**Protocol Number: AVXS-101-CL-303**

**Official Title:**

# Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

**NCT Number: NCT03306277**

**Document Date: 4 October 2018**

# AVXS-101
# AVXS-101-CL-303

| | |
|---|---|
| **IND Number:** | 15699 |
| **Protocol Title:** | Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion |
| **Indication Studied:** | Spinal Muscular Atrophy Type 1 |
| **Sponsor Address:** | AveXis, Inc.<br>2275 Half Day Road<br>Bannockburn, IL 60015 |
| **Protocol Version/Date:** | 4.0 / 4 October 2018 |

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

# 1. ADMINISTRATIVE INFORMATION

## 1.1. Approval

**REPRESENTATIVES FROM AVEXIS:**

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization and the Harmonized Tripartite Guideline for Good Clinical Practice E6
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

**SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):**

[redacted]
Vice President Clinical Development
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Executive Director Clinical Development
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Senior Vice President Regulatory Affairs, AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Vice President Clinical Operations
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Sr. Director, Head of Biostatistics
AveXis, Inc.

Date (ddMmmyyyy)

## 1.2. Investigator's Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-CL-303 protocol and agree to conduct the study in accordance with the relevant current protocol(s). I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of study participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Informed Consent 21 CFR Part 56, Institutional Review Board Review in 21 CRF Part 56, Adverse Event Reporting as defined in Section 13.4 and in 21 CFR 312.64, Adequate/accurate and accessible records in accordance with 21CFR 312.62 and 312.68.
- Terms outlined in the study site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations) I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

**Confidentiality Statement**

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date (ddMmmyyyy)

## 1.3. Contact Information

**Table 1: Important Study Contact Information**

| Role in Study | Name/Address and Telephone Number |
|---|---|
| Clinical Study Leader | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Responsible Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Drug Safety Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Serious Adverse Event Reporting | Please see Project Management Plan in TMF or Study Contact list in ISF |
| 24-Hour Emergency Contact | Please see Study Contact List in ISF |

**Table 2: Study Vendor Listing**

| Role in Study | Name/Address |
|---|---|
| Clinical Research Organization | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Investigational Product Shipment | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Video | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Independent Video Review | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Holter Monitor and 12-lead Electrocardiogram | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-immunoassays | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-viral shedding studies | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Autopsy | Please see Project Management Plan in TMF or Study Contact list in ISF |

ISF = Investigator site file; TMF = trial master file

# 2. SYNOPSIS

**Name of Sponsor/Company:** AveXis, Inc.

**Name of Investigational Product:** AVXS-101

**Name of Active Ingredient:** Survival Motor Neuron Gene by Self-Complementary Adeno-Associated Virus Serotype 9 (AAV9)

**Title of Study:** Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

**Study Center(s):** 10 to 20 United States (US) Investigators

| **Studied Period (years):** | **Phase of Development:** 3 |
|---|---|
| Estimated date first patient enrolled: 2Q 2017<br>Estimated date last patient completed: 4Q 2019 | |

**Objectives:**

**Co-Primary**

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

**Co-Secondary**

- Determine effect of AVXS-101 on the ability to thrive defined as achieving all of the following at 18 months of age:
  - Does not receive nutrition through mechanical support (e.g., feeding tube) or other non-oral method
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age

[redacted]

[redacted]

**Safety**

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity

**Methodology:**

Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least 15 patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first 3 patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at 1-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial

(AVXS-101-CL-101).

The study includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a 1-time intravenous (IV) infusion of AVXS-101 and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age. After the End of Study visit, eligible patients will be asked to rollover into the long-term follow up study.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first 3 patients to allow review of the safety analysis from 6-time points (day 1, 2, 7, 14, 21, and 30 visits) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient. The first 3 patients enrolled must meet the criteria for the Intent-to-Treat Population. AveXis will compare the CHOP-INTEND-1 month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first 3 patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first 3 ITT patients, AveXis will remove the 4-week interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria. If the expected CI improvements are not observed for the first 3 ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to AVXS-101 infusion until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values, aspartate aminotransferase (AST) values, and T-cell response are below the threshold of 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline: 1 mg/kg/day until at least 30 days post-infusion, 0.5 mg/kg/day at Weeks 5 and 6, 0.25 mg/kg/day at Weeks 7 and 8, and discontinued at Week 9.

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age. The ability to thrive (as defined above) and the ability to remain independent of ventilatory support (as defined above) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development (Version 3). Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or

definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

**Number of Patients (planned):** Up to twenty (20) patients that meet the study enrollment criteria to enable at least 15 patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

1. Patients with SMA Type 1 as determined by the following features:
   a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))2.
2. The first 3 patients enrolled must meet the criteria for the Intent-To-Treat Population.
3. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (26)
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

**Exclusion Criteria:**

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

   Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened- liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards[25]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within

2 weeks prior to screening

8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (gamma glutamyl- transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational Cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)
16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form
19. Gestational age at birth < 35 weeks (245 days)

**Investigational Product, Dosage and Mode of Administration:**

Patients will receive a 1-time dose of AVXS-101 at $1.1 \times 10^{14}$ vg/kg, a dose determined to be equivalent to the dose received by the Cohort 2 patients in the Phase 1 study (AVXS-101-CL-101) by direct testing using improved analytical methods.

**Duration of Treatment:**

AVXS-101 will be administered as a 1-time IV infusion over approximately 30-60 minutes, dependent upon the volume required.

**Reference Therapy, Dosage and Mode of Administration:** Not Applicable

**Criteria for Evaluation:**

**Efficacy:**

**Co-Primary**

- Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 seconds
- Survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death

**Co-Secondary**

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [25] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)

[redacted]

**Safety:**

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated liver function tests (LFTs) and/or unresolved liver function enzymes (LFEs)
- Incidence of CTCAE Grade 3 or higher toxicity, treatment emergent- adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFNγ Enzyme-linked ImmunoSpot (ELISpot) to detect -T-cell- responses to AAV9 and SMN

**Statistical Methods:**

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least 15 patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first 3 patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at 1-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

Based upon widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [21], it is expected that no patient meeting the study entrance criteria (*SMN2* copy number of 2 without the *SMN2* gene modifier mutation (c.859G>C)) would be expected to attain the ability to sit without support for at least 30 seconds at or before the 18 months of age study visit or other milestones (rolling over, standing, walking) assessed as part of the study.

Assuming the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis is whether the AVXS-101 treated patients achieve a response rate greater than 0.1%. Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated patients in the ITT population are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age visit. With the assumption for the true response rate of AVXS-101 for the primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients

are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with $\alpha = 0.025$ using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint of survival at 14 months of age will be evaluated by comparing the results observed in the ITT population with the results from the age and gender-matched control patients selected from existing natural history data sets (PNCR) [*Neurol*. 2014; 83(9):810-817]. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. Based upon preliminary results from the ongoing Phase 1 clinical study (AVXS-101-CL-101), at least 80% of patients in the ITT population are expected to survive, as defined, through 14 months of age. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with $\alpha = 0.05$ using a 2-sided Fisher's Exact test.

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AAV | Adeno-associated virus |
| AAV9 | Adeno-associated virus serotype 9 |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ASO | Antisense oligonucleotide |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CB | Chicken-β-actin-hybrid |
| CDC | Center for Disease Control |
| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| CI | CHOP-INTEND |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CK | Creatine kinase |
| CK-MB | Creatine kinase isoenzyme |
| CLIA | Clinical Laboratory Improvement Amendment |
| CMAP | Compound motor action potential |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Day 1 | First 24-hour interval after the start of gene replacement therapy infusion |
| Day –1 | 24-hour interval prior to the start of gene replacement therapy infusion |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-linked Immunosorbent Assay |
| ELISpot | Enzyme-linked ImmunoSpot |
| ET | Early termination |
| FVB | Friend Virus B-Type |
| GCP | Good Clinical Practice |
| GFP | Green fluorescent protein |
| GGT | Gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| HEENT | Head, eyes, ears, nose, and throat |
| HgB | Hemoglobin |
| HIV | Human Immunodeficiency Virus |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ICD-10 code | International Statistical Classification of Diseases and Related Health Problems |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon gamma |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| ITR | Inverted terminal repeat |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LFE | Liver function enzymes |
| LFT | Liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NHP | Non-human primates |
| NOAEL | No Observable Adverse Effect Level |
| OAE | Other significant Adverse Event |
| PBMC | Peripheral blood mononuclear cells |
| PICU | Pediatric intensive care unit |
| PNCR | Pediatric Neuromuscular Clinical Research Network |
| RNA | Ribonucleic acid |
| RSV | Respiratory syncytial virus |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | Self-complementary |
| scAAV | Self-complimentary adeno-associated virus |
| scAAV9.CB.SMN | Self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron |
| SMA | Spinal muscular atrophy |
| SMN | Survival motor neuron |
| *SMN1* | Survival motor neuron 1 gene |
| *SMN2* | Survival motor neuron 2 gene |
| SOC | System Organ Class |
| TMF | Trial master file |
| US | United States |
| vg/kg | Vector genome per kilogram |
| WBC | White blood cell |
| WHO | World Health Organization |
| WT | Wild type |

# 5. INTRODUCTION

Study AVXS-101-CL-303 is a pivotal Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* as well as 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least 15 patients that meet the Intent-to-Treat Population (ITT) criteria. The first 3 patients enrolled must meet the ITT criteria to enable a comparison of CHOP-INTEND scores at 1-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

In this study, the survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMNΔ7 mouse model for SMA from a median of 15.5 days to over 1 year, following IV delivery to a facial vein. Additionally, preliminary results from an ongoing Phase 1 clinical study (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function (Section 5.4).

## 5.1. Background

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1: 10,000 live births [1]. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*SMN2*). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis before 6 months of age and early death due to respiratory failure before 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the prenatal period), whereas motor neurons in SMA Type 2 and Type 3 patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of *SMN1* in hopes of rescuing neurons at this critical stage. The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in

increased full-length SMN protein in SMA animal models [5,6], however, clinical studies employing several of these agents, most notably phenylbutyrate, valproic acid, and hydroxyurea, have not resulted in clinical benefit [7,8]. FDA recently approved Nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some modest promise in improving motor function; however, the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring. A single-dose IV administration study of AVXS-101 will provide information on the potential gene transfer has in treating SMA Type 1 patients and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose study that will include up to 20 Type 1 patients with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

## 5.2. Rationale for Gene Transfer to SMA Type 1 Patients

Patients with SMA Type 1 have been chosen as the target population for this gene therapy study based on studies of the natural history of this disease. The classification of SMA is shown below (Table 4) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

**Table 4: Spinal Muscular Atrophy Classification**

| Type | Age at Symptom Onset | | Maximum Motor Function | Life Expectancy | *SMN2* Copy No. |
|---|---|---|---|---|---|
| 0 | Fetal | | Nil | Days – Weeks | 1 |
| 1 | < 6 months | 1A: B-2 Weeks<br>1B: < 3 Months<br>1C: > 3 Months | Never sits | < 2 years | 1, 2, 3 |
| 2 | 6 – 18 months | | Never walks | 20 – 40 years | 2, 3, 4 |
| 3 | 1.5 – 10 Years | 3A: < 3 Years<br>3B: > 3 Years | Walks, regression | Normal | 3, 4, 5 |
| 4 | > 35 Years | | Slow decline | Normal | 4, 5 |

Source: Adapted from Kolb 2011 [10]
*SMN2* = survival motor neuron 2 gene

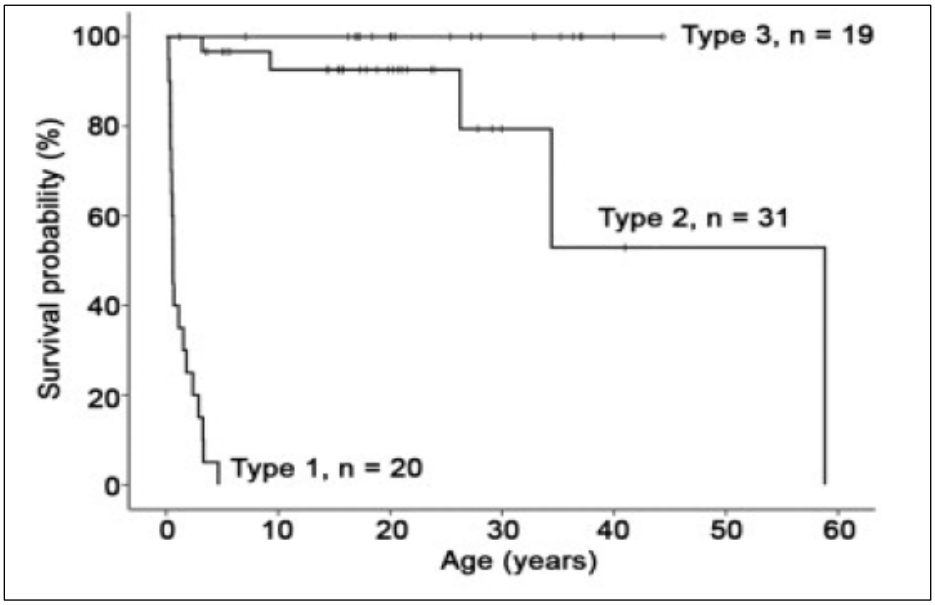
Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 month of age (Table 4). In contrast, SMA

Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3 patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [11]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10 to 15% of that produced by *SMN1* [11,12,13]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms of SMA generally have higher *SMN2* copy numbers [14,15]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, 2, or 3 SMA showed a significant correlation between *SMN2* copy number and SMA Type, as well as, duration of survival. In a large early study by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [16]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [17], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with 2 *SMN2* copies lived < 21 months, and 8/10 with 3 *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated and has also influenced our choice of the study target group.

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

**Figure 1: Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3**




n = number of patients

Source: Farrar 2013 [18]

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the prenatal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [2,3,4].

There is reason to believe that there are few safety issues to be concerned about when targeting the SMA Type 1 group in this gene therapy clinical study. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans, a high copy number of *SMN2* poses no risk (as seen in Type 2, 3, and 4 patients who have high *SMN2* copy number), allowing for use of robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV can be employed for this study because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded adeno-associated virus (AAV) vectors.

Recent studies using self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron (scAAV9.CB.SMN) show a robust post-natal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology and survival after a 1-time delivery of vector [19]. Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

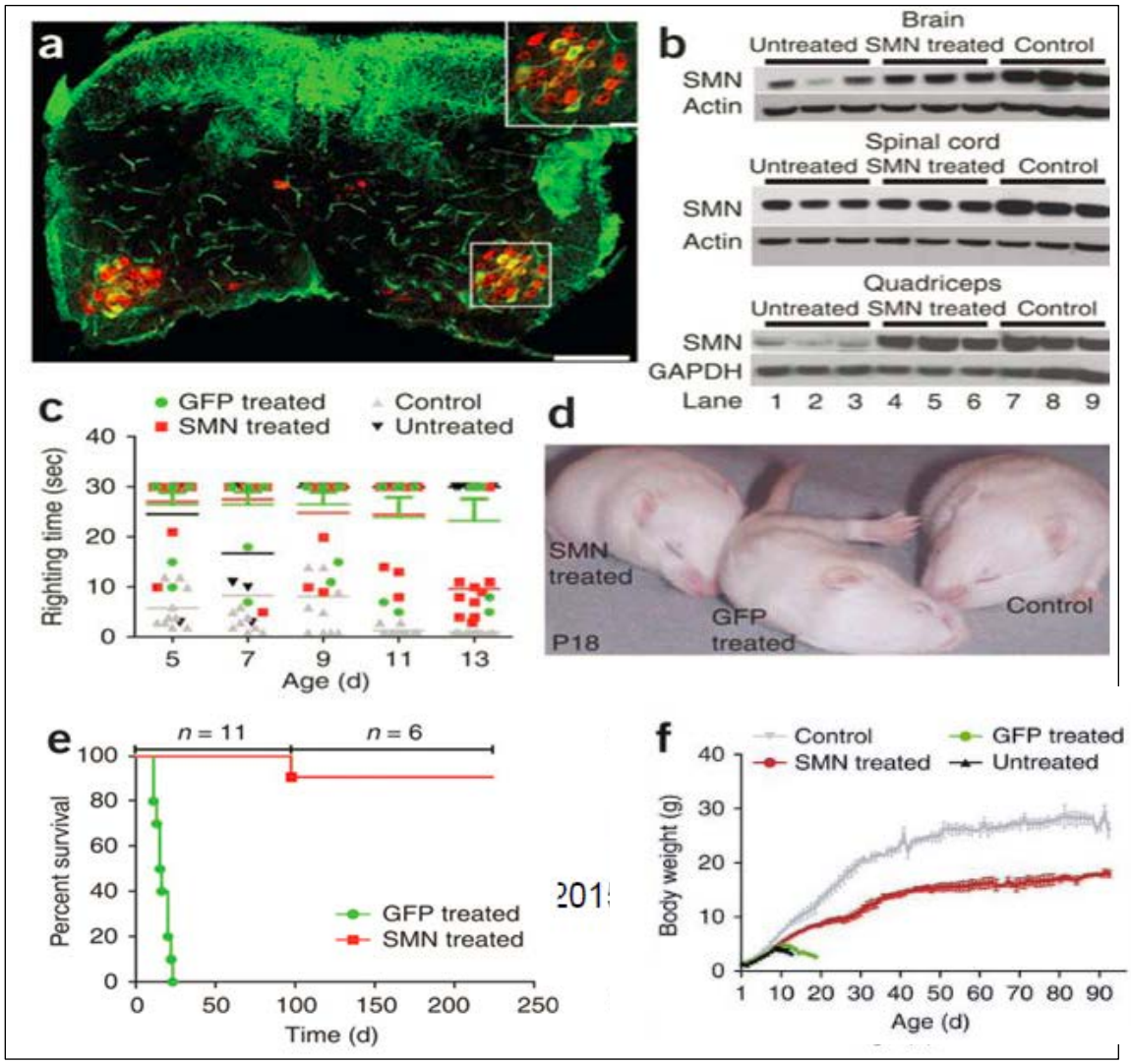
## 5.3. Non-clinical Studies

A mouse model was developed by the [redacted] after a generation of multiple variants. It was found that the double transgenic, referred to as the SMNΔ7 mouse, provided the most suitable model to study gene transfer [20]. Studies performed in the [redacted] have shown that injecting $5 \times 10^{11}$ viral genomes of scAAV9.CB.SMN into the facial vein on Day 1 old mice rescues the SMNΔ7 mouse model [19]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.GFP treated mice. SMN transduction was shown by real time polymerase chain reaction (RT-PCR) in the mice. GFP transduction was observed by microscopy. Both constructs were in AAV9 and had transduction of motor neurons. SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMNΔ7 mice (although lower than wild type [WT] controls). SMNΔ7 animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on post-natal Day 1 were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and green fluorescent protein (GFP)-treated SMA animals showed difficulty at P5, however, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated

controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMNΔ7 animals compared with GFP-treated SMNΔ7 animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a 'chimeric' animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

**Figure 2: Study Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves**

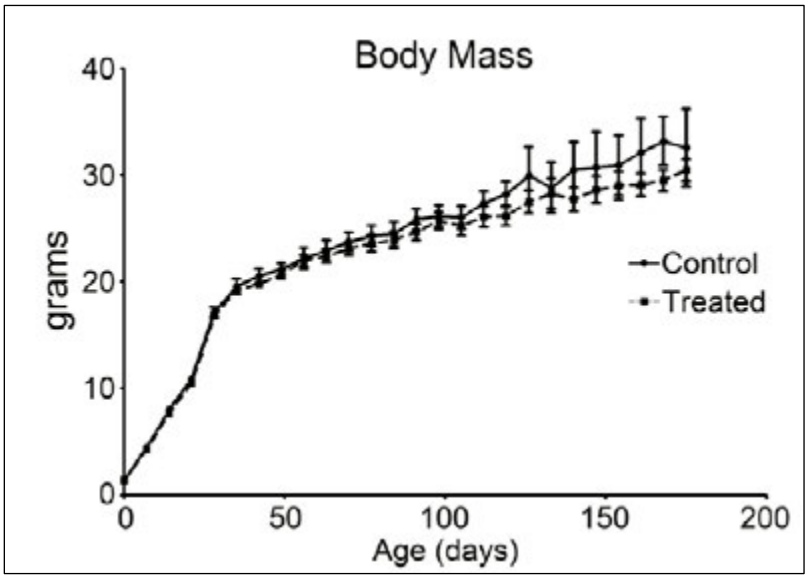



Source: Foust 2010 [19]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type
a)Shows transduced motor neurons in lumbar spinal cord

b) Western Blots of SMN expression in CNS and muscle
c)Improved righting ability of SMN-treated- similar to WT controls by P13
d) SMN-treated are larger than GFP-treated at P18
e)Survival of SMN-treated markedly improved compared to GFP- treated
f) Body weight increased in SMN-treated vs GFP

Toxicology biodistribution studies were generated by the [redacted] [data on file]. In the non-Good Laboratory Practice (GLP) studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with AVXS-101. To assess toxicity and safety, AVXS-101 was injected into P1 wild type Friend Virus B-Type (FVB) mice with either vehicle (3 males/6 females) or $3.3 \times 10^{14}$ vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the SMNΔ7 mouse model [19]. P1 mice were used in anticipation of simulating potential clinical studies in infants. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

**Figure 3 Body Mass of Treated and Control Mice Showed No Difference**




At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies including complete blood counts with differentials. At 90, 120 and 180 days post-injection, blood was collected for clinical chemistries assessment (alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase, creatinine, blood urea nitrogen [BUN], electrolytes, and creatine kinase [CK]). For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. There were no clinically significant results observed during from the hematology, clinical chemistry, and histopathology portions of the study and trends of both groups were comparable. Of note, no significant lesions were present in any brain or spinal cord sections, although, the sections were frozen and thicker than 5 microns which made cellular morphology obscure and subtle changes may not have been identified.

In the safety study for the 4 male Cynomolgus Macaques, animals were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The AVXS-101 vector was administered 1 time by catheterization of the saphenous vein with a dose of $6.7 \times 10^{13}$ vg/kg, which corresponds to the lowest dose tested for which SMNΔ7 mice showed a significant increase of survival. Animals were followed for 6 months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using Enzyme-linked ImmunoSpot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

In these non-GLP studies, the serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The NHP patient animals mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [data on file].

In pivotal GLP compliant 3-month mouse toxicology studies, the main target organs of toxicity were the heart and liver. Following intravenous infusion in the mouse, vector and transgene were widely distributed with the highest expression generally observed in heart and liver, and substantial expression in the brain and spinal cord. AVXS-101-related findings in the ventricles of the heart were comprised of dose-related inflammation, edema and fibrosis, and in the atrium, inflammation and thrombosis. Liver findings were comprised on hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. A no observable adverse effect level (NOAEL) was not identified for AVXS-101-related heart and liver findings in the mouse, and the Maximum Tolerated Dose was defined as $1.5 \times 10^{14}$ vg/kg, providing a safety margin of approximately 1.4-fold relative to the recommended therapeutic dose of $1.1 \times 10^{14}$ vg/kg. The translatability of the observed findings in mice to primates is not known at this time.

## 5.4. Clinical Studies

First-in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received the low dose used in this study (equivalent to a dose that doubled mouse lifespan in the SMNΔ7 Mouse potency assay) and Cohort 2 (n = 12) received the high dose used in this study (equivalent to a dose that restored mouse lifespan to greater than 200 days or "full life" in the SMNΔ7 Mouse potency assay). The dose received by Cohort 2 patients in AVXS-101-CL-101 (proposed therapeutic dose) has been demonstrated to be equivalent to the dose to be used in the AVXS-101-CL-303 study by direct testing using improved analytical methods.

Preliminary data as of 15 September 2016 indicate that treatment with AVXS-101 results in broad improvements in survival, motor function, pulmonary function, and nutritional function. All patients in Cohort 2 (proposed therapeutic dose) showed improvements in survival, as defined by Finkel et al 2014 [21], with no deaths or requirements for permanent ventilation ≥ 16 hours/day for ≥ 14 consecutive days through 15 September 2016. The median age at last follow-up for Cohort 2 was 17.3 months, with the oldest patient at 27.4 months of age. One patient in Cohort 1 (low dose–cohort) had a pulmonary event of increased use of bi-level

positive airway pressure in advance of surgery related to hypersalivation, a condition experienced by some SMA patients. The event was determined by independent review to represent progression of disease and not related to AVXS-101.

As of September 15, 2016, improvements in motor function, as assessed by the CHOP-INTEND scores, were observed with mean increases of 9.0 points in Cohort 1 and 24.8 points in Cohort 2. The CHOP-INTEND scores in Cohort 2 were ≥ 40 points for 11/12 patients, ≥ 50 points for 9/12 patients, and ≥ 60 points (normal) for 3/12 patients.

As of September 15, 2016, patients in Cohort 2 consistently achieved and maintained key developmental motor milestones as summarized below:

- 11/12 patients achieved head control, 7/12 patients could roll, 11/12 patients could sit with support, and 8/12 patients could sit unassisted, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016
- 7 patients were able to feed themselves, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016, and 5 patients were speaking (1 bilingual)
- 2 patients were walking independently, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016. These 2 patients each achieved earlier and important developmental milestones such as crawling, standing with support, standing alone, and walking with support

As of September 15, 2016, AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in this study. A total of 118 treatment-related AEs were reported (34 serious adverse events [SAEs] and 84 non-serious- adverse events [AEs]). Two SAEs were deemed treatment-related in 2 patients, and 3 AEs were deemed treatment-related in 2 patients. All treatment-related events consisted of clinically asymptomatic liver enzyme elevations that resolved with prednisolone treatment. There were no clinically significant elevations of gamma glutamyl transferase (GGT), alkaline phosphatase or bilirubin, and as such, Hy's Law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

In summary, through September 15, 2016, the consistently positive clinical observations are remarkably different from that described in extensive natural history studies, clinical publications, the experience of seasoned clinicians, and concurrent SMA Type 1 studies with other therapies. These significant and clinically meaningful responses in patients treated with AVXS-101 indicate preliminary clinical evidence of a treatment effect that addresses an unmet need in this devastating pediatric disease.

A full understanding of all the risks associated with AVXS-101 is not known at this time. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 study, which is believed to be a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the study were accompanied by clinical sequelae. Patients could experience an allergic response to AVXS-101. Patients could also develop an immune response to the AAV9 viral vector, which could prevent future use of gene transfers using this vector.

Taken together, results from the clinical and non-clinical studies support further clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objectives

The co-primary objectives are to:

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

## 6.2. Secondary Objective

The co-secondary objectives are to:

- Determine the effect of AVXS-101 on the on the ability to thrive defined as achieving all of the following at 18 months of age
  - Does not receive nutrition through mechanical support (e.g., feeding tube)
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device, for patients issued a Trilogy 100 BiPAP device

## 6.4. Safety Objectives

The safety objectives are to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) [9] Grade 3 or higher, unanticipated, treatment-related toxicity.

# 7. INVESTIGATIONAL PLAN

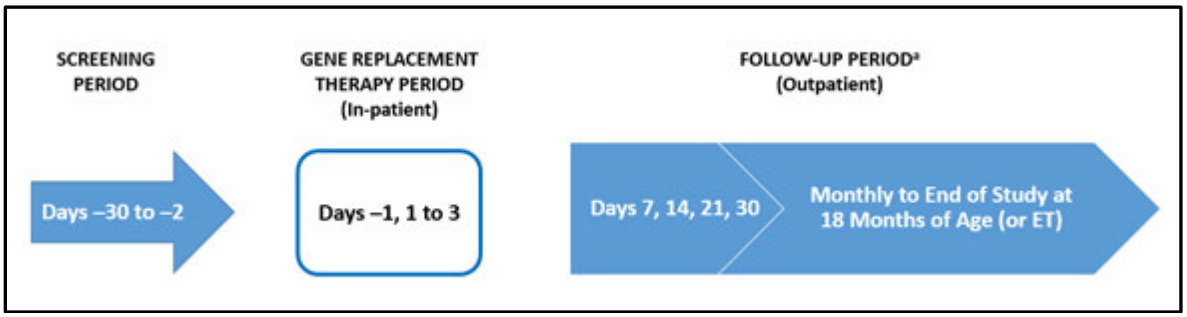
## 7.1. Overall Study Design

This is a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) that will enroll up to twenty (20) patients with SMA Type 1who may be either symptomatic or pre-symptomatic with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least 15 patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first 3 patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at 1-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

The study includes 3 study periods: screening, gene replacement therapy, and follow-up (Figure 4). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a 1-time IV infusion of AVXS-101 at a dose equivalent to the dose received by the second dosing Cohort in the Phase 1 study over approximately 60 minutes and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within 7 days.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days **after** the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients will be asked to roll over into the long-term follow-up study.

**Figure 4: Study Design**




Note: After the End of Study visit at 18 months of age, eligible patients will be asked to roll over into the long-term follow-up study.
ET = early termination
[a] All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first 3 patients to allow review of the safety analysis from 6 time points (day 1, 2, 7, 14, 21, and 30 visits) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

The first 3 patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-1-month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first 3 patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first 3 ITT patients, AveXis will remove the 4-week interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first 3 ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion in accordance with the specified guidelines for tapering (Section 9.2.1).

A schedule of study assessments is provided in Appendix 5. Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined in Section 14.1.1.2) will also be assessed. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development© (Version 3) (Section 11). Safety will be assessed through monitoring AEs, concomitant

medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (Section 12). Additionally, a Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment (Section 13.1.1.1 and Section 15). This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

## 7.2. Number of Patients

Up to twenty (20) patients that meet the study entry criteria will be enrolled to enable enrollment of at least 15 patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

## 7.3. Criteria for Study Termination

An independent DSMB will conduct quarterly and ad hoc reviews of the emerging safety data throughout the study as described in Section 15.

The study will be completed as planned but may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment
- DSMB can recommend early termination of the study for safety reasons
- Study is terminated by Sponsor
- Regulatory Authority recommendation

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients with SMA Type 1 who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) with proven biallelic- mutations of the *SMN1* gene and 1 or 2 copies of the *SMN2* will be enrolled in this study. Patients may be of any racial, ethnic, or gender background.

## 8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Patients with SMA Type 1 as determined by the following features:
    a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))
2. The first 3 patients enrolled must meet the criteria for the Intent-To-Treat population
3. Patients must be < 6 months (< 180 days) of age at the time of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics [26]
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

## 8.2. Patient Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

    Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours/day over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing

4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards [25]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for the treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (GGT, ALT, and AST > 3 × ULN; bilirubin ≥ 3.0 mg/dL; creatinine ≥ 1.0 mg/dL; hemoglobin < 8 or > 18 g/dL; white blood cells [WBC] > 20,000/cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational Cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing. Inhaled albuterol specifically

prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study

15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)
16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form
19. Gestational age at birth < 35 weeks (< 245 days)

## 8.3. Patient Withdrawal Criteria

Patients may be discontinued from the study for the following reasons:

- Death

– An autopsy will be requested for any patient who expires following participation in a gene replacement study [25] (see Autopsy Plan in Appendix 1)

- Failure to comply with protocol-required visits or study procedures for 3 or more consecutive visits that are not rescheduled, unless due to hospitalization
- Parent(s)/legal guardian(s) withdraws consent
- Investigator discretion

Early termination procedures should be completed within 14 days for any patient who prematurely discontinues the study for any reason, as indicated in Appendix 5.

# 9. TREATMENT OF PATIENTS

It is the responsibility of the Investigator to ensure the safe storage and administration of gene replacement therapy.

## 9.1. Description of Product

The biological product is a non-replicating recombinant AAV9 containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed, and the resulting protein is produced. The biological product, called AVXS-101 (formerly scAAV9.CB.hSMN), expresses the human SMN protein in transduced cells.

**Table 5: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name:** | AVXS-101 |
| **Dosage Form:** | Equivalent to the dose received by the second dosing Cohort in the Phase 1 study |
| **Unit Dose** | $1.1 \times 10^{14}$ vg/kg; Equivalent to the dose received by the Cohort 2 in the Phase 1 study (AVXS-101-CL-101) as determined by direct product testing with improved analytical methods. |
| **Route of Administration** | Intravenous infusion |
| **Physical Description** | AVXS-101 is a clear, colorless liquid. |

## 9.2. Prior and Concomitant Medications

Prior and concomitant medications will be captured in the electronic Case Report Form (eCRF) from 2 weeks prior to administration of gene replacement therapy through the last study visit.

### 9.2.1. Prophylactic Administration of Prednisolone

An antigen specific T-cell response to the AAV vector was observed in the ongoing Phase 1 clinical study (AVXS-101-CL-101) investigating AVXS-101 treatment via IV infusion. This is an expected response between 2 to 4 weeks following gene replacement therapy. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression.

In an attempt to dampen the host immune response to the AAV based- therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell

response are ≤ 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline:

- Until at least 30 days post-infusion: 1 mg/kg/day
- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/day
- Week 9: prednisolone discontinued

If the AST or ALT values are > 2 X ULN, or if T-cell response is ≥ 100 SFC/$10^6$ PBMCs after 30 days of treatment, the dose of prednisolone will be maintained until the AST and ALT values decrease below threshold. If T-cell- response continues past Day 60, Investigator discretion should be used considering risk benefit for maintaining prednisolone. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient.

### 9.2.2. Prohibited Medications

Concomitant use of any of the following medications is prohibited:

- Drugs for treatment of diabetes, myopathy or neuropathy
- Therapy received with the intent to treat SMA (e.g., nusinersen, valproic acid)
    - Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing.
    - Inhaled β-agonists may be used to treat respiratory complications of SMA provided such medications are dosed at clinically appropriate levels
- Any investigational medication other than AVXS-101 is prohibited during the study
- Ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of starting the study (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)

Corticosteroid usage following completion of the prednisolone taper is permissible as part of routine clinical management. The use of corticosteroids in such circumstances should be documented appropriately as a concomitant medication, and the event precipitating its usage should be appropriately documented as an adverse event.

Should the use of corticosteroids (aside from inhaled corticosteroids for bronchospasm) be considered as part of care during the course of the prednisolone taper, this medical management should be discussed with the medical monitor.

## 9.3. Treatment Compliance

AVXS-101 will be administered as a 1-time IV injection.

## 9.4. Randomization and Blinding

This is an open-label study.

# 10. STUDY PRODUCT MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in accordance with current Good Manufacturing Practices (cGMP). Investigational product accountability logs will be maintained by the clinical pharmacy.

## 10.1. Study Product

AVXS-101

## 10.2. Study Product Dose and Dose Justification

Patients will receive a 1-time dose of AVXS-101 at $1.1 \times 10^{14}$ vg/kg, equivalent to the dose received by Cohort 2 in the Phase 1 study via IV infusion administered in the ongoing Phase 1 clinical study (AVXS-101-CL-101).

Two doses are being studied in the ongoing Phase 1 clinical study (AVXS-101-CL-101); the higher dose (dose received by the Cohort 2 patients) was chosen for the present study as preliminary data demonstrated both a dose response and significant clinical benefit thus identifying it as the proposed therapeutic dose. In the Phase 1 study, AVXS-101 demonstrated a dose response, with efficacy greater as observed by motor milestone achievement and CHOP-INTEND scores at the higher dose (received by Cohort 2) than the lower dose (received by Cohort 1). Direct testing of the actual lot of Investigational Medicinal Product (IMP) used in the AVXS-101-CL-101 study by an improved and more fully qualified analytical method has assigned a value of $1.1 \times 10^{14}$ vg/kg to the actual dose received by Cohort 2 in this Phase 1 study. The same method has been used to establish an equivalent dose for the Phase 3 IMP. This vg/kg value has been further verified in an improved and more fully qualified SMNΔ7 Mouse Biopotency assay to support a similar extension of mouse life time in direct comparative assessment between the Phase 1 and Phase 3 IMP.

## 10.3. Study Product Packaging and Labeling

AVXS-101 kits are labeled with a specific kit number and batch/lot number assigned at the cGMP facility. The content of the labeling is in accordance with the local regulatory specifications and requirements.

## 10.4. Study Product Storage

AVXS-101 kits will be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared AVXS-101 should be managed in accordance with the Pharmacy Manual.

The vessel used for delivery of the vector should be resealed in the procedure room and processed for destruction and/or return to AveXis in accord with the Pharmacy manual and applicable biohazardous waste guidelines for disposal.

## 10.5. Study Product Preparation

Preparation of AVXS-101 will be done aseptically under sterile conditions by a pharmacist and will arrive at the clinical site ready for infusion.

AVXS-101 will be received diluted with normal saline, as outlined in the Pharmacy Manual.

The total vector genome dose will be calculated based on the patient's body weight.

The dose-delivery vessel will be delivered to the designated pediatric intensive care unit (PICU) patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. The vessel will be delivered in accord with the Pharmacy Manual.

## 10.6. Study Product Administration

AVXS-101 infusion will be administered under sterile conditions in a PICU or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered 1-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose equivalent to the dose received by the second dosing Cohort in the Phase 1 study. AVXS-101 should be slowly infused over approximately 30-60 minutes, dependent upon total volume in accord with the Pharmacy Manual, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, patients should return to an appropriate designated setting to ensure close monitoring of vital signs and adverse events. Vital signs will be continuously monitored throughout the gene replacement therapy infusion as described in Section 12.1.3. Patients should be maintained in the PICU or other appropriate setting for 48 hours after the start of gene replacement therapy.

## 10.7. Dose Adjustment Criteria

The study investigates a 1-time IV infusion of AVXS-101; no dose adjustments are possible.

## 10.8. Study Product Accountability

The pharmacist or designee will maintain accurate records of the quantities of AVXS-101 received, dispensed, destroyed, and/or returned to AveXis. The pharmacist or designee will document the date and time of delivery of the dose vessel to the dose procedure room as well as the time the used vessel was returned to AveXis or destroyed as per the Pharmacy Manual.

## 10.9. Study Product Handling and Disposal

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof containers. All waste must be sealed in bags bearing the biohazard symbol and disposed of in a biohazard waste container.

All transfers must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment, such as gloves.

Any quality issue noticed with the receipt or use of AVXS-101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accord with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply AVXS-101 to a third party, allow AVXS-101 to be used other than as directed by this clinical trial protocol, or dispose of AVXS-101 in any other manner.

# 11. ASSESSMENT OF EFFICACY

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined Section14.1.1.2) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using the Bayley Scales of Infant and Toddler Development (version 3©). Efficacy assessments will be performed at the times specified in the Table of Assessments (Appendix 5) and should be the first assessments performed at any scheduled visit. All post-treatment visits will be relative to the date on which gene replacement therapy is administered except the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

## 11.1. Developmental Milestones

Developmental milestones will be assessed using relevant definitions obtained from the Bayley Scales of Infant and Toddler Development (version 3), and will be analyzed to assess efficacy (Appendix 2 and Appendix 3). Achievement of each developmental milestone will be determined by the Physical Therapist and confirmed by the central reader (as may be necessary) based on an assessment of the submitted videos (Section 11.3). Developmental milestones will be determined at each monthly visit as listed in Section 11.2.1.

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement in accordance with Appendix 5; this assessment must address all milestones/items noted on Appendix 5 that are at or below the child's expected function for age, and be recorded on video. The findings must be documented in the source. Items that are below the expected function for age that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestones of sitting independently (items 22 and 26) should be assessed at every subsequent visit, until attainment of milestone, regardless of starting point on the scale. These milestones must also be assessed at the 18 months of age visit, regardless of previous attainment.

As the Bayley Scales do not necessarily require the child to repeat previously attained milestones, it is essential that each attained milestone be captured on video.

A milestone will be considered achieved when demonstrated by a patient and observed with video capture confirmation during a physical therapy assessment or observed with video as provided by the patient's family at the patient's visit at 18 months of age.

## 11.2. Motor Function Tests

### 11.2.1. Bayley Scales of Infant and Toddler Development/Developmental Milestones

The Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 2) is a standardized, norm-referenced infant assessment of developmental functioning across 5 domains of cognitive, language, motor, social-emotional, and adaptive behavior. The Bayley Scales will be administered by a qualified Physical Therapist.

The full Bayley Scales will be administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain will be administered at each monthly visit. For patients in which English is not their first language, the language subtests (receptive communication and expressive communication) and cognitive scale portions of the Bayley will not be performed.

Each Bayley Scales/developmental milestone assessment will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and may be submitted to the vendor for review by a central reader (Section 11.3).

The following developmental milestones will be assessed:

- Ability to hold head erect without support
- Ability to roll from back to both sides
- Ability to sit with support
- Ability to sit independently, > 10 seconds; WHO [22]
- Ability to sit without support for at least 30 seconds
- Ability to crawl
- Ability to pull to stand
- Ability to stand with assistance
- Ability to stand alone
- Ability to walk with assistance
- Ability to walk alone

### 11.2.2. CHOP-INTEND

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA Type 1, and will be administered by a qualified Physical Therapist.[23,24] The CHOP-INTEND scale examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions (Appendix 4). Anti-gravity movements in assisted rolling, ventral suspension, and supported standing will also be measured.

The CHOP-INTEND will be performed at screening, Day -1, and at each scheduled visit from Day 7 through the End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5). If Day -1 CHOP-INTEND assessment cannot be conducted, a CHOP-INTEND assessment must be completed on Day 1 prior to dose administration.

Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not undergo any additional CHOP-INTEND examinations.

Each CHOP-INTEND exam will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and submitted to the vendor for review by a central reader as may be necessary (Section 11.3).

## 11.3. Video Evidence

Physical therapy assessments (Bayley Scales and CHOP-INTEND) required at each study visit will be video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

## 11.4. Compound Motor Action Potential

Peroneal nerve CMAP amplitude will be measured by a qualified electrophysiologist, at all clinical sites capable of performing this assessment, using the procedures as described in the CMAP Manual (Appendix 5). CMAP will be measured at screening, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5).

The CMAP data will be collected for centralized review and interpretation.

Sites that do not have equipment or appropriately experienced personnel required to perform CMAP measurements will not be required to perform these assessments.

# 12. ASSESSMENT OF SAFETY

## 12.1. Safety Parameters

Safety parameters include physical examinations, pulmonary examinations, vital signs, capillary blood gas assessments, weight and length measurements, 12-lead electrocardiograms (ECGs), 12-lead Holter monitor recordings, echocardiograms, swallowing tests, laboratory assessments, adverse event monitoring, and photographs of the infusion site. In general, safety assessments will be performed at the times specified in the Table of Assessments (Appendix 5). All post-treatment visits are relative to the date on which gene replacement therapy is administered until the patient reaches 14 months of age, at which point all visits are relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

### 12.1.1. Demographic/Medical History

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/weight/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any
- Historical feeding support, if any

Patients are encouraged to follow all routinely scheduled immunizations, as recommended by the Center for Disease Control (CDC), throughout the study. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics [26].

### 12.1.2. Physical Examinations

Physical examinations will be conducted by the Investigator or Sub-Investigator at each scheduled visit, except Day –1 (Appendix 5). The Day 1 physical examination will be

performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

### 12.1.3. Vital Signs/Weight and Length

Vital sign parameters include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry. Vital signs will be obtained at each study visit (as specified in Appendix 5). On Day 1, vital signs will be continuously monitored throughout the gene replacement therapy infusion and recorded pre-dose and every 15 (± 5) minutes for the first 4 hours after the start of infusion, and then every hour (± 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.

Weight and length will be measured at each study visit (as specified in Appendix 5). On Day 1, weight and length will be measured pre-dose.

### 12.1.4. Electrocardiogram

A 12-lead ECG will be performed at screening, Day –1, pre-dose on Day 1, Day 2, Months 3, 6, 9, and 12 visits and every 6 months thereafter. A 12-lead ECG will also be performed at the End of Study visit when the patient reaches 18 months of age (or early termination) (Appendix 5). For patients enrolled in the study prior to amendment 3 and irrespective of the study schedule, after signing an updated informed consent form, a 12-lead ECG will be conducted at the next scheduled visit and then in accordance with the Schedule of Assessments (Appendix 5). Additional ECG monitoring will be at the discretion of the Investigator as per local institutional guidelines.

The ECG will be interpreted locally by a cardiologist. The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

### 12.1.5. 12-Lead Holter Monitor

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 72 hours from Day –1 (24 hours prior to the start of gene replacement therapy infusion) through 48 hours after the start of infusion. On Days -1 to Day 3, serial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours

- 48 hours

Twenty-four-hour Holter monitoring will also be performed at the 3, 6, 9, and 12-month visits and every 6 months thereafter. Twenty-four-hour Holter monitoring will also be performed at the End of Study visit when the patient reaches 18 months of age (or early termination). For patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent form, a 24-hour Holter monitor will be performed at the next scheduled visit and then in accordance with the Schedule of Assessments (Appendix 5).

Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist within 24 hours of data upload. The Sponsor physician or designee will be notified of any safety concerns from the centralized review, and the safety management plan will be followed for documenting and reporting of AEs/SAEs.

### 12.1.6. Echocardiogram

A standard transthoracic echocardiogram will be performed at screening, at 3, 6, 9, and 12-month visits and every 6 months thereafter. An echocardiogram will also be performed at the End of Study visit when the patient reaches 18 months of age (or early termination) (Appendix 5). For patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent form, an echocardiogram will be performed at the next scheduled visit and then in accordance with the Schedule of Assessments (Appendix 5).

### 12.1.7. Pulmonary Examinations

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit except Day 1 (Appendix 5). Prior to study entry, a pulmonologist or appropriate individual as per standard institutional practice will review and document ventilator usage in the 2 weeks prior to screening.

Patients may be fitted with non-invasive ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Non-invasive ventilatory support equipment will be provided by AveXis through a third-party vendor. Should the patient require non-invasive ventilatory support at any time during the study, the equipment provided by AveXis must be used.

Patients requiring non-invasive ventilatory support will be asked to bring their machine(s) to each study visit such that the study staff can remove an SD card which captures actual usage data. The hours per day usage data for each day between visits will be extracted with software provided by the device manufacturer into a format that will be transferred/transcribed to the clinical database.

### 12.1.8. Swallowing Test

A swallowing test will be performed at screening (at the Investigator site), every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5) to determine if the patient has signs of aspiration. If the test is positive for aspiration, there may be a recommendation for the patient to use an alternate method

to oral feeding for the duration of the study at the determination of the Investigator and treating clinician.

### 12.1.9. Photographs of Infusion Site

Photographs will be taken of the infusion site at each scheduled visit from Day 1 (pre-dose) through Day 30 (Appendix 5) to monitor healing of the infusion site. AveXis will provide a secure and confidential upload process for transfer and storage of the photographs from the investigative sites to a contracted third-party vendor that will compile and arrange photographs as per AveXis requirements. Any/all photographs received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

### 12.1.10. Laboratory Assessments

Blood samples will be collected at each scheduled visit, except Day 1 and Day 3 (as specified in Appendix 5). On Day -1, blood and urine samples will be processed locally for receipt of results prior to the start of gene replacement therapy infusion. Any clinically significant laboratory value will be repeated at the discretion of the Investigator.

In most instances, blood samples will be collected and shipped to a central laboratory, however, at the discretion of the Investigator, samples may be processed locally for emergent safety monitoring or other logistical or technical reasons that warrant samples to be processed locally. Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's Clinical Laboratory Improvement Amendment (CLIA) CLIA-certified local laboratory to ensure receipt of results prior to dosing.

**Table 6: Total Blood Volume**

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Screening | Hematology, chemistry/CK-MB, virus serology, immunology sample (AAV9 Ab only), diagnostic confirmation sample | 16.9 |
| Day –1 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 2 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 7 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 14 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 21 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 30 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 60 | Hematology, chemistry/CK-MB, | 3.6 |
| Month 3/4/5/7/8/10/11/13/14/16/17 | Hematology, chemistry | 25.3 |
| Month 6/9/12/15 | Hematology, chemistry/CK-MB | 14.4 |
| End of Study/ET | Hematology, chemistry/CK-MB | 3.6 |
| | **Maximum Total Volume for Study [a]** | **96.2** |

ET = early termination

[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits, provided T-cell responses are not elevated at Day 30 requiring additional surveillance samples and virus serology is not positive at screening requiring additional testing

[b] Immunology sample for IFNγ- ELISpots requires 4-6 mL whole blood. Immunology sample for ELISA requires 1 mL whole blood. When drawn at the same visit, 4-6 mL is sufficient for both assays.

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety labs
    a. Chemistry
    b. Hematology
    c. CK-MB
2. Interferon gamma (IFNγ) ELISpots to detect -T-cell responses
3. Serum antibody to AAV9 and SMN
4. Genetic reconfirmation testing

If there is not sufficient blood volume to include the genetic reconfirmation testing sample at the screening visit, patient must return before Visit 2. All patients must have genetic reconfirmation testing completed.

#### 12.1.10.1. Hematology

Hematology analysis will include a complete blood count with differential and platelet count with smear. Samples will be collected and shipped in accordance with the laboratory manual

provided by the central laboratory. Blood samples for hematology analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 5).

Immediate/same-day hematology analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory. Investigators will receive hematology results from all study visits from the central laboratory.

#### 12.1.10.2. Blood Chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 5).

Immediate/same-day chemistry analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory.

- Chemistry analysis will include the following at all study visits:
- Serum GGT
- AST/ALT
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Total creatine kinase
- Creatinine
- BUN
- Electrolytes
- Alkaline phosphatase

Creatine kinase (CK-MB) will be collected at Screening, Day 7, Day 30, Day 60, Month 6, 9, 12, 15 months of age, and at 18 months of age/End of Study.

Investigators will receive chemistry results from all study visits from the central laboratory (except Day -1).

#### 12.1.10.3. Urinalysis

Urine samples will be collected in accordance with the laboratory manual provided by the central laboratory at all study visits except Day 1 and Day 3 (Appendix 5). Day -1 urinalysis will be performed as per investigational site standard procedures at the local laboratory. Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin
- Blood
- Protein
- Red Blood Cell
- White Blood Cell
- Squamous epithelial cells
- Casts
- Crystals
- Bacteria
- Yeast

#### 12.1.10.4. Virus Serology

The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have HIV or positive serology for hepatitis B or C or Zika virus, administration of AAV vector may represent an unreasonable risk; therefore, negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected at screening (Appendix 5) and shipped in accordance with the laboratory manual provided by the central laboratory.

#### 12.1.10.5. Capillary Blood Gas

Capillary blood gas will be completed locally at Day –1 and Day 2 (Appendix 5). A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the

patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

#### 12.1.10.6. Immunology Testing (ELISA and IFNγ- ELISpots)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA), and to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN. Blood samples will be collected at screening (ELISA anti-AAV9 only), Day 7, Day 14 (ELISA anti-AAV9/SMN only), Day 21 (ELISA anti-AAV9/SMN only), and Day 30 (Appendix 5). Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.

#### 12.1.10.7. AAV9 Antibody Screen in Mother

There is potential that the biological mother of the patient may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or, theoretically, via placental transfer in utero. Informed consent will be requested from the biological mother of the patient to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein at screening and shipped to the central laboratory for screening of anti-AAV9 antibodies. Mothers who test positive for antibodies to AAV9 will be asked to refrain from further feedings with breast milk.

If AAV9 antibodies are identified, the patient must desist in consuming breast milk from the biological mother.

Patients consuming banked breast milk from donor sources that cannot be test for anti-AAV9 antibodies must be transitioned to formula prior to participation.

#### 12.1.10.8. Blood for Diagnostic Confirmation Testing

A blood sample will be collected during the screening visit and shipped to the central laboratory in accordance with the laboratory manual for reconfirmation of *SMN1* deletions/mutations, *SMN2* copy number, and absence of exon 7 gene modifier mutation (c.859G>C). This will be done to ensure consistency in diagnostic testing practices.

#### 12.1.10.9. Saliva, Urine, and Stool Collection

Studies have shown that some vector can be excreted from the body for up to a few weeks after injection; this is called "viral shedding." Vector shedding can be found in the blood, urine, saliva, and stool for up to 1 week following infusion. The potential health risks associated with the shed vector are not fully known at this time; however, the health risk is thought to be low as the vector cannot replicate. Regardless, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved instructions should be provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of 2 weeks (14 days) after gene replacement therapy. Additionally, patients are prohibited from donating blood for 2 years following the vector infusion.

Saliva, urine, and stool samples will be collected for viral shedding studies at screening, 24 hours postdose-, 48 hours post-dose, Day 7, Day 14, Day 21, and Day 30 (Appendix 5). Samples will be collected, prepared, and shipped as per the laboratory manual.

A subset of patients at sites opting to participate in the viral shedding sub-study will have 24-hour total volume urine and fecal samples collected through 24 hour post-dose and through 48 hours-post dose.

# 13. ADVERSE AND SERIOUS ADVERSE EVENTS

## 13.1.1. Definition of Adverse Events

### 13.1.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur from the start of gene replacement therapy infusion through the last study visit will be collected and recorded in the eCRF.

All adverse events will be classified in accordance with the CTCAE version 4.03 outlined in Table 7.

**Table 7: Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 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 selfcare -ADL. [b] |
| 4 | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death related to AE. |

Source: Common Terminology Criteria for Adverse Events (version 4.03) [9]

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

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

Study enrollment will be interrupted should any patient experience an unanticipated CTCAE Grade 3, or higher adverse event toxicity that is possibly, probably, or definitely related to the gene replacement therapy. The event will then be reviewed by the DSMB and an evaluation will be made as to whether the study should be terminated early following the discontinuation rules.

Unanticipated CTCAE Grade 3 or higher adverse events that are possibly, probably, or definitely related to the gene replacement therapy must be reported within 24 hours to Sponsor and/or designee as per study safety management plan to ensure timely escalation to the DSMB.

#### 13.1.1.2. Serious Adverse Event

A SAE is an AE occurring during any study phase (e.g., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or comparator that fulfils 1 or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above.

All SAEs that occur after signing of the informed consent through the last study visit, whether or not they are related to the study product, must be collected and recorded on forms provided by the Contract Research Organization.

#### 13.1.1.3. Other Adverse Event

The following specific treatment-emergent AE of special interest, which may be searched using Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries, will be summarized:

- Elevated liver enzymes

Other adverse events (OAE) will be identified by the Drug Safety Physician and, if applicable, also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

## 13.2. Relationship to Study Product

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related, Probably Related, or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” then the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 13.3. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the time of vector infusion until the end of the study. Serious Adverse Event information will be collected from signing of consent form until the last study visit. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date (and time if during Visit 2)), resolution (date (and time if start date during Visit 2)), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.1.2. An AE of severe intensity may not be considered serious.

## 13.4. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of consent form until the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or e-mail to AveXis or designee.

Additional follow-up information, if required or available, should all be faxed or e-mailed to AveXis or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

AveXis is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, product-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

# 14. STATISTICS

This section summarizes key aspects of the analysis plan including definitions of co-primary, co-secondary, and [redacted] and safety endpoints, and the methods to be used to test the primary effectiveness hypothesis. Additional details regarding methods for the final data analysis will be provided in a separate Statistical Analysis Plan (SAP) which will be finalized and submitted to the Investigational New Drug application prior to the enrollment of the first patient. The SAP will detail all analyses and data displays and will be executed according to Standard Operating Procedures in a controlled environment.

## 14.1. Study Endpoints and Populations

### 14.1.1. Study Endpoints

The primary and efficacy endpoint will be compared to the null. The survival co-primary efficacy variable will be evaluated relative to literature-based historical controls (such as the Pediatric Neuromuscular Clinical Research Network [PNCR] [21]. These were selected on the basis of comparability to the target population and similarity to the investigational device.

#### 14.1.1.1. Co-Primary Efficacy Endpoint

The co-primary efficacy endpoints are:

- The proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 2), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds.
- The survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

An "acute reversible illness" is defined as any condition other than SMA that results in increased medical intervention (e.g., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (e.g., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (e.g., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of "acute." The date of "definitive intervention" shall be defined as the date of provision of a procedure (e.g., surgery, etc.) or medication (e.g., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of "definitive intervention" shall be considered the date of hospitalization or substantial escalation of care.

"Perioperative" use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.

For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

#### 14.1.1.2. Co-Secondary Efficacy Endpoint

The co-secondary efficacy endpoints are:

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [25] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy).

#### 14.1.1.4. Safety Endpoints

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated LFTs and/or unresolved LFEs
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ ELISpot to detect T cell responses to AAV9 and SMN

### 14.1.2. Statistical Analysis Populations

#### 14.1.2.1. Intent-to-Treat Population (ITT)

The ITT population will consist of symptomatic patients with biallelic- deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at < 180 days of age. The first 3 patients enrolled must meet the criteria for the Intent-to-Treat Population.

#### 14.1.2.2. Efficacy Completers Population

The efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE or experience death

#### 14.1.2.3. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101. Analyses of endpoints in this population are considered descriptive.

#### 14.1.2.4. Safety Population

The safety analysis population will consist of all patients who receive an IV infusion of AVXS-101. All safety analyses will be conducted on the safety analysis population.

