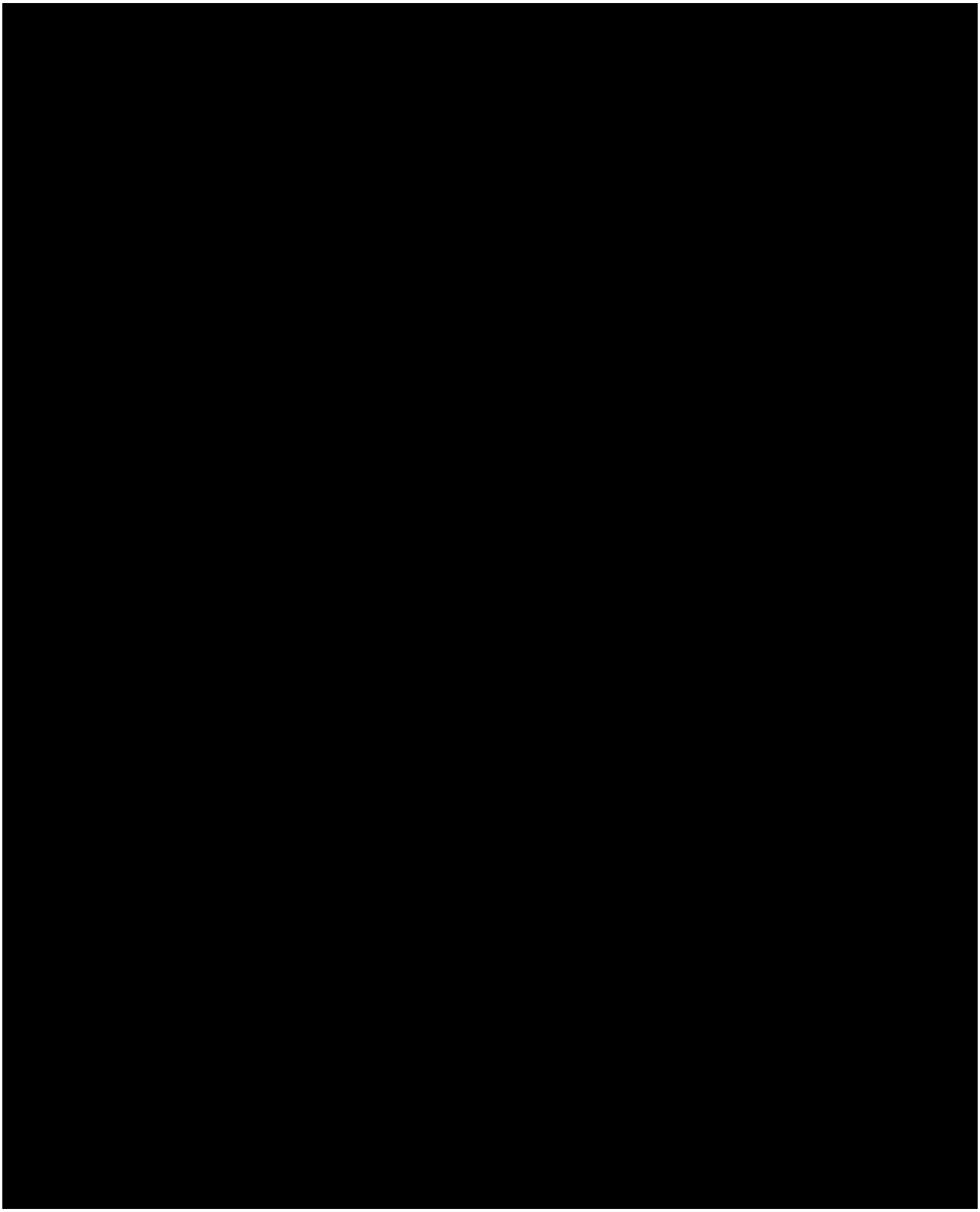


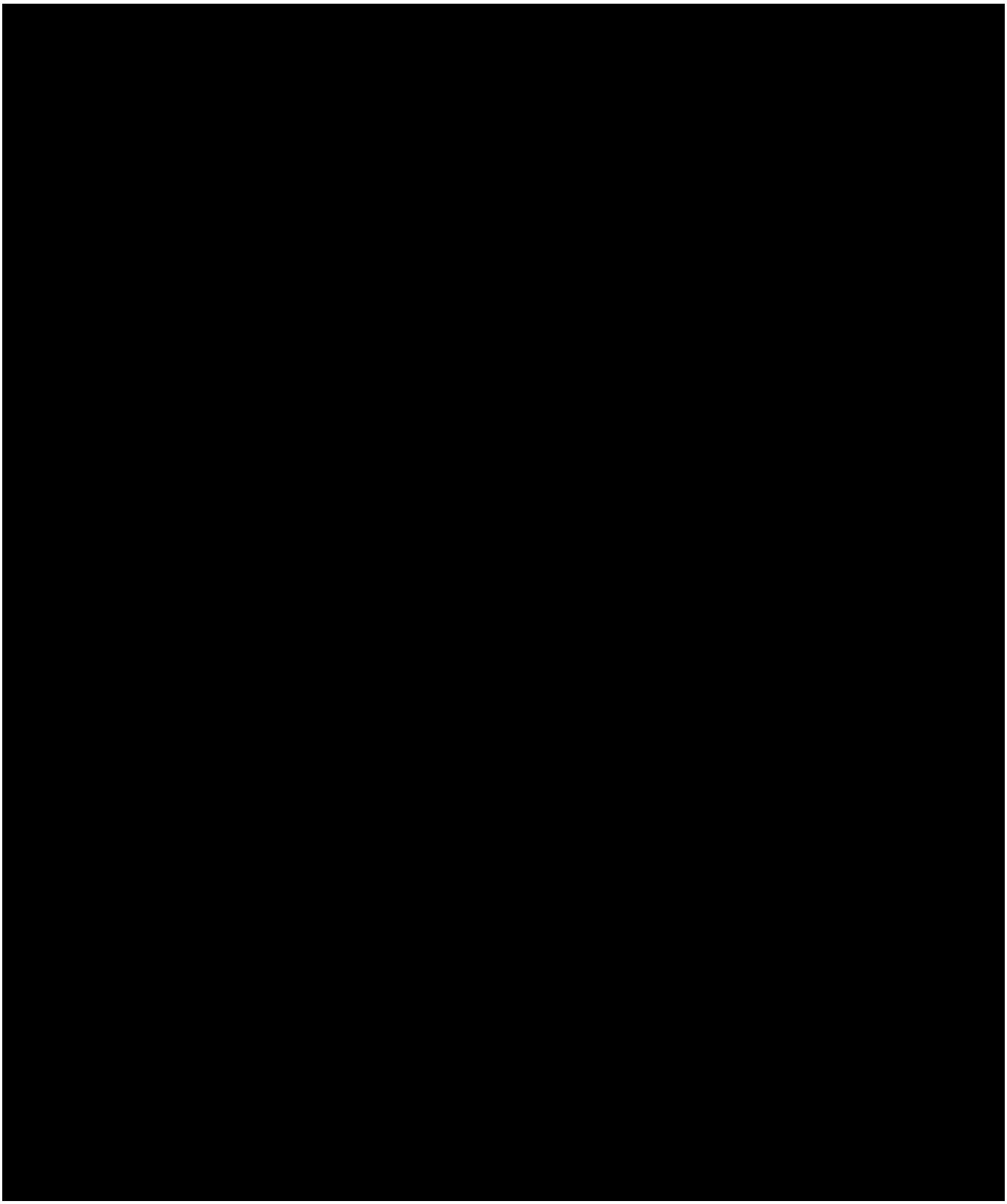


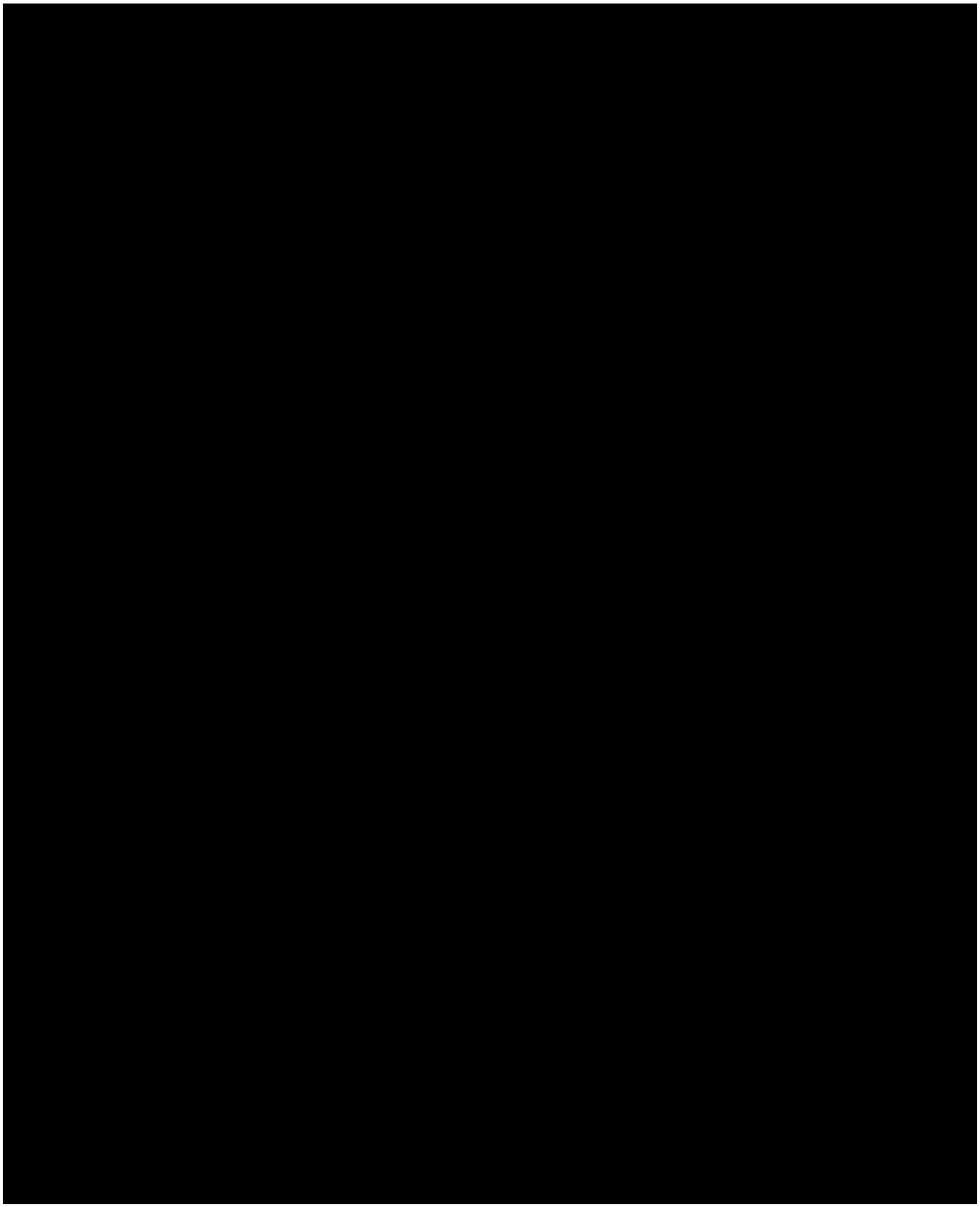


