annexon biosciences	**Review and Approval of Clinical Documents and Disseminated Information**	**CO110-F1**
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Form CO110-F1

Clinical Document and Disseminated Information Approval Form

DOCUMENT TYPE:	Protocol Amendment
DOCUMENT TITLE:	A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects with, or at Risk for, Manifest Huntington's Disease
STUDY # (if applicable)	ANX005-HD-01
VERSION / DATE:	Version 6.0 / 16 December 2020

APPROVAL SIGNATURES REQUIRED:
Clinical Development: **Signature**: [redacted] **Date**: 12/18/2020 **Name**: [redacted] **Title**: [redacted] Annexon Inc.
Clinical Operations: **Signature**: [redacted] **Date**: 12/18/2020 **Name**: [redacted] **Title**: [redacted] Annexon Inc.
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CLINICAL STUDY PROTOCOL

Version 6

Title:	A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects with, or at Risk for, Manifest Huntington's Disease
Protocol No:	ANX005-HD-01
Study Drug:	ANX005
Development Phase:	Phase 2a
Country/Region:	North America
Sponsor:	Annexon, Inc. 180 Kimball Way, 2nd floor South San Francisco, CA 94080 Phone: [redacted] Fax: [redacted]
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Study Trial Manager:	[redacted] Annexon, Inc Phone: [redacted]
Date of Protocol:	Version 6: 16 December 2020 Version 5: 27 April 2020 Version 4: 08 April 2020 Version 3: 06 March 2020 Version 2: 31 January 2020 Version 1: 14 November 2019

SYNOPSIS

Protocol Title	A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects with, or at Risk for, Manifest Huntington's Disease
Protocol Number	ANX005-HD-01
Development Phase	Phase 2a
Sponsor	Annexon, Inc.
Study Centers	Multi-center
Subject Population	Subjects with, or at risk for, manifest Huntington's Disease (HD) Total cytosine, adenine, and guanine [CAG] Age Product (CAP) score > 400 Unified Huntington's Disease Rating Scale '99 (UHDRS) independence score ≥ 80
Number of Study Subjects	Up to approximately 24 total subjects will be enrolled
Study Duration	Each subject will participate for approximately 42 weeks • Screening: approximately 6 weeks • Treatment: approximately 22 weeks • Follow up: approximately 14 weeks Long-Term follow-up: 6 months after study completion
Study Objectives	**Primary Objectives:** • To assess the safety and tolerability of intravenous ANX005 administered for up to 22 weeks in subjects with, or at risk for, manifest HD • To assess the pharmacokinetics (PK) of ANX005 in the serum and cerebrospinal fluid (CSF) • To assess the pharmacodynamic (PD) effects of ANX005 in blood and/or CSF through the assessment of C1q, C4a, and neurofilament light chain (NfL) levels **Exploratory Objectives:** [redacted]

	[redacted]
Study Design	This study is a multi-center, open label, proof-of-biology study of intravenous ANX005 in subjects with, or at risk for, manifest HD. Subjects will receive induction dosing of ANX005 at 75 mg/kg administered by intravenous (IV) infusion on Days 1 and 5 or 6 (5/6), followed by maintenance dosing at 100 mg/kg every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22) with follow up visits on Weeks 24, 28, and 36. All ANX005 infusions will be administered at in clinic visits. The first infusion will be given over approximately 21 hours with subsequent infusions expected to be completed in approximately 4 or up to 5 hours. All subjects will be contacted (in clinic visit or phone call) 6 months after study completion to gather information focused towards clinical signs and symptoms suggestive of autoimmunity, e.g., fatigue, muscle aches, swelling, redness, low-grade fever, trouble concentrating, numbness and tingling, hair loss, or skin rashes. If clinically indicated, appropriate clinic visits may be scheduled depending on the information gathered during this visit. Blood samples for PK/PD assessments will be collected for serial sampling following the first and last dose. Pre-dose samples will be collected at all dosing visits (Days 1 and 5/6 and Weeks 2 through 22) prior to beginning the ANX005 infusion. Blood samples will be collected after completing the infusion on Day 5/6, and Weeks 2, 6, 10, 14, and 18. PK/PD samples will also be collected at the Week 24, 28, and 36 visits. Additional PK/PD samples will be collected (via home visit, if preferred) on other study days as described in Table 1 (Schedule of Assessments). Cerebrospinal fluid sampling for PK and PD assessments will be conducted at Screening, pre-dose at Week 6 and Week 12, and at Weeks 24 and 36.

	[redacted] Only after obtaining informed consent may subjects begin Screening procedures and required study interventions including administration of required vaccinations, infusion with ANX005, observation, and follow-up care. Subjects will be admitted to the clinic for the Day 1 ANX005 infusion which is expected to last for approximately 21 hours. Subjects will be observed for 1 hour after each infusion and may be released once all required end of infusion procedures have been conducted. Subjects are expected to return to clinic for all subsequent visits and ANX005 infusions through the end of the study. At home health care visits may be made by appropriately trained health care professionals to collect blood samples and/or complete assessments if necessary, to maintain the study visit schedule. Subjects who do not receive all scheduled infusions of ANX005 may be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator (PI). Similarly, if a subject discontinues from the study prior to the end-of-study visit, an additional subject may be enrolled at the discretion of the Sponsor to replace the discontinued subject. Up to 5 replacement subjects may be enrolled. Table 1 describes study assessments for subjects enrolled in the study.
Safety Evaluations	The PI and medical monitor review safety data on an ongoing basis to evaluate the frequency and severity of the following events and findings: • Serious adverse events (SAEs) • Discontinuation of participation due to an adverse event (AEs) • Adverse events graded according to NCI-CTCAE V5.0 • Adverse events of special interest (AESI), such as hypersensitivity and infusion-related reactions, evidence of an infection, hemolytic anemia, autoimmune disorder, new or worsening clinically significant findings from Columbia Suicide Severity Rating Scale (C-SSRS), physical examinations, and laboratory tests A safety review team (SRT), consisting of relevant study team members of the Sponsor and independent external experts (including an immunologist and a hematologist) will monitor the emerging safety

	data throughout the study and will meet after the first subject enrolled has completed the Week 4 visit (4 doses of ANX005) and then after the first 4 subjects enrolled have completed the Week 4 visit and periodically or for cause thereafter to review available safety data. The SRT charter will describe the committee structure and details for the conduct and rules of the meetings. *Ad hoc* meetings will be conducted should events relating to study stopping rules or AESI occur. The naming, composition, and members' roles and responsibilities of the SRT may be modified in regions where local regulatory practices require the Sponsor to do so. The SRT will review all pertinent safety information including adverse events with close attention to emerging safety signals suggestive of autoimmunity or infections, infusion related reactions, hemolytic anemia, hypersensitivity, safety laboratory assessments (serum chemistry, hematology, urine analysis, ADA, and antinuclear antibody [ANA]), vital signs, and the C-SSRS. Stopping rules for this study include two or more occurrences of any of the following within a given category: • Serious adverse events with signs, symptoms and concurrent serologic evidence (Section 7.2.13.1) consistent with an autoimmune disease considered related to study drug treatment. • Serious adverse events of infection considered related to study drug treatment. • Systemic life-threatening infusion-related or hypersensitivity reactions resulting in hospitalizations, admittance to the intensive care unit (ICU), or death considered related to study drug treatment. • Other occurrences of the same or a similar SAE assessed as related to study drug treatment. Should these events occur at any time during the study, the SRT will be notified immediately and will meet within 5 business days of becoming aware of the events to review all applicable medical and clinical information and observations in order to determine if study stopping rules have been met. Causality of adverse events is determined by the study Investigator (Section 9.2.2). The study may also be terminated if the Sponsor and SRT determine that AEs are occurring that are intolerable or pose a medically unacceptable safety risk.

	The study will continue for subject follow-up visits as described and for safety observations in the event the study stopping rules are met (Section 3.4).
Study Medication Dose, and Route of Administration	ANX005: The Sponsor provides ANX005 in sterile, single-use, 20 mL vials containing 20 mg/mL ANX005. All study doses are based on subject body weight recorded at the previous study visit. No modification of the assigned dose is allowed. Details on preparation and infusion of ANX005 are provided in the pharmacy manual and ANX005 Infusion Plan (Appendix F). All subjects should receive [redacted] within 2 hours prior to the start of the first IV infusion of ANX005. [redacted] Modification to the recommended medication guideline is acceptable based on individual subject condition and characteristics. Addition or substitution with alternative [redacted] is acceptable based on Investigator discretion. The PI or medically qualified designee may choose lower or omit doses of [redacted] if discussed and approved by the medical monitor.

	[redacted] may be repeated during the infusion of ANX005 at the discretion of the PI or medically qualified designee. If infusion related reactions (IRRs) occur during the infusion, the infusion rate may be stopped temporarily until symptoms have resolved, or discontinued altogether depending on the severity of symptoms that develop during the infusion (refer to Section 9.10 for details on monitoring infusion reactions). Infusions subsequent to the first infusion can be expected to be completed over approximately 4 or up to 5 hours. Pre-medication for subsequent IV infusions of ANX005 is not required.
Study Population	**Inclusion Criteria:** Subjects must meet all of the following criteria: 1. Males or females aged 18 and above at the time of informed consent. 2. Diagnosis of or at risk for HD, as defined by: a. Genetically confirmed disease by direct DNA testing. b. Total CAG-Age Product (CAP) score > 400. Only subjects with a prior history of a positive genetic test for HD are eligible to participate in the trial. Documentation of the number of CAG repeats in a subject's huntingtin gene is required either through prior genetic testing or through genetic testing included as part of the Screening process. c. UHDRS independence score ≥ 80. 3. Able to walk independently and self-sufficient in basic activities of daily living (e.g. eating, dressing, bathing) 4. All HD concomitant medications stable for 3 months prior to Screening 5. All other concomitant medications must be stable for 30 days prior to Screening. 6. If female, must be postmenopausal (no menses for at least 2 years without an alternative medical cause), surgically sterilized (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or agree to use highly effective methods of contraception from Screening through Week 36 (Section 6.3). 7. Males with a woman of childbearing potential partner must agree to use highly effective methods of contraception from Screening through Week 36 (Section 6.3).

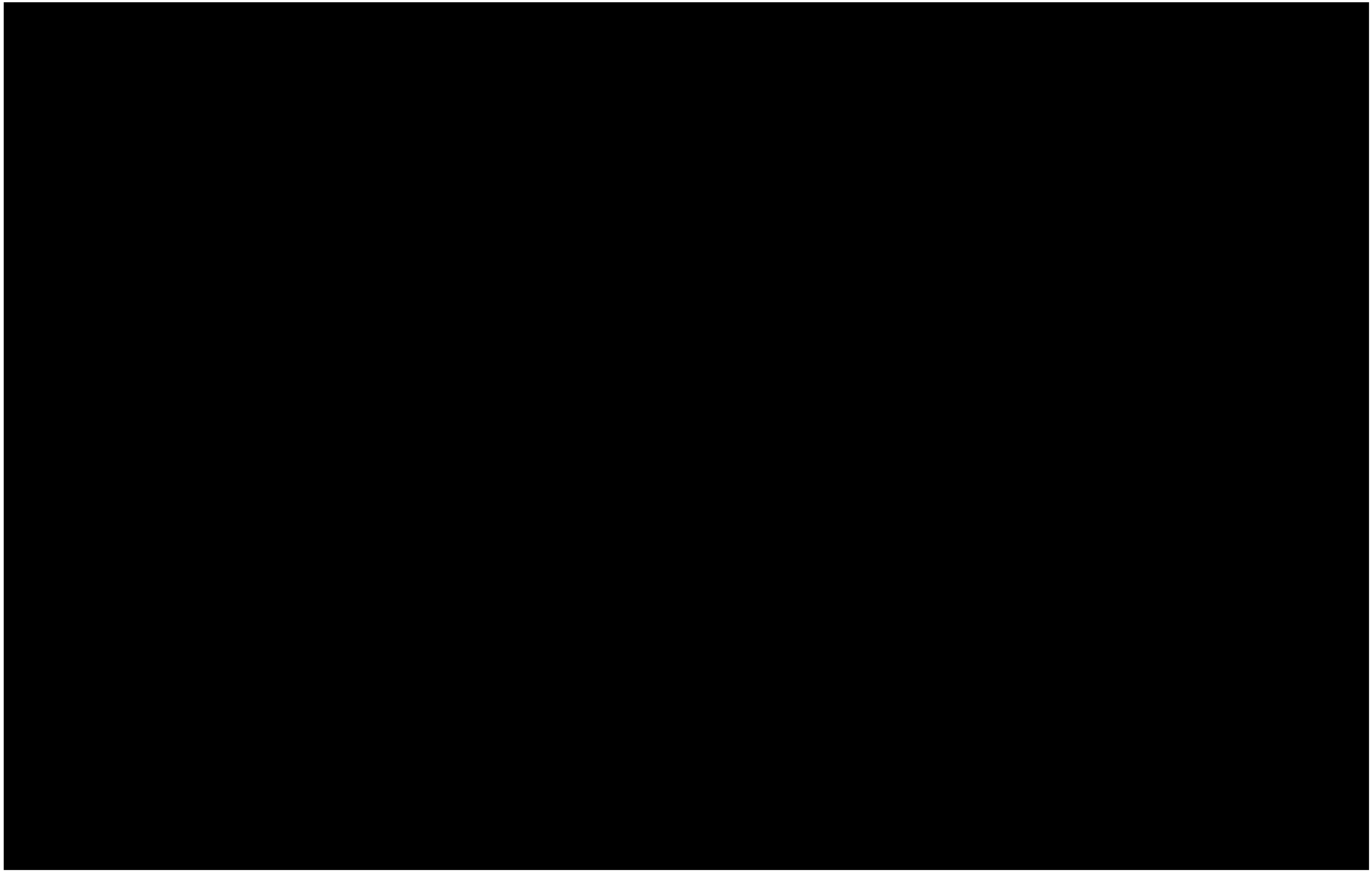
	8. Willing to have drug of abuse testing at Screening and at later time points if drug abuse is suspected during the study. 9. Previously vaccinated against encapsulated bacterial pathogens (*Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) or willing to undergo vaccination. 10. Able to comply with the requirements of the study and complete the full sequence of protocol-related procedures and evaluations, including lumbar punctures (LPs) for collection of CSF. 11. If a caregiver/study partner is required, per Investigator discretion, must be a competent caregiver/study partner who is at least 18 years of age and is willing to accompany the subject to select trial visits and to be available by phone if needed, and who is and will remain sufficiently knowledgeable of subject's ongoing condition to respond to Study Center inquiries about the subject. 12. Able to tolerate [redacted] and LP procedures. 13. Able to understand and provide written, informed consent. **Exclusion Criteria:** Subjects must not meet any of the following criteria: 1. Be at risk of suicide or self-harm within the preceding 12 months, in the opinion of the Investigator. 2. Chorea and/or cognitive deficits severe enough to interfere with study assessments. 3. Subjects with body weight > 150 kg. 4. Clinically significant findings on the Screening laboratory testing or physical examination that are not specific to HD and may interfere with the conduct of the study or the interpretation of the data or increase subject risk. 5. Signs and symptoms of, or a diagnosis consistent with a chronic autoimmune disorder and/or an ANA titer ≥ 1:160. 6. History of previous infusion reactions, sensitivities, allergic, or anaphylactic reactions to previous medications, environmental stimuli or other substances. 7. Receipt of an experimental agent within 60 days or five half-lives prior to Screening or anytime over the duration of this study. 8. Prior treatment with any monoclonal antibody within 6 months of Screening. 9. Presence of an implanted deep brain stimulation device.

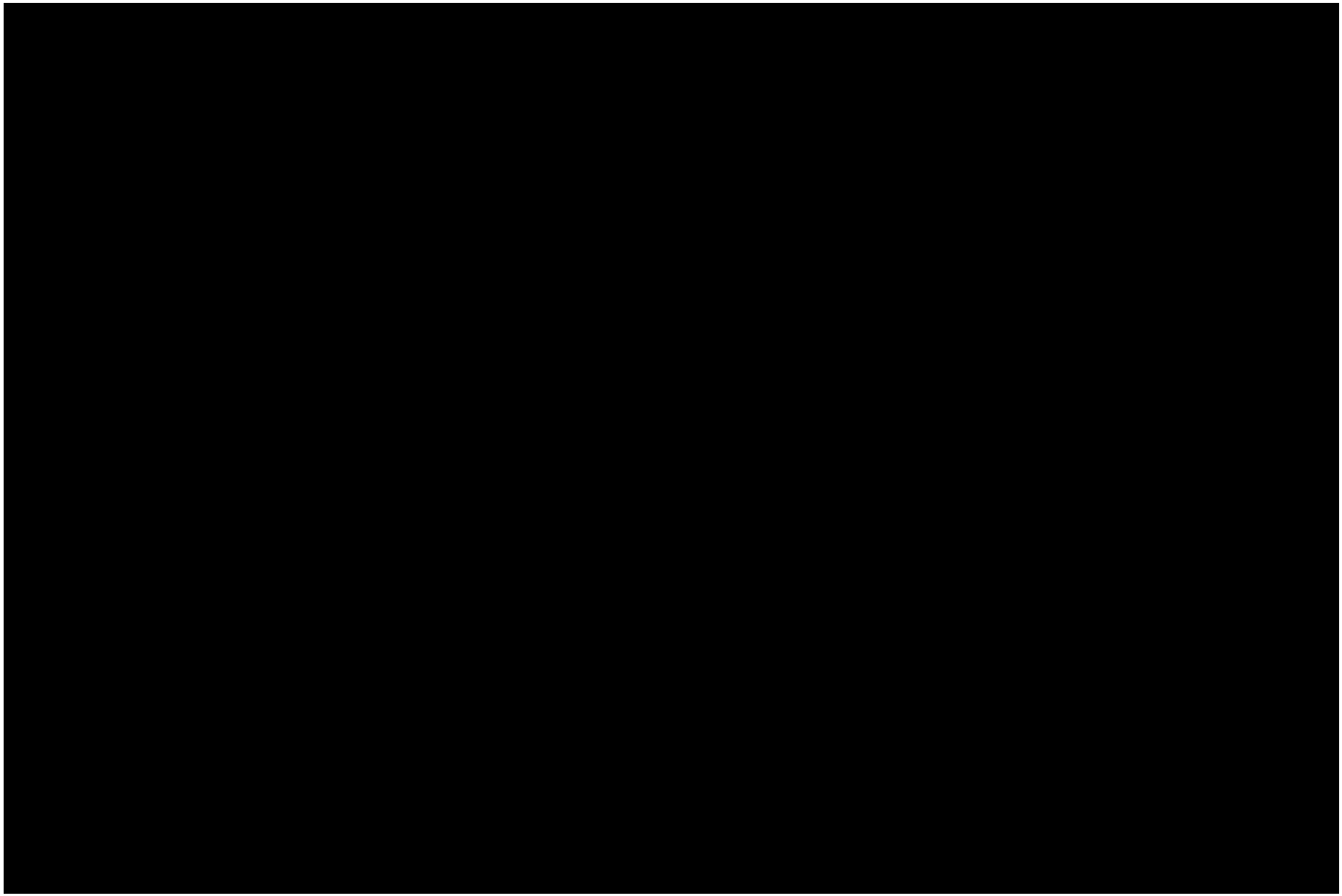
	10. Any history of gene therapy, RNA or DNA targeted HD specific investigational agents such as antisense oligonucleotides, cell transplantation or any experimental brain surgery. 11. Brain and spinal pathology that may interfere with CSF homeostasis and circulation, increases intracranial pressure (implanted shunt or catheter), malformations or tumor. 12. Contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; international normalized ratio (INR) > 1.4 or other coagulopathy; platelet count of < 120,000/μL; infection at the desired lumbar puncture site; taking anti-platelet or anti-coagulant medication within 90 days of Screening (low dose aspirin is permitted), degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma. 13. Hypersensitivity to any of the excipients in the ANX005 drug product 14. Clinically significant intercurrent illness, medical condition, or medical history (including neurological or mental illness, HIV, any active infection, including Hepatitis B or C) that would jeopardize the safety of the subject, limit participation, or compromise the interpretation of the data derived from the subject. 15. Any known genetic deficiencies of the complement-cascade system. 16. Clinically significant laboratory or vital sign abnormalities at Screening. 17. History of chronic oral or IV steroid use or immunosuppressant medication ending less than 1 month prior to Screening. 18. Active alcohol, drug abuse or substance abuse, or any other reason that makes it unlikely that the subject will comply with study procedures. If positive drug screen results are obtained due to the use of a concomitant medication for a therapeutic indication, the result may be flagged and discussed with Sponsor and will not necessarily be exclusionary. 19. Females who are pregnant (positive pregnancy test at Screening or prior to infusion of ANX005), breast feeding, or unable or unwilling to use highly effective methods of contraception (Section 6.3) throughout the study. 20. Hemoglobin, bilirubin, or lactate dehydrogenase (LDH) values that are outside normal limits and clinically significant or suggestive of hemolytic anemia.

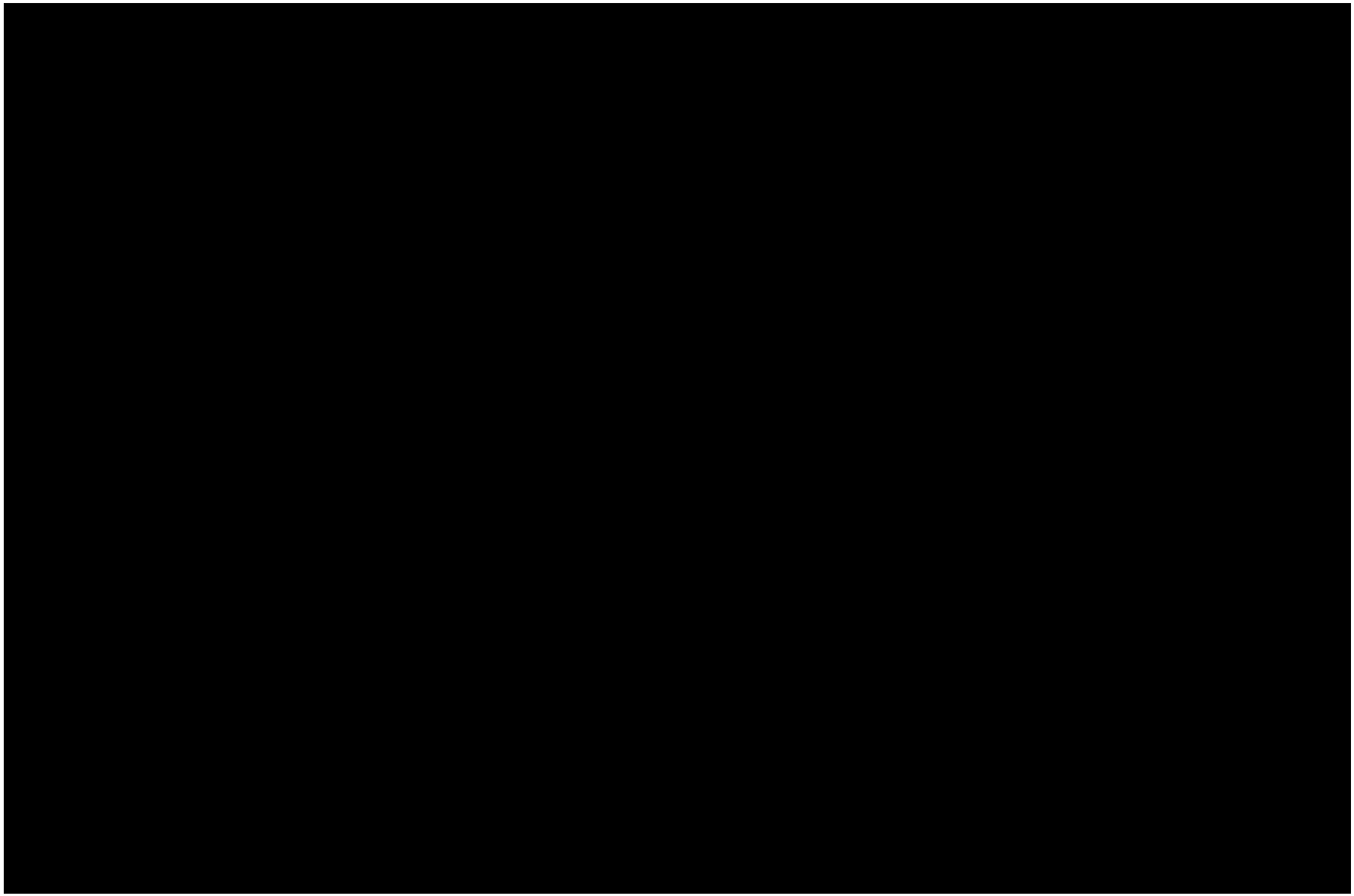
Study Assessments	Safety: Safety is assessed during the study via monitoring of AEs, AESIs, infusion-related reactions, vital signs, assessment of clinical or laboratory evidence of an autoimmune disease or infection, hemolytic anemia, Columbia Suicide Severity Rating Scale results, clinical laboratory tests, concomitant medication review, and physical examinations. [redacted] Pharmacokinetics and Pharmacodynamics: PK of ANX005 will be assessed during the study by serum sampling prior to infusion and with sequential sampling after select infusions of ANX005. PD will be assessed during the study by measurement of C1q, C4a, 50% hemolytic complement activity (CH50), NfL, and other complement biomarkers in blood and/or CSF with sampling at specified timepoints. See Table 1 for details of assessments performed.
Statistical Methods	**Analysis Populations:** • The safety population (SAF) includes all subjects who received any amount of ANX005 and will be the population for safety, and immunogenicity endpoints. • The Full Analysis Set (FAS) includes all subjects who received at least 1 completed infusion of ANX005 and have at least one post infusion assessment and will be used for clinical and functional assessments, and biomarker endpoints. These assessments will be repeated for the Per Protocol (PP) set, defined as those who completed all infusions and do not have major protocol violations. • The PK analysis set includes all subjects who received any ANX005 and have evaluable PK data. **Methods:** Descriptive statistics will be provided for demographic, safety, PK, PD, immunogenicity data, and other clinical data. For continuous variables, descriptive statistics will include means, medians, standard deviations, and ranges. The descriptive summaries for the categorical variables will include frequency counts and percentages.

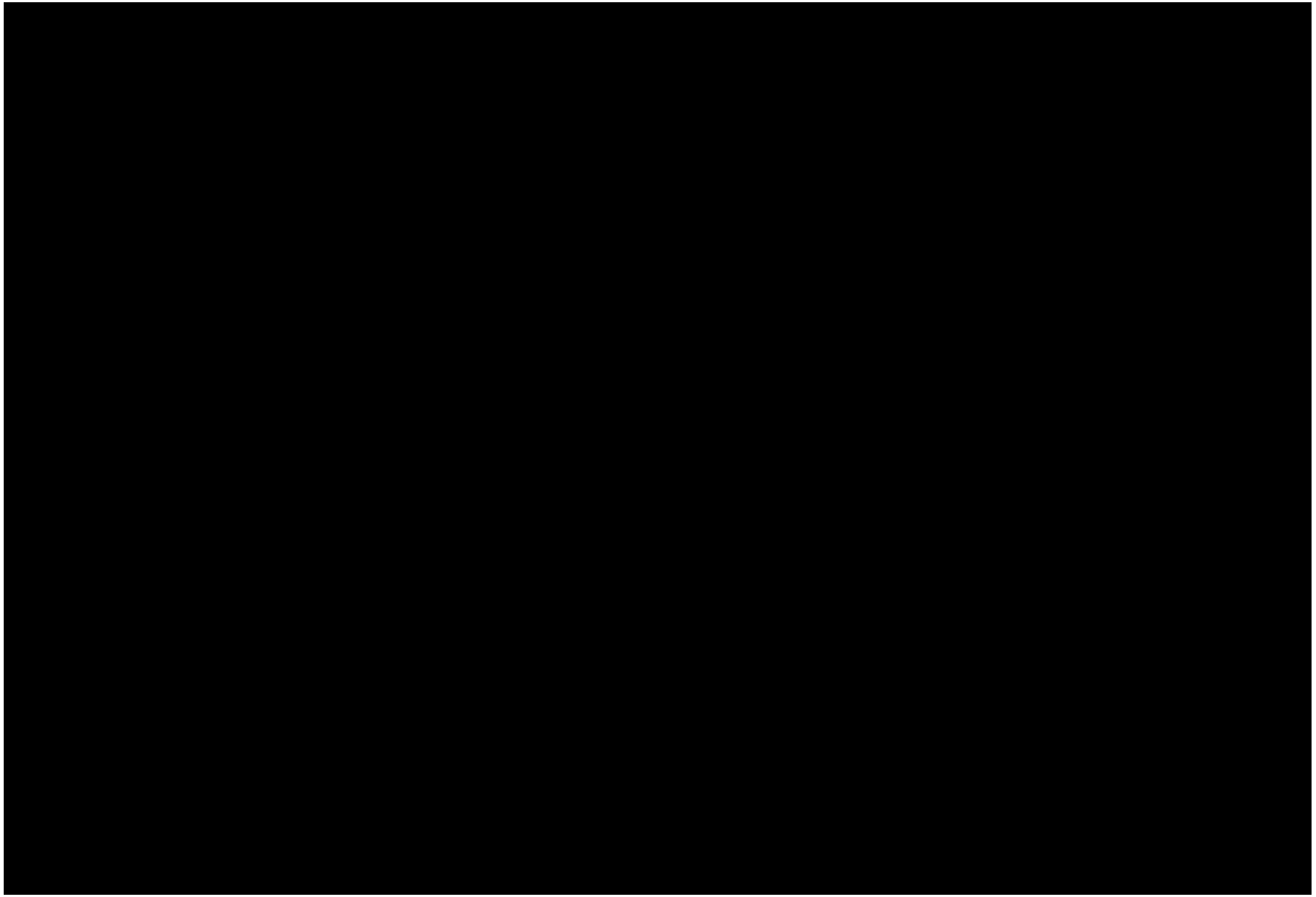
	Safety analyses will be performed using the SAF. Safety and tolerability endpoints will be summarized using descriptive statistics. AEs and AESIs will be included in by-subject listings and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. AEs will be summarized overall, by relationship, and by severity. AEs will be listed individually by subject. AEs leading to death, SAEs, and AEs resulting in discontinuation will be listed or tabulated separately. All laboratory results will be listed individually by subject and time point. Laboratory values and changes from baseline will be summarized at each time point. Shift tables from baseline to each post-baseline time point will be presented for selected variables.

Table 1: Schedule of Assessments









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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ADA	Antidrug (ANX005) antibodies
ANA	Antinuclear antibody
AUC	Area under the curve
C1q	Component of complement complex
C4a	Component of complement complex
CAG	Cytosine-adenine-guanine
CAP	CAG age product
CH50	50% hemolytic complement activity
Cmax	Maximum concentration
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DAT	Direct antiglobulin test
DMP	Data management plan
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
EOI	End of infusion
FAS	Full analysis set
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HD	Huntington's Disease
Hgb	Hemoglobin
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IgG4	Immunoglobulin gamma 4
INR	International Normalized Ratio
IRR	Infusion-related reaction
IV	Intravenous
LDH	Lactate dehydrogenase
LP	Lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
Men ACWY	Meningococcal vaccine to protect against disease caused by serogroups A, C, W, and Y

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NfL	Neurofilament light chain
PCV13	Pneumococcal conjugate vaccine
PD	Pharmacodynamic or pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic or pharmacokinetics
PKAP	PK analysis plan
PP	Per protocol set
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SDMT	Symbol digit modalities test
SLE	Systemic lupus erythematosus
SRT	Safety Review Team
[redacted]	[redacted]
TMS	Total motor score
UDS	Urine drug screening
UHDRS	Unified Huntington's Disease Rating Scale
WHO-DD	World Health Organization Drug Dictionary

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the PI must provide to a Sponsor representative a current, signed curriculum vita.

The clinical study is administered and monitored by representatives of Annexon, Inc (the Sponsor). Clinical research associates monitor the site on a periodic basis and perform verification of source documentation for each subject.

Sponsor representatives are responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities.

Clinical laboratory safety evaluations are performed at the central laboratory specified by the study Sponsor.

1 INTRODUCTION

1.1 Background

Huntington's Disease (HD) is an autosomal-dominant progressive neurodegenerative condition that is characterized by chorea and dystonia, cognitive decline and psychiatric disorder[1,2]. The specific genetic mutation involves expansion of a trinucleotide (cytosine, adenine, and guanine [CAG]) repeat in the huntingtin gene (Htt) on chromosome 4p[3]. The unstable CAG repeat is translated into a polyglutamine stretch in the huntingtin protein[4]. The age of onset and severity of disease is found to be linked to the number of CAG repeats in the Htt gene with those individuals with the earliest onset having the largest repeat number[1]. The normal function of the huntingtin protein is not known but current understanding supports the mutant protein with the expanded polyglutamine sequence as toxic to brain cells[4].

In general HD symptoms worsen progressively and invariably lead to death[2,5]. HD is often divided into three broad phases. In early stage HD patients experience minor symptoms but are largely functional and able to work and live independently. In middle stage HD, patients' symptoms are more prominent including chorea and cognitive decline and they may not be able to work or care for themselves. In late stage HD, patients require assistance for all aspects of daily living, with dementia, mutism, dystonia, and bradykinesia predominating in advanced disease. Death typically occurs within 15–20 years of disease onset, and is usually related to complications of immobility, infection, especially pneumonia, and cardiac disease. The Unified Huntington's Disease Rating scale (UHDRS)[6] first published in 1996 and revised in 1999 and 2005 is often used to stage patients with HD based on assessing motor function, cognition, behavior, independence, functional ability and a total functional capacity.

Neuropathologically, HD is primarily characterized by neuronal loss in the striatum and cerebral cortex[7]. Certain neuronal populations are more affected including those within the corpus striatum of the basal ganglia. The mechanism by which polyglutamine aggregation leads to neurodegeneration has been elusive, although insight has emerged from animal models regarding HD pathophysiology[5]. Early synaptic dysfunction is a key characteristic and is manifested by dysregulated glutamate release in striatum followed by progressive disconnection between cortex and striatum[5]. Some of the alterations in late HD could be compensatory mechanisms designed to cope with early synaptic and receptor dysfunctions[5]. These findings suggest that HD treatments need to be designed according to the stage of disease progression, however synaptic dysfunction and loss occur early and continue throughout disease progression.

Complement activation has been implicated in the aberrant removal of synapses during neurodegenerative disease, and in conjunction with its associated inflammation may contribute to ongoing neuronal loss. Complement expression and activation are elevated in many neurodegenerative diseases, including HD and Alzheimer's disease (AD) patients[8, 9, 10]. Therapies targeting the complement pathway may inhibit the complement driven functional synapse loss and neuronal damage in HD and reduce disease progression.

To date, no treatment has been shown to delay the onset of HD or slow its progression[2, 11]. Treatment is focused on specific symptom management and remains supportive. A patient's care may include a broad range of physicians to address the various physical and psychological symptoms. Chorea is often linked to cognitive and psychological aspects of the disease such as anxiety and depression. Disabilities in one area usually lead to problems in another.