## 14.2. Sample Size Calculation

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least 15 patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first 3 patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at 1-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

The 2 co-primary efficacy endpoints will be assessed in sequence: The endpoint of functional independent sitting will be assessed first and, only if this assessment meets statistical significance will the endpoint of survival be assessed.

Based upon the widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patients in this population would be expected to attain the ability to sit without support or accomplish other milestones (rolling over, standing, walking) prior to 18 months of age. Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age study visit. With the assumption for the true response rate of AVXS-101 for

the primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with α = 0.025 using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion of patients surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with biallelic- *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with α = 0.05 using a 2-sided Fisher's Exact test, comparing to the 26 age and gender matched patients from a published natural history observational study performed at 3 large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

## 14.3. Efficacy Analysis

### 14.3.1. General Considerations

This study will compare the activity of AVXS-101 administered IV versus the natural observational results from PNCR [21] in terms of functional independent sitting and survival rate. The ability to thrive and the ability remain independent of ventilatory support will also be assessed.

The analysis of the co-primary and co-secondary efficacy endpoints will be performed for the ITT and efficacy completers population. The analysis based on the ITT population will be considered as the primary analysis. In the case of missing data, observed data will be used for the analyses.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (e.g., on or before Day 1 visit).

### 14.3.2. Primary and Secondary Efficacy Analysis

Primary and secondary efficacy analyses will be based on the ITT population, those patients that are symptomatic with biallelic- deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 to the results from natural observation study (PNCR) [21].

The first co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion surviving at 14 months of age.

Primary efficacy endpoints will be examined on the ITT population. Testing for the first co-primary endpoint, functional independent sitting will first be performed using 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at $p<0.025$, will the co-primary endpoint survival improvement be tested using 2-sided Fisher's Exact test on the ITT population, comparing to matched patients from natural observational study (PNCR). This hierarchy approach strongly protects the Type I error rate.

The hypothesis for both co-secondary efficacy endpoints to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where *p* is the proportion of patients maintaining the ability to thrive/are independent of ventilatory support.

One-sided exact binomial tests will be executed for secondary efficacy analyses on the ITT population.

A sensitivity analysis will be conducted by repeating the primary efficacy analysis on the efficacy completers analysis population.

## 14.4. CHOP-INTEND Comparison

A comparison will be performed of the first 3 patients CHOP-INTEND scores to the AVXS-101-CL-101 CHOP-INTEND scores. The first 3 patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-1 month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first 3 patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first 3 ITT patients, AveXis will remove the 4-week interval between patients and proceed to dose at least

12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first 3 ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

## 14.5. Safety Analysis

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, urinalysis, immunology), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary.

Safety analyses will be conducted on safety population and summarized by subgroup and overall.

# 15. DATA SAFETY MONITORING BOARD

The DSMB is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, have experience in the management of patients with SMA Type 1 and other diseases, and in the conduct and monitoring of randomized clinical studies with interim analyses. The DSMB will be chartered to oversee the safety of patients during the conduct of the study and will act in an advisory capacity to AveXis. A detailed description of the DSMB, its role in this study, and the timing of the scheduled reviews will be described in a DSMB Charter.

The DSMB will routinely convene on a quarterly basis to review emerging safety data from the study. All available safety data from all enrolled patients will be included in such reviews, which include, but are not limited to, screen failures, enrollment status, data from safety parameters, all SAEs, and other AEs. Following each meeting, the DSMB will make a recommendation as to whether or not the accumulated safety data warrants a suspension or discontinuation of the study, a modification to the study, or any additional comments or recommendations related to safety. The DSMB will prepare and provide minutes of their meetings to AveXis who will provide copies to the regulatory authorities as appropriate.

The DSMB will also convene on an ad hoc basis within 48 hours should any patient experience an unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation.

# 16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 16.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of AveXis will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AveXis or its representatives. This will be documented in a Clinical Study Agreement between AveXis and the Investigator.

During the study, a monitor from AveXis or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts, electronic medical records)
- Record and report any protocol deviations not previously sent to AveXis
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to AveXis and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

## 16.2. Audits and Inspections

Authorized representatives of AveXis, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact AveXis immediately if contacted by a regulatory agency about an inspection.

### 16.3. Institutional Biosafety Committee

As this study involves gene therapy, the Principal Investigator must obtain approval/favorable opinion for the investigation from a designated institutional or independent biosafety committee in accordance with institutional requirements and/or guidelines.

### 16.4. Institutional Review Board/Institutional Ethics Committee

The Principal Investigator must obtain IRB/IEC approval for the investigation (Section 18.1). Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

# 17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. AveXis may also conduct a quality assurance audit any time during or after the completion of the study. Please see Section 16.2 for more details regarding the audit process.

The Investigator agrees to allow these Sponsor representatives direct access to the clinical data and supplies, dispensing and storage areas and if requested, agrees to cooperate fully or assist the Sponsor representative. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, site staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/IEC and relevant regulatory authority will also be informed.

# 18. ETHICS

## 18.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to AveXis before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## 18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 6) and are consistent with ICH/GCP, applicable regulatory requirements and the AveXis' policy on Bioethics.

## 18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the parent(s)/legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent(s)/legal guardian(s) must also be notified that they are free to discontinue the patient from the study at any time. The parent(s)/legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the parent(s)/legal guardian(s).

There will be 3 informed consent forms:

- Parent(s)/legal guardian(s) informed consent form
- Biological mother baseline AAV9 antibody screening informed consent form

- Autopsy informed consent form (Appendix 1; if the parent(s)/legal guardian(s) decline an autopsy, it will not prevent the patient from participating in the study)

# 19. DATA HANDLING AND RECORDKEEPING

## 19.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained, and all relevant observations and data related to the study will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion criteria, product administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

## 19.2. Inspection of Records

AveXis or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the product storage area, study product stocks, product accountability records, patient charts and study source documents, and other records relative to study conduct.

## 19.3. Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not < 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years included in ICH shall be followed.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, patient / subject screening records, patient / subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB/IEC documentation, an approved sample ICF, drug / product accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

# 20. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

# 21. LIST OF REFERENCES

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# 22. APPENDICES

# APPENDIX 1. AUTOPSY PLAN

An autopsy will be requested for any patient who receives gene replacement therapy and expires. The autopsy and tissue collection will be performed by a contracted vendor who will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions will be used to perform the autopsy and pathology necessary to determine the cause of death.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes, including up to 7 sections or pieces from each organ and each region of the spinal cord. Upon collection, these tissue samples will be provided to AveXis for analysis. Tissue analysis will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results will demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

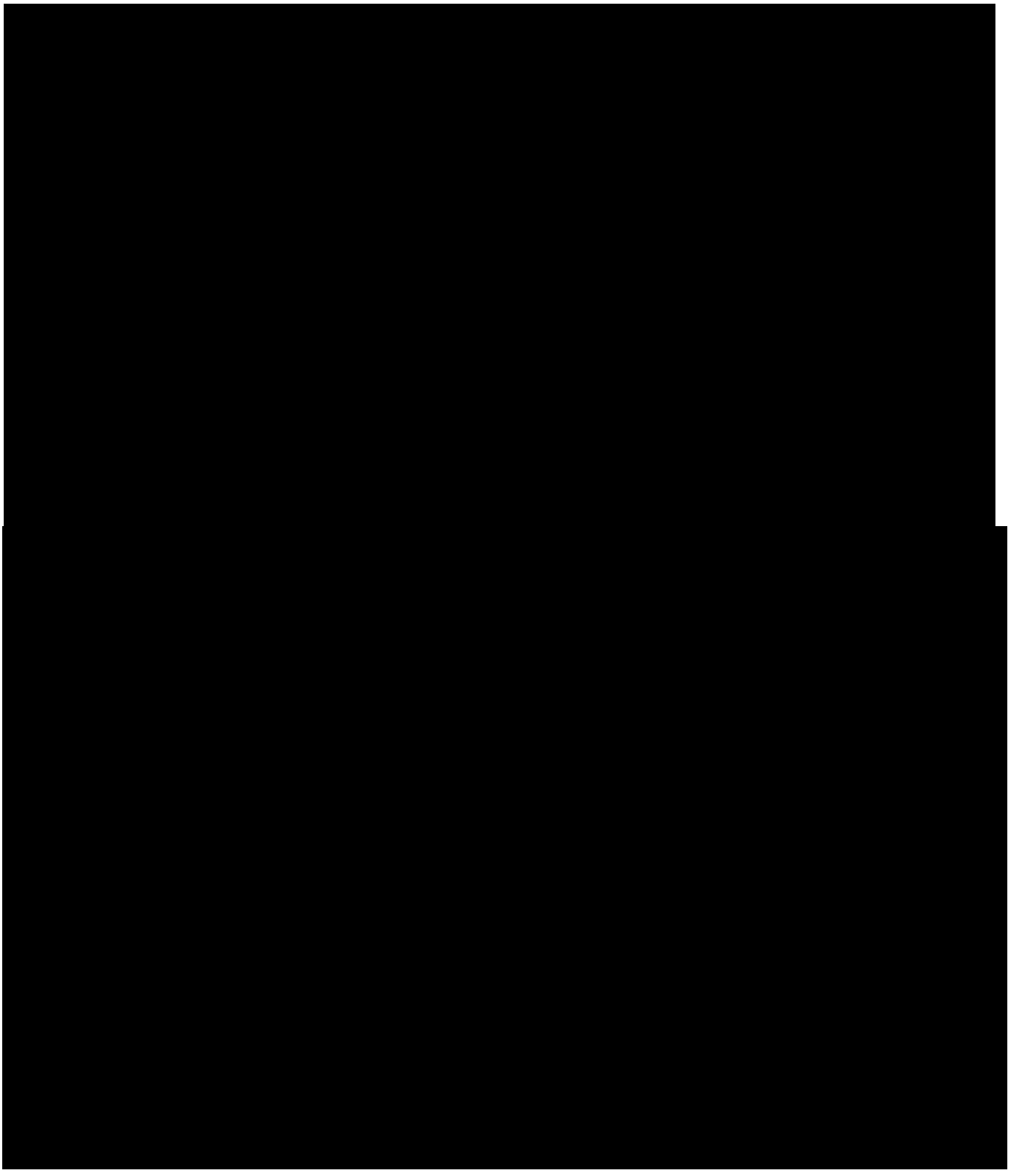
Specifically, tissue samples from the spinal cord, muscles, and organs will be collected as indicated in Table 8. Tissue samples will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

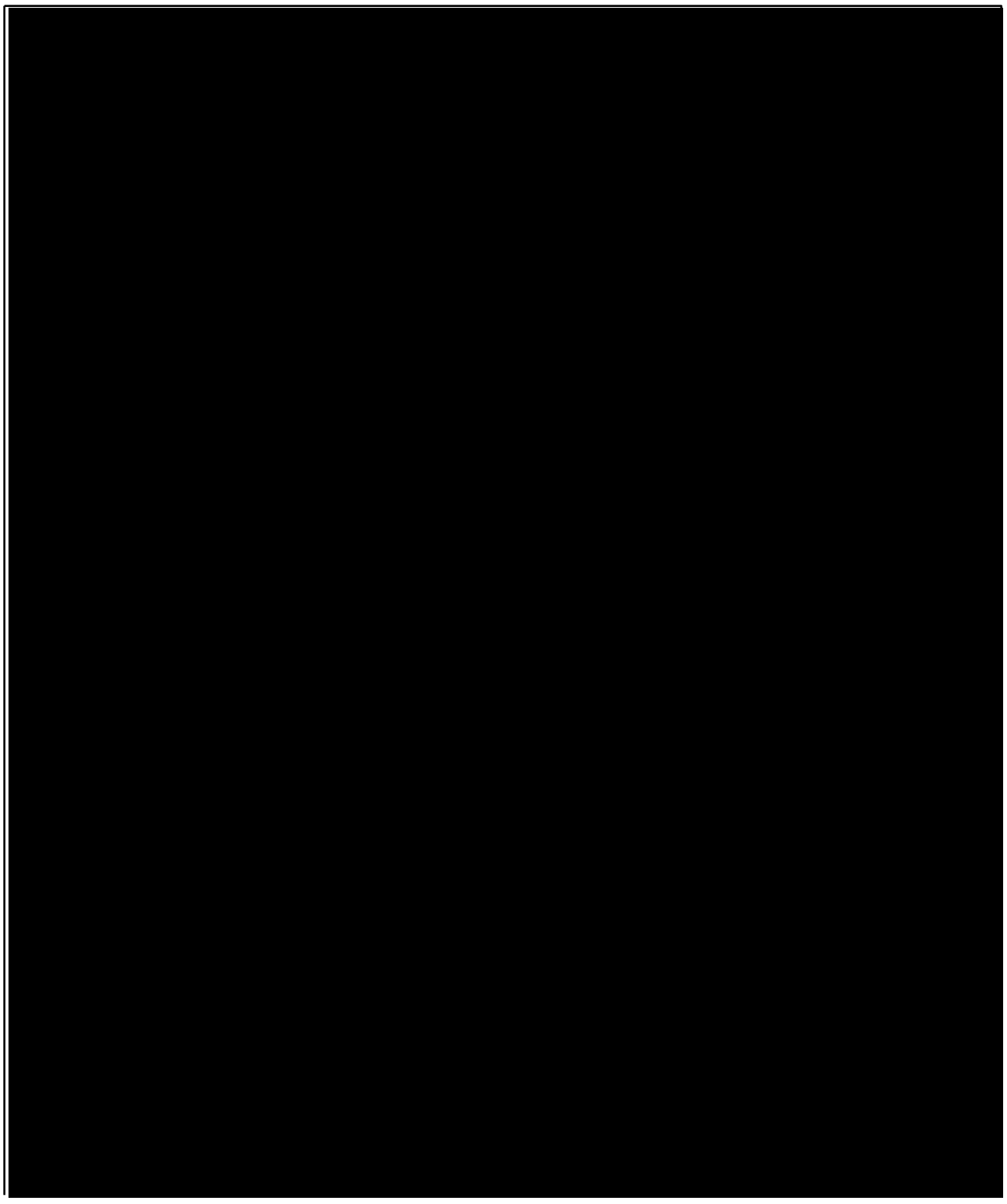
Families will be asked to consent to the autopsy and authorize tissue collection prior to any sign of moribund or death by the clinical team conducting the study. There are distinct forms for the formal autopsy and for the research tissue collection. This will allow families the flexibility to participate in one or both of the research activities. Declining an autopsy will not prevent patients from participating in the study.

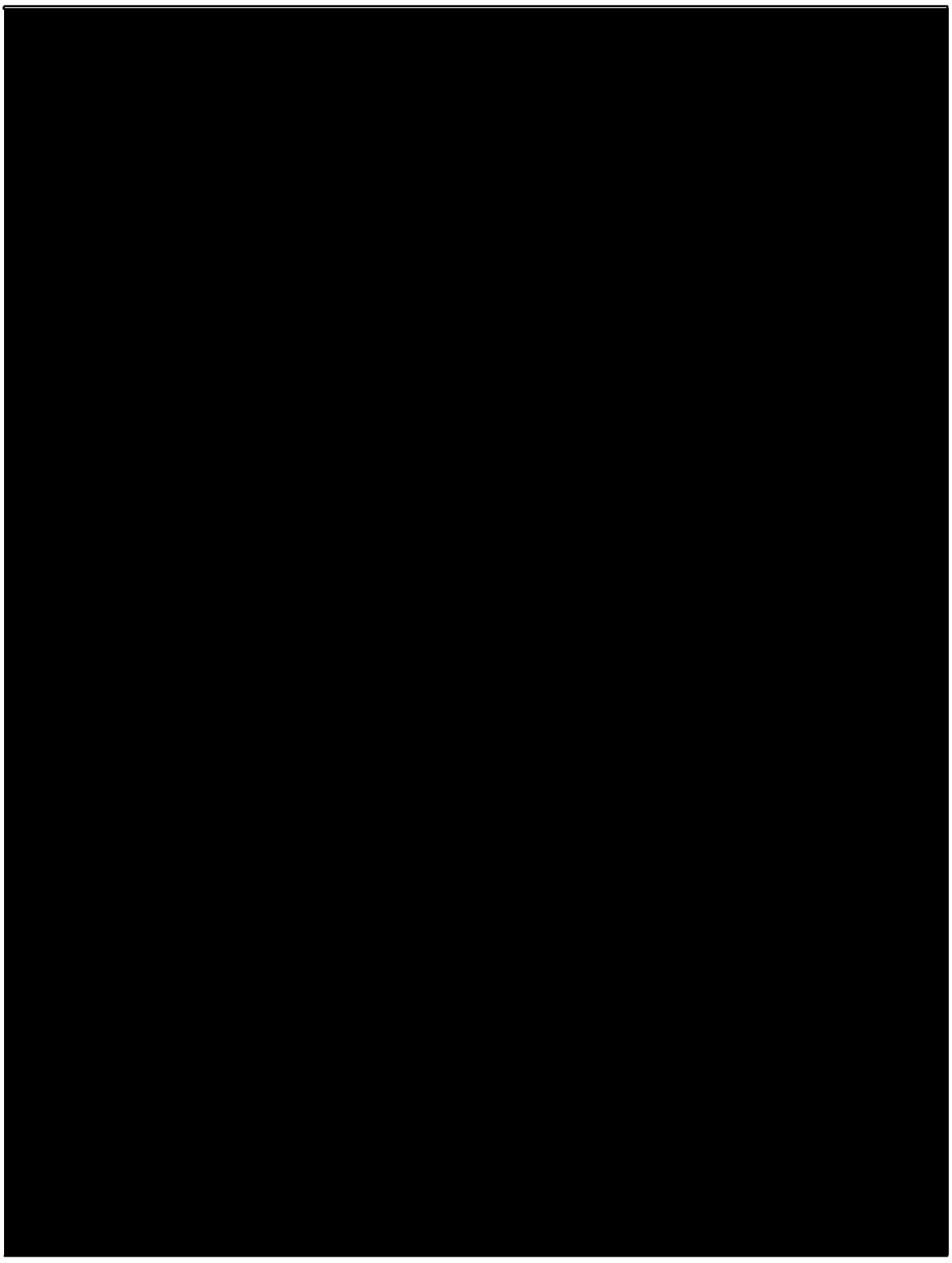
**Table 8: Tissue Sample for Analysis**

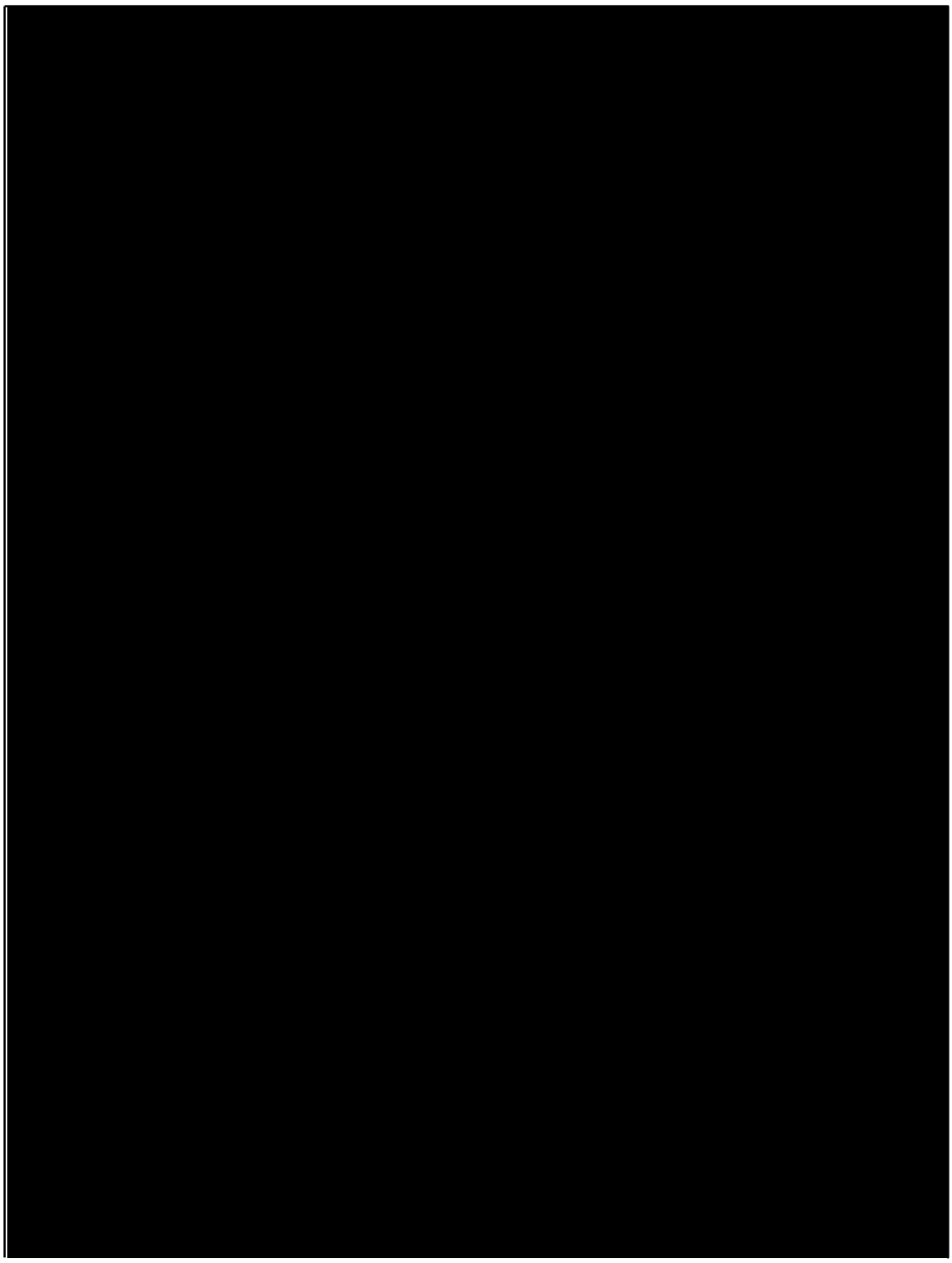
| Brain | Spinal Cord | Muscles | Organs |
|---|---|---|---|
| Motor cortex | Cervical spinal cord | Diaphragm | Spleen |
| Layer 5 motor cortex | Thoracic spinal cord | #6/#7 Rib with intercostal muscle and nerve | Kidney |
| Brain stem | Lumbar spinal cord | Psoas muscle | Small intestine |
| | Sacral spinal cord | | Large intestine |
| | Dorsal root | | Pancreas |
| | Cervical level | | Stomach |
| | Ventral root | | Lung |
| | Cervical level | | Heart |
| | DRG root | | Liver |
| | Cervical level | | Inguinal lymph node |
| | Cerebrospinal fluid | | Gonads |

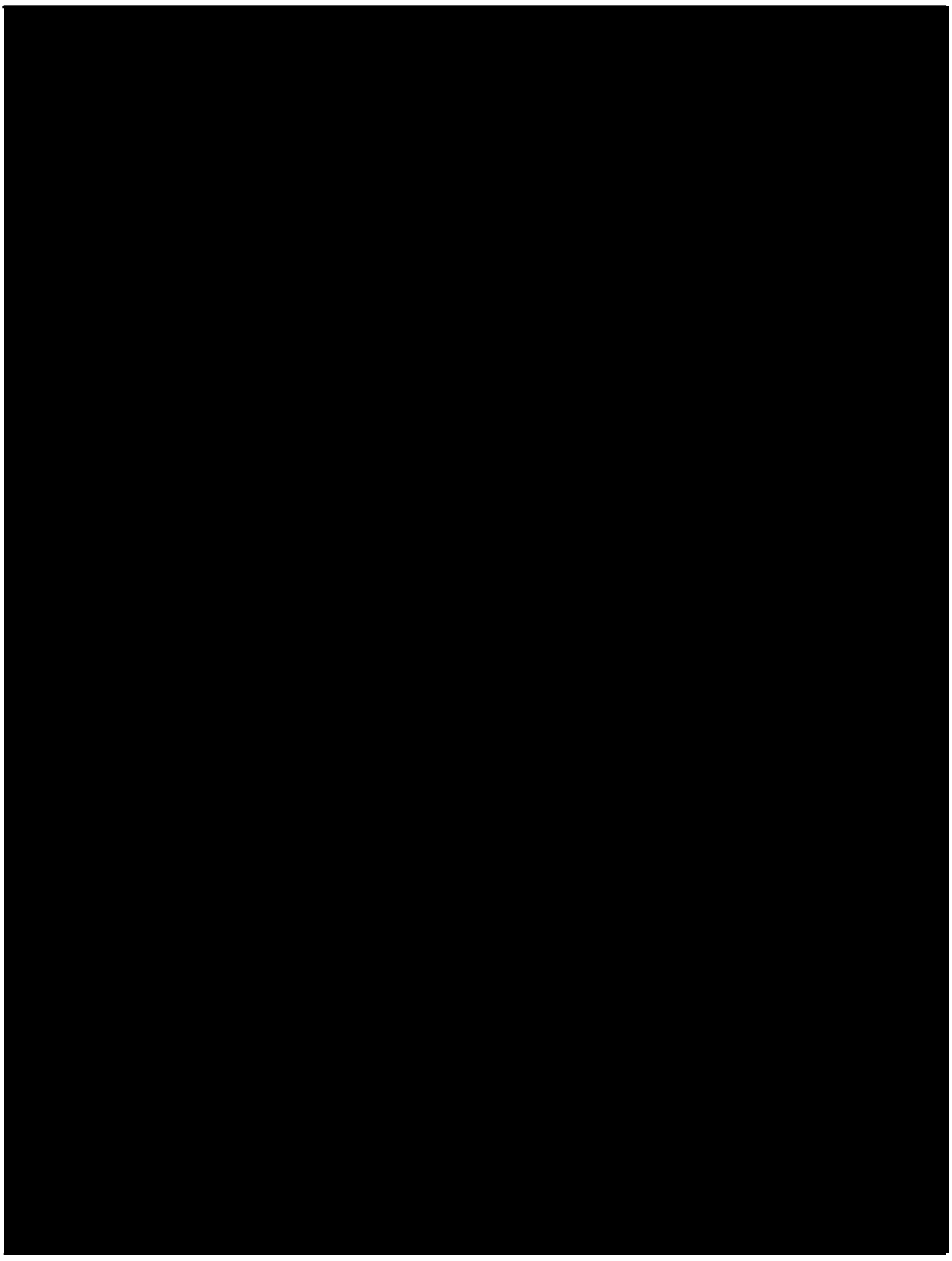
# APPENDIX 2. BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