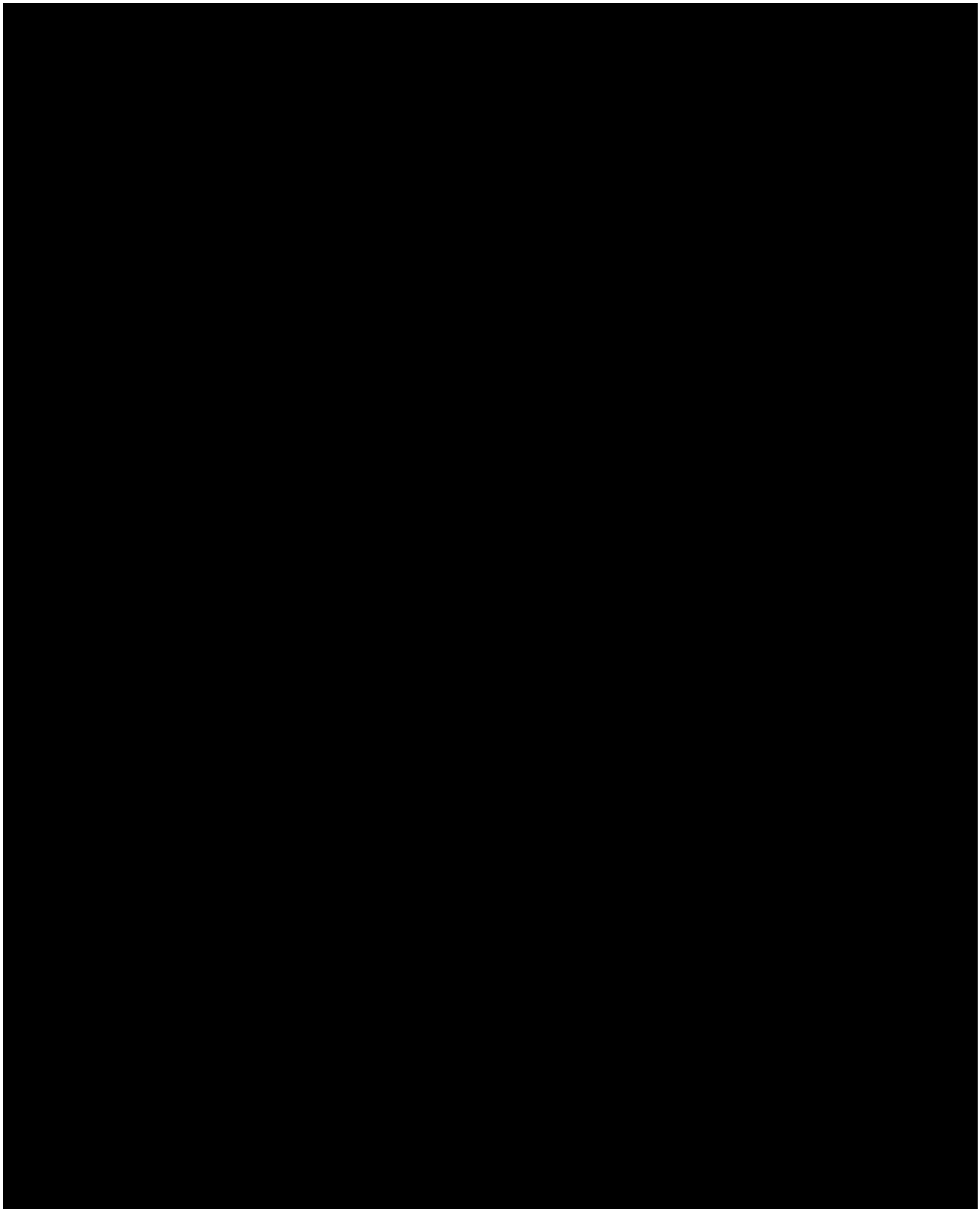


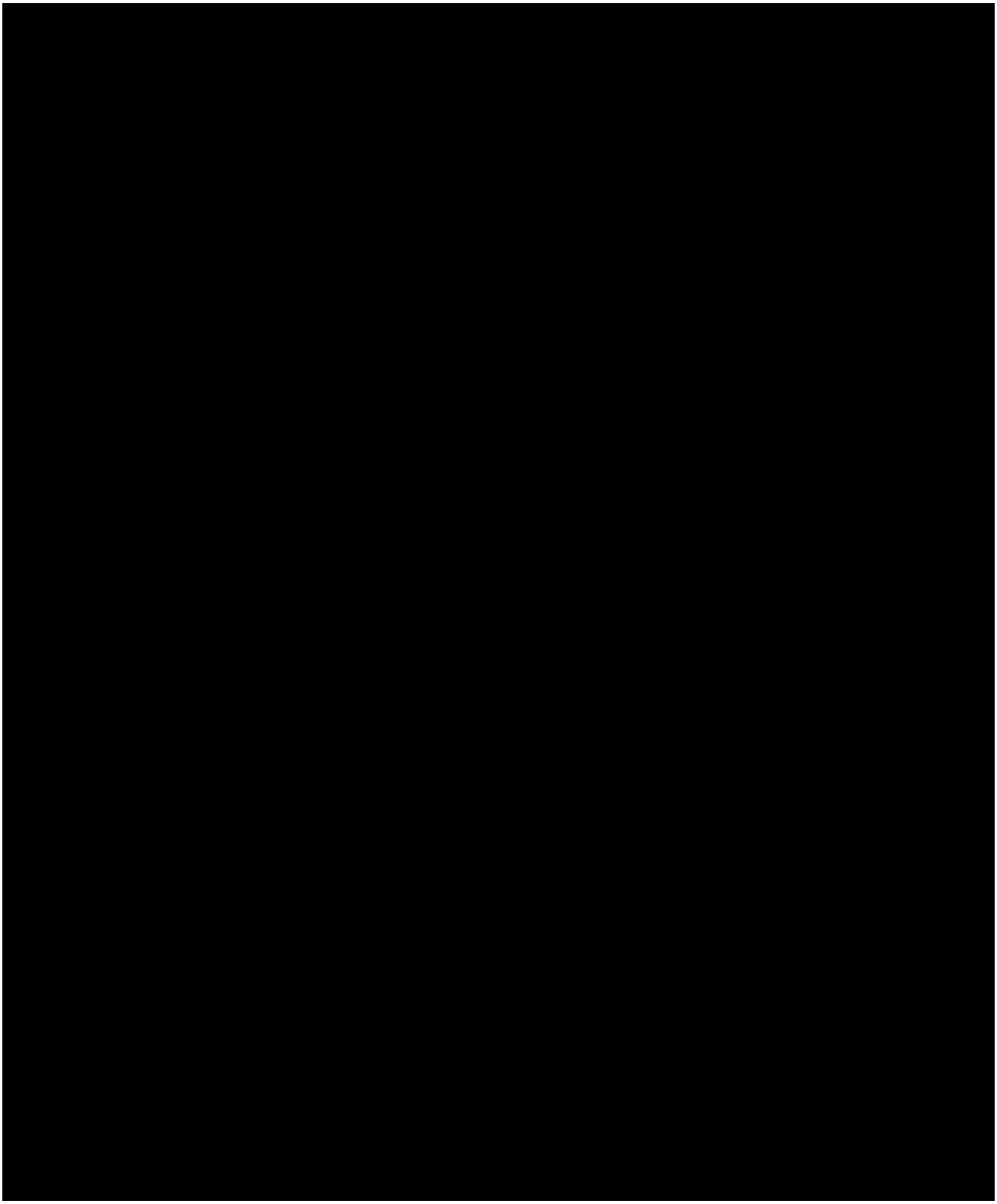