Investigational treatments are in development that may provide symptomatic relief or modify the course of the disease. Ultimately a treatment paradigm that incorporates disease modifying drugs that can be administered together with symptomatic drugs will be a significant advance in the treatment of HD[12].

Annexon, Inc. is developing therapies targeting the complement cascade for neurological and ophthalmological disorders. ANX005 is a monoclonal antibody that targets C1q to block the initial activation step of the classical complement pathway, prevent the generation of multiple downstream pathogenic components, and thus block broader aspects of complement signaling than other downstream approaches. Annexon has studied intravenous ANX005 dosing in Guillain-Barré Syndrome (GBS) subjects in an ongoing Phase 1b/2a clinical trial (Protocol ANX005-GBS-01) which has provided safety and tolerability data for dosing of up to 100 mg/kg. [redacted] hese data suggest that ANX-005 may be beneficial in the treatment of neurodegeneration in HD. If Annexon can develop clinical biomarker evidence for engaging the complement mediated neurodegeneration cascade in patients with HD, ANX005 could be tested in larger disease modification trials for subjects with symptomatic and pre-manifest HD.

1.1.1 ANX005 Description and Mechanism of Action

ANX005 is a human IgG4 monoclonal antibody (mAb) that binds to and functionally inhibits human C1q, the initiating molecule of the classical complemen cascade. Thereby, ANX005 can selectively block activation of the entire classical complement cascade. ANX005 is composed of two heavy chains of the IgG4 isotype and two light chains of the kappa isotype. ANX005 has a molecular weight of approximately 150K Da and binds to C1q with high affinity.

Inhibiting C1q in a model of HD (zQ175 KI mouse) have led to synapse protection in the striatum along with functional recovery. In a different mouse model (R6/2), C1q inhibition led to a reduction in CSF NfL levels, consistent with neuronal protection. Inhibiting the first

step in the classical complement cascade can prevent C1q binding to synapses and reduce downstream complement activation and thereby protect vulnerable synapses and neurons in HD. ANX005 is a specific inhibitor of the classical complement cascade and preserves the immune function of the lectin and alternative complement pathways that will allow the body to deal with infectious agents and other cellular debris required for homeostasis.

1.1.2 Nonclinical

Pharmacology, pharmacokinetic (PK), and toxicology studies with ANX005 have been completed or are ongoing. This nonclinical program is consistent with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines S6(R1). The Investigator brochure provides more detailed and the most current information.

The Investigator brochure provides the tables and figures displaying the data summarized below.

1.1.2.1 [redacted]

1.1.2.2 [redacted]

[redacted]

1.1.2.3 [redacted]

[redacted]

[redacted]

[redacted]

1.1.3 Previous Human Experience

1.1.3.1 ANX005 in Healthy Volunteers

A Phase 1 study (ANX005-CP-01) in healthy volunteers was initiated to evaluate the safety, PK, and PD of ANX005 infusion. Study medication (ANX005 and placebo) was administered to healthy volunteers at single, ascending dose levels of 1, 3, and 10 mg/kg, with 6 subjects receiving ANX005 and 2 subjects receiving placebo per dose level. The study was discontinued by the Sponsor after 27 subjects were dosed with ANX005 or placebo in doses up to 8.2 mg/kg.

1.1.3.2 ANX005 in Guillain Barré Subjects

A Phase 1/2 study (ANX005-GBS-01), the first study conducted in patients, is a double-blind placebo-controlled dose escalation study in GBS subjects. This study is ongoing with the

objectives to obtain information on the safety, tolerability, efficacy, PK, and PD of ANX005 administered as a single or two infusions to subjects recently diagnosed with GBS. Cohorts completed (through 8 weeks of follow-up) include 3 subjects who received ANX005 or placebo at 3 mg/kg (2:1), 4 subjects at 9 mg/kg (3:1), 8 subjects at 18 mg/kg (3:1), 8 subjects at 36 mg/kg (3:1), 8 subjects at 75 mg/kg (3:1), 11 subjects at 2 x 75 mg/kg (75 mg/kg ANX005 dose, administered on Day 1 and Day 8, 3:1). In addition to completed subjects, 8 subjects have enrolled to date at 100 mg/kg (3:1). At all doses tested ANX005 has been shown to be safe and well-tolerated as a monotherapy.

1.2 Potential Risks and Benefits

1.2.1 Potential Risks of ANX005

While ANX005 has to date been generally well tolerated, a potential risk of infection with encapsulated organisms, e.g., *Neisseria meningitidis*, including serogroup B *meningococcus, Haemophilus influenzae,* and *Streptococcus pneumoniae,* may exist due to its blockade of the classical complement pathway via inhibition of C1q. Since the other two initiator pathways of the complement cascade, the lectin and the alternative pathways, remain intact, subjects receiving ANX005 may still possess alternative bacteriolytic capability to ward off against infections. There have been no reported cases of infections with encapsulated organisms (*Neisseria meningitidis*, including serogroup B *meningococcus, Haemophilus influenzae,* and *Streptococcus pneumoniae)* in vaccinated normal healthy volunteers and unvaccinated subjects with an acute disease such as GBS. With a more chronic dosing regimen, however, subjects will be vaccinated prior to study entry or must have documented evidence of vaccination. They will be closely monitored for infections during study participation. Subjects will be instructed to report infections immediately.

Development of an autoimmune disease may be a potential risk of ANX005-mediated inhibition of C1q. Autoimmune diseases have developed in subjects with genetic C1q deficiency. Autoimmunity in subjects with inherited C1q deficiency typically occurs in mid-childhood or later, following many years of significant C1q deficiency. Based on these observations, autoimmunity would not be expected following short-term suppression of C1q. [redacted]
Clinical trial data to date do not suggest that ANX005 is associated with an increased risk of autoimmunity; nevertheless, the protocol includes detailed information with respect to monitoring for autoimmunity through a combination or clinical vigilance, Screening laboratory data, and more specific autoimmunity panels.

Infusion related reactions are common adverse drug reactions that occur with the administration of monoclonal antibodies such as ANX005 and have the potential to cause local or systemic infusion reactions[15]. [redacted]

[redacted]

[redacted]

[redacted]

Refer to Section 5.4 for details on recommended [redacted] and Section 9.10 for further information on IRRs. Please see the ANX005 Investigator brochure for further details.

1.2.2 Potential Benefits of ANX005

We believe that progressive synaptic changes, linked to the underlying mutant huntingtin protein, drive local activation of the classical complement cascade which promotes microglial assisted removal of corticostriatal synapses. We further hypothesize that blockade of C1q with ANX005 in HD will reduce downstream complement components, lower microglial activation and potentially decrease neurodegeneration. As previously described in detail in Section 1.1.2.1, ANX005 has demonstrated desired biomarker and pharmacologic activity in 2 HD-relevant disease models, e.g., the zQ175 knock-in HD mouse and the R6/2 mouse model with overexpression of N-terminally truncated mHtt with CAG repeat expansion. By empirically establishing a relationship between the serum and CSF pharmacokinetics of ANX005, changes in CSF complement components and NfL levels, and [redacted] we hope to establish biologic proof of principle with ANX005 in HD.

Annexon proposes the dosing schedule in ANX005-HD-01 in Table 2 to optimize the potential for benefit vs risk in subjects with Huntington's disease, a fatal, neurodegenerative disease with no currently available disease modifying therapies. In GBS subjects, treatment with ANX005 single doses up to 100 mg/kg and two weekly doses of 75 mg/kg have generally been safe and well-tolerated, and dosing as proposed in ANX005-HD-01 is projected to fall to within acceptable safety margins established by chronic toxicology studies. Benefit is expected to require inhibition of C1q in deep brain structures, such as the caudate nucleus and putamen. Given the expected relatively low brain penetration of a monoclonal antibody such as ANX005, doses that fully engage peripheral C1q and maximize CNS penetration are required to maximize the potential for benefit, as demonstrated in preclinical models of HD. Annexon proposes to treat HD subjects with ANX005 for approximately 6 months in this clinical study. Given that HD is a slowly progressing disease and CNS damage accumulates over time, longer treatment durations are anticipated to have a greater effect on circulating C1q and modulation of NfL (a biomarker of neurodegeneration), as well as other biomarkers involved in classical complement activation (e.g. C4a).

2 STUDY OBJECTIVES

2.1 Primary Objectives:

- To assess the safety and tolerability of intravenous ANX005 administered for up to 22 weeks in subjects with, or at risk for, manifest Huntington's Disease
- To assess the pharmacokinetics (PK) of ANX005 in the serum and cerebrospinal fluid (CSF)
- To assess the pharmacodynamic (PD) effects of ANX005 in blood and/or CSF through the assessment of C1q, C4a, and NfL levels

2.2 Exploratory Objectives:

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This study is a multi-center, open label, proof-of-biology study of intravenous ANX005 in subjects with, or at risk for, manifest Huntington's Disease.

Subjects will receive induction dosing of ANX005 at 75 mg/kg administered by IV infusion on Days 1 and 5 or 6 (5/6), followed by maintenance dosing at 100 mg/kg every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22) with follow up visits on Weeks 24, 28, and 36. All ANX005 infusions will be administered at in clinic visits. The first infusion will be given over approximately 21 hours with subsequent infusions expected to be completed in approximately 4 hours (Day 5/6) or up to 5 hours (Weeks 2 through 22).

All subjects will be contacted (in clinic visit or phone call) 6 months after study completion to gather information focused towards clinical signs and symptoms suggestive of autoimmunity, e.g., fatigue, muscle aches, swelling, redness, low-grade fever, trouble concentrating, numbness and tingling, hair loss, or skin rashes. If clinically indicated, appropriate clinic visits may be scheduled depending on the information gathered during this visit.

Blood samples for PK/PD assessments will be collected for serial sampling following the first and last dose. Pre-dose samples will be collected at all dosing visits (Days 1 and 5/6 and Weeks 2 through 22) prior to beginning the ANX005 infusion. Blood samples will be collected after completing the infusion on Day 5/6, and Weeks 2, 6, 10, 14, and 18. PK/PD samples will also be collected at the Week 24, 28, and 36 visits. Additional PK/PD samples will be collected (via home visit, if preferred) on other study days as described in Table 1.

Cerebrospinal fluid sampling for PK and PD assessments will be conducted at Screening, pre-dose at Week 6 and Week 12, and at Weeks 24 and 36.

[redacted]

Only after obtaining informed consent may subjects begin Screening procedures and required study interventions including administration of required vaccinations, infusion with ANX005, observation, and follow-up care.

Subjects will be admitted to the clinic for the Day 1 ANX005 infusion which is expected to last for approximately 21 hours. Subjects will be observed for 1 hour after each infusion and may be released once all required end of infusion procedures have been conducted. Subjects are expected to return to clinic for all subsequent visits and ANX005 infusions through the end of the study. At home health care visits may be made by appropriately trained health care professionals to collect blood samples and/or complete assessments if necessary, to maintain the study visit schedule.

Subjects who do not receive all scheduled infusions of ANX005 may be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator (PI). Similarly, if a subject discontinues from the study prior to the end of study visit, an additional subject may be enrolled at the discretion of the Sponsor to replace the discontinued subject. Up to 5 replacement subjects may be enrolled.

The study assessments for subjects enrolled in the study are shown in Table 1.

3.2 Safety Review

The PI and the medical monitor will review safety data on an ongoing basis to evaluate the frequency and severity of the following events and findings:

- Serious AEs
- Discontinuation of participation due to an AE
- Adverse events
- Adverse events of special interest (AESI), such as hypersensitivity and infusion-related reactions, evidence of an infection, hemolytic anemia, or autoimmune disorder (see protocol Sections 9.7, 9.8, and 9.9 for additional details on how such events will be monitored)
- New or worsening, clinically significant findings from Columbia Suicide Severity Rating Scale, physical examinations, and laboratory test

See Section 3.4 for a description of Stopping Rules.

3.3 Data Safety Monitoring

A safety review team (SRT), consisting of relevant study team members of the Sponsor and independent external experts (including an immunologist and hematologist), will monitor the emerging safety data throughout the study and will meet after the first subject enrolled has completed the Week 4 visit (4 doses of ANX005) and then after the first 4 subjects enrolled have completed the Week 4 visit and periodically or for cause thereafter to review available safety data. The SRT charter will describe the committee structure and details for the conduct and rules of the meetings. SRT meetings will be conducted when events related to study stopping rules occur or when indicated by surveillance for AESI. The naming, composition, and members' roles and responsibilities of the SRT may be modified in regions where local regulatory practices require the Sponsor to do so.

The SRT will review all pertinent safety information including adverse events with close attention to emerging safety signals suggestive of autoimmunity or infections, infusion related reactions, hemolytic anemia, hypersensitivity, safety laboratory assessments (serum chemistry, hematology, urine analysis, ADA, and ANA), vital signs, and the Columbia Suicide Severity Rating Scale (C-SSRS).

3.4 Stopping Rules

Dosing of ANX005 on Day 1 will require subjects to be housed for approximately 21 hours for IV infusion. It is expected that subsequent IV infusions of ANX005 will be completed within approximately 4 hours (Day 5/6) or up to 5 hours (Weeks 2 through 22). This schedule has been successfully implemented in the ongoing clinical trial in GBS subjects (Protocol ANX005-GBS-01). Individual subjects will be monitored during study drug infusions and may experience study drug interruptions or discontinuation based on immediate observations (refer to Section 5.4 and Section 9.10 for information on study drug administration and management of IRRs). All subjects will be followed for safety and with attention towards AESI as described in Sections 9.7, 9.8, and 9.9 which provide details for monitoring for infection, autoimmunity, and hemolytic anemia respectively.

Stopping rules for this study include two or more occurrences of any of the following within a given category:

- Serious adverse events with signs, symptoms and concurrent serologic evidence (Section 7.2.13.1) consistent with an autoimmune disease considered related to study drug treatment.
- Serious adverse events of infection considered related to study drug treatment.
- Systemic life-threatening infusion-related or hypersensitivity reactions resulting in hospitalizations, admittance to the intensive care unit (ICU), or death considered related to study drug treatment.
- Other occurrences of the same or a similar SAE assessed as related to study drug treatment.

Should these events occur at any time during the study, the SRT will be notified immediately and will meet within 5 business days of becoming aware of the events to review all applicable medical and clinical information and observations in order to declare if study stopping rules have been met. Causality of adverse events is determined by the study Investigator (Section 9.2.2). The study may also be terminated if the Sponsor and SRT determine that AEs are occurring that are intolerable or pose a medically unacceptable safety risk.

The study will continue to allow for subject follow-up visits as described and for safety observations in the event the study stopping rules are met.

3.5 Replacement Subjects

Subjects who do not receive their complete assigned doses of ANX005 may be replaced at the discretion of the Sponsor and in consultation with the PI. Similarly, if a subject discontinues from the study prior to the Week 36 visit, an additional subject may be enrolled at the discretion of the Sponsor to replace the discontinued subject. Up to 5 replacement subjects may be enrolled.

3.6 Duration of Participation

The total duration for individual participation in the study may be up to 42 weeks (screening, treatment, and follow-up), not including the long-term follow-up (6 months after Week 36 or EOS). The subjects are expected to follow the schedule of assessments (Table 1) through the End of Study visit (Week 36).

3.7 Study Visits

Subjects will be admitted to the clinic for the Day 1 ANX005 infusion which is expected to last for approximately 21 hours. Subjects may be released after the first ANX005 infusion is completed and all required end of infusion procedures have been conducted. All subjects are expected to return to the study site for all subsequent study visits. At home health care visits may be made by appropriately trained health care professionals to collect blood samples and/or complete assessments if necessary, to maintain study visit schedules.

4 STUDY POPULATION

The study population consists of male and female subjects aged 18 and above, inclusive, at the time of consent with, or at risk for, manifest Huntington's Disease

4.1 Number of Subjects

Up to approximately 24 subjects are expected to take part in the study.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Subjects must meet **ALL** the following criteria to be eligible to participate in the study:

1. Males or females aged 18 and above at the time of informed consent.
2. Diagnosis of or at risk for Huntington's disease, as defined by:
   a. Genetically confirmed disease by direct DNA testing.
   b. Total CAG-Age Product (CAP) score > 400. Only subjects with a prior history of a positive genetic test for HD are eligible to participate in the trial. Documentation of the number of CAG repeats in a subject's huntingtin gene is required either through prior genetic testing or through genetic testing included as part of the Screening process.
   c. UHDRS independence score ≥ 80.
3. Able to walk independently and self-sufficient in basic activities of daily living (e.g. eating, dressing, bathing)
4. All HD concomitant medications stable for 3 months prior to Screening.
5. All other concomitant medications must be stable for 30 days prior to Screening.
6. If female, must be postmenopausal (no menses for at least 2 years without an alternative medical cause), surgically sterilized (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or agree to use highly effective methods of contraception from Screening through Week 36 (Section 6.3).
7. Males with a woman of childbearing potential partner must agree to use highly effective methods of contraception from Screening through Week 36 (Section 6.3).
8. Willing to have drug of abuse testing at Screening and at later time points if drug abuse is suspected during the study.
9. Previously vaccinated against encapsulated bacterial pathogens (*Neisseria meningitidis, Haemophilus influenzae,* and *Streptococcus pneumoniae*) or willing to undergo vaccination.
10. Able to comply with the requirements of the study and complete the full sequence of protocol-related procedures and evaluations, including lumbar punctures (LPs) for collection of CSF.

11. If a caregiver/study partner is required, per Investigator discretion, must be a competent caregiver/study partner who is at least 18 years of age and is willing to accompany the subject to select trial visits and to be available by phone if needed, and who is and will remain sufficiently knowledgeable of subject's ongoing condition to respond to Study Center inquiries about the subject.
12. Able to tolerate [redacted] and LP procedures.
13. Able to understand and provide written, informed consent.

4.2.2 Exclusion Criteria

Subjects must **NOT** meet any of the following criteria to be eligible to participate in the study:

1. Be at risk of suicide or self-harm within the preceding 12 months, in the opinion of the Investigator.
2. Chorea and/or cognitive deficits severe enough to interfere with study assessments.
3. Subjects with body weight > 150 kg.
4. Clinically significant findings on the Screening laboratory testing or physical examination that are not specific to HD and may interfere with the conduct of the study or the interpretation of the data or increase subject risk.
5. Signs and symptoms of, or a diagnosis consistent with a chronic autoimmune disorder and/or an ANA titer ≥ 1:160.
6. History of previous infusion reactions, sensitivities, allergic, or anaphylactic reactions to previous medications, environmental stimuli or other substances.
7. Receipt of an experimental agent within 60 days or five half-lives prior to Screening or anytime over the duration of this study.
8. Prior treatment with any monoclonal antibody within 6 months of Screening.
9. Presence of an implanted deep brain stimulation device.
10. Any history of gene therapy, RNA or DNA targeted HD specific investigational agents such as antisense oligonucleotides, cell transplantation or any experimental brain surgery.
11. Brain and spinal pathology that may interfere with CSF homeostasis and circulation, increases intracranial pressure (implanted shunt or catheter), malformations or tumor.
12. Contraindication to undergoing an LP including, but not limited to: inability to tolerate an appropriately flexed position for the time necessary to perform an LP; international normalized ratio (INR) > 1.4 or other coagulopathy; platelet count of < 120,000/μL; infection at the desired lumbar puncture site; taking anti-platelet or anti-coagulant medication within 90 days of Screening (low dose aspirin is permitted), degenerative arthritis of the lumbar spine; suspected non-communicating hydrocephalus or intracranial mass; prior history of spinal mass or trauma.
13. Hypersensitivity to any of the excipients in the ANX005 drug product.

14. Clinically significant intercurrent illness, medical condition, or medical history (including neurological or mental illness, HIV, any active infection, including Hepatitis B or C) that would jeopardize the safety of the subject, limit participation, or compromise the interpretation of the data derived from the subject.
15. Any known genetic deficiencies of the complement-cascade system.
16. Clinically significant laboratory or vital sign abnormalities at Screening.
17. History of chronic oral or intravenous steroid use or immunosuppressant medication ending less than 1 month prior to Screening.
18. Active alcohol, drug abuse or substance abuse, or any other reason that makes it unlikely that the subject will comply with study procedures. If positive drug screen results are obtained due to the use of a concomitant medication for a therapeutic indication, the result may be flagged and discussed with Sponsor and will not necessarily be exclusionary.
19. Females who are pregnant (positive pregnancy test at Screening or prior to infusion of ANX005), breast feeding, or unable or unwilling to use highly effective methods of contraception (Section 6.3) throughout the study.
20. Hemoglobin, bilirubin, or lactate dehydrogenase (LDH) values that are outside normal limits and clinically significant or suggestive of hemolytic anemia.

5 STUDY MEDICATION AND ADMINISTRATION

ANX005 is the only study medication used in this open label study. Details on preparation of ANX005 are provided in the pharmacy manual.

5.1 ANX005 Description

ANX005 is a recombinant, humanized, monoclonal antibody. The drug product composition is [redacted] ANX005, [redacted] The ANX005 formulation is [redacted].

[redacted]

All study doses are based on subject body weight recorded at the previous visit. No modification of the assigned dose is allowed.

5.2 Packaging, Labeling, and Storage

ANX005 packaging consists of supply cartons containing ANX005 vials. The cartons are tamper-seal protected for shipment. Labels are present on both the cartons and the vials.

Do not remove vials from their cartons prior to infusion preparation. Store ANX005 in a secure area with controlled access, under monitored refrigeration (2°C to 8°C) and protect from light. Excursions from these limits should be reported to Sponsor representatives to determine whether the affected vials can be used.

Details on ANX005 preparation are provided in the pharmacy manual.

Pharmacy records must document storage temperatures.

5.3 Preparation of Study Medication

Details for preparing ANX005 are provided in the pharmacy manual.

5.4 Dosage and Administration

Infusions of ANX005 must take place by an appropriately trained health care provider, who is a member of the site personnel under the medical supervision of the PI or PI designee. See Table 2 for dosing schedule.

Table 2: ANX005 Dosing Schedule

[redacted]

For the first ANX005 infusion, all subjects should receive [redacted] within 2 hours prior to the start of the infusion. [redacted]

[redacted]

[redacted]

[redacted]

Modification to the recommended medication guideline is acceptable based on individual subject condition and characteristics. Addition or substitution with alternative [redacted] is acceptable based on Investigator discretion. The PI or medically qualified designee may choose lower or omit doses of pre-medications if discussed and approved by the medical monitor. [redacted] may be repeated during the infusion of ANX005 at the discretion of the PI or medically qualified designee. If IRRs occur during the infusion, the infusion rate may be stopped temporarily until symptoms have resolved, or discontinued altogether depending on the severity of symptoms that develop during the infusion (refer to Section 9.10 for details on monitoring infusion reactions).

Site personnel administer ANX005 via IV infusion following the Sponsor-provided infusion plan such that each subject receives the assigned dose of ANX005. No modification of the assigned dose is allowed. The ANX005 infusion plan (Appendix F) provides details on the preparation of ANX005 for injection including drug concentrations, saline dilution, and

infusion rates. The Day 1 infusion is expected to take approximately 21 hours to administer. Subsequent infusions are expected to take approximately 4 hours (Day 5/6) or up to 5 hours (Weeks 2 through 22) to administer.

Monitor subject with a transcutaneous pulse oximeter during each ANX005 infusion.

Subjects are allowed normal meals prior to and during the infusion of ANX005. Water use prior to, during, or after the infusion is unrestricted. Subjects are monitored closely for detection of infusion-related reactions during and following completion of the infusion of ANX005. See Section 9.10 for details on monitoring for infusion reactions.

5.5 Study Medication Accountability

Site personnel must maintain adequate records of the receipt and disposition of all vials of ANX005. Records must include dates, lot numbers, quantities received, quantities dispensed, and the subject identification code associated with each infusion. Site personnel may destroy used vials of ANX005 per site standard operating procedures (SOPs).

5.6 Overdose

An accidental overdose is highly unlikely, because a pharmacist or qualified designee prepares ANX005 dilutions for infusion. In the event of an accidental overdose, contact the medical monitor immediately to discuss an appropriate course of action and follow-up.

5.7 Missed Doses

If a subject misses a scheduled dose of ANX005 (failure to administer the scheduled dose in the specified interval) the subject will be discontinued from further ANX005 treatments and will continue with all scheduled study visits including the Long-Term Follow-up visit. Subjects who do not complete all scheduled dosing visits and assessments may be replaced. Up to 5 replacement subjects may be enrolled.

6 MEDICATIONS AND RESTRICTIONS

6.1 Permitted Medications

Record all medications on the Concomitant Medications case report form (CRF), including all medications taken within 3 months before the Screening visit and through the final study visit. Permitted concomitant medications (CMs) include all vitamins, herbal remedies, nutritional supplements, and over-the-counter and prescription medications, unless listed under Section 6.2.

6.2 Prohibited Medications and Supplements

Prohibited medications include, but are not limited to the following:

- Drugs of abuse
- Steroid or immunosuppressant medication use ending less than 1 month prior to Screening
- Any medication that suppresses the immune system
- Other investigational drugs

6.3 Contraceptive Methods

Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to use highly effective methods of contraception from Screening through Week 36. Highly effective methods of contraception result in a failure rate less than 1% per year when used consistently and correctly.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral[d] – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral[d] – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Effective Methods Used in Combination
• Double Barrier Method When used consistently and correctly "double barrier" methods (eg, use of male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Effective methods may include barrier methods of contraception (eg, male condom, female condom, cervical cap, diaphragm, contraceptive sponge). – *No barrier method by itself achieves a highly effective standard of contraception.* – *The proper use of a diaphragm or cervical cap includes use of spermicide and is considered one barrier method.* – *The cervical cap and contraceptive sponge are less effective in parous women.* – *The use of spermicide alone is not considered a suitable barrier method of contraception.*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d) For oral contraception, the same pill at the same dosage for at least 3 months before taking the study medication.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together due to risk of failure from friction

6.4 Restrictions

Alcohol use is prohibited throughout the duration of housing in the study (Day 1–2).

7 [redacted]

All assessments and procedures are listed in the recommended order for each visit.

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7.1.1 [redacted]

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7.1.24 [redacted]

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7.2 Study Procedures

7.2.1 Informed Consent

Prior to any protocol-related activities or Screening evaluations, obtain informed consent from each potential subject in accordance with Good Clinical Practice (GCP) and local regulatory requirements. The format and content of the informed consent form (ICF) must be approved by the appropriate independent ethics committee (IEC) prior to implementation.

7.2.2 Genetic Testing and CAP Score Calculation

Subjects are required to have documented genetic test results indicating the number of CAG repeats present in order to confirm eligibility for the study and calculation of CAP score.

$$\text{CAP Score} = \text{Age} \times (\text{CAG} - 33.66)$$

Subjects that do not have documented genetic test results available are required to have genetic testing conducted to confirm eligibility criteria are met. Repeat genetic testing is not required if subjects have confirmed genetic test results available.

7.2.3 Vaccinations

Complement activation results in the rapid clearance of bacteria by immune cells and direct bacterial killing via large pore forming terminal complement complex. Long-term complement inhibition may increase the risk of infection with encapsulated bacteria, particularly Neisseria meningitis, including serogroup B *meningococcus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. While the overall risk of infection risk appears low with short-term and selective blockade of the classical complement pathway that leaves the immune function of the lectin and alternative pathways intact, an appropriate program of prophylactic vaccinations will be instituted. Vaccination reduces but may not prevent the risk of infections and therefore subjects must be advised that vaccination may not prevent serious infections with encapsulated organisms and that they should immediately report fevers or other symptoms consistent with acute infection to the Investigator.

Subjects who do not have a documented history of vaccination against encapsulated bacterial pathogens (*Neisseria meningitis*, including serogroup B *meningococcus, Haemophilus influenzae,* and *Streptococcus pneumoniae*) within 5 years prior to Screening, are required to receive the following vaccinations:

- One dose of a *meningococcal* conjugate vaccine
- Two doses of *meningococcal* serotype B vaccine series
- One dose of a *pneumococcal* vaccine
- One dose of *Haemophilus influenzae* type b

Completion of the primary vaccine series should occur at the Week -6 Screening visit and at a minimum of 42 (±3) days prior to Day 1 dosing with ANX005. The second (booster) dose with the same vaccine should be completed 14 (±3) days prior to Day 1 (if required). Vaccinations should comply with routine vaccination guidelines, vaccine availability and be in accordance with respective labels, as applicable.

Subjects who develop symptoms consistent with an infection due to encapsulated bacterial pathogens during the study period will have a blood sample collected to test for confirmation of infection.

7.2.4 Subject Identification Number

Assign a unique, sequential number to each subject upon signature of an ICF. Subject numbers consist of 6 digits; the first 3 digits identify the study site, and the last 3 digits identify the subject screened at the site, in ascending order.

Do not enroll subjects who fail Screening.

If an enrolled subject does not receive infusion of ANX005, do not reuse the same enrollment number for another subject.

7.2.5 Rescreening Criteria

Subjects who do not meet all inclusion and exclusion criteria may rescreen once, with the medical monitor's prior approval, if there is cause to believe that the subject will be eligible upon rescreen. If a subject is rescreened, reuse the same Screening number.

7.2.6 Medical History and Demographic Data

Medical history includes an assessment of past and present, clinically significant diseases and surgeries, as well as an assessment of current reproductive status. Record all medications (e.g., prescription and over-the-counter medications, hormonal birth control, herbal or homeopathic remedies, and nutritional supplements) used by the subject within 3 months prior to the Screening visit.

Demographic data include age, sex, and self-reported race or ethnicity.

7.2.7 Physical Examinations

The physical examination includes height (Screening only), body weight, and an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record any abnormality identified prior to infusion of ANX005 as medical history.

Record any clinically significant, new or worsened abnormalities that occur after infusion of ANX005 as AEs.

Body weight will be collected at visits on Day 1, Day 5/6, applicable visits from Week 2 through Week 22, Week 24, and Week 28 when physical examinations are not performed (Table 1).

7.2.8 Vital Signs

Measure vital signs at the time points as indicated in the Schedule of Assessments (Table 1). Vital signs include body temperature, respiratory and heart rates, and systolic and diastolic blood pressures (blood pressure). Heart rate, respiration rate, and blood pressure should be measured after the subject has rested for at least 5 minutes. Monitor subject with a transcutaneous pulse oximeter during each ANX005 infusion (approximately 21 hours for Day 1 dosing and approximately 4 or up to 5 hours for all subsequent doses).

7.2.8.1 Vital Signs and Dosing

Seated or semi-recumbent vital signs (blood pressure, heart rate, respiration rate, and body temperature) should be collected within 30 minutes prior to start of infusion, 15 minutes after the start of the infusion, and then every 30 minutes and as needed during the initial 4 hours of the infusion. Vital signs may then be collected every 4 hours and as needed until the infusion is completed and within 1 hour after the end of the infusion.

Should an IRR occur; seated or semi-recumbent vital signs should be collected at the onset of the IRR, 15 minutes later, and then every 30 minutes and as needed until the IRR is stabilized. Once the IRR is stabilized, vital signs should be collected every 4 hours until the end of the infusion or the IRR is fully resolved. Vital sign measurement time window is ±15 minutes.

7.2.8.2 Vital Signs and Orthostatic Hypotension

To assess for the presence of orthostatic hypotension, additional blood pressure and pulse rate will be assessed at Screening, pre-infusion, every 4 hours during the infusion, and post-infusion on Day 1; pre- and post-infusion at all other dosing visits (Day 5/6 and Weeks 2 through 22); and as needed at the discretion of the Investigator. BP (systolic and diastolic) and pulse rate will be evaluated in the seated, semi-recumbent, or supine position after at least 5 minutes rest. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the seated/semi-recumbent/supine measurement). During the night of the first infusion, one scheduled orthostatic blood pressure measurement may be missed if the subject is sleeping and if blood pressure measurements are otherwise stable. Vital sign measurement time window ± 15 minutes.

7.2.9 Drug of Abuse Testing

All subjects undergo testing for drugs of abuse during Screening via dipstick Screening.

Subjects found to be positive for one or more substances are not eligible to participate in the study. Repeat testing can be performed in the event of a suspected false-positive, at the discretion of the study physician.

7.2.10 [redacted]

[redacted]

7.2.11 [redacted]

[redacted]

7.2.12 [redacted]

[redacted].

7.2.13 Blood Samples

7.2.13.1 Safety Laboratory Assessments

[redacted]

[redacted]

7.2.13.2 Blood Samples for PK, PD, and ANX005 Immunogenicity

- [redacted]

7.2.14 CSF Samples for PK and PD

ANX005 and biomarkers will be measured in CSF collected through lumbar punctures (LPs) performed according to standard procedures for the study site. Detailed information on equipment, LP procedures, and CSF handling and storage are documented in the laboratory manual. The collection timepoints are provided in the schedule of assessments (Table 1). In brief, up to 15 mL of CSF will be collected at each timepoint. CSF quality analysis for evidence of blood contamination (visual inspection and analysis for hemoglobin, protein and cells) will take place after collection. Instructions for shipment of CSF to the bioanalytical laboratories are detailed in the laboratory manual.

7.2.15 Diagnostic and Quality of Life Assessments

Conduct assessments according to Table 1. A trained health care provider who has been approved to conduct the assessments must administer each questionnaire. When possible, the same health care provider should administer each questionnaire at all time points for each subject. The questionnaires should not be administered over the phone.

- **Columbia Suicide Severity Rating Scale:** The C-SSRS is an instrument that assesses suicidal ideation and behavior[16].The baseline/Screening version of the instrument is administered at the Screening visit. The since-last-visit version is administered at the Week 4, 12, 20, 24, and 36 visits. Samples of the 2 versions of the C-SSRS can be found in Appendix C. In between protocol-specified C-SSRS collections, Investigator will

remain vigilant for any signs and symptoms suggestive of active suicidal intent, significant suicidal behavior, or the subject is dangerous to himself or herself, the subject should be referred for immediate psychiatric evaluation. Individuals who score a 4 or 5 on the C-SSRS, whether at Screening or during the study should be assessed promptly by a psychiatrist and be reviewed for potential discontinuation.

8 STUDY COMPLETION AND WITHDRAWAL

8.1 Subject Completion

Subjects complete study visits as defined in Table 1, culminating with the Week 36 end-of-study visit. An additional Long-Term Follow-up visit (phone call or in clinic visit) will occur for all enrolled subjects 6 months after study completion. Additional follow-up visits may be conducted if required for safety assessments.

8.2 Subject Withdrawal

A subject may withdraw from the study at any time. Site personnel must make every effort to determine why a subject withdraws from the study early. Any subject who withdraws from the study with an ongoing AE that is considered related to ANX005 must be followed until the event is resolved or deemed stable. For subjects who refuse further study visits, attempt to obtain an end-of-study evaluation at Week 36, with a total of 2 documented attempts of contact with the subject to review ongoing or new AEs that may have occurred since the infusion of ANX005.