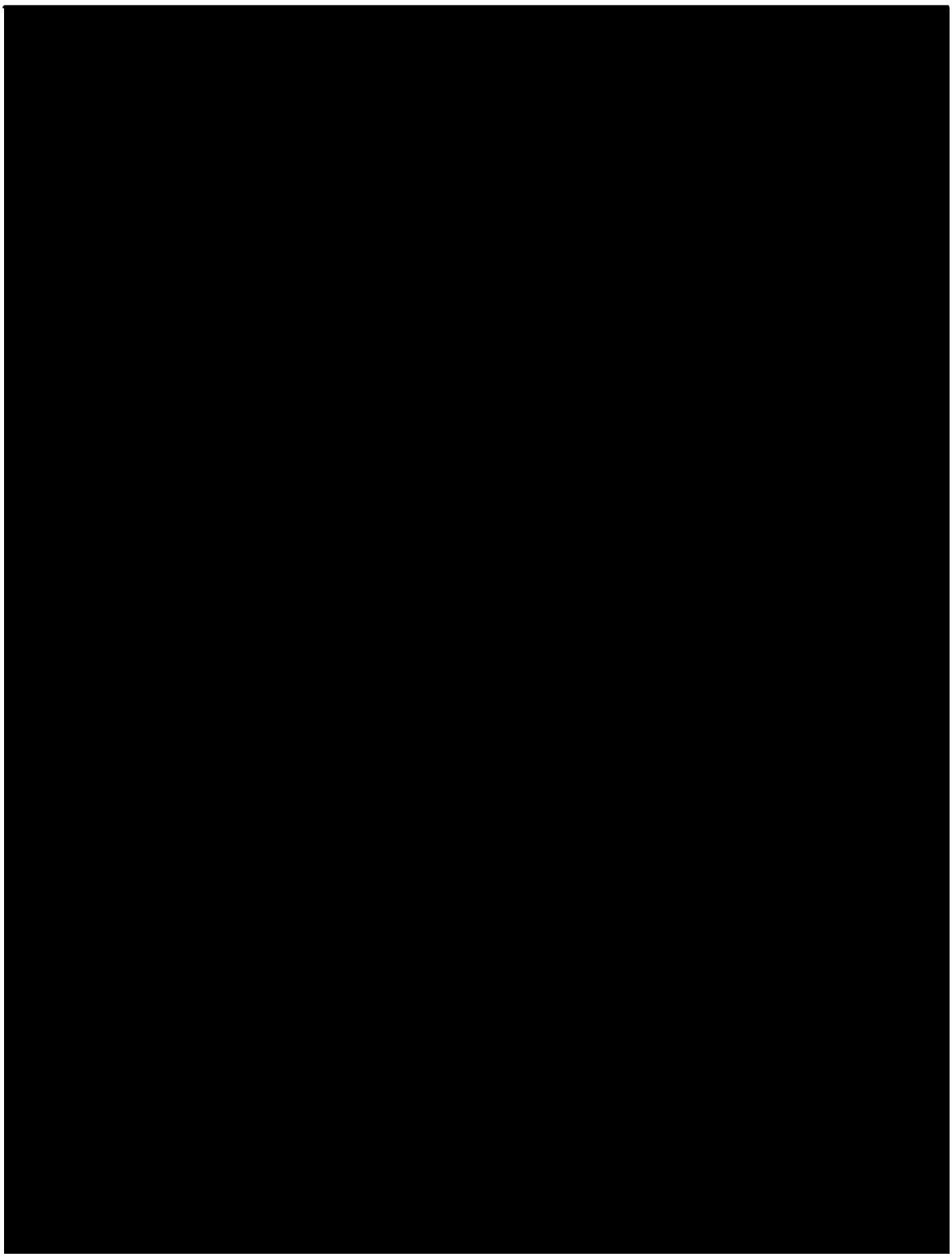


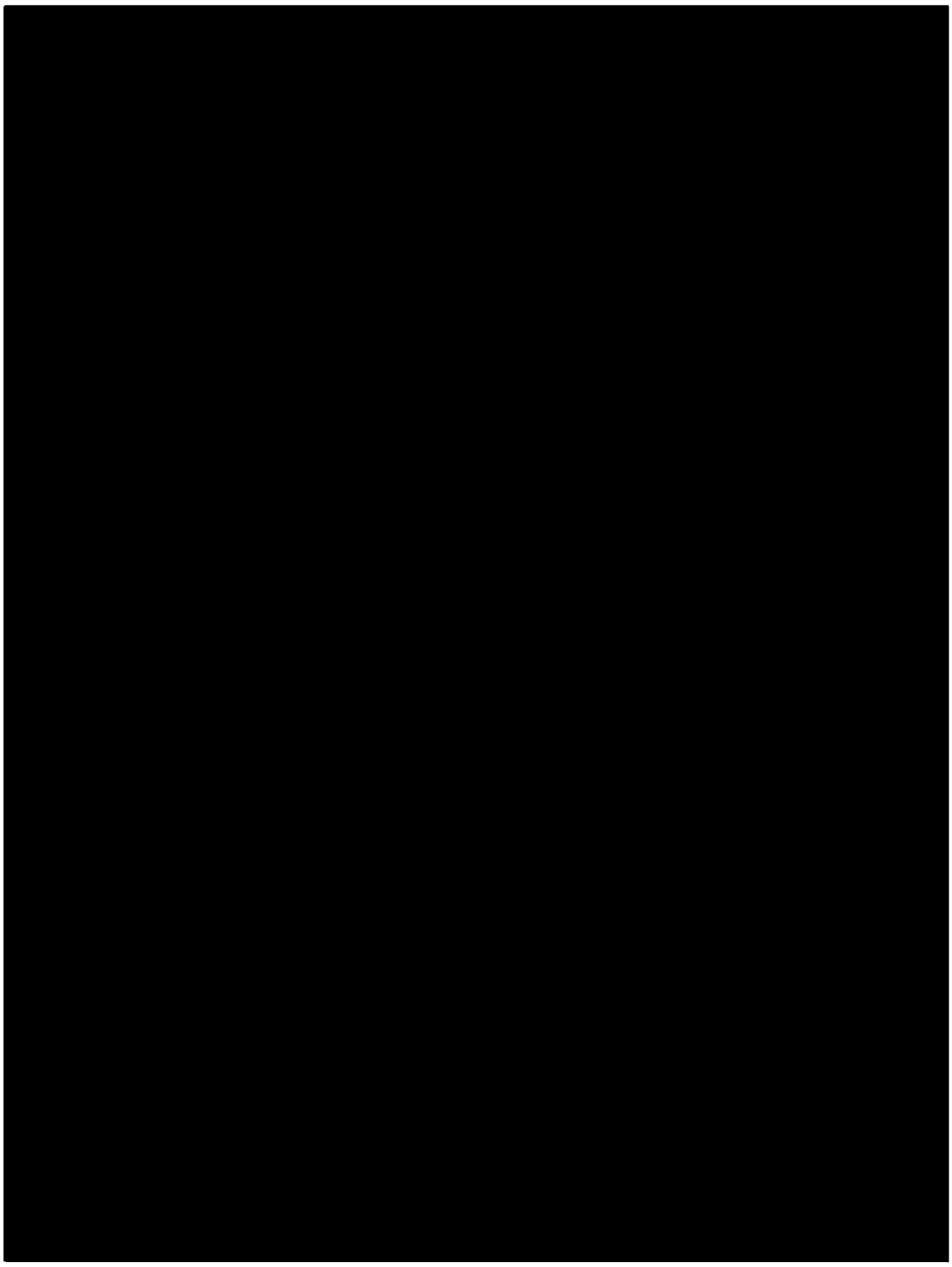


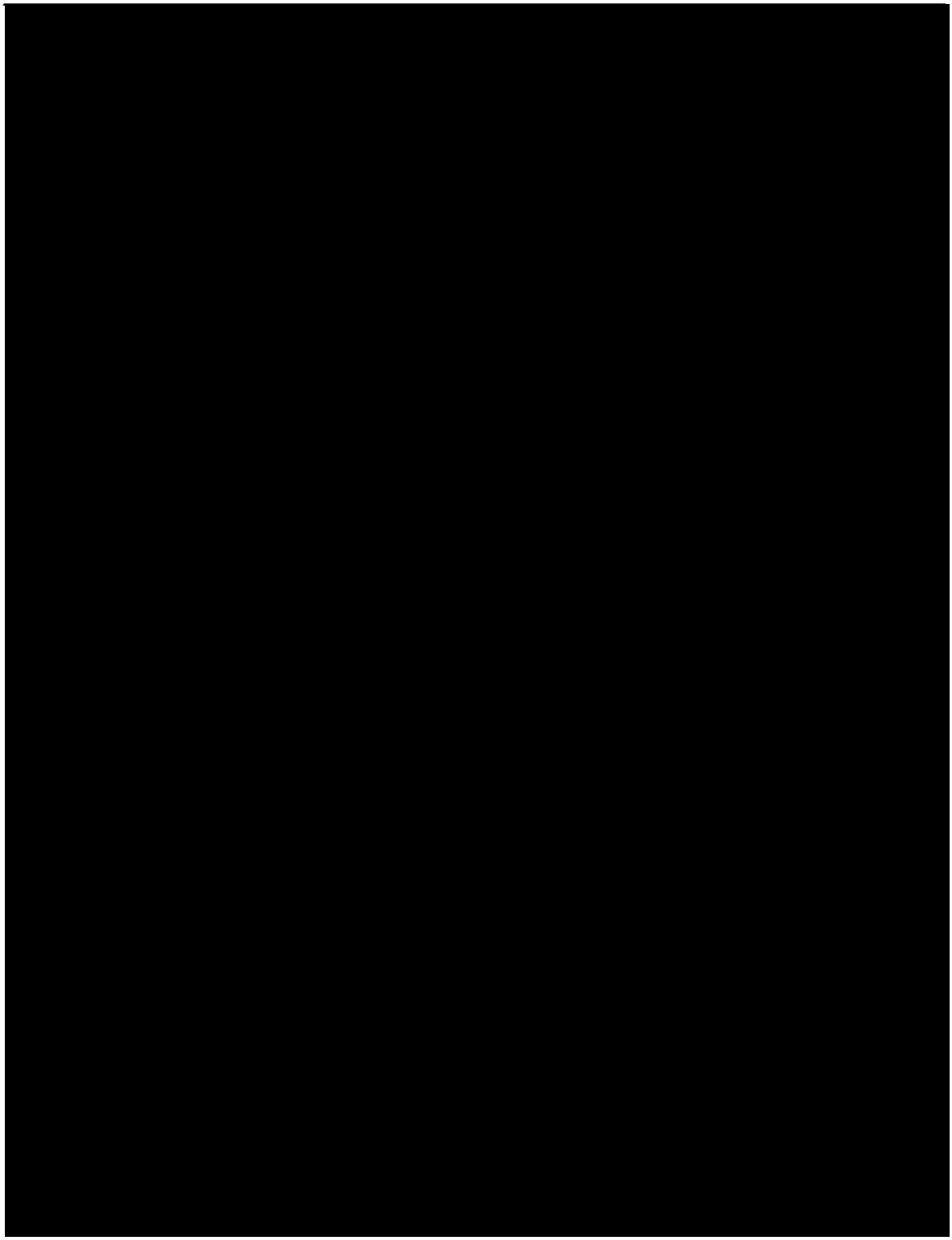


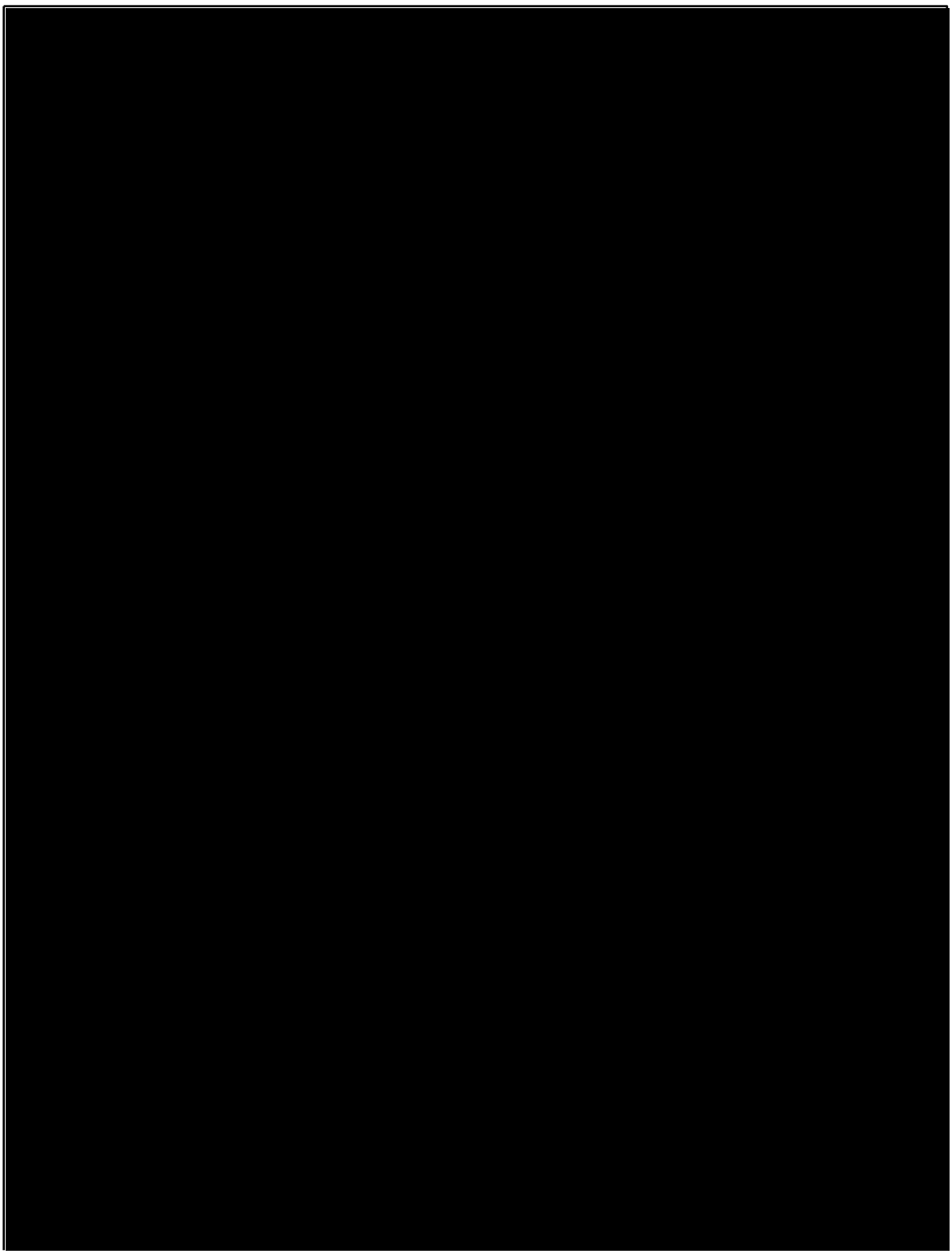


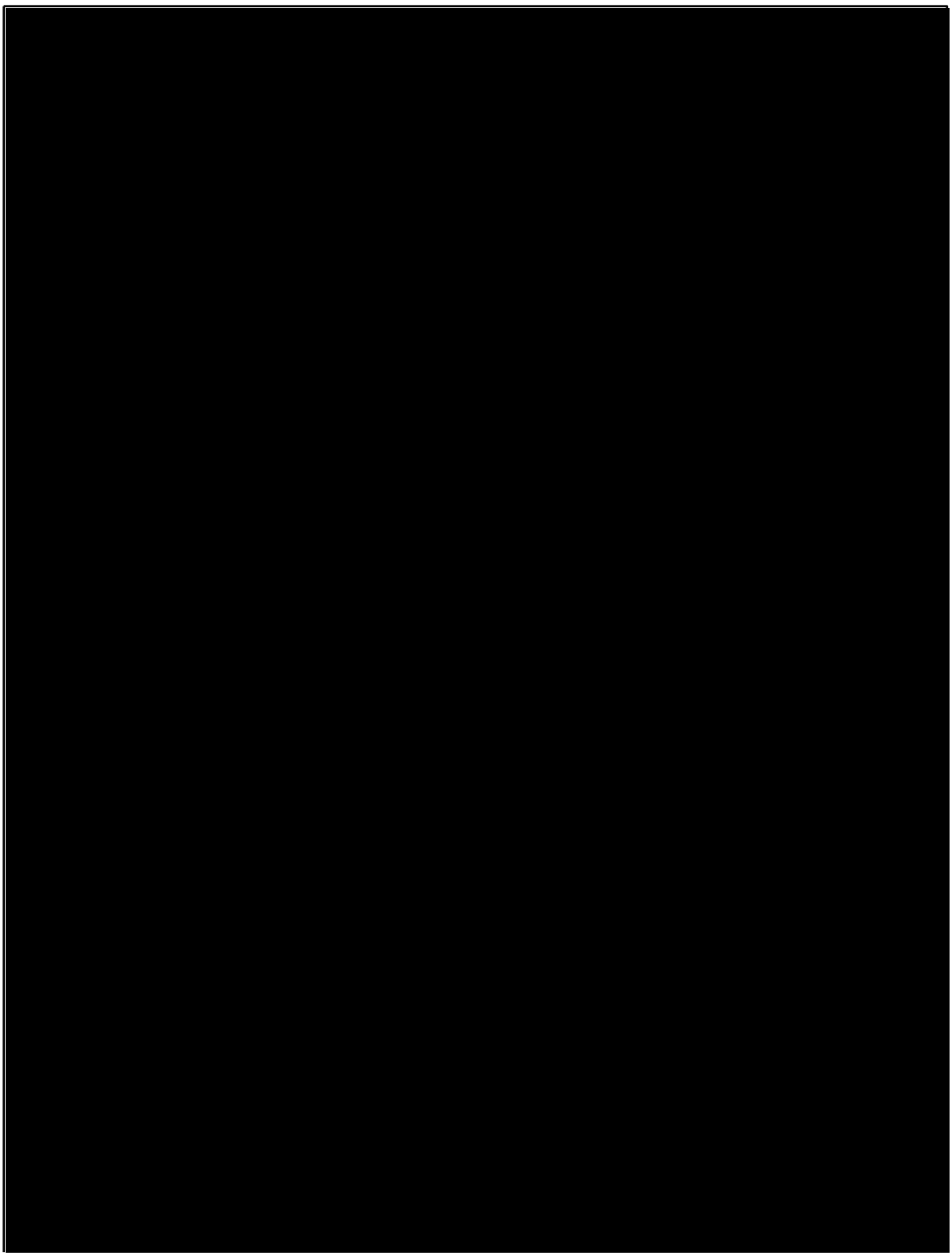


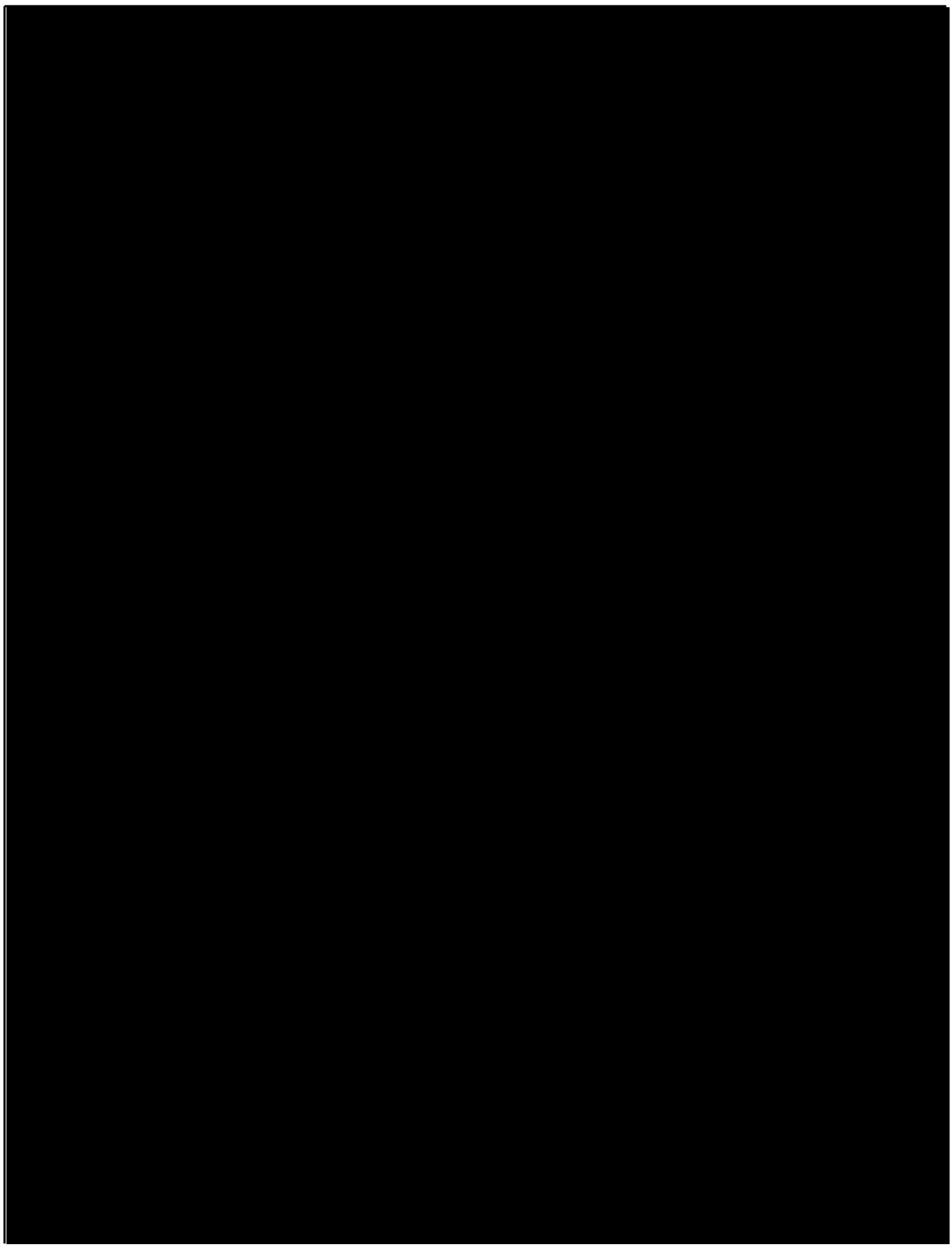


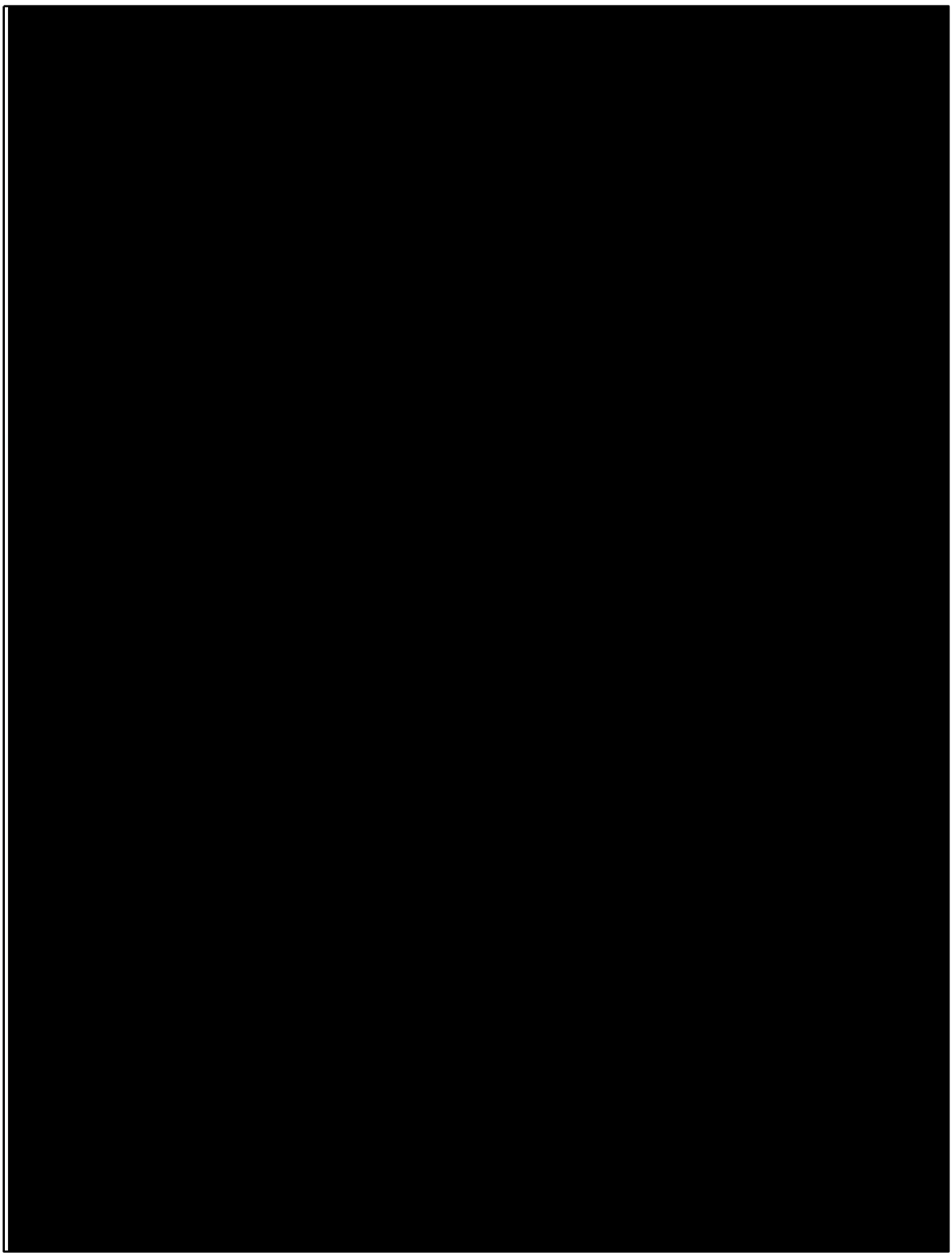


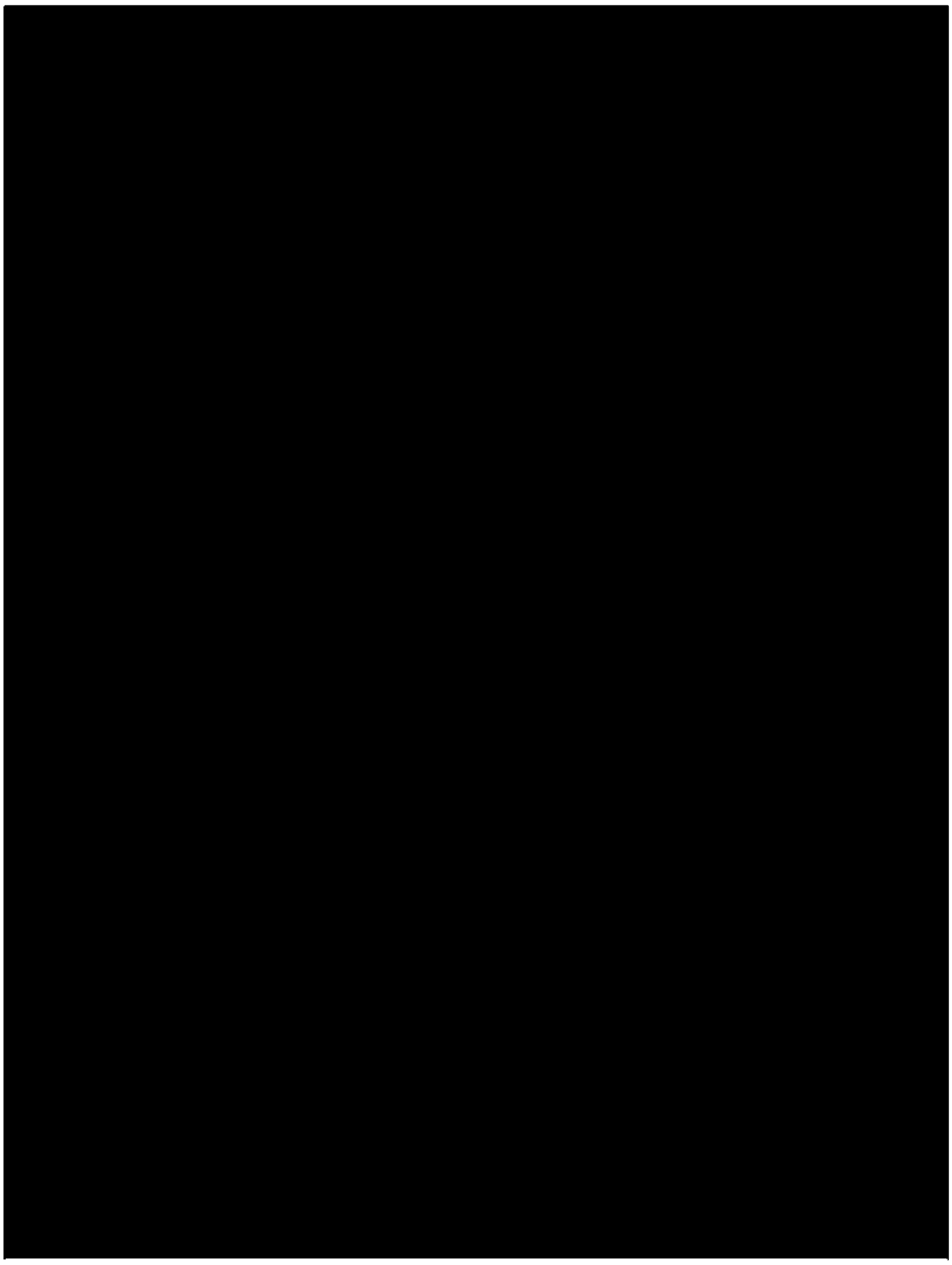


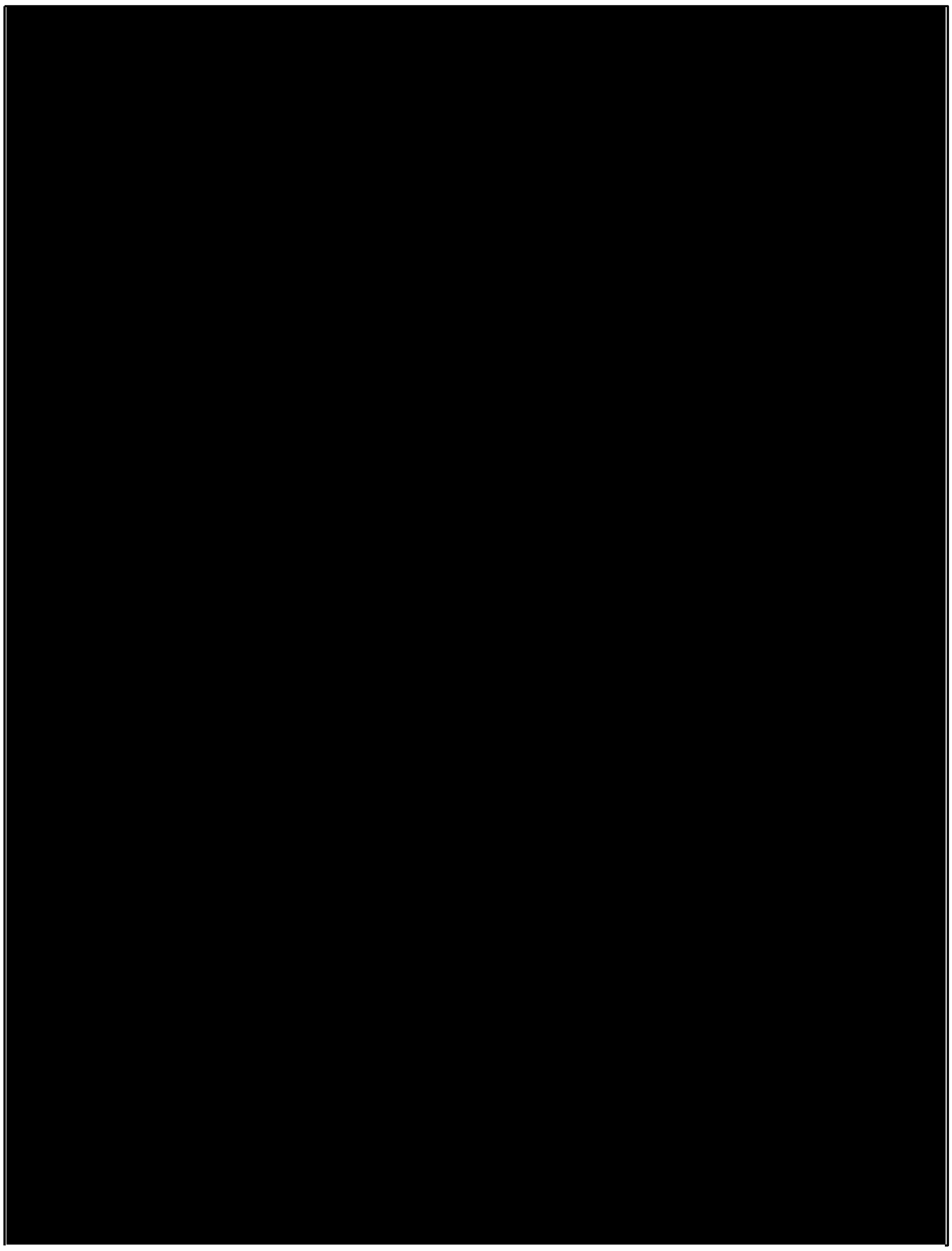


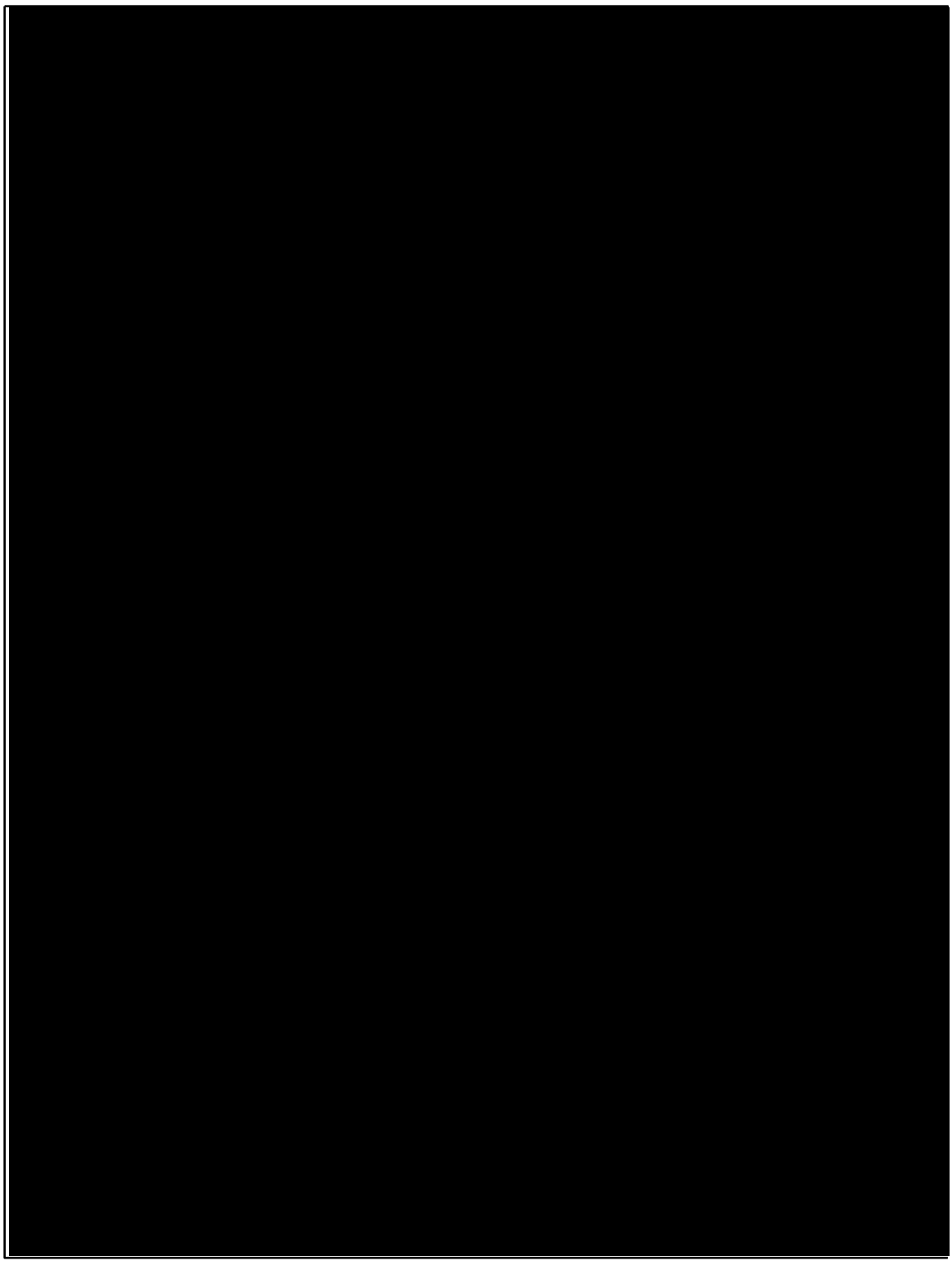


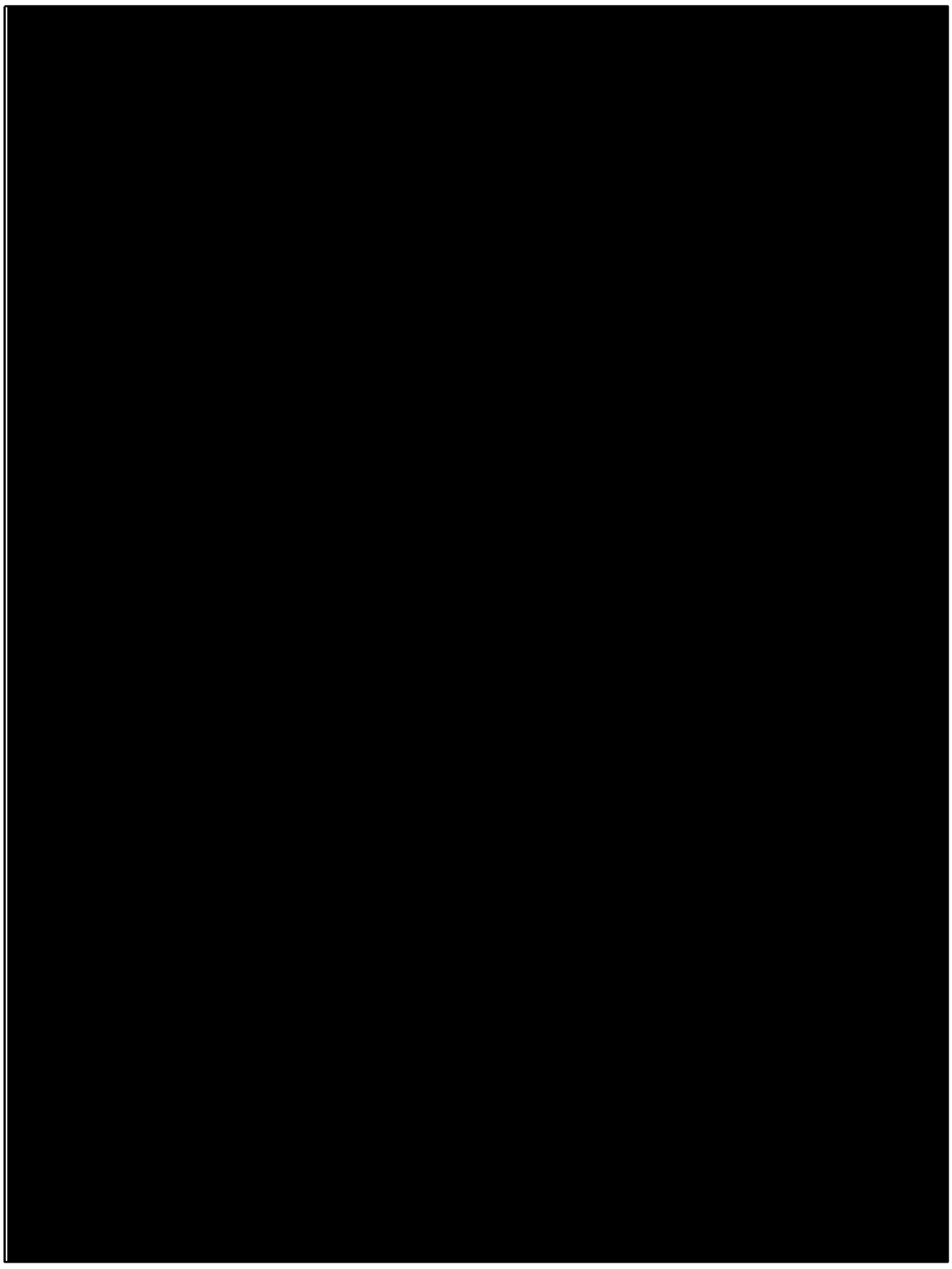


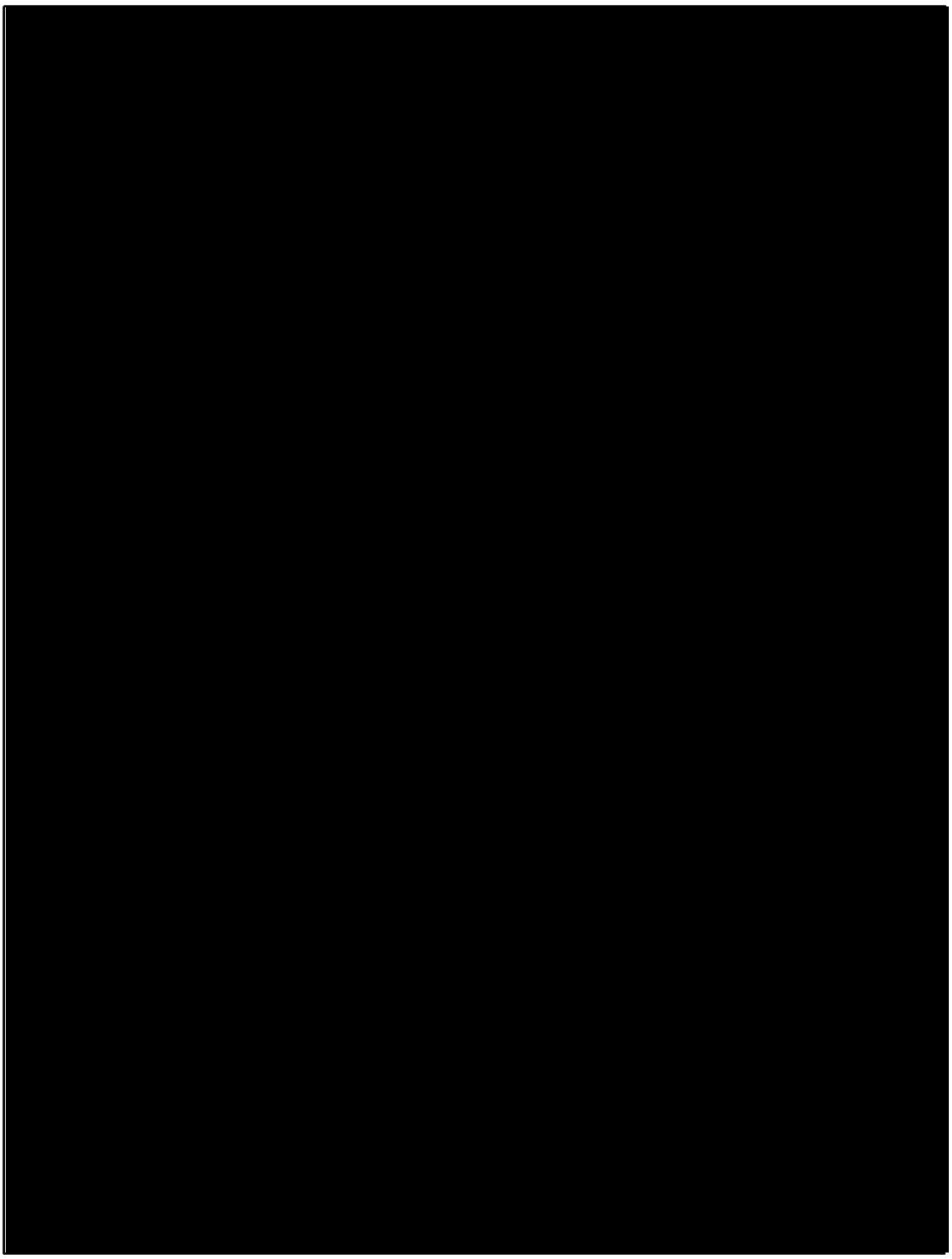


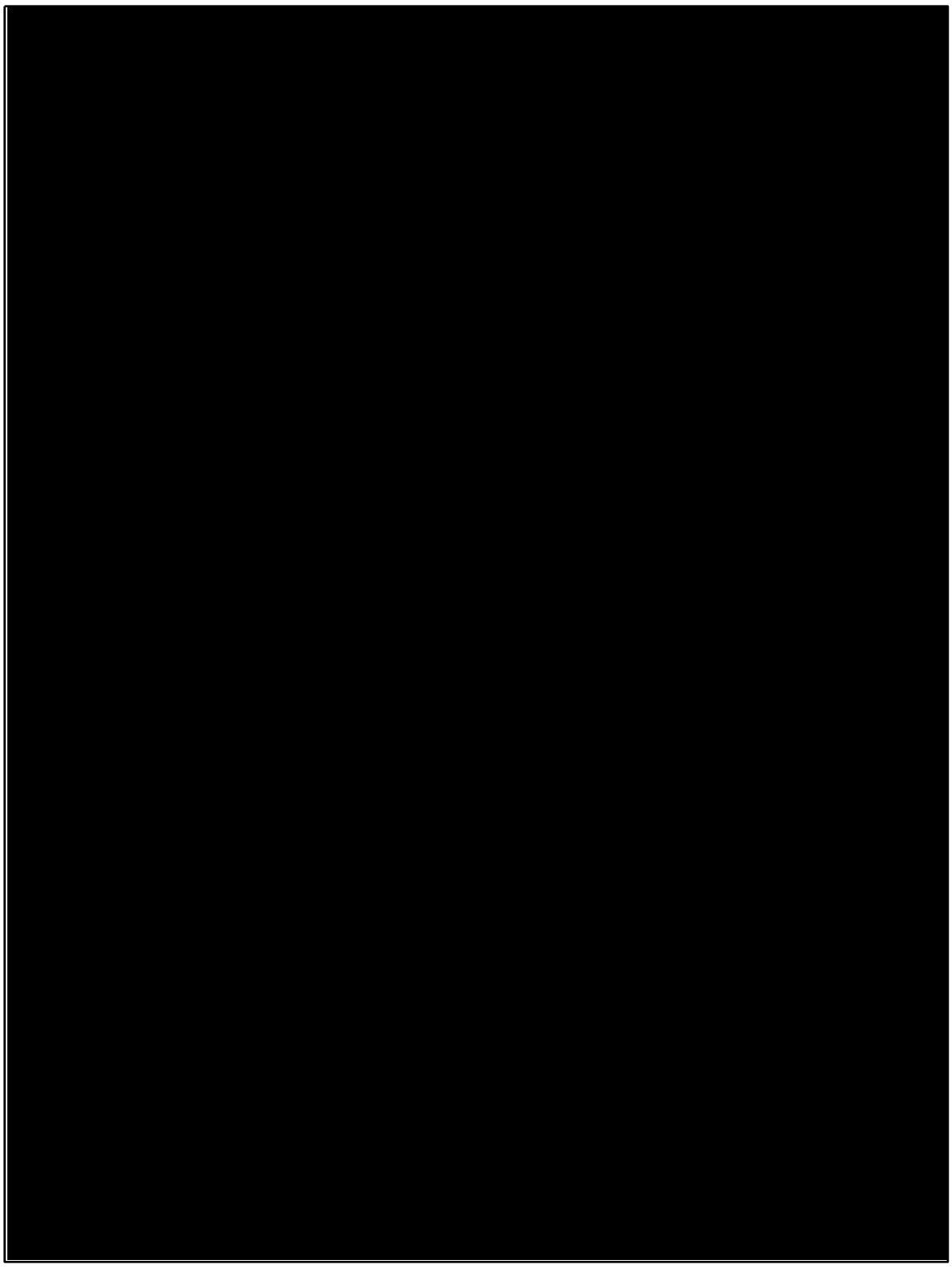


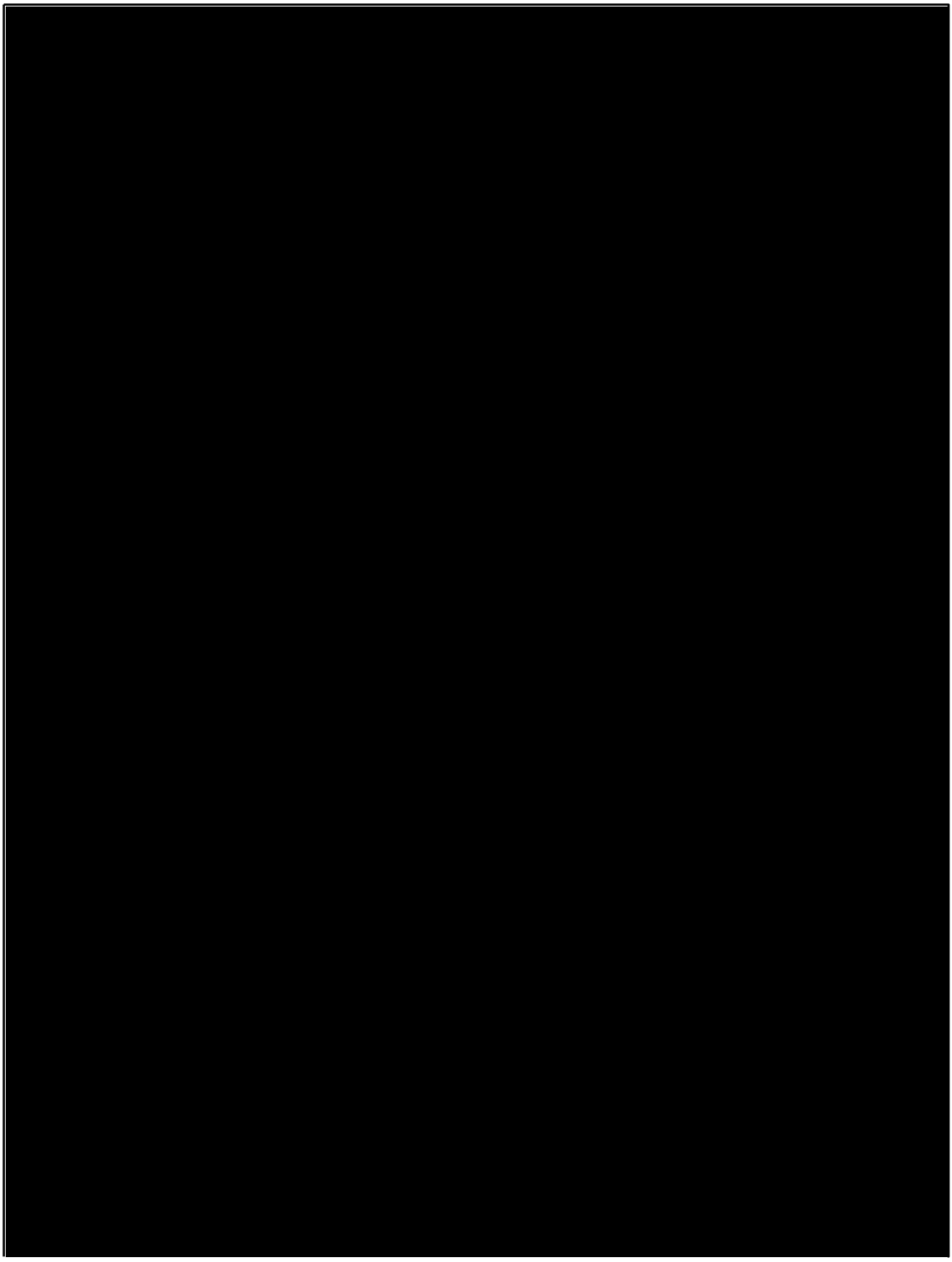


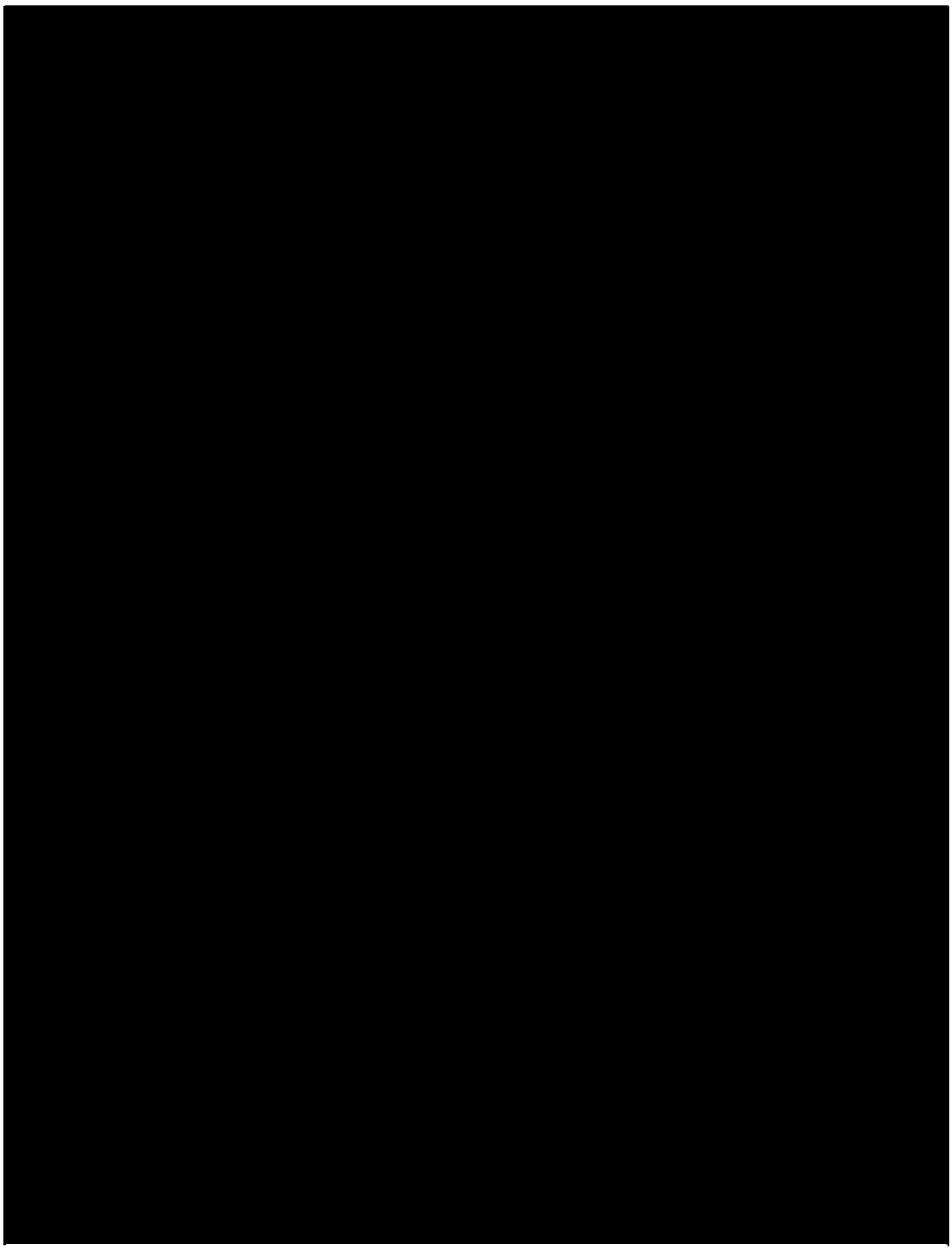


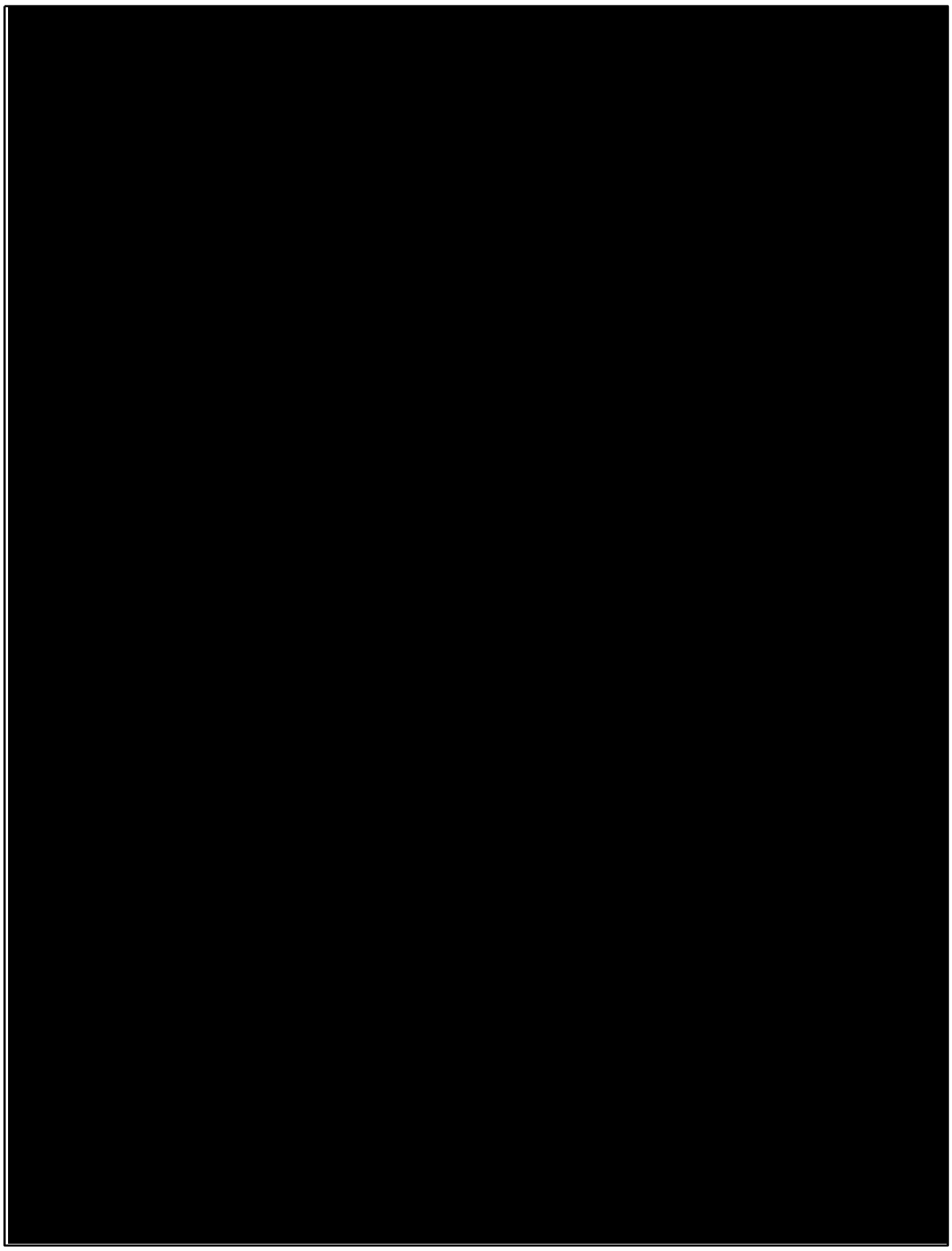


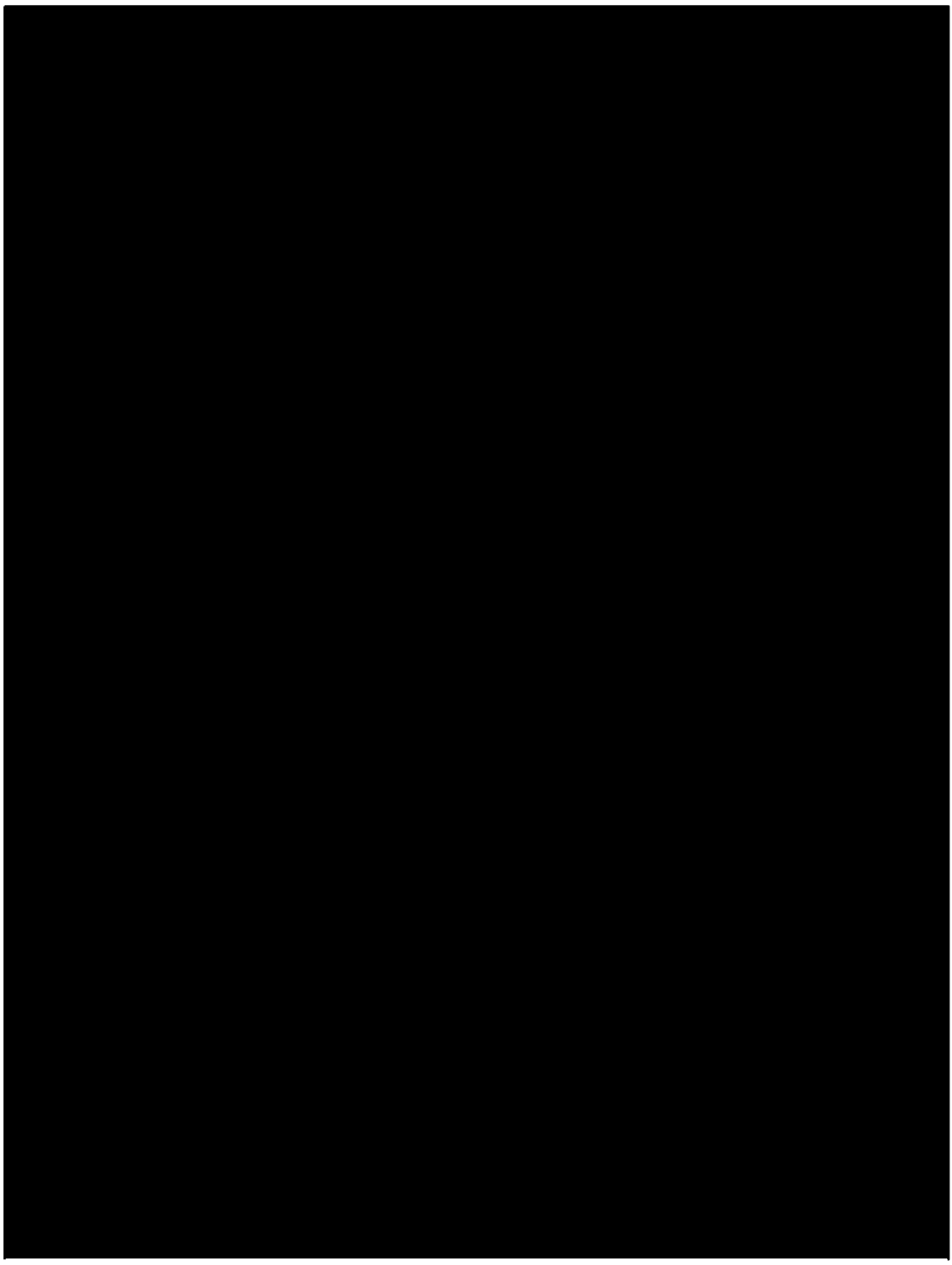


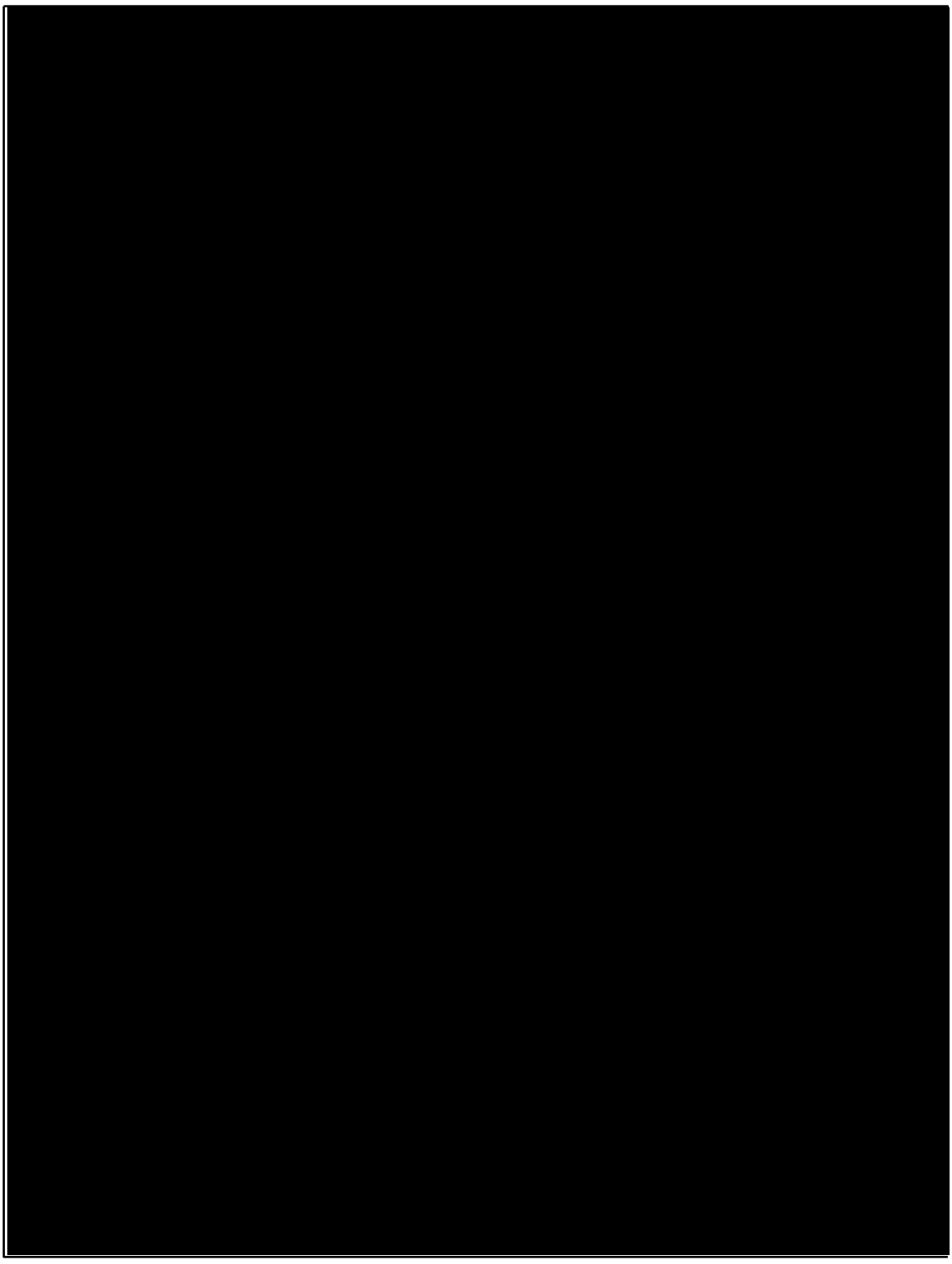


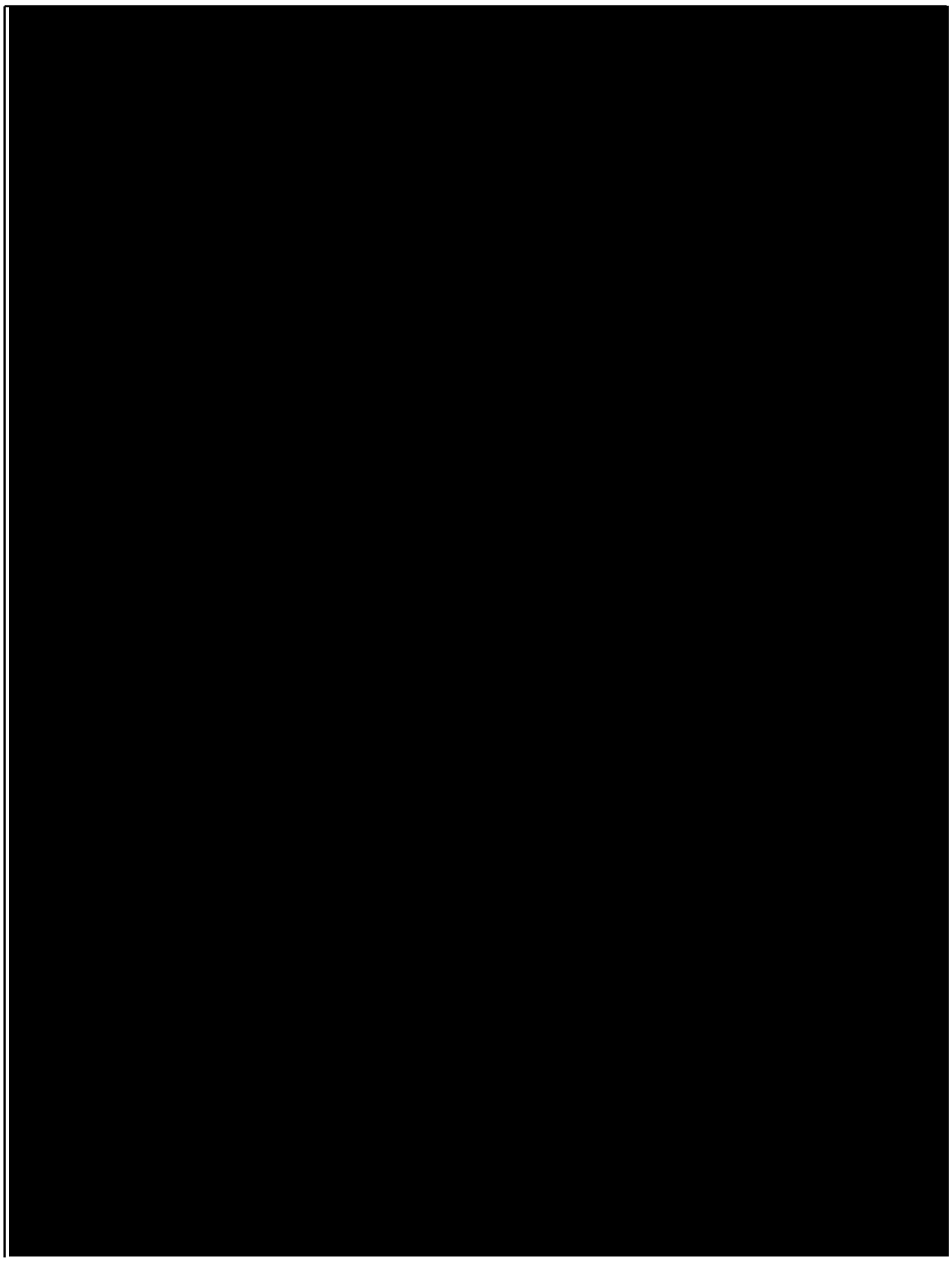


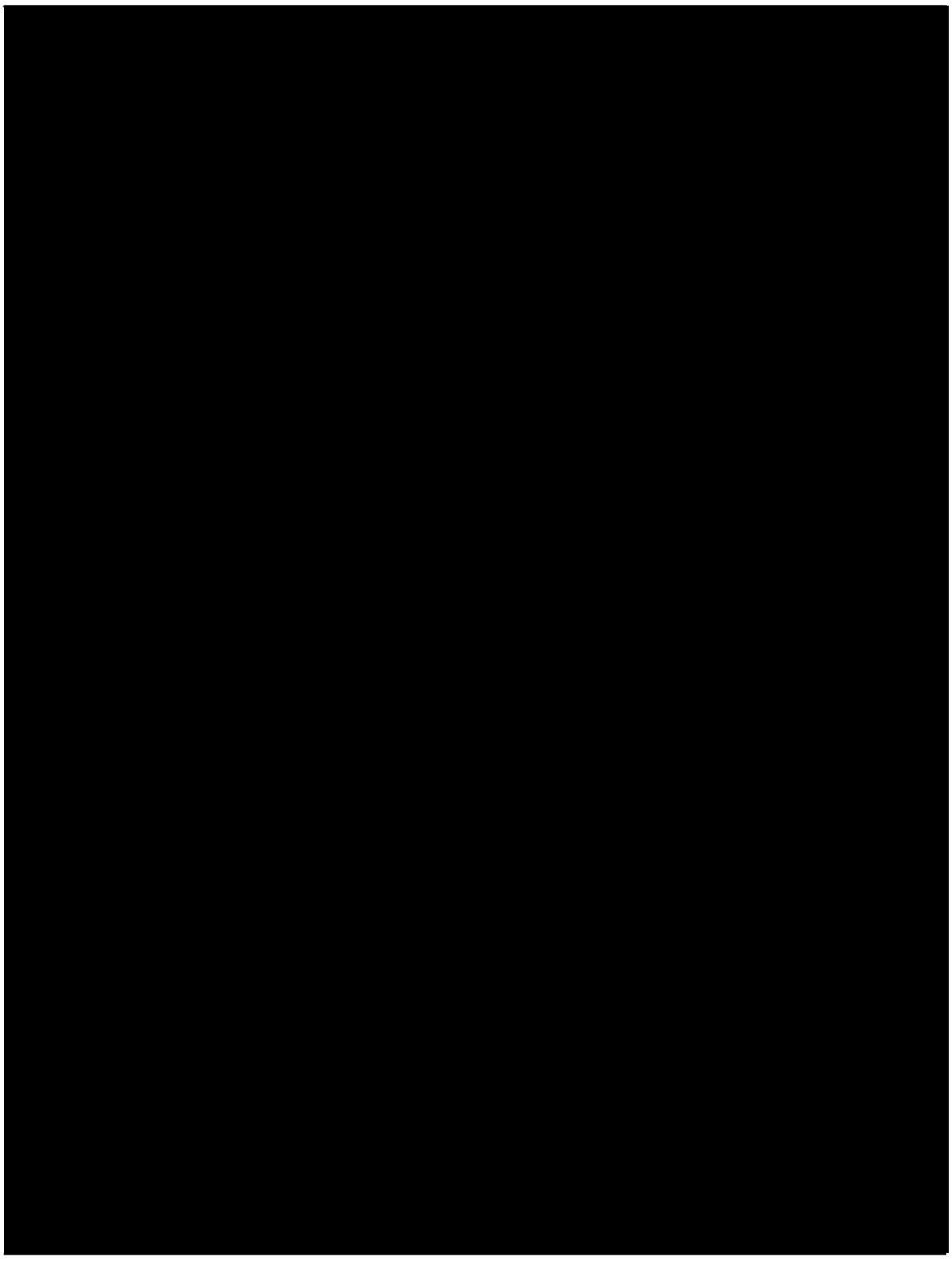


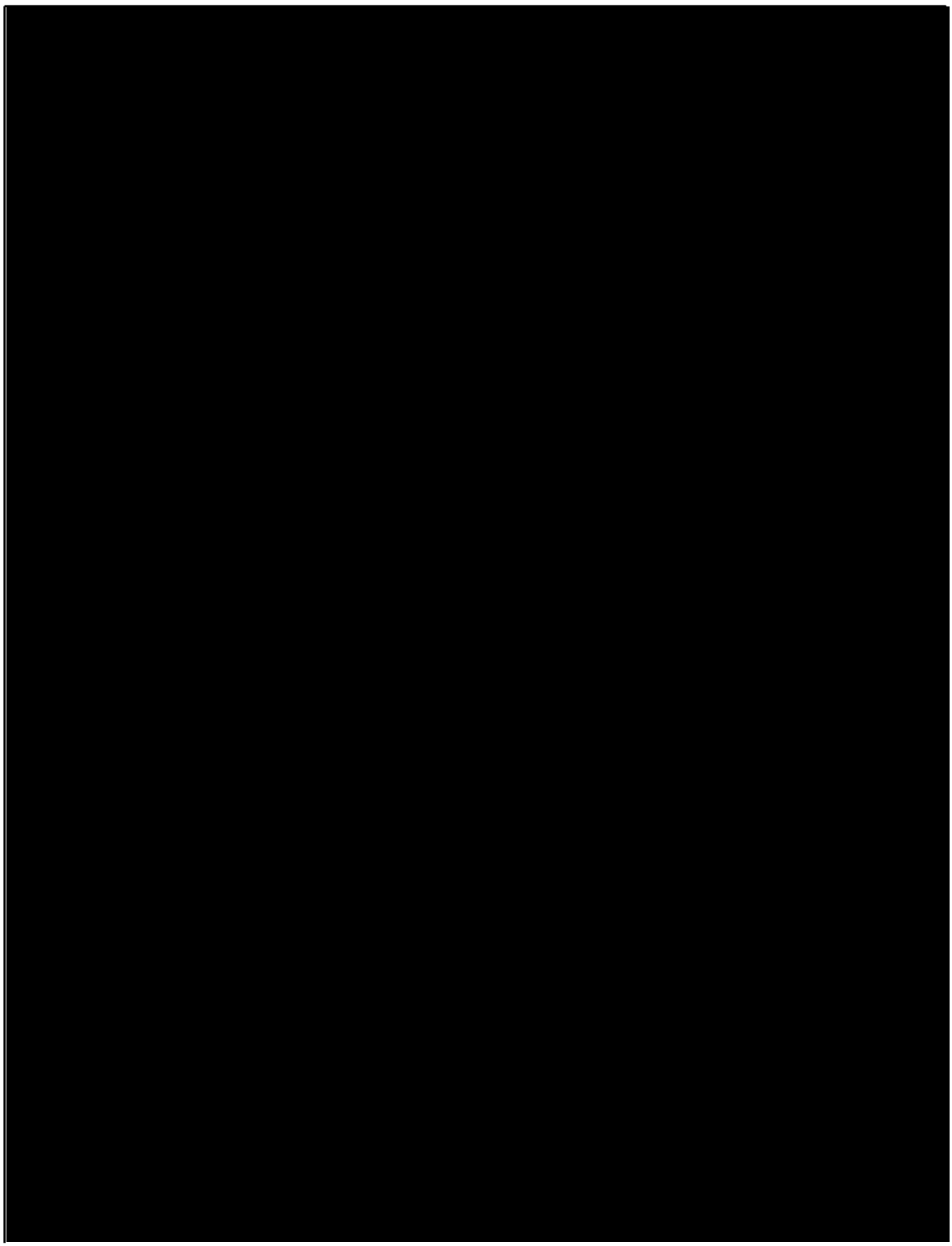


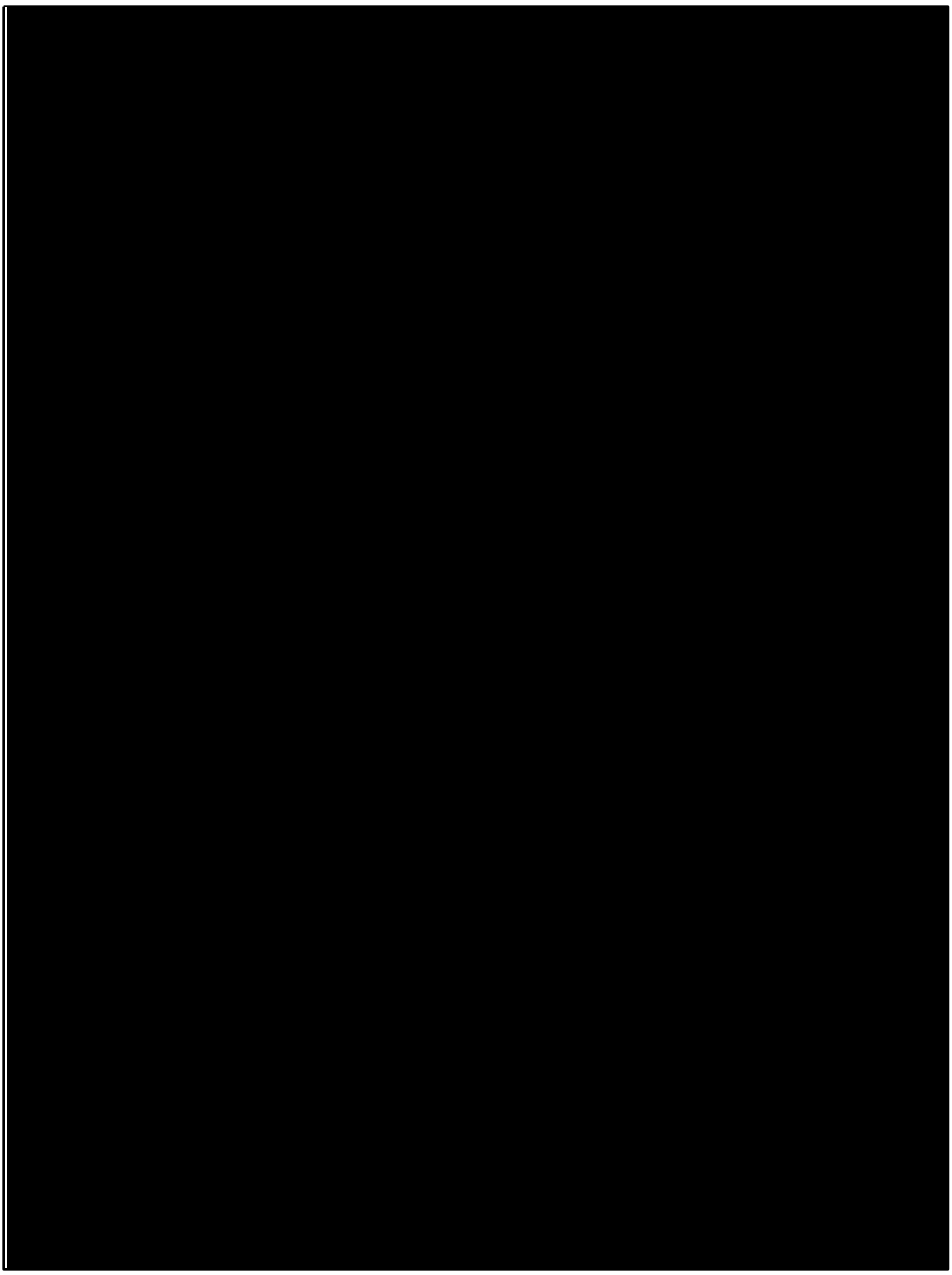


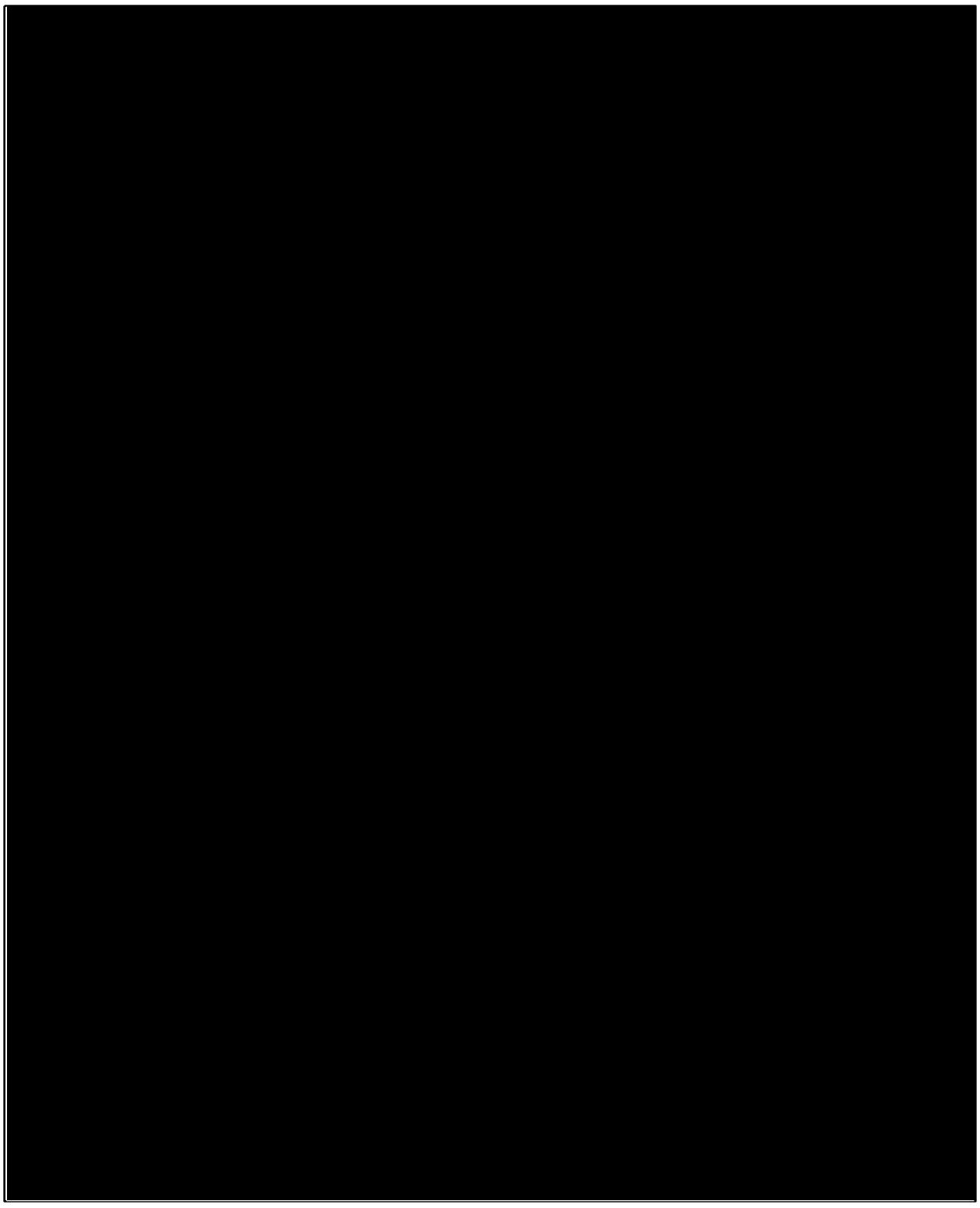


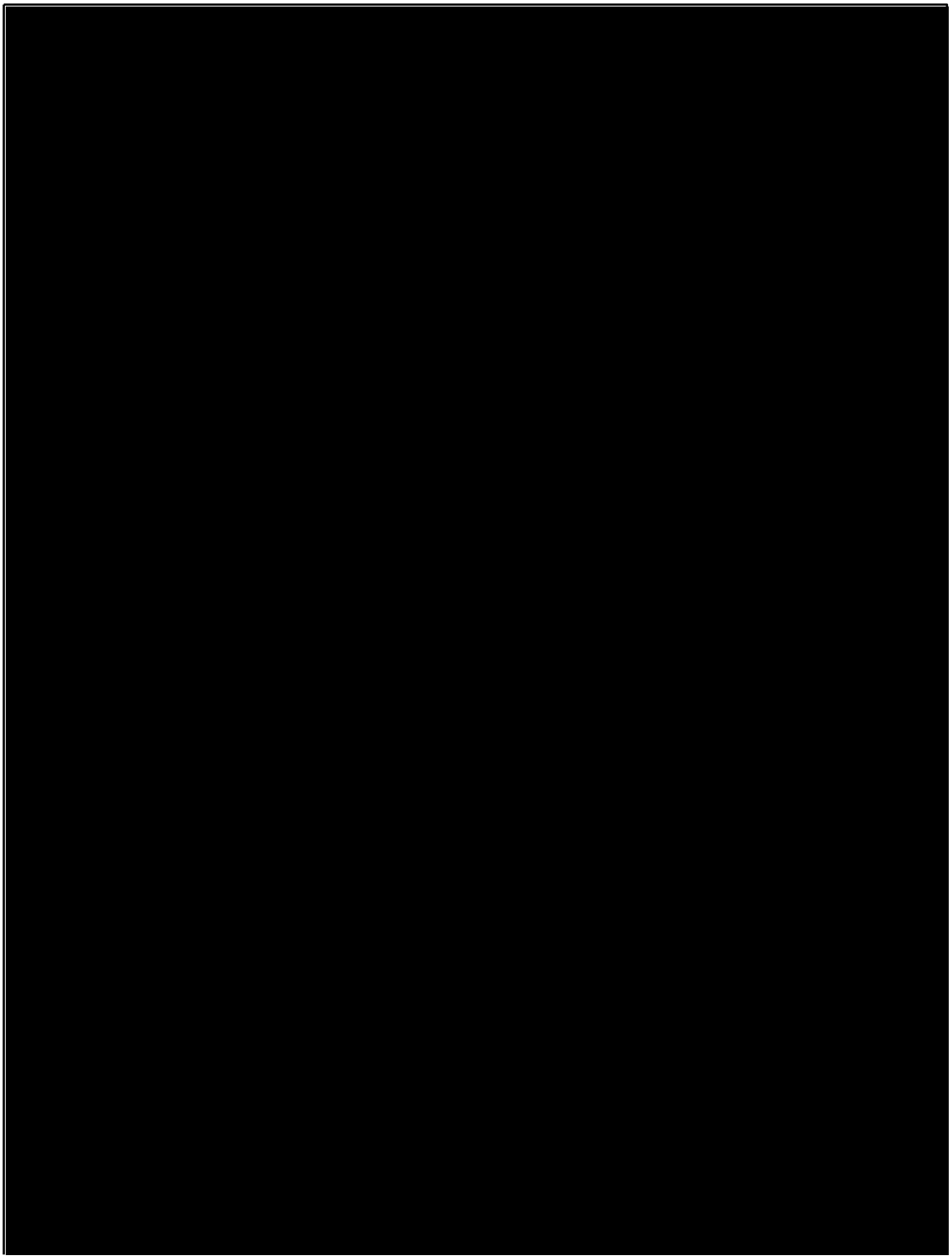


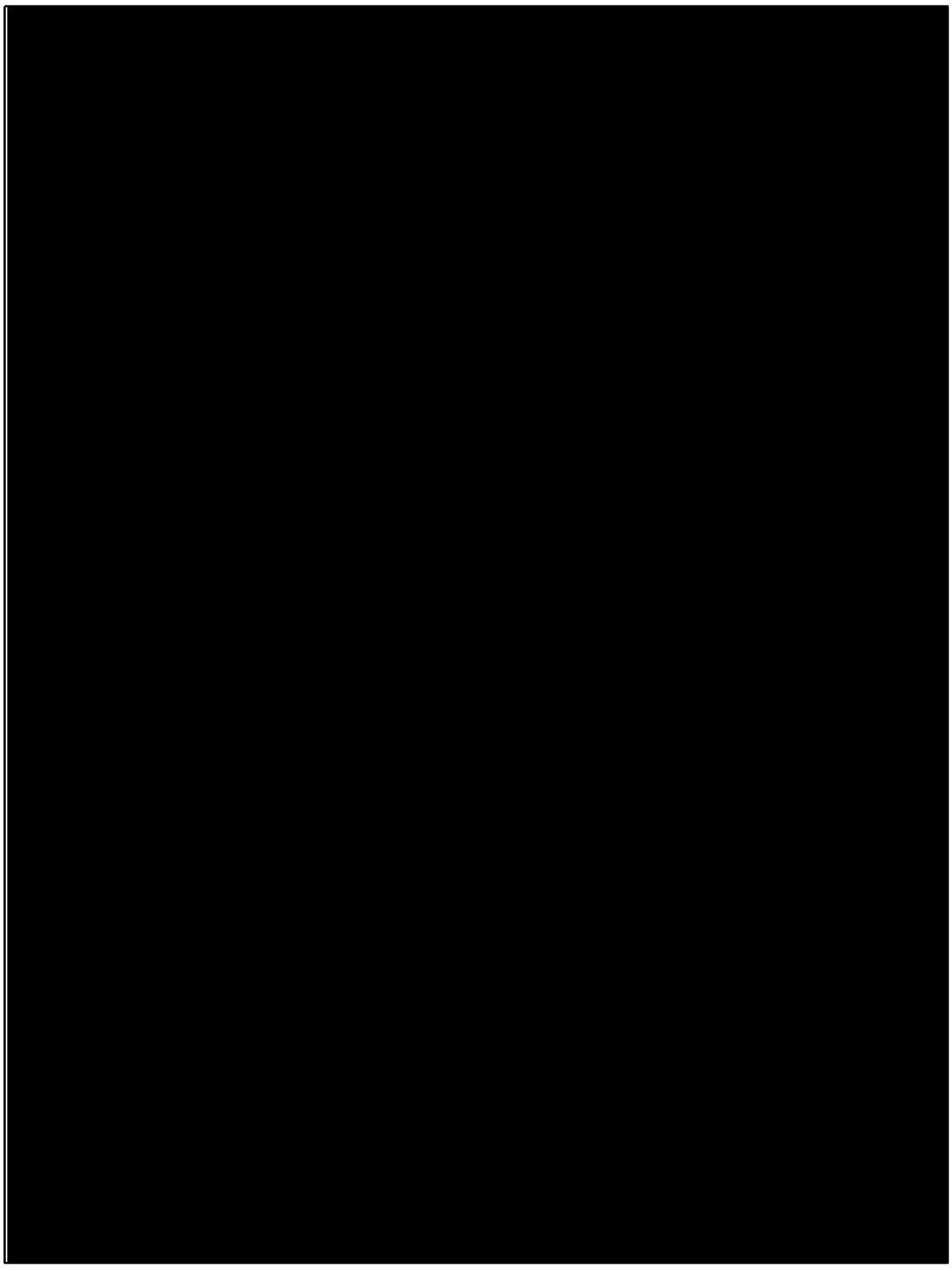


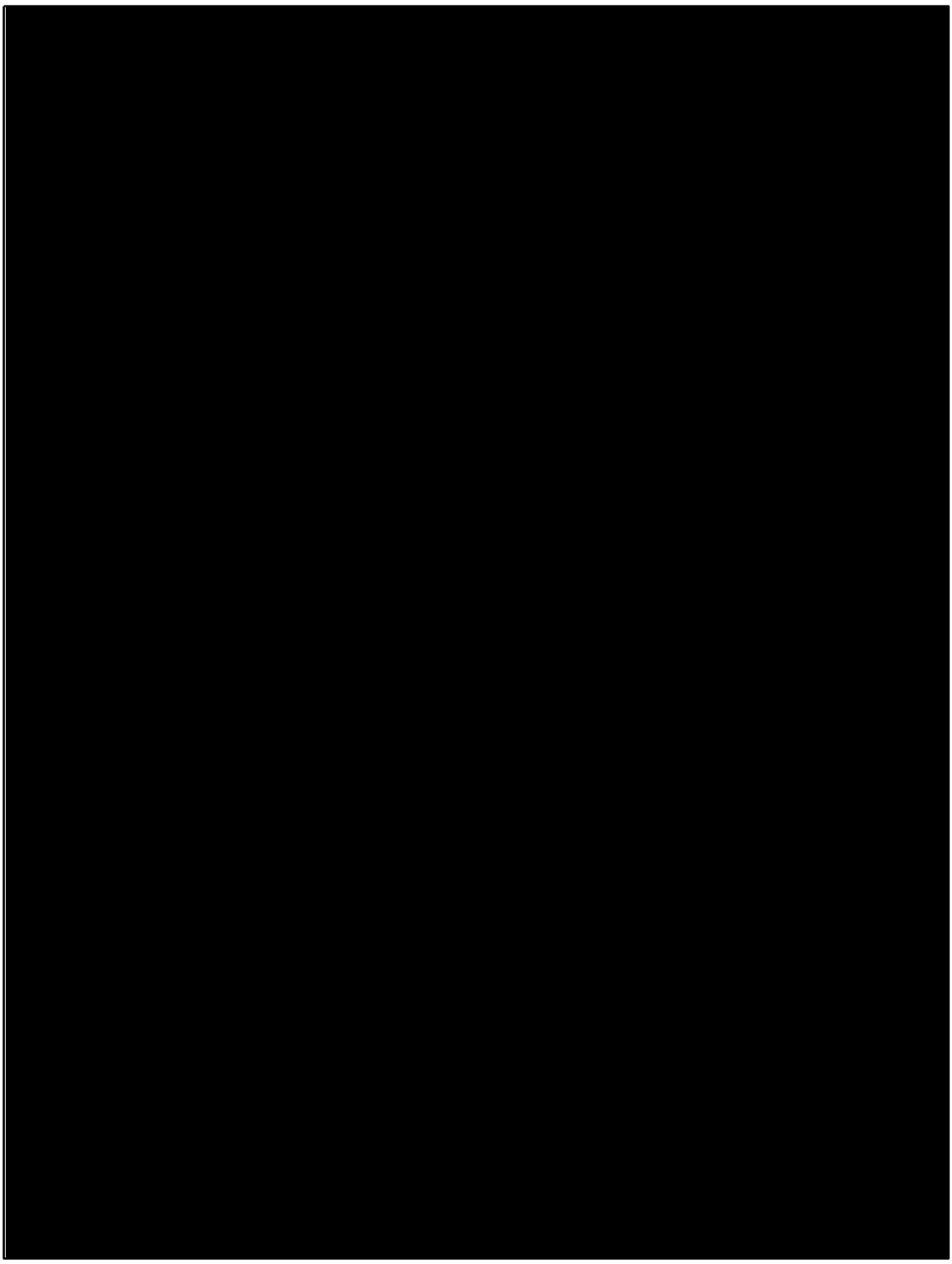


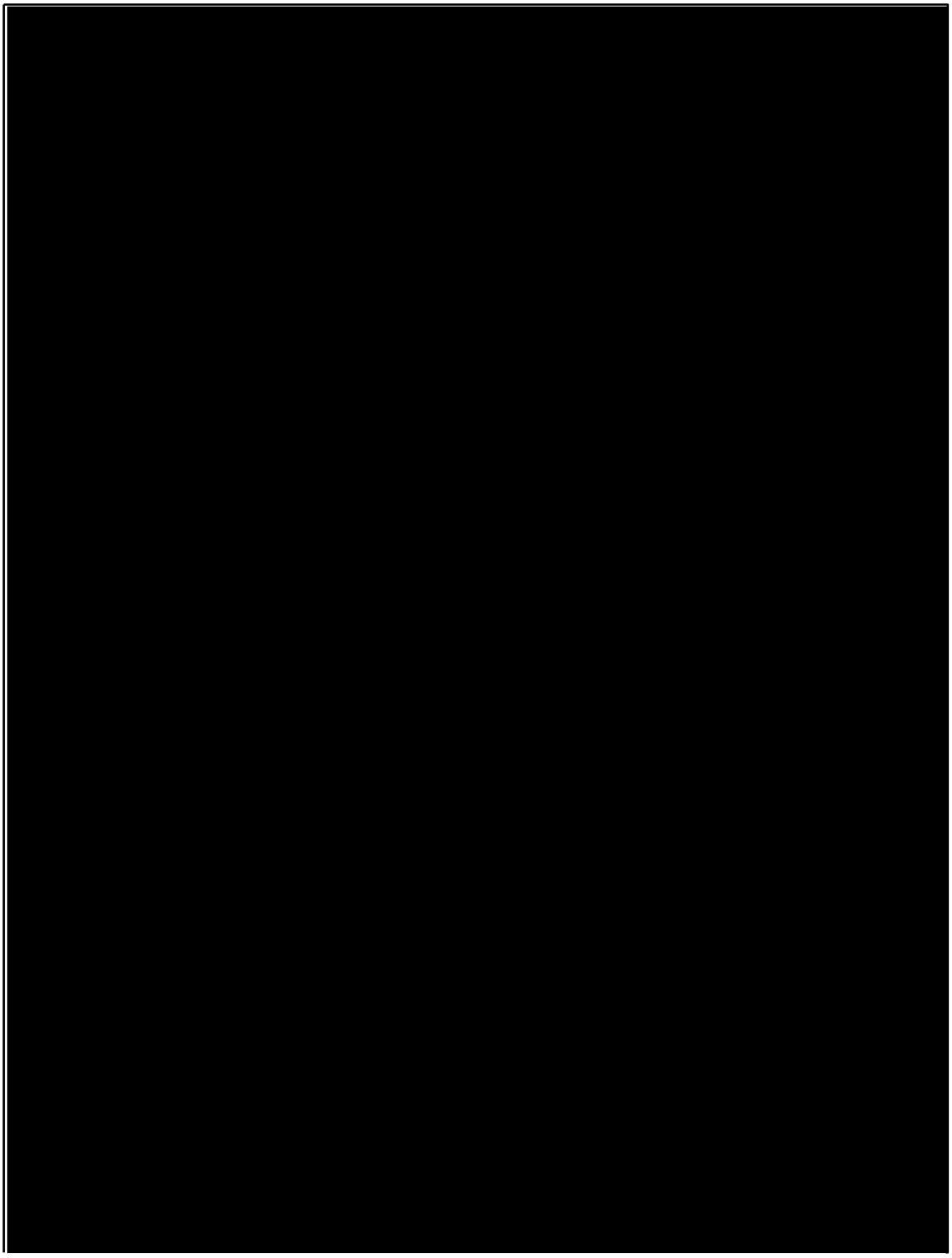


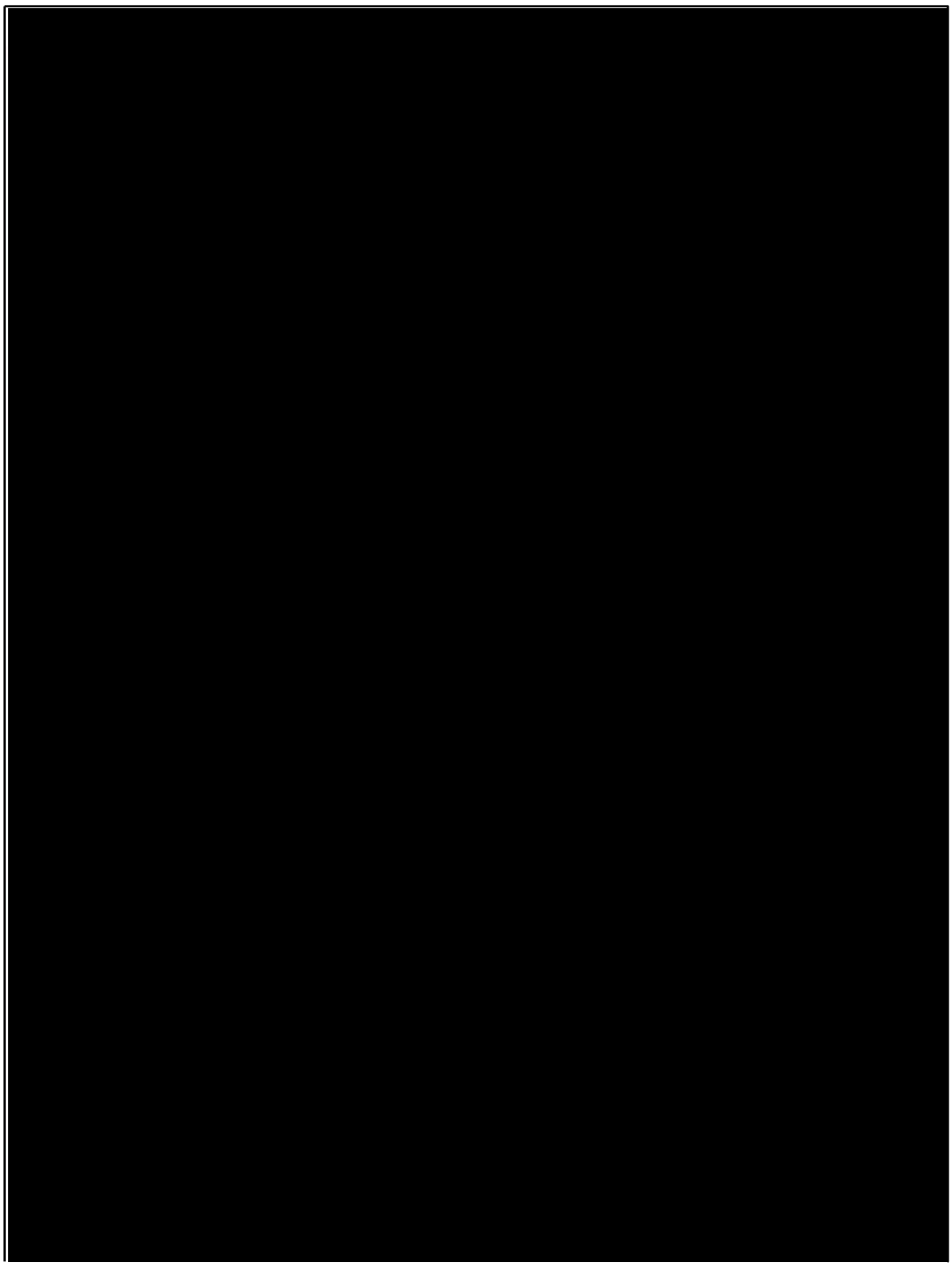


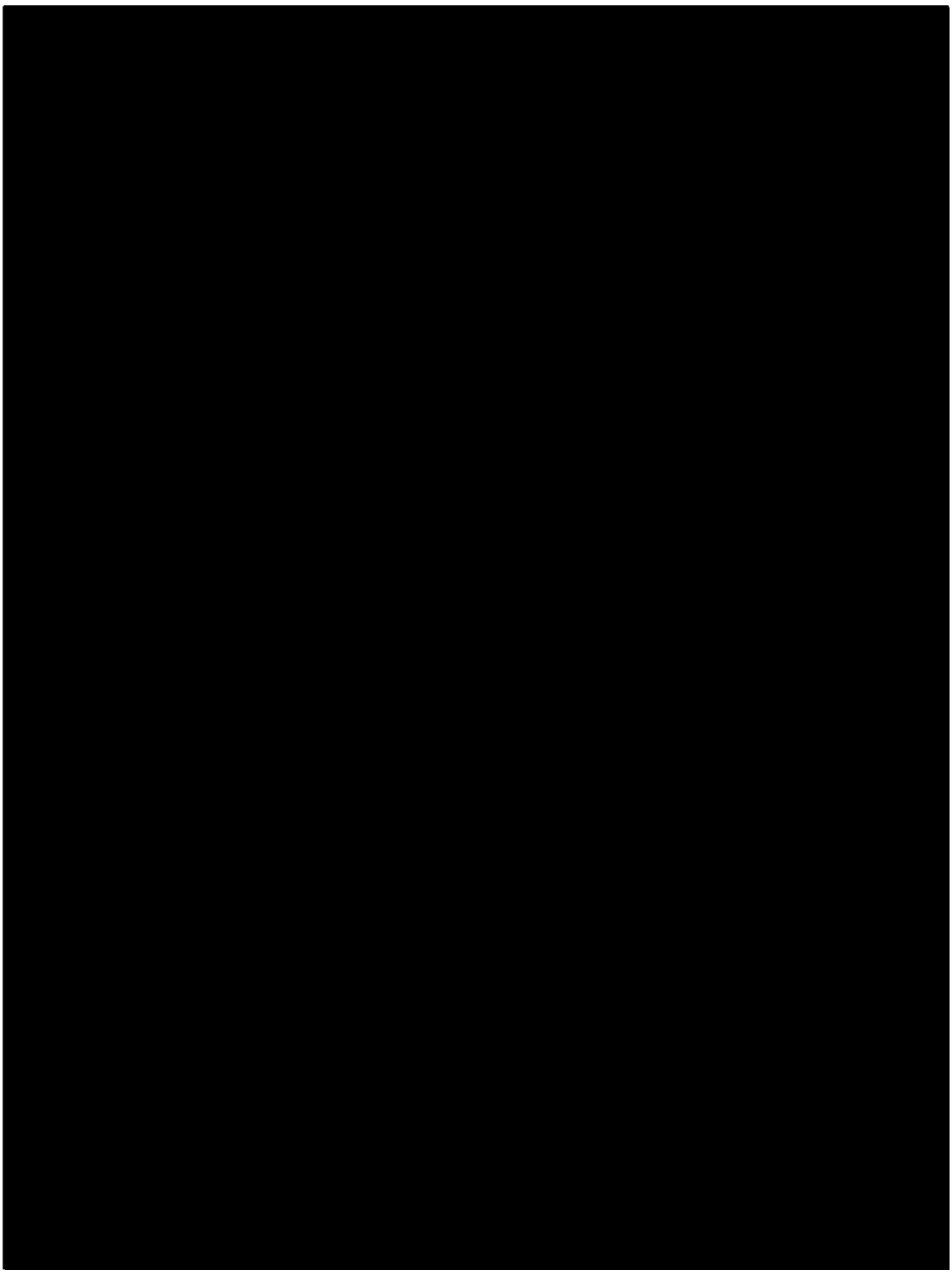


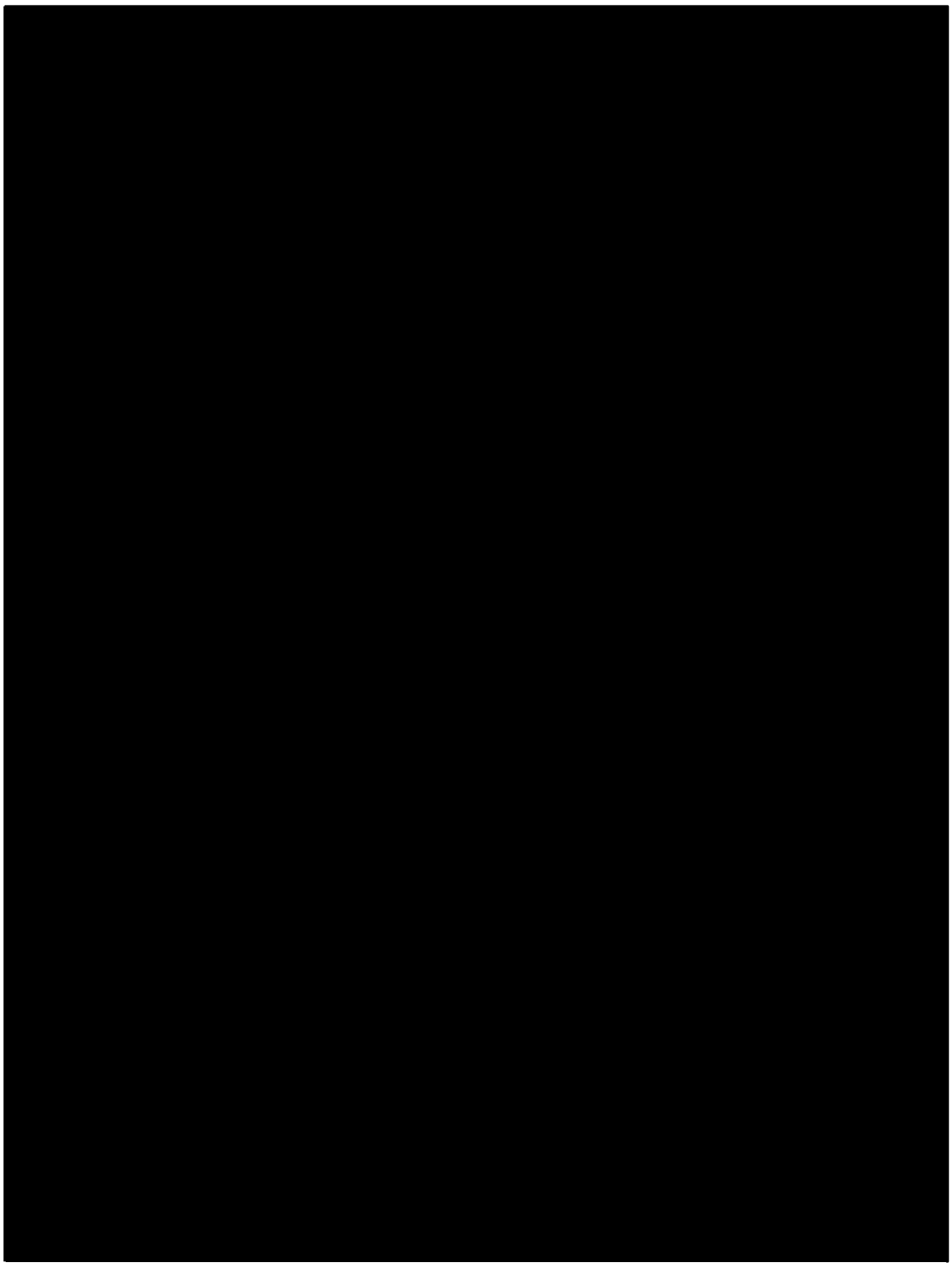


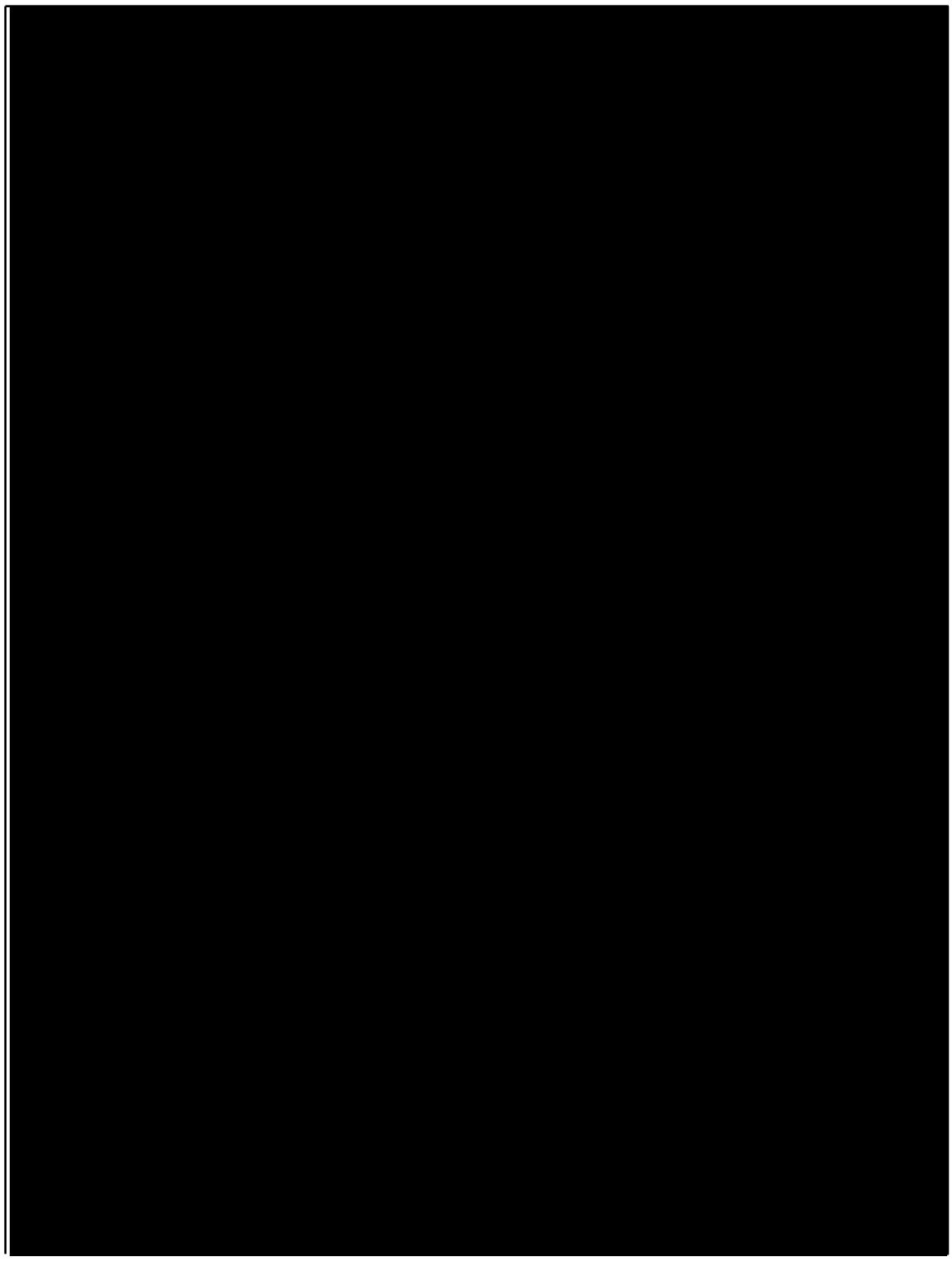


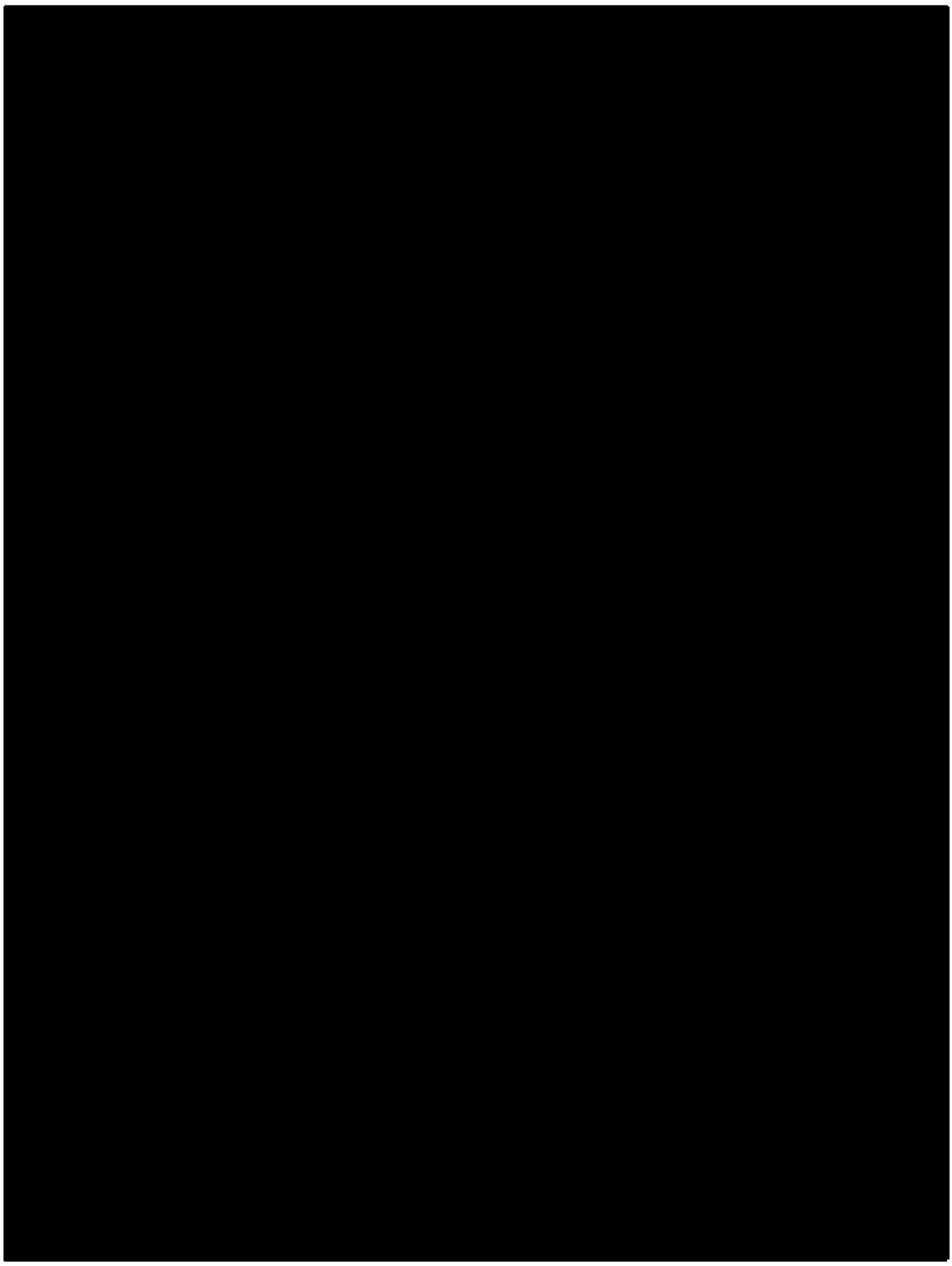


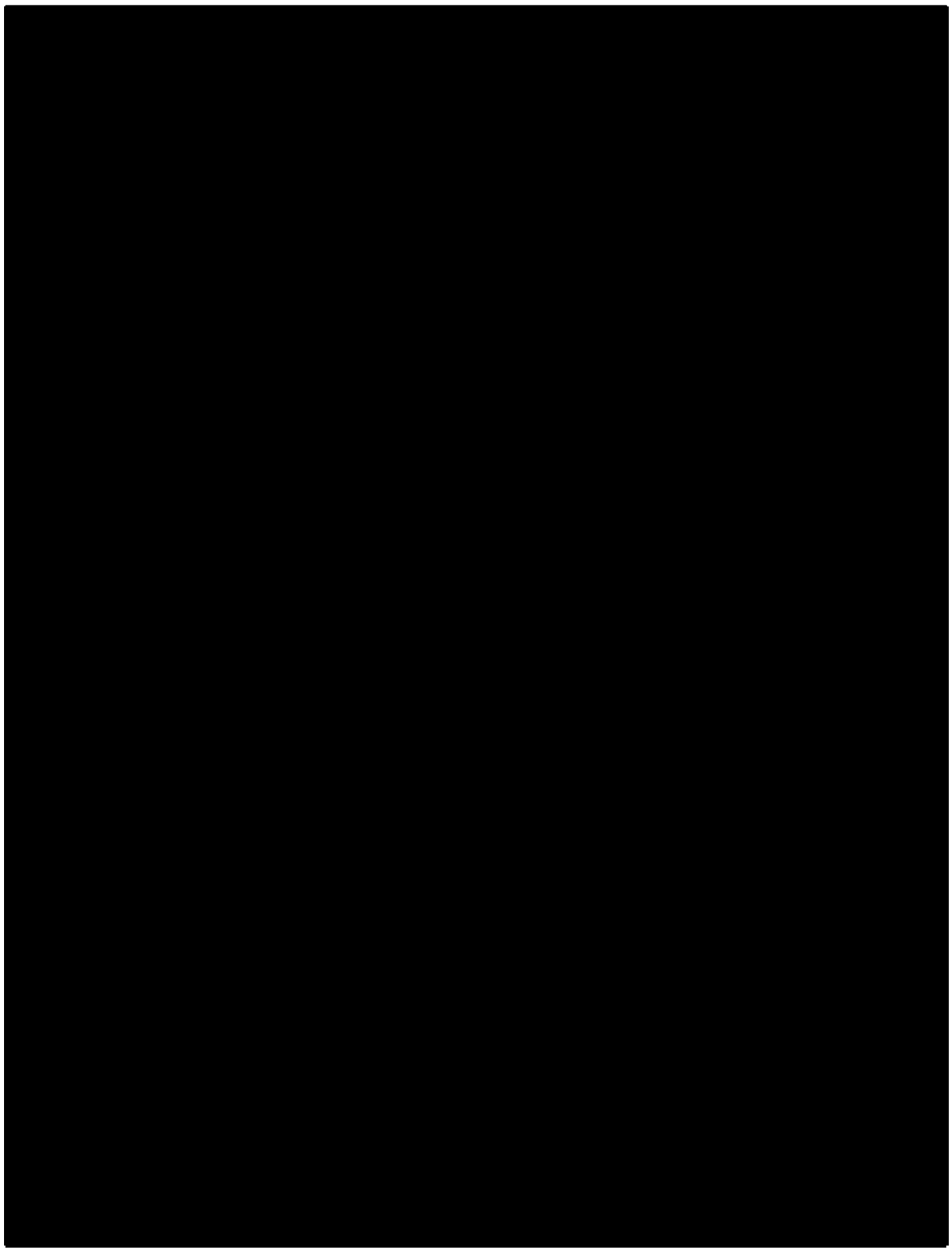


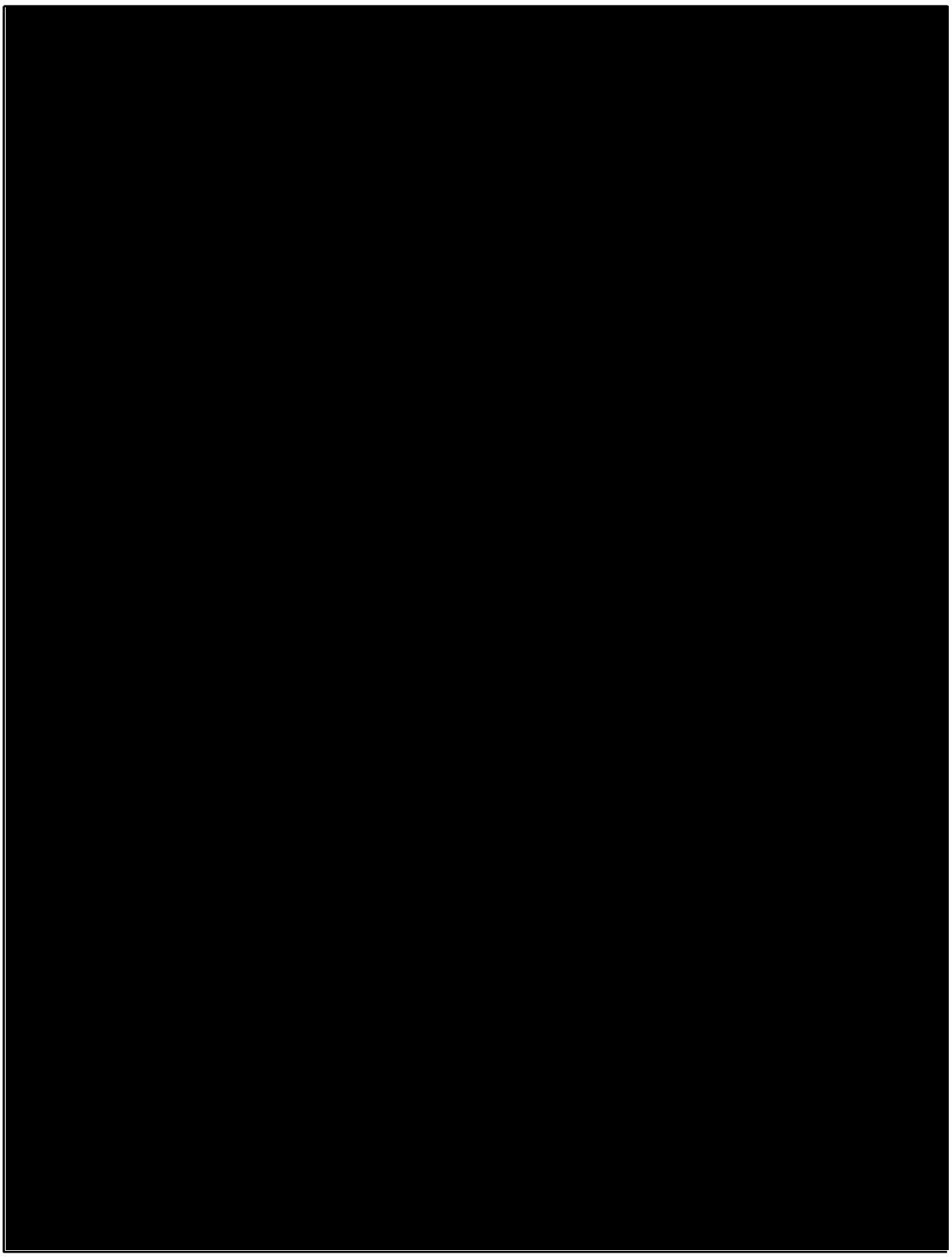


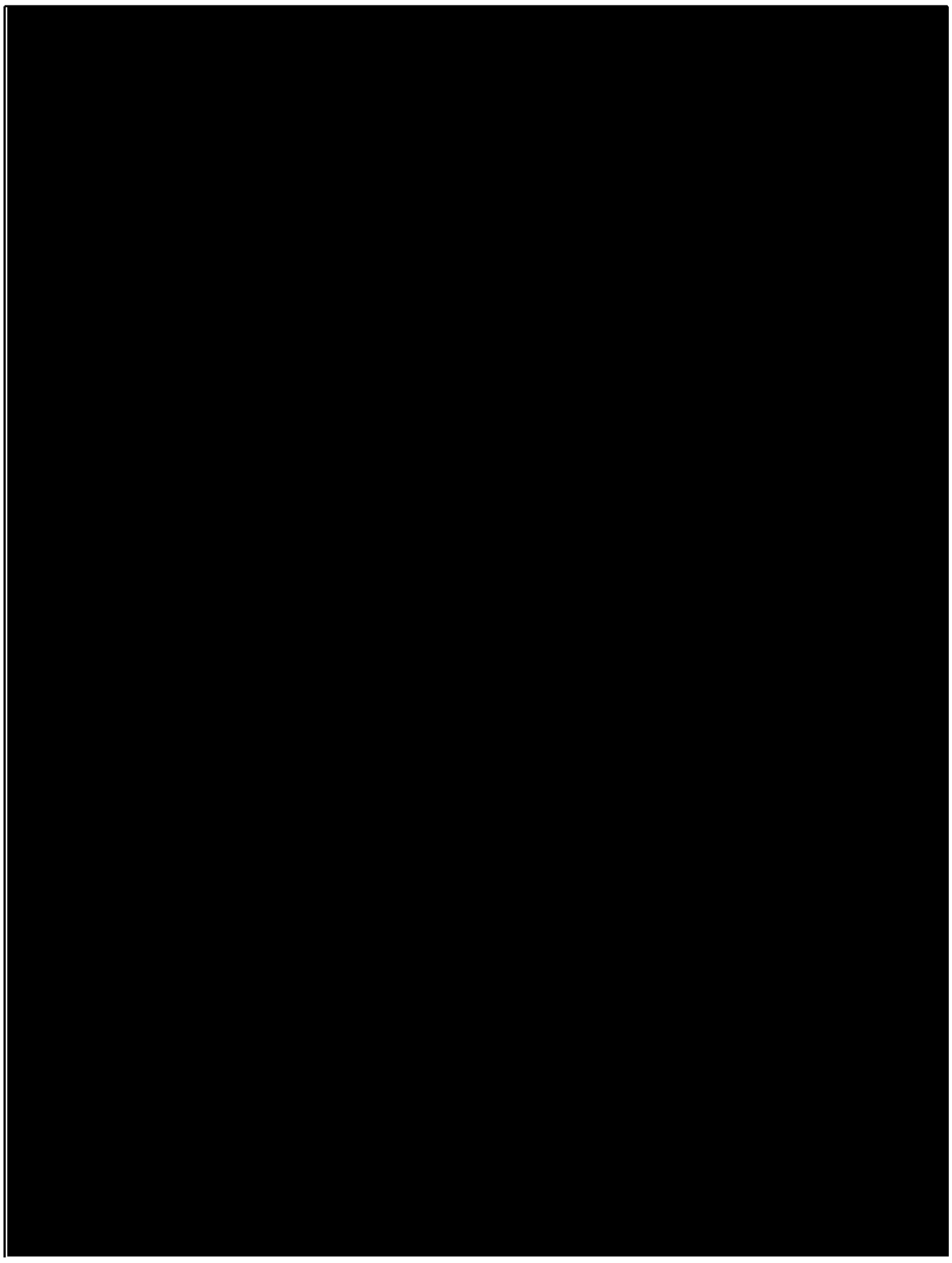


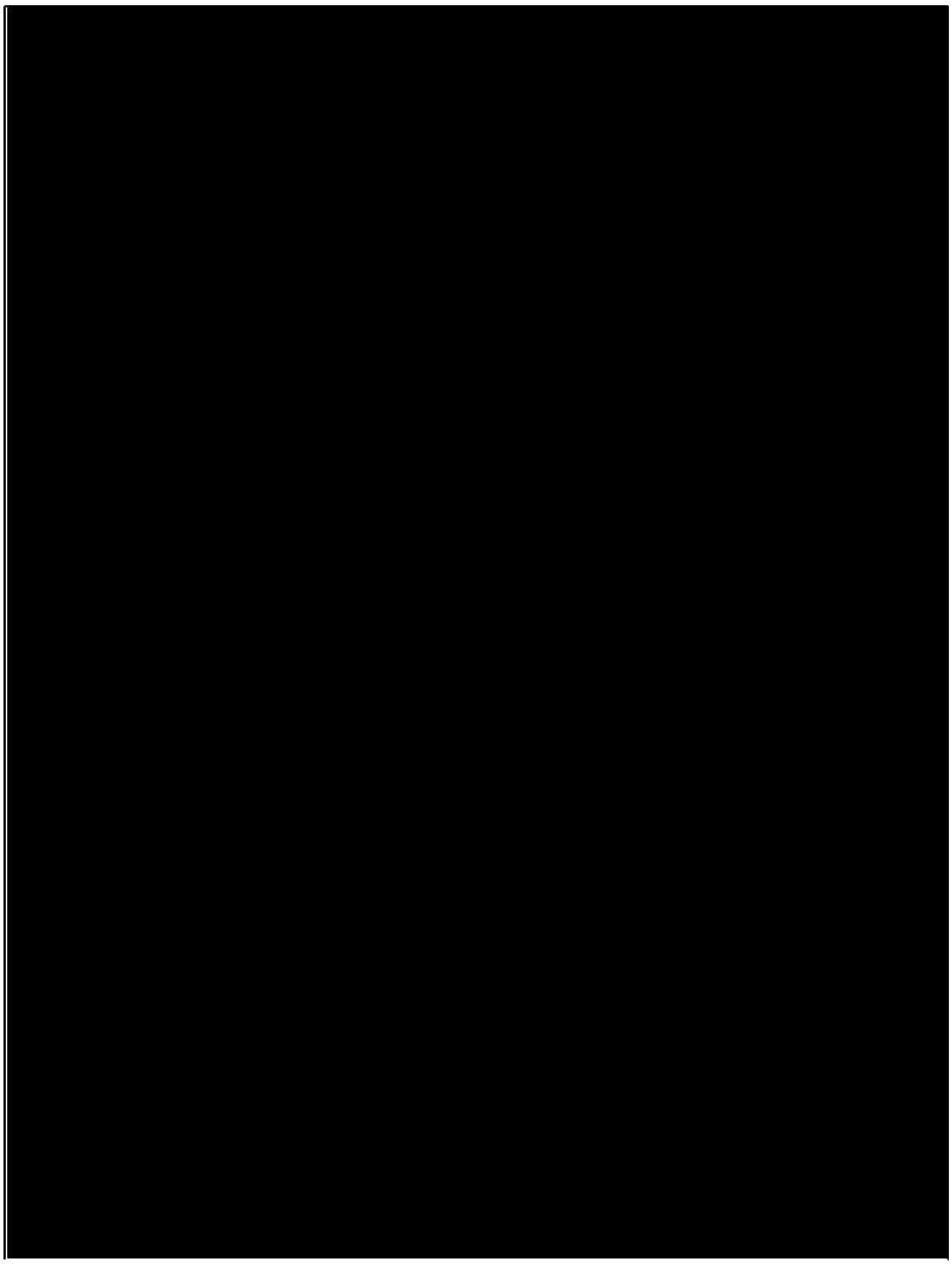


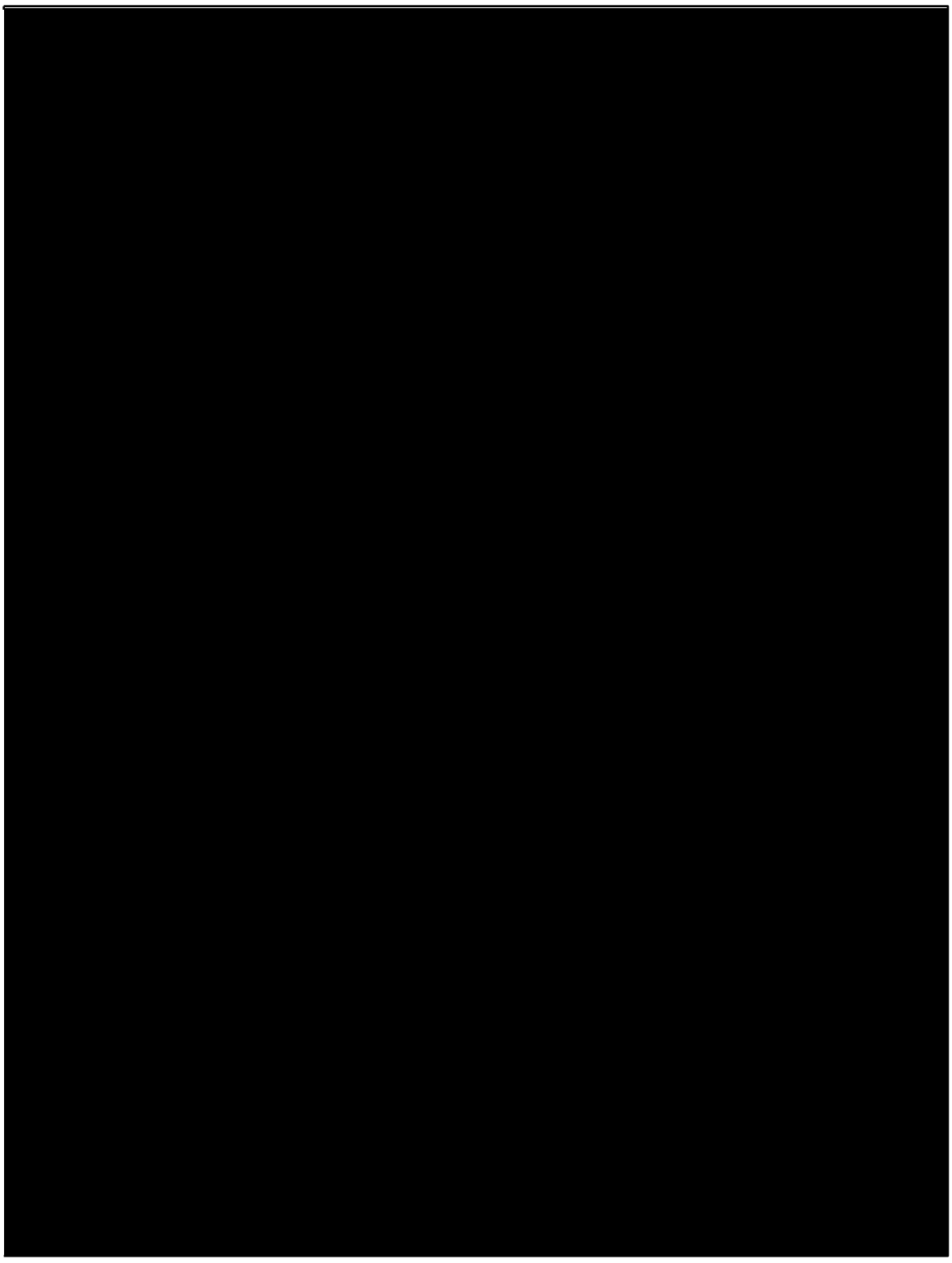


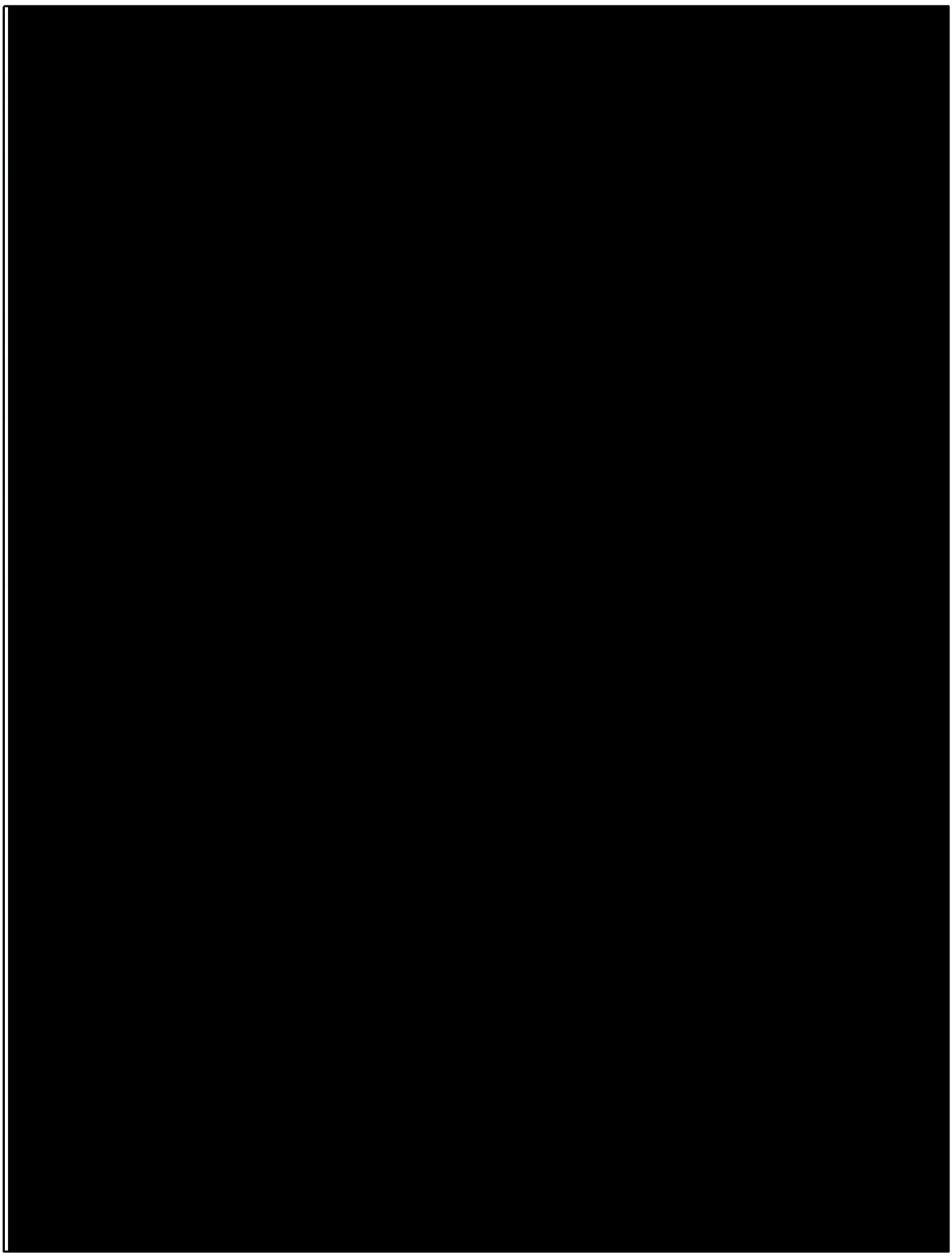


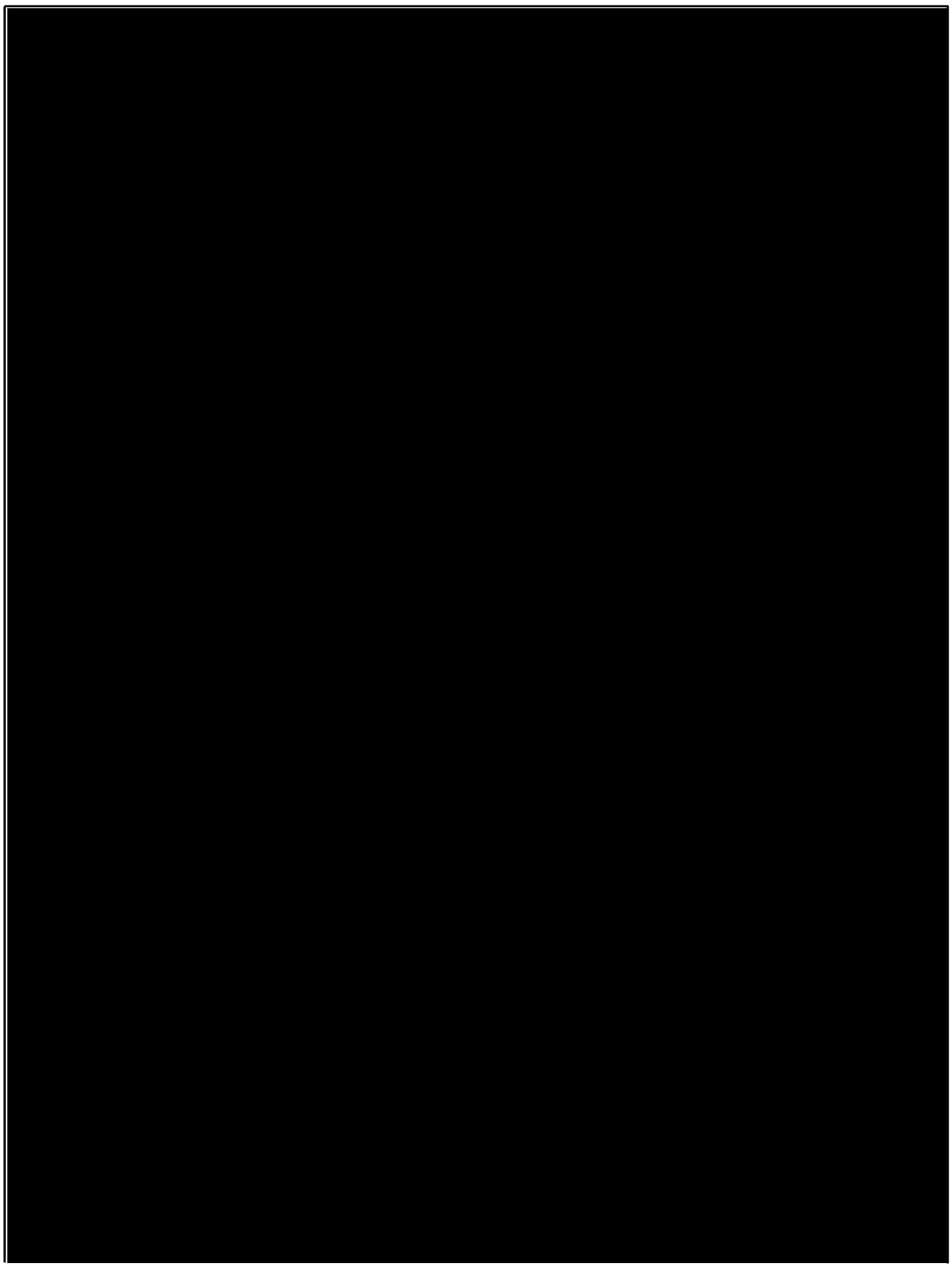


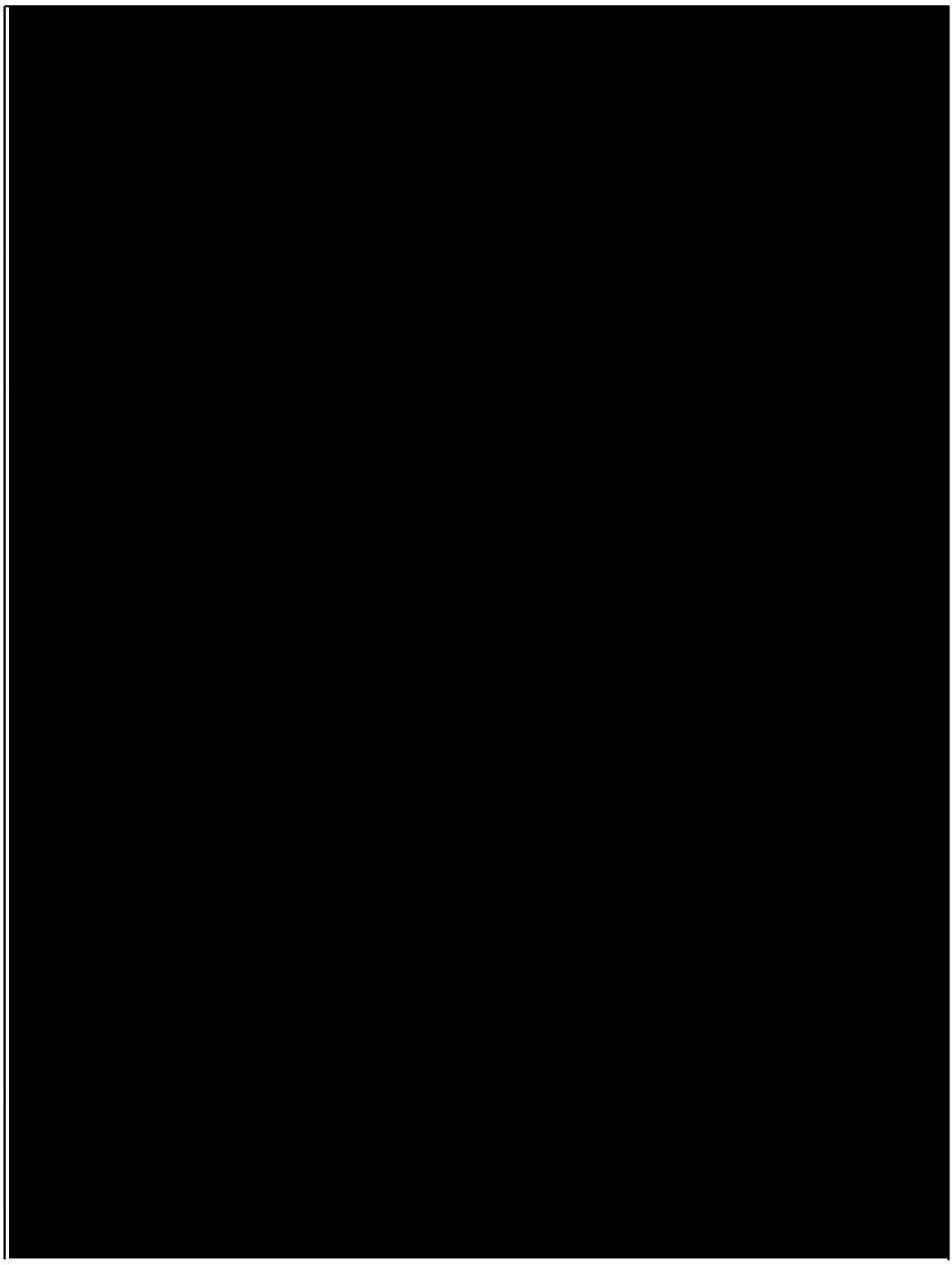








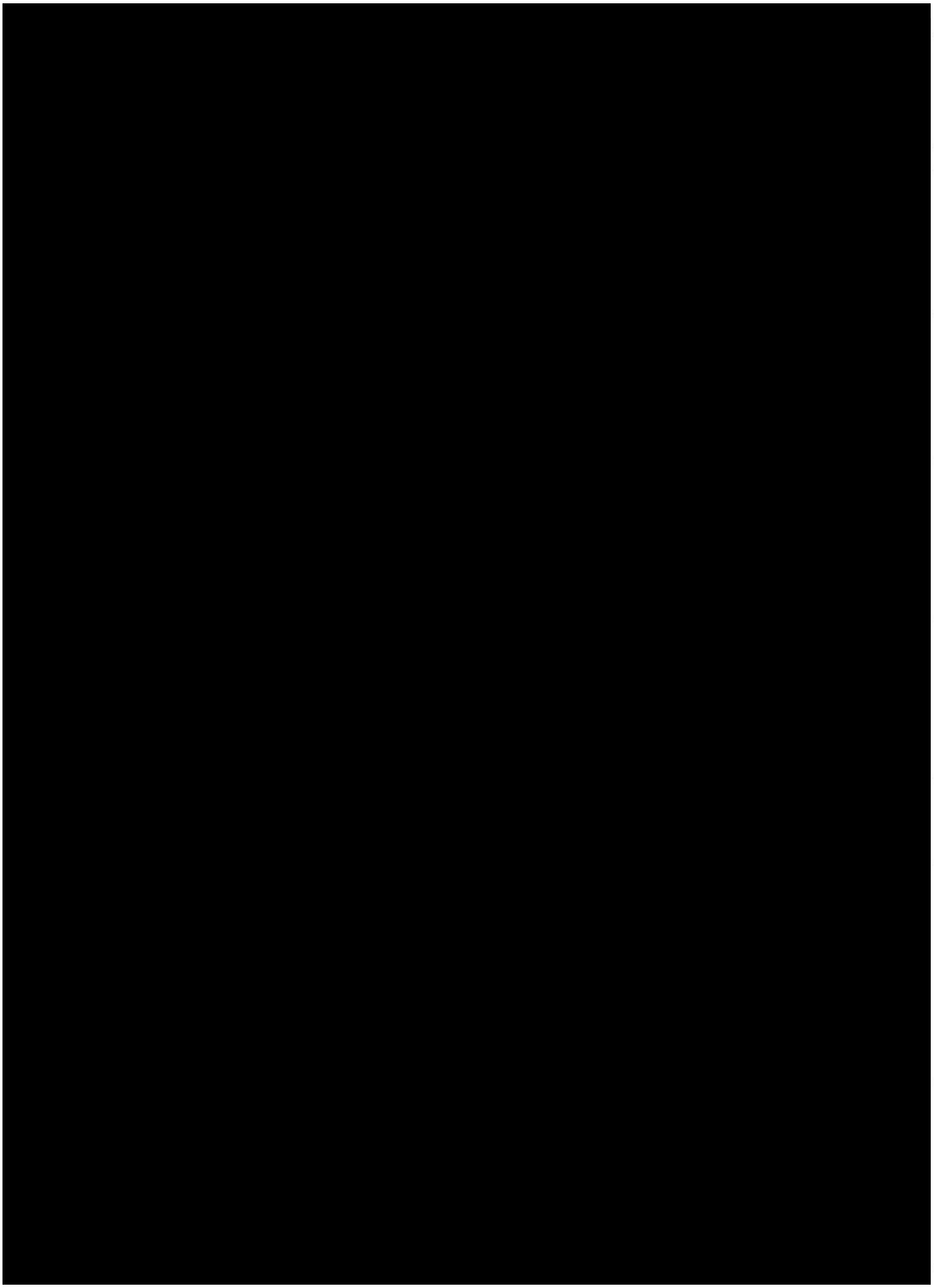


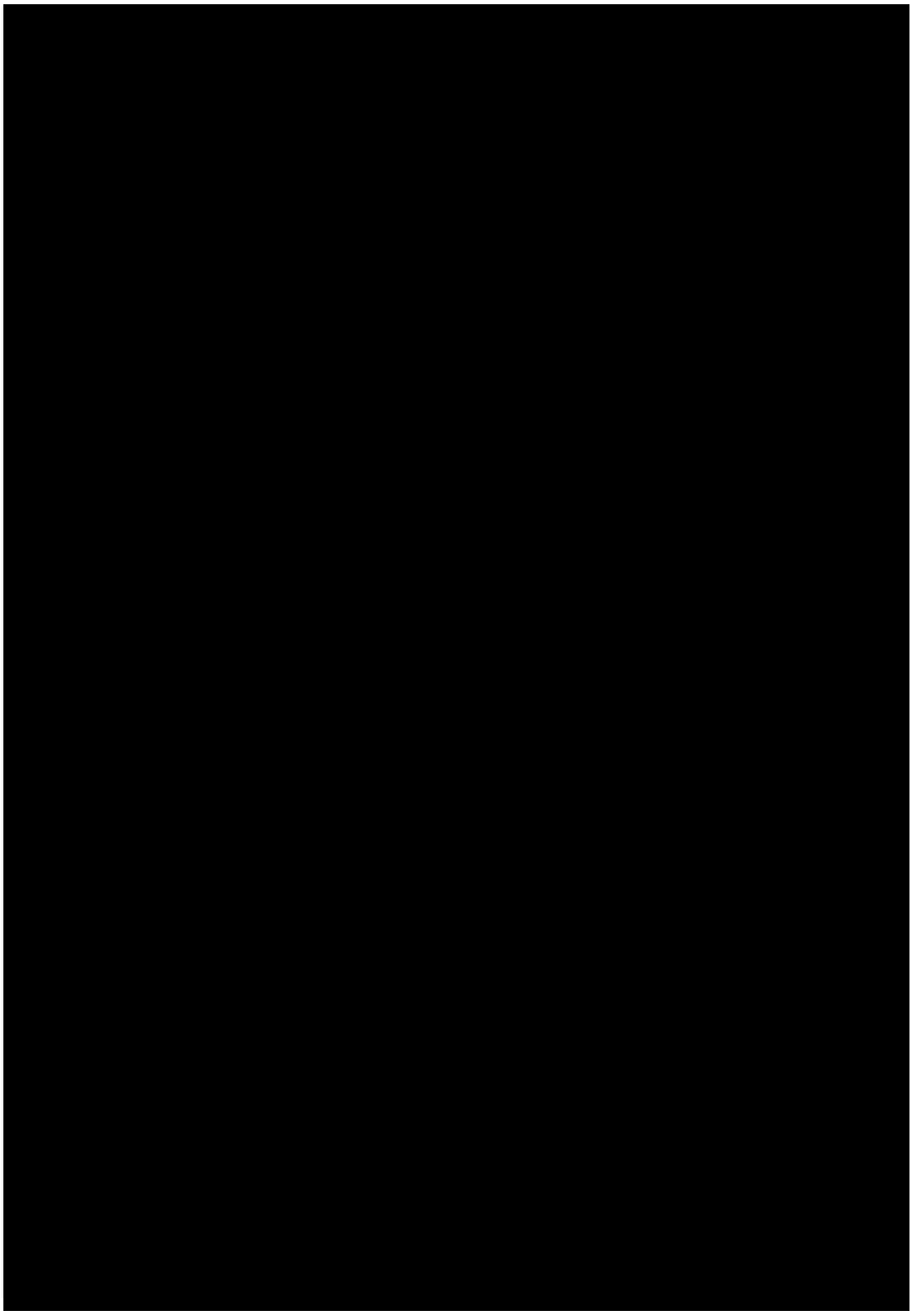


# APPENDIX 3. PERFORMANCE CRITERIA FOR BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3) DEVELOPMENTAL MILESTONES

| **Developmental Milestone** | [redacted] |
|---|---|
| Head Control – Gross Motor Subtest Item #4 | |
| Rolls from Back to Sides – Gross Motor Subtest Item #20 | |
| Sits Without Support – Gross Motor Subtest Item #26 | |
| Stands With Assistance - Gross Motor Subtest Item #33 | |
| Crawls – Gross Motor Subtest Item #34 | |
| Pulls to Stand – Gross Motor Subtest Item #35 | |
| Walks With Assistance – Gross Motor Subtest Item #37 | |
| Stands Alone – Gross Motor Subtest Item #40 | |
| Walks Alone – Gross Motor Subtest Item #43 | |

# APPENDIX 4. CHOP-INTEND





# APPENDIX 5. SCHEDULE OF ASSESSMENTS

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study [a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly [c]** | **18 months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones [d] (with video) [e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND [g] (with video) [e] | X | X[s] | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs [h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j, t] | X |
| 12-Lead Holter Monitoring [k] | | X | X | X | X | | | | | X[j, t] | X |
| Echocardiogram | X | | | | | | | | | X[j, t] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| CK-MB | X | | | | | X | | | X | X[r] | X |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | | X | | X | | | | | | | |
| ELISA anti-AAV9/SMN Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISpot) | | | | | | X | | | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding) [p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events [n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.

[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed at Months 3, 6, 9, and 12 and every 6 months thereafter.
[k] On Days -1 to Day 3, serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing and continued as per protocol Section 9.2.1.
[r] CK-MB to be performed at Day 60, and Month 6, 9, 12, 15 months of age, 18 months of age/EOT).
[s] If a Day -1 CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Day 1 prior to dose administration.
[t] For patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent form, an echocardiogram, 24-hour Holter monitoring, and 12-lead ECG will be performed at the next scheduled visit and then in accordance with the Schedule of Assessments Compound Motor Action Potential Manual

**Phase 3 Gene Transfer Clinical Study for Spinal Muscular Atrophy Type 1 Delivering AVXS-101**

# CMAP Manual
# Compound Motor Action Potential (CMAP)

## Materials Needed for the Process

- Carefusion Disposable Ring Electrode with Leads (order number 019-439300) (4 per visit)
- Carefusion Tab Electrodes 1.0 meter leads (order number 019-406600) (1 or 2 per visit)
- CMAP case report form
- Infrared temperature probe
- Electrode gel
- Warming packs or some other warming source
- Transpore adhesive tape
- Alcohol skin prep pads
- EMG machine

### Temperature and Warming

As only the peroneal motor study will be performed, only lower extremity temperatures will need to be assessed. The temperature should be measured on the surface of the anterior calf distal to the recording electrodes and proximal to the ankle. As the protocol only refers to measurement of upper extremity temperatures, by convention a temperature threshold that is 2 degrees lower, i.e., ≥ 31 degrees Centigrade, should be sufficient. When the temperature is measured to be below 31 degrees, a warming procedure should be performed, either with heated towels or other authorized devices. Care must be taken not to apply towels or other devices at temperatures that would put the infants at risk of burns, the examiner must test the temperature of the warming device against his/her own skin and/or the skin of a parent prior to application. As a general rule, the warming device should feel lukewarm, not hot, against an adult's skin, and it should be expected that the warming procedure will take 3–5 minutes. Scheduling of this procedure should allow for both temperature recording and warming procedures.

### Preparation of Skin

The skin should be cleaned with alcohol (or equivalent) as needed to improve contact with the electrodes.

**EMG machine settings**

For the peroneal CMAP measures the filter settings should be 10 Hz to 10 kHz.

**Tibialis Anterior (TA) CMAP Electrode Placement**

For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed over the tendon above the ankle in a standard "belly-tendon" arrangement. An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode. Adhesive tape may be used to secure any loose electrodes in place. Adhesive tape should not touch other electrodes or other pieces of adhesive tape.

**Supramaximal Nerve Stimulation for TA CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at or proximal to the fibular head. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. Maximum CMAP amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

**Alternate G1 Electrode Placements and Repetition of Motor Study**

As the motor point of the tibialis anterior does not have precise landmarks, there is a possibility that the G1 electrode will not be placed exactly over the motor point without testing multiple sites. Thus, as tolerated by the patient, the CMAP should be recorded at least 3 times, with a different placement of the G1 electrode each time. The CMAP with the highest amplitude among the trials should be reported.

# APPENDIX 6. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving Human subjects.
6. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.
    Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving Human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.
    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research patients should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

# APPENDIX 7. SUMMARY OF CHANGES

The section below highlights content changes represented in this version of the protocol. Language deleted from Protocol version 3.0 appears in ~~red strike through~~. Language added to Protocol version 4.0 appears in **bold**.

The Amendment 3 version of the protocol (Protocol version 4.0) is updated to included updated and recent GLP toxicology data, to provide additional cardiac monitoring for patient safety, standardize infusion times within protocol, and to exclude patients from Bayley scales where English is not their first language to preserve the validity of the Bayley scales. Additionally, minor editorial edits were included where applicable.

**Section 1.1 Approval**

[redacted] _____ _____

~~Chief Medical Officer~~
~~AveXis, Inc.~~

~~Date (ddMmmyyyy)~~

[redacted] _____ _____

~~Senior Vice President, Chief Regulatory and Quality Officer~~
~~AveXis, Inc.~~

~~Date (ddMmmyyyy)~~

**Rationale for Change**

Administrative change.

**Section 2 Synopsis, Duration of Treatment**

AVXS-101 will be administered as a 1-time IV infusion over approximately ~~30~~ 60 minutes, dependent upon the volume required.

**Section 5.3 Non-clinical Studies**

~~These mouse and monkey studies can be summarized as follows.~~ **In these non-GLP studies,** ~~T~~the serum chemistry and hematology studies were unremarkable as was the histopathology assessment.

**Rationale for Change**

Updated to include GLP toxicology data.

**Section 5.3 Non-clinical Studies**

**In pivotal GLP compliant 3-month mouse toxicology studies, the main target organs of toxicity were the heart and liver. Following intravenous infusion in the mouse, vector and transgene were widely distributed with the highest expression generally observed in heart**

**and liver, and substantial expression in the brain and spinal cord. AVXS-101-related findings in the ventricles of the heart were comprised of dose-related inflammation, edema and fibrosis, and in the atrium, inflammation and thrombosis. Liver findings were comprised on hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. A no observable adverse effect level (NOAEL) was not identified for AVXS-101-related heart and liver findings in the mouse, and the Maximum Tolerated Dose was defined as $1.5 \times 10^{14}$ vg/kg, providing a safety margin of approximately 1.4-fold relative to the recommended therapeutic dose of $1.1 \times 10^{14}$ vg/kg. The translatability of the observed findings in mice to primates is not known at this time.**

**Rationale for Change**

Updated to include GLP toxicology data.

**Section 5.3 Non-clinical Studies**

~~When newborn FVB mice were given a single IV injection of AVXS-101 at levels up to $3.3 \times 10^{14}$ vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of AVXS-101 was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given $3.3 \times 10^{14}$ vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses. Based on these results, the no observable adverse effect level (NOAEL) of AVXS-101 in newborn male and female mice is considered to be $3.3 \times 10^{14}$ vg/kg.~~

~~Intravenous administration of AAV9 has been shown to be safe and well tolerated when administered to mice and monkeys. The vector has also demonstrated the ability to cross the blood brain barrier in both species following IV administration. Body weight increased, righting behavior improved, survival was extended and cardiac deficits returned toward normal in treated SMNΔ7 mice when compared to untreated SMNΔ7 mice. Toxicology studies determined the NOAEL of AVXS-101 was $3.3 \times 10^{14}$ vg/kg and there was no test article mortality or toxicity observed up to 24 weeks following IV administration in mice. Biodistribution to the brain and spinal cord was reconfirmed and low levels of antibodies to the AAV9 capsid were observed at 12 and 24 weeks following the $3.3 \times 10^{14}$ vg/kg dose. No alteration was observed in clinical pathology and histopathology analyses.~~

**Rationale for Change**

Updated to reflect recent GLP toxicology data.

**Section 10.6 Study Product Administration**

AVXS-101 should be slowly infused over approximately ~~30~~ 60 minutes, dependent upon total volume in accord with the Pharmacy Manual, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

**Rationale for Change**

Standardization of infusion time within the study.

**Section 11.2.1 Bayley Scales of Infant and Toddler Development/Developmental Milestones**

The full Bayley Scales will be administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain will be administered at each monthly visit. **For patients which English is not their first language, the language subtests (receptive communication and expressive communication) and cognitive scale portions of the Bayley will not be performed.**

**Rationale for Change**

For the purposes of this study, the Bayley Scales are only conducted in English. Administering in a second or non-native language would jeopardize the validity of these portions of the Bayley Scales.

**Section 12.1.4 Electrocardiogram**

A 12-lead ECG will be performed at screening, Day –1, pre-dose on Day 1, Day 2, **Months 3, 6, 9, and 12 visits and** every 6 months **thereafter. A 12-lead ECG will also be performed**~~starting~~ at ~~Month 6, and~~ **the** End of Study **visit** when the patient reaches 18 months of age (or early termination) (Appendix 5). **For patients enrolled in the study prior to amendment 3 in the study and irrespective of the study schedule, after signing an updated informed consent, all patients should have a 12-lead ECG at their next scheduled visit and then in conformity with the Schedule of Assessments (**Appendix 5**).** Additional ECG monitoring will be at the discretion of the Investigator as per local institutional guidelines.

**Rationale for Change**

Added to provide additional cardiac monitoring to assure patient safety.

**Section 12.1.5 12-Lead Holter Monitor**

**On Days -1 to Day 3, s**~~S~~erial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours

- 36 hours
- 48 hours

**Twenty-four hour Holter monitoring will also be performed at the 3, 6, 9, and 12 month visits and every 6 months thereafter. For patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent, all patients should have a 24-hour Holter monitor at their next scheduled visit and then in conformity with the Schedule of Assessments (Appendix 5).**

**Rationale for Change**

Added to provide additional cardiac monitoring to assure patient safety.

**Section 12.1.6 Echocardiogram**

A standard transthoracic echocardiogram will be performed at screening, **at 3, 6, 9, and 12 month visits and** every 6 months **thereafter. An echocardiogram will also be performed** ~~starting at Month 6, and~~ at **the** End of Study **visit** when the patient reaches 18 months of age (or early termination) (Appendix 5). **For patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent, all patients should have an echocardiogram performed at their next scheduled visit and then in conformity with the Schedule of Assessments (Appendix 5).**

**Rationale for Change**

Added to provide additional cardiac monitoring to assure patient safety.

**Section 12.1.10 Laboratory Assessments**

**In most instances, B**~~b~~lood samples will be collected and shipped to a central laboratory, however, **at the discretion of the Investigator, samples may be processed locally for emergent safety monitoring or other logistical or technical reasons that warrant samples to be processed locally.** Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's Clinical Laboratory Improvement Amendment (CLIA) CLIA-certified local laboratory to ensure receipt of results prior to dosing.

**Rationale for Change**

Allowance for samples to be processed locally provides additional options and flexibility for safety monitoring.

## Appendix 5 Schedule of Assessments

| Study Period | Screening | Gene Replacement Therapy (In-patient) | | | | Follow-up (Outpatient) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | X[s] | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j, t] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | X[j, t] | |
| Echocardiogram | X | | | | | | | | | X[j, t] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| CK-MB | X | | | | | X | | | X | X[r] | X |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | | X | | X | | | | | | | |
| ELISA anti-AAV9/SMN Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISpot) | | | | | | X | | | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed at Months 3, 6, 9, and 12 and every 6 months thereafter~~, starting at Month 6~~.
[k] On Days -1 to Day 3, ~~S~~serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
[r] CK-MB to be performed at Day 60, and Month 6, 9, 12, 15 months of age, 18 months of age/EOT).
[s] If a Day -1 CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Day 1 prior to dose administration.
[t] Irrespective of study schedule, after signing the updated informed consent, all enrolled patients should have 12-lead ECG, 24-hour Holter monitoring, and echocardiogram done at the next scheduled visit and then in conformity with the study Schedule of Assessments.

## Rationale for Change

Added to provide additional cardiac monitoring to assure patient safety.