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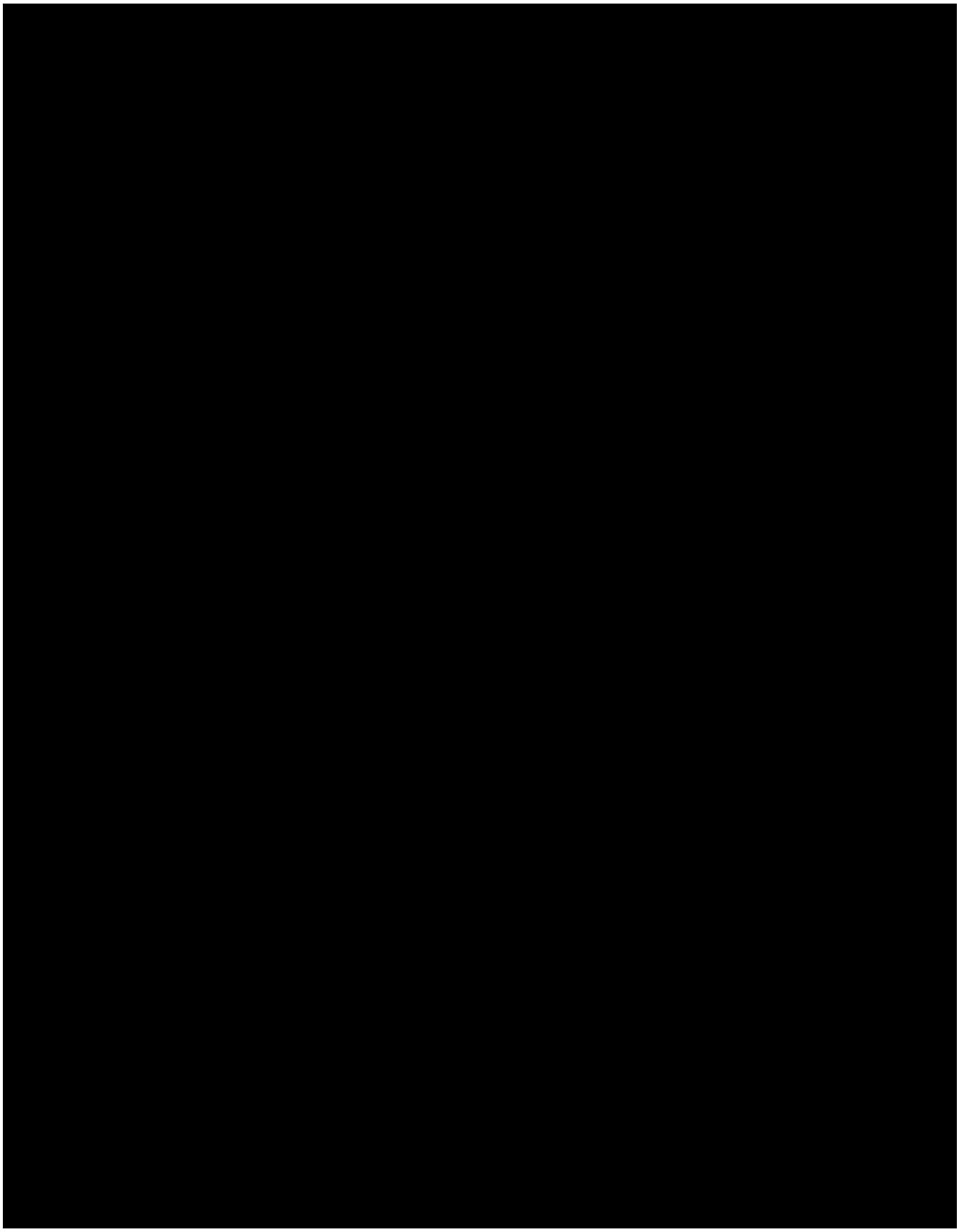