The Sponsor and/or Investigator may choose to discontinue study treatment for subjects who are determined to be at risk for continued treatment. These subjects should continue in the study with all scheduled visits and at a minimum return for evaluations at the Week 36 visit and the Long-Term Follow-up visit 6 months after study completion. Reasons for discontinuing treatment of individual subjects may include:

- Subject experiences any dose-limiting toxicity
- Subject withdraws consent
- Investigator or Sponsor considers that the subject will not benefit from further study drug administration
- Subject becomes pregnant
- Subject is unable to comply with the protocol requirements

8.3 Termination of the Study

If the Investigators, the medical monitor, or other Sponsor representatives become aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, the clinical study may be terminated by the Sponsor after appropriate consultation between the involved parties. The clinical study may also be terminated at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to the following examples:

- The discovery of an unexpected, relevant, or unacceptable risk to subjects related to ANX005 enrolled in the clinical study
- Failure to enroll subjects at the required rate
- A decision of the Sponsor to suspend or discontinue the study

Should the study be terminated, or the study site closed for any reason, all documentation pertaining to the study must be forwarded to Sponsor representatives. The study physician must continue to assess and maintain subject safety as required, despite termination of the study by the Sponsor.

9 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

9.1 Adverse Events

9.1.1 Definition

An AE is any untoward medical occurrence in a subject who has been administered a pharmaceutical product. An AE does not necessarily have a causal relationship with the product and therefore can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product. An AE can arise with any use, route of administration, formulation, dose (including an overdose), or when used in combination with another pharmaceutical product.

Events occurring after signing the informed consent but prior to first administration of ANX005 should be documented as medical history unless the event is study procedure-related, in which case it should be reported as a non-treatment-emergent AE. Events observed during or following the first administration of ANX005 until the end-of-study visit, are to be recorded as AEs.

An AE includes any of the following:

- An exacerbation or an unexpected increase in frequency or intensity of a pre-existing condition, including intermittent or episodic conditions
- New conditions or intercurrent illnesses detected or diagnosed after the first administration of ANX005
- A suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either ANX005 or a concurrent medication
- Any clinically significant laboratory abnormality or physical examination finding that was not present prior to the first administration of ANX005

An AE does not include:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study (HD)
- Medical or surgical procedure (e.g., colonoscopy, hernia repair); the condition that leads to the procedure may be an AE, if not present in medical history
- Hospitalizations where an untoward medical occurrence did not occur (social or convenience admission to a hospital, such as the admission the night prior to an outpatient visit)

- Pre-existing diseases or conditions that were present before the start of ANX005 administration that do not worsen
- Overdose of either study drug or concomitant medication without any signs or symptoms

9.2 Severity and Causality Assessment

9.2.1 Severity Rating

The severity of each AE should be characterized and then classified according to National Cancer Institute Common Terminology Criteria for Adverse Events, (NCI-CTCAE v5.0), Adverse Event Severity Grading (Appendix A). For infusion related reaction severity grading please refer to Appendix B.

9.2.2 Causality Rating

An event is considered related to ANX005 if there is a reasonable possibility that there is a causal relationship between the ANX005 and the event. Any AE judged by the Investigator or Sponsor representatives as having a reasonably suspected, causal relationship to ANX005 qualifies as a related AE.

Adverse events are categorized as having one of the following relationships to study treatment:

Not Related: The AE is not related to ANX005 if any of the following exists:

- An event that is considered part of natural history of HD in intensity and frequency
- Another cause of the event is most plausible
- A clinically plausible temporal sequence is inconsistent with the onset of the event and the ANX005 administration
- A causal relationship is considered biologically implausible

Related: The AE is possibly or probably related if any of the following exists:

- The event is uncommon in the subject population and follows a reasonable, temporal sequence from administration of ANX005
- The event cannot readily have been produced by the clinical state of the subject, environmental factors, concomitant medication, or other modes of concomitant therapy
- The event improves on stopping ANX005 and reappears on subsequent exposure to ANX005

Relationship assessment for individual AEs is part of the Investigator responsibilities. Regardless of relationship, Sponsor representatives review all AEs against cumulative experience of ANX005 to identify and communicate new safety findings to the Investigators and regulatory authorities, as applicable.

9.3 Documentation

An event that occurs after a subject signs the ICF, but prior to first administration of ANX005 should be documented as medical history, unless the event is study procedure-related, in which case it should be reported as a non-treatment-emergent AE. Any new event or worsening, pretreatment event that occurs from the time of the first administration of ANX005 until the final study visit is recorded as an AE, irrespective of whether the event is considered to be related to ANX005.

Adverse events are reported at the maximum intensity experienced. If a previously recorded pretreatment condition increases in severity or frequency, it is recorded as a new AE. All AEs are considered ongoing until they have completely resolved or, in the case of a pretreatment condition, returned to baseline status recorded prior to administration of ANX005. At the time of the final study evaluation, all AEs should have a statement regarding resolution. Any AE that is assessed as related to ANX005 is followed until resolution or stabilization.

The following information is collected on all AEs experienced during this clinical study:

Event Term

- Whenever possible, report an AE as a specific diagnosis or syndrome using the most medically appropriate term rather than as signs or symptoms. If no specific diagnosis or syndrome can be identified, the AE symptoms should be recorded as separate and individual events.

Onset Date

- Report the date on which the AE was first experienced
- For AEs experienced during infusion of ANX005, report the date and time, using the infusion reaction CRF page.

Resolution Date

- Report the date on which the AE was last experienced, completely resolved, or if for a pretreatment condition, returned to the baseline status

Severity

- Determine the worst grade as defined by NCI CTCAE v 5.0 (Appendix A)

Seriousness

- Confirm whether or not the AE meets the definition of an SAE (Section 9.4.1)

Causality

- Determine the relatedness of the AE to ANX005 (Section 9.2.2)

Action Taken

- Report the action taken with ANX005 in response to the AE
  - Dose Not Changed (No action taken)
  - Drug Interrupted (infusion interrupted)
  - Drug Withdrawn (infusion discontinued)
  - Not applicable

Outcome

- Report the outcome of the AE
  - Ongoing
  - Fatal
  - Not recovered/not resolved
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Recovering/resolving
  - Unknown

Caused Discontinuation from Study

- Report whether the AE was the cause of the subject discontinuing from the study

Record clinically significant, abnormal, laboratory, or physical examination findings discovered during the Screening period on the Medical History CRF as a diagnosis whenever possible. Record clinically significant, abnormal findings after the start of infusion of ANX005, throughout the study, until the final visit on the AE CRF as a diagnosis.

9.4 Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

The Investigator classifies each AE as serious or not serious.

The medical monitor determines the expectedness of AEs assessed as related to ANX005.

9.4.1 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence that meets 1 or more of the following criteria:

1. Is fatal
2. Is life threatening, (i.e., subject was at risk of death at the time of the event)
3. Requires or prolongs in-subject hospitalization (unless related to an elective surgery, a routine procedure to treat a pre-existing condition that did not worsen or an admission for non-medical reasons such as respite care)
4. Results in persistent or significant incapacity or disability
5. Is a congenital anomaly/birth defect in the child of a subject exposed to ANX005 prior to conception, or during pregnancy
6. Is a medically important event (i.e., events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition)

An SAE may also include any other event that the Investigator or the medical monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

In addition, any event that occurs after the subject signs an ICF and the first infusion of ANX005 that is assessed by the Investigator as both serious and related to a protocol-mandated procedure must be documented as an SAE.

9.4.2 Suspected Unexpected Serious Adverse Reaction Definition

A suspected, unexpected, serious, adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the ANX005 and the AE, and which is both assessed as unexpected and serious. An unexpected adverse reaction (i.e. any untoward and unintended response to the ANX005), is one for which the nature and severity is inconsistent with the applicable Reference Safety Information (RSI). The ANX005 Investigator Brochure contains RSI that should be referenced for assessing expectedness of adverse events with ANX005 administration.

SUSARs are subject to expedited reporting to applicable regulatory authorities.

9.5 Reporting

Site personnel must provide subjects with contact information for the PI and study physician for reporting SAEs.

The reporting period for SAEs begins from the time of infusion of ANX005 through study completion. If an ongoing SAE that is thought to be related to ANX005 remains unresolved at the conclusion of the study additional follow-up must continue until resolution or stabilization of the SAE.

All initial and follow-up information regarding SAEs including those related to protocol-mandated procedures, must be reported by the PI or study physician immediately (within 1 business day of discovery) to a Sponsor representative and the SRT. Reporting must not be delayed by waiting for additional information. Additional information can be reported in a follow-up report. Forms and instructions for completion and submission of SAE report forms are provided as part of the study instructions.

It is the responsibility of the medical monitor to assess expectedness and Sponsor representatives report SUSARs to regulatory authorities within the time frames required by applicable regulations. It is the responsibility of the PI to notify the regional IEC of SAEs and any new and significant safety information. At a minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

9.5.1 Reporting for Disease Under Study

The Investigator will assess if any worsening of HD leading to prolongation of hospitalization that is considered part of natural history of HD in intensity and frequency should be reported as an SAE.

An overnight stay in the hospital for social convenience the night prior to follow-up visits is not reported as an SAE.

Failure to respond to treatment for HD is not reported as an SAE.

9.6 Clinically Significant Findings and Safety Monitoring

Sponsor representatives conduct an ongoing review of all study data, with particular attention given to laboratory findings, AEs, and concomitant medication data. Any significant trends in safety observations or other findings of significance that are considered related to ANX005 are reported to the Investigator and regulatory authorities.

Safety data include, but are not limited to, SAEs, AEs, physical examinations, vital signs, C-SSRS, and laboratory data (protocol-specified or ad hoc), as well as additional information provided by the Investigator.

9.7 Monitoring for Infection

Patients receiving the classical complement inhibitor ANX005 are potentially at risk of infections with encapsulated organisms that are mainly, but not exclusively community-acquired. These pathogens include *Neisseria meningitidis*, including serogroup B *meningococcus, Haemophilus influenzae,* and *Streptococcus pneumoniae*. All subjects enrolled in this study are required to receive vaccinations for these pathogens or provide documented evidence of vaccination prior to enrolment. Although vaccination against these organisms is highly effective in reducing the risk of infections, subjects will be monitored for signs and symptoms of infection throughout the study.

As an additional precaution during the study, whether an in-patient or out-patient, subjects must carry a detailed patient card describing the "alert" symptoms for infections at all times. The triggers for seeking immediate medical attention are any of the following symptoms:

- Fever
- Fever and a cough
- Flu like symptoms
- Sore throat
- Ear infection or pain
- Headache with nausea and vomiting
- Headache and fever
- Headache with a stiff neck or stiff back
- Fever and a rash
- Confusion
- Eyes sensitive to light

Any subject experiencing any of the above noted symptoms needs to follow the instructions displayed on the patient card and be seen by a physician as quickly as possible. Early recognition of a bacterial infection with encapsulated organisms and the identification of the causative pathogen by culture is important to optimize outcomes. After an initial work-up, instituting appropriate antimicrobial treatment and monitoring of the subject's condition is recommended.

The Investigator's Brochure contains detailed information on the safety profile of ANX005 (Section 6).

9.8 Monitoring for Autoimmunity

Subjects will have regular safety laboratory evaluations conducted (Table 1) with results assessed for signs of potentially developing an autoimmune disease.

Assessed at every visit:

- Treatment-emergent white blood cell (WBC) count < 4,000/mm^3 OR
- Treatment-emergent ANC of < 1,500/mm^3 OR
- Treatment-emergent lymphocyte count of < 1,000/mm^3 OR
- Platelet count of < 100,000/mm^3 OR
- Urinalysis (including pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, urobilinogen, blood, and leukocyte esterase) will be performed to assess for any significant changes from baseline. If urinalysis parameters show potentially new clinically significant abnormalities, reflex microscopy will be performed and a determination of whether a clinically significant change from baseline based on reflex microscopy and clinical correlation will be made by the Investigator.

Assessed every 4 weeks:

- ANA ≥ 1:160 and an increase from baseline of 2 dilutions
  - If any of these lab criteria are met on 2 or more separate assessments in the absence of a known cause of the observed lab abnormality prompt further tests for autoimmunity will be done.
  - At each visit subjects will also be assessed for signs and symptoms suggestive of an autoimmune disease such as systemic lupus erythematosus (SLE), including seizures, psychosis, pleuritis, pericarditis, persistent hypertension, or new onset arthritis. The development of any of these signs or symptoms or persistent mucocutaneous SLE symptoms (mucosal ulceration, alopecia, photosensitive rash, malar rash,) in conjunction with abnormal clinical laboratory evaluations will prompt further laboratory work-up and/or a referral to rheumatologist.
  - Subjects who met the lab criteria on 2 or more separate assessments or develop signs and symptoms of suggestive of autoimmunity, will have further laboratory tests conducted on the stored and current sample that may include:
    - Antinuclear antibodies (ANA)
    - Multiplex with anti-double-stranded DNA antibody (anti-dsDNA)
    - Antiphospholipid antibody (APL)
    - Ribosome P antibody
    - RNP (also called nRNP and U1RNP) antibody
    - Sm (Smith) antibody

- SS-A/Ro antibody
- SS-B/La antibody
- Scl 70 (topoisomerase 1) antibody
- Chromatin (histone autoantibodies)
- Jo 1 (histidyl tRNA synthetase) antibody
- Centromere B (CENP-B) antibody
- CIC = circulating immune complex

If the further laboratory work-up is suggestive for autoimmune disorder or any of the follow-up labs are persistently abnormal, the subject will be referred to a rheumatologist and information provided to the SRT. Further treatment with ANX005 will be discontinued at this point for such subjects. If restoration of C1q function is deemed necessary, plasmapheresis with albumin or saline replacement may be utilized to eliminate ANX005. Fresh frozen plasma should not be given as a source of C1q in the presence of therapeutic levels of circulating ANX005; C1q levels will recover by endogenous production.

9.9 Monitoring for Hemolytic Anemia

At the Screening visit and all dosing visits Days 1 and 5/6, and Weeks 2 through 22 prior to dosing, subjects will be evaluated for anemia by a complete blood count (CBC), which includes hemoglobin (Hgb) level, as well as for evidence of hemolysis by testing for serum lactate dehydrogenase (LDH), serum indirect bilirubin (calculated from total and direct bilirubin), serum haptoglobin, peripheral blood smear, absolute reticulocyte count, and testing for anti-RBC antibodies using the Direct Antiglobulin Test (DAT).

Prior to dosing, the determination of anemia and hemolysis will be based on a local lab result demonstrating a decrease of > 2 g/dL in Hgb from the subject's last study visit as well as evidence of hemolysis (LDH > ULN and indirect bilirubin > ULN with associated increases from the last study visit). If these lab criteria are met, dosing on the day will not occur and further dosing with ANX005 will be discontinued. Any subject with suspected hemolytic anemia will be followed and appropriately diagnosed and managed until resolution. It is expected that any hemolytic issues would resolve upon drug cessation. Depending upon the severity of the hemolytic anemia, other measures may include RBC transfusion and, if needed, plasmapheresis to rapidly/urgently clear ANX005 and ADAs. The local pre-dose safety labs (Hgb, LDH and bilirubin) may be drawn on the day prior to dosing to facilitate the infusions being administered as planned on the scheduled dosing day.

This monitoring plan will allow for early detection and treatment of any cases of hemolytic anemia that do occur, potentially even before patients become symptomatic, and ensure the systematic collection of relevant safety data. Additionally, the 'real-time' Screening prior to each dose provides further protection for patients, since it will reduce any further drug exposure, expediting the recovery expected once study drug is cleared. Subjects will also be evaluated for the emergence of ADAs but due to the relatively long turn-around time for ADA results, hematological parameters will be the primary Screening tool.

Subjects who are discontinued from further ANX005 dosing due to results from monitoring for hemolytic anemia will be requested to remain in the study and complete all study visits and activities per protocol (with the exception of further ANX005 dosing).

9.10 Infusion Reactions

The ANX005 Infusion-Related Reaction Management Plan provides details and objective criteria regarding the management of IRRs. This plan was developed and implemented in 51 patients with GBS, to mitigate the risk of IRRs. For the first infusion an initial infusion rate of 0.75 mg/kg/hr and [redacted] prior to administration is used. With these measures, transient mild to moderate IRRs occur in approximately 75% of subjects during the first administration of ANX005. These IRRs mainly consist of non-pruritic localized macular rash without systemic adverse reactions. Rashes have occurred at various timepoints during ANX005 infusion and may reoccur during the initial infusion. More extensive maculopapular rashes with pruritic symptoms and serpentine presentation have also occurred infrequently. At initial high infusion rates ≥ 5 mg/kg/hr during the first infusion of ANX005, hypotension and tachycardia have been observed in 2 normal healthy volunteers that had not received [redacted]

Resting vital signs are obtained before, during, and after infusion of ANX005 to monitor for infusion related reactions at scheduled timepoints. A transcutaneous pulse oximeter is used to monitor pulse rate and oxygenation during the first 4–5 hours of each ANX005 infusion.

In the event of any AE of any grade, the Investigator may stop the infusion, if the AE is viewed as a precursor or is indicative of developing anaphylaxis or hemodynamic instability. The subject should receive symptomatic treatment until complete resolution of symptoms before attempting to resume the infusion. In case of a life-threatening event, including anaphylaxis, all appropriate standard measures, including full resuscitation medications and equipment, should be used as clinically indicated.

After completion of the infusion of ANX005, the IV cannula or line should remain in situ for at least 1 hour, to facilitate administration of IV medications, if necessary, in the event of a delayed reaction. If no AEs occur during this period of time, the IV cannula or line may be removed.

9.10.1 Day 1 Dosing (approximately 21-hour infusion)

Administration of [redacted] may reduce IRR symptoms and is required for Day 1 infusion (Section 5.4). For subjects experiencing trace or mild macular rashes, or moderate maculo-papular rashes, and without systemic signs and symptoms, such as abnormal vital signs or any cardiac or respiratory symptoms, the infusion rate should continue as per the infusion plan.

For subjects experiencing or developing any systemic signs or symptoms related to the infusion (i.e., headache, fever, chills, syncope, seizure, hypertension, hypotension, tachycardia, vomiting, dyspnea, tachypnea, etc.), the ANX005 infusion should be immediately interrupted. Appropriate medical intervention with rescue medications as

needed for IRR rescue management should be administered at the discretion of the Investigator and institutions IRR and emergency management policies.

Upon resolution of the systemic adverse events the infusion may begin or resumed at half of the original rate, after a minimum of one hour hold, and be returned to normal rate slowly and in one-to-two hour steps (i.e. 50%,75%, 100%), only if symptoms do not worsen or recur during half rate infusion and IRR symptoms have improved or resolved. Prescribed target infusion rate may be reinstituted after at least 1 hour at half rate as long as signs and symptoms do not worsen or recur.

9.10.2 Dosing on Day 5/6 and Weeks 2 through 22 (approximately 4–5 hour infusion)

[redacted] is not expected to be needed for subsequent infusions of ANX005 but is not prohibited based on Investigator discretion and after appropriate risk benefit assessment.

For subjects experiencing trace or mild macular rashes, or moderate maculo-papular rashes, and without systemic signs and symptoms, such as abnormal vital signs or any cardiac or respiratory symptoms, the infusion rate should continue as per the infusion plan.

For subjects experiencing or developing any systemic signs or symptoms related to the infusion (i.e., headache, fever, chills, syncope, seizure, hypertension, hypotension, tachycardia, vomiting, dyspnea, tachypnea, other), the ANX005 infusion should be immediately interrupted. Appropriate medical intervention with rescue medications as needed for IRR rescue management should be administered at the discretion of the Investigator and institutions IRR and emergency management policies. The subject may not be rechallenged and should complete all scheduled study visits.

9.11 Pregnancy

Pregnancies that occur in enrolled subjects, or the partners of enrolled subjects, while not considered AEs, must be reported by the Investigator to Sponsor representatives within 1 business day of awareness, using the pregnancy report form provided in the study instructions. The pregnancy should be followed until there is a pregnancy outcome. Following delivery or termination of the pregnancy, the Investigator must report the pregnancy outcome within 1 business day of awareness, using the pregnancy report form. Any AEs observed during pregnancy or any abnormality in the newborn are evaluated for potential SAE reporting. Newborns should be followed for at least 6 months, whenever possible, for any potential, congenital anomalies. In the case of a partner pregnancy. Partner informed consent must be attained prior to collecting information on the pregnancy and outcome.

Sponsor representatives ensure due diligence to collect the outcome of the pregnancy (e.g., term or preterm delivery, induced abortion, stillbirth, spontaneous abortion), details of the birth if available, and additional relevant information.

10 STATISTICAL METHODS

Full details on the statistical analyses to be performed will be provided in a separate statistical analysis plan (SAP) or a PK analysis plan (PKAP) as appropriate. The SAP will be finalized prior to database lock.

10.1 Timing of Analyses

The Investigator and the medical monitor jointly monitor safety data for purposes of safety on an ongoing basis as described in Section 3.2.

The final analysis will occur after the last subject completes the end-of-study visit (Week 36).

10.2 Sample Size and Power

Approximately 24 total subjects will be treated in the study. The sample size for this study is determined by practical clinical methods rather than statistical considerations. Descriptive statistics will be used to characterize the results, with a focus on the percent change from the pre-treatment values. A sample size of 24 will provide 2-sided 95% confidence interval half widths of 6 to 12%, assuming observed SD of 15 to 30%.

10.3 General Considerations

10.3.1 Analysis Populations and Sets

The safety population (SAF) includes all subjects who received any amount of ANX005 and will be the population for safety and immunogenicity endpoints.

The full analysis set (FAS) includes all subjects who received at least 1 completed infusion of ANX005 and have at least one post infusion assessment. The FAS will be the population for clinical and functional assessments and biomarker endpoints.

A per protocol set (PP) includes all subjects who completed all infusions of ANX005 and do not have major protocol violations. Major protocol violations may include, but are not limited to, violations of eligibility criteria, receipt of incorrect dose of ANX005, use of prohibited medications, and non-compliance with study assessments. A final determination of inclusion in the PP will be made prior to database lock. The PP set will be used for clinical and functional assessments and biomarker endpoints.

The pharmacokinetic analysis set includes all subjects who received any amount of ANX005 and have evaluable ANX005 concentration data.

10.3.2 General Considerations for Data Analysis

All statistical analyses will be performed using SAS® version 9.4 or higher.

Descriptive summaries for the categorical variables will include frequency counts and percentages. Descriptive summaries for the continuous variables will include means, medians, standard deviations, 25th and 75th quartiles, and minimum and maximum values. Summaries may include 95% confidence intervals (CIs) for point estimates.

Data will be summarized at each scheduled time point. Additional unscheduled data will not be included in the summaries at each time point, but adverse events or lab abnormal results will be included in subject level summaries. Unless specified otherwise, all data will be listed for all subjects.

There is no planned formal hypothesis testing. Descriptive statistics will be used to describe the results of this study.

Further details of the analysis, including the handling of missing data, subgroups, transformations and other data handling procedures will be provided in the SAP and/or PKAP. Exploratory analyses of the data will be conducted as deemed appropriate.

10.3.3 Missing Data

Efforts will be made to collect data at Month 6, even if the subject has discontinued from treatment. Methods for handling missing data will be described in the SAP.

10.4 Subject Disposition

Subject disposition, including receipt of intended ANX005, early discontinuation, and reason for discontinuation will be summarized using all enrolled subjects.

10.5 Baseline and Demographic Characteristics

Subject demographics (gender, age, ethnicity, and race) and clinical baseline characteristics (height, baseline weight, HD type, presence of antecedent event, baseline CH50, baseline C1q, and other key complement parameters at baseline as applicable) will be summarized using the SAF and PP. If the SAF and FAS differ, the summaries will be repeated in the FAS. Similarly, if the SAF and PK analysis set differ, the summaries will be repeated in the PK analysis set.

Baseline disease characteristics, including baseline scores for [redacted] and C-SSRS will be summarized as described above.

Medical history and prior medications will be listed.

10.6 Primary Endpoints

10.6.1 Safety Endpoints

The safety analyses will be performed in the SAF. Safety will be assessed by AEs, infusion related reactions, safety laboratory assessments (serum chemistry, hematology, urine analysis), vital signs, ECGs, and the C-SSRS.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergence is defined as any AE with an onset on or after the day of infusion through Week 36 (EOS). The number and percentage of subjects experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated and summarized by severity and relationship to ANX005.

Each AE will be counted only once for a given subject at each level of summarization. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to ANX005 will be used in the applicable summaries. If grade or relationship are missing in analyses of grade and causality, the missing grade will be set to Grade 3 and relationship will be set to related. Infusion-related and immune reactions will be summarized as the number and percent of subjects with these reactions and will be presented in data listings. Summaries will also be provided for AESIs, SAEs, Grade 3 and higher AEs, Grade 3 AEs and higher related to ANX005, AEs leading to study discontinuation, and AEs leading to discontinuation of ANX005. The number and percentage of subjects that died on study, from any cause, will be summarized.

Results and changes from baseline in vital signs, and hematology and clinical chemistry parameters will be tabulated at each visit (and time point when applicable). Laboratory values above or below the normal range will be flagged as such in the data listings.

Concomitant medications are considered medications that are taken during or after infusion up through Week 36 (EOS). All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant medications will be summarized by anatomical therapeutic chemical level, using frequency and percentage of subjects.

ANX005 administration will be summarized with number and duration of infusions, volume administered, and dose administered. The number of subjects with an infusion interruption or incomplete administration will also be summarized.

Other safety data will be presented in data listings only: C-SSRS, physical examinations, pregnancy tests, and illicit drug tests.

10.6.2 Pharmacokinetic Endpoints

Pharmacokinetic analyses of ANX005 will be based on the PK analysis set. ANX005 serum and CSF concentration data will be tabulated descriptively, summarized by nominal sampling time, and will include number of subjects, arithmetic mean, standard deviation, coefficient of variation (CV%), minimum, median, maximum, and geometric mean. Data will be displayed graphically by visit and time point, as appropriate. Noncompartmental analyses on serial serum data will be applied as data allow. PK parameters and analysis methods will be described in a PK Analysis Plan (PKAP). Parameters may include but are not limited to:

- Maximum observed serum concentration (C_{max})
- Observed time to Cmax (T_{max})

- Area under the ANX005 serum concentration-time curve to the last sample (AUC_{0-t}) and extrapolated through infinity ($AUC_{0-\infty}$)
- Accumulation ratio
- Terminal half-life ($t_{1/2}$)
- Terminal elimination rate constant (λ_z)
- Clearance (CL)
- Volume of distribution (Vss)

10.6.3 Primary Pharmacodynamic Endpoints

Serum or plasma and CSF C1q and NfL levels and CSF C4a will be analyzed for the FAS and for PP. Observed values, changes and percent changes from baseline will be summarized at each visit (and time point where applicable).

The number and percentage of subjects experiencing C1q inhibition, expressed as a percentage decrease from baseline, will be summarized at each visit.

10.7 Exploratory Endpoints

[redacted]

10.7.1 [redacted]

[redacted]

10.7.2 [redacted]

[redacted]

10.7.3 [redacted]

[redacted]

[redacted]

[redacted]

10.7.4 ***Efficacy -*** [redacted]

[redacted]

11 DATA MANAGEMENT

11.1 Data Collection and Management

Clinical data are collected through an electronic data capture system. The handling and management of data, including data quality assurance, must comply with regulatory guidelines and are defined in a study-specific data management plan (DMP). The DMP must include procedures for all aspects of the processing of the data from this study and, if clinical data management is outsourced, the responsibilities of Sponsor representatives. In particular, the DMP includes a list of the SOPs that apply to this study.

Data collection processes and procedures are reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail is maintained of all data changes.

Adverse events and medications are coded using MedDRA and WHO-DD respectively. The DMP specifies the versions used.

The PI must ensure the accuracy, completeness, and timeliness of the data reported to a Sponsor representative. Data reported on the electronic CRFs must be verifiable to source data, which necessitates access to all original recordings, laboratory reports and subject records as specifically related to the subject's participation in this study (i.e. medical history, genetic test results and diagnosis of HD/risk of HD, inclusion and exclusion criteria, adverse events, concomitant medications, study activities, and other pertinent medical information or procedures occurring during the study period). The PI and site personnel must cooperate with Sponsor representatives for the periodic review of study documents, to ensure the accuracy and completeness of the data reported in the electronic CRFs.

12 STUDY ADMINISTRATION

12.1 Ethical and Regulatory Considerations

The study is conducted in accordance with the following:

- Protocol and study-related plans and documents
- Local regulations, as applicable
- Good Clinical Practices, as outlined in the ICH Harmonized Tripartite Guideline for GCP (ICH E6)
- The ethical principles established by the Declaration of Helsinki
- Regional subject data protection laws and regulations
- Local IEC requirements

12.2 Independent Ethics Committee

The IEC must be constituted according to ICH and GCP requirements as well as the local laws and regulations of each participating country. Sponsor representatives supply relevant documents for the Investigator to submit to the IEC for review and approval. This protocol, the Investigator brochure and any relevant safety updates not contained in the Investigator brochure, the ICF template, and any other applicable documents must be submitted to an appropriate IEC by the Investigator. Written, unconditional, IEC approval must be obtained and submitted to Sponsor representatives before commencement of the study (i.e., shipment of ANX005 and activation of the study site). This approval must refer to the study by protocol title and Sponsor protocol number whenever possible, identify the documents reviewed, and indicate the date of review and approval. Sponsor representatives must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study at each site.

Sponsor representatives provide appropriate updates and reports on the progress of the study to the Investigator and ensures that such are provided to the IEC in accordance with applicable local requirements and regulations. The Investigator must supply ongoing study progress reports to the IEC, per local requirements, such as updates on SAEs or SUSARs, protocol deviations and amendments, ICF revisions, relevant Sponsor communication, enrollment updates, etc. In addition, the Investigator must notify the IEC at the closure of the study.

12.3 Informed Consent

The study physician obtains a properly written and executed ICF from each subject, prior to commencing any Screening procedures, and in accordance with the Declaration of Helsinki, ICH E6, and other applicable local regulations.

Sponsor representatives provide a template ICF to site personnel for modification into the format required by the site SOPs. Site personnel must submit a draft ICF to and receive approval from Sponsor representatives prior to submission to the IEC. Upon approval by the IEC, site personnel forward a copy of the ICF approved by the review board to Sponsor representatives prior to performing any study-specific procedures, including any copies of approved subject information sheets or ICFs translated to another language.

The ICF template documents the subject's informed agreement to participate. The study physician must fully explain the content of the ICF and the study in layman's terms, including study goals, tests, anticipated benefits, and potential risks that participation might entail. The ICF must be appropriately signed and dated before the subject undergoes any study-related procedure. The original and any amended, signed, and dated ICFs must be retained in the subject's file at the study site, and a copy of each provided to the subject. Site personnel must also fully document the informed consent process in the subject's source documents.

Separate, additional ICFs may be required as part of the study to collect consent for optional protocol tests, or specific country or local requirements.

12.4 Protocol Amendments

This protocol must be followed as written. Any change or addition to this protocol requires a written protocol amendment that must be approved in writing by the IEC and any required regulatory authorities before implementation.

Sponsor representatives may decide to amend the protocol, or the Investigator may suggest protocol amendments. Sponsor representatives must notify the applicable regulatory authorities of all amendments to the protocol.

These requirements for amendment approval should in no way prevent any immediate action from being taken by the Investigator or by Sponsor representatives in the interests of preserving the safety of an individual, or all subjects included in the study. If an immediate change to the protocol is deemed necessary by Sponsor representatives or the Investigator and is implemented for safety reasons, the IEC as well as applicable regulatory agencies must be notified.

12.5 Retention of Documents

The Investigator must retain all study records required by the Sponsor and by applicable regulations in a secure and safe location for as long as needed to comply with national and international regulations, but not less than 2 years after (1) the last approval of a marketing application in an ICH region, (2) there are no pending marketing applications, or (3) the discontinuation of a development plan for the ANX005.

Subject hospital records and source data must be kept for the maximum period required by the study site, but not less than 15 years.

The Investigator must consult Sponsor representatives before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or change of custody. If the Investigator or study site is unable to continue maintenance of the study records for the full 15 years, the Investigator must notify Sponsor representatives for assistance with retention.

Sponsor representatives notify the Investigator and study site when the retention of study-related records is no longer required.

Study records include the following:

- Approvals by the IEC for the study protocol, ICF, and amendments
- All subject source documents, laboratory records, and applicable diaries, etc.
- Case report form copies
- Informed consent forms
- Essential documents such as curricula vitae, financial disclosure forms, and other local or national regulatory approvals
- All other pertinent study documentation

12.6 Monitoring Procedures

Sponsor representatives schedule monitoring visits to take place throughout the study at appropriate intervals as outlined in the monitoring plan.

These visits are to confirm that the study is conducted in compliance with the relevant GCP regulations and guidelines, verifying adherence to the protocol, and the completeness and accuracy of data entered on the source records, CRF, and drug accountability forms. The study monitor verifies CRF entries by comparing them with the source records, which must be available for this purpose. The Investigator must ensure adequate time and space availability for these visits. The Investigator and site personnel are responsible for being present or available for consultation during monitoring visits.

12.7 Quality Control and Quality Assurance

Prior to participation, Sponsor representatives evaluate potential study sites and Investigators for appropriate qualifications and ability to conduct the study. Study training must take place at each study site before any subjects may be enrolled at that site. Study initiation visits and Investigator meetings (if applicable) may include a review of GCP guidelines, study protocol and procedures review, management of AEs, preparation and administration of ANX005, and data collection and subject eligibility requirements.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by Sponsor and competent authority representatives at any time. The Investigator must agree to the inspection of study-related records by competent authority representatives and audits by Sponsor representatives.

Sponsor representatives may conduct a quality assurance audit at a study site at any time before, during, or after completion of the study. Sponsor representatives inform the Investigator if an audit is to take place and advise him or her as to the scope of the audit. Representatives of regulatory agencies may also conduct an audit of the study site. If informed of such an inspection, the Investigator should notify Sponsor representatives immediately. The Investigator must ensure that auditors have access to study supplies, site facilities, original source documentation, and all study records.

12.8 Confidentiality

All clinical study findings and documents are regarded as confidential. Study documents (protocols, Investigator brochures, and other material) must be stored appropriately to ensure their confidentiality. The Investigators, site personnel, and members of the IEC must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to comply with applicable regulatory requirements.

The anonymity of participating subjects must be maintained per applicable local and national laws. Subjects are specified on all documents by subject number and, whenever possible, initials, but not by name. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by site personnel.

Site personnel must obliterate subject names from study-required documents that identify the subject by name (e.g., hospital records) prior to transmitting these documents to Sponsor representatives.

Site personnel also acknowledge that United States securities law prohibits any party who receives material non-public information about the Sponsor from purchasing or selling securities of the Sponsor or from communicating such information to any other person under circumstances in which it is reasonably foreseeable that such person is likely to purchase or sell such securities in reliance on such information.

12.9 Publication

The data and information generated in this study are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required before disclosing any information relative to this clinical study, and no publications initiated by site personnel may be published until all protocol-defined results are published in a manuscript. Publications of the results must be based on appropriate analyses and review of the complete data. Authorship may be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the study.