# AVXS-101

# AVXS-101-CL-303

| | |
|---|---|
| **IND Number:** | 15699 |
| **Protocol Title:** | Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion |
| **Indication Studied:** | Spinal Muscular Atrophy Type 1 |
| **Sponsor Address:** | AveXis, Inc.<br>2275 Half Day Road<br>Bannockburn, IL 60015 |
| **Protocol Version/Date:** | 3.0 / 21 December 2017 |

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

## Confidentiality Statement

# 1. ADMINISTRATIVE INFORMATION

## 1.1. Approval

**REPRESENTATIVES FROM AVEXIS:**

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization and the Harmonized Tripartite Guideline for Good Clinical Practice E6
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

**SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):**

[redacted]
Vice President Clinical Development
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Chief Medical Officer
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Senior Vice President, Chief Regulatory and Quality Officer
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Vice President Clinical Operations
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Sr. Director, Head of Biostatistics
AveXis, Inc.

Date (ddMmmyyyy)

## 1.2. Investigator's Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-CL-303 protocol and agree to conduct the study in accordance with the relevant current protocol(s). I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of study participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Informed Consent 21 CFR Part 56, Institutional Review Board Review in 21 CRF Part 56, Adverse Event Reporting as defined in Section 13.4 and in 21 CFR 312.64, Adequate/accurate and accessible records in accordance with 21CFR 312.62 and 312.68.
- Terms outlined in the study site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations) I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

**Confidentiality Statement**

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date (ddMmmyyyy)

## 1.3. Contact Information

**Table 1: Important Study Contact Information**

| Role in Study | Name/Address and Telephone Number |
|---|---|
| Clinical Study Leader | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Responsible Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Drug Safety Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Serious Adverse Event Reporting | Please see Project Management Plan in TMF or Study Contact list in ISF |
| 24-Hour Emergency Contact | Please see Study Contact List in ISF |

**Table 2: Study Vendor Listing**

| Role in Study | Name/Address |
|---|---|
| Clinical Research Organization | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Investigational Product Shipment | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Video | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Independent Video Review | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Holter Monitor and 12-lead Electrocardiogram | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-immunoassays | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-viral shedding studies | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Autopsy | Please see Project Management Plan in TMF or Study Contact list in ISF |

ISF = Investigator site file; TMF = trial master file

# 2. SYNOPSIS

**Name of Sponsor/Company:** AveXis, Inc.

**Name of Investigational Product:** AVXS-101

**Name of Active Ingredient:** Survival Motor Neuron Gene by Self-Complementary Adeno-Associated Virus Serotype 9 (AAV9)

**Title of Study:** Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

**Study Center(s):** 10 to 20 United States (US) Investigators

| **Studied Period (years):** | **Phase of Development:** 3 |
|---|---|
| Estimated date first patient enrolled: 2Q 2017<br>Estimated date last patient completed: 4Q 2019 | |

**Objectives:**

**Co-Primary**

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

**Co-Secondary**

- Determine effect of AVXS-101 on the ability to thrive defined as achieving all of the following at 18 months of age:
  - Does not receive nutrition through mechanical support (e.g., feeding tube) or other non-oral method
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age

[redacted]

**Safety**

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity

**Methodology:**

Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

The study includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of AVXS-101, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age. After the End of Study visit, eligible patients will be asked to rollover into the long-term follow up study.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (day 1, 2, 7, 14, 21, and 30 visits) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient. The first three patients enrolled must meet the criteria for the Intent-to-Treat Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 4-week interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to AVXS-101 infusion until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values, aspartate aminotransferase (AST) values, and T-cell response are below the threshold of 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline: 1 mg/kg/day until at least 30 days post-infusion, 0.5 mg/kg/day at Weeks 5 and 6, 0.25 mg/kg/day at Weeks 7 and 8, and discontinued at Week 9.

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age. The ability to thrive (as defined above) and the ability to remain independent of ventilatory support (as defined above) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development (Version 3). Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires

medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

**Number of Patients (planned):** Up to twenty (20) patients that meet the study enrollment criteria to enable at least fifteen (15) patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

1. Patients with SMA Type 1 as determined by the following features:
   a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))2.
2. The first three patients enrolled must meet the criteria for the Intent-To-Treat Population.
3. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (26)
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

**Exclusion Criteria:**

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

   Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate nonthickened- liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards[25]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening

8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values ( gammaglutamyl- transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)
16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form
19. Gestational age at birth < 35 weeks (245 days)

**Investigational Product, Dosage and Mode of Administration:**

Patients will receive a one-time dose of AVXS-101 at 1.1 X $10^{14}$ vg/kg, a dose determined to be equivalent to the dose received by the Cohort 2 patients in the Phase 1 study (AVXS-101-CL-101) by direct testing using improved analytical methods.

**Duration of Treatment:**

AVXS-101 will be administered as a one-time IV infusion over approximately 30-60 minutes, dependent upon the volume required.

**Reference Therapy, Dosage and Mode of Administration:** Not Applicable

**Criteria for Evaluation:**

**Efficacy:**

**Co-Primary**

- Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 seconds
- Survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death

**Co-Secondary**

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [25] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)

- [redacted]

**Safety:**

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated liver function tests (LFTs) and/or unresolved liver function enzymes (LFEs)
- Incidence of CTCAE Grade 3 or higher toxicity, treatment emergent- adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN, as well as IFNγ Enzyme-linked ImmunoSpot (ELISpot) to detect T-cell responses to AAV9 and SMN

**Statistical Methods:**

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

Based upon widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patient meeting the study entrance criteria (*SMN2* copy number of 2 without the *SMN2* gene modifier mutation (c.859G>C)) would be expected to attain the ability to sit without support for at least 30 seconds at or before the 18 months of age study visit or other milestones (rolling over, standing, walking) assessed as part of the study.

Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis is

whether the AVXS-101 treated patients achieve a response rate greater than 0.1%. Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated patients in the ITT population are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age visit. With the assumption for the true response rate of AVXS-101 for the primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with $\alpha = 0.025$ using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint of survival at 14 months of age will be evaluated by comparing the results observed in the ITT population with the results from the age and gender-matched control patients selected from existing natural history data sets (PNCR) [*Neurol*. 2014; 83(9):810-817]. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. Based upon preliminary results from the ongoing Phase 1 clinical study (AVXS-101-CL-101), at least 80% of patients in the ITT population are expected to survive, as defined, through 14 months of age. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with $\alpha = 0.05$ using a 2-sided Fisher's Exact test.

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## TABLE OF CONTENTS

# LIST OF TABLES



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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AAV | Adenoassociated- virus |
| AAV9 | Adeno-associated virus serotype 9 |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ASO | Antisense oligonucleotide |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CB | Chicken-β-actin-hybrid |
| CDC | Center for Disease Control |
| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| CI | CHOP-INTEND |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CK | Creatine kinase |
| CK-MB | Creatine kinase isoenzyme |
| CLIA | Clinical Laboratory Improvement Amendment |
| CMAP | Compound motor action potential |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Day 1 | First 24-hour interval after the start of gene replacement therapy infusion |
| Day –1 | 24-hour interval prior to the start of gene replacement therapy infusion |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-linked Immunosorbent Assay |
| ELISpot | Enzyme-linked ImmunoSpot |
| ET | Early termination |
| FVB | Friend Virus B-Type |
| GCP | Good Clinical Practice |
| GFP | Green fluorescent protein |
| GGT | Gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| HEENT | Head, eyes, ears, nose, and throat |
| HgB | Hemoglobin |
| HIV | Human Immunodeficiency Virus |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ICD-10 code | International Statistical Classification of Diseases and Related Health Problems |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon gamma |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| ITR | Inverted terminal repeat |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LFE | Liver function enzymes |
| LFT | Liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NHP | Non-human primates |
| NOAEL | No Observable Adverse Effect Level |
| OAE | Other significant Adverse Event |
| PBMC | Peripheral blood mononuclear cells |
| PICU | Pediatric intensive care unit |
| PNCR | Pediatric Neuromuscular Clinical Research Network |
| RNA | Ribonucleic acid |
| RSV | Respiratory syncytial virus |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | Self-complementary |
| scAAV | Self-complimentary adeno-associated virus |
| scAAV9.CB.SMN | Self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron |
| SMA | Spinal muscular atrophy |
| SMN | Survival motor neuron |
| *SMN1* | Survival motor neuron 1 gene |
| *SMN2* | Survival motor neuron 2 gene |
| SOC | System Organ Class |
| TMF | Trial master file |
| US | United States |
| vg/kg | Vector genome per kilogram |
| WBC | White blood cell |
| WHO | World Health Organization |
| WT | Wild type |

# 5. INTRODUCTION

Study AVXS-101-CL-303 is a pivotal Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* as well as 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The first three patients enrolled must meet the ITT criteria to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

In this study, the survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMNΔ7 mouse model for SMA from a median of 15.5 days to over 1 year, following IV delivery to a facial vein. Additionally, preliminary results from an ongoing Phase 1 clinical study (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function (Section 5.4).

## 5.1. Background

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births [1]. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*SMN2*). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis before 6 months of age and early death due to respiratory failure before 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the prenatal period), whereas motor neurons in SMA Type 2 and Type 3 patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of *SMN1* in hopes of rescuing neurons at this critical stage. The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [5,6]. However, clinical studies employing several of these agents, most notably phenylbutyrate, valproic acid, and hydroxyurea,

have not resulted in clinical benefit [7,8]. FDA recently approved Nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some modest promise in improving motor function; however the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring. A single-dose IV administration study of AVXS-101 will provide information on the potential gene transfer has in treating SMA Type 1 patients, and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose study that will include up to 20 Type 1 patients with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

## 5.2. Rationale for Gene Transfer to SMA Type 1 Patients

Patients with SMA Type 1 have been chosen as the target population for this gene therapy study based on studies of the natural history of this disease. The classification of SMA is shown below (Table 4) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

**Table 4: Spinal Muscular Atrophy Classification**

| Type | Age at Symptom Onset | | Maximum Motor Function | Life Expectancy | *SMN2* Copy No. |
|---|---|---|---|---|---|
| 0 | Fetal | | Nil | Days – Weeks | 1 |
| 1 | < 6 Months | 1A: B-2 Weeks<br>1B: < 3 Months<br>1C: > 3 Months | Never sits | < 2 years | 1, 2, 3 |
| 2 | 6 – 18 Months | | Never walks | 20 – 40 years | 2, 3, 4 |
| 3 | 1.5 – 10 Years | 3A: < 3 Years<br>3B: > 3 Years | Walks, regression | Normal | 3, 4, 5 |
| 4 | > 35 Years | | Slow decline | Normal | 4, 5 |

Source: Adapted from Kolb 2011 [10]
*SMN2* = survival motor neuron 2 gene

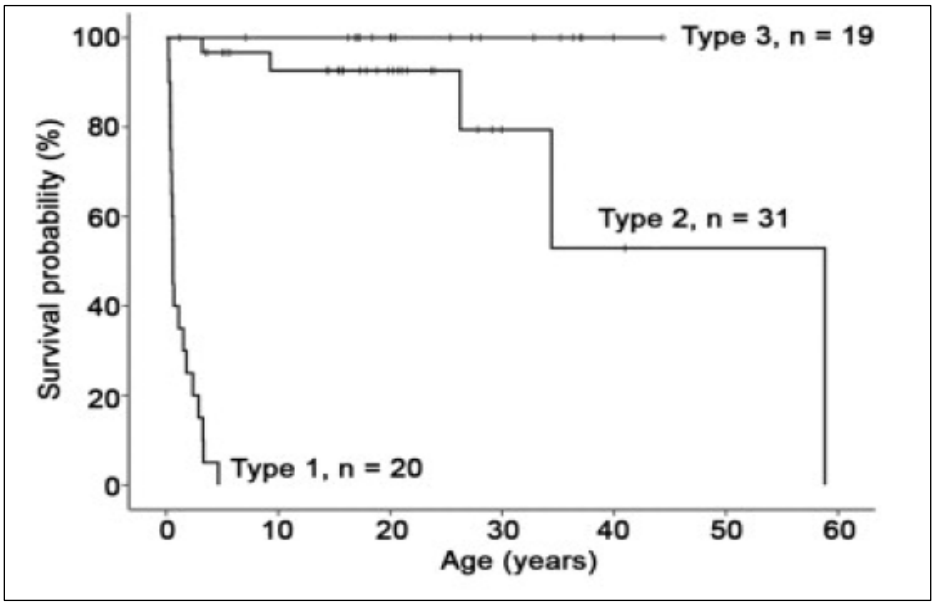
Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 months of age (Table 4). In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3

patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [11]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10 to 15% of that produced by *SMN1* [11,12,13]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms of SMA generally have higher *SMN2* copy numbers [14,15]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, 2, or 3 SMA showed a significant correlation between *SMN2* copy number and SMA Type, as well as, duration of survival. In a large early study by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [16]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [17], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with two *SMN2* copies lived < 21 months, and 8/10 with three *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated, and has also influenced our choice of the study target group.

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

**Figure 1: Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3**




n = number of patients
Source: Farrar 2013 [18]

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the prenatal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [2,3,4].

There is reason to believe that there are few safety issues to be concerned about when targeting the SMA Type 1 group in this gene therapy clinical study. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans, a high copy number of *SMN2* poses no risk (as seen in Type 2, 3, and 4 patients who have high *SMN2* copy number), allowing for use of robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV can be employed for this study because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded adeno-associated virus (AAV) vectors.