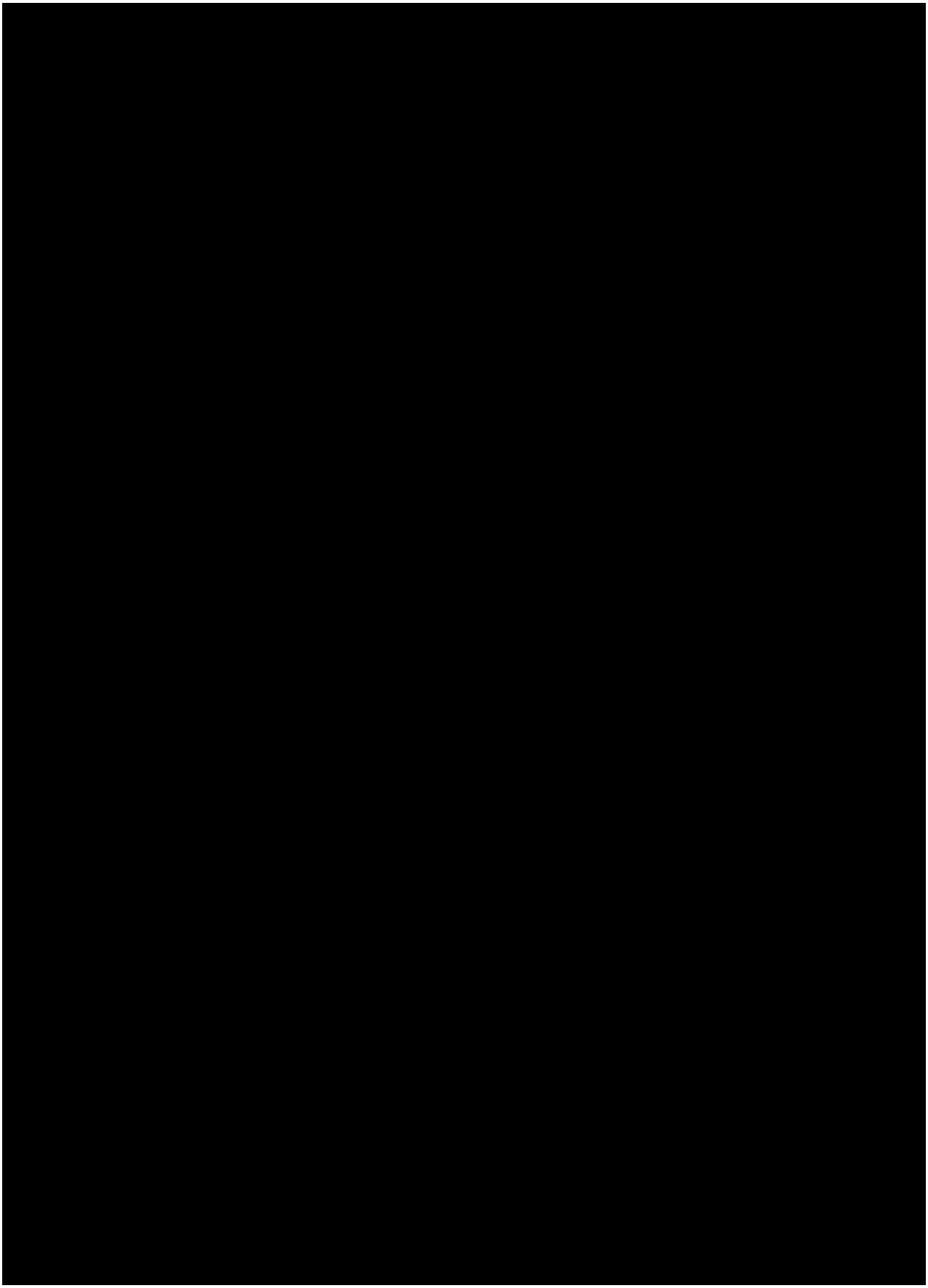

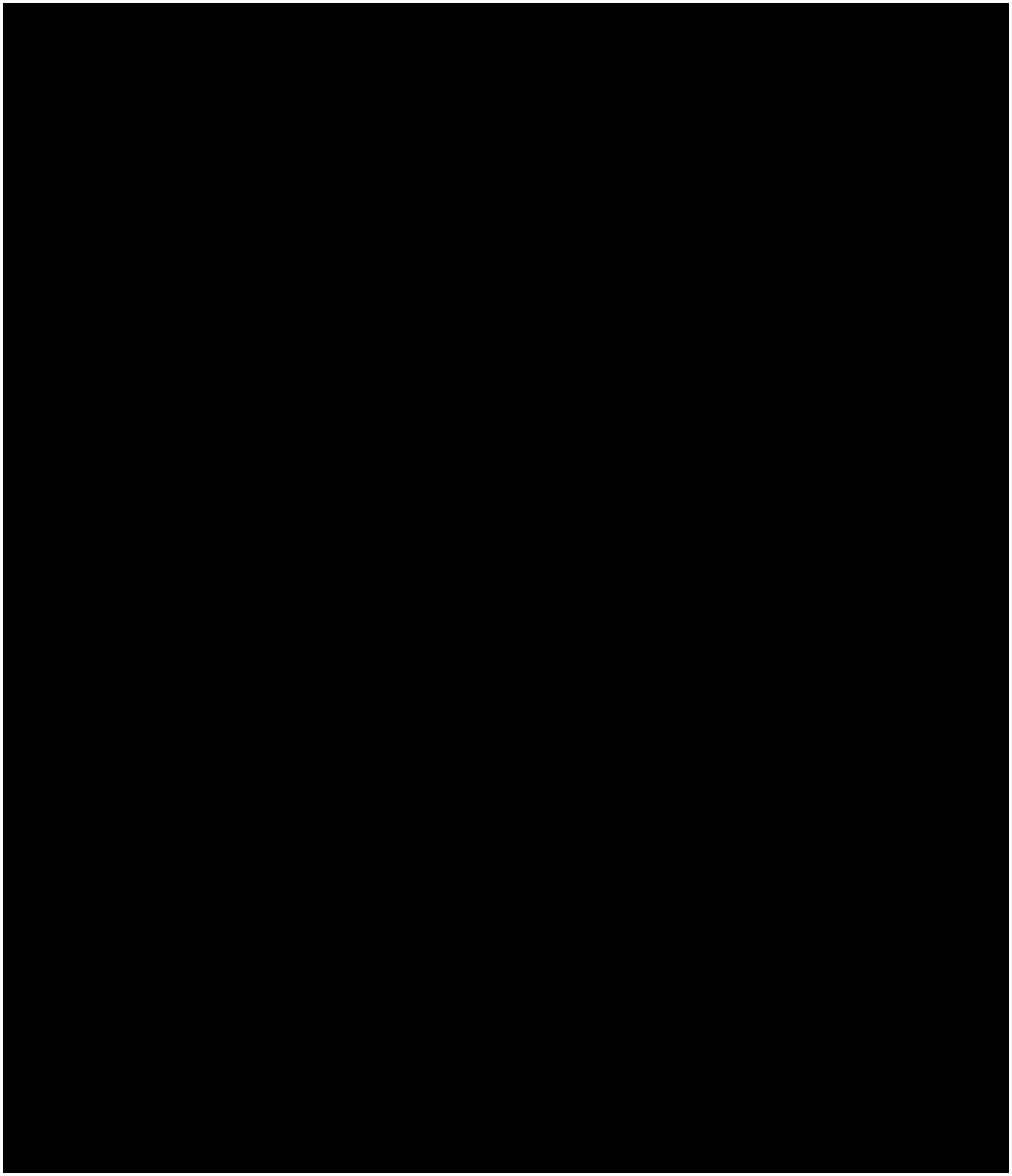

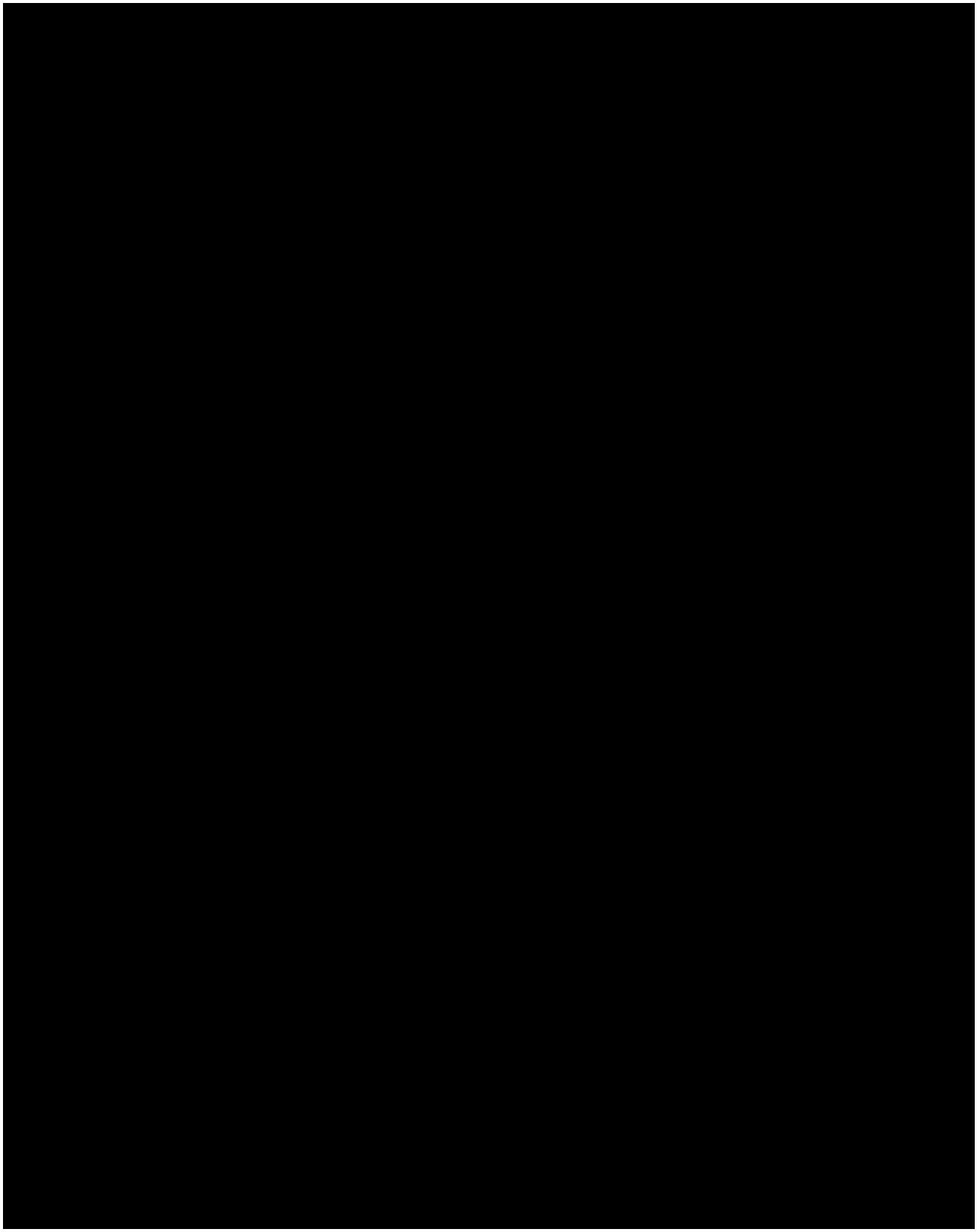