Investigators agree to have their names listed as an Investigator in any publication reporting the results from this study, whether or not they are an author on the publication.

The preparation and submittal for publication of manuscripts and presentations containing the study results shall be in accordance with a process determined by mutual written agreement between the Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

The details and processes of producing and reviewing reports, manuscripts and presentations based on the data from this study are described in the clinical trial agreement between the Sponsor and the institution of the Investigators.

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects With, or At Risk For, Manifest Huntington's Disease

Protocol Number: ANX005-HD-01

Date: 16 December 2020

Declaration of the Principal Investigator

I have read this protocol and agree to conduct the study as outlined herein, in accordance with GCP and the Declaration of Helsinki, and complying with the obligations and requirements of clinical Investigators and all other requirements listed in 21 CFR Part 312.

Principal Investigator

Print Name	Site Number
Signature	Date

APPENDIX A: ADVERSE EVENT SEVERITY GRADING

Adverse event grading gives an assessment of the severity of an AE. The NCI-CTCAE provides a common system for AE grading, and is based on the guidelines shown in the table below.

Grade	*Description*
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting, age-appropriate, instrumental ADL.[a]
3	Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

Source: NCI-CTCAE v 5.0

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using a telephone, managing money, etc.

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

ADL = activities of daily living, AE = adverse event, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events

APPENDIX B: GRADING FOR INFUSION-RELATED REACTIONS

An infusion-related reaction is a disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances. The NCI-CTCAE provides a common system for grading infusion-related reactions, as shown in the table below.

Grade	*Description*
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); [redacted] indicated for ≤24 hours.
3	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
4	Life-threatening consequences; urgent intervention indicated.
5	Death

Source: NCI-CTCAE v 5.0

IV = intravenous, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events, NSAID = nonsteroidal anti-inflammatory drug.

APPENDIX C: COLUMBIA SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this **becomes an attempt rather than an interrupted** attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow **prevented from pulling** trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but **stops** themselves **before** they **actually have** engaged in any self-destructive behavior. Examples are similar to interrupted attempts, **except that** the individual **stops** him/**herself**, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a **suicide attempt. This** can **include anything** beyond a verbalization or thought, such as assembling a specific method (e.g. buying **pills**, purchasing a **gun**) **or preparing** for **one's** death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior **was present during the** assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead — Yes ☐ No ☐
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

2. Non-Specific Active Suicidal Thoughts — Yes ☐ No ☐
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — Yes ☐ No ☐
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than **a specific plan** with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would **say**, ***"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".***
Have you been thinking about how you might do this?
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — Yes ☐ No ☐
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to ***"I have the thoughts but I definitely will not do anything about them".***
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — Yes ☐ No ☐
Thoughts of killing oneself with details of plan fully or partially worked out **and subject has some intent to carry it out.**
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Frequency — ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration — ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability — ____
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents — ____
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation — ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

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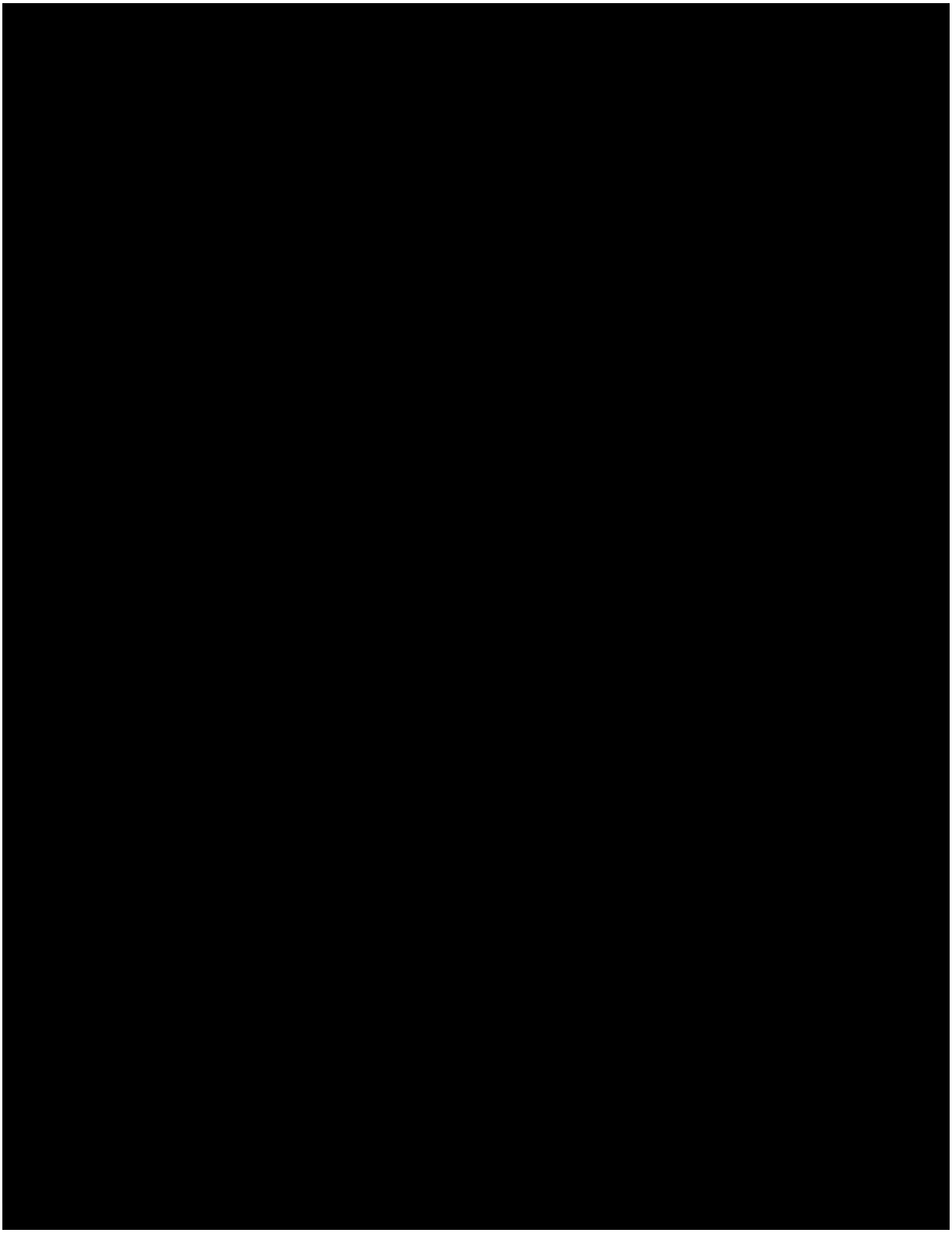
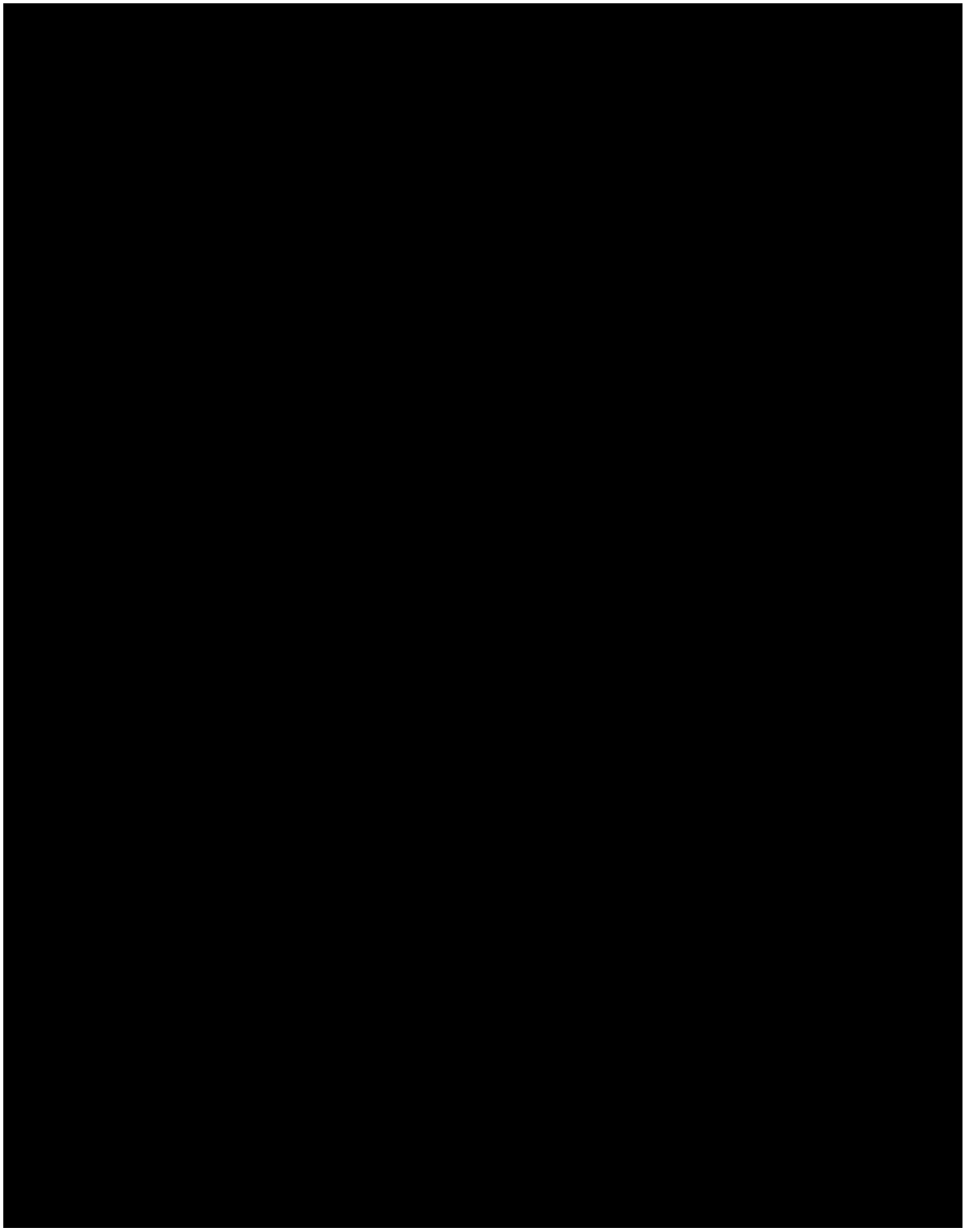
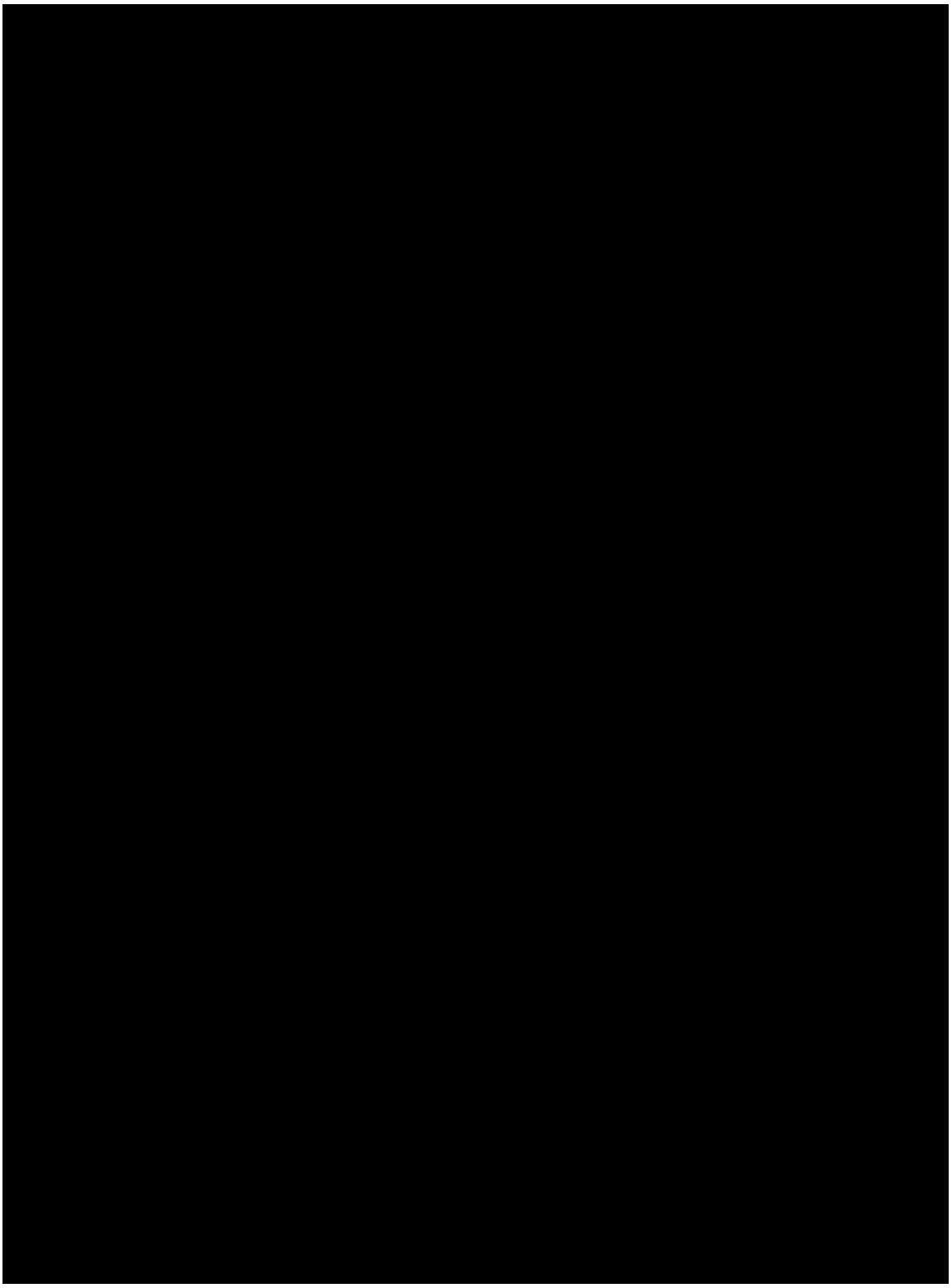
SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

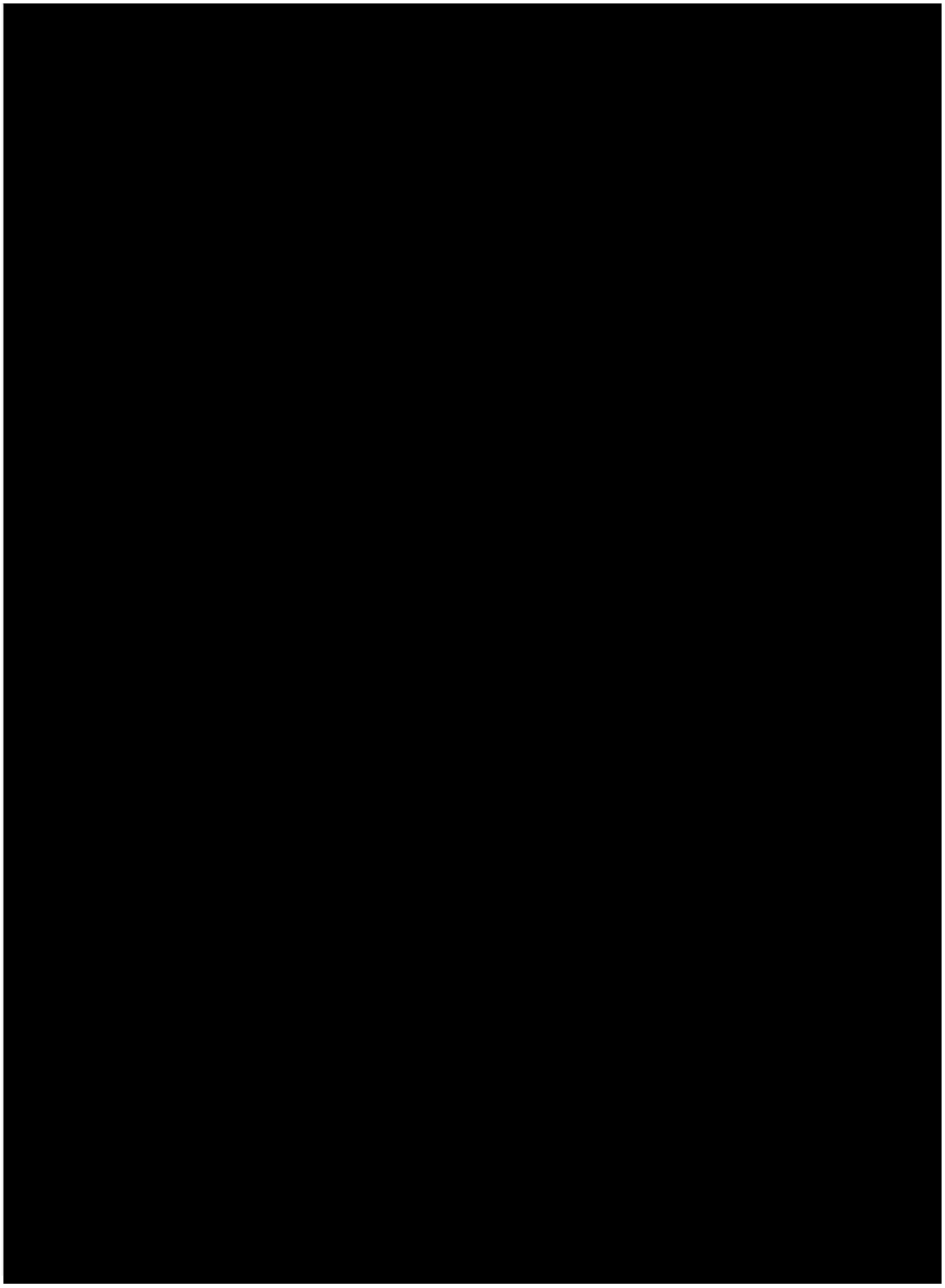
APPENDIX D: [redacted]

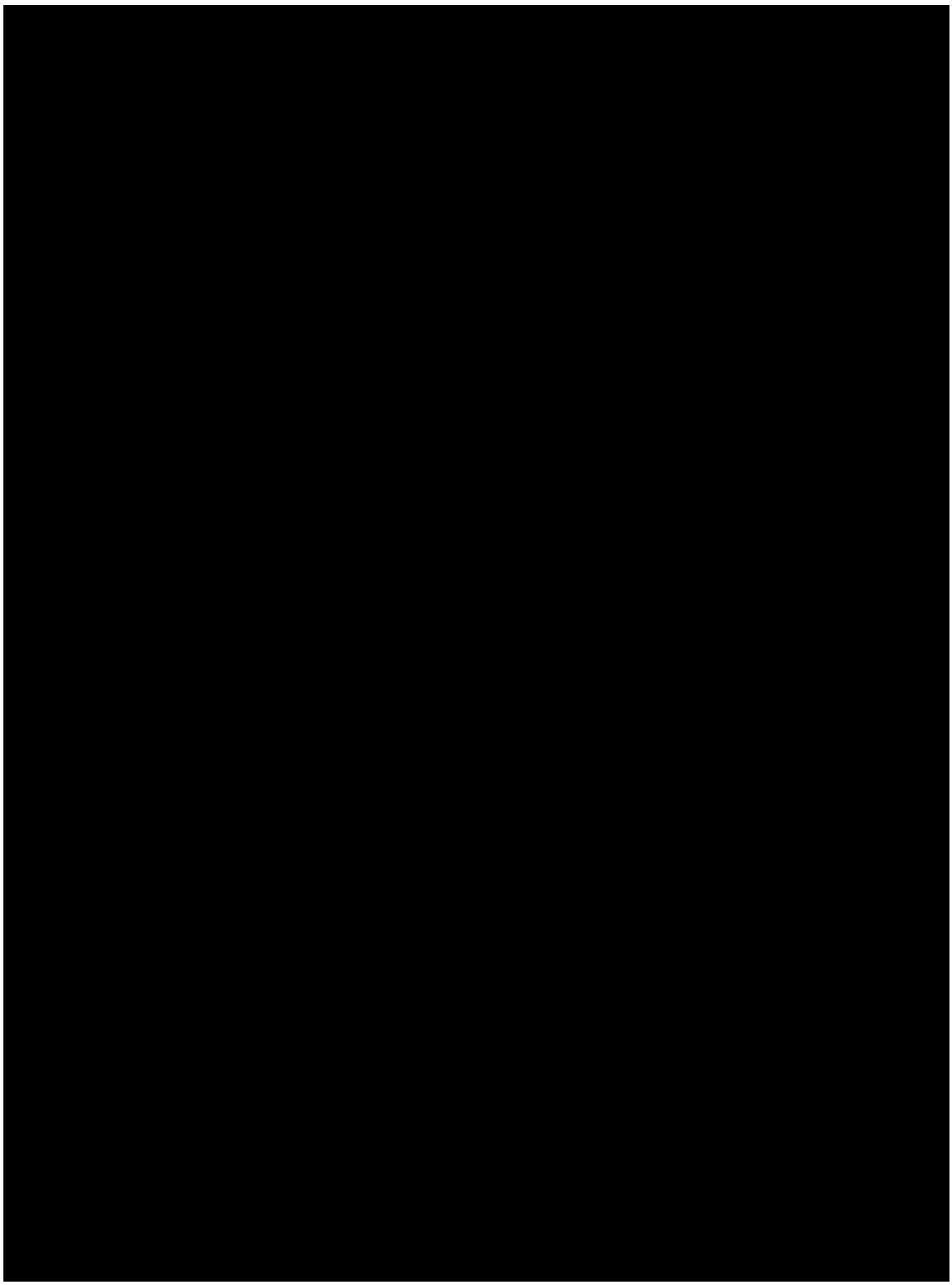
[redacted]