Recent studies using self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron (scAAV9.CB.SMN) show a robust post-natal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology and survival after a one-time delivery of vector [19]. Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

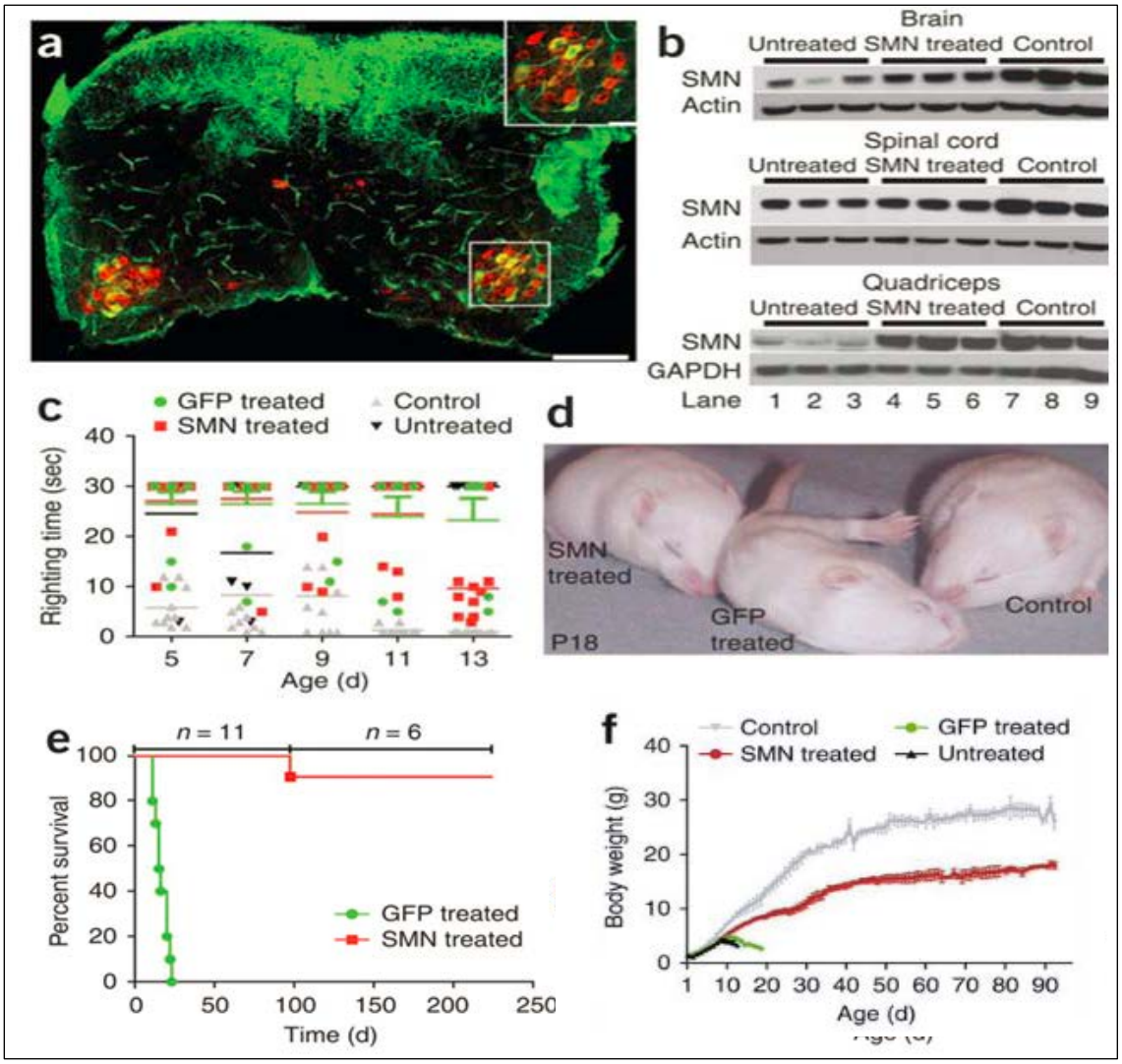
## 5.3. Non-clinical Studies

A mouse model was developed by the [redacted] after a generation of multiple variants. It was found that the double transgenic, referred to as the SMNΔ7 mouse, provided the most suitable model to study gene transfer [20]. Studies performed in the [redacted] have shown that injecting $5 \times 10^{11}$ viral genomes of scAAV9.CB.SMN into the facial vein on Day 1 old mice rescues the SMNΔ7 mouse model [19]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.GFP treated mice. SMN transduction was shown by real time polymerase chain reaction (RT-PCR) in the mice. GFP transduction was observed by microscopy. Both constructs were in AAV9 and had transduction of motor neurons. SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMNΔ7 mice (although lower than wild type [WT] controls). SMNΔ7 animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on post-natal Day 1 were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and green fluorescent protein (GFP)-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than

GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMNΔ7 animals compared with GFP-treated SMNΔ7 animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a 'chimeric' animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

**Figure 2: Study Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves**

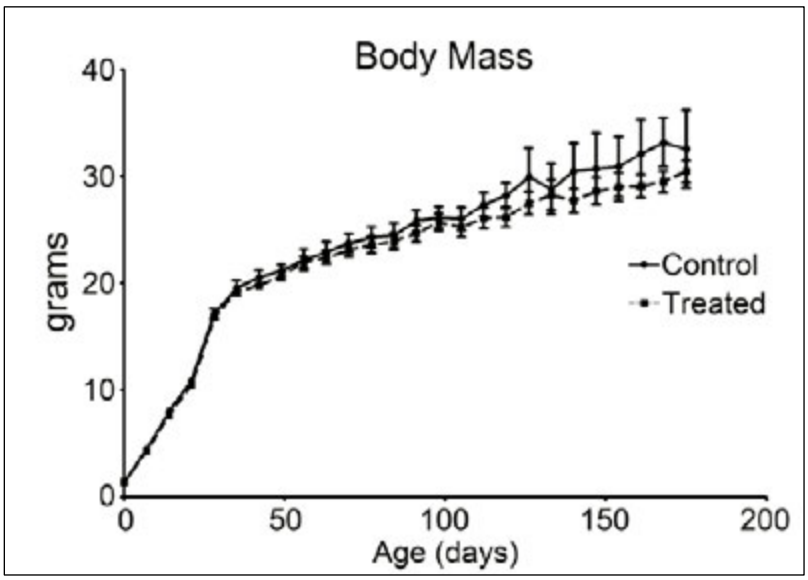



Source: Foust 2010 [19]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type
a)Shows transduced motor neurons in lumbar spinal cord
b) Western Blots of SMN expression in CNS and muscle

c)Improved righting ability of SMN-treated- similar to WT controls by P13
d) SMN-treated are larger than GFP-treated at P18
e)Survival of SMN-treated markedly improved compared to GFP- treated
f) Body weight increased in SMN-treated vs GFP

Toxicology biodistribution studies were generated by the [redacted] [data on file]. In the non-Good Laboratory Practice (GLP) studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with AVXS-101. To assess toxicity and safety, AVXS-101 was injected into P1 wild type Friend Virus B-Type (FVB) mice with either vehicle (3 males/6 females) or $3.3 \times 10^{14}$ vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the SMNΔ7 mouse model [19]. P1 mice were used in anticipation of simulating potential clinical studies in infants. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

**Figure 3 Body Mass of Treated and Control Mice Showed No Difference**




At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies including complete blood counts with differentials. At 90, 120 and 180 days post-injection, blood was collected for clinical chemistries assessment (alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase, creatinine, blood urea nitrogen [BUN], electrolytes, and creatine kinase [CK]). For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. There were no clinically significant results observed during from the hematology, clinical chemistry, and histopathology portions of the study and trends of both groups were comparable. Of note, no significant lesions were present in any brain or spinal cord sections, although, the sections were frozen and thicker than 5 microns which made cellular morphology obscure and subtle changes may not have been identified.

In the safety study for the 4 male Cynomolgus Macaques, animals were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The AVXS-101 vector was administered one time by catheterization of the saphenous vein with a dose of $6.7 \times 10^{13}$ vg/kg, which corresponds to the lowest dose tested for which SMNΔ7 mice showed a significant increase of survival. Animals were followed for six months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using Enzyme-linked ImmunoSpot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

These mouse and monkey studies can be summarized as follows. The serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The NHP patients animals mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [data on file].

When newborn FVB mice were given a single IV injection of AVXS-101 at levels up to $3.3 \times 10^{14}$ vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of AVXS-101 was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given $3.3 \times 10^{14}$ vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses. Based on these results, the no observable adverse effect level (NOAEL) of AVXS-101 in newborn male and female mice is considered to be $3.3 \times 10^{14}$ vg/kg.

Intravenous administration of AAV9 has been shown to be safe and well tolerated when administered to mice and monkeys. The vector has also demonstrated the ability to cross the blood brain barrier in both species following IV administration. Body weight increased, righting behavior improved, survival was extended and cardiac deficits returned toward normal in treated SMNΔ7 mice when compared to untreated SMNΔ7 mice. Toxicology studies determined the NOAEL of AVXS-101 was $3.3 \times 10^{14}$ vg/kg and there was no test article mortality or toxicity observed up to 24 weeks following IV administration in mice. Biodistribution to the brain and spinal cord was reconfirmed and low levels of antibodies to the AAV9 capsid were observed at 12 and 24 weeks following the $3.3 \times 10^{14}$ vg/kg dose. No alteration was observed in clinical pathology and histopathology analyses.

## 5.4. Clinical Studies

First-in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received the low dose used in this study (equivalent to a dose that doubled mouse lifespan in the SMNΔ7 Mouse potency assay) and Cohort 2 (n = 12) received the high dose used in this study (equivalent to a dose that restored mouse lifespan to greater than 200 days or "full life" in the SMNΔ7 Mouse

potency assay). The dose received by Cohort 2 patients in AVXS-101-CL-101 (proposed therapeutic dose) has been demonstrated to be equivalent to the dose to be used in the AVXS-101-CL-303 study by direct testing using improved analytical methods.

Preliminary data as of 15 September 2016 indicate that treatment with AVXS-101 results in broad improvements in survival, motor function, pulmonary function, and nutritional function. All patients in Cohort 2 (proposed therapeutic dose) showed improvements in survival, as defined by Finkel et al 2014 [21], with no deaths or requirements for permanent ventilation ≥ 16 hours/day for ≥ 14 consecutive days through 15 September 2016. The median age at last follow-up for Cohort 2 was 17.3 months, with the oldest patient at 27.4 months of age. One patient in Cohort 1 (lowdose–cohort) had a pulmonary event of increased use of bi-level positive airway pressure in advance of surgery related to hypersalivation, a condition experienced by some SMA patients. The event was determined by independent review to represent progression of disease and not related to AVXS-101.

As of September 15, 2016, improvements in motor function, as assessed by the CHOP-INTEND scores, were observed with mean increases of 9.0 points in Cohort 1 and 24.8 points in Cohort 2. The CHOP-INTEND scores in Cohort 2 were ≥ 40 points for 11/12 patients, ≥ 50 points for 9/12 patients, and ≥ 60 points (normal) for 3/12 patients.

As of September 15, 2016, patients in Cohort 2 consistently achieved and maintained key developmental motor milestones as summarized below:

- 11/12 patients achieved head control, 7/12 patients could roll, 11/12 patients could sit with support, and 8/12 patients could sit unassisted, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016
- 7 patients were able to feed themselves, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016, and 5 patients were speaking (1 bilingual)
- 2 patients were walking independently, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016. These 2 patients each achieved earlier and important developmental milestones such as crawling, standing with support, standing alone, and walking with support

As of September 15, 2016, AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in this study. A total of 118 treatment-related AEs were reported (34 serious adverse events [SAEs] and 84 nonserious- adverse events [AEs]). Two SAEs were deemed treatment-related in 2 patients, and 3 AEs were deemed treatment-related in 2 patients. All treatment-related events consisted of clinically asymptomatic liver enzyme elevations that resolved with prednisolone treatment. There were no clinically significant elevations of gammaglutamyl transferase (GGT), alkaline phosphatase or bilirubin, and as such, Hy's- Law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

In summary, through September 15, 2016, the consistently positive clinical observations are remarkably different from that described in extensive natural history studies, clinical publications, the experience of seasoned clinicians, and concurrent SMA Type 1 studies with other therapies. These significant and clinically meaningful responses in patients treated with

AVXS-101 indicate preliminary clinical evidence of a treatment effect that addresses an unmet need in this devastating pediatric disease.

A full understanding of all the risks associated with AVXS-101 is not known at this time. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 study, which is believed to be a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the study were accompanied by clinical sequelae. Patients could experience an allergic response to AVXS-101. Patients could also develop an immune response to the AAV9 viral vector, which could prevent future use of gene transfers using this vector.

Taken together, results from the clinical and non-clinical studies support further clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objectives

The co-primary objectives are to:

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

## 6.2. Secondary Objective

The co-secondary objectives are to:

- Determine the effect of AVXS-101 on the on the ability to thrive defined as achieving all of the following at 18 months of age
  - Does not receive nutrition through mechanical support (e.g., feeding tube)
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device, for patients issued a Trilogy 100 BiPAP device

## 6.4. Safety Objectives

The safety objectives are to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) [9] Grade 3 or higher, unanticipated, treatment-related toxicity.

# 7. INVESTIGATIONAL PLAN

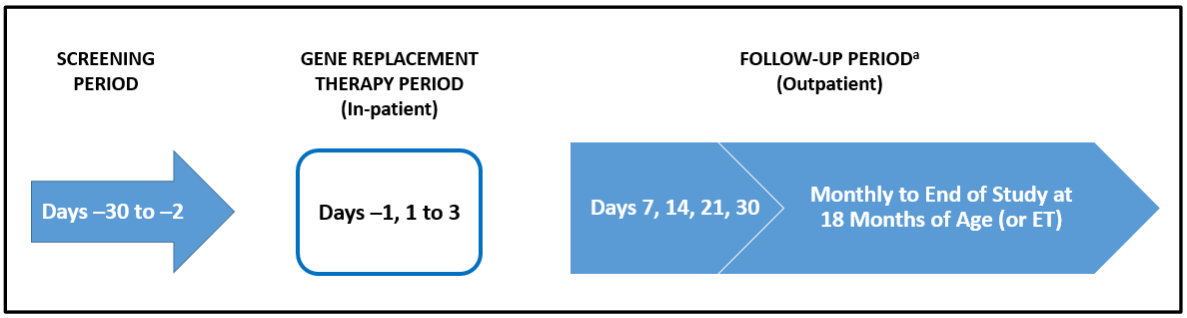
## 7.1. Overall Study Design

This is a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) that will enroll up to twenty (20) patients with SMA Type 1who may be either symptomatic or pre-symptomatic with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

The study includes 3 study periods: screening, gene replacement therapy, and follow-up (Figure 4). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time IV infusion of AVXS-101 at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study over approximately 60 minutes, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within 7 days.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days **after** the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients will be asked to roll over into the long-term follow-up study.

**Figure 4: Study Design**




Note: After the End of Study visit at 18 months of age, eligible patients will be asked to roll over into the long-term follow-up study.
ET = early termination
[a] All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (day 1, 2, 7, 14, 21, and 30 visits) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 4-week interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion in accordance with the specified guidelines for tapering (Section 9.2.1).

A schedule of study assessments is provided in Appendix 5. Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined in Section 14.1.1.2) will also be assessed. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development© (Version 3) (Section 11). Safety will be assessed through monitoring AEs, concomitant

medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (Section 12). Additionally, a Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment (Section 13.1.1.1 and Section 15). This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

## 7.2. Number of Patients

Up to twenty (20) patients that meet the study entry criteria will be enrolled to enable enrollment of at least fifteen (15) patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

## 7.3. Criteria for Study Termination

An independent DSMB will conduct quarterly and ad hoc reviews of the emerging safety data throughout the study as described in Section 15.

The study will be completed as planned but may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment
- DSMB can recommend early termination of the study for safety reasons
- Study is terminated by Sponsor
- Regulatory Authority recommendation

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients with SMA Type 1 who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) with proven biallelic- mutations of the *SMN1* gene and 1 or 2 copies of the *SMN2* will be enrolled in this study. Patients may be of any racial, ethnic, or gender background.

## 8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Patients with SMA Type 1 as determined by the following features:
    a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))
2. The first three patients enrolled must meet the criteria for the Intent-To-Treat population
3. Patients must be < 6 months (< 180 days) of age at the time of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics [26]
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

## 8.2. Patient Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

    Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours/day over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study

5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards [25]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non- respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for the treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (GGT, ALT, and AST > 3 × ULN; bilirubin ≥ 3.0 mg/dL; creatinine ≥ 1.0 mg/dL; hemoglobin < 8 or > 18 g/dL; white blood cells [WBC] > 20,000/cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)

16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form
19. Gestational age at birth < 35 weeks (< 245 days)

## 8.3. Patient Withdrawal Criteria

Patients may be discontinued from the study for the following reasons:

- Death

– An autopsy will be requested for any patient who expires following participation in a gene replacement study [25] (see Autopsy Plan in Appendix 1)

- Failure to comply with protocol-required visits or study procedures for 3 or more consecutive visits that are not rescheduled, unless due to hospitalization
- Parent(s)/legal guardian(s) withdraws consent
- Investigator discretion

Early termination procedures should be completed within 14 days for any patient who prematurely discontinues the study for any reason, as indicated in Appendix 5.

# 9. TREATMENT OF PATIENTS

It is the responsibility of the Investigator to ensure the safe storage and administration of gene replacement therapy.

## 9.1. Description of Product

The biological product is a non-replicating recombinant AAV9 containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed and the resulting protein is produced. The biological product, called AVXS-101 (formerly scAAV9.CB.hSMN), expresses the human SMN protein in transduced cells.

**Table 5: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name:** | AVXS-101 |
| **Dosage Form:** | Equivalent to the dose received by the second dosing cohort in the Phase 1 study |
| **Unit Dose** | 1.1 X $10^{14}$ vg/kg; Equivalent to the dose received by the Cohort 2 in the Phase 1 study (AVXS-101-CL-101) as determined by direct product testing with improved analytical methods. |
| **Route of Administration** | Intravenous infusion |
| **Physical Description** | AVXS-101 is a clear, colorless liquid. |

## 9.2. Prior and Concomitant Medications

Prior and concomitant medications will be captured in the electronic Case Report Form (eCRF) from 2 weeks prior to administration of gene replacement therapy through the last study visit.

### 9.2.1. Prophylactic Administration of Prednisolone

An antigen specific T-cell response to the AAV vector was observed in the ongoing Phase 1 clinical study (AVXS-101-CL-101) investigating AVXS-101 treatment via IV infusion. This is an expected response between 2 to 4 weeks following gene replacement therapy. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression.