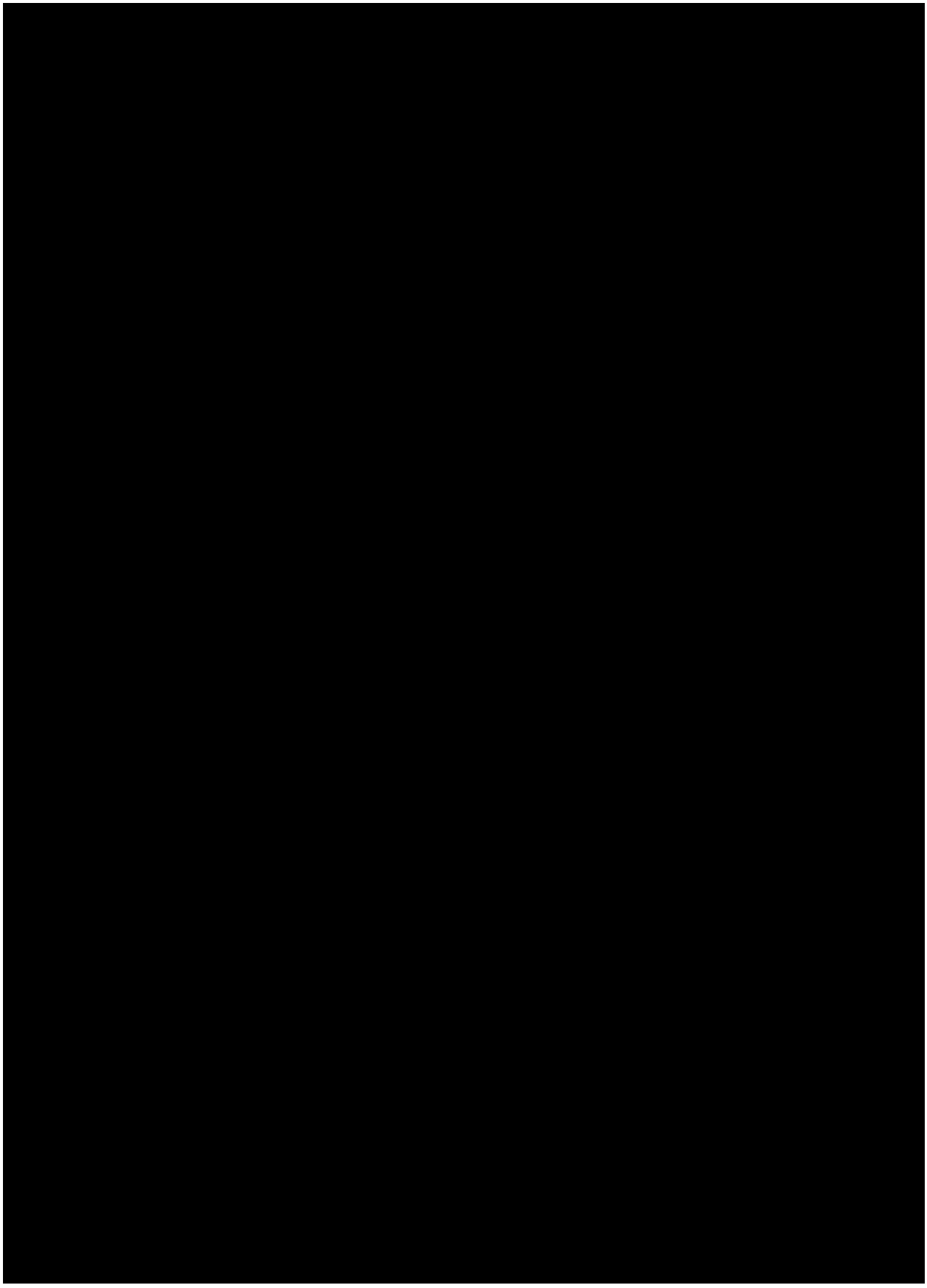

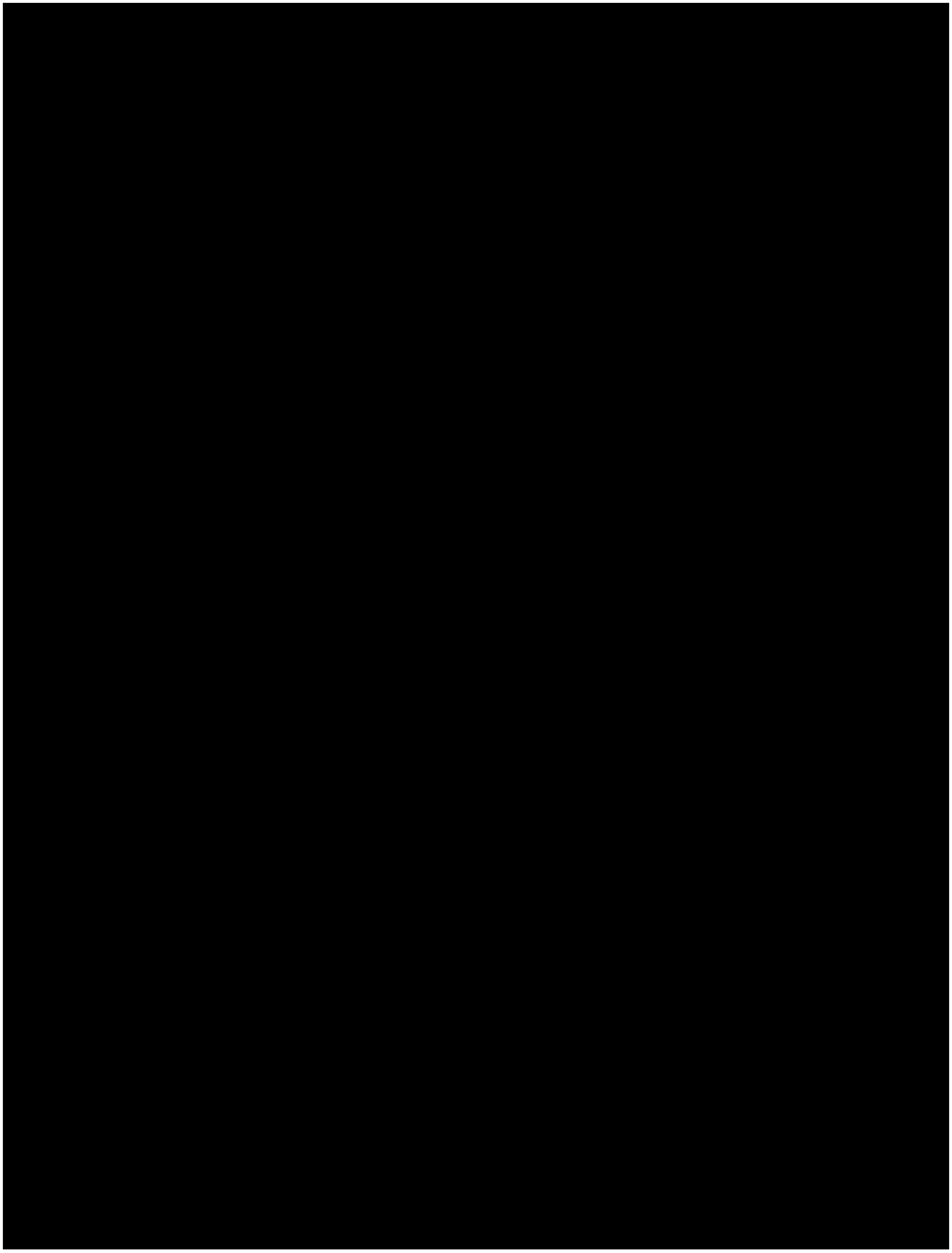

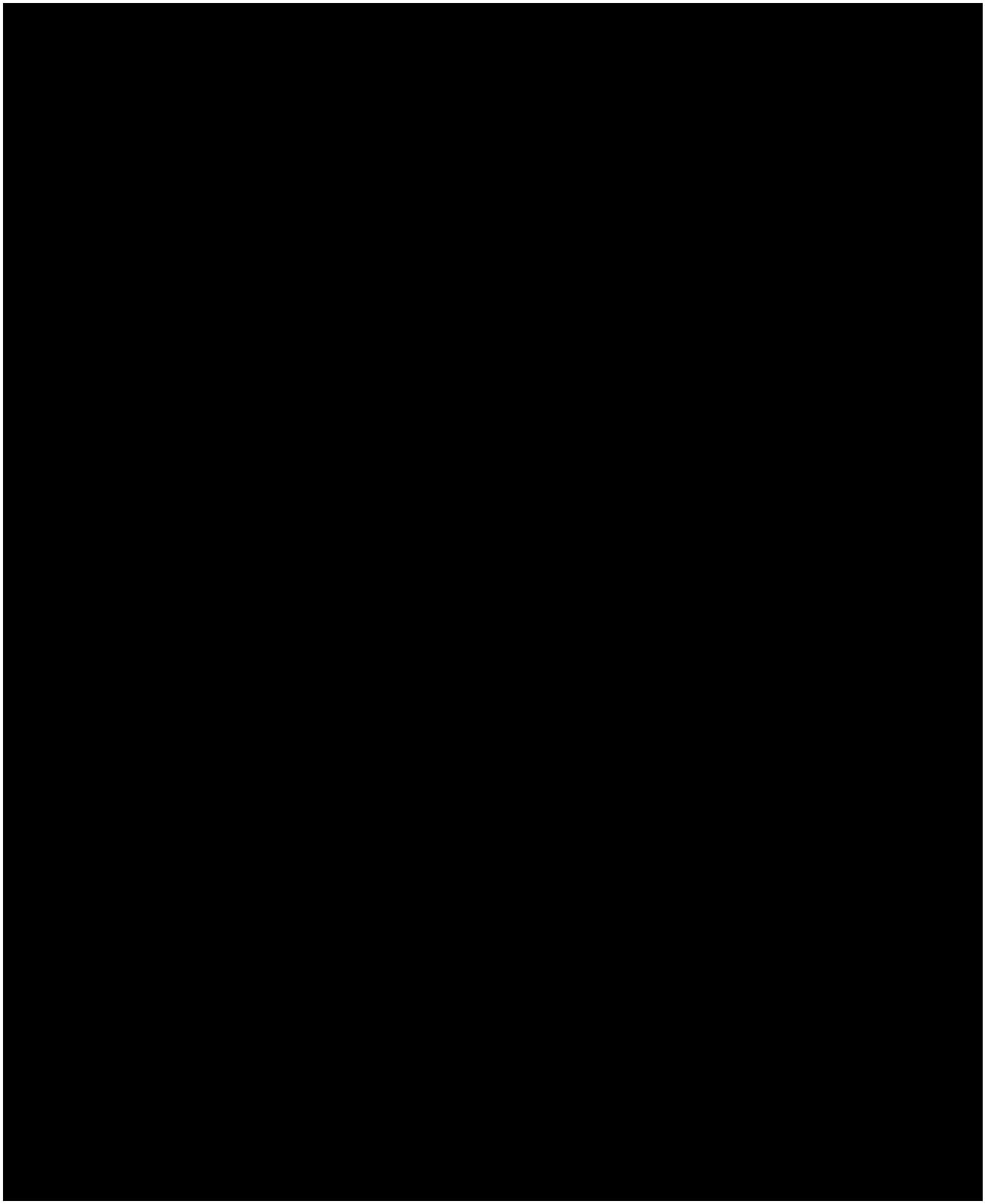