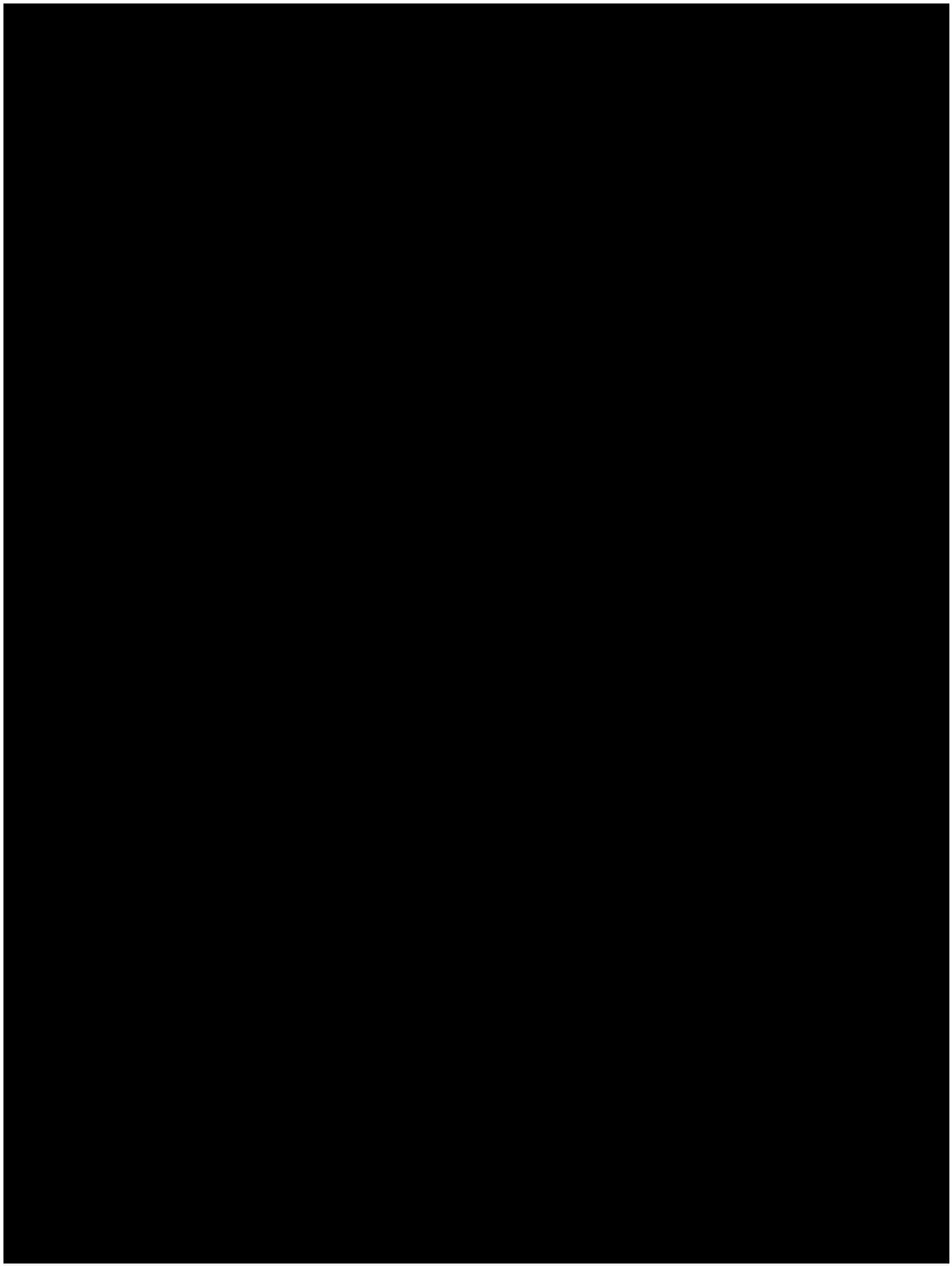


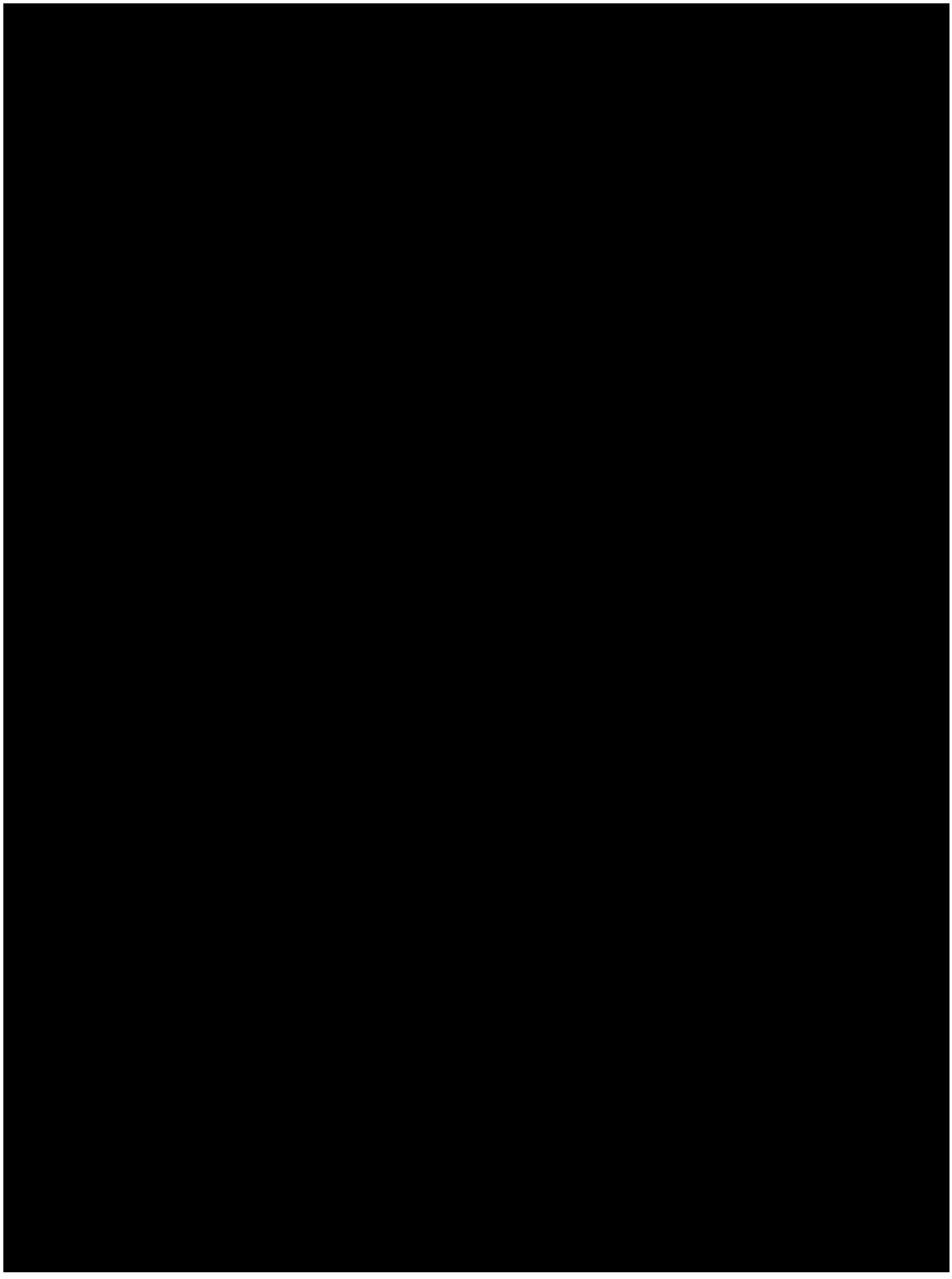


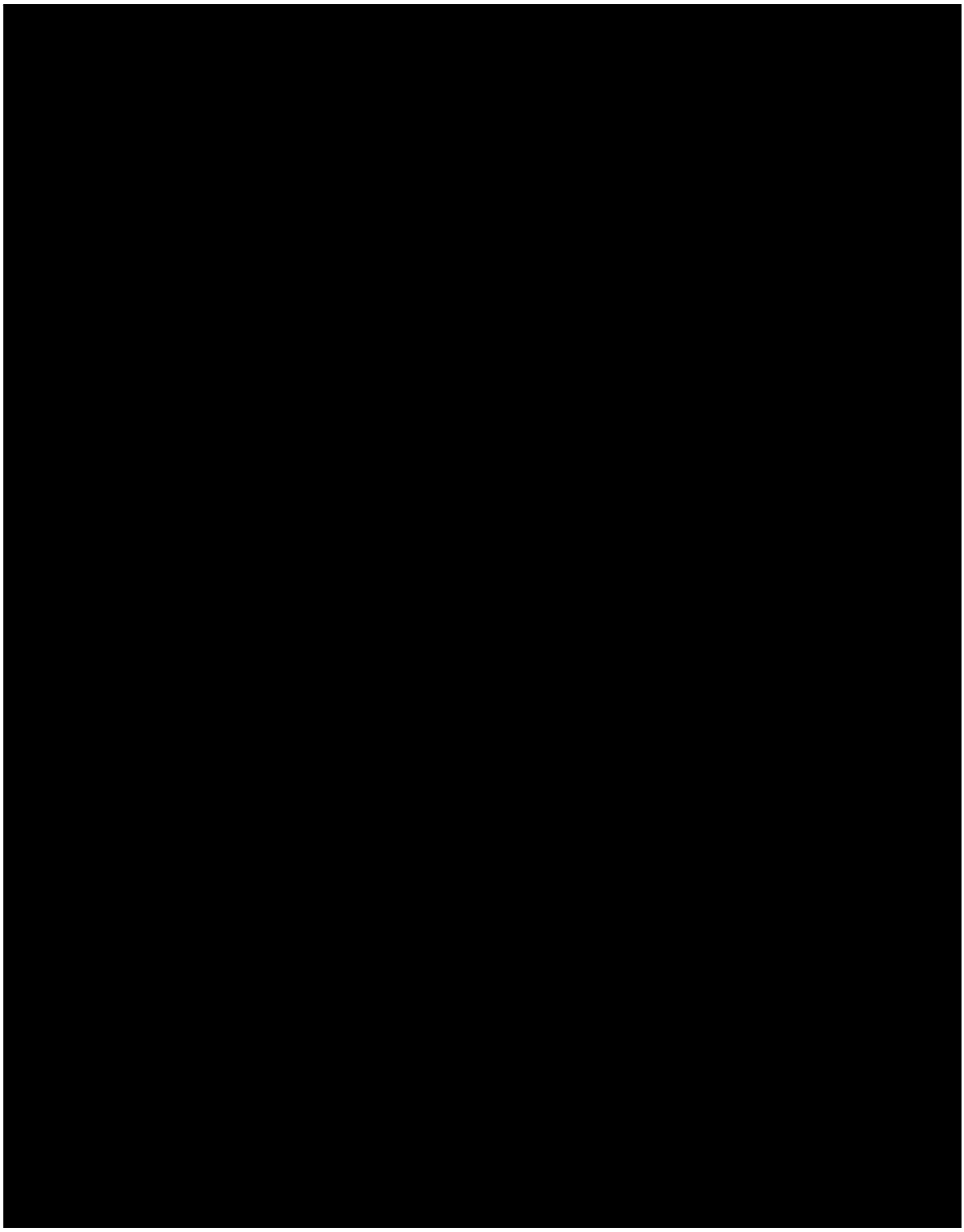


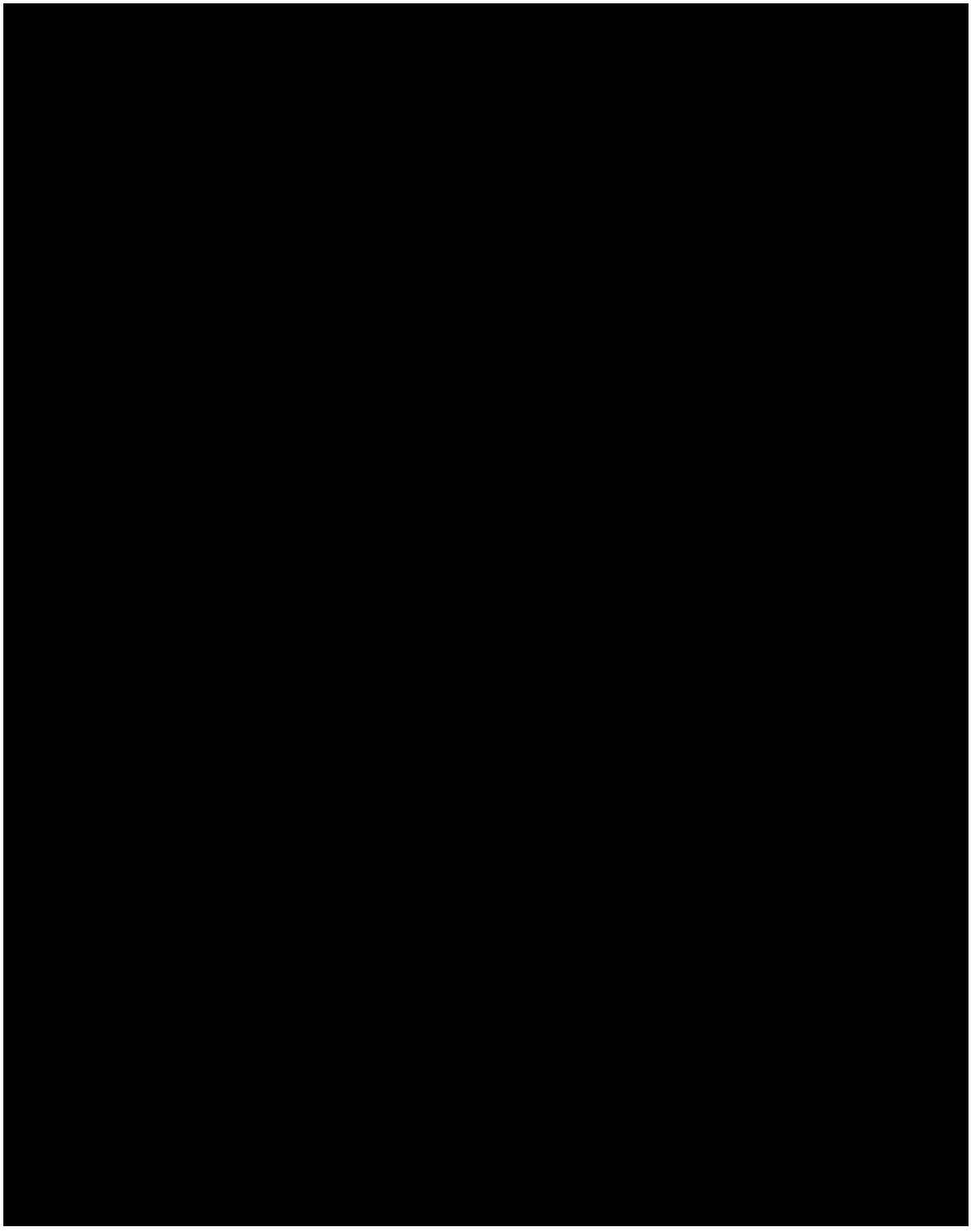


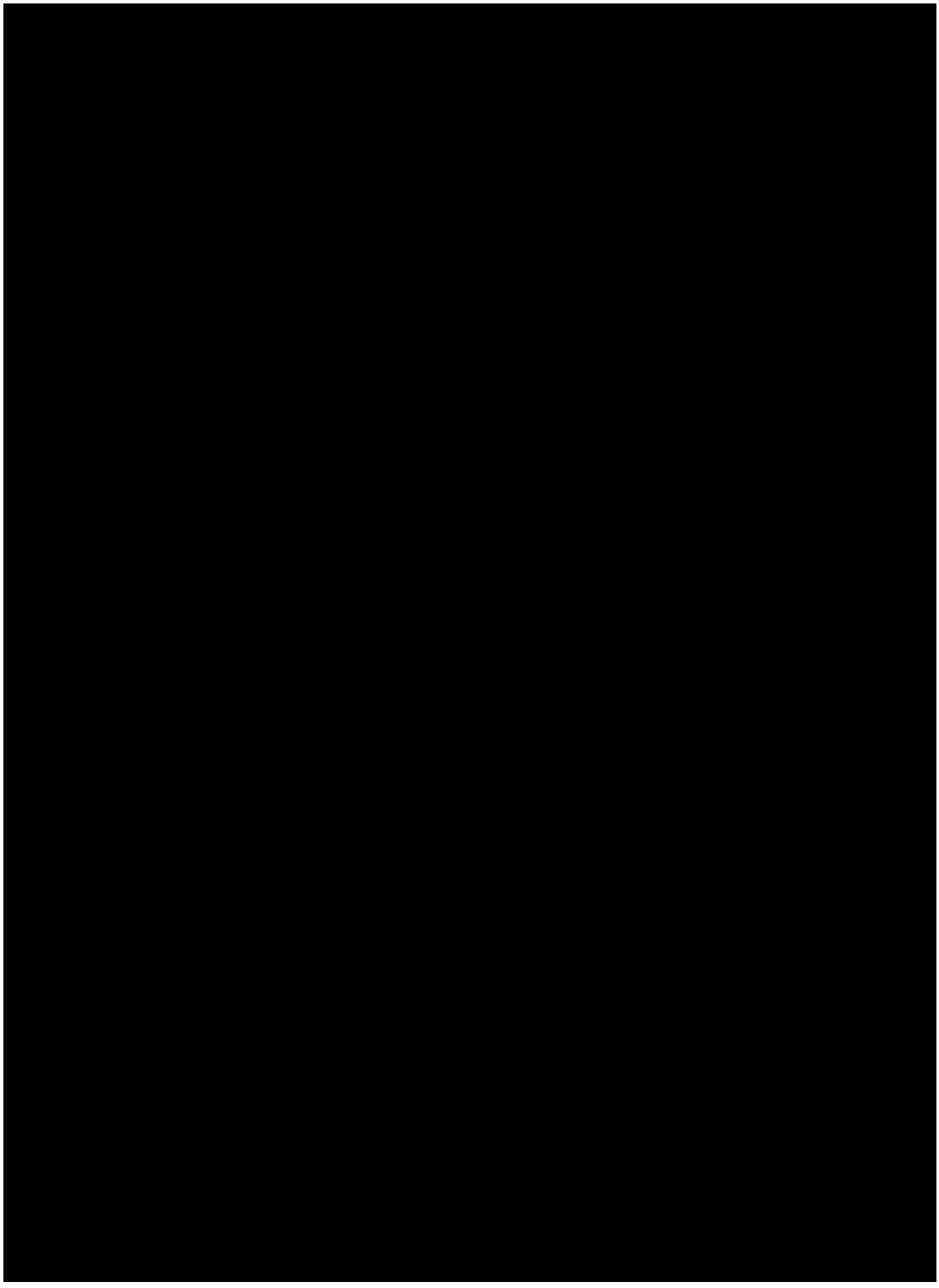


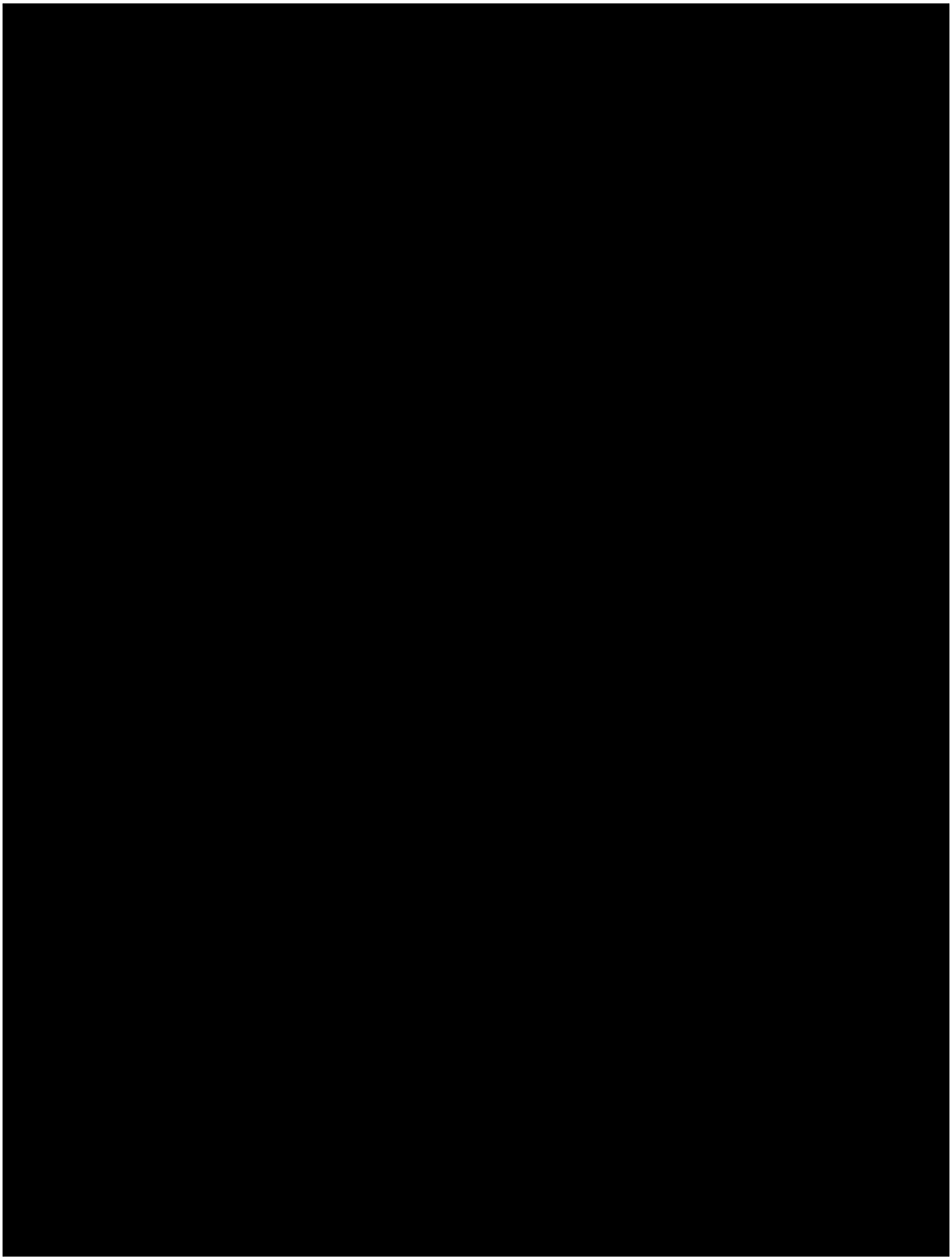


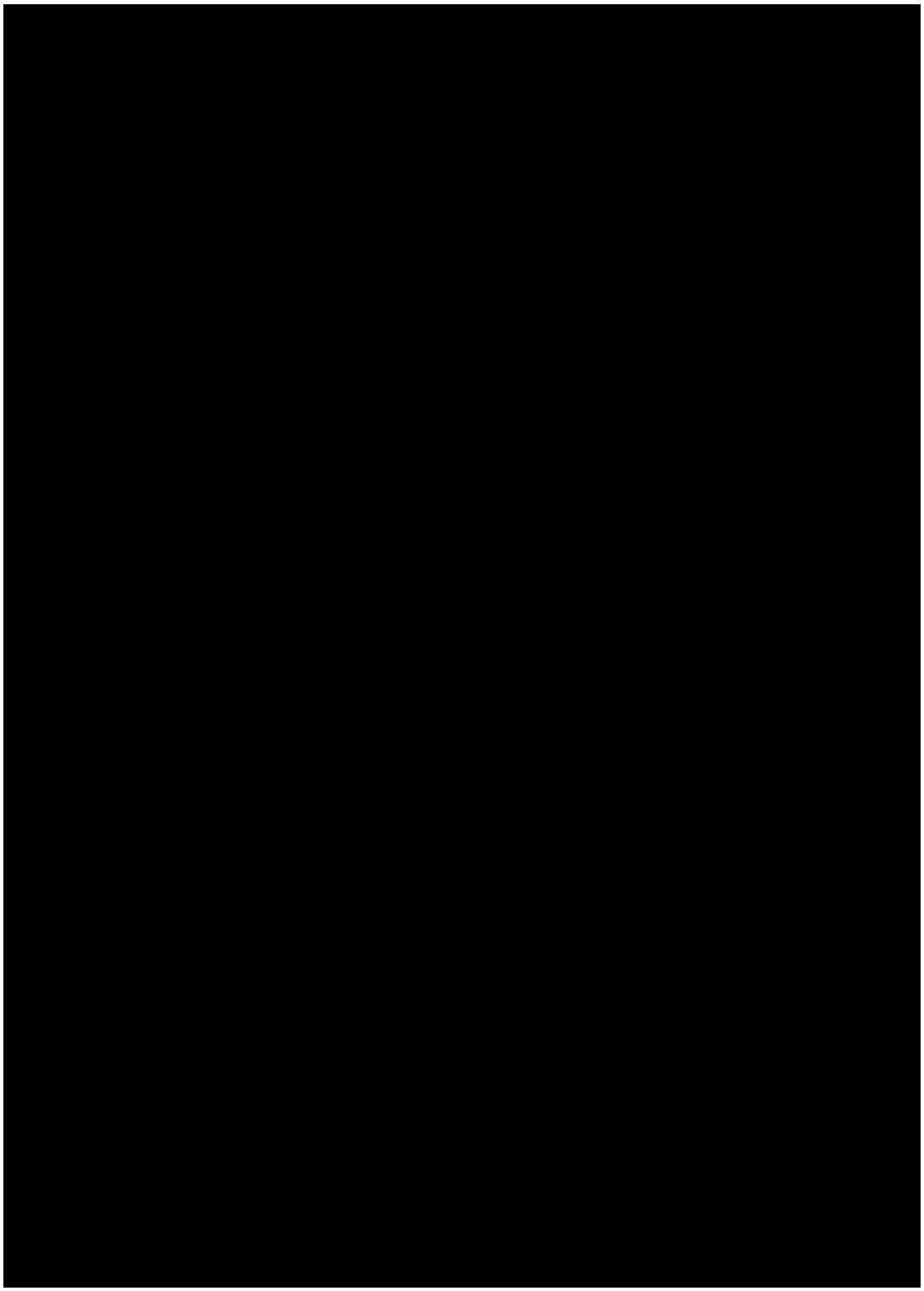


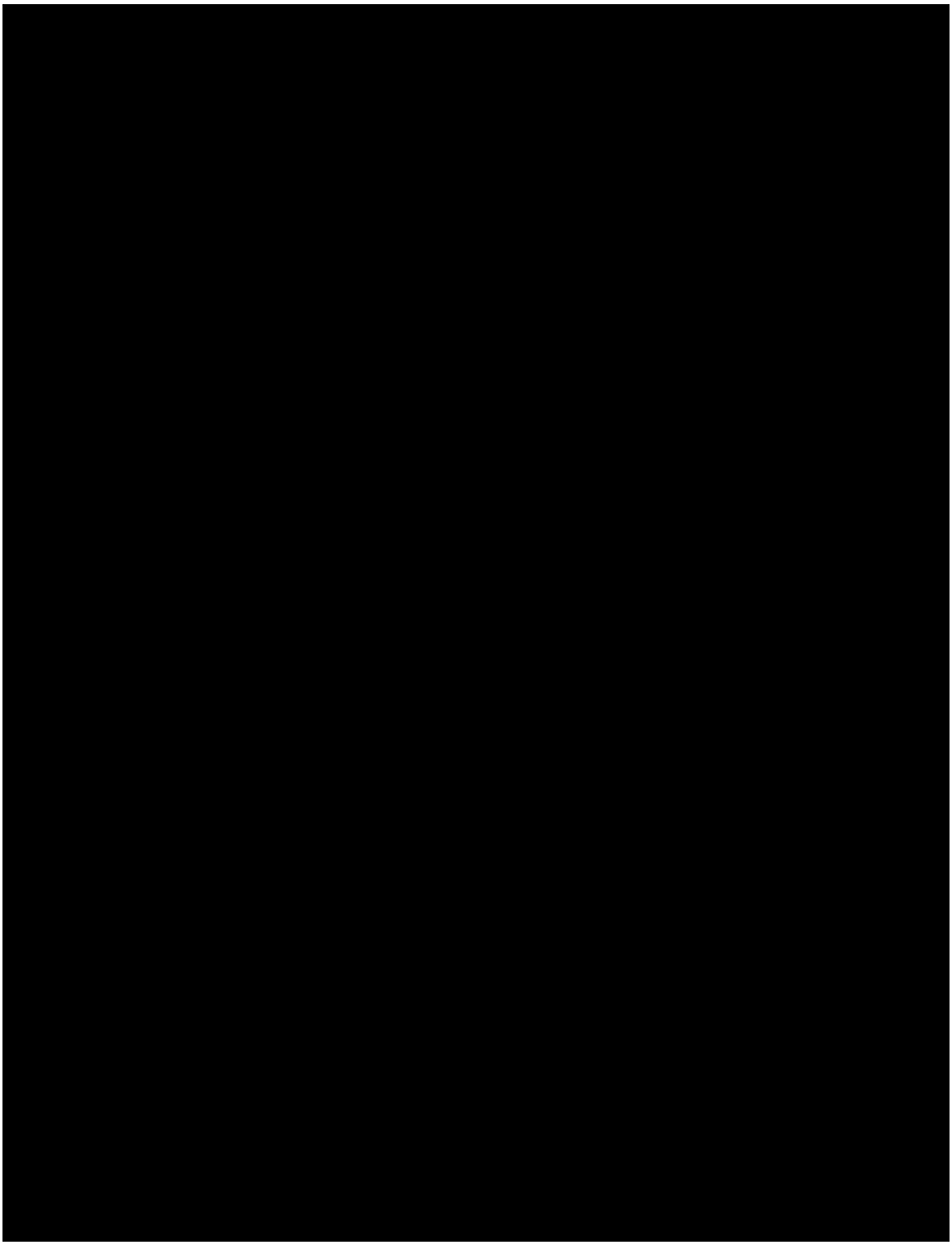


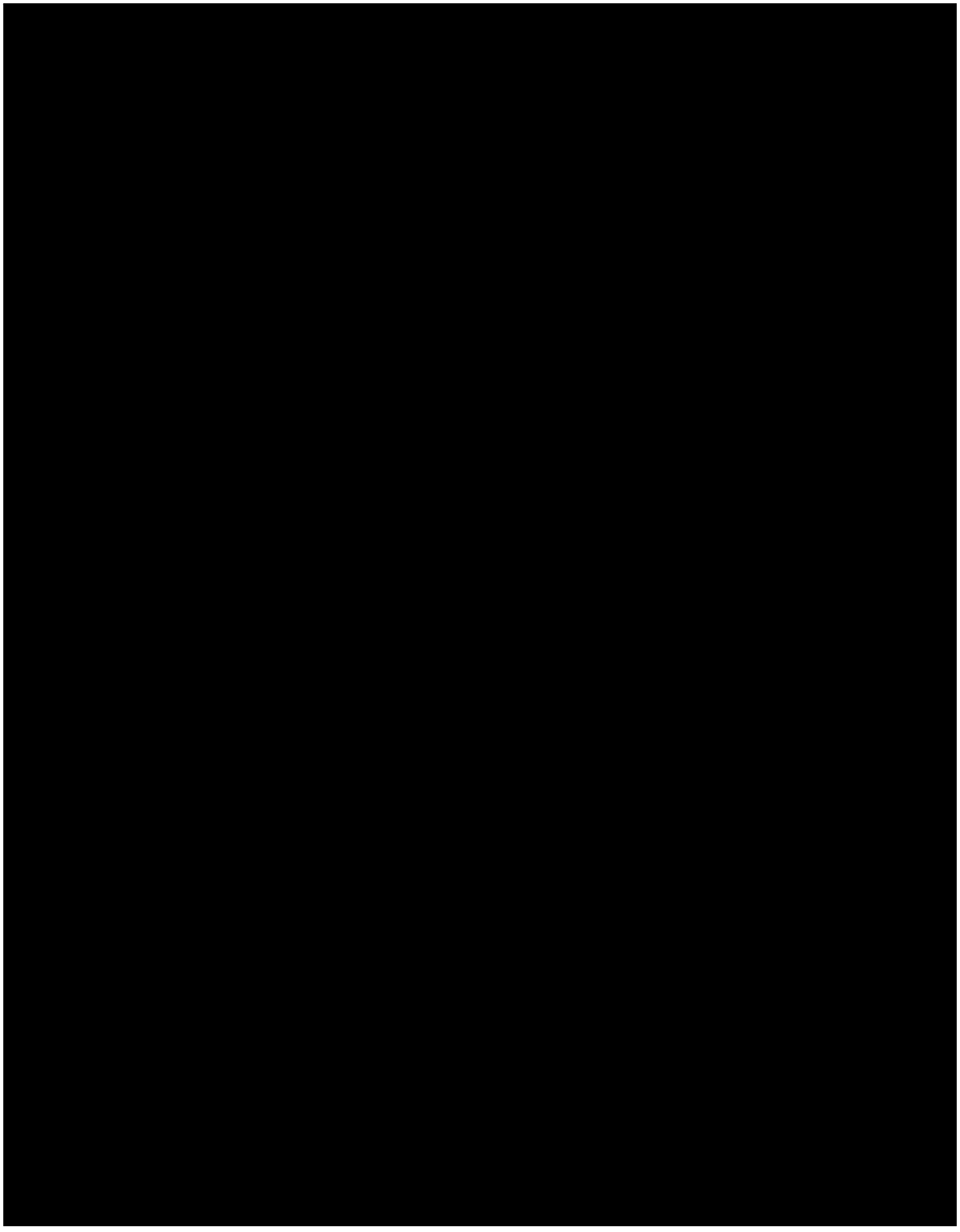


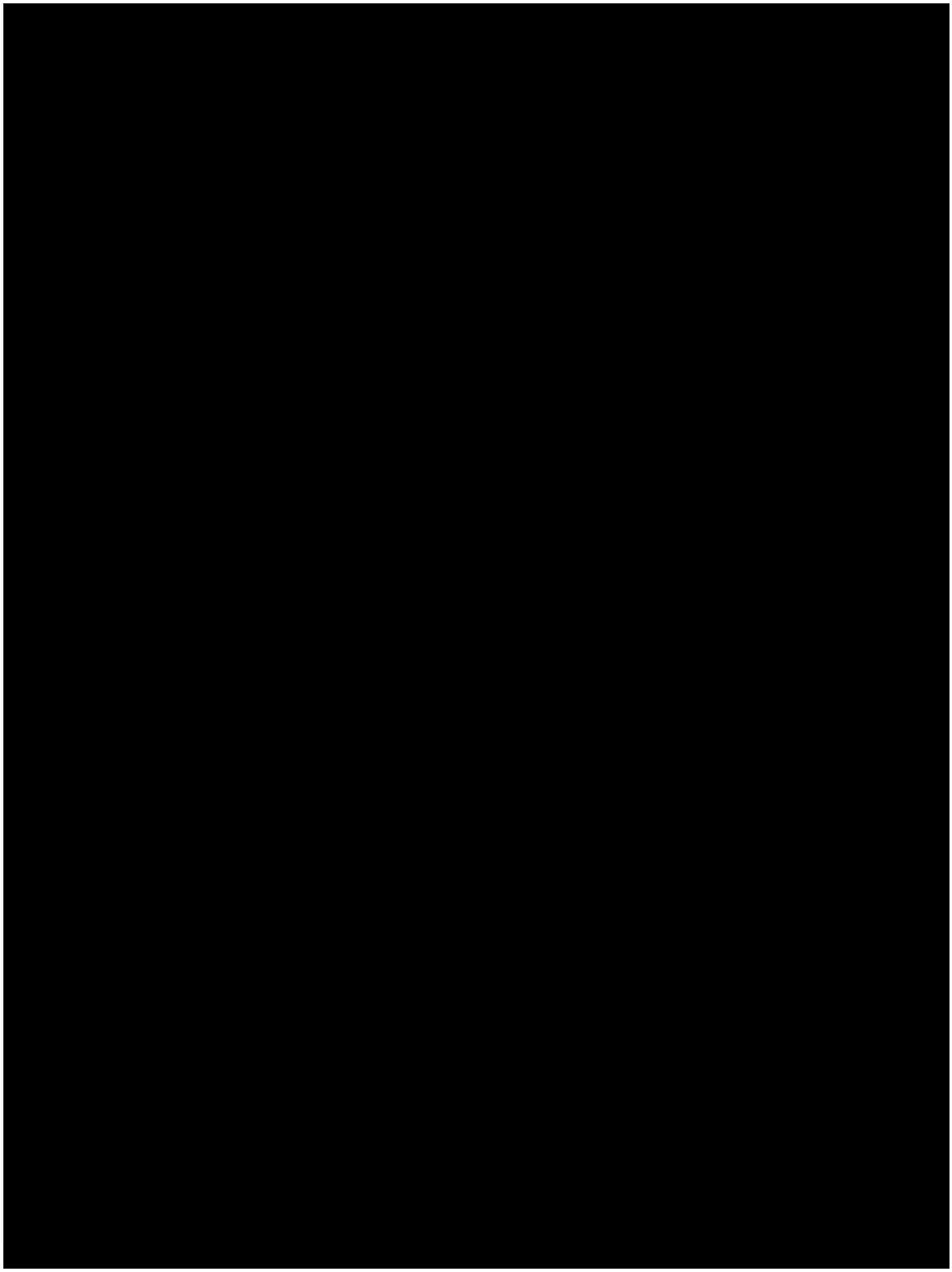


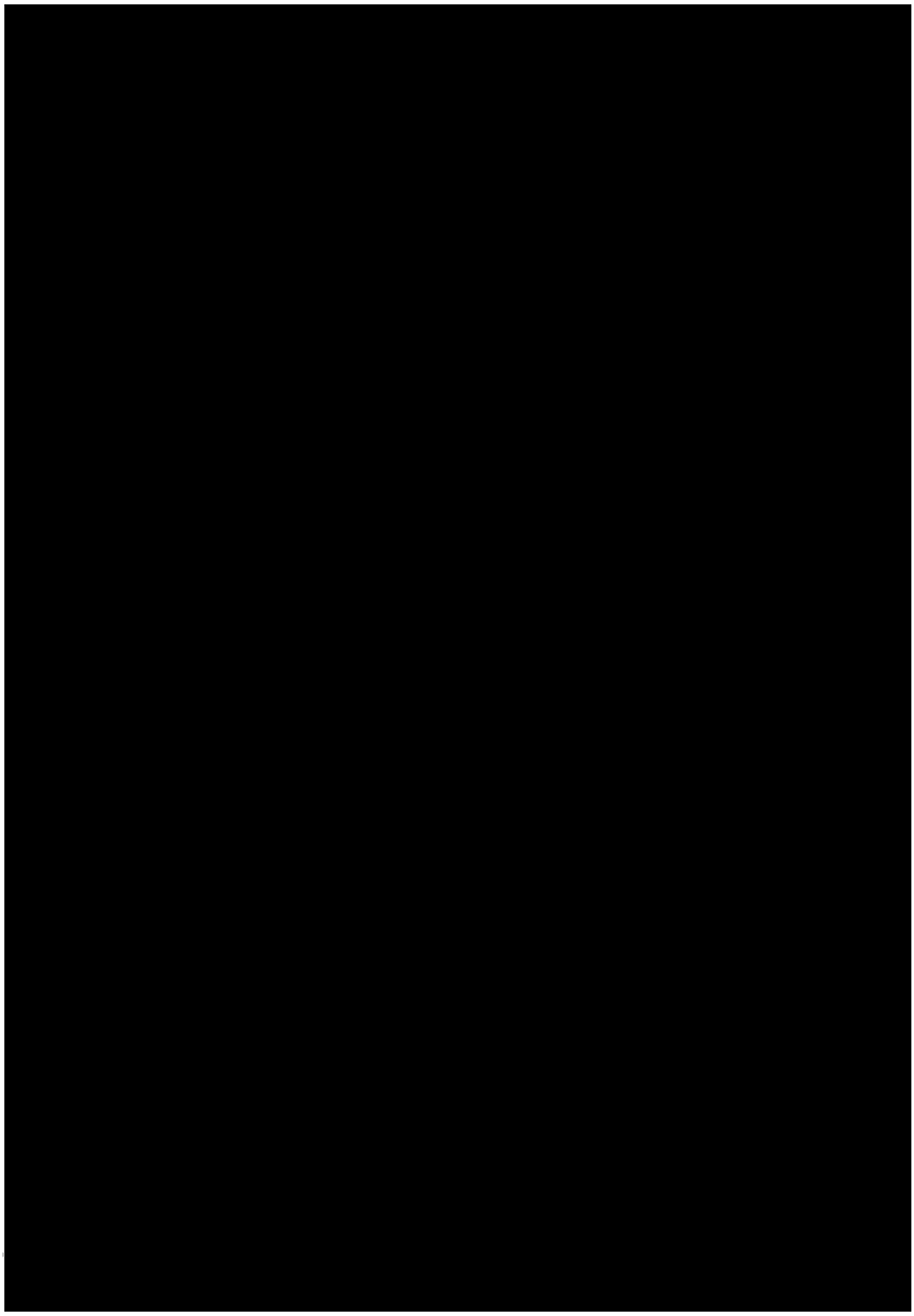


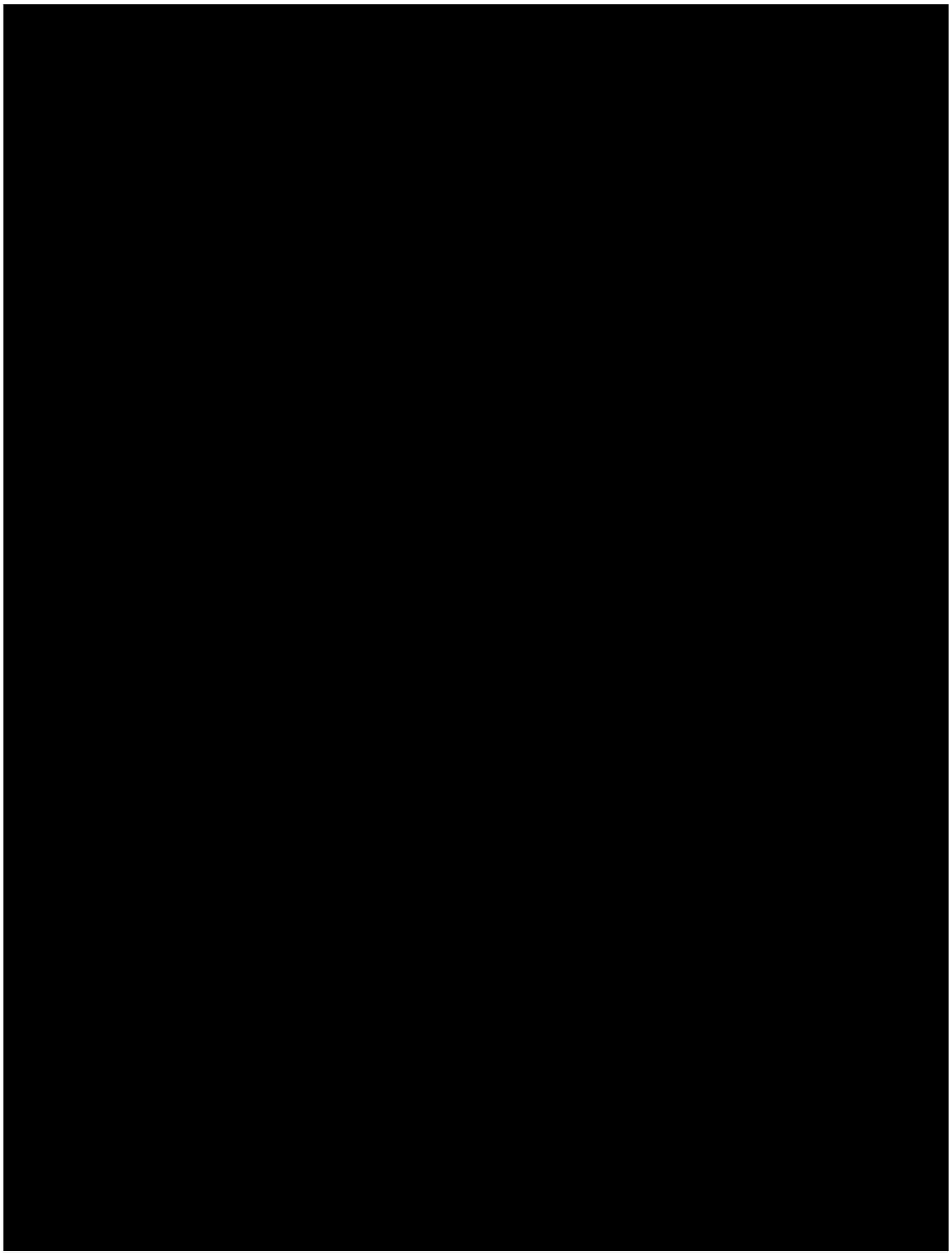


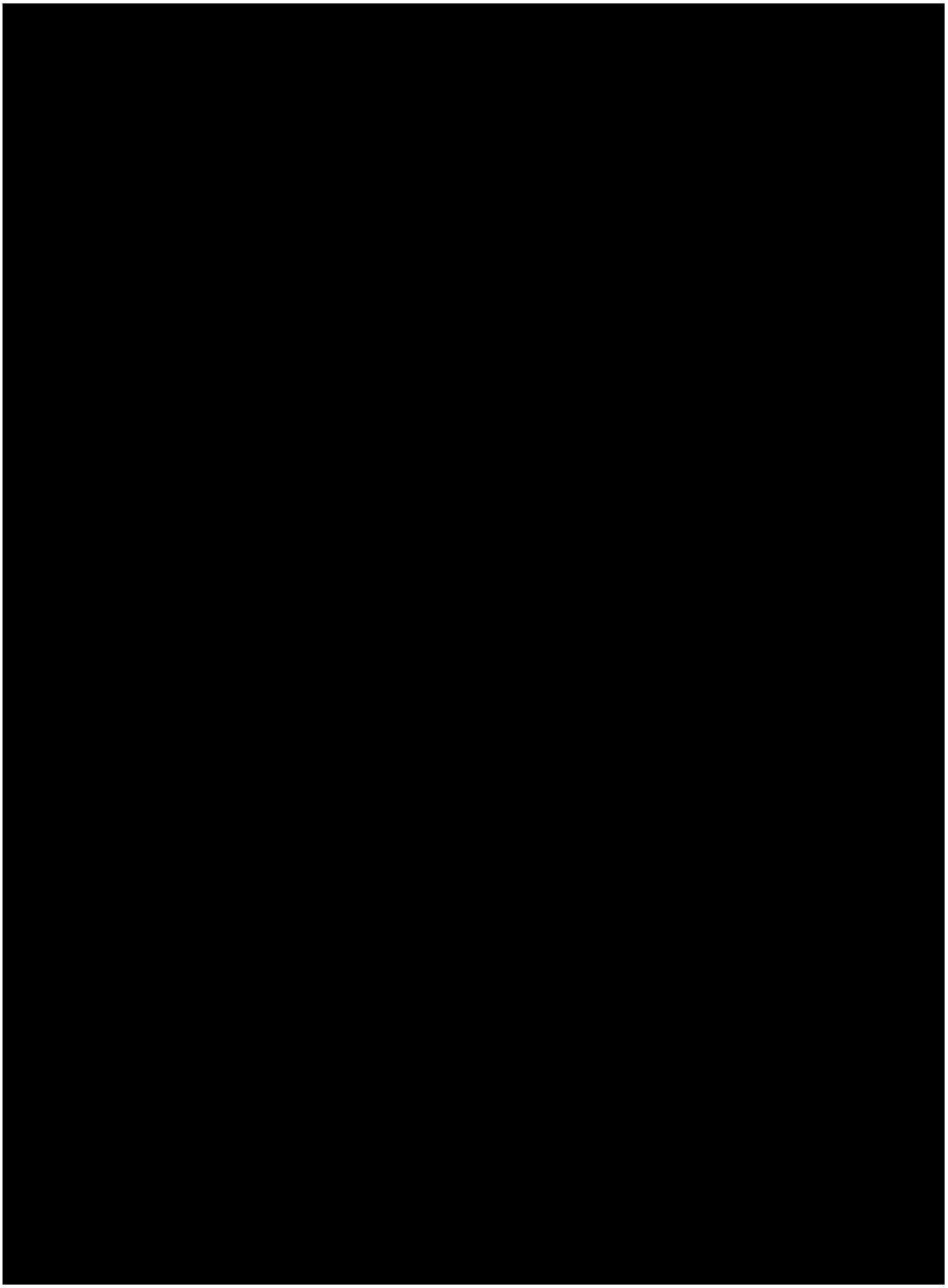


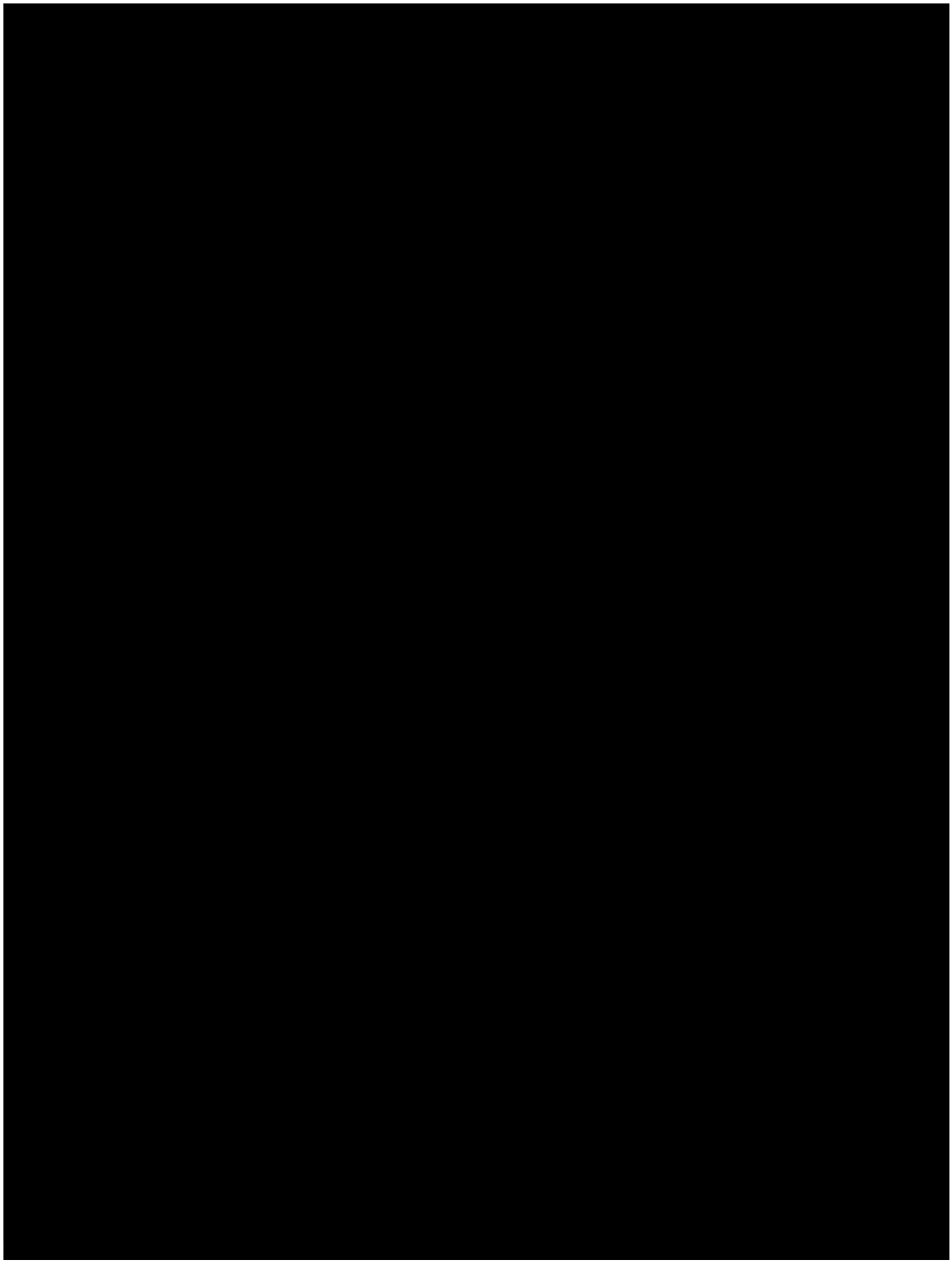


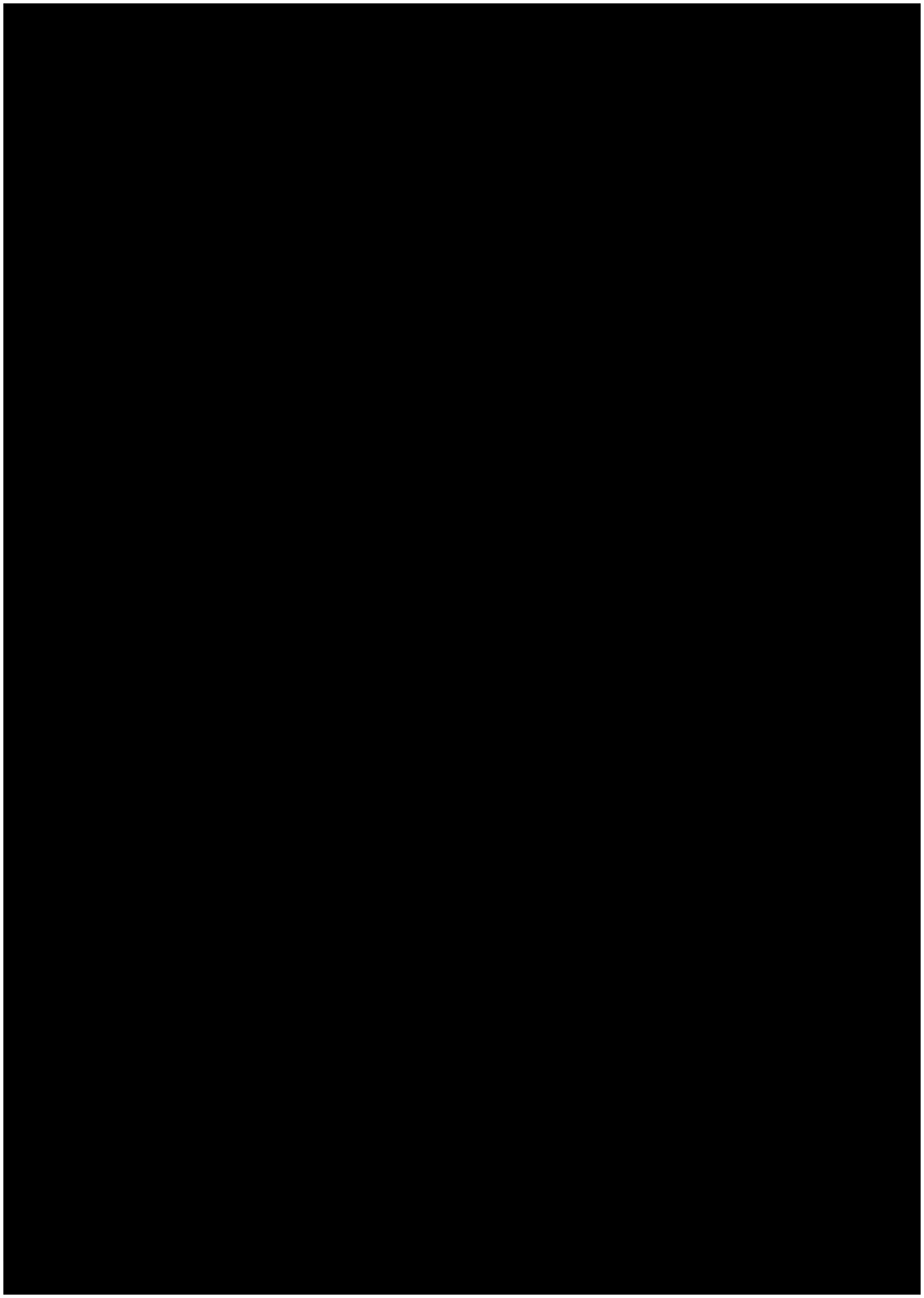


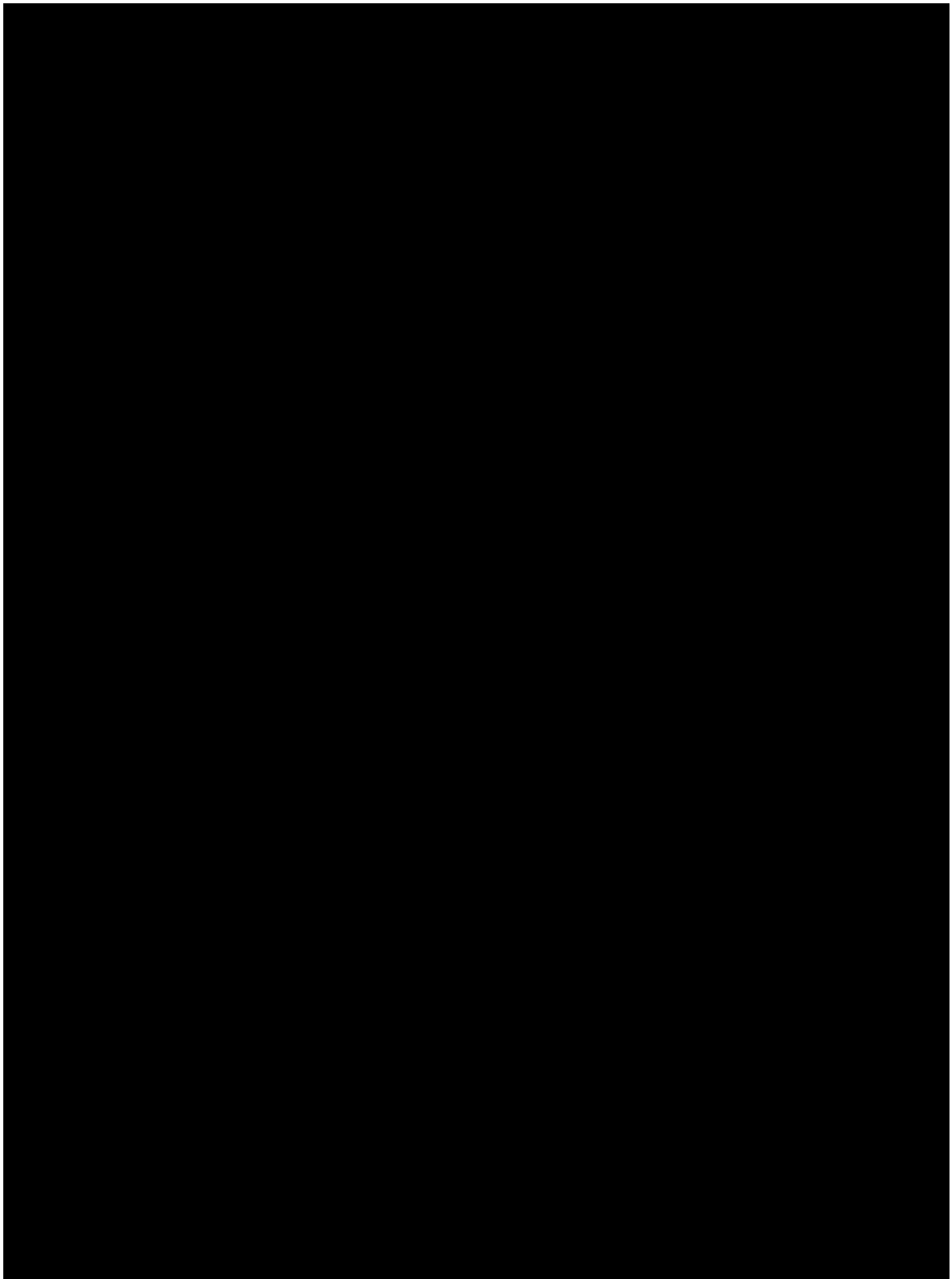


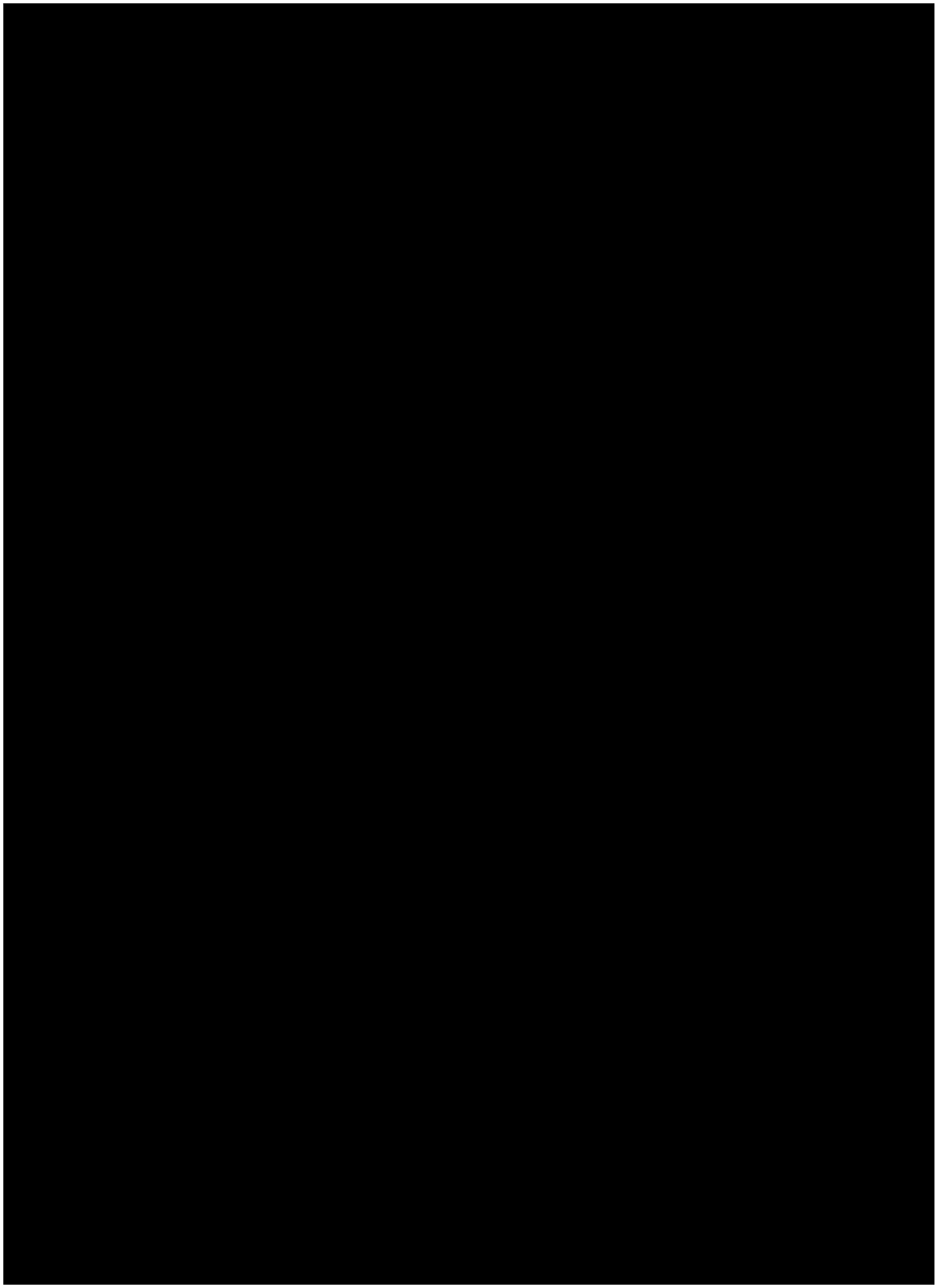


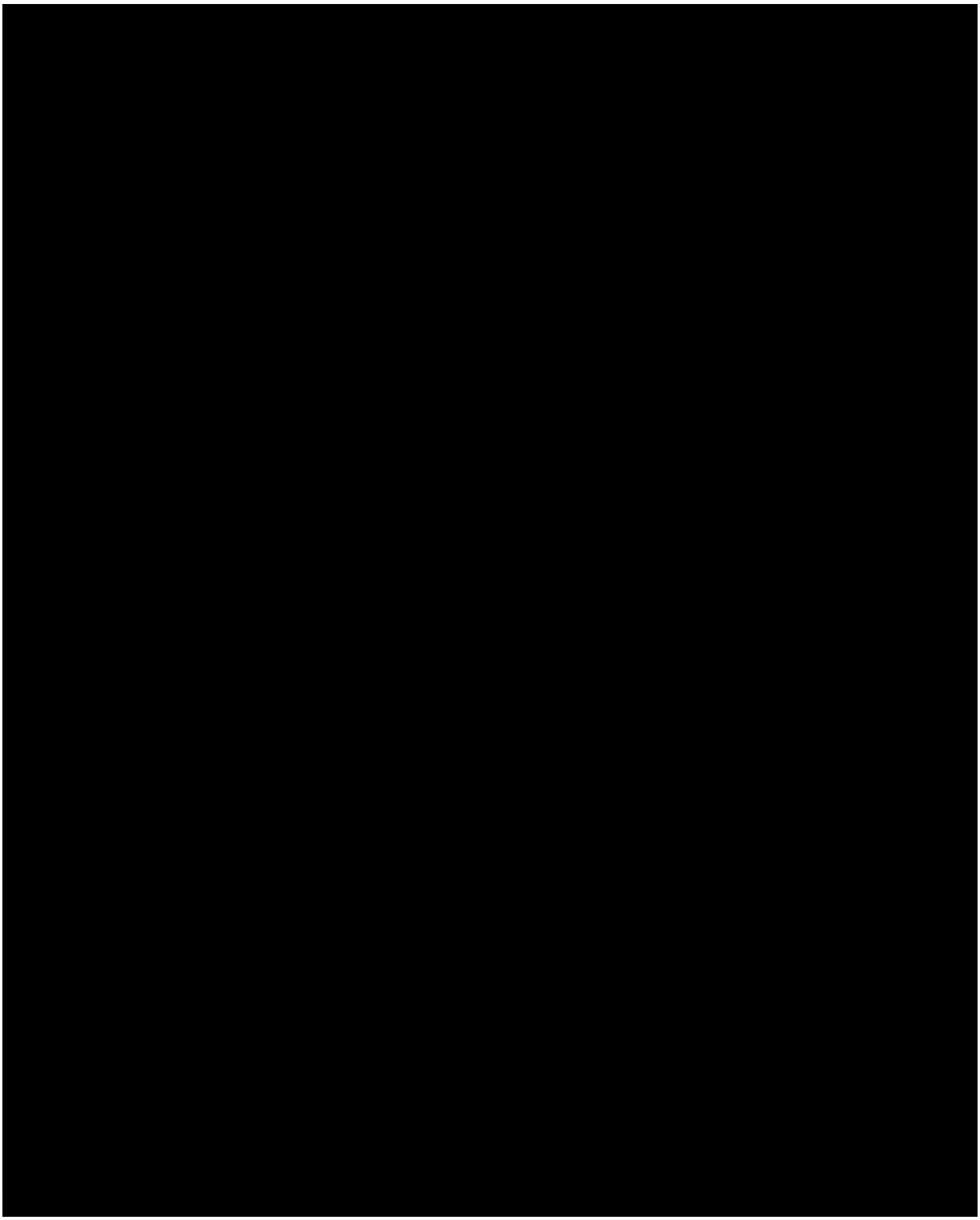


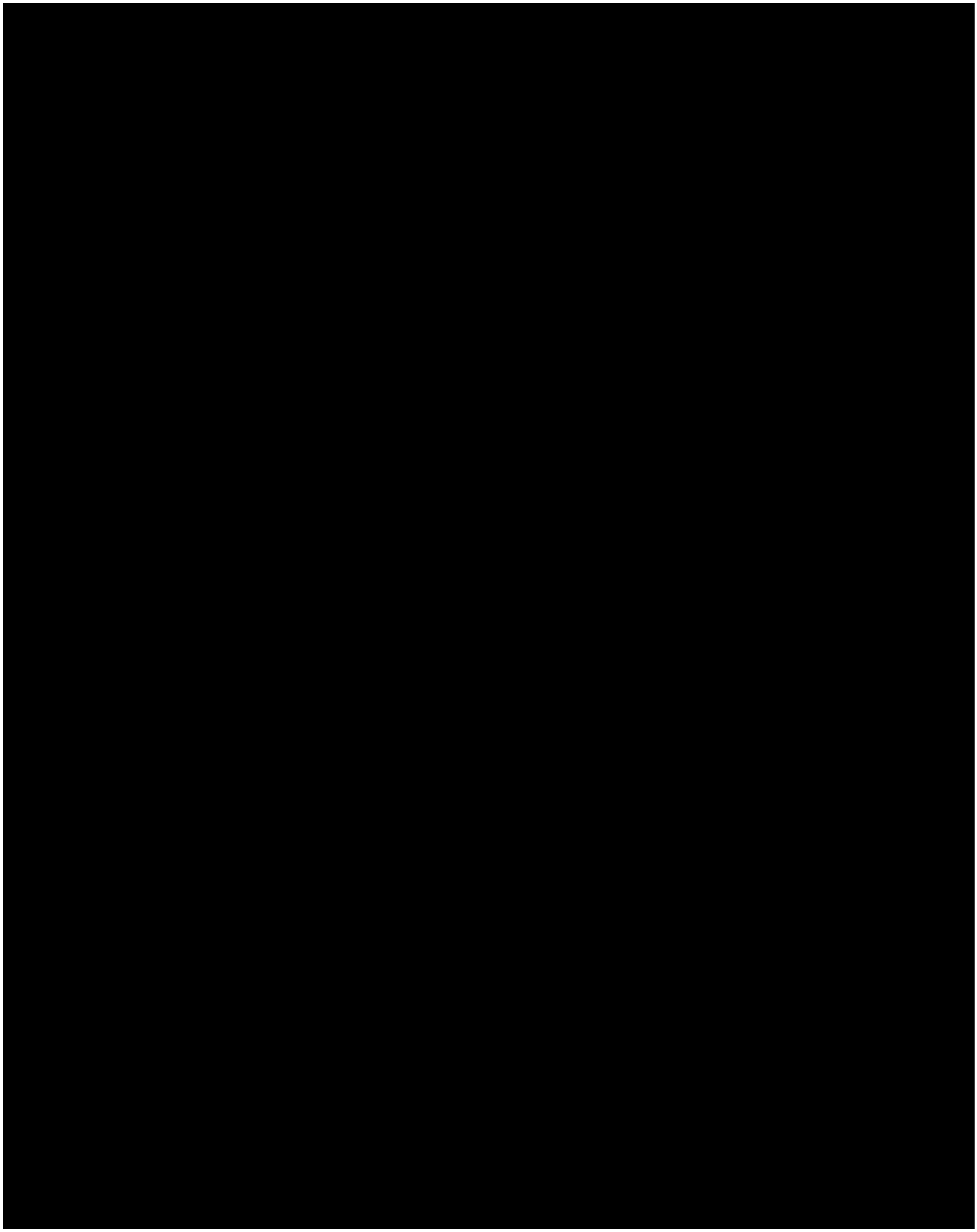


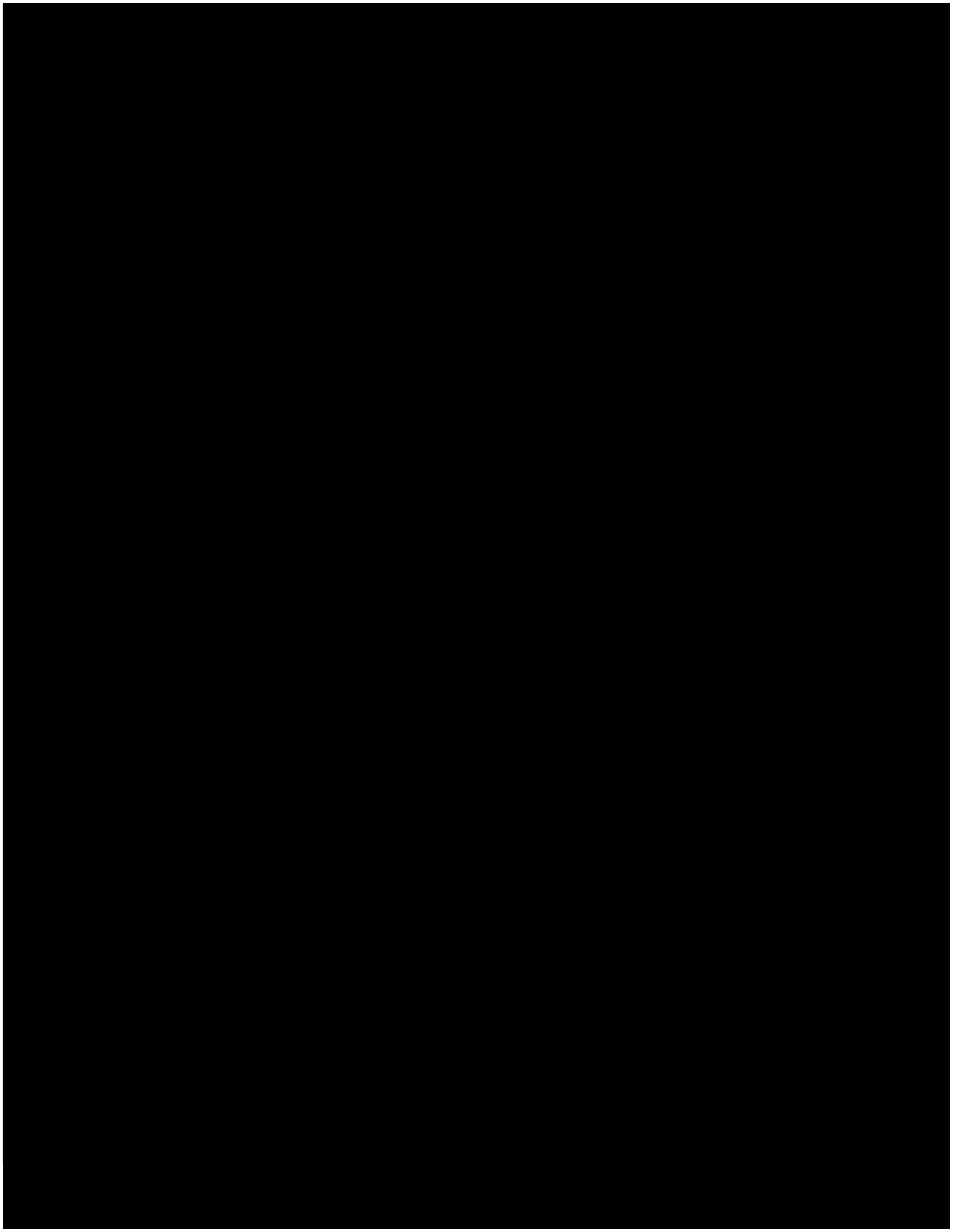


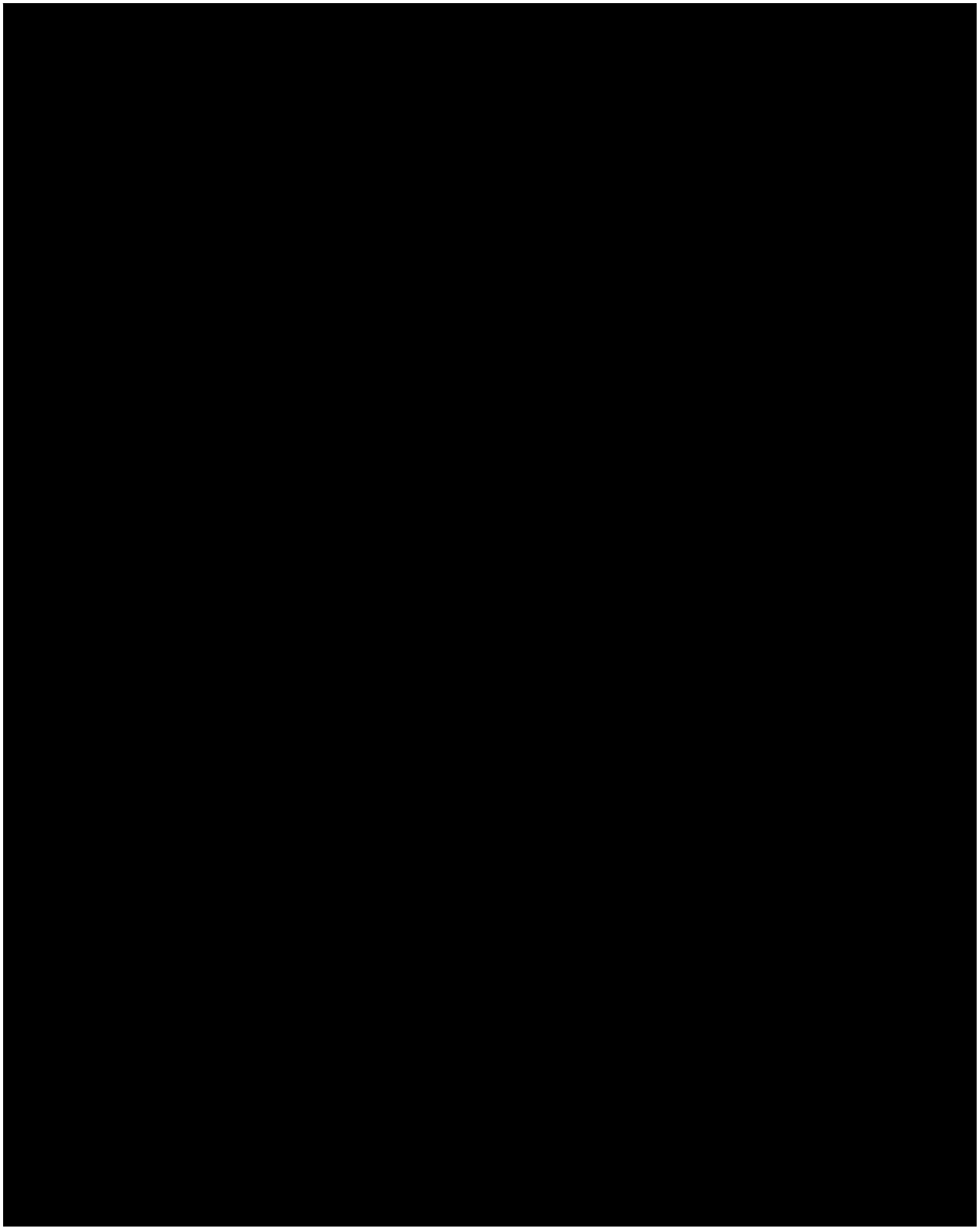


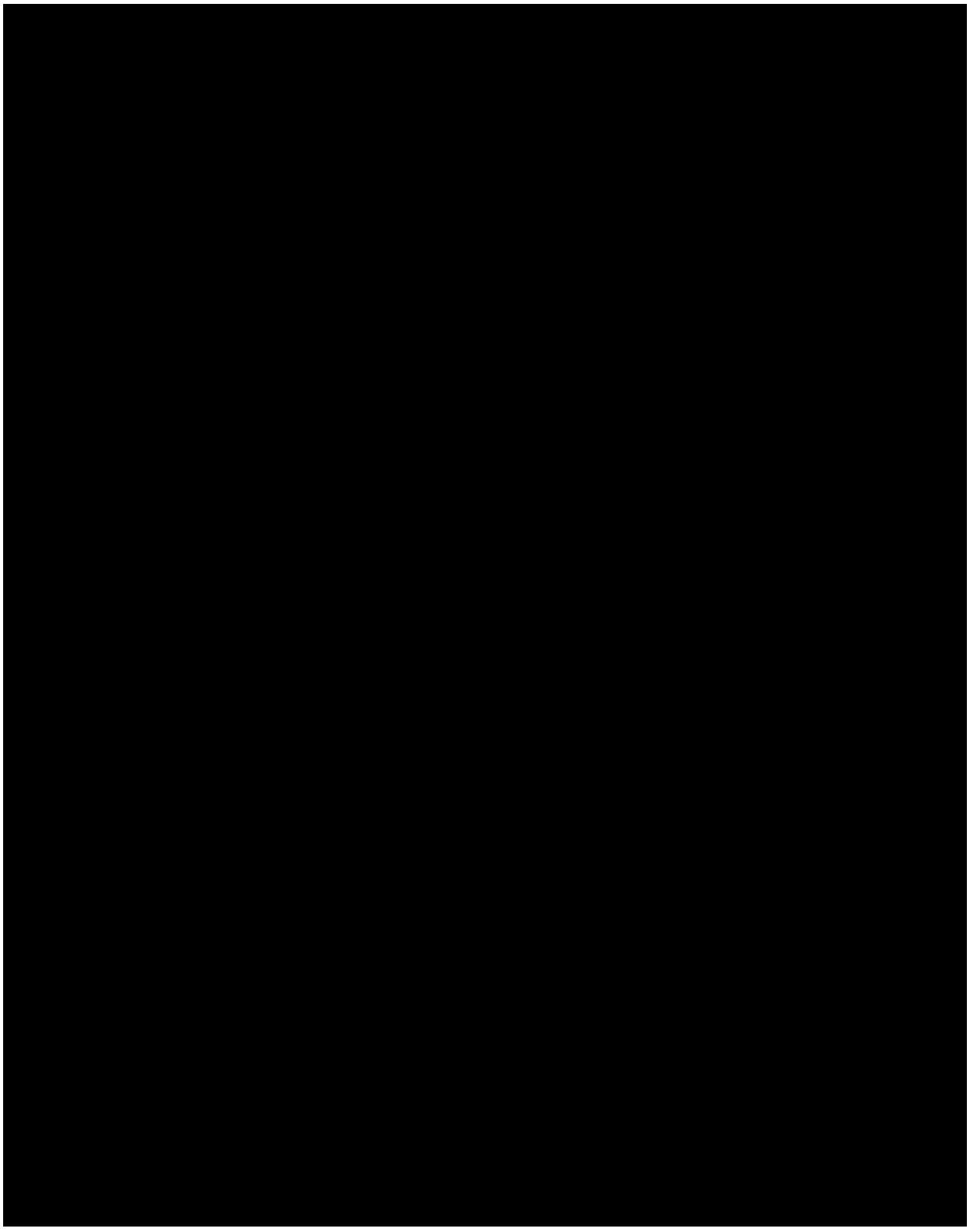


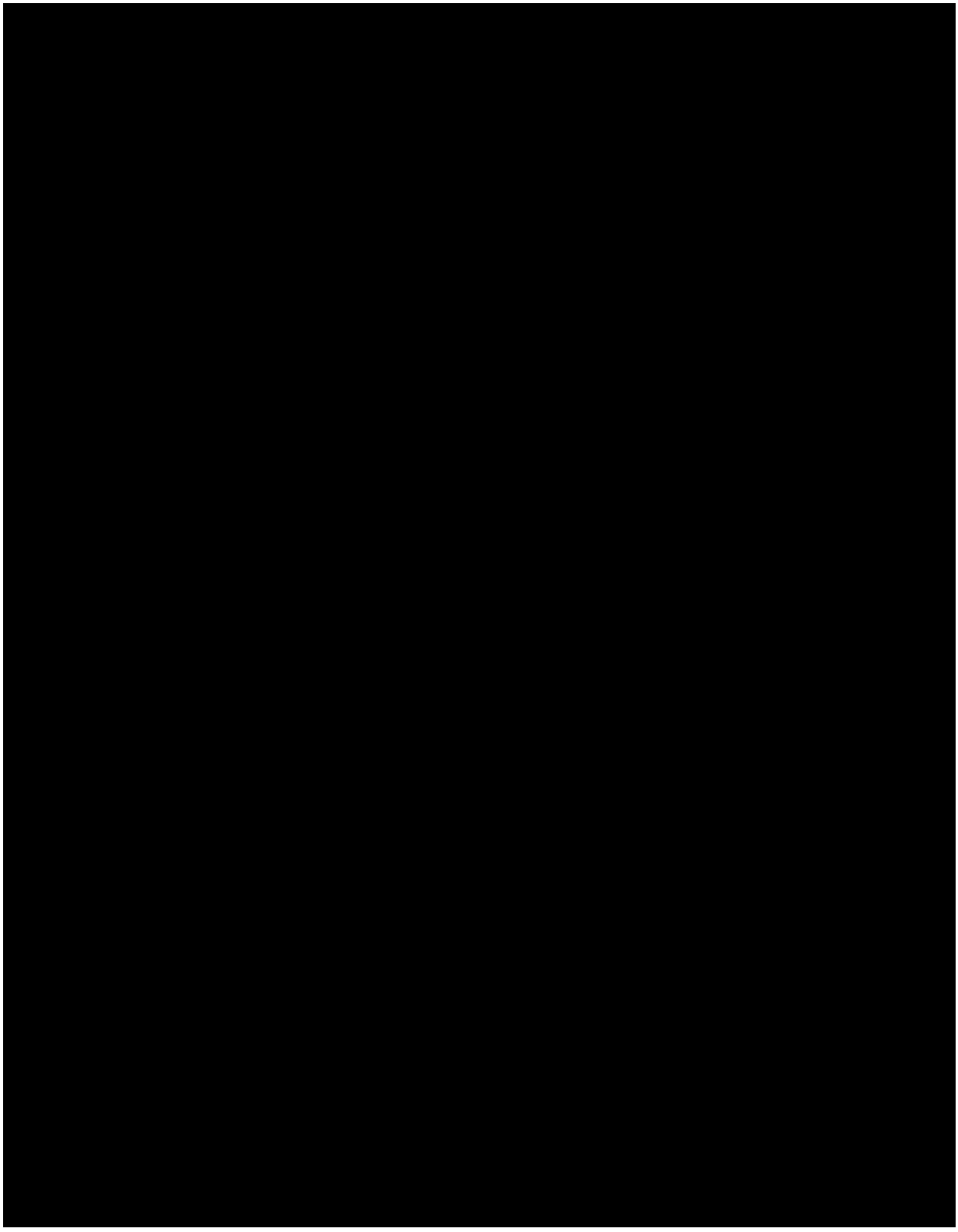


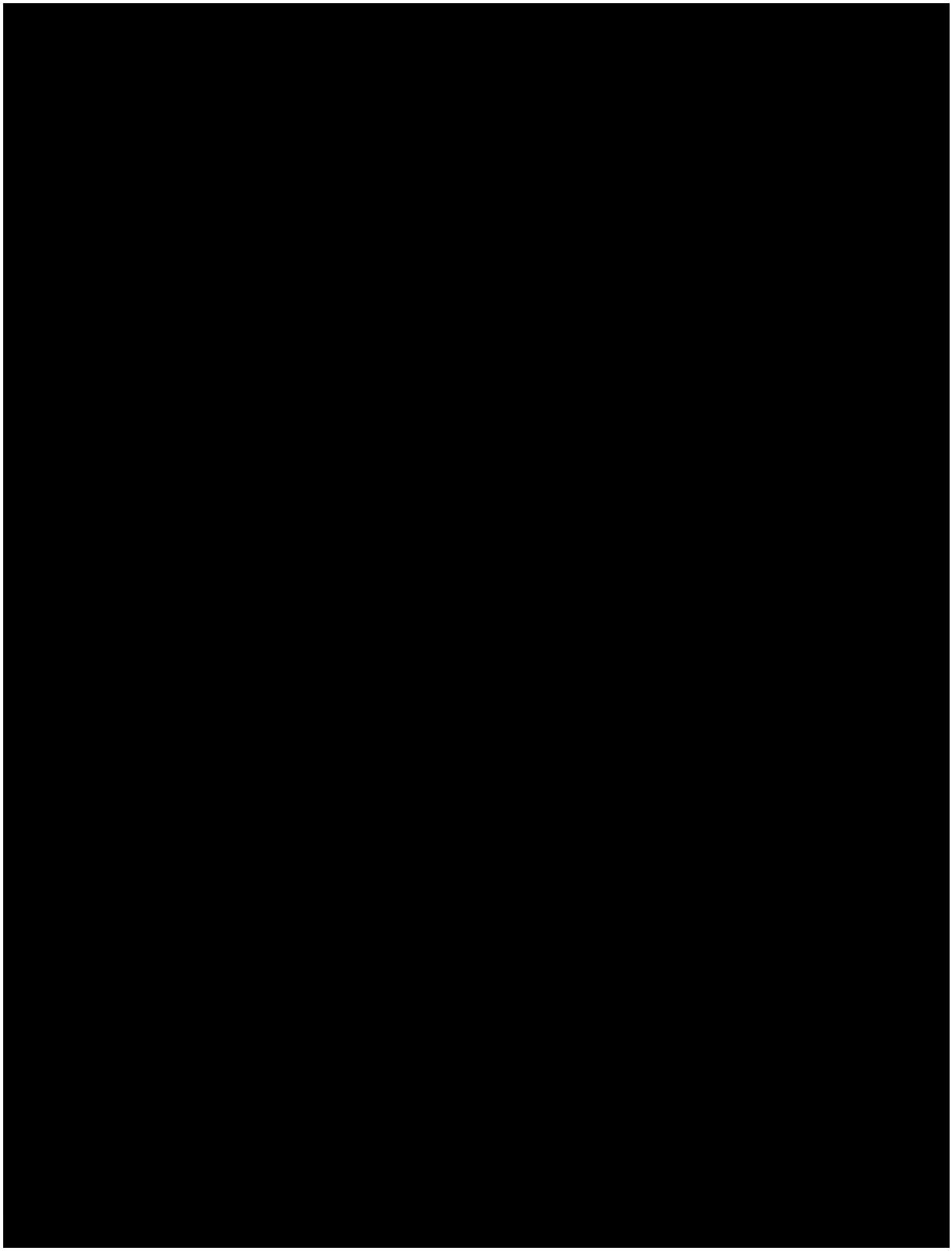


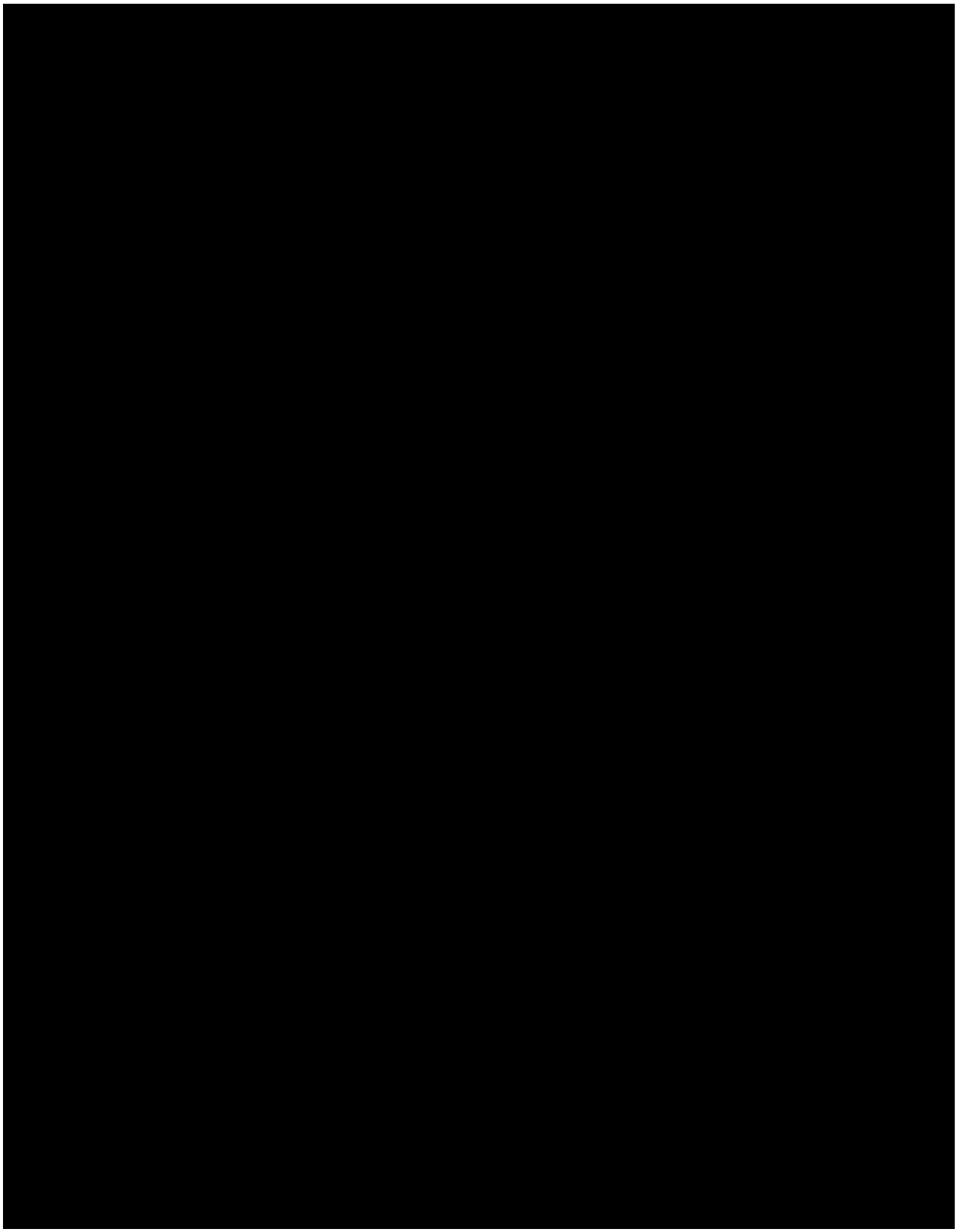