In an attempt to dampen the host immune response to the AAV based- therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell response are ≤ 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline:

- Until at least 30 days post-infusion: 1 mg/kg/day
- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/day
- Week 9: prednisolone discontinued

If the AST or ALT values are > 2 X ULN, or if T-cell response is ≥ 100 SFC/$10^6$ PBMCs after 30 days of treatment, the dose of prednisolone will be maintained until the AST and ALT values decrease below threshold. If T-cell response continues past Day 60, Investigator discretion should be used considering risk benefit for maintaining prednisolone. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient.

### 9.2.2. Prohibited Medications

Concomitant use of any of the following medications is prohibited:

- Drugs for treatment of diabetes, myopathy or neuropathy
- Therapy received with the intent to treat SMA (e.g., nusinersen, valproic acid)
    - Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing.
    - Inhaled β-agonists may be used to treat respiratory complications of SMA provided such medications are dosed at clinically appropriate levels
- Any investigational medication other than AVXS-101 is prohibited during the study
- Ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of starting the study (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)

Corticosteroid usage following completion of the prednisolone taper is permissible as part of routine clinical management. The use of corticosteroids in such circumstances should be documented appropriately as a concomitant medication, and the event precipitating its usage should be appropriately documented as an adverse event.

Should the use of corticosteroids (aside from inhaled corticosteroids for bronchospasm) be considered as part of care during the course of the prednisolone taper, this medical management should be discussed with the medical monitor.

## 9.3. Treatment Compliance

AVXS-101 will be administered as a one-time IV injection.

## 9.4. Randomization and Blinding

This is an open-label study.

# 10. STUDY PRODUCT MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in accordance with current Good Manufacturing Practices (cGMP). Investigational product accountability logs will be maintained by the clinical pharmacy.

## 10.1. Study Product

AVXS-101

## 10.2. Study Product Dose and Dose Justification

Patients will receive a one-time dose of AVXS-101 at 1.1 X $10^{14}$ vg/kg, equivalent to the dose received by Cohort 2 in the Phase 1 study via IV infusion administered in the ongoing Phase 1 clinical study (AVXS-101-CL-101).

Two doses are being studied in the ongoing Phase 1 clinical study (AVXS-101-CL-101); the higher dose (dose received by the Cohort 2 patients) was chosen for the present study as preliminary data demonstrated both a dose response and significant clinical benefit thus identifying it as the proposed therapeutic dose. In the Phase 1 study, AVXS-101 demonstrated a dose response, with efficacy greater as observed by motor milestone achievement and CHOP-INTEND scores at the higher dose (received by Cohort 2) than the lower dose (received by Cohort 1). Direct testing of the actual lot of Investigational Medicinal Product (IMP) used in the AVXS-101-CL-101 study by an improved and more fully qualified analytical method has assigned a value of 1.1 x $10^{14}$ vg/kg to the actual dose received by Cohort 2 in this Phase 1 study. The same method has been used to establish an equivalent dose for the Phase 3 IMP. This vg/kg value has been further verified in an improved and more fully qualified SMNΔ7 Mouse Biopotency assay to support a similar extension of mouse life time in direct comparative assessment between the Phase 1 and Phase 3 IMP.

## 10.3. Study Product Packaging and Labeling

AVXS-101 kits are labeled with a specific kit number and batch/lot number assigned at the cGMP facility. The content of the labeling is in accordance with the local regulatory specifications and requirements.

## 10.4. Study Product Storage

AVXS-101 kits will be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared AVXS-101 should be managed in accordance with the Pharmacy Manual.

The vessel used for delivery of the vector should be resealed in the procedure room and processed for destruction and/or return to AveXis in accord with the Pharmacy manual and applicable biohazardous waste guidelines for disposal.

## 10.5. Study Product Preparation

Preparation of AVXS-101 will be done aseptically under sterile conditions by a pharmacist and will arrive at the clinical site ready for infusion.

AVXS-101 will be received diluted with normal saline, as outlined in the Pharmacy Manual.

The total vector genome dose will be calculated based on the patient's body weight.

The dose-delivery vessel will be delivered to the designated pediatric intensive care unit (PICU) patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. The vessel will be delivered in accord with the Pharmacy Manual.

## 10.6. Study Product Administration

AVXS-101 infusion will be administered under sterile conditions in a PICU or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study. AVXS-101 should be slowly infused over approximately 30-60 minutes, dependent upon total volume in accord with the Pharmacy Manual, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, patients should return to an appropriate designated setting to ensure close monitoring of vital signs and adverse events. Vital signs will be continuously monitored throughout the gene replacement therapy infusion as described in Section 12.1.3. Patients should be maintained in the PICU or other appropriate setting for 48 hours after the start of gene replacement therapy.

## 10.7. Dose Adjustment Criteria

The study investigates a one-time IV infusion of AVXS-101; no dose adjustments are possible.

## 10.8. Study Product Accountability

The pharmacist or designee will maintain accurate records of the quantities of AVXS-101 received, dispensed, destroyed, and/or returned to AveXis. The pharmacist or designee will document the date and time of delivery of the dose vessel to the dose procedure room as well as the time the used vessel was returned to AveXis or destroyed as per the Pharmacy Manual.

## 10.9. Study Product Handling and Disposal

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof containers. All waste must be sealed in bags bearing the biohazard symbol and disposed of in a biohazard waste container.

All transfers must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment, such as gloves.

Any quality issue noticed with the receipt or use of AVXS-101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accord with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply AVXS-101 to a third party, allow AVXS-101 to be used other than as directed by this clinical trial protocol, or dispose of AVXS-101 in any other manner.

# 11. ASSESSMENT OF EFFICACY

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined Section14.1.1.2) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using the Bayley Scales of Infant and Toddler Development (version 3©). Efficacy assessments will be performed at the times specified in the Table of Assessments (Appendix 5), and should be the first assessments performed at any scheduled visit. All post-treatment visits will be relative to the date on which gene replacement therapy is administered except the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

## 11.1. Developmental Milestones

Developmental milestones will be assessed using relevant definitions obtained from the Bayley Scales of Infant and Toddler Development (version 3), and will be analyzed to assess efficacy (Appendix 2 and Appendix 3). Achievement of each developmental milestone will be determined by the Physical Therapist and confirmed by the central reader (as may be necessary) based on an assessment of the submitted videos (Section 11.3). Developmental milestones will be determined at each monthly visit as listed in Section 11.2.1.

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement in accordance with Appendix 5; this assessment must address all milestones/items noted on Appendix 5 that are at or below the child's expected function for age, and be recorded on video. The findings must be documented in the source. Items that are below the expected function for age that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestones of sitting independently (items 22 and 26) should be assessed at every subsequent visit, until attainment of milestone, regardless of starting point on the scale. These milestones must also be assessed at the 18 months of age visit, regardless of previous attainment.

As the Bayley Scales do not necessarily require the child to repeat previously attained milestones, it is essential that each attained milestone be captured on video.

A milestone will be considered achieved when demonstrated by a patient and observed with video capture confirmation during a physical therapy assessment or observed with video as provided by the patient's family at the patient's visit at 18 months of age.

## 11.2. Motor Function Tests

### 11.2.1. Bayley Scales of Infant and Toddler Development/Developmental Milestones

The Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 2) is a standardized, norm-referenced infant assessment of developmental functioning across 5 domains of cognitive, language, motor, social-emotional, and adaptive behavior. The Bayley Scales will be administered by a qualified Physical Therapist.

The full Bayley Scales will be administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain will be administered at each monthly visit.

Each Bayley Scales/developmental milestone assessment will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and may be submitted to the vendor for review by a central reader (Section 11.3).

The following developmental milestones will be assessed:

- Ability to hold head erect without support
- Ability to roll from back to both sides
- Ability to sit with support
- Ability to sit independently, > 10 seconds; WHO [22]
- Ability to sit without support for at least 30 seconds
- Ability to crawl
- Ability to pull to stand
- Ability to stand with assistance
- Ability to stand alone
- Ability to walk with assistance
- Ability to walk alone

### 11.2.2. CHOP-INTEND

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA Type 1, and will be administered by a qualified Physical Therapist.[23,24] The CHOP-INTEND scale examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions (Appendix 4). Anti-gravity movements in assisted rolling, ventral suspension, and supported standing will also be measured.

The CHOP-INTEND will be performed at screening, Day -1, and at each scheduled visit from Day 7 through the End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5). If Day -1 CHOP-INTEND assessment cannot be conducted, a CHOP-INTEND assessment must be completed on Day 1 prior to dose administration.

Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not undergo any additional CHOP-INTEND examinations.

Each CHOP-INTEND exam will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and submitted to the vendor for review by a central reader as may be necessary (Section 11.3).

## 11.3. Video Evidence

Physical therapy assessments (Bayley Scales and CHOP-INTEND) required at each study visit will be video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

## 11.4. Compound Motor Action Potential

Peroneal nerve CMAP amplitude will be measured by a qualified electrophysiologist, at all clinical sites capable of performing this assessment, using the procedures as described in the CMAP Manual (Appendix 6). CMAP will be measured at screening, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5).

The CMAP data will be collected for centralized review and interpretation.

Sites that do not have equipment or appropriately experienced personnel required to perform CMAP measurements will not be required to perform these assessments.

# 12. ASSESSMENT OF SAFETY

## 12.1. Safety Parameters

Safety parameters include physical examinations, pulmonary examinations, vital signs, capillary blood gas assessments, weight and length measurements, 12-lead electrocardiograms (ECGs), 12-lead Holter monitor recordings, echocardiograms, swallowing tests, laboratory assessments, adverse event monitoring, and photographs of the infusion site. In general, safety assessments will be performed at the times specified in the Table of Assessments (Appendix 5). All post-treatment visits are relative to the date on which gene replacement therapy is administered until the patient reaches 14 months of age, at which point all visits are relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

### 12.1.1. Demographic/Medical History

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/weight/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any
- Historical feeding support, if any

1. Patients are encouraged to follow all routinely scheduled immunizations, as recommended by the Center for Disease Control (CDC), throughout the study. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics [26].

### 12.1.2. Physical Examinations

Physical examinations will be conducted by the Investigator or Sub-Investigator at each scheduled visit, except Day –1 (Appendix 5). The Day 1 physical examination will be

performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

### 12.1.3. Vital Signs/Weight and Length

Vital sign parameters include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry. Vital signs will be obtained at each study visit (as specified in Appendix 5). On Day 1, vital signs will be continuously monitored throughout the gene replacement therapy infusion, and recorded pre-dose and every 15 (± 5) minutes for the first 4 hours after the start of infusion, and then every hour (± 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.

Weight and length will be measured at each study visit (as specified in Appendix 5). On Day 1, weight and length will be measured pre-dose.

### 12.1.4. Electrocardiogram

A 12-lead ECG will be performed at screening, Day –1, pre-dose on Day 1, Day 2, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5). Additional ECG monitoring will be at the discretion of the Investigator as per local institutional guidelines.

The ECG will be interpreted locally by a cardiologist. The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

### 12.1.5. 12-Lead Holter Monitor

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 72 hours from Day –1 (24 hours prior to the start of gene replacement therapy infusion) through 48 hours after the start of infusion. Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours
- 48 hours

Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist within 24 hours of data upload. The Sponsor physician or designee will be notified of any safety concerns from the centralized review, and the safety management plan will be followed for documenting and reporting of AEs/SAEs.

### 12.1.6. Echocardiogram

A standard transthoracic echocardiogram will be performed at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5).

### 12.1.7. Pulmonary Examinations

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit except Day 1 (Appendix 5). Prior to study entry, a pulmonologist or appropriate individual as per standard institutional practice will review and document ventilator usage in the 2 weeks prior to screening.

Patients may be fitted with non-invasive ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Non-invasive ventilatory support equipment will be provided by AveXis through a third-party vendor. Should the patient require non-invasive ventilatory support at any time during the study, the equipment provided by AveXis must be used.

Patients requiring non-invasive ventilatory support will be asked to bring their machine(s) to each study visit such that the study staff can remove an SD card which captures actual usage data. The hours per day usage data for each day between visits will be extracted with software provided by the device manufacturer into a format that will be transferred/transcribed to the clinical database.

### 12.1.8. Swallowing Test

A swallowing test will be performed at screening (at the Investigator site), every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 5) to determine if the patient has signs of aspiration. If the test is positive for aspiration, there may be a recommendation for the patient to use an alternate method to oral feeding for the duration of the study at the determination of the Investigator and treating clinician.

### 12.1.9. Photographs of Infusion Site

Photographs will be taken of the infusion site at each scheduled visit from Day 1 (pre-dose) through Day 30 (Appendix 5) to monitor healing of the infusion site. AveXis will provide a secure and confidential upload process for transfer and storage of the photographs from the investigative sites to a contracted third-party vendor that will compile and arrange photographs as per AveXis requirements. Any/all photographs received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with

regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

### 12.1.10. Laboratory Assessments

Blood samples will be collected at each scheduled visit, except Day 1 and Day 3 (as specified in Appendix 5). On Day -1, blood and urine samples will be processed locally for receipt of results prior to the start of gene replacement therapy infusion. Any clinically significant laboratory value will be repeated at the discretion of the Investigator.

Blood samples will be collected and shipped to a central laboratory. Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's Clinical Laboratory Improvement Amendment (CLIA) CLIA-certified local laboratory to ensure receipt of results prior to dosing.

**Table 6: Total Blood Volume**

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Screening | Hematology, chemistry/CK-MB, virus serology, immunology sample (AAV9 Ab only), diagnostic confirmation sample | 16.9 |
| Day –1 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 2 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 7 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 14 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 21 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 30 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 60 | Hematology, chemistry/CK-MB, | 3.6 |
| Month 3/4/5/7/8/10/11/13/14/16/17 | Hematology, chemistry | 25.3 |
| Month 6/9/12/15 | Hematology, chemistry/CK-MB | 14.4 |
| End of Study/ET | Hematology, chemistry/CK-MB | 3.6 |
| | **Maximum Total Volume for Study[a]** | **96.2** |

ET = early termination

[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits, provided T-cell responses are not elevated at Day 30 requiring additional surveillance samples and virus serology is not positive at screening requiring additional testing

[b] Immunology sample for IFNγ- ELISpots requires 4-6 mL whole blood. Immunology sample for ELISA requires 1 mL whole blood. When drawn at the same visit, 4-6 mL is sufficient for both assays.

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety labs
    a. Chemistry
    b. Hematology
    c. CK-MB
2. Interferon gamma (IFNγ) ELISpots to detect -T-cell responses
3. Serum antibody to AAV9 and SMN
4. Genetic reconfirmation testing

If there is not sufficient blood volume to include the genetic reconfirmation testing sample at the screening visit, patient must return before Visit 2. All patients must have genetic reconfirmation testing completed.

#### 12.1.10.1. Hematology

Hematology analysis will include a complete blood count with differential and platelet count with smear. Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for hematology analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 5).

Immediate/same-day hematology analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory. Investigators will receive hematology results from all study visits from the central laboratory.

#### 12.1.10.2. Blood Chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 5).

Immediate/same-day chemistry analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory.

Chemistry analysis will include the following at all study visits:

- Serum GGT
- AST/ALT
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Total creatine kinase

- Creatinine
- BUN
- Electrolytes
- Alkaline phosphatase

Creatine kinase (CK-MB) will be collected at Screening, Day 7, Day 30, Day 60, Month 6, 9, 12, 15 months of age, and at 18 months of age/End of Study.

Investigators will receive chemistry results from all study visits from the central laboratory (except Day -1).

#### 12.1.10.3. Urinalysis

Urine samples will be collected in accordance with the laboratory manual provided by the central laboratory at all study visits except Day 1 and Day 3 (Appendix 5). Day -1 urinalysis will be performed as per investigational site standard procedures at the local laboratory. Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin
- Blood
- Protein
- Red Blood Cell
- White Blood Cell
- Squamous epithelial cells
- Casts
- Crystals
- Bacteria
- Yeast

#### 12.1.10.4. Virus Serology

The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have HIV or positive serology for hepatitis B or C or Zika virus, administration of AAV vector may represent an unreasonable risk; therefore negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected at screening (Appendix 5) and shipped in accordance with the laboratory manual provided by the central laboratory.

#### 12.1.10.5. Capillary Blood Gas

Capillary blood gas will be completed locally at Day –1 and Day 2 (Appendix 5). A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

#### 12.1.10.6. Immunology Testing (ELISA and IFNγ- ELISpots)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA), and to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN. Blood samples will be collected at screening (ELISA anti-AAV9 only), Day 7, Day 14 (ELISA anti-AAV9/SMN only), Day 21 (ELISA anti-AAV9/SMN only), and Day 30 (Appendix 5). Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.

#### 12.1.10.7. AAV9 Antibody Screen in Mother

There is potential that the biological mother of the patient may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or, theoretically, via placental transfer in utero. Informed consent will be requested from the biological mother of the patient to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein at screening and shipped to the central laboratory for screening of anti-AAV9 antibodies. Mothers who test positive for antibodies to AAV9 will be asked to refrain from further feedings with breast milk.

If AAV9 antibodies are identified, the patient must desist in consuming breast milk from the biological mother.

Patients consuming banked breast milk from donor sources that cannot be test for anti-AAV9 antibodies must be transitioned to formula prior to participation.

#### 12.1.10.8. Blood for Diagnostic Confirmation Testing

A blood sample will be collected during the screening visit and shipped to the central laboratory in accordance with the laboratory manual for reconfirmation of *SMN1* deletions/mutations, *SMN2* copy number, and absence of exon 7 gene modifier mutation (c.859G>C). This will be done to ensure consistency in diagnostic testing practices.

#### 12.1.10.9. Saliva, Urine, and Stool Collection

Studies have shown that some vector can be excreted from the body for up to a few weeks after injection; this is called "viral shedding." Vector shedding can be found in the blood, urine, saliva, and stool for up to 1 week following infusion. The potential health risks associated with the shed vector are not fully known at this time; however the health risk is thought to be low as the vector cannot replicate. Regardless, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved instructions should be provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of 2 weeks (14 days) after gene replacement therapy. Additionally, patients are prohibited from donating blood for 2 years following the vector infusion.

Saliva, urine, and stool samples will be collected for viral shedding studies at screening, 24 hours postdose-, 48 hours post-dose, Day 7, Day 14, Day 21, and Day 30 (Appendix 5). Samples will be collected, prepared, and shipped as per the laboratory manual.

A subset of patients at sites opting to participate in the viral shedding sub-study will have 24-hour total volume urine and fecal samples collected through 24 hour post-dose and through 48 hours-post dose.

# 13. ADVERSE AND SERIOUS ADVERSE EVENTS

### 13.1.1. Definition of Adverse Events

#### 13.1.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur from the start of gene replacement therapy infusion through the last study visit will be collected and recorded in the eCRF.

All adverse events will be classified in accordance with the CTCAE version 4.03 outlined in Table 7.

**Table 7: Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 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 selfcare -ADL.[b] |
| 4 | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death related to AE. |

Source: Common Terminology Criteria for Adverse Events (version 4.03) [9]

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

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

Study enrollment will be interrupted should any patient experience an unanticipated CTCAE Grade 3, or higher adverse event toxicity that is possibly, probably, or definitely related to the gene replacement therapy. The event will then be reviewed by the DSMB and an evaluation will be made as to whether the study should be terminated early following the discontinuation rules.

Unanticipated CTCAE Grade 3 or higher adverse events that are possibly, probably, or definitely related to the gene replacement therapy must be reported within 24 hours to Sponsor and/or designee as per study safety management plan to ensure timely escalation to the DSMB.

#### 13.1.1.2. Serious Adverse Event

A SAE is an AE occurring during any study phase (e.g., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or comparator that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after signing of the informed consent through the last study visit, whether or not they are related to the study product, must be collected and recorded on forms provided by the Contract Research Organization.

#### 13.1.1.3. Other Adverse Event

The following specific treatment-emergent AE of special interest, which may be searched using Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries, will be summarized:

- Elevated liver enzymes

Other adverse events (OAE) will be identified by the Drug Safety Physician and, if applicable, also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

## 13.2. Relationship to Study Product

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related, Probably Related, or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” then the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 13.3. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the time of vector infusion until the end of the study. Serious Adverse Event information will be collected from signing of consent form until the last study visit. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date (and time if during Visit 2)), resolution (date (and time if start date during Visit 2)), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.1.2. An AE of severe intensity may not be considered serious.

## 13.4. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of consent form until the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or e-mail to AveXis or designee.

Additional follow-up information, if required or available, should all be faxed or e-mailed to AveXis or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

AveXis is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, product-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

# 14. STATISTICS

This section summarizes key aspects of the analysis plan including definitions of co-primary, co-secondary, and [redacted] and safety endpoints, and the methods to be used to test the primary effectiveness hypothesis. Additional details regarding methods for the final data analysis will be provided in a separate Statistical Analysis Plan (SAP) which will be finalized and submitted to the Investigational New Drug application prior to the enrollment of the first patient. The SAP will detail all analyses and data displays, and will be executed according to Standard Operating Procedures in a controlled environment.

## 14.1. Study Endpoints and Populations

### 14.1.1. Study Endpoints

The primary and efficacy endpoint will be compared to the null. The survival co-primary efficacy variable will be evaluated relative to literature-based historical controls (such as the Pediatric Neuromuscular Clinical Research Network [PNCR] [21]. These were selected on the basis of comparability to the target population and similarity to the investigational device.

#### 14.1.1.1. Co-Primary Efficacy Endpoint

The co-primary efficacy endpoints are:

- The proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 2), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds.
- The survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

An "acute reversible illness" is defined as any condition other than SMA that results in increased medical intervention (e.g., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (e.g., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (e.g., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of "acute." The date of "definitive intervention" shall be defined as the date of provision of a procedure (e.g., surgery, etc.) or medication (e.g., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of "definitive intervention" shall be considered the date of hospitalization or substantial escalation of care.

"Perioperative" use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.

For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

#### 14.1.1.2. Co-Secondary Efficacy Endpoint

The co-secondary efficacy endpoints are:

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [25] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy).

- [redacted]

#### 14.1.1.4. Safety Endpoints

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated LFTs and/or unresolved LFEs
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ ELISpot to detect T cell responses to AAV9 and SMN

### 14.1.2. Statistical Analysis Populations

#### 14.1.2.1. Intent-to-Treat Population (ITT)

The ITT population will consist of symptomatic patients with biallelic- deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at less than 180 days of age. The first three patients enrolled must meet the criteria for the Intent-to-Treat Population.

#### 14.1.2.2. Efficacy Completers Population

The efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE or experience death

#### 14.1.2.3. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101. Analyses of endpoints in this population are considered descriptive.

#### 14.1.2.4. Safety Population

The safety analysis population will consist of all patients who receive an IV infusion of AVXS-101. All safety analyses will be conducted on the safety analysis population.

## 14.2. Sample Size Calculation

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

The two co-primary efficacy endpoints will be assessed in sequence: The endpoint of functional independent sitting will be assessed first and, only if this assessment meets statistical significance will the endpoint of survival be assessed.

Based upon the widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patients in this population would be expected to attain the ability to sit without support or accomplish other milestones (rolling over, standing, walking) prior to 18 months of age. Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age study visit. With the assumption for the true response rate of AVXS-101 for the

primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with α = 0.025 using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion of patients surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with biallelic- *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with α = 0.05 using a 2-sided Fisher's Exact test, comparing to the 26 age and gender matched patients from a published natural history observational study performed at 3 large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

## 14.3. Efficacy Analysis

### 14.3.1. General Considerations

This study will compare the activity of AVXS-101 administered IV versus the natural observational results from PNCR [21] in terms of functional independent sitting and survival rate. The ability to thrive and the ability remain independent of ventilatory support will also be assessed.

The analysis of the co-primary and co-secondary efficacy endpoints will be performed for the ITT and efficacy completers population. The analysis based on the ITT population will be considered as the primary analysis. In the case of missing data, observed data will be used for the analyses.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (e.g., on or before Day 1 visit).

### 14.3.2. Primary and Secondary Efficacy Analysis

Primary and secondary efficacy analyses will be based on the ITT population, those patients that are symptomatic with biallelic- deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 to the results from natural observation study (PNCR) [21].

The first co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion surviving at 14 months of age.

Primary efficacy endpoints will be examined on the ITT population. Testing for the first co-primary endpoint, functional independent sitting will first be performed using 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at $p<0.025$, will the co-primary endpoint survival improvement be tested using 2-sided Fisher's Exact test on the ITT population, comparing to matched patients from natural observational study (PNCR). This hierarchy approach strongly protects the Type I error rate.

The hypothesis for both cosecondary- efficacy endpoints to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of patients maintaining the ability to thrive/are independent of ventilatory support.

One-sided exact binomial tests will be executed for secondary efficacy analyses on the ITT population.

A sensitivity analysis will be conducted by repeating the primary efficacy analysis on the efficacy completers analysis population.

## 14.4. CHOP-INTEND Comparison

A comparison will be performed of the first three patients CHOP-INTEND scores to the AVXS-101-CL-101 CHOP-INTEND scores. The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 4-week interval between patients and

proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

## 14.5. Safety Analysis

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, urinalysis, immunology), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary.

Safety analyses will be conducted on safety population, and summarized by subgroup and overall.

# 15. DATA SAFETY MONITORING BOARD

The DSMB is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, have experience in the management of patients with SMA Type 1 and other diseases, and in the conduct and monitoring of randomized clinical studies with interim analyses. The DSMB will be chartered to oversee the safety of patients during the conduct of the study, and will act in an advisory capacity to AveXis. A detailed description of the DSMB, its role in this study, and the timing of the scheduled reviews will be described in a DSMB Charter.

The DSMB will routinely convene on a quarterly basis to review emerging safety data from the study. All available safety data from all enrolled patients will be included in such reviews, which include, but are not limited to, screen failures, enrollment status, data from safety parameters, all SAEs, and other AEs. Following each meeting, the DSMB will make a recommendation as to whether or not the accumulated safety data warrants a suspension or discontinuation of the study, a modification to the study, or any additional comments or recommendations related to safety. The DSMB will prepare and provide minutes of their meetings to AveXis who will provide copies to the regulatory authorities as appropriate.

The DSMB will also convene on an ad hoc basis within 48 hours should any patient experience an unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation.

# 16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 16.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of AveXis will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AveXis or its representatives. This will be documented in a Clinical Study Agreement between AveXis and the Investigator.

During the study, a monitor from AveXis or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts, electronic medical records)
- Record and report any protocol deviations not previously sent to AveXis
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to AveXis and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

## 16.2. Audits and Inspections

Authorized representatives of AveXis, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact AveXis immediately if contacted by a regulatory agency about an inspection.

### 16.3. Institutional Biosafety Committee

As this study involves gene therapy, the Principal Investigator must obtain approval/favorable opinion for the investigation from a designated institutional or independent biosafety committee in accordance with institutional requirements and/or guidelines.

### 16.4. Institutional Review Board/Institutional Ethics Committee

The Principal Investigator must obtain IRB/IEC approval for the investigation (Section 18.1). Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

# 17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. AveXis may also conduct a quality assurance audit any time during or after the completion of the study. Please see Section 16.2 for more details regarding the audit process.

The Investigator agrees to allow these Sponsor representatives direct access to the clinical data and supplies, dispensing and storage areas and if requested, agrees to cooperate fully or assist the Sponsor representative. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, site staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/IEC and relevant regulatory authority will also be informed.

# 18. ETHICS

## 18.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to AveXis before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## 18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 7) and are consistent with ICH/GCP, applicable regulatory requirements and the AveXis' policy on Bioethics.

## 18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the parent(s)/legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent(s)/legal guardian(s) must also be notified that they are free to discontinue the patient from the study at any time. The parent(s)/legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the parent(s)/legal guardian(s).

There will be 3 informed consent forms:

- Parent(s)/legal guardian(s) informed consent form
- Biological mother baseline AAV9 antibody screening informed consent form
- Autopsy informed consent form (Appendix 1; if the parent(s)/legal guardian(s) decline an autopsy, it will not prevent the patient from participating in the study)

# 19. DATA HANDLING AND RECORDKEEPING

## 19.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion criteria, product administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

## 19.2. Inspection of Records

AveXis or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the product storage area, study product stocks, product accountability records, patient charts and study source documents, and other records relative to study conduct.

## 19.3. Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years included in ICH shall be followed.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, patient / subject screening records, patient / subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB/IEC documentation, an approved sample ICF, drug / product accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

# 20. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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# 22. APPENDICES

# APPENDIX 1. AUTOPSY PLAN

An autopsy will be requested for any patient who receives gene replacement therapy and expires. The autopsy and tissue collection will be performed by a contracted vendor who will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions will be used to perform the autopsy and pathology necessary to determine the cause of death.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes, including up to 7 sections or pieces from each organ and each region of the spinal cord. Upon collection, these tissue samples will be provided to AveXis for analysis. Tissue analysis will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results will demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

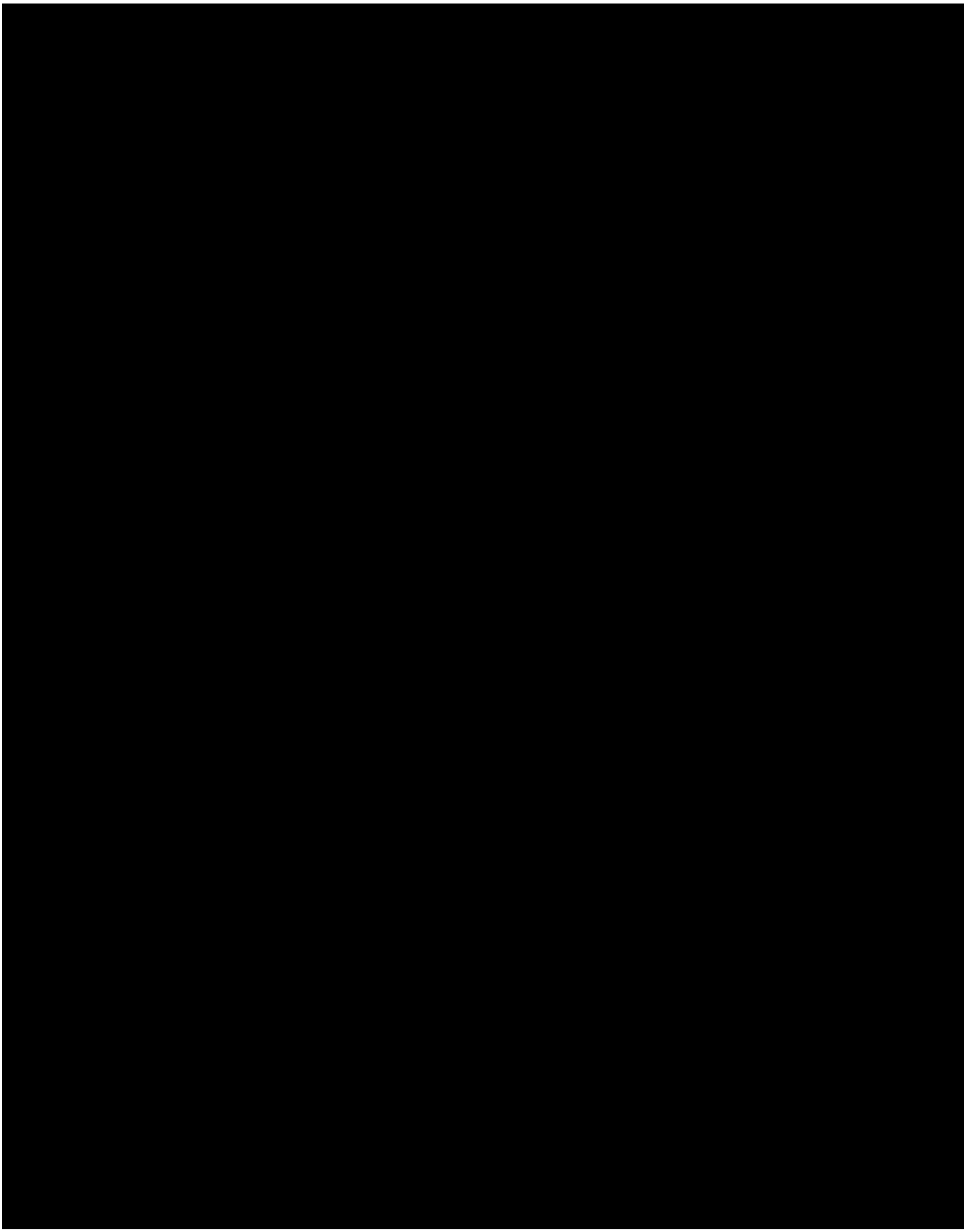
Specifically, tissue samples from the spinal cord, muscles, and organs will be collected as indicated in Table 8. Tissue samples will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

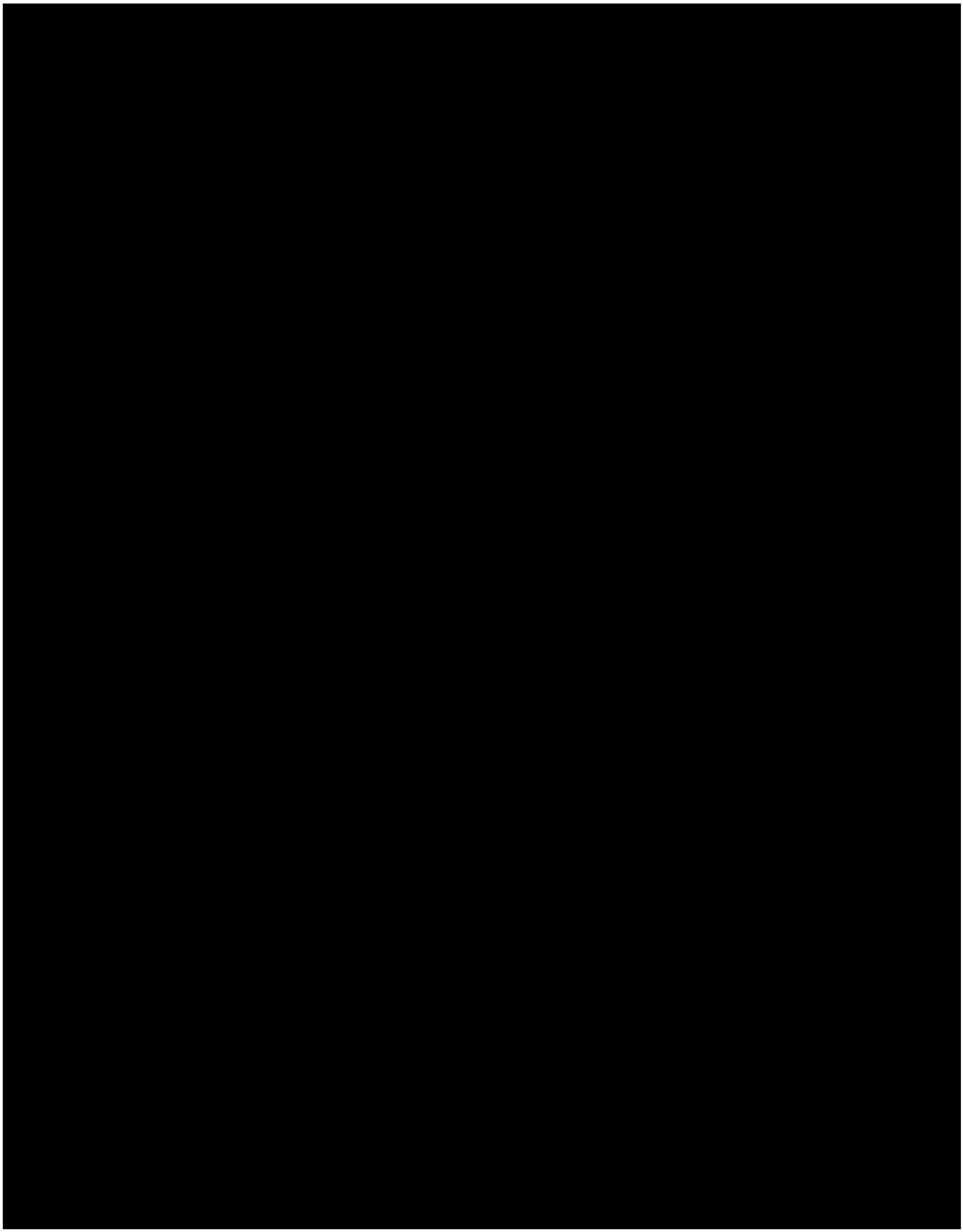
Families will be asked to consent to the autopsy and authorize tissue collection prior to any sign of moribund or death by the clinical team conducting the study. There are distinct forms for the formal autopsy and for the research tissue collection. This will allow families the flexibility to participate in one or both of the research activities. Declining an autopsy will not prevent patients from participating in the study.

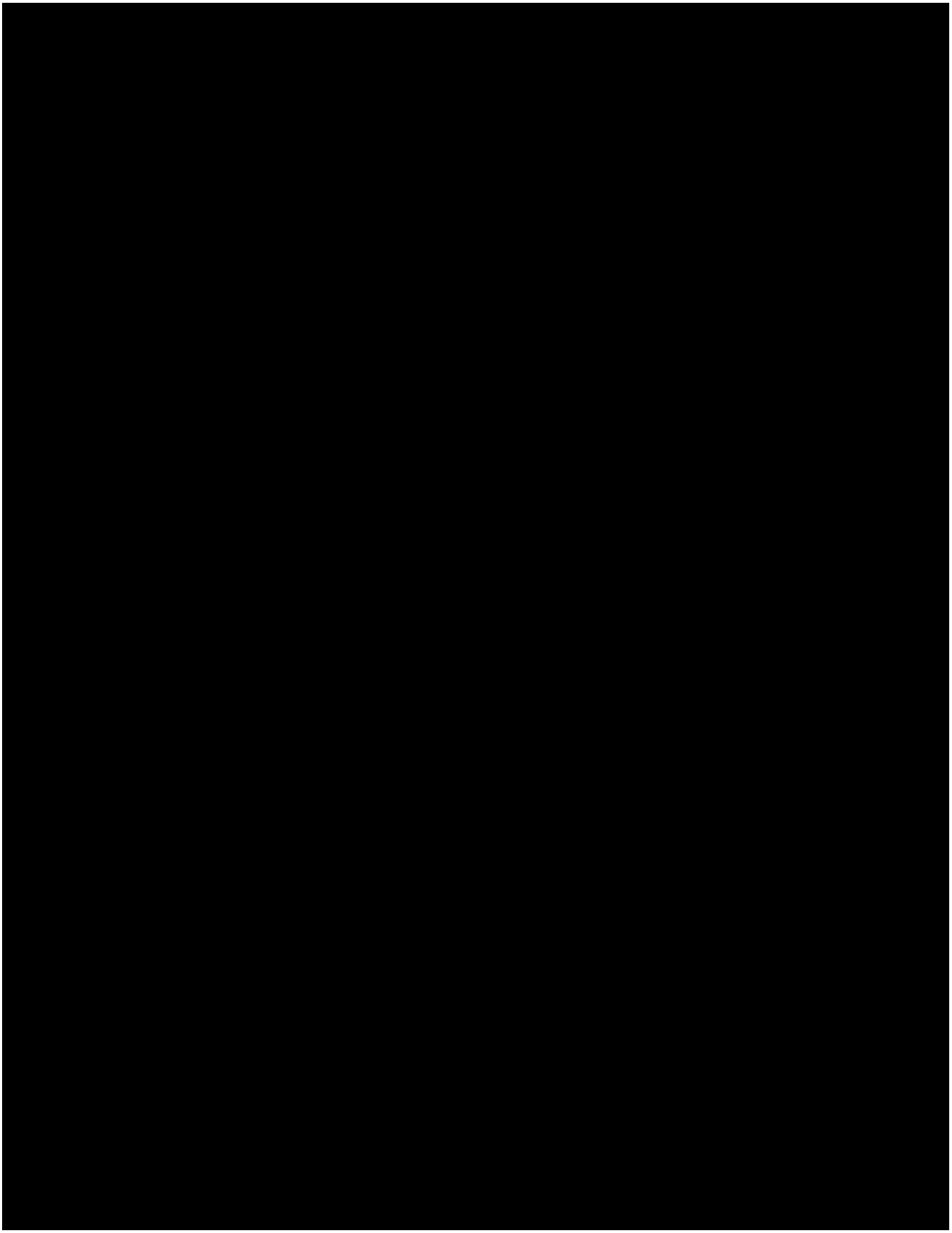
**Table 8: Tissue Sample for Analysis**

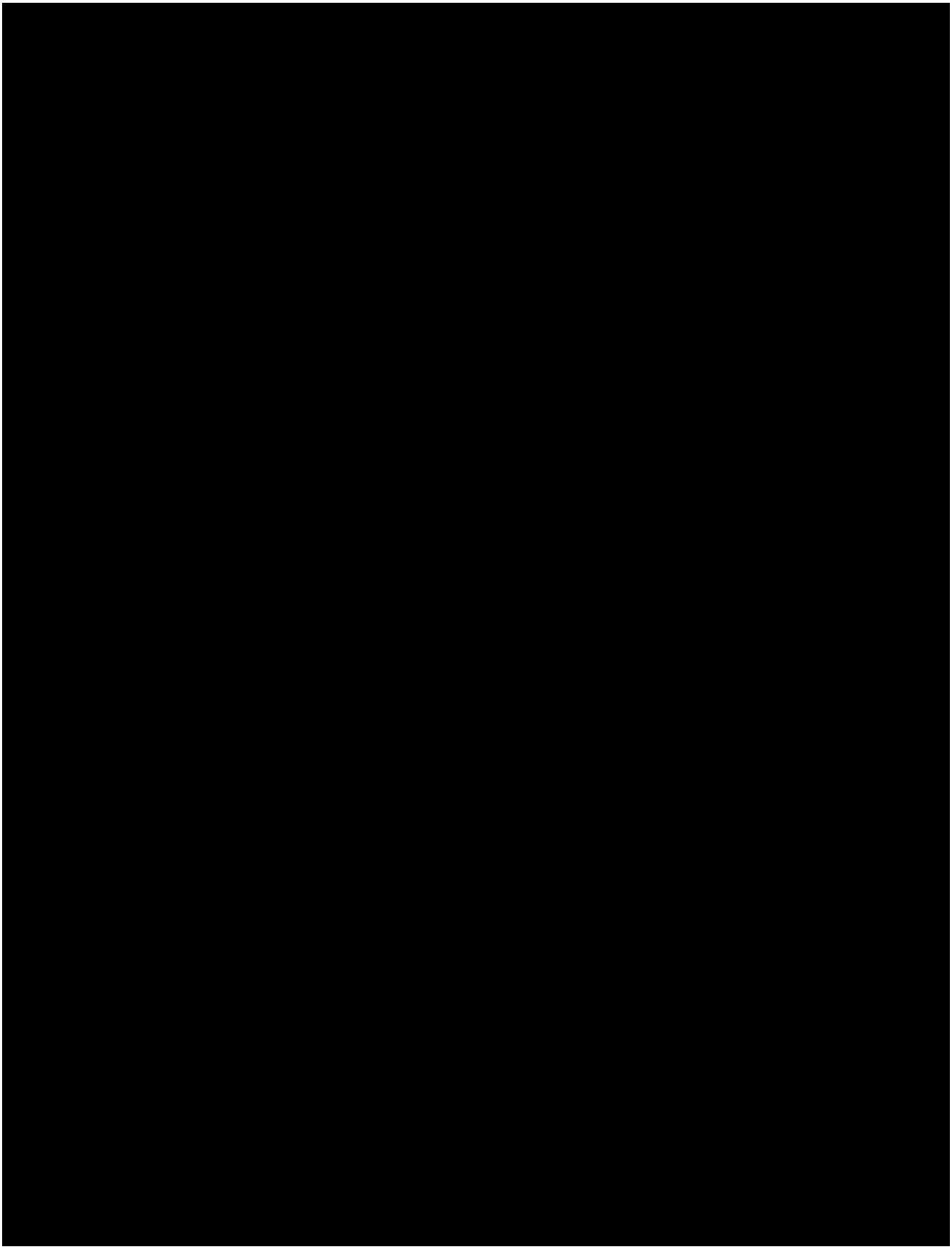
| Brain | Spinal Cord | Muscles | Organs |
|---|---|---|---|
| Motor cortex | Cervical spinal cord | Diaphragm | Spleen |
| Layer 5 motor cortex | Thoracic spinal cord | #6/#7 Rib with intercostal muscle and nerve | Kidney |
| Brain stem | Lumbar spinal cord | Psoas muscle | Small intestine |
| | Sacral spinal cord | | Large intestine |
| | Dorsal root | | Pancreas |
| | Cervical level | | Stomach |
| | Ventral root | | Lung |
| | Cervical level | | Heart |
| | DRG root | | Liver |
| | Cervical level | | Inguinal lymph node |
| | Cerebrospinal fluid | | Gonads |

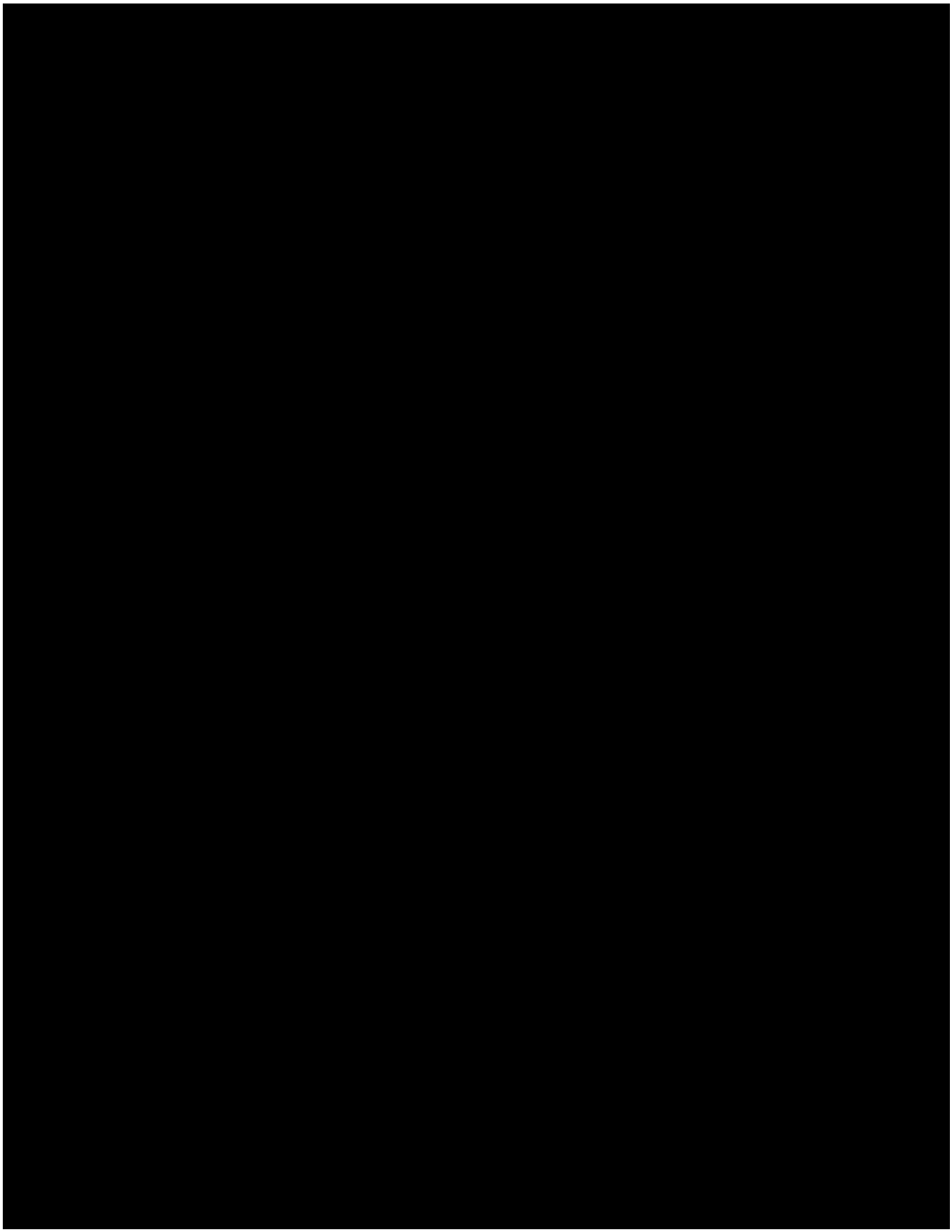
# APPENDIX 2. BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