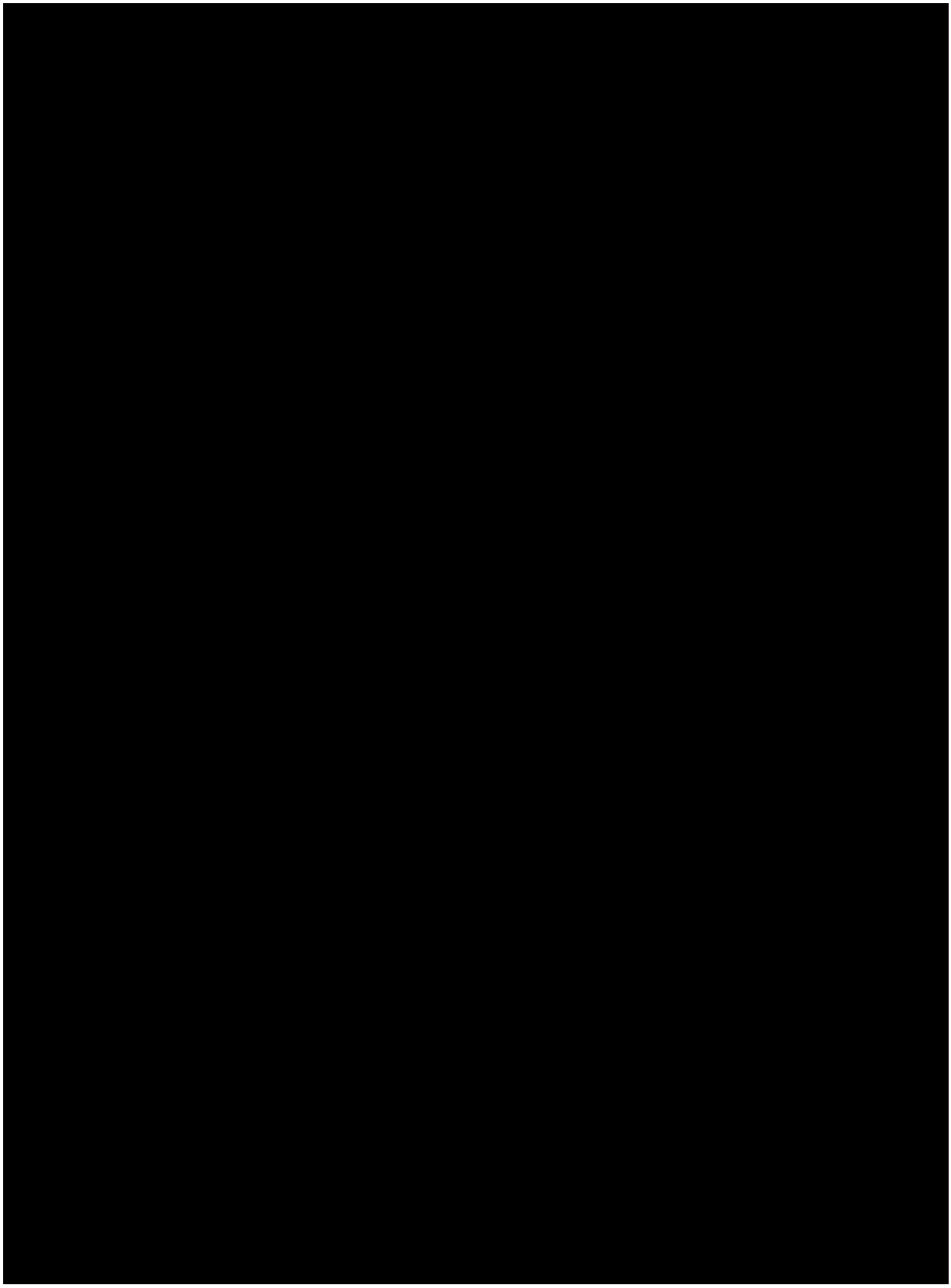

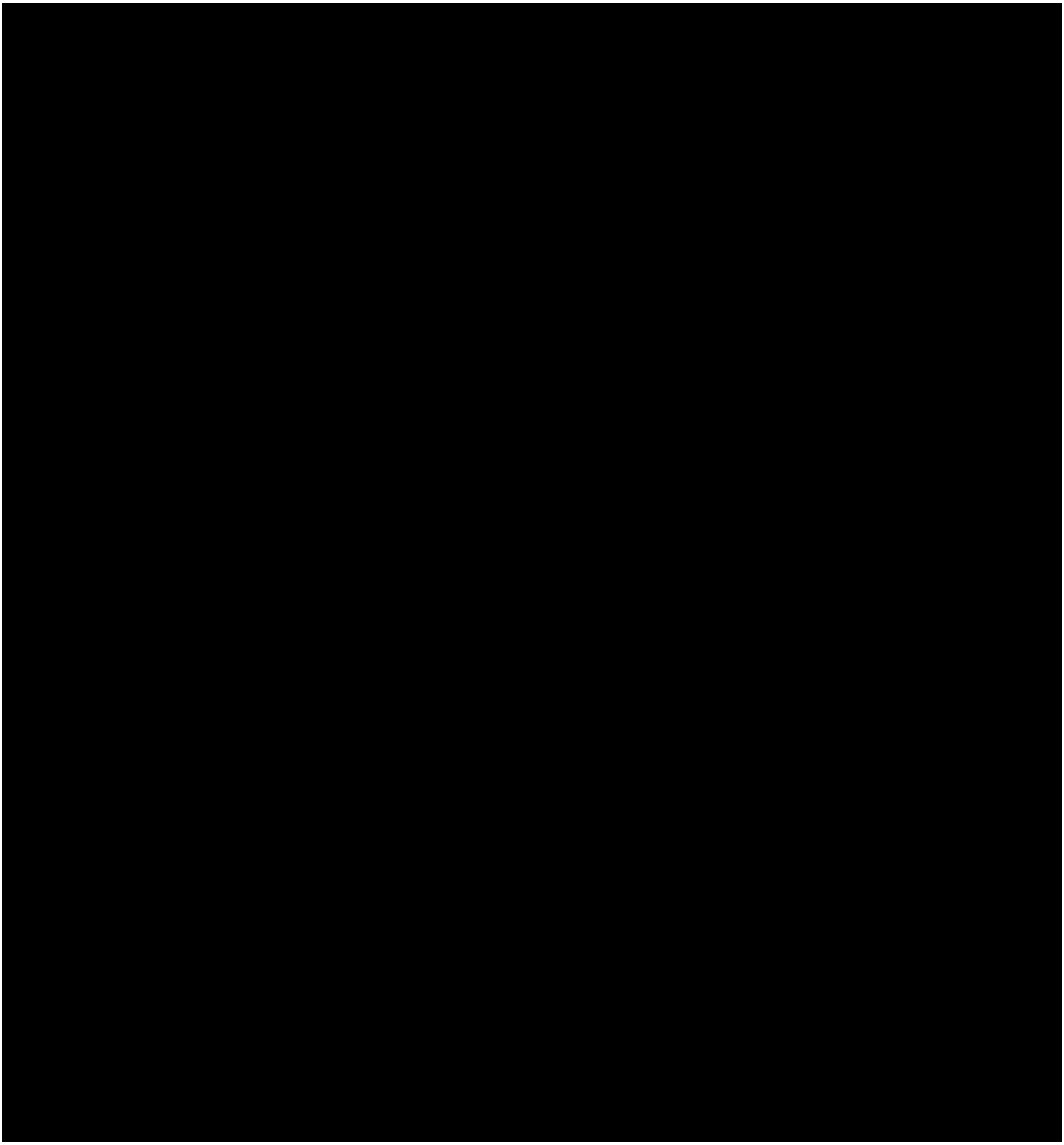

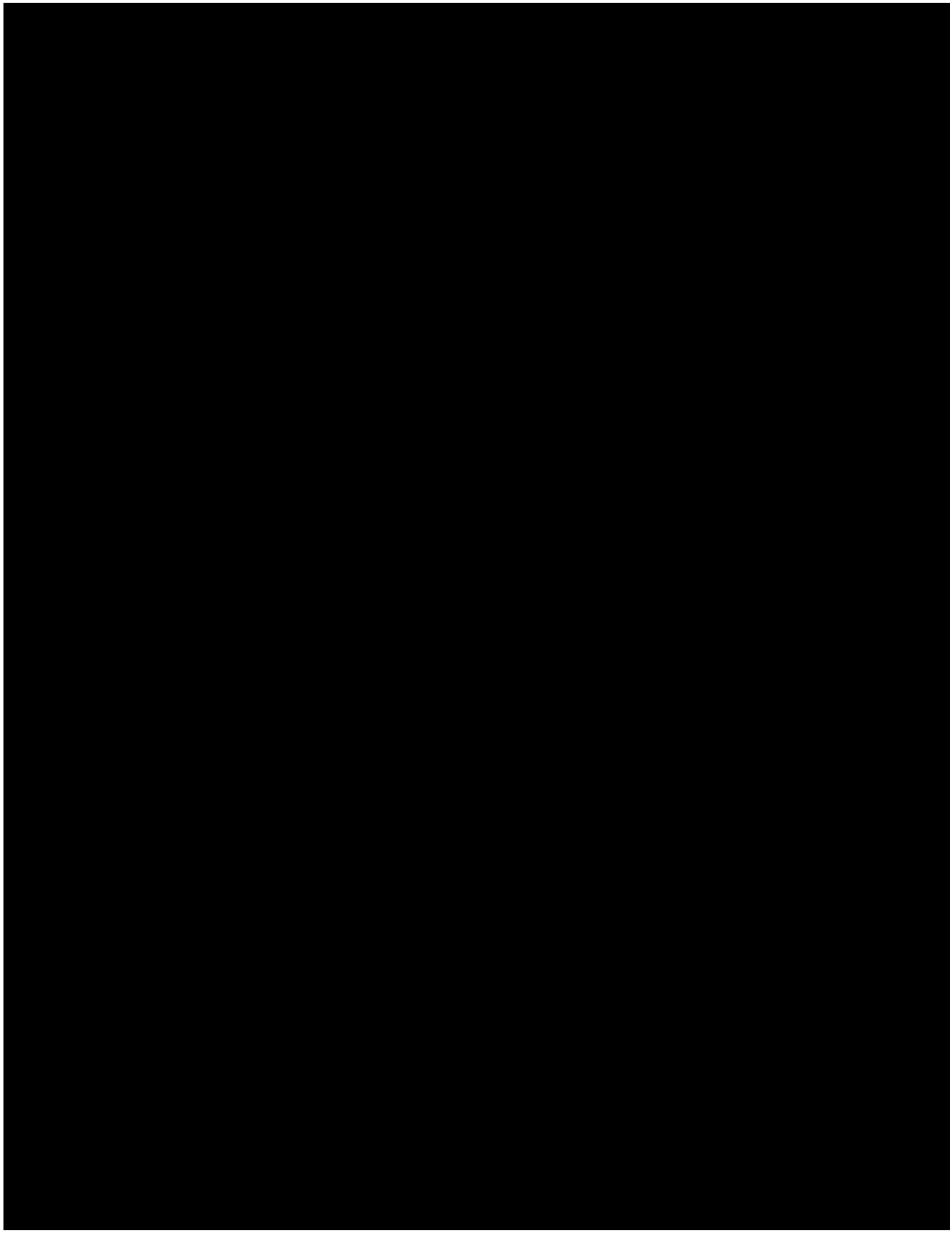