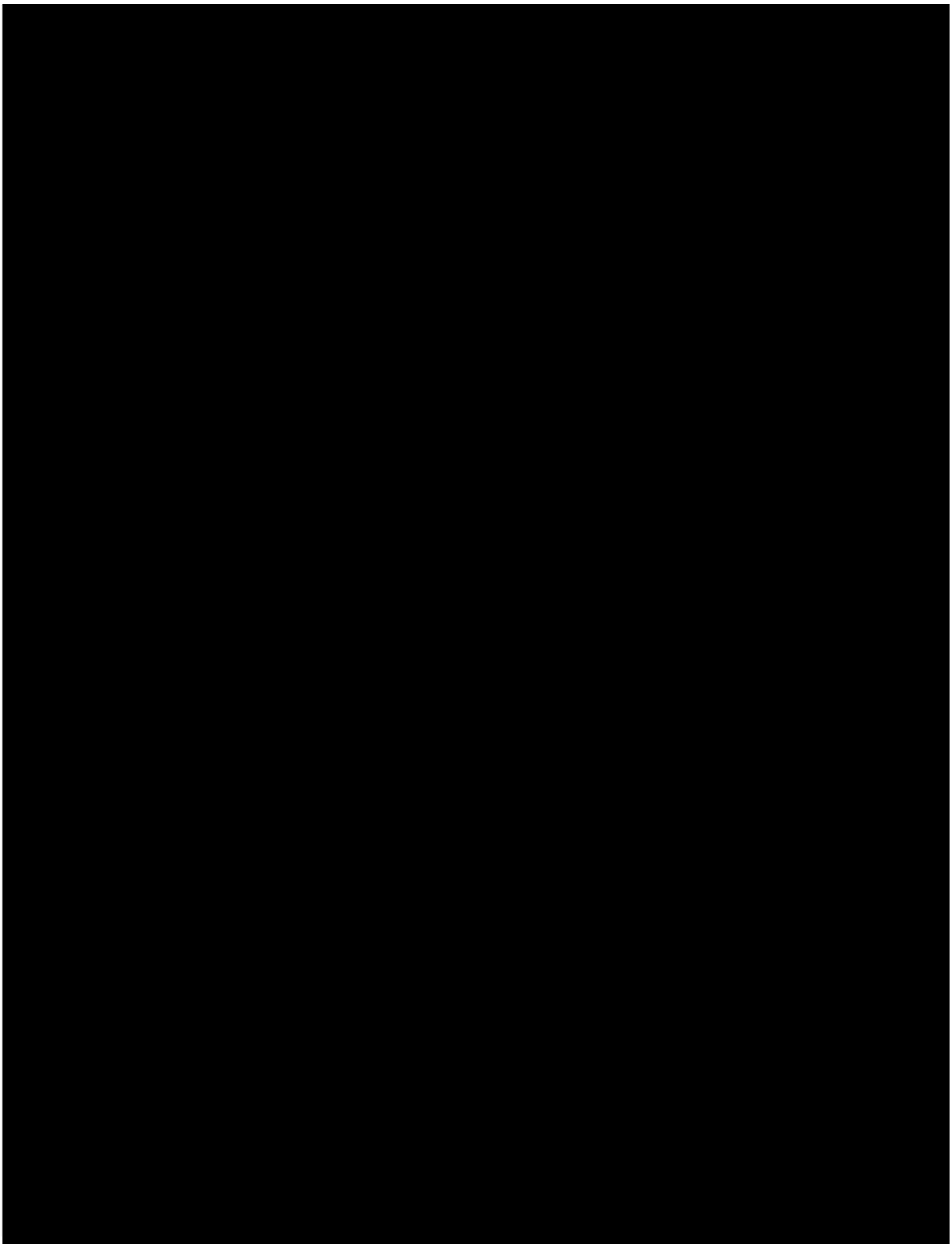


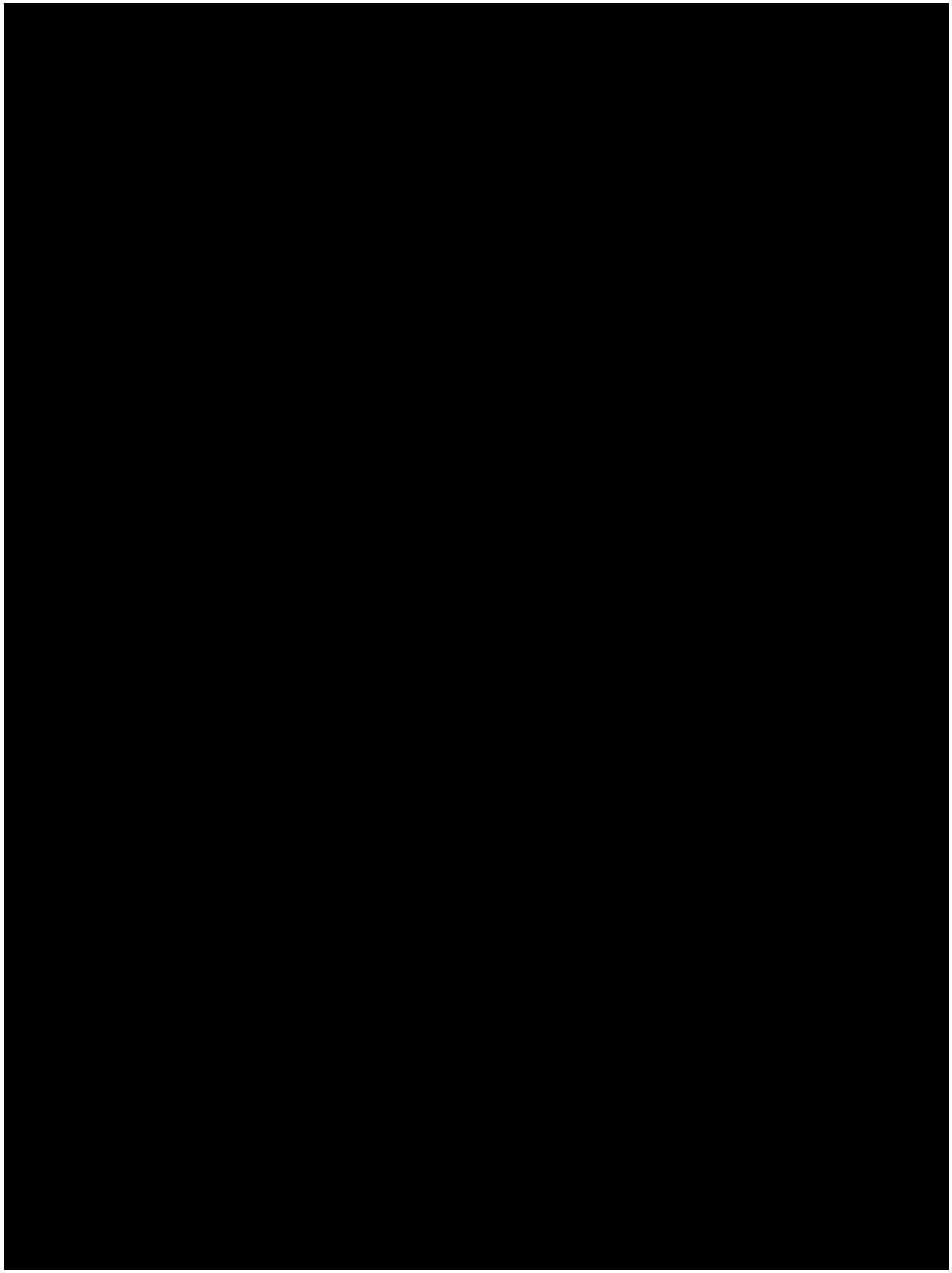


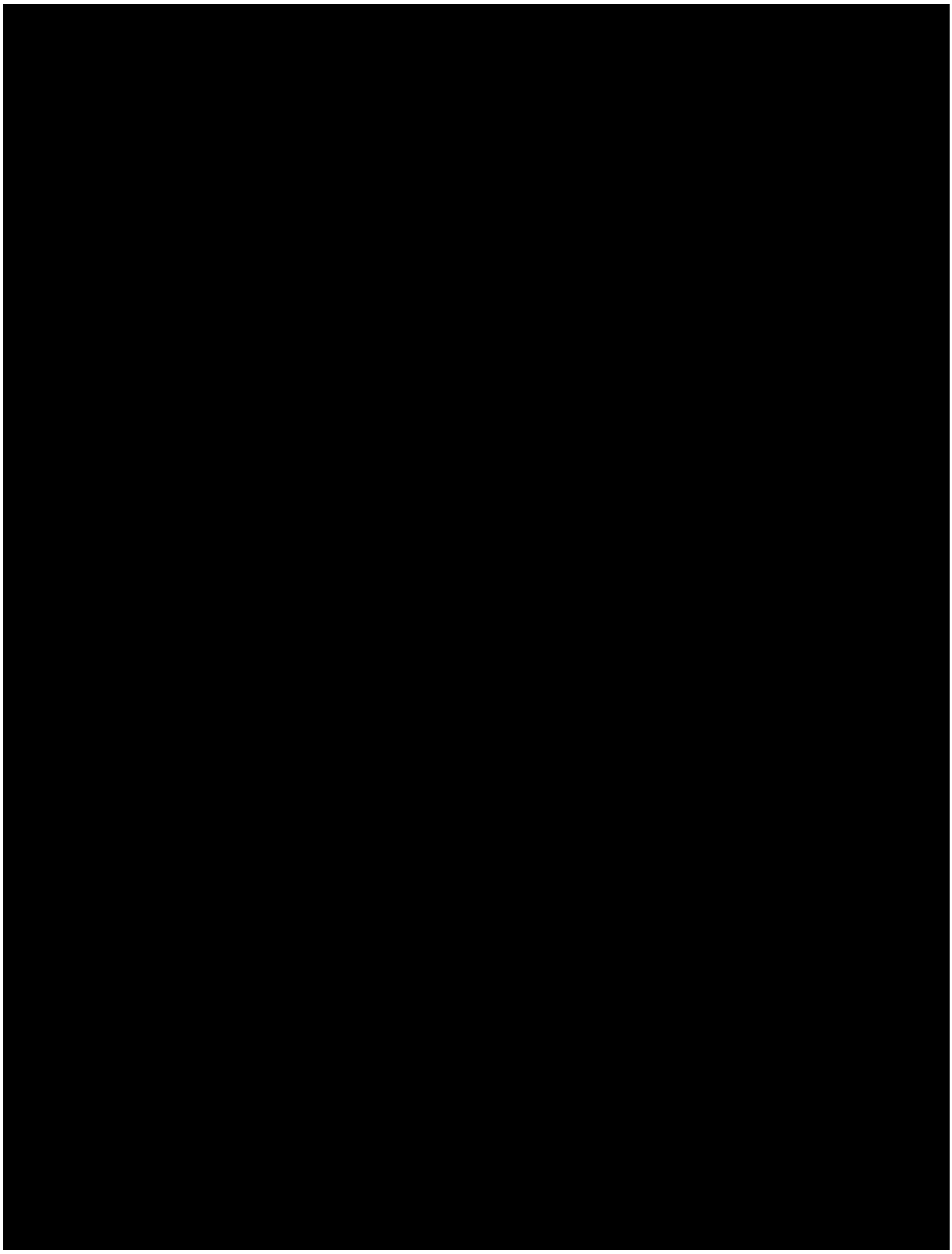


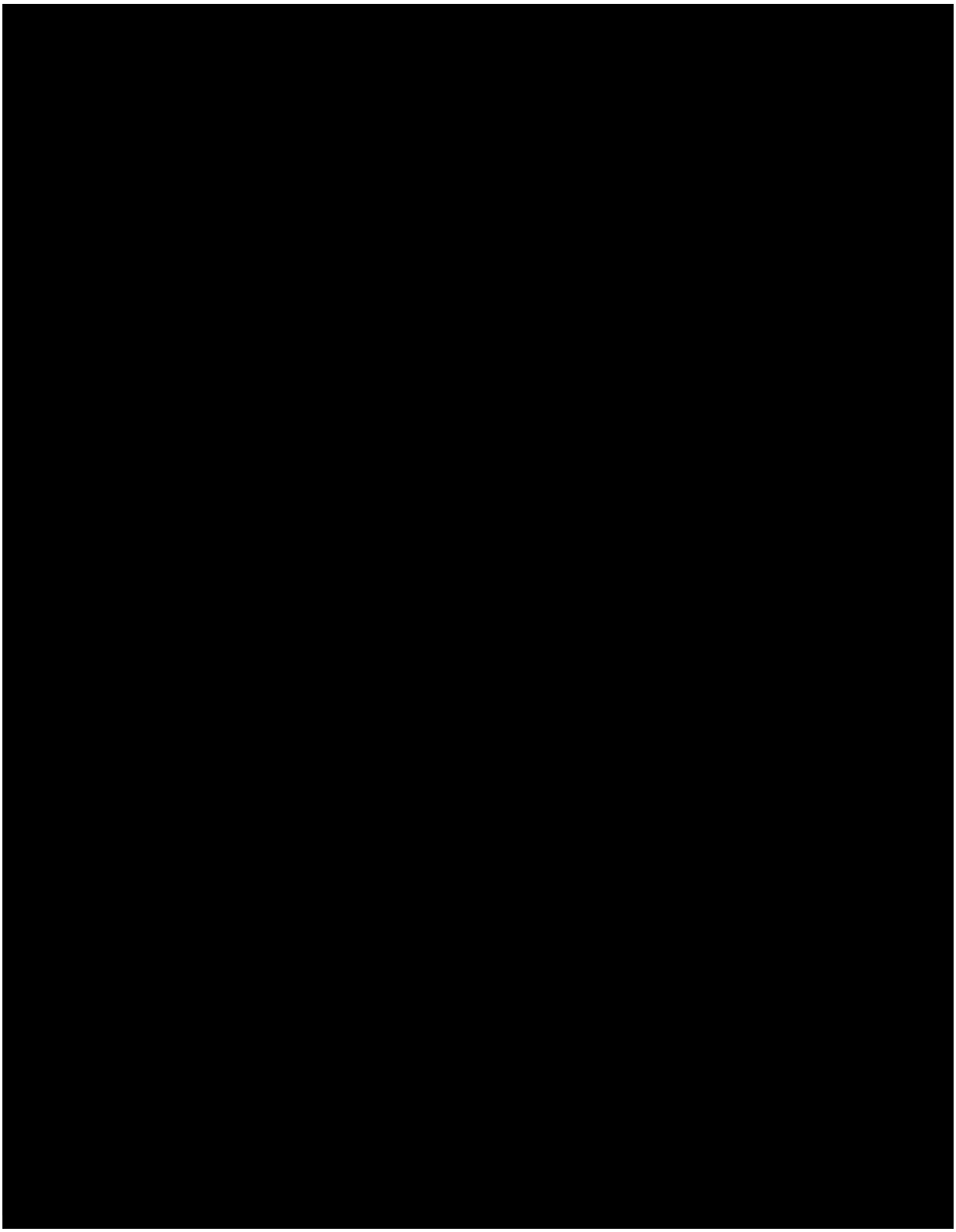


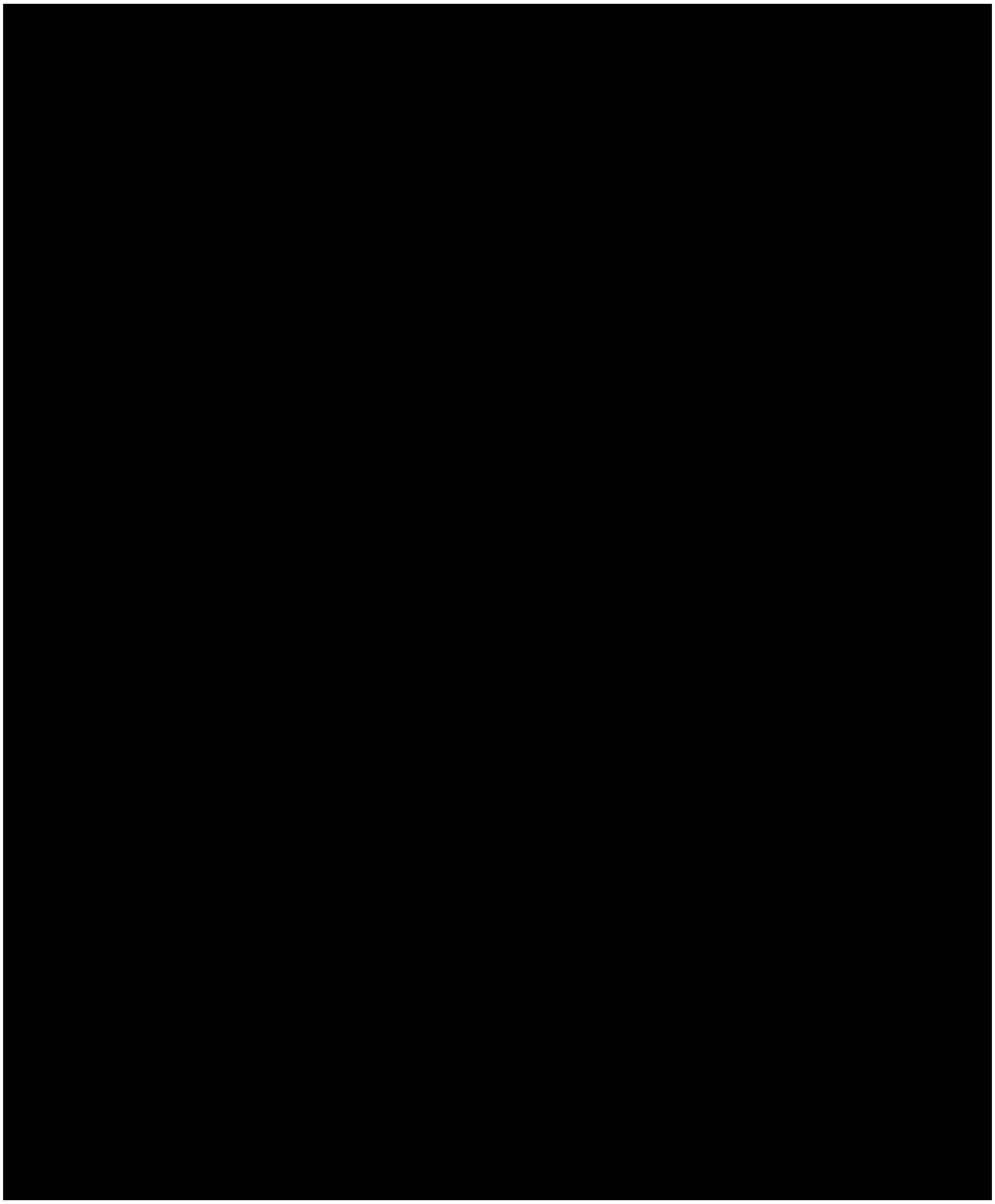


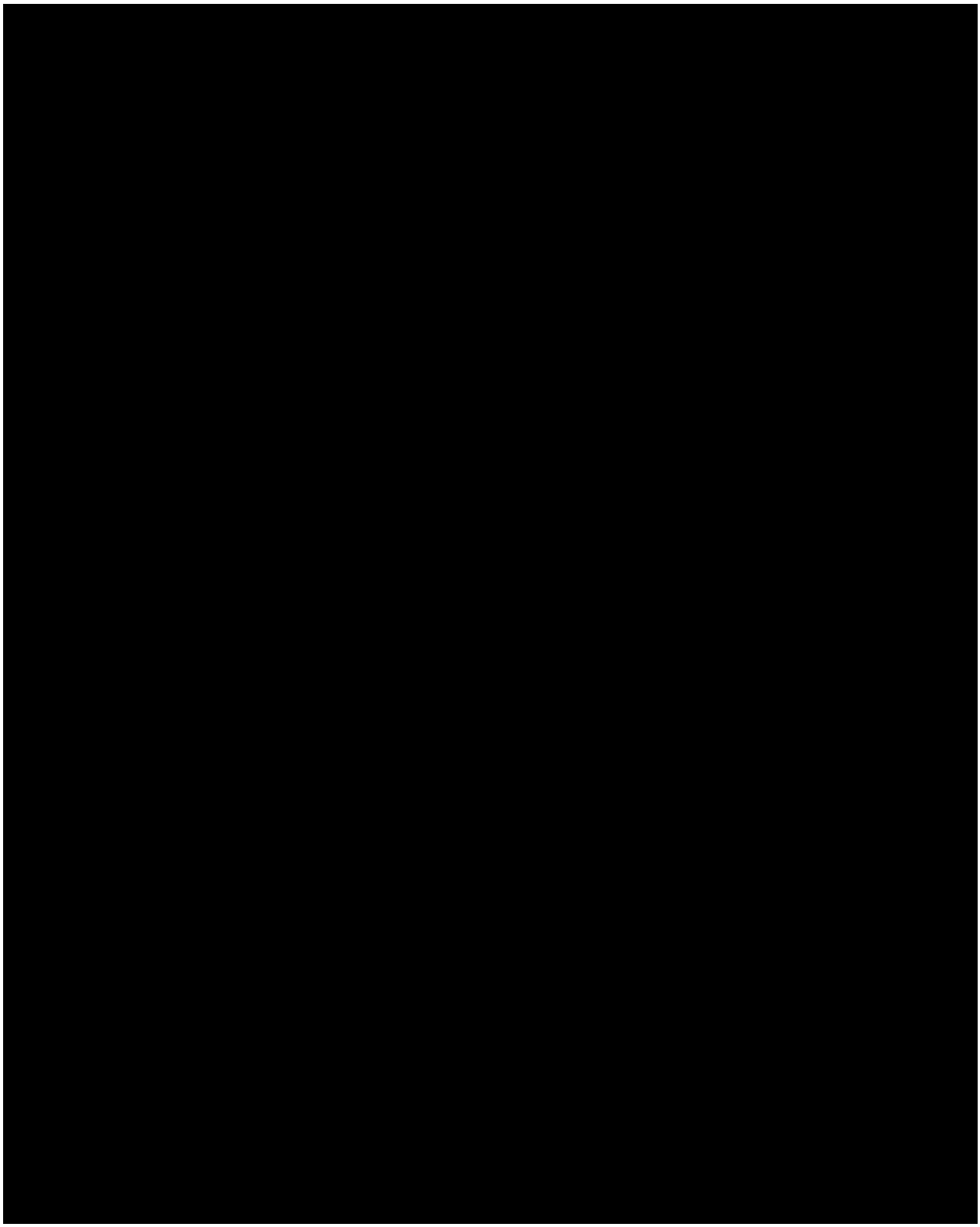


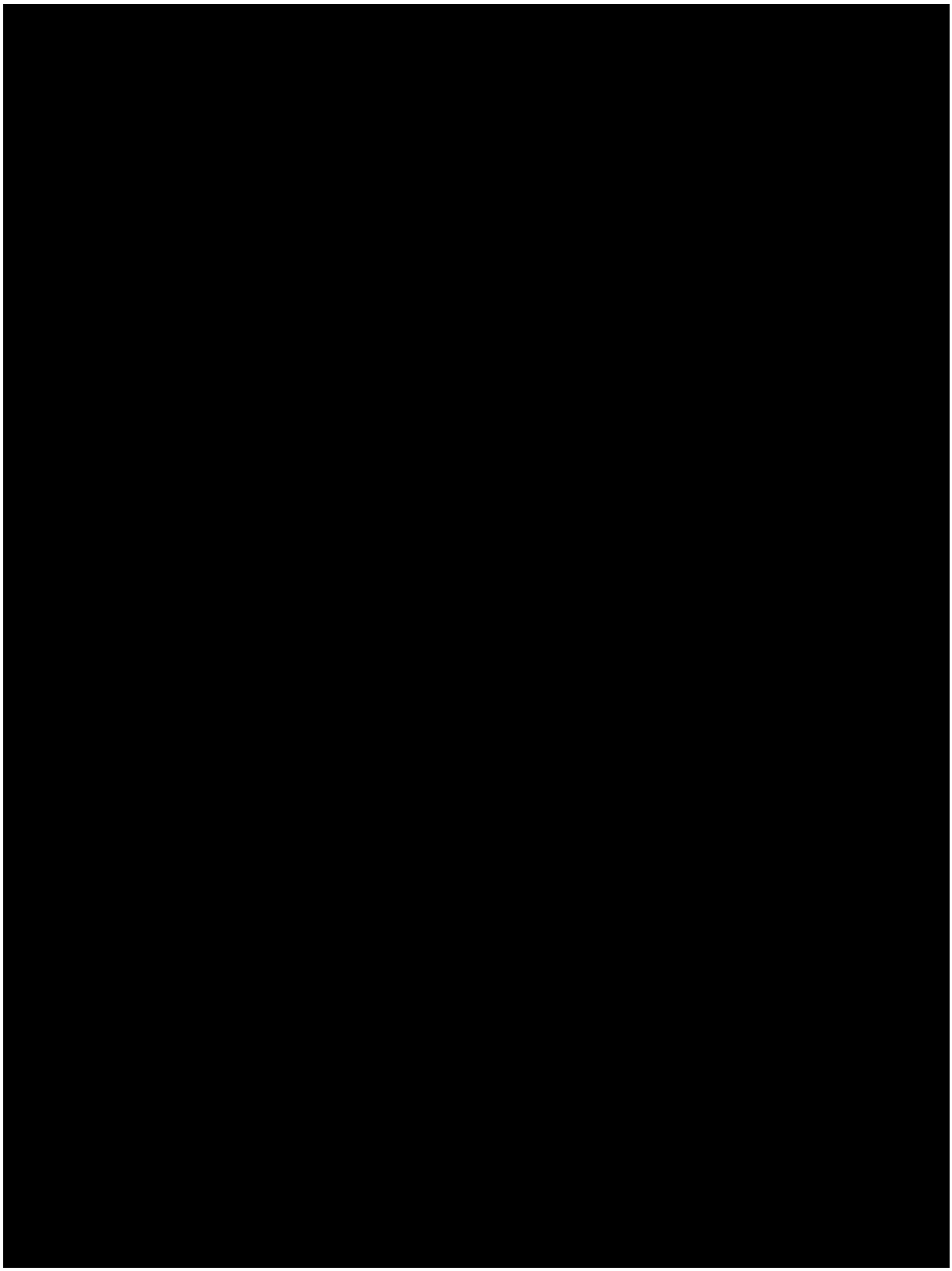


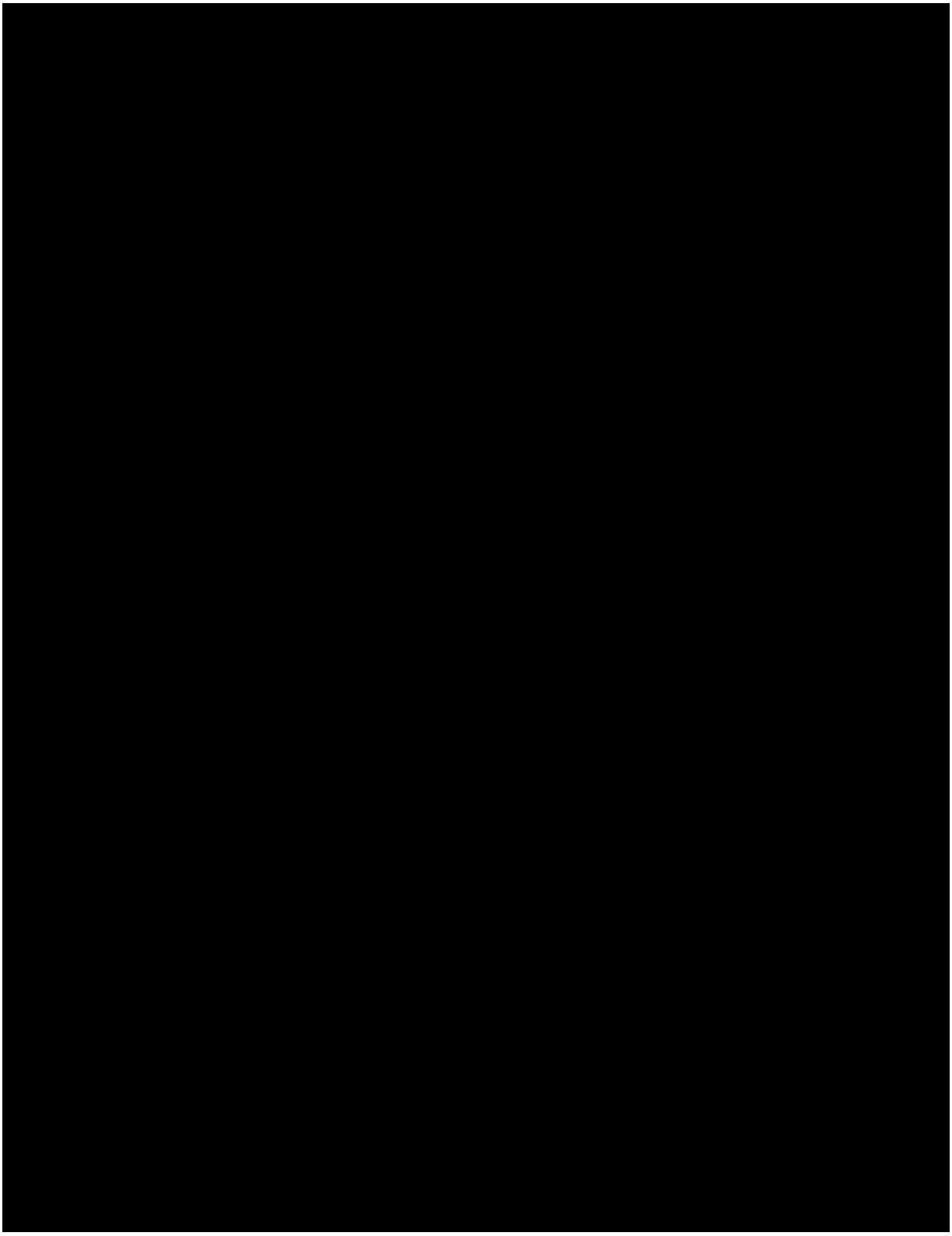


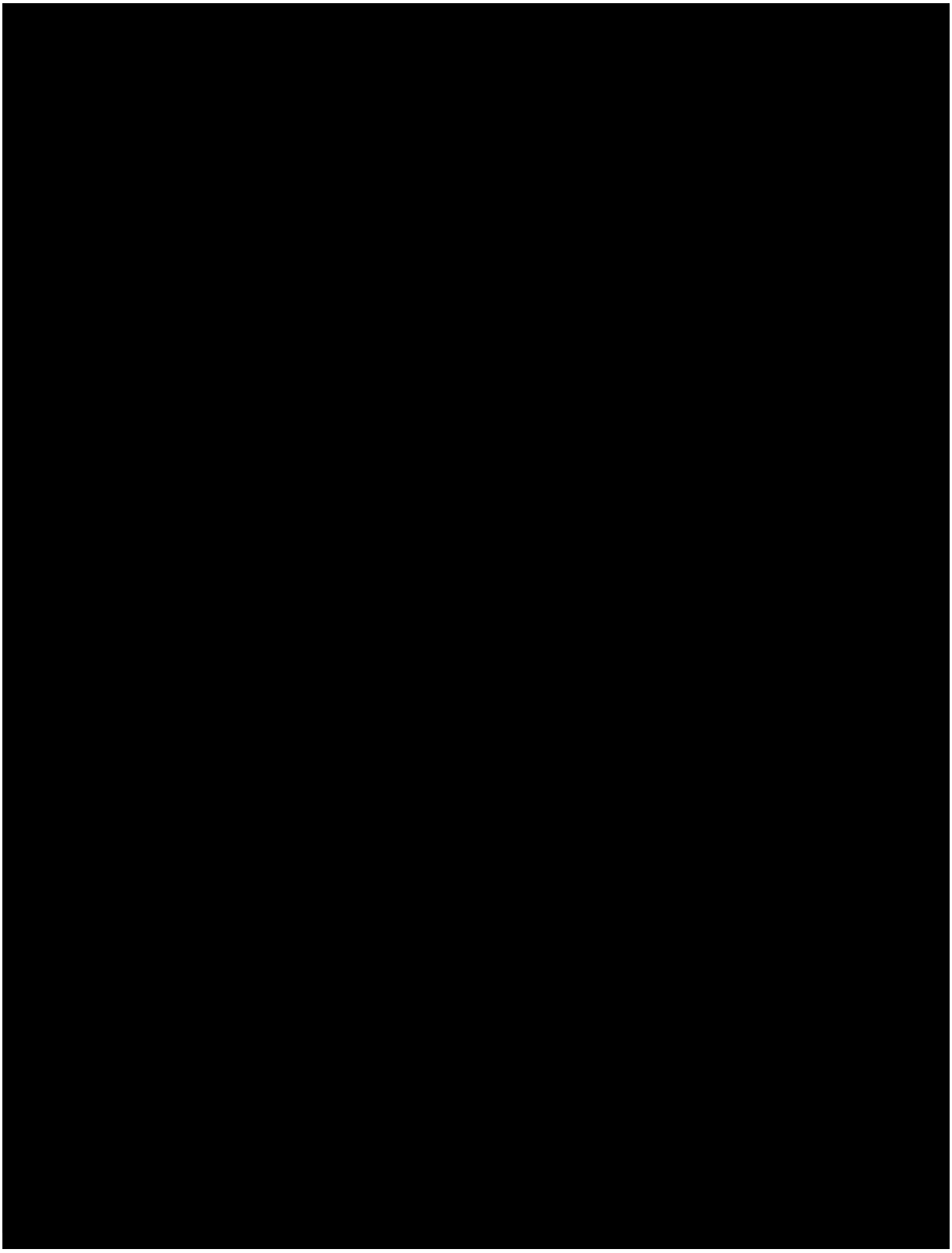


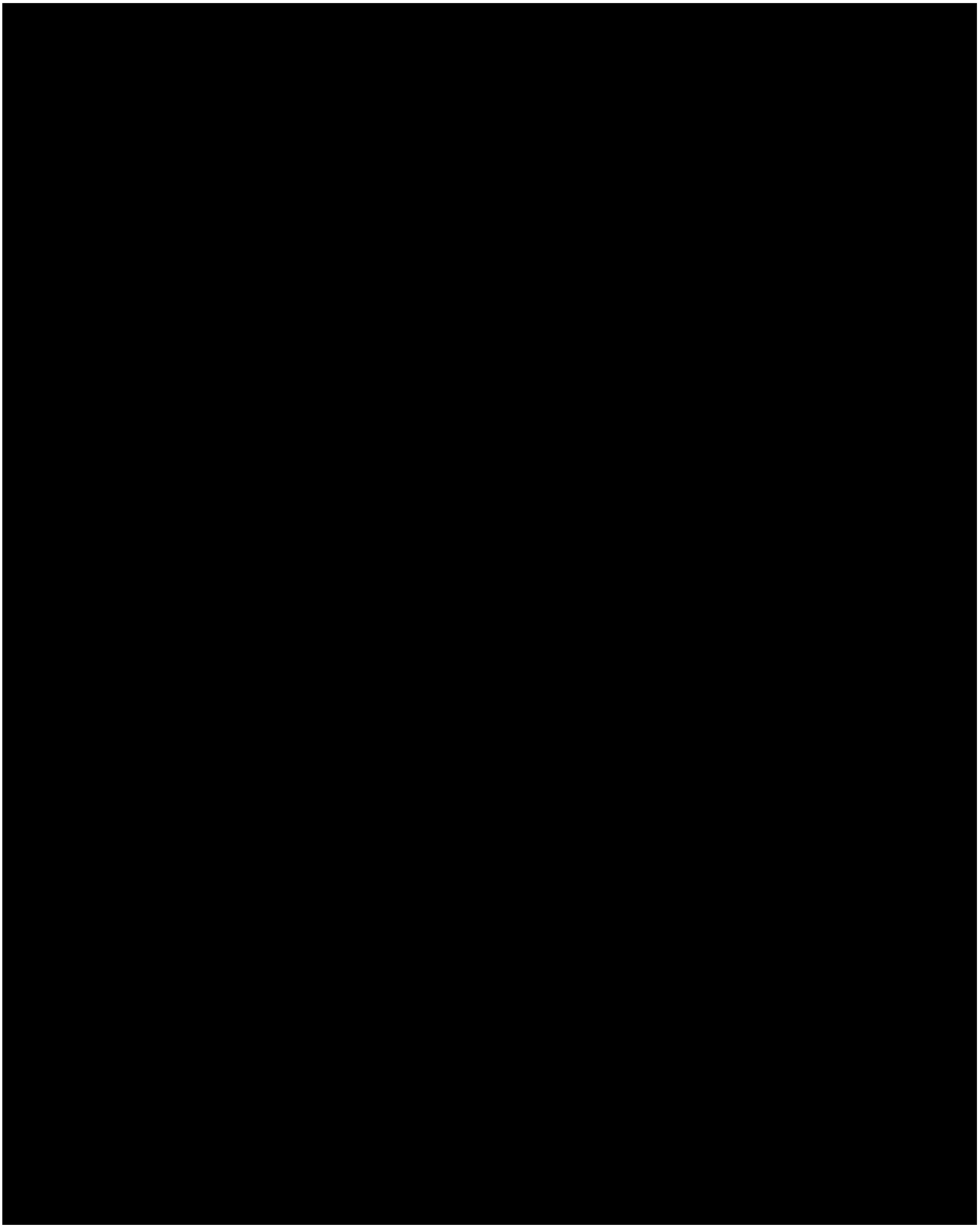


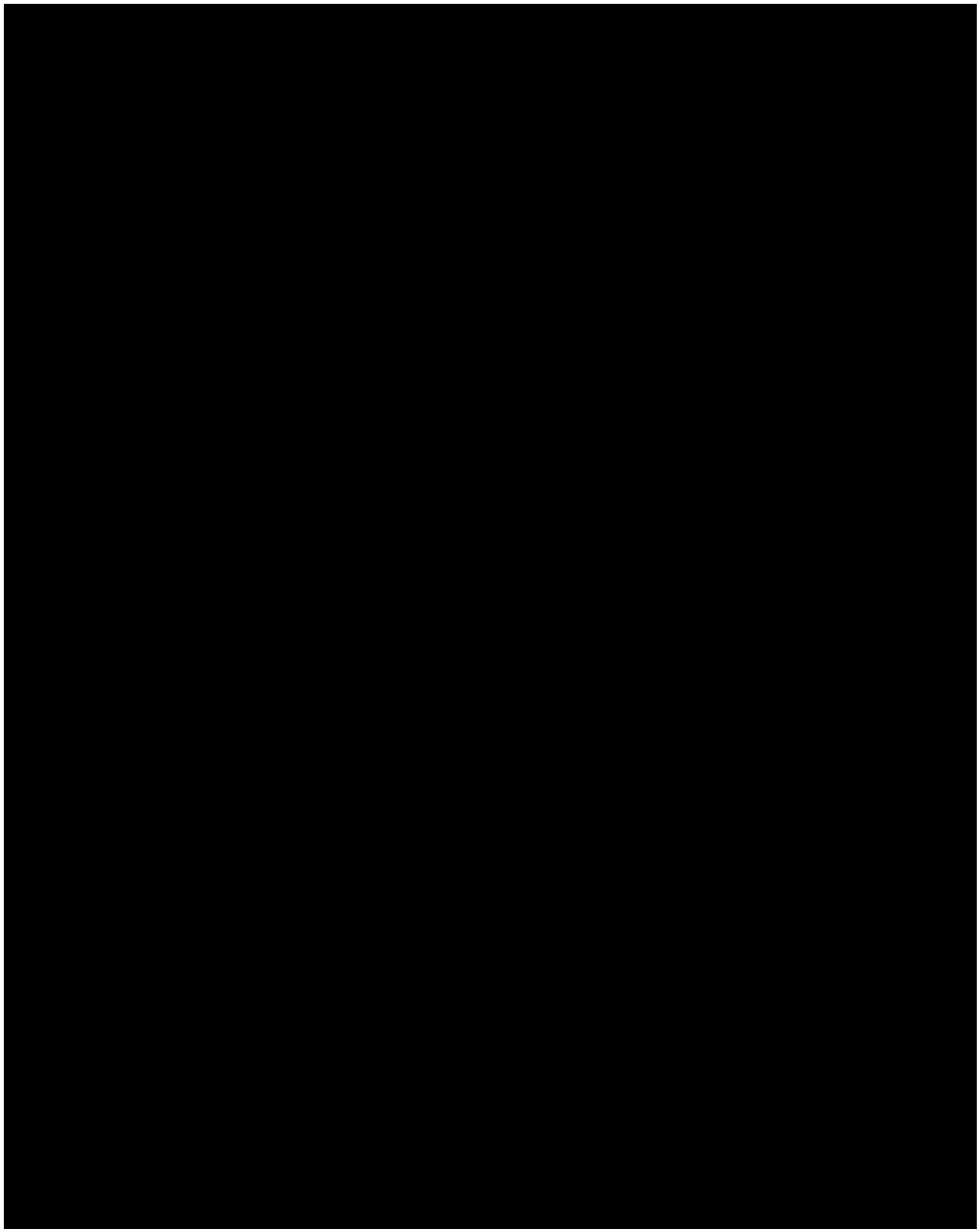


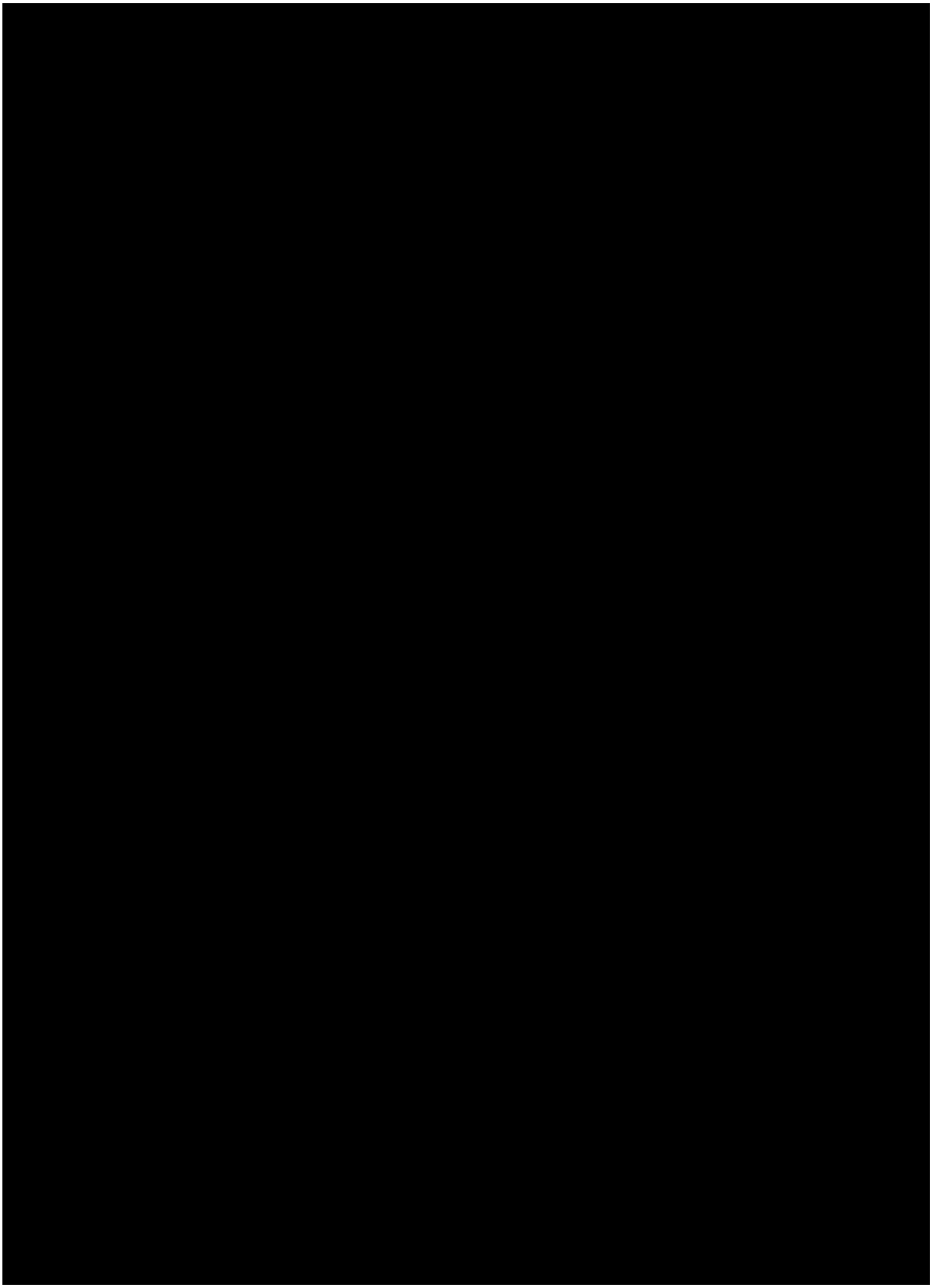


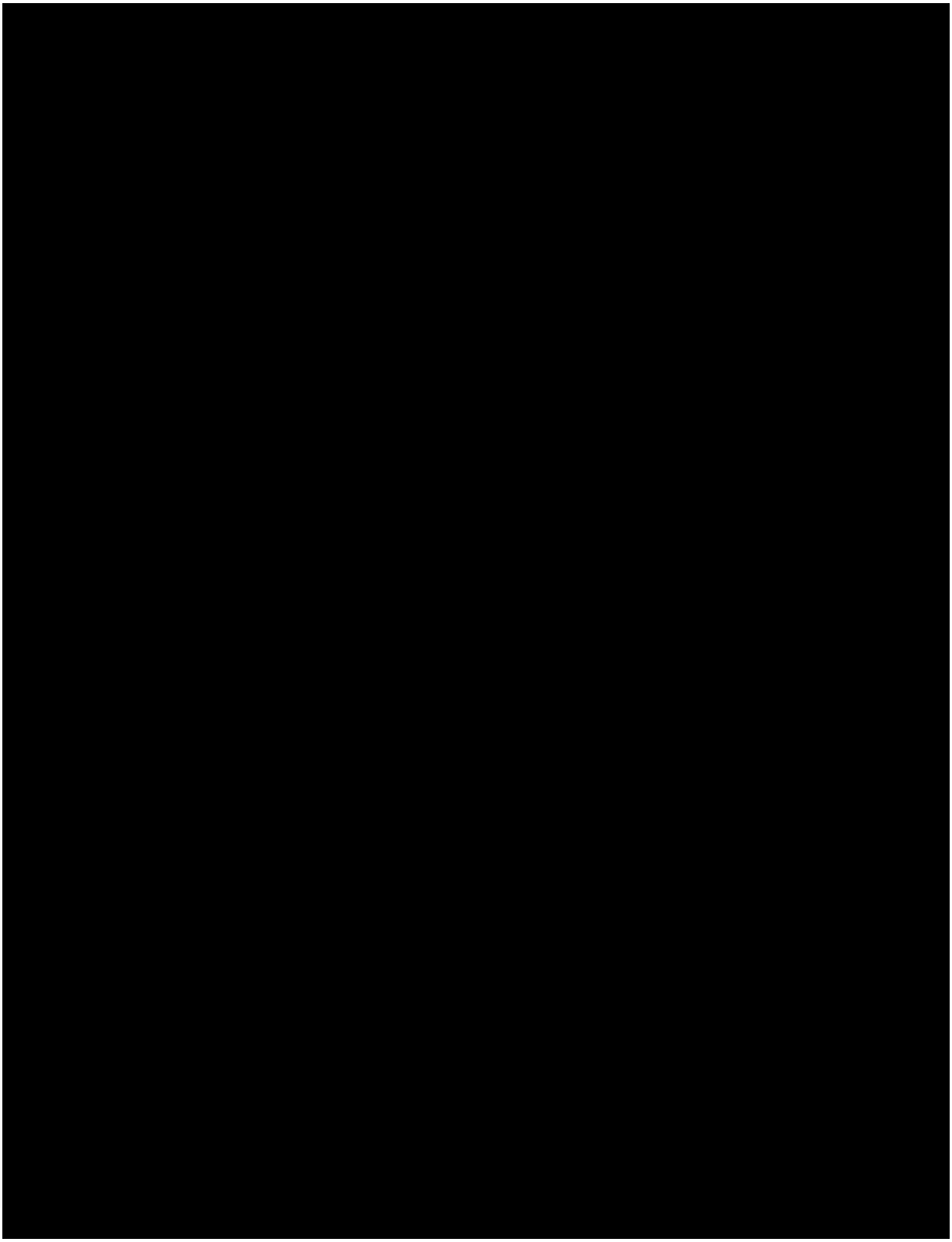


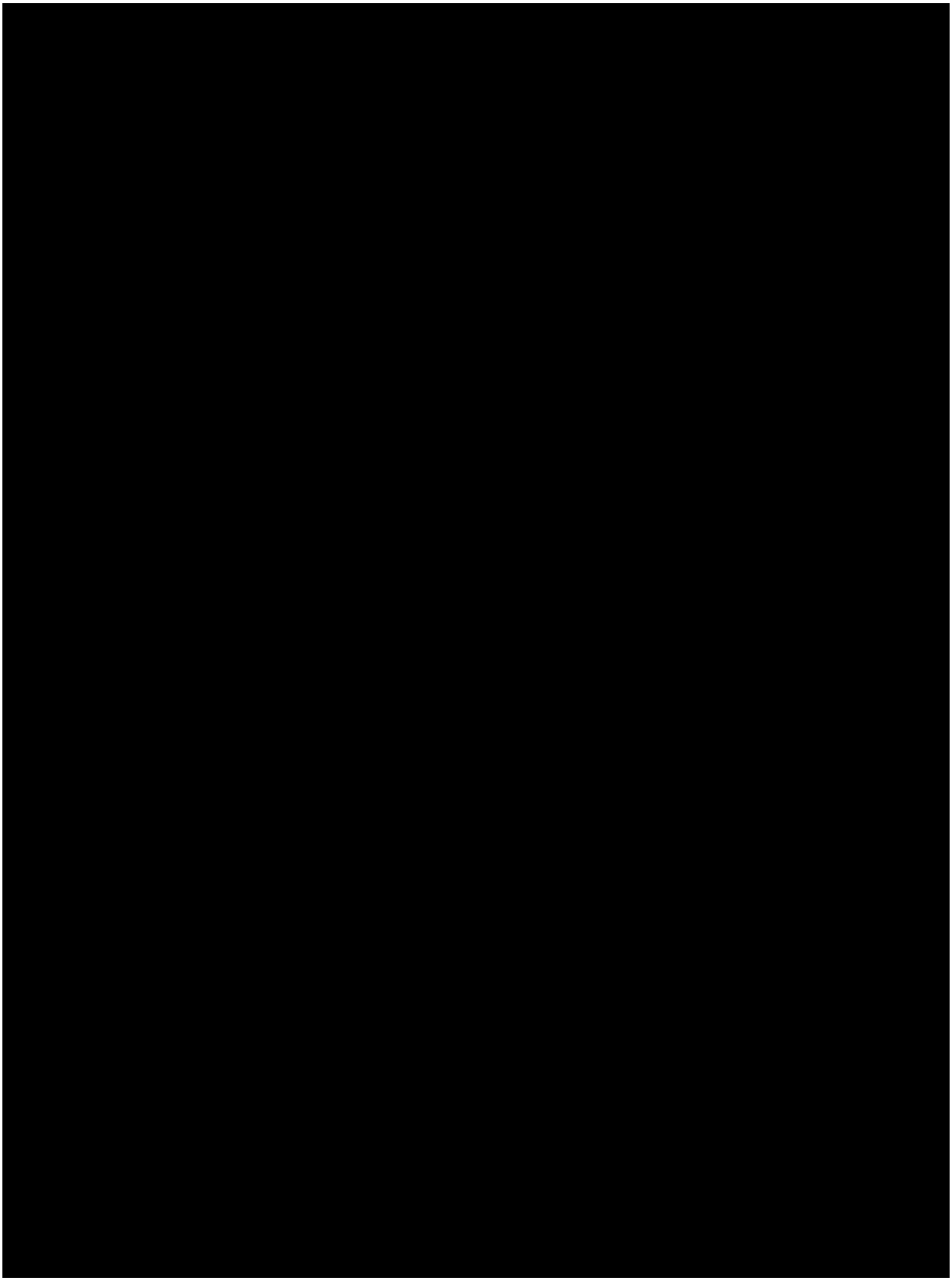


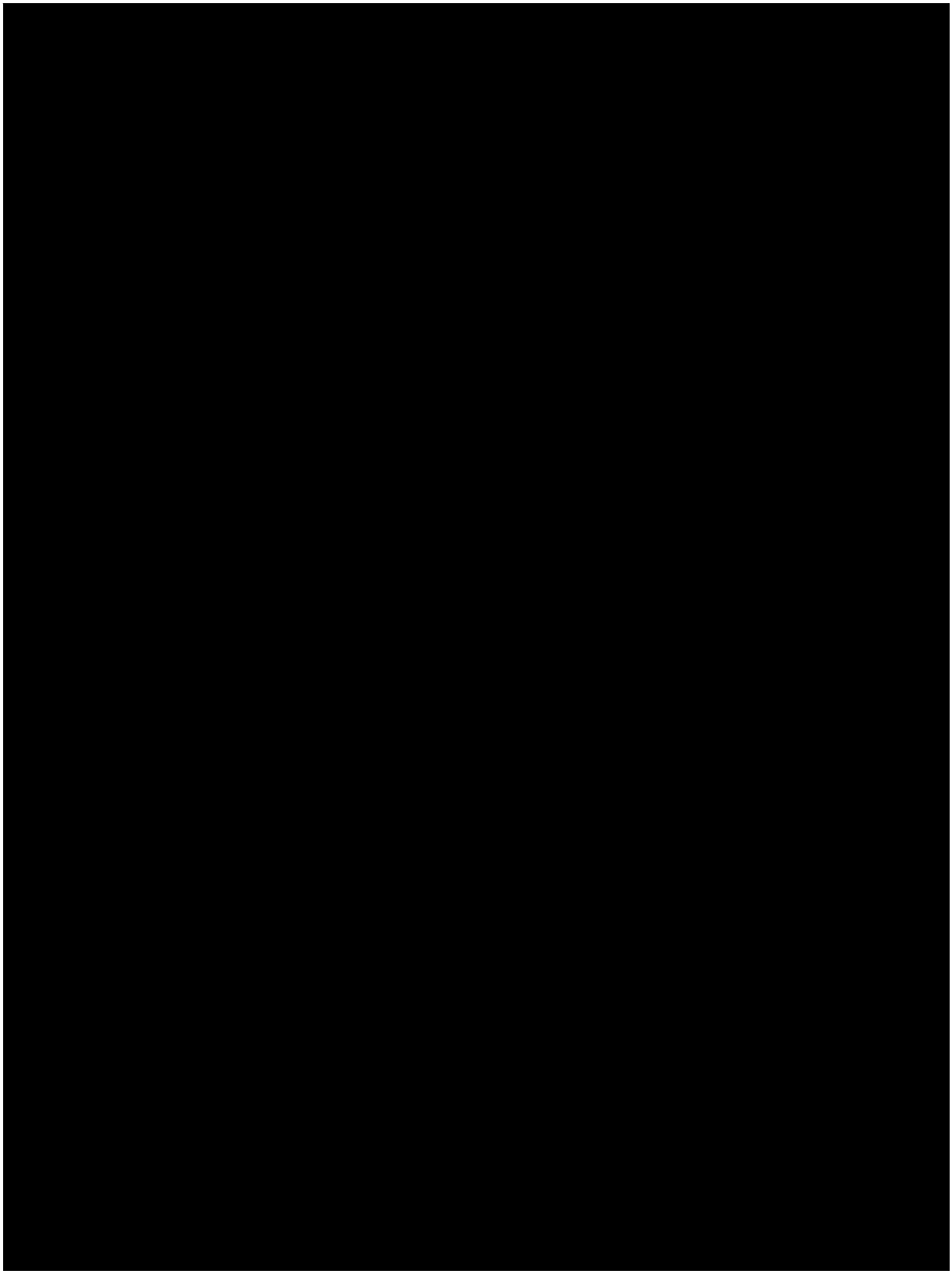












APPENDIX E: [redacted]

[redacted]

APPENDIX F: ANX005 SAMPLE INFUSION PLAN

ANX005-HD-01 Sample Infusion Plan

Day 1 Dosing: All Subjects

Mg/kg Dose	75						
Body Weight (kg)	87.0						
Total Mg Dose	6525						
Divided by 20 (20 mg/ml)							
Total ml required	**326**						
						Total	
		Bag 1	**Bag 2**	**Bag 3**	**Bag 4**		
	Mg/kg	9.0	6.0	25.0	35.0	**75.0**	
	Mg/bag	783.0	522.0	2175.0	3045.0	**6525**	