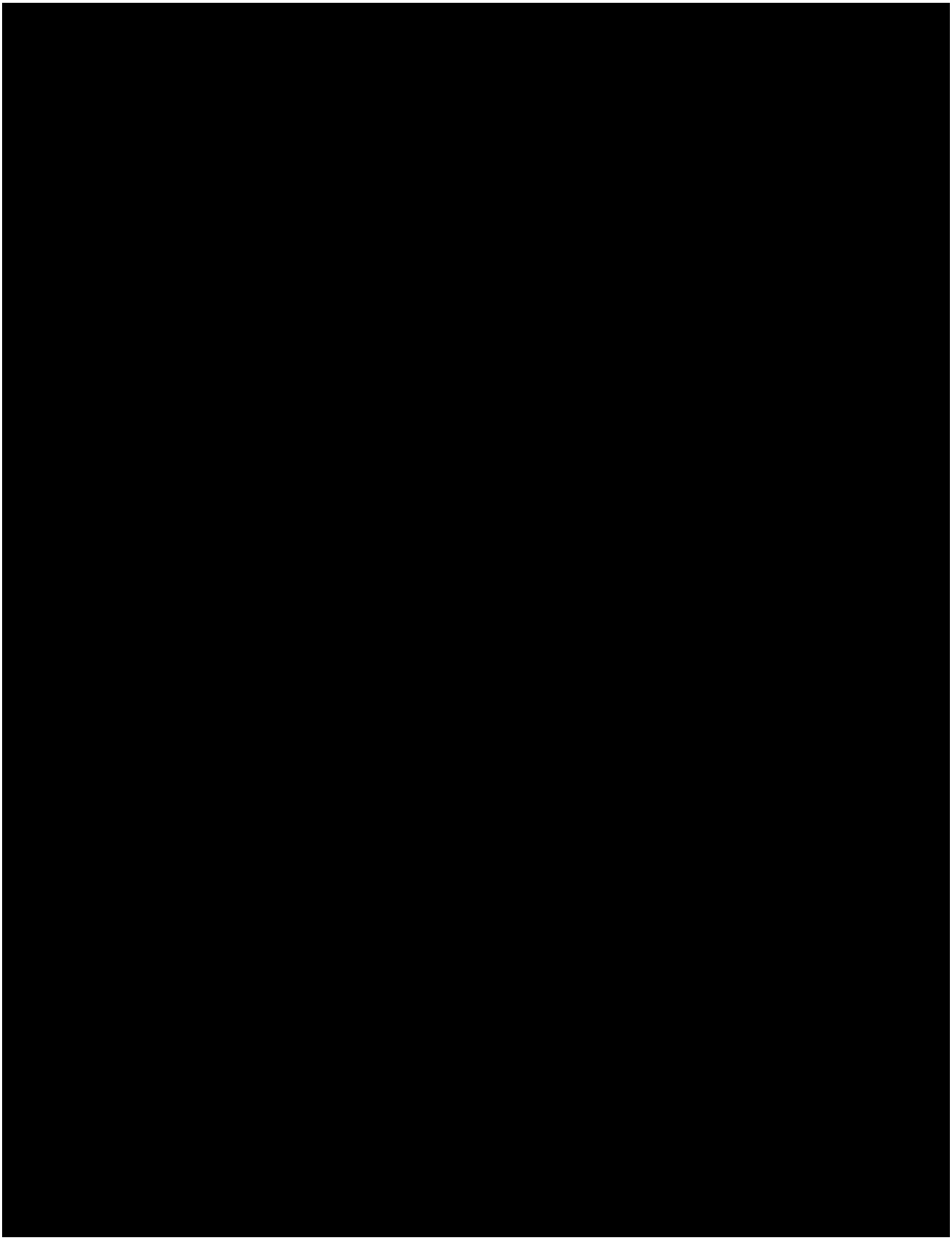


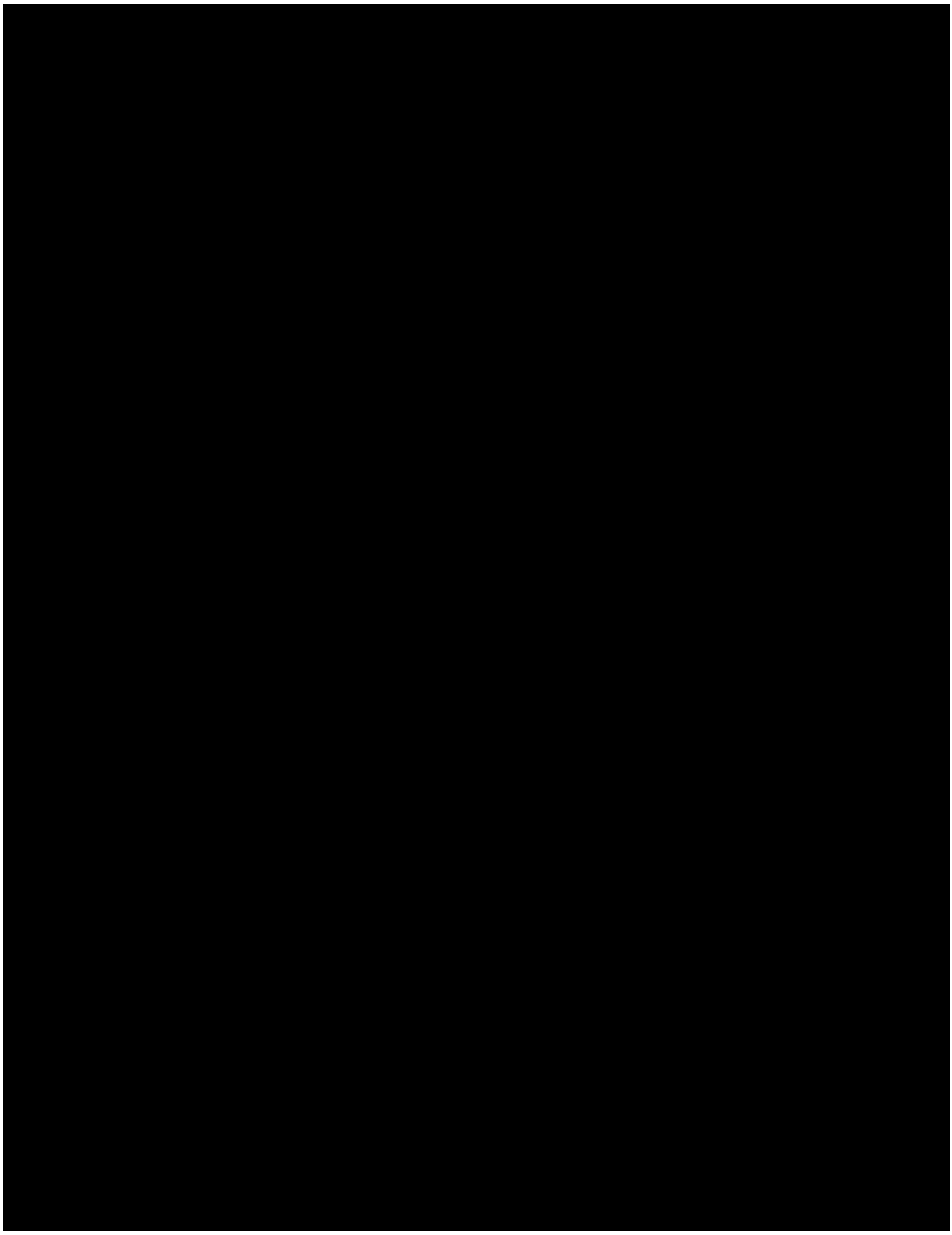


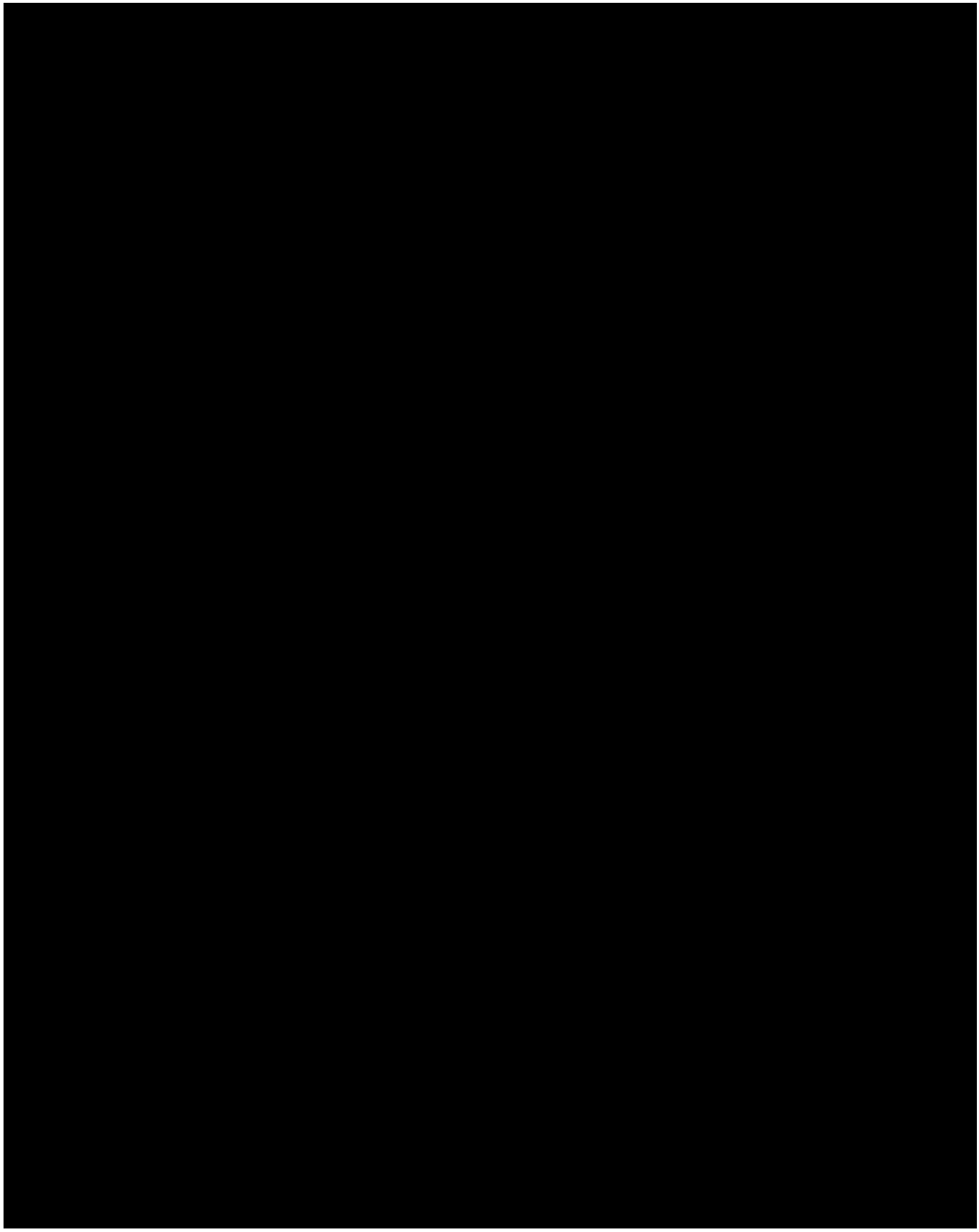


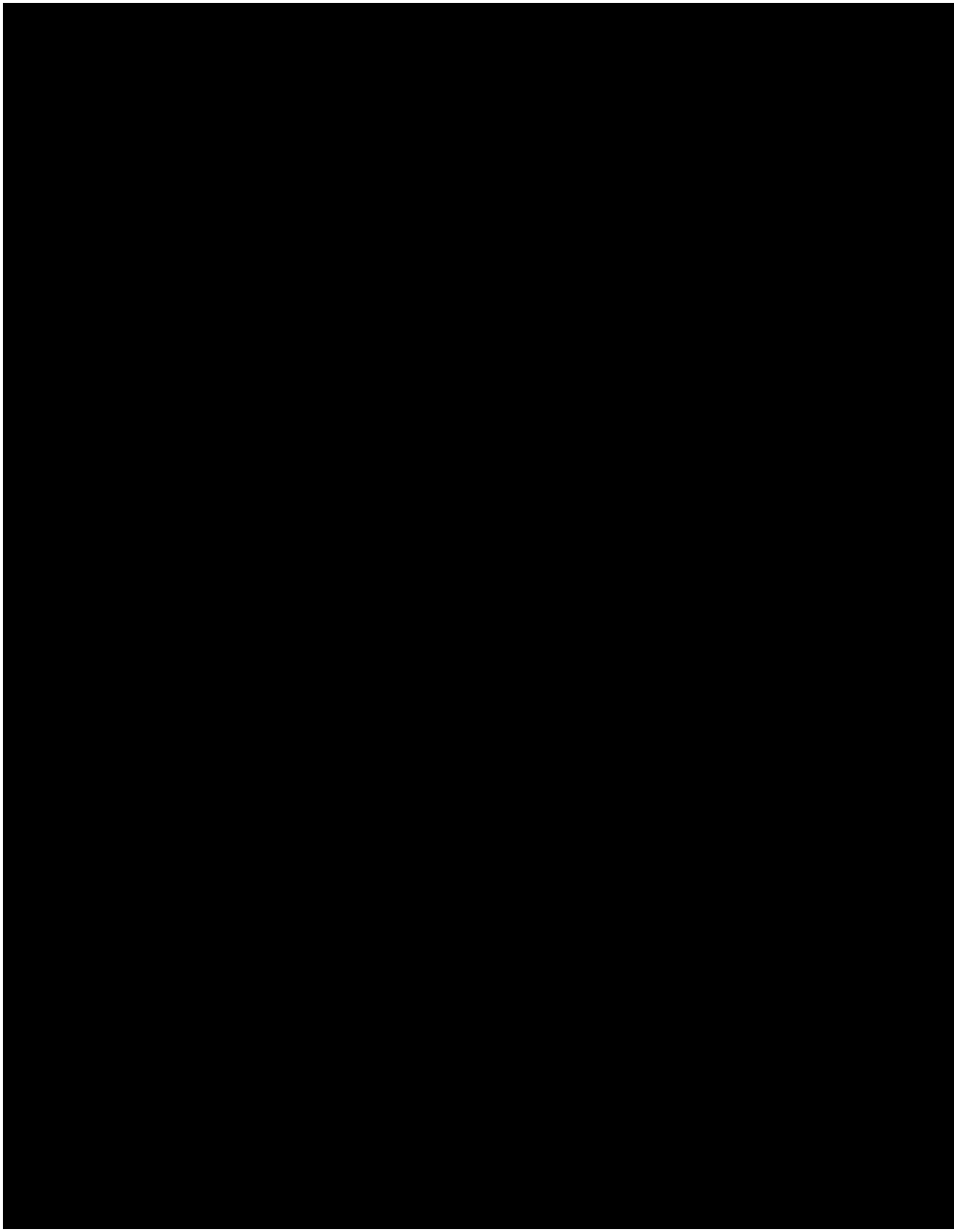


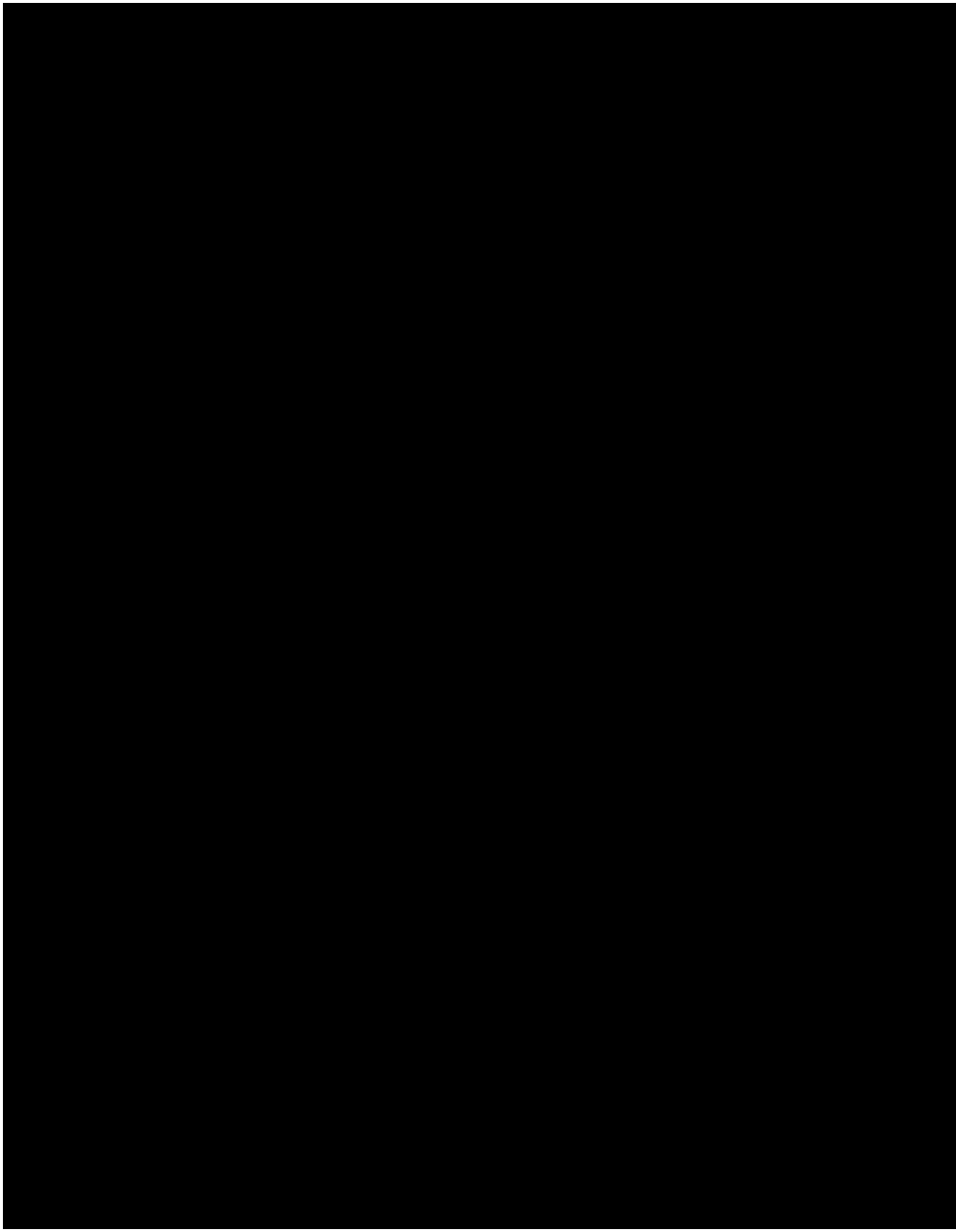


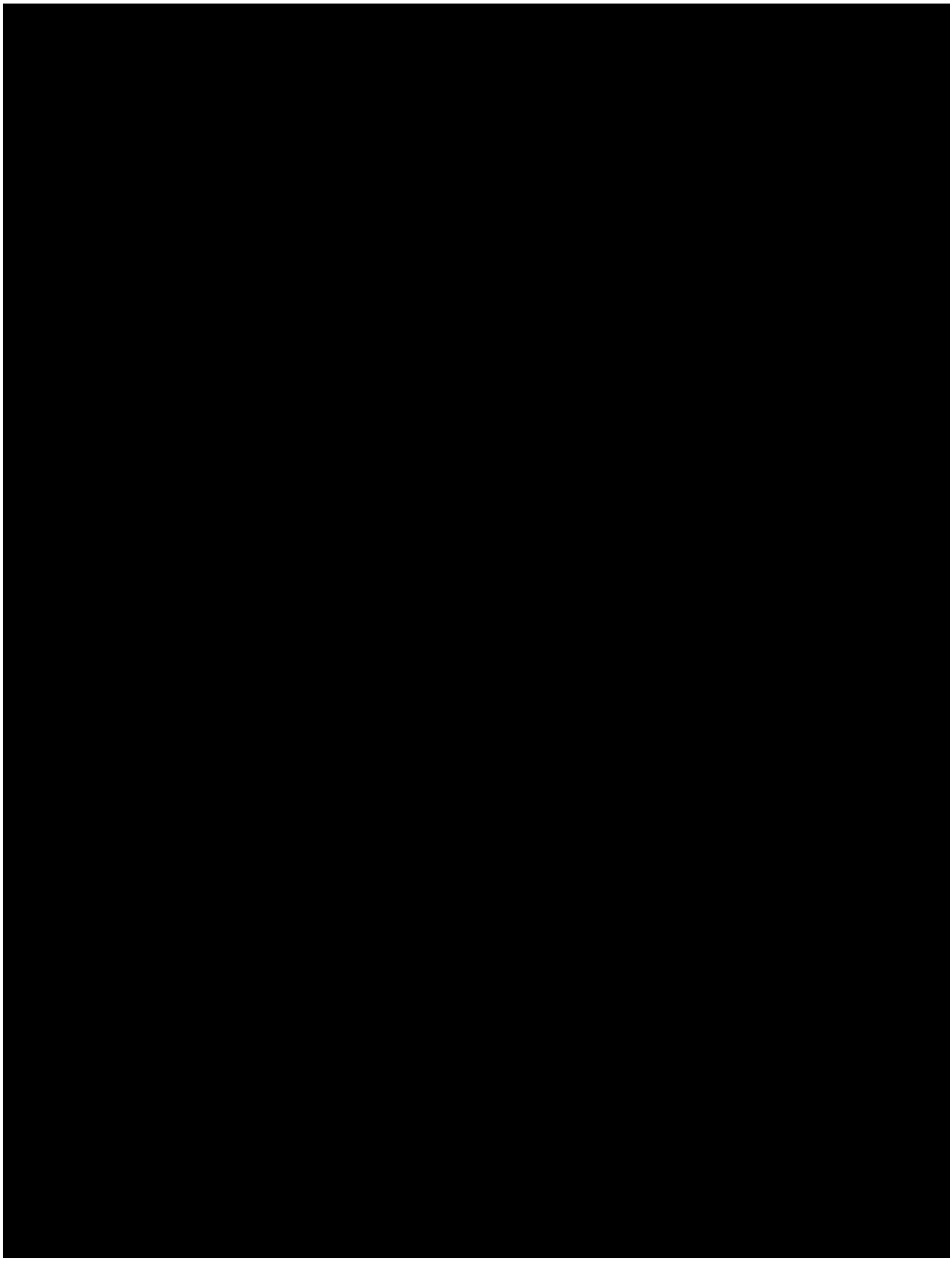


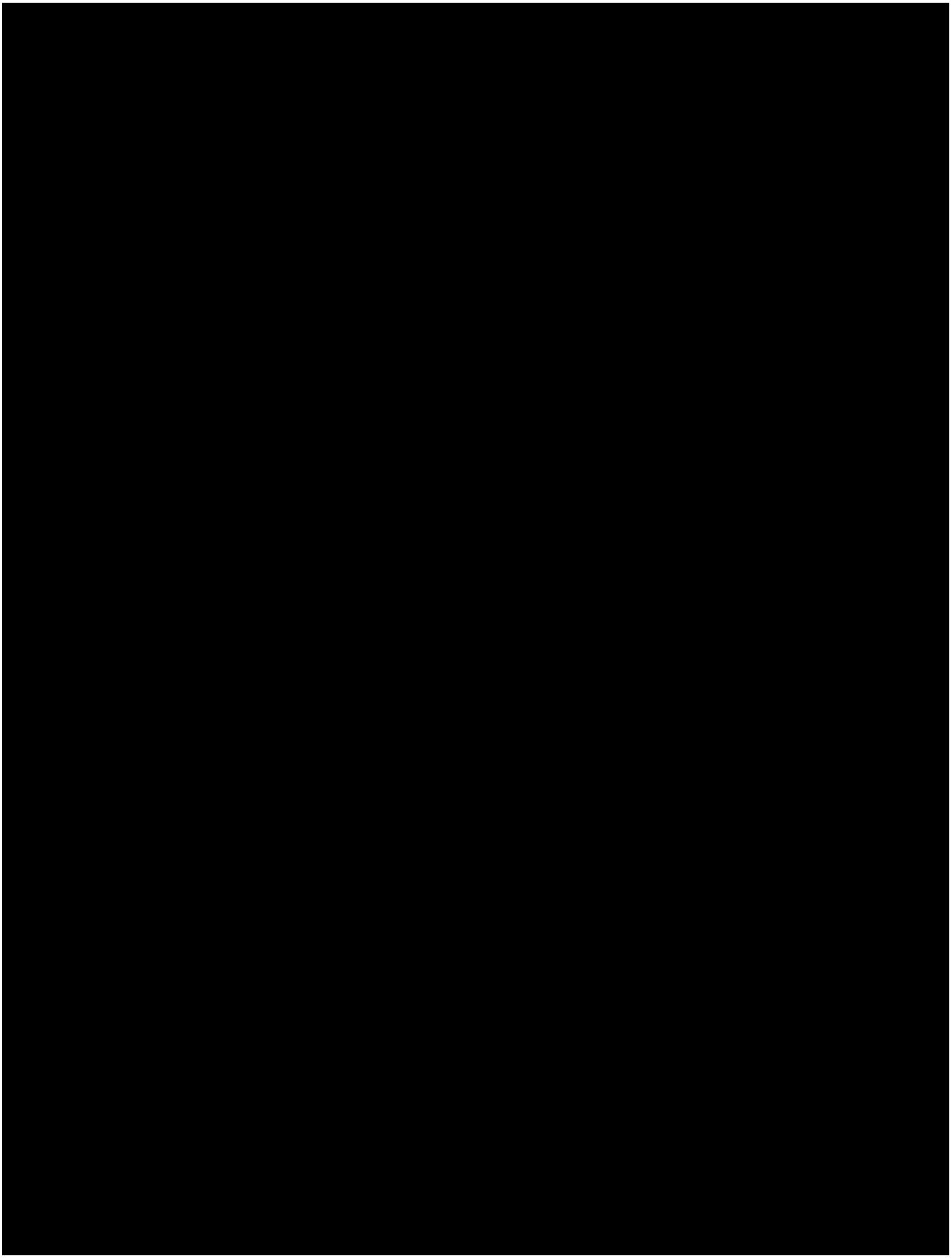


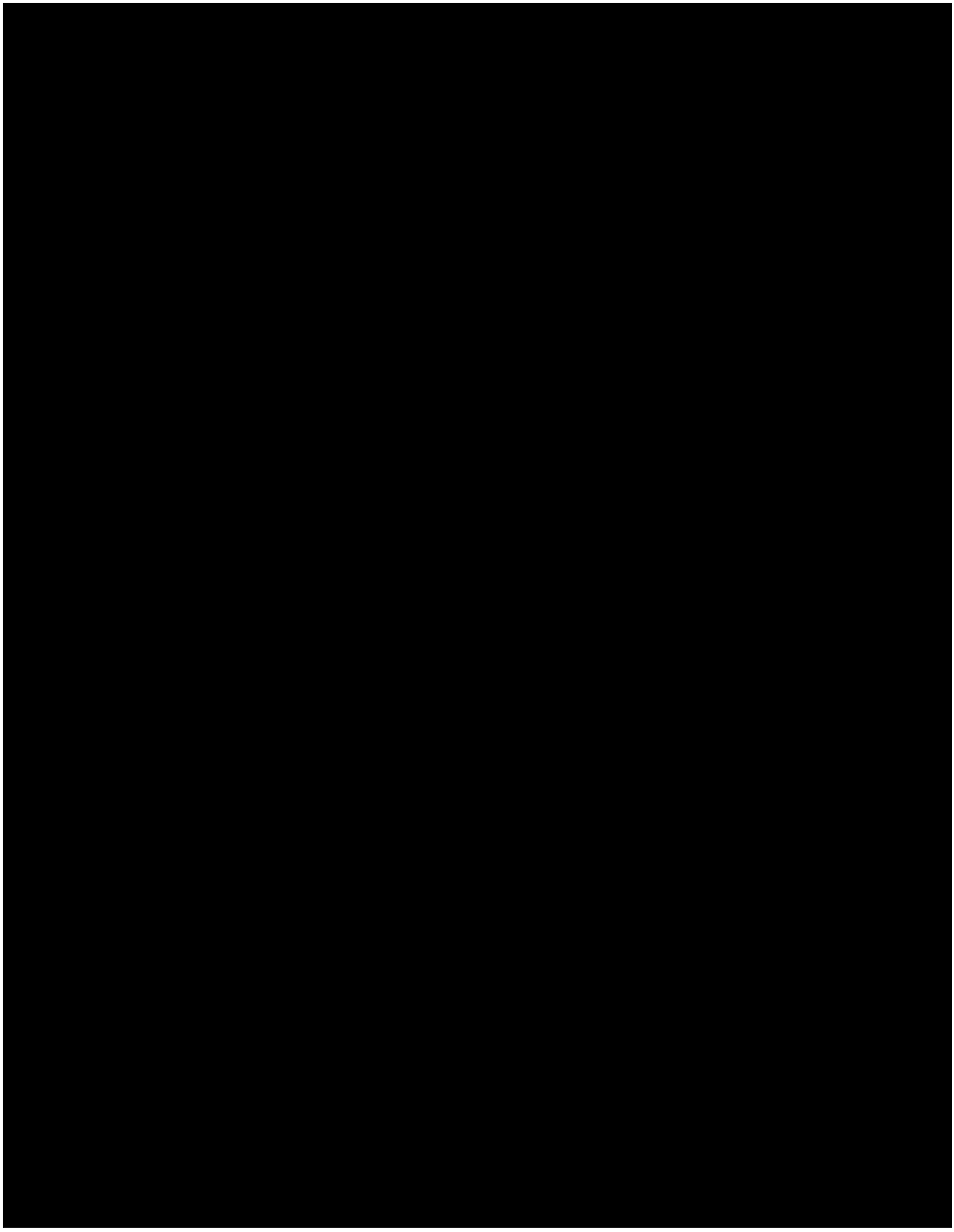


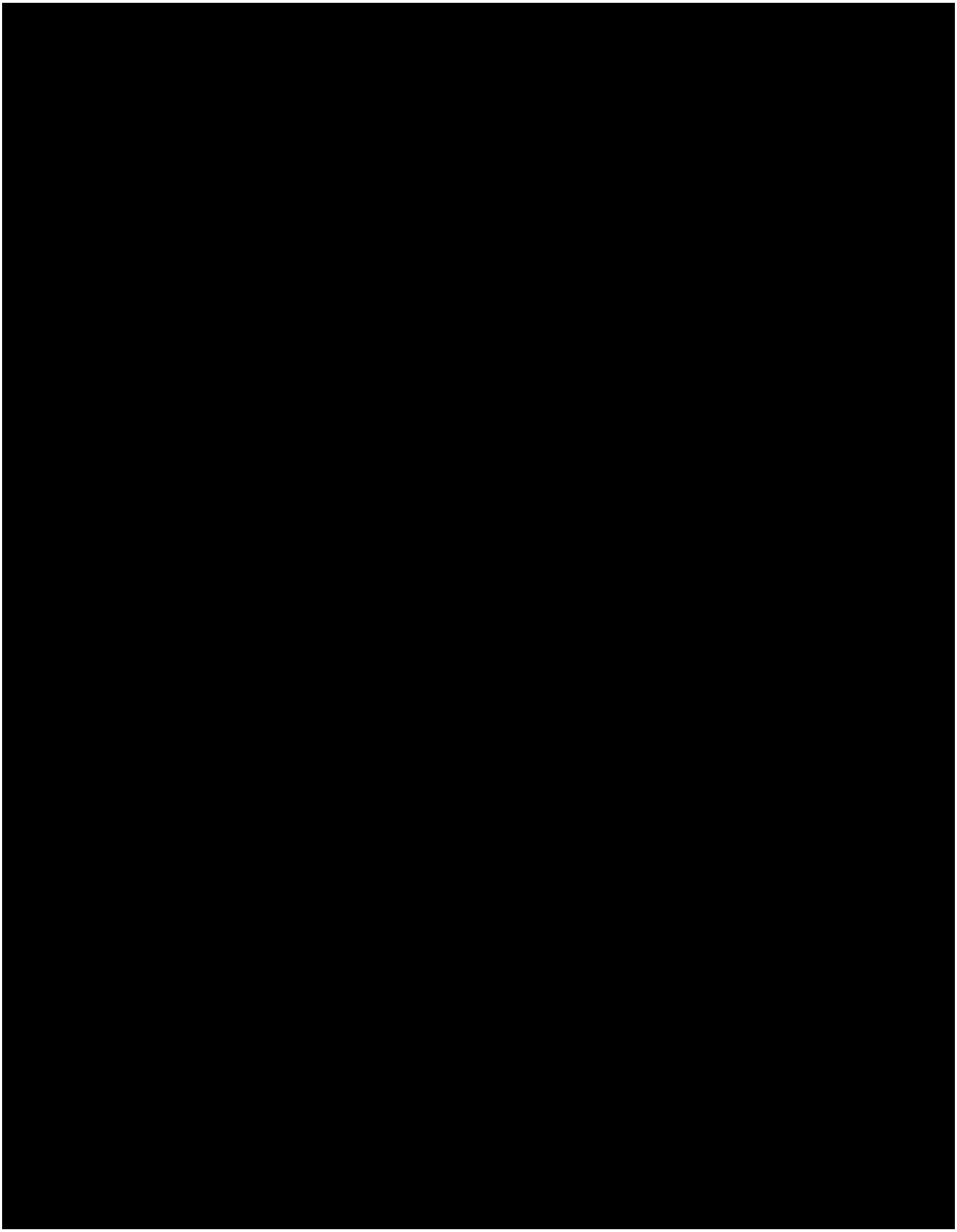


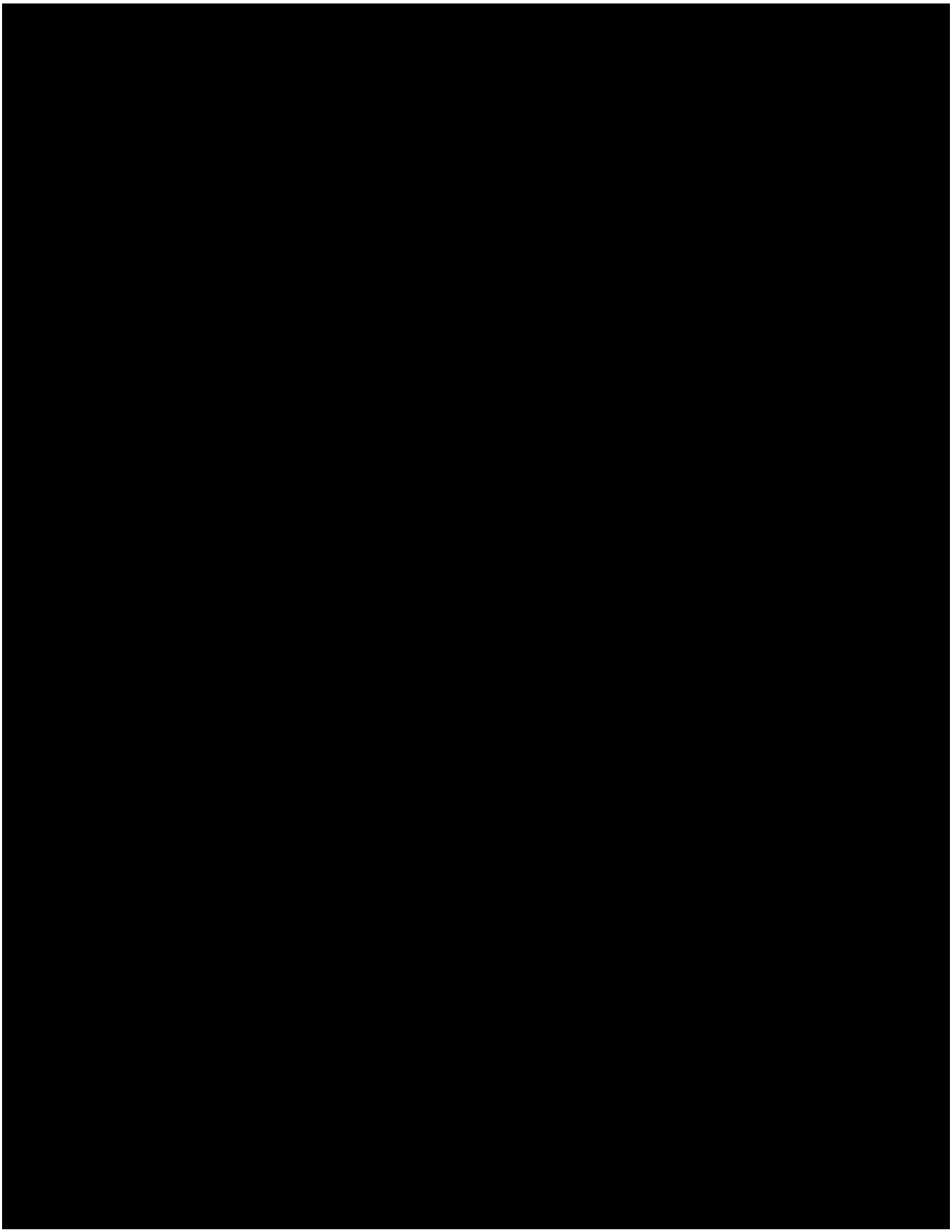


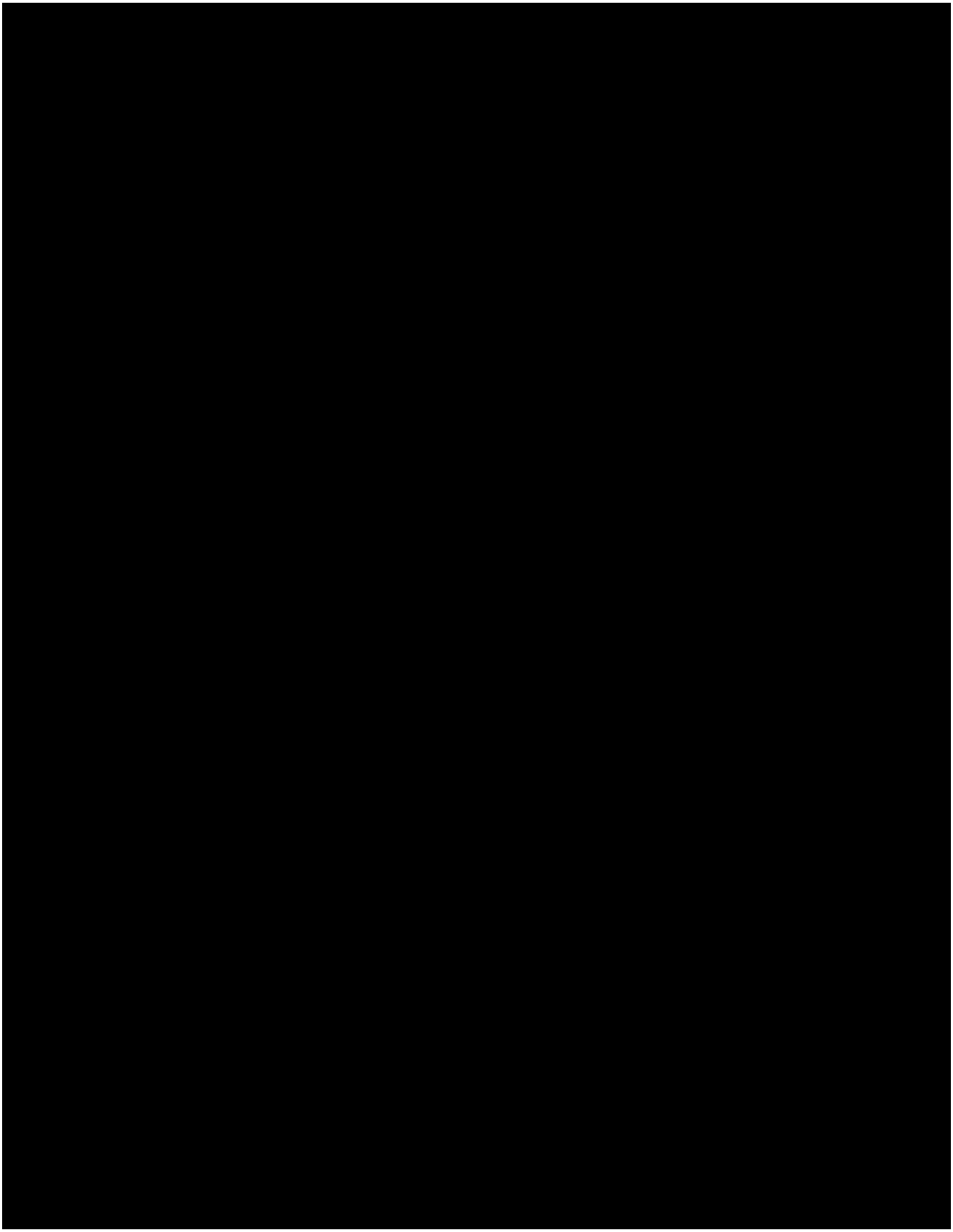


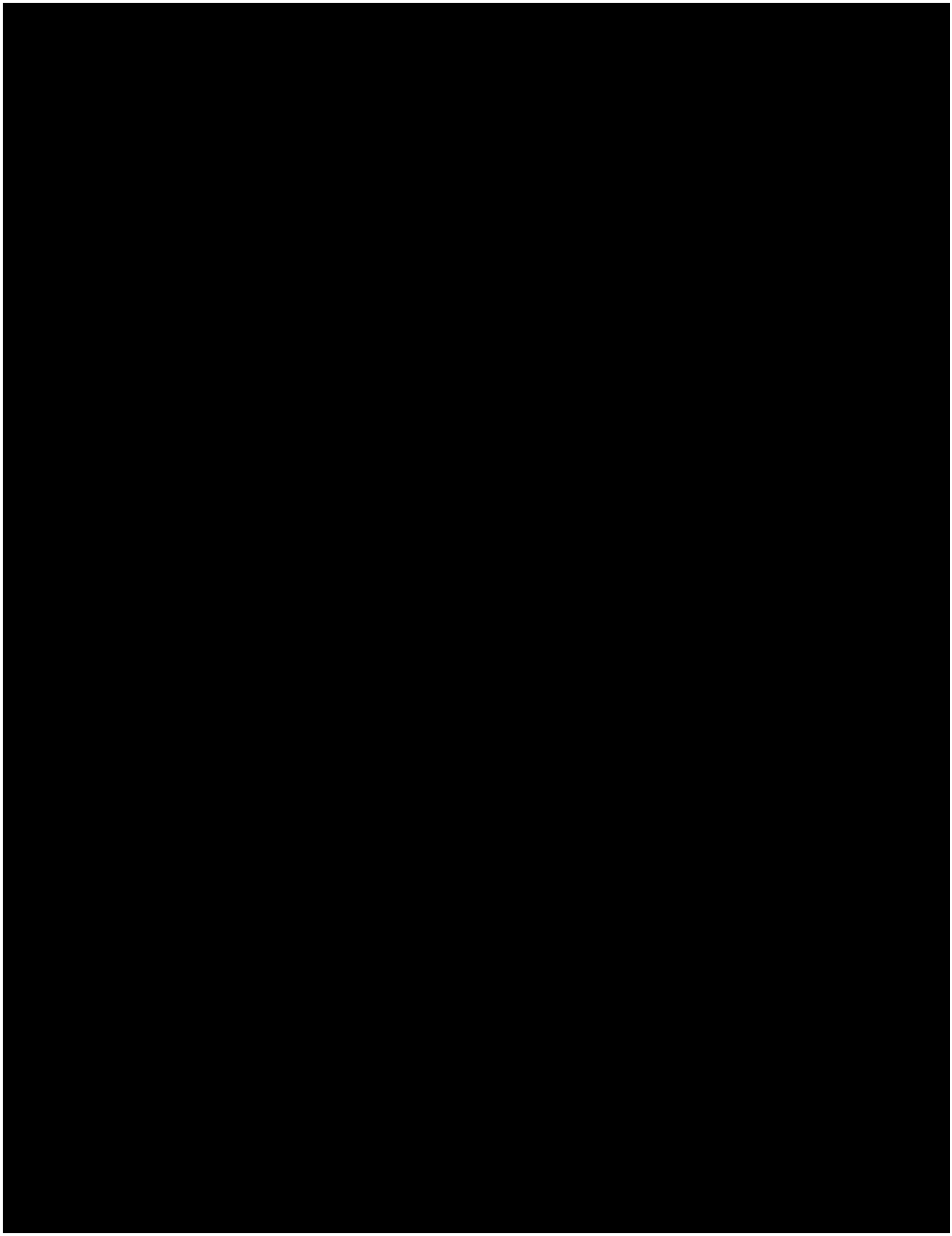


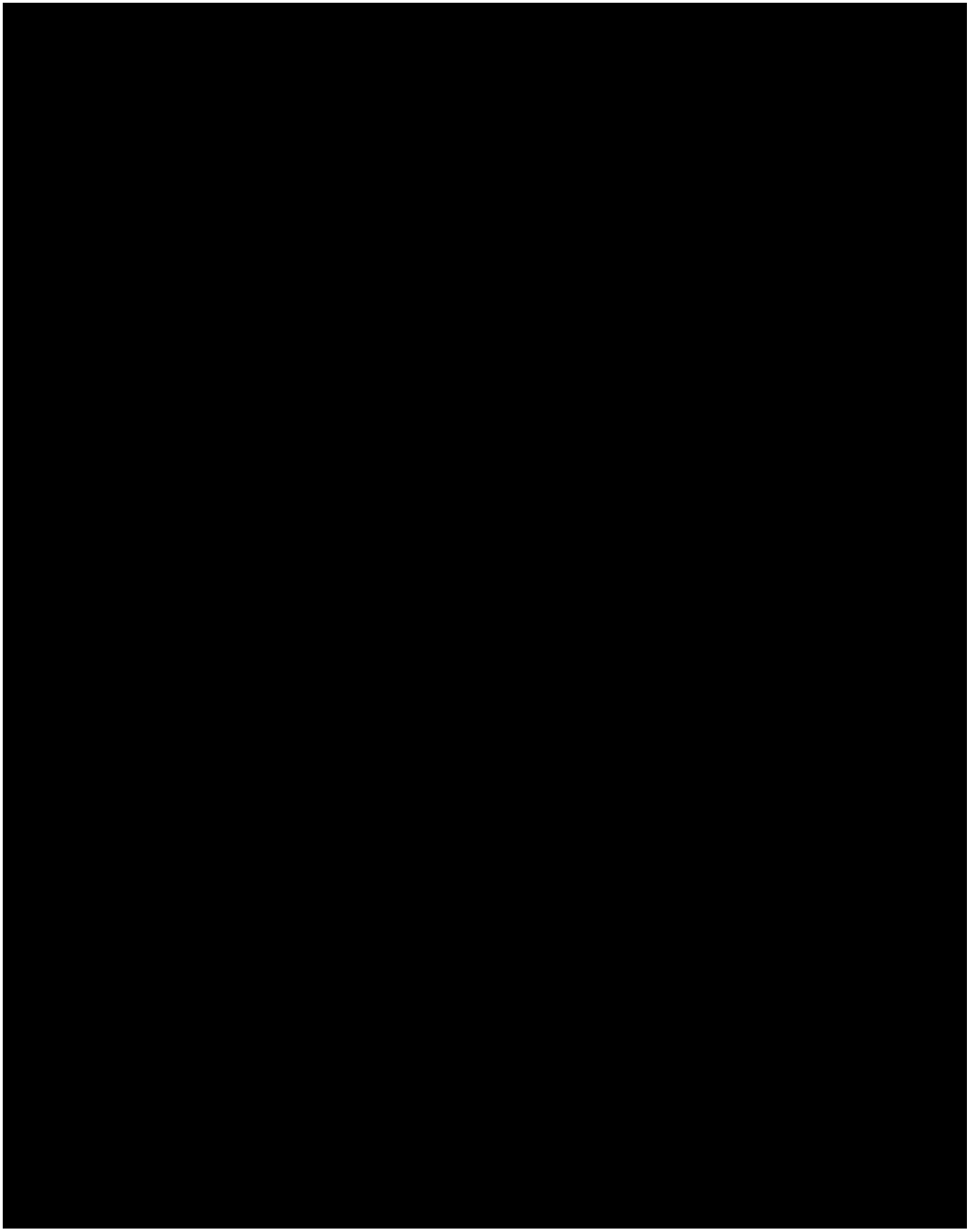


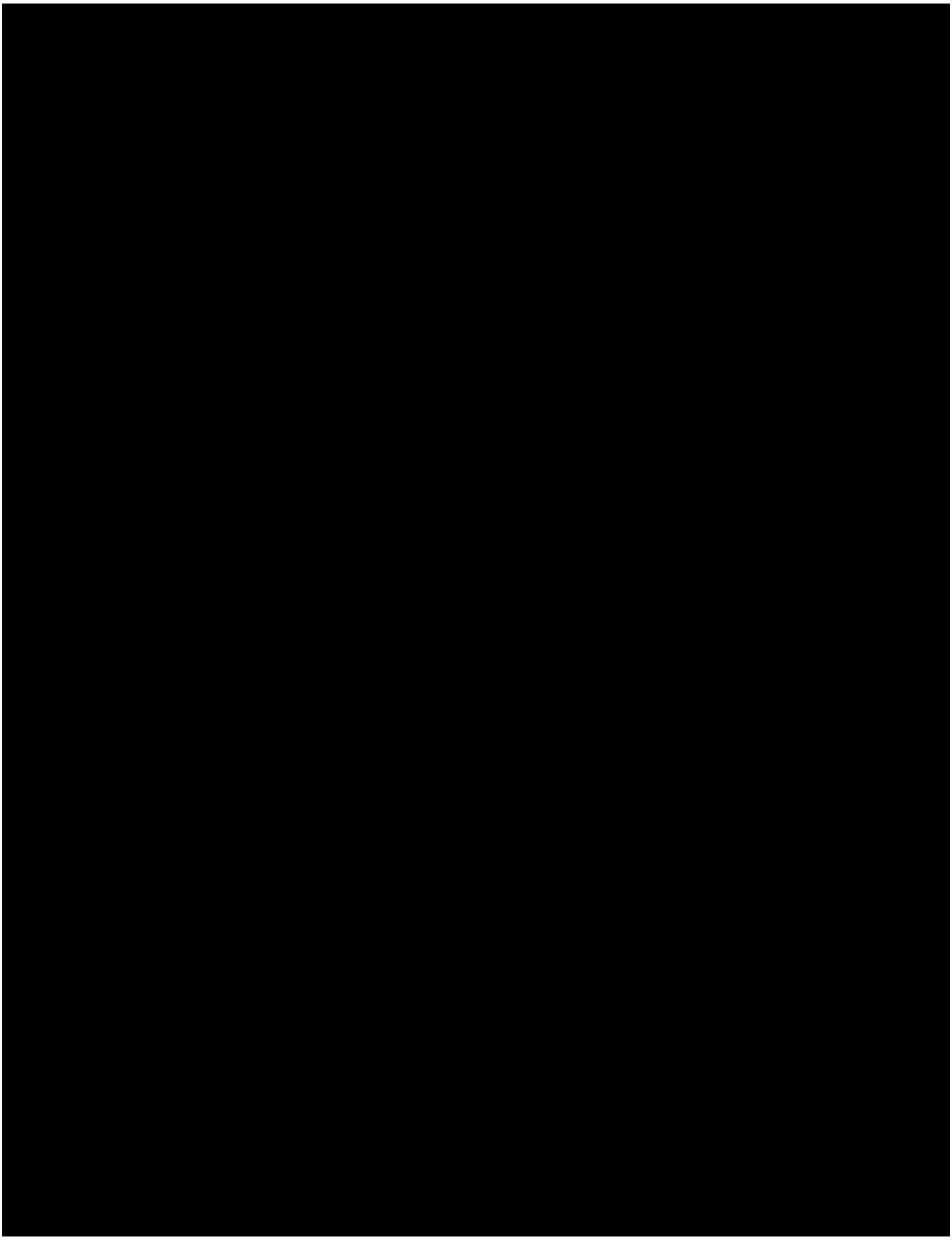


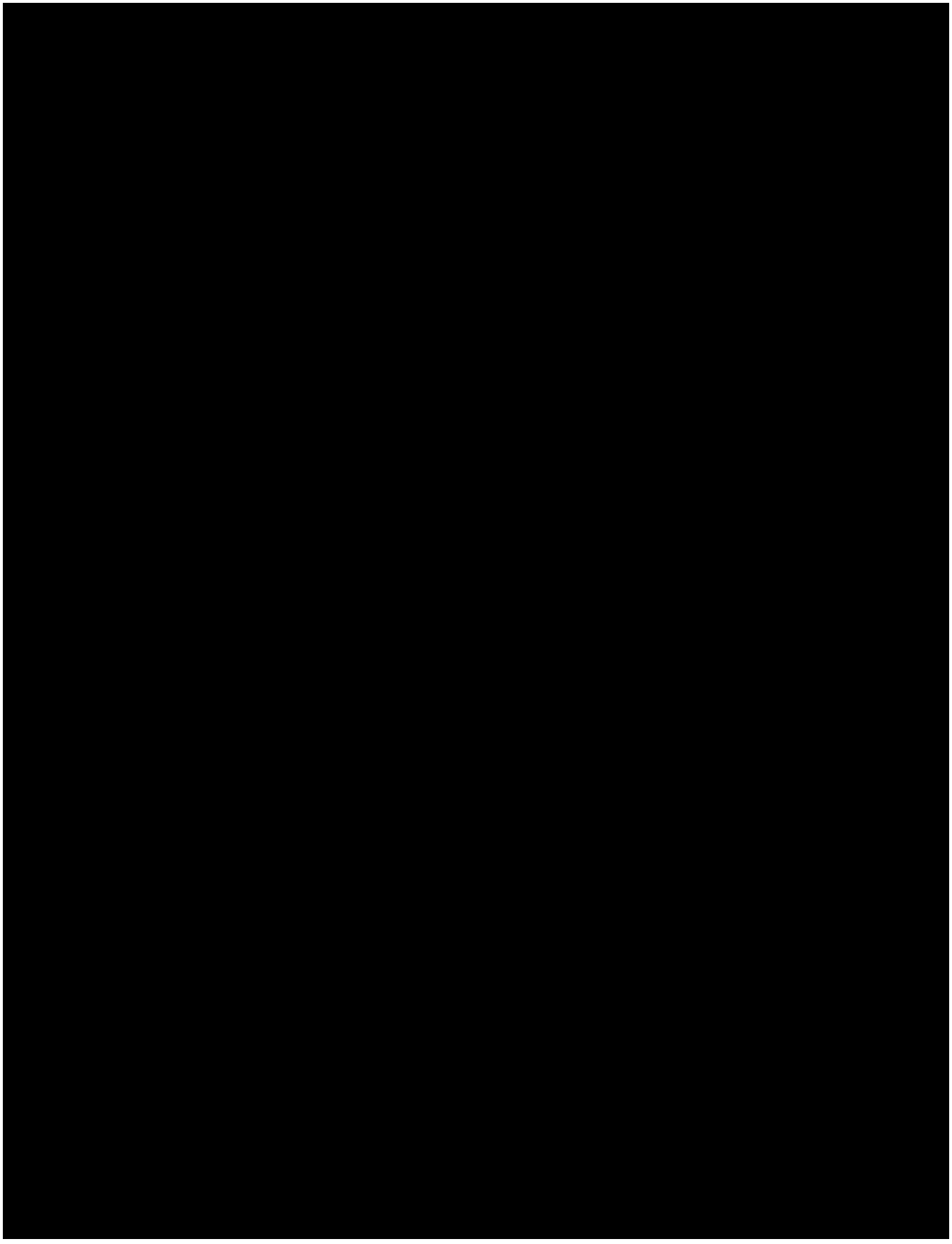


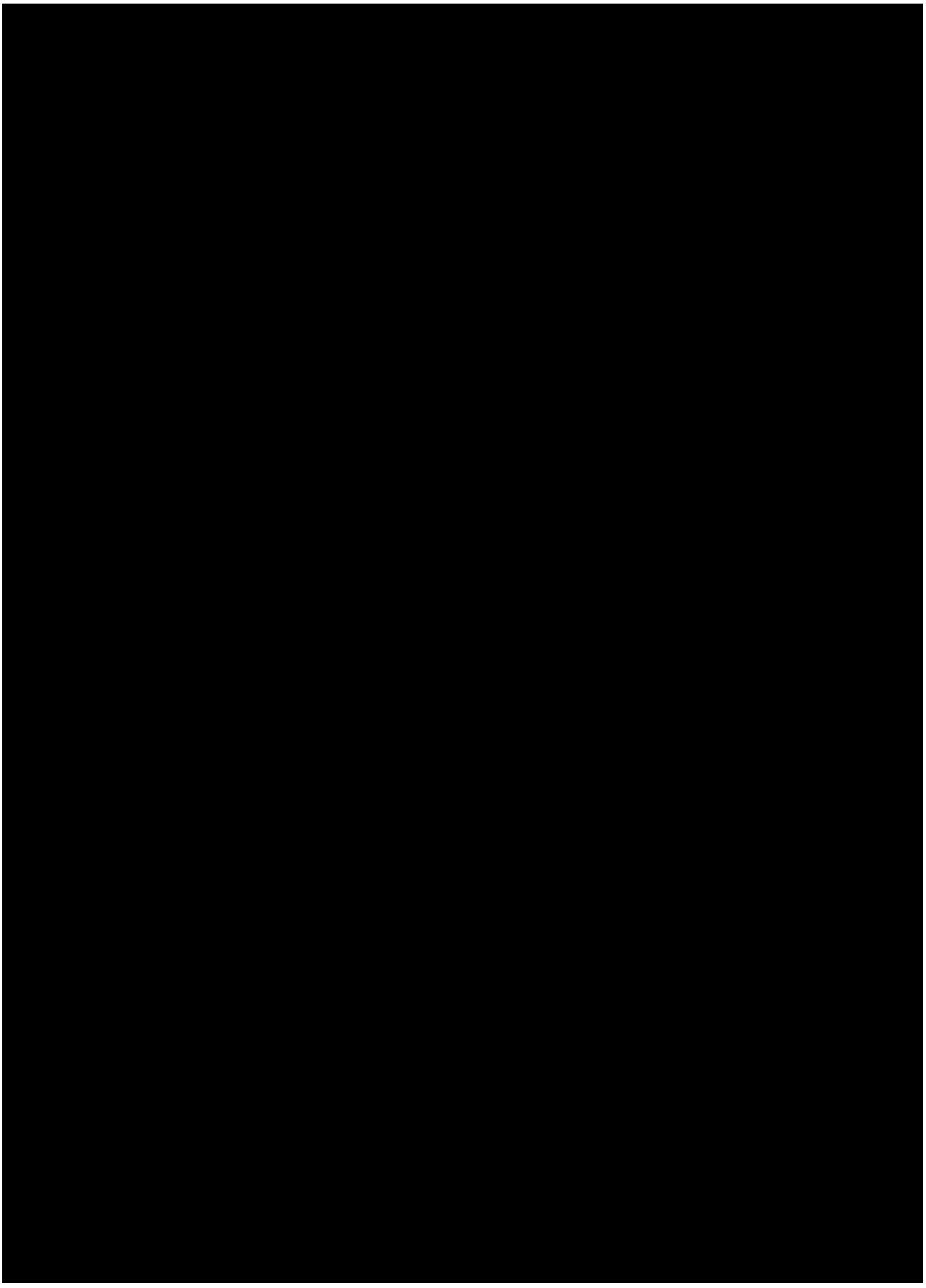


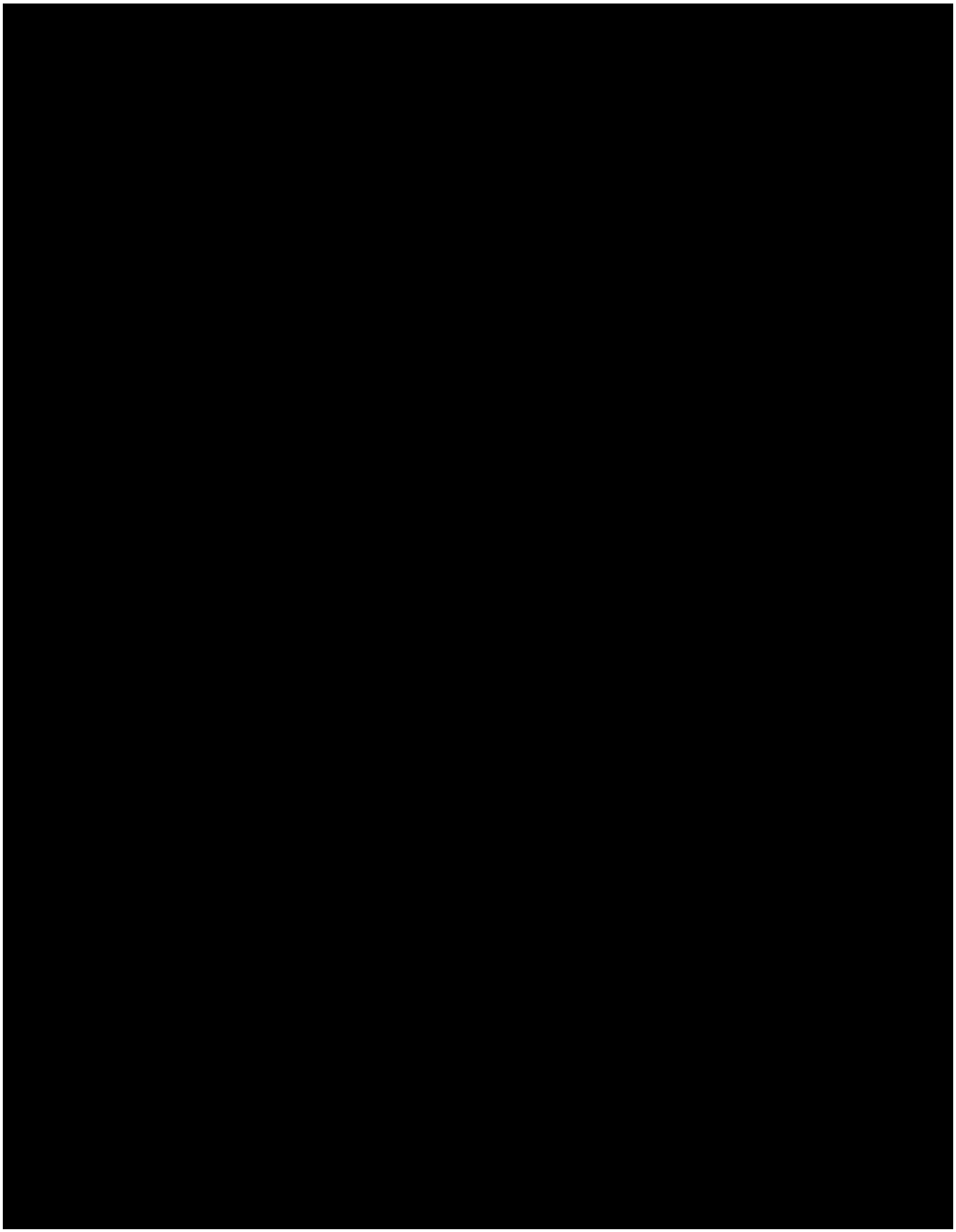