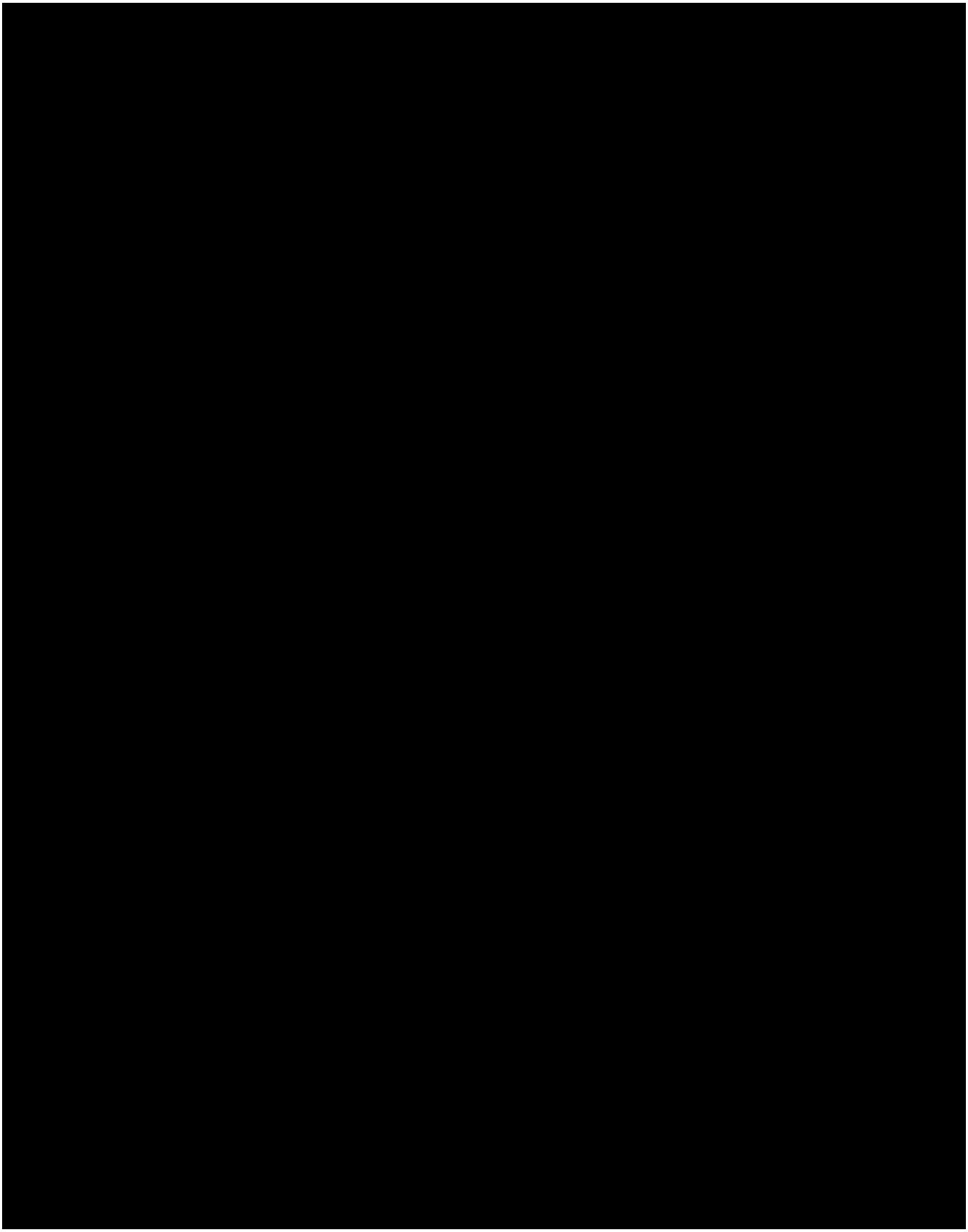

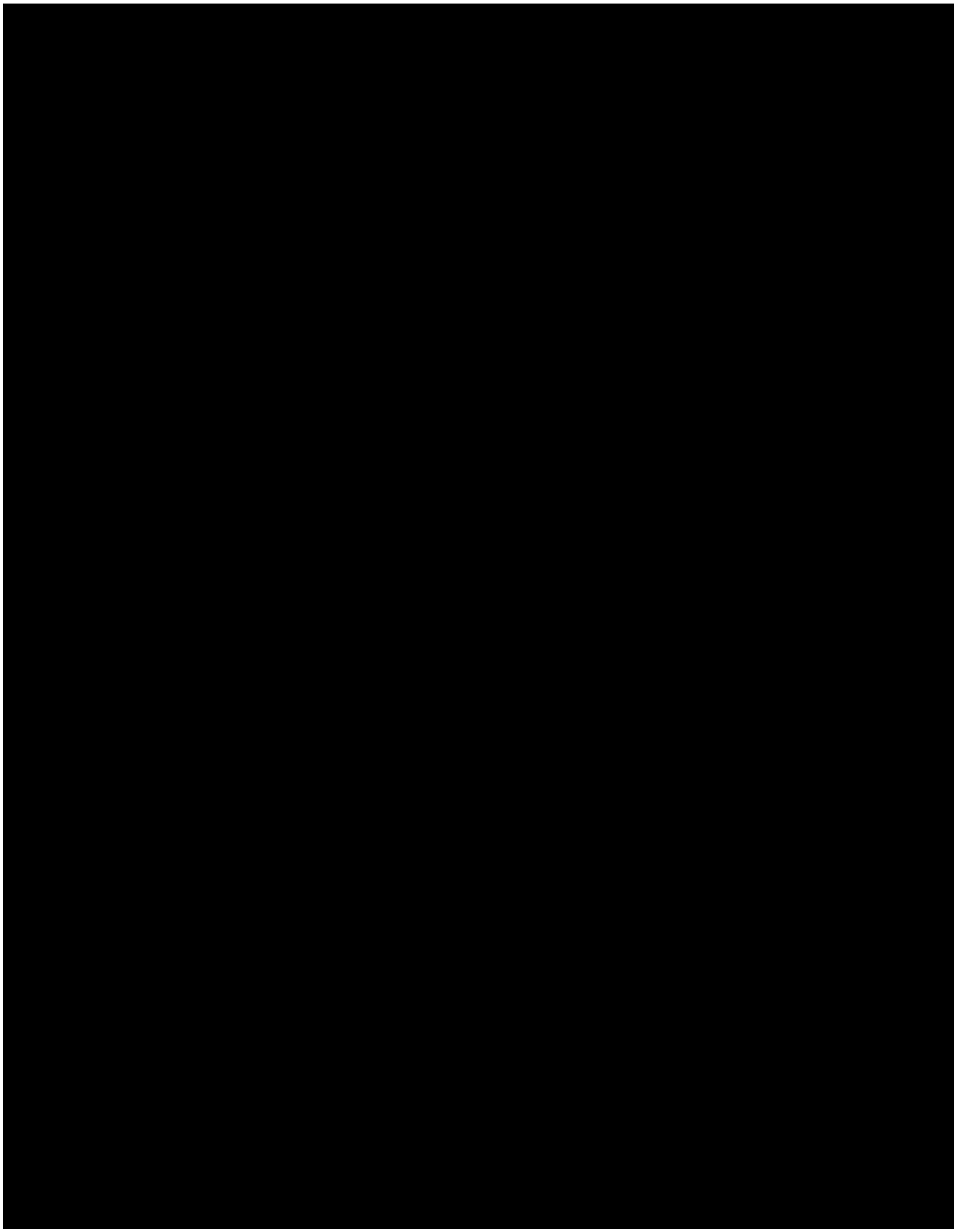