Total ml drug required per bag		**39**	**26**	**109**	**152**	**326**	
	Vials Required	2.0	1.3	5.4	7.6	**16.3**	
	Rounded up	2	2	6	8	**18**	
Rate:	Infusion Rate in ml/hr	44	131	175	263		**Total Volume**
Volume:	Total volume(mL) per bag	525	525	525	525	**2100**	**(mL)**
Time:	Intended Hours per bag	12	4	3	2	**21**	**Total Hours**
	Mg/kg/hr	0.75	1.5	8.3	17.5		

Each 0.9 % NaCl bag should contain approximately 525 total ml after preparation: remove appropriate saline volume prior to preparing study drug for infusion

Day 5/6 Dosing: All Subjects

Mg/kg Dose	75					
Body Weight (kg)	87.0					
Total Mg Dose	6525					
Divided by 20 (20 mg/ml)						
Total ml required	**326**					
					Total	
		Bag 1	**Bag 2**			
	Mg/kg	37.5	37.5		**75.0**	
	Mg/bag	3263	3263		**6525**	
Total ml drug required per bag		**163**	**163**		**326**	
	Vials Required	8.2	8.2		**16.3**	
	Rounded up	9	9		**18**	
Rate:	Infusion Rate in ml/hr	263	263			**Total Volume (mL)**
Volume:	Total volume (mL) per bag	525	525		**1050**	
Time:	Intended Hours per bag	2	2		**4**	**Total Hours**
	Mg/kg/hr	18.75	18.75			

Each 0.9 % NaCl bag should contain approximately 525 total ml after preparation: remove appropriate saline volume prior to preparing study drug for infusion

Dosing on Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22 For All Subjects

Mg/kg Dose	100					
Body Weight (kg)	100.0					
Total Mg Dose	10000.0					
Divided by 20 (20 mg/ml)						
Total ml required	**500.0**					
					Total	
		Bag 1	**Bag 2**			
	Mg/kg	50.0	50		**100.0**	
	Mg/bag	5000.0	5000.0		**10000.0**	
Total ml drug required per bag		**250**	**250**		**500**	
	Vials Required	12.5	12.5		**25.0**	
	Rounded up	13	13		**26**	
Rate:	Infusion Rate in ml/hr	210.0	210.0			**Total Volume (mL)**
Volume:	Total volume (mL)per bag	525	525		**1050**	
Time:	Intended Hours per bag	2.5	2.5		**5**	**Total Hours**
	Mg/kg/hr	20	20			

Each 0.9 % NaCl bag should contain approximately 525 total ml after preparation: remove appropriate saline volume prior to preparing study drug for infusion

Note: Review and follow procedures detailed in Section 9.10 for management of ANX005 infusion in subjects experiencing IRR