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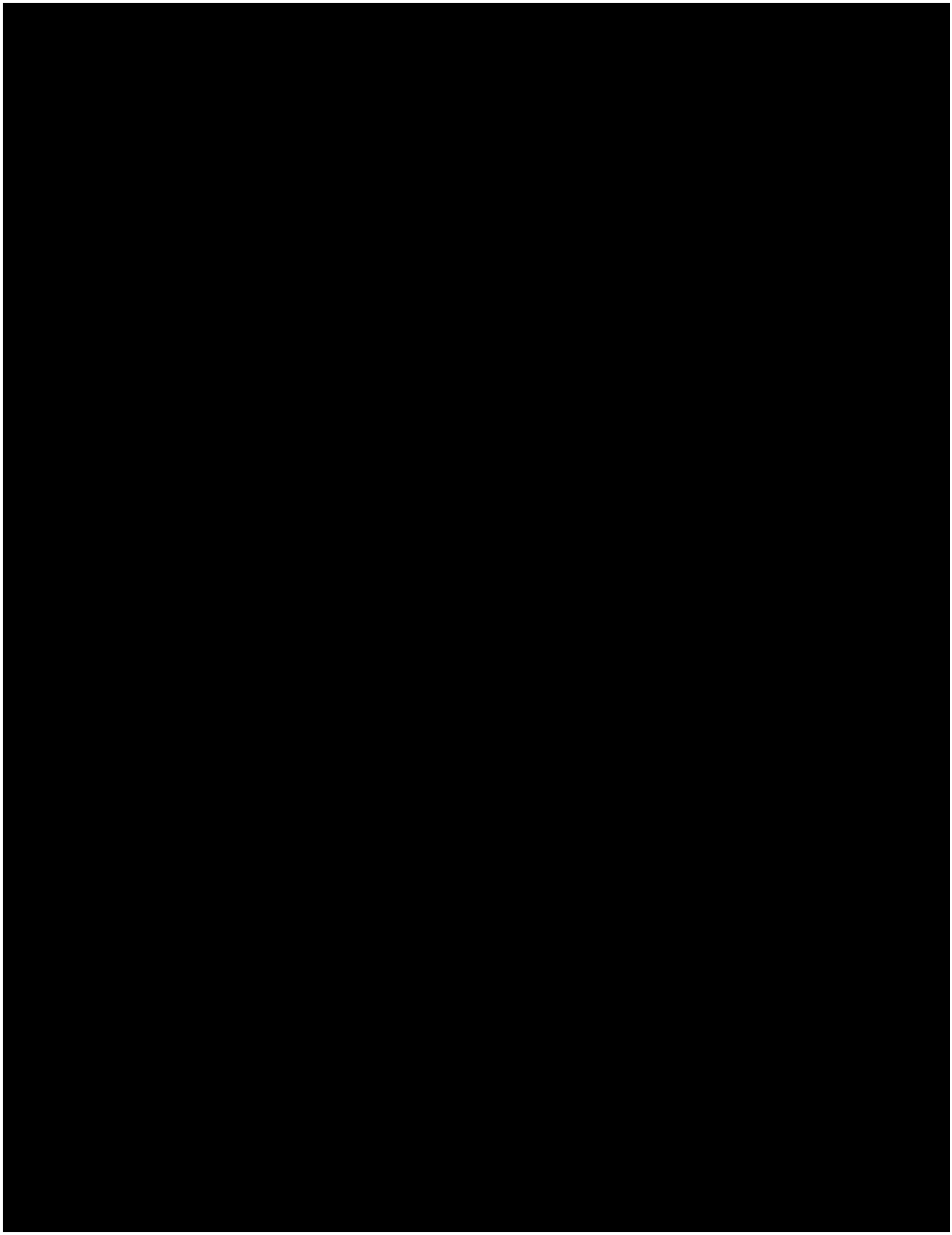
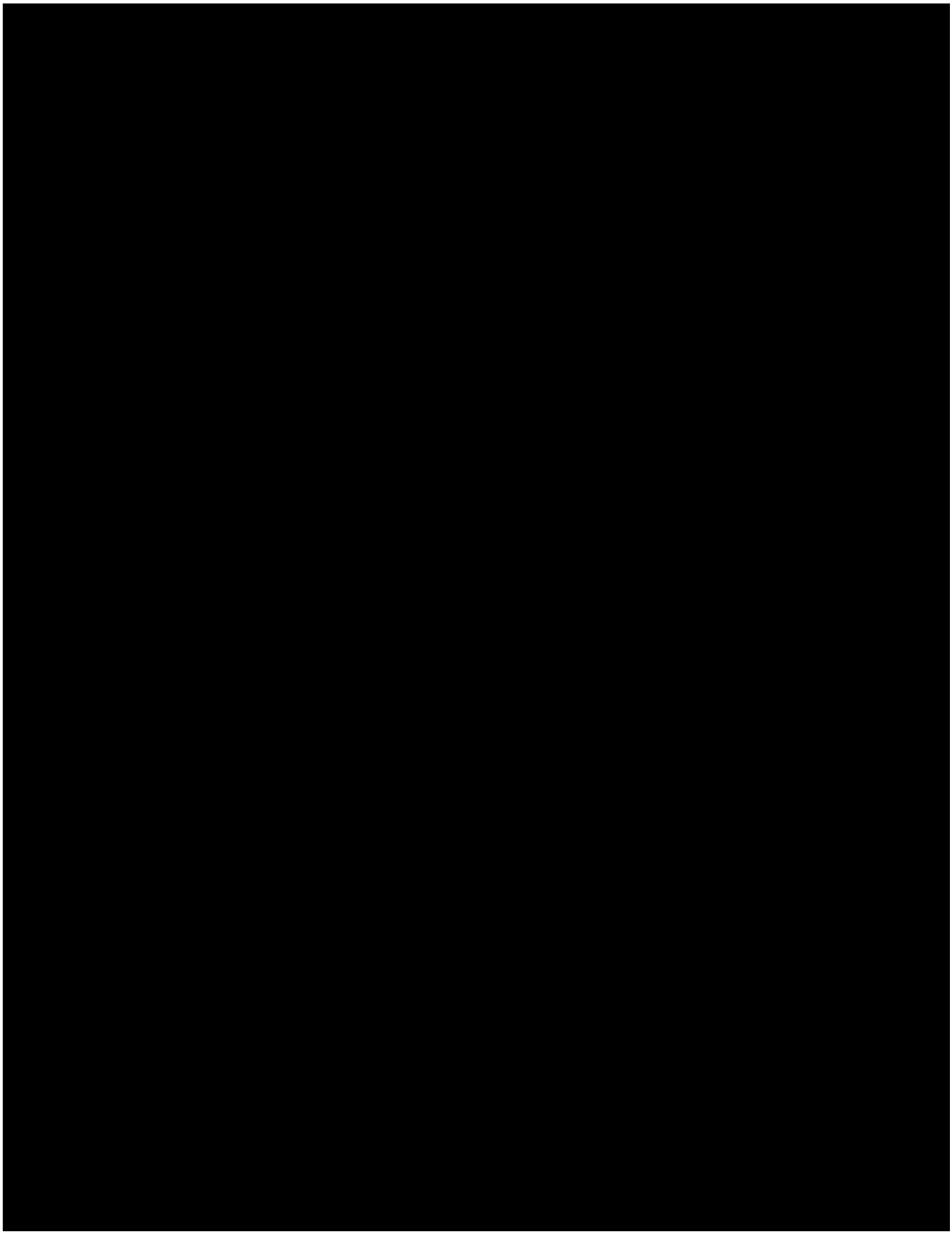
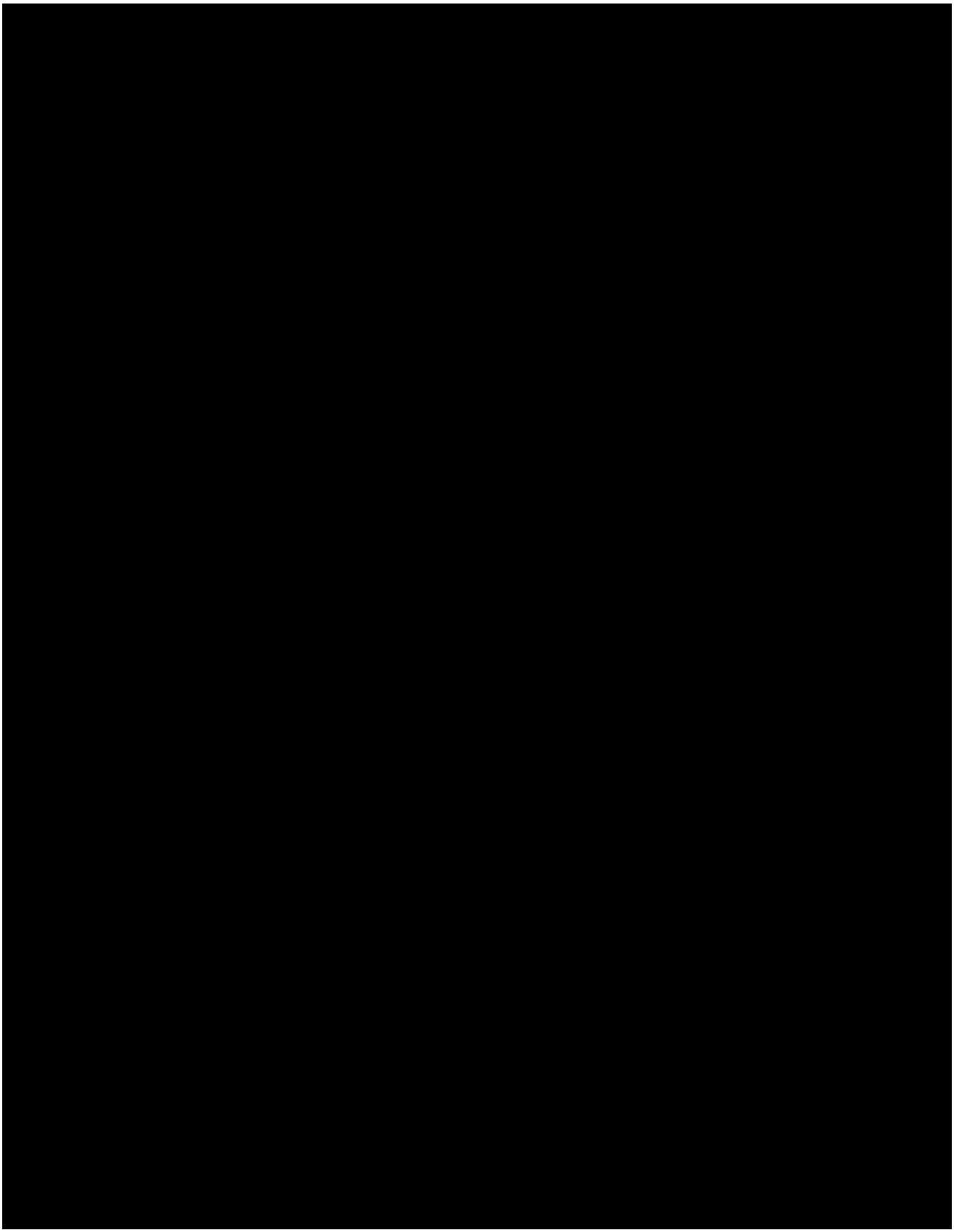
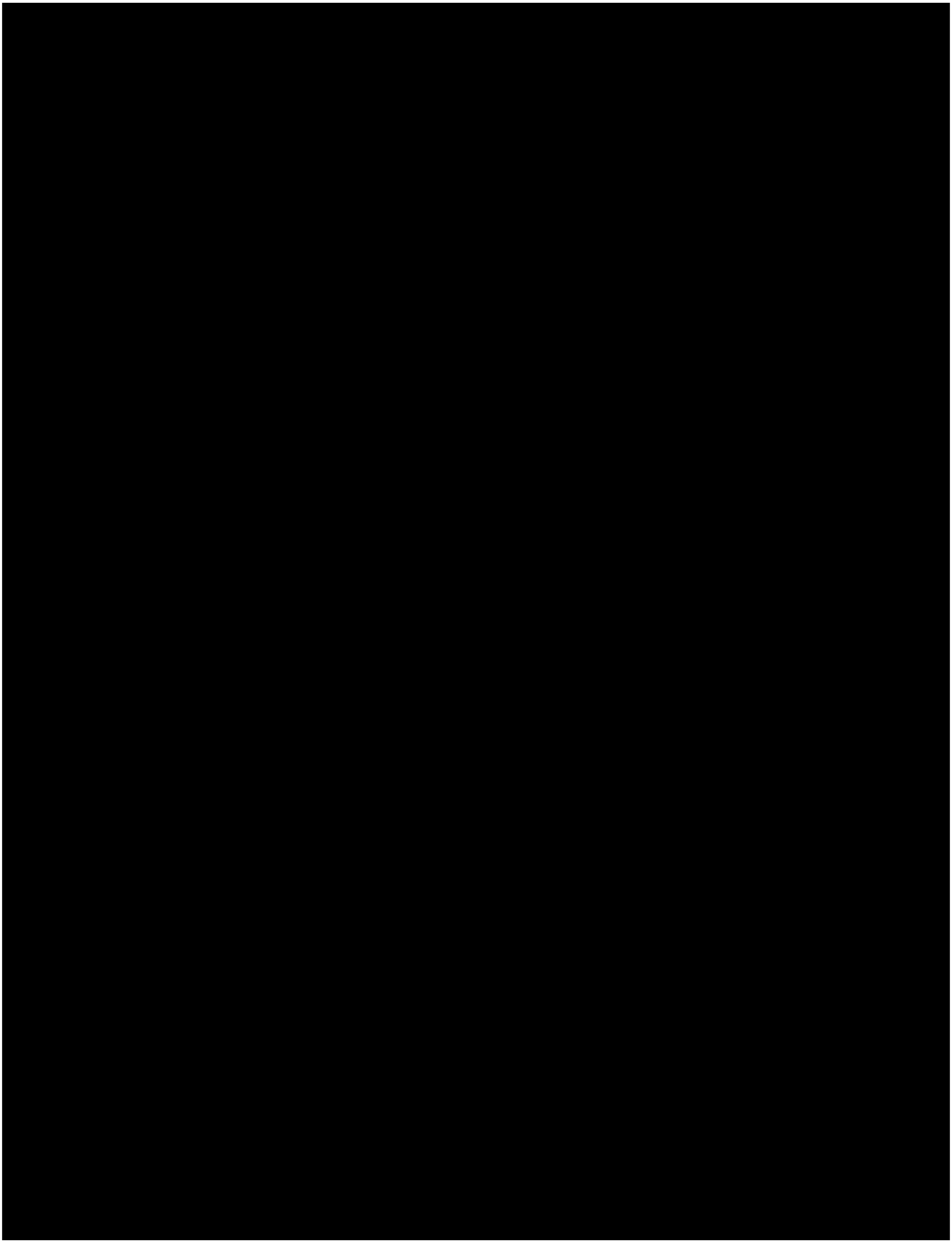
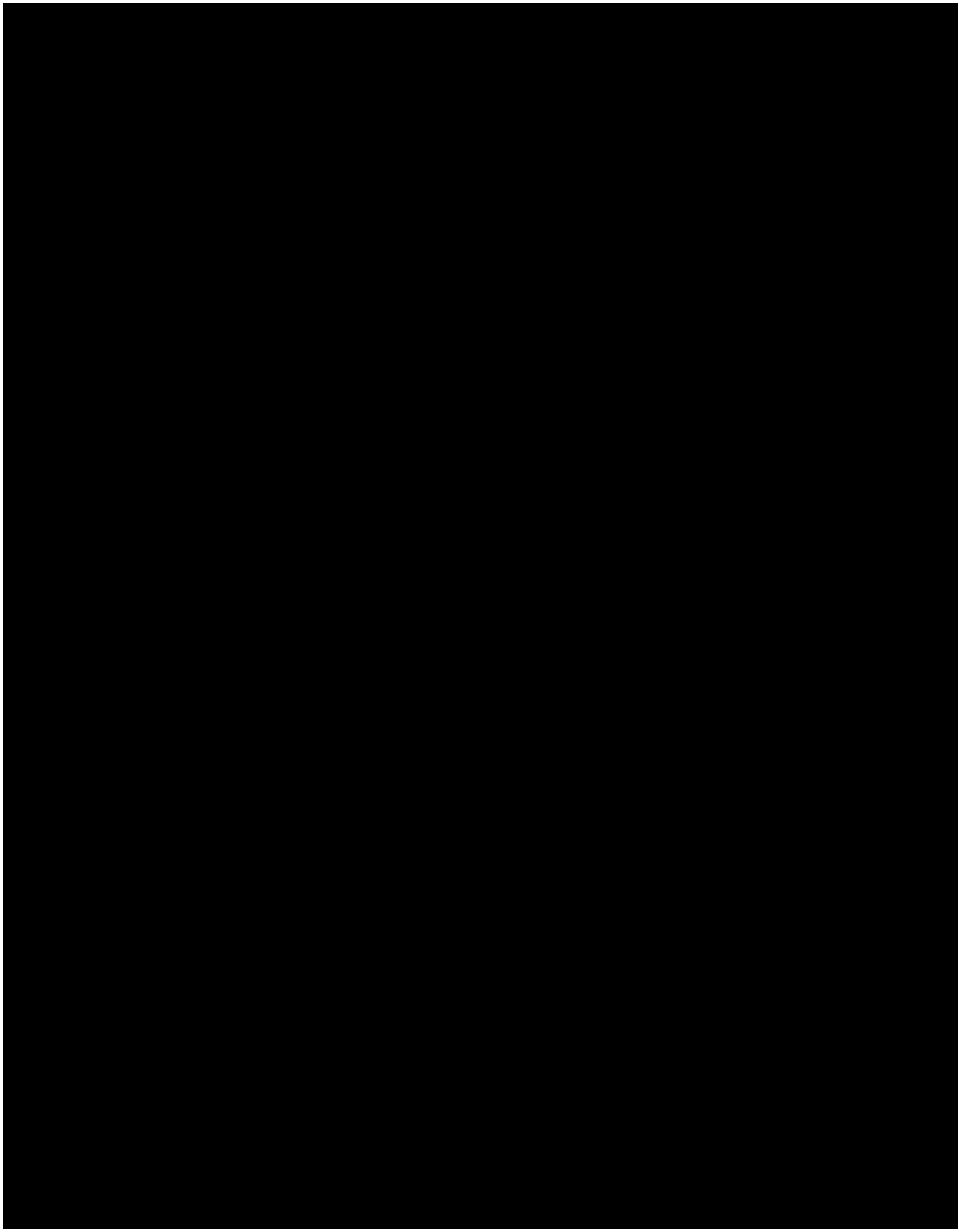
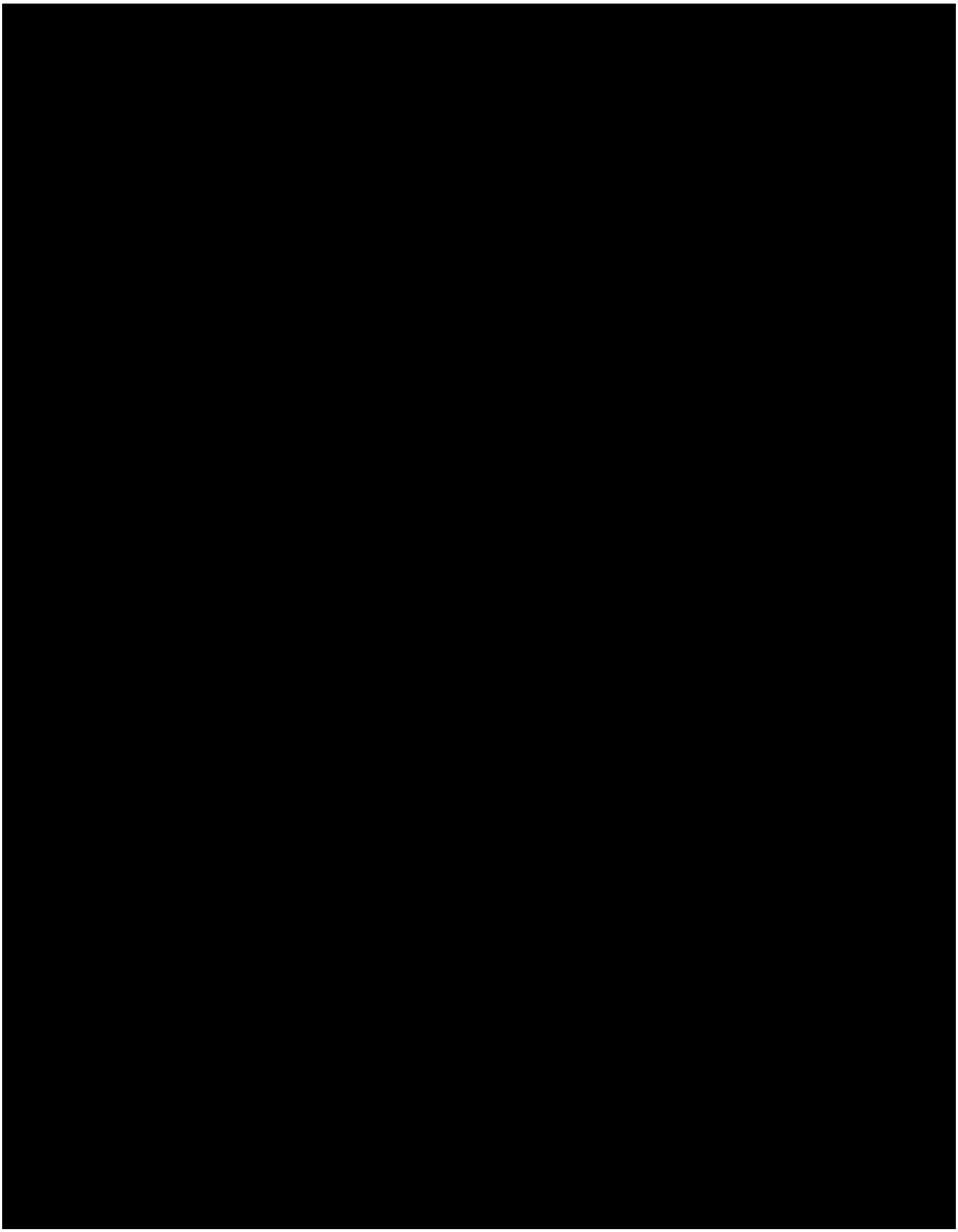


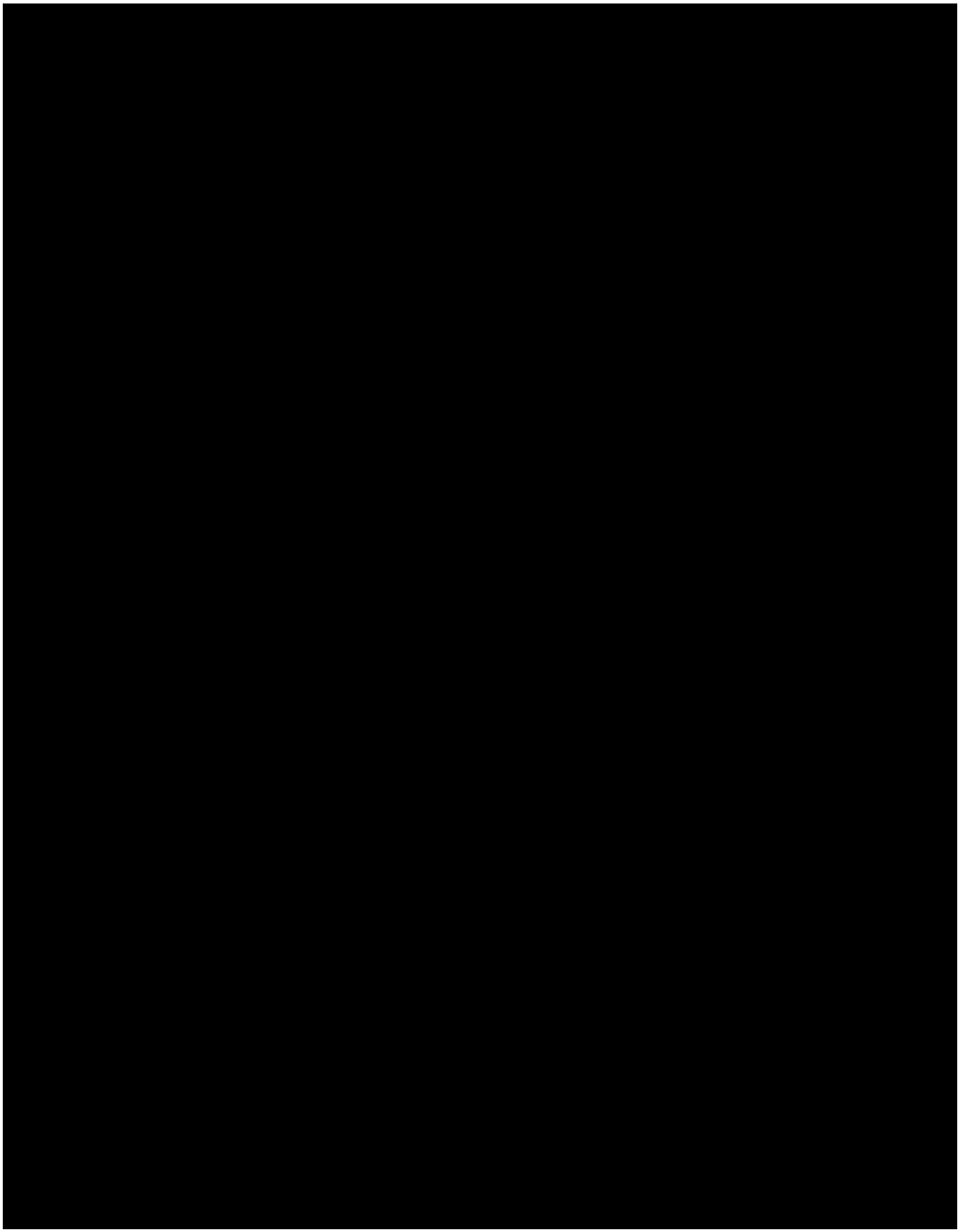


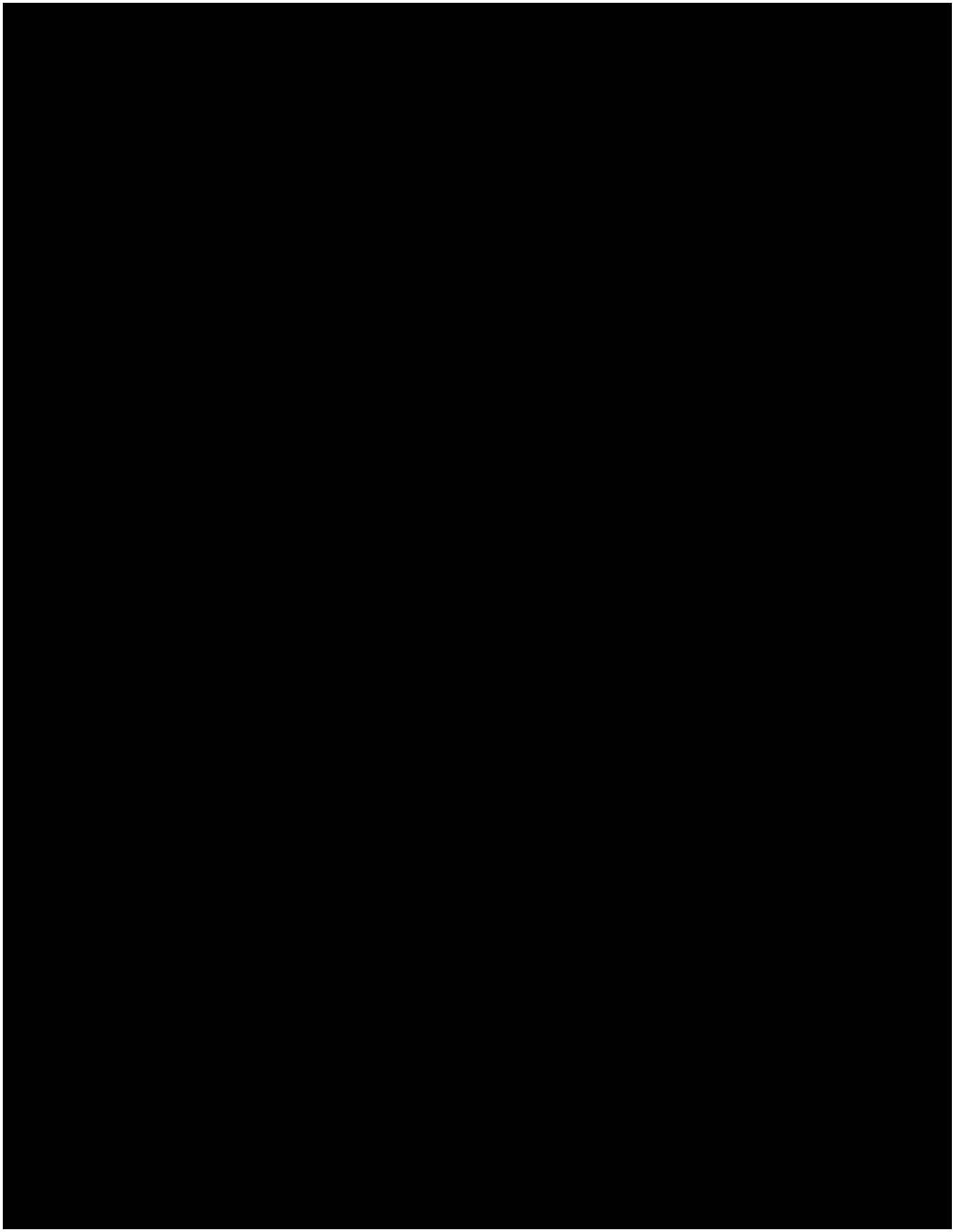


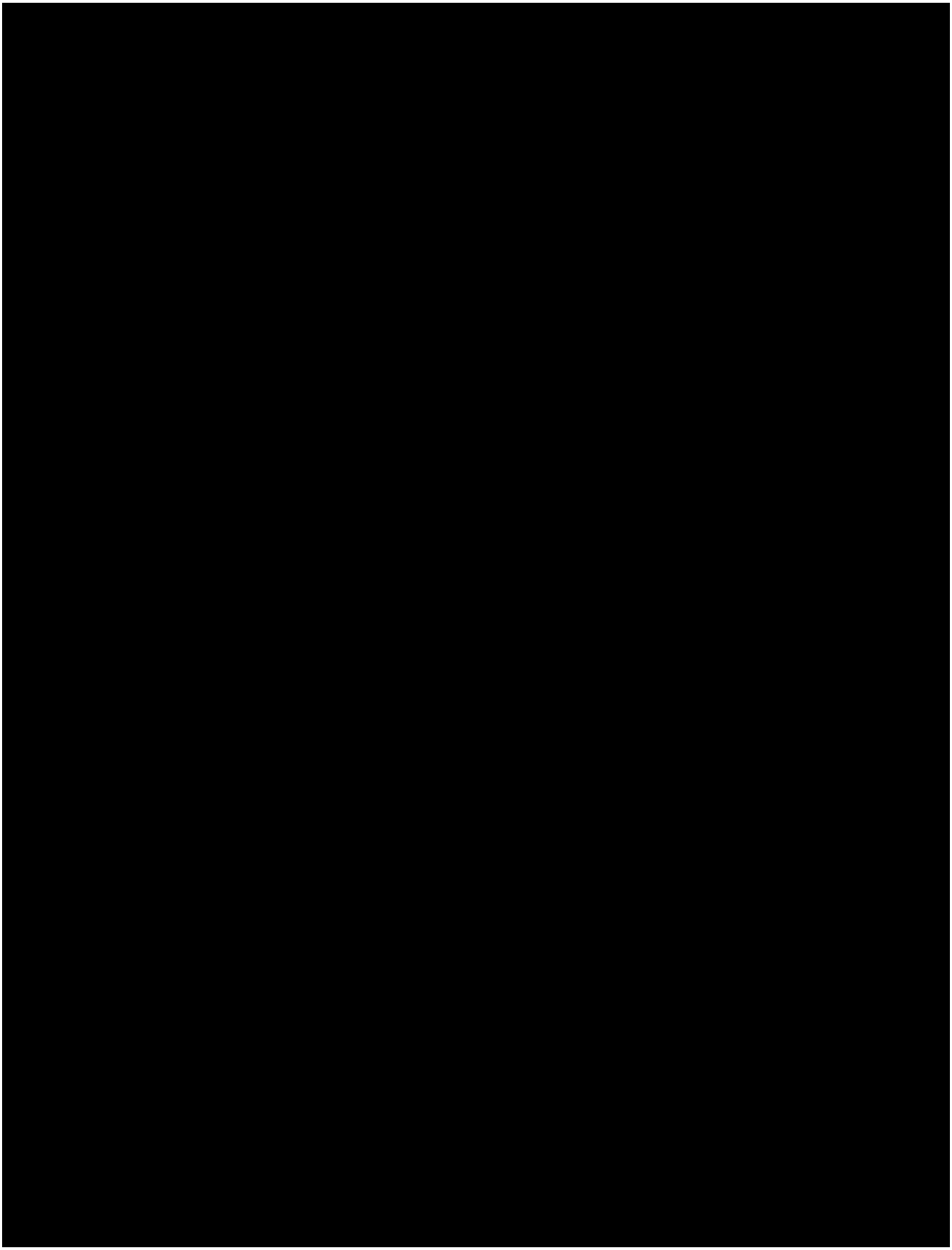


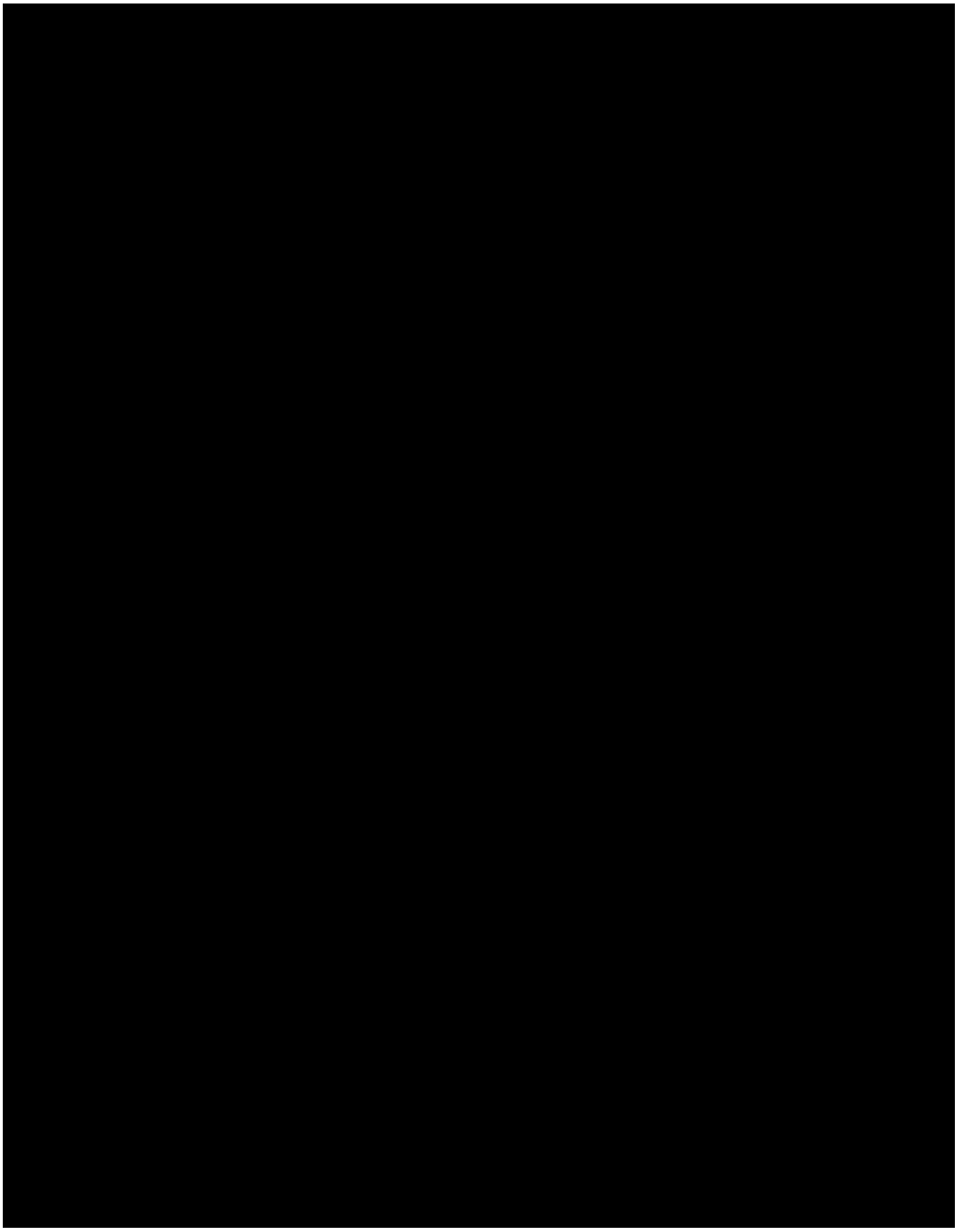


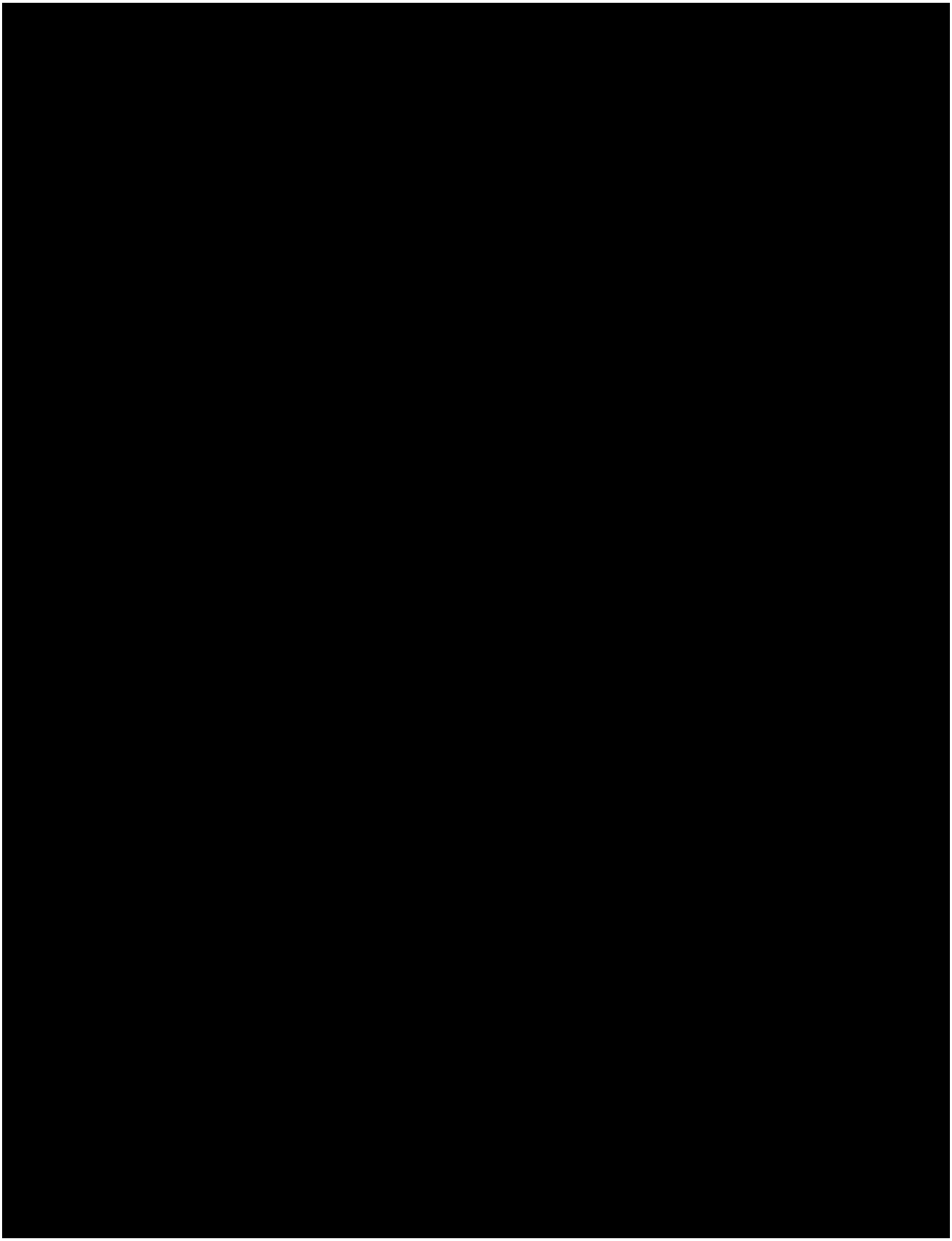


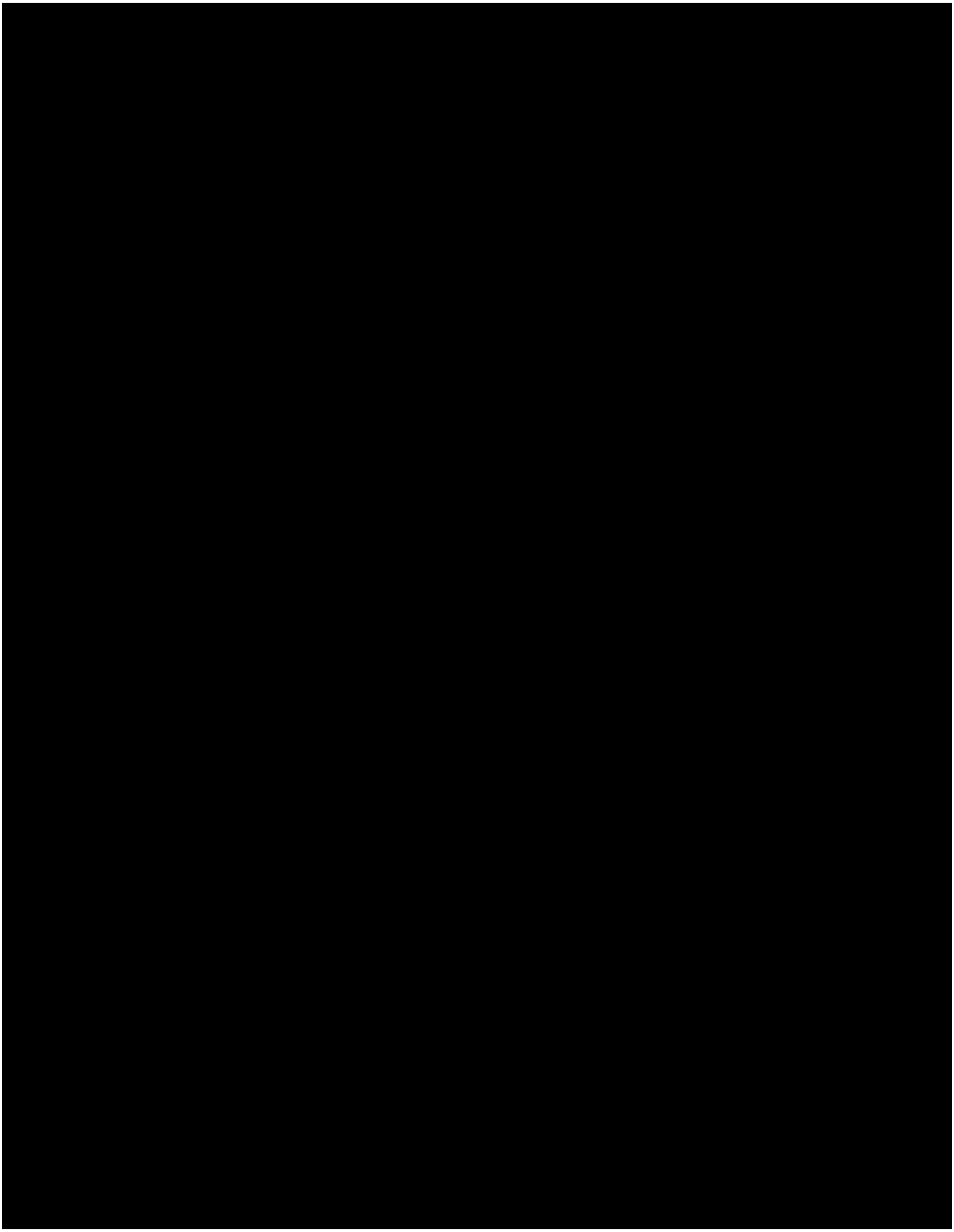


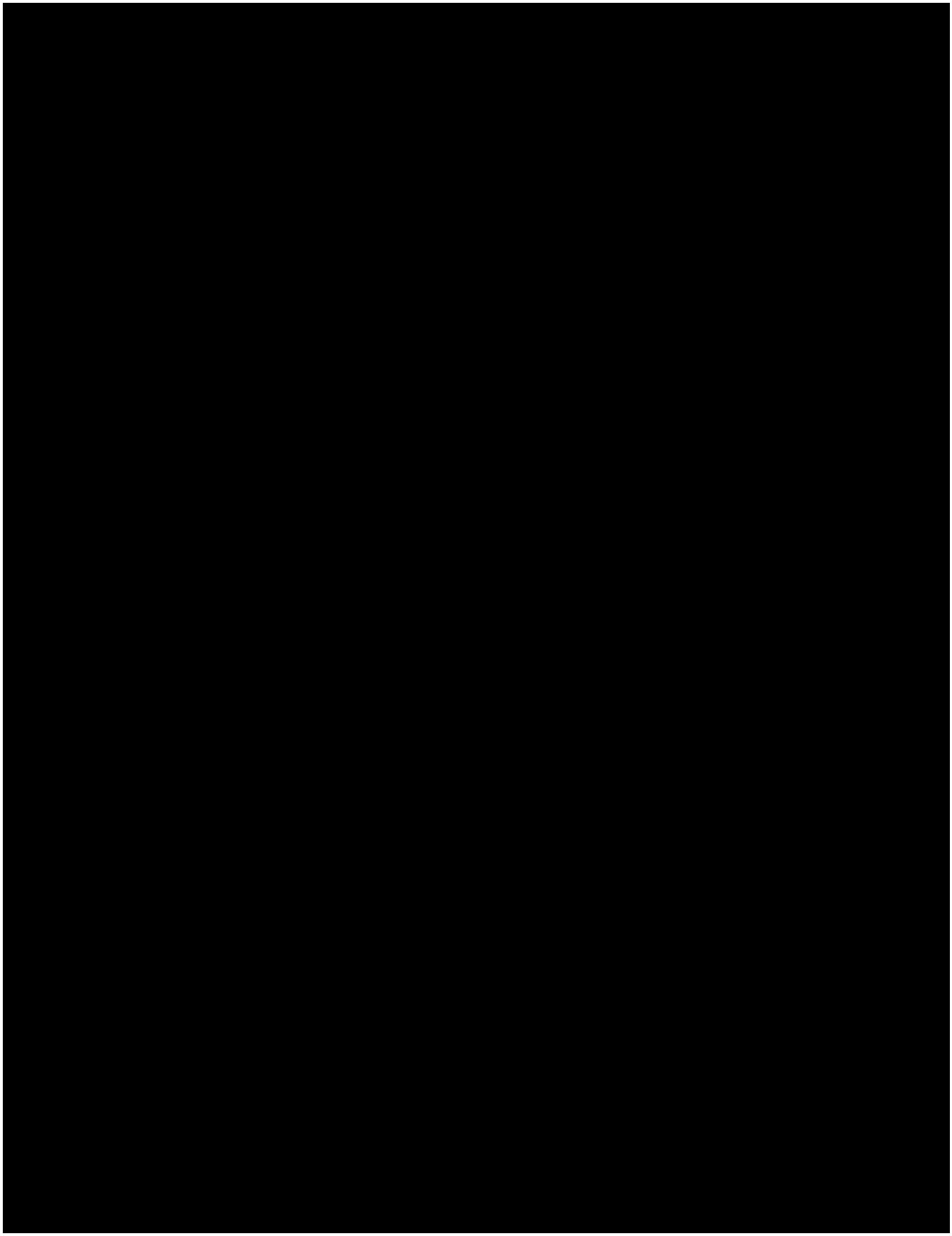


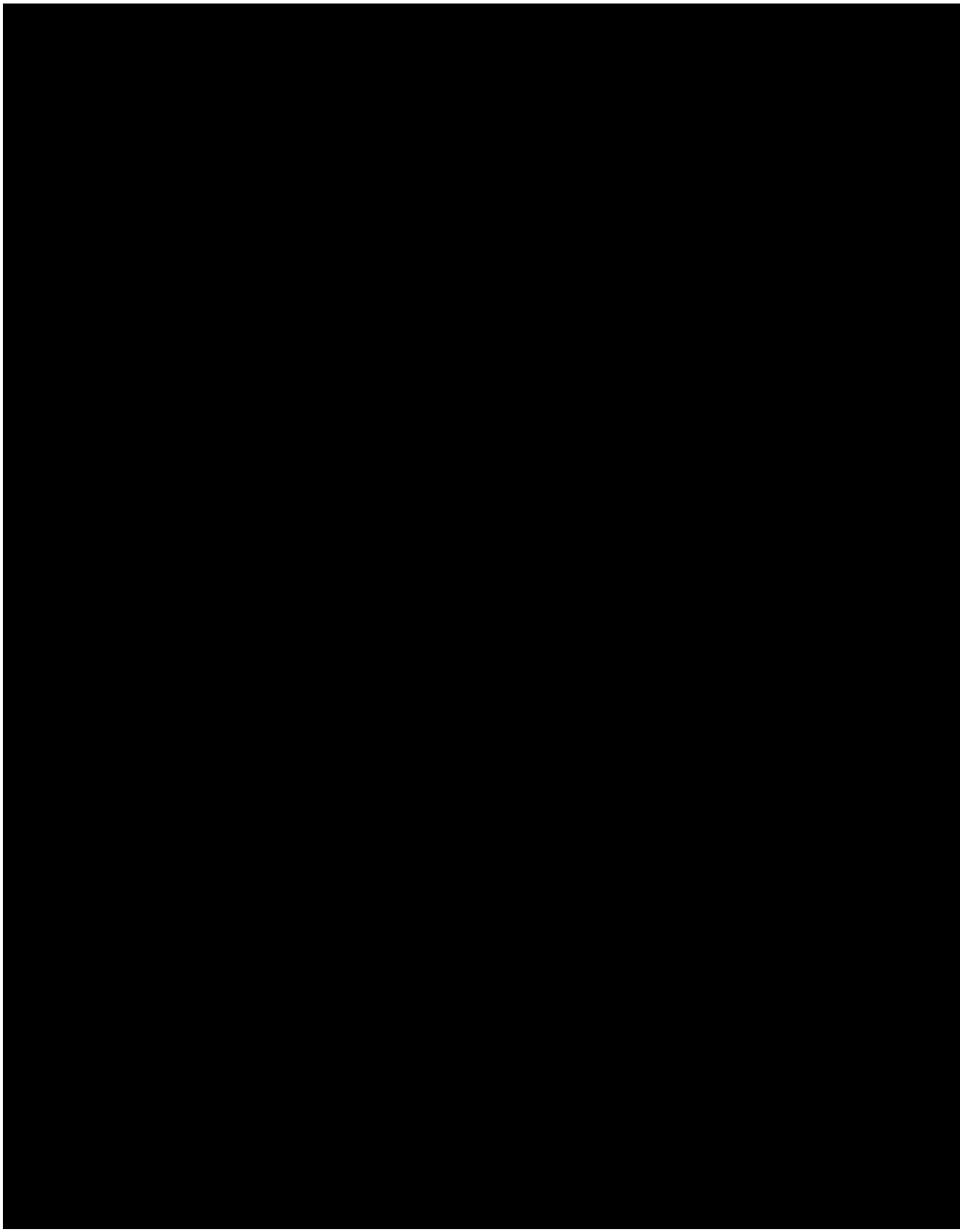


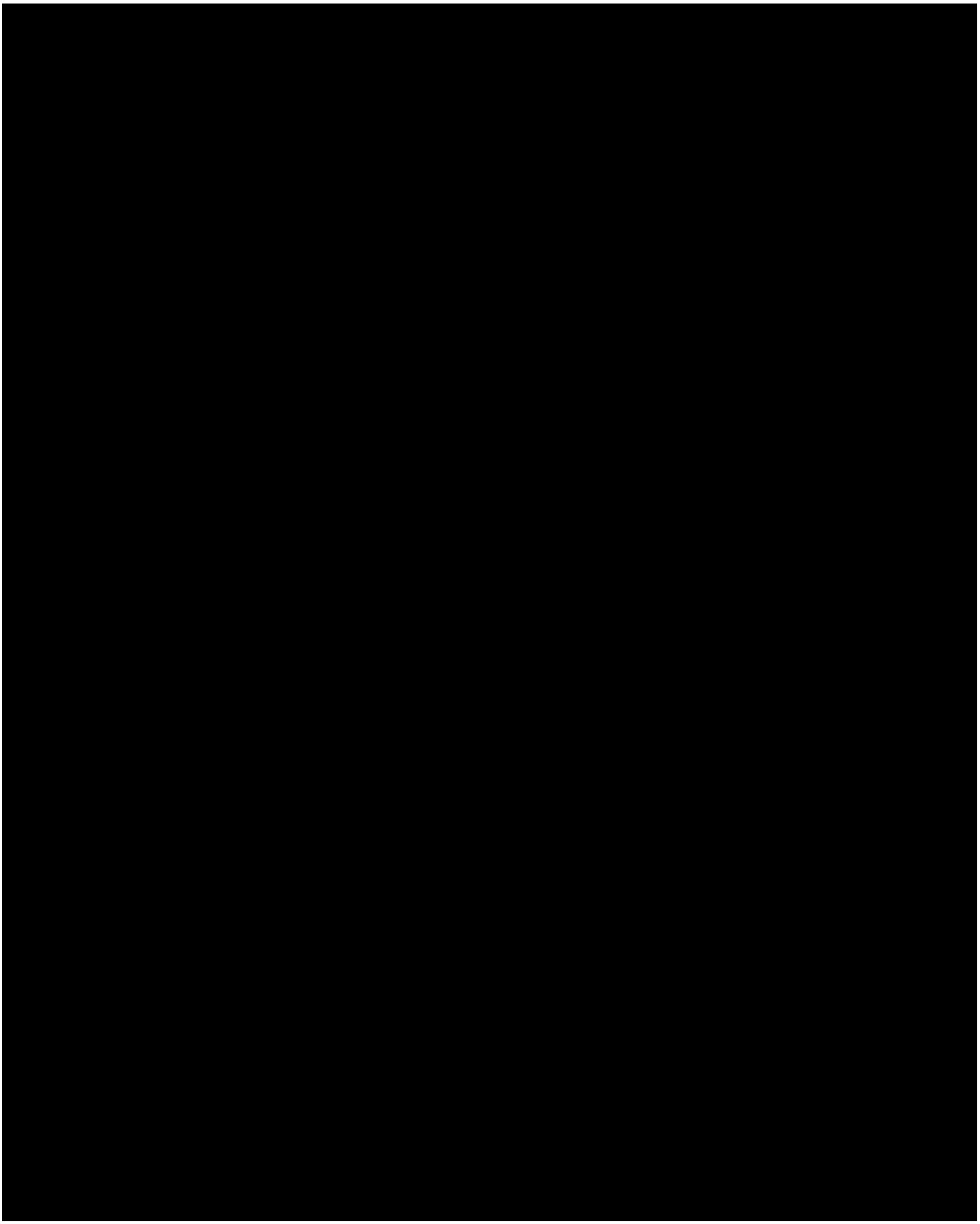


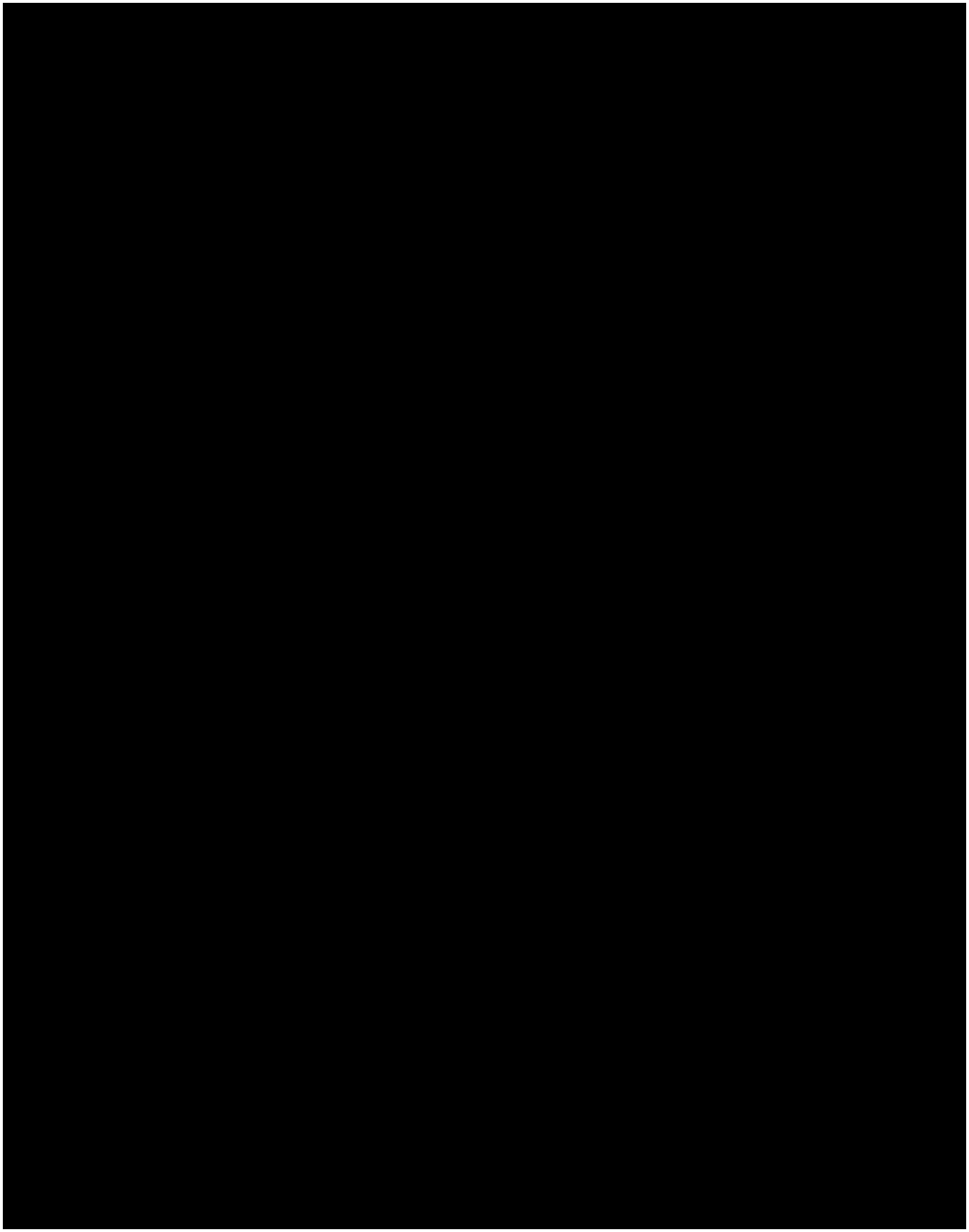