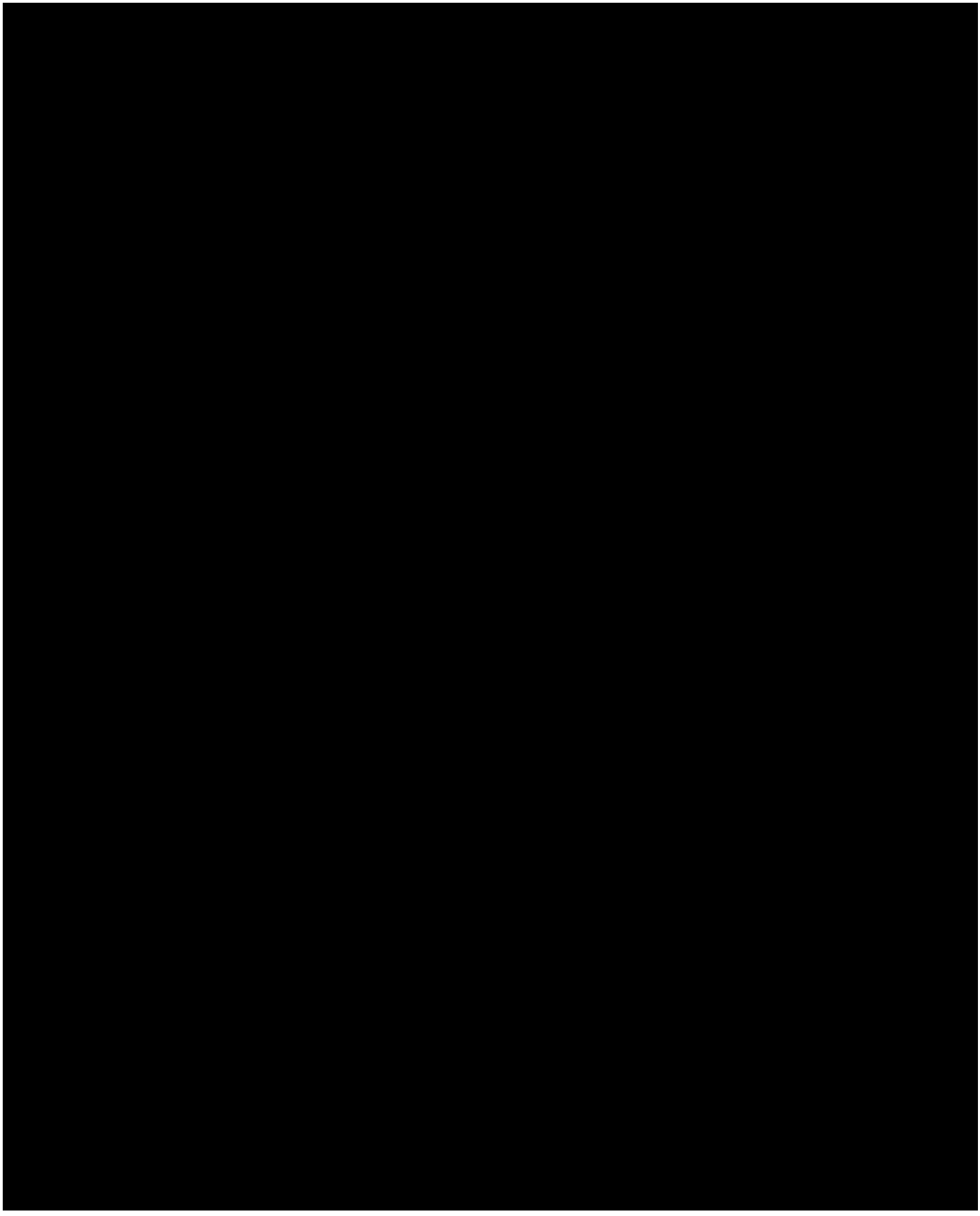

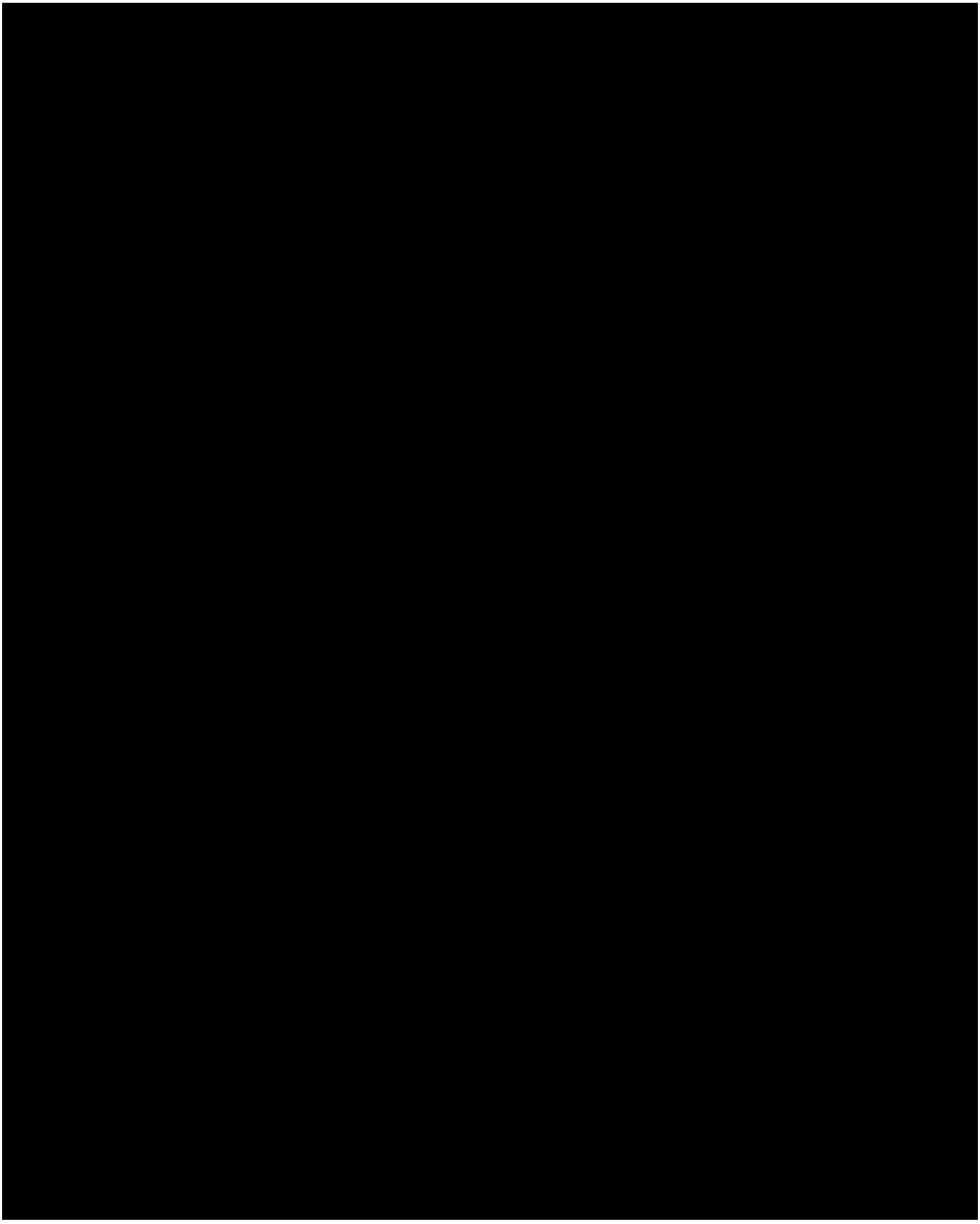

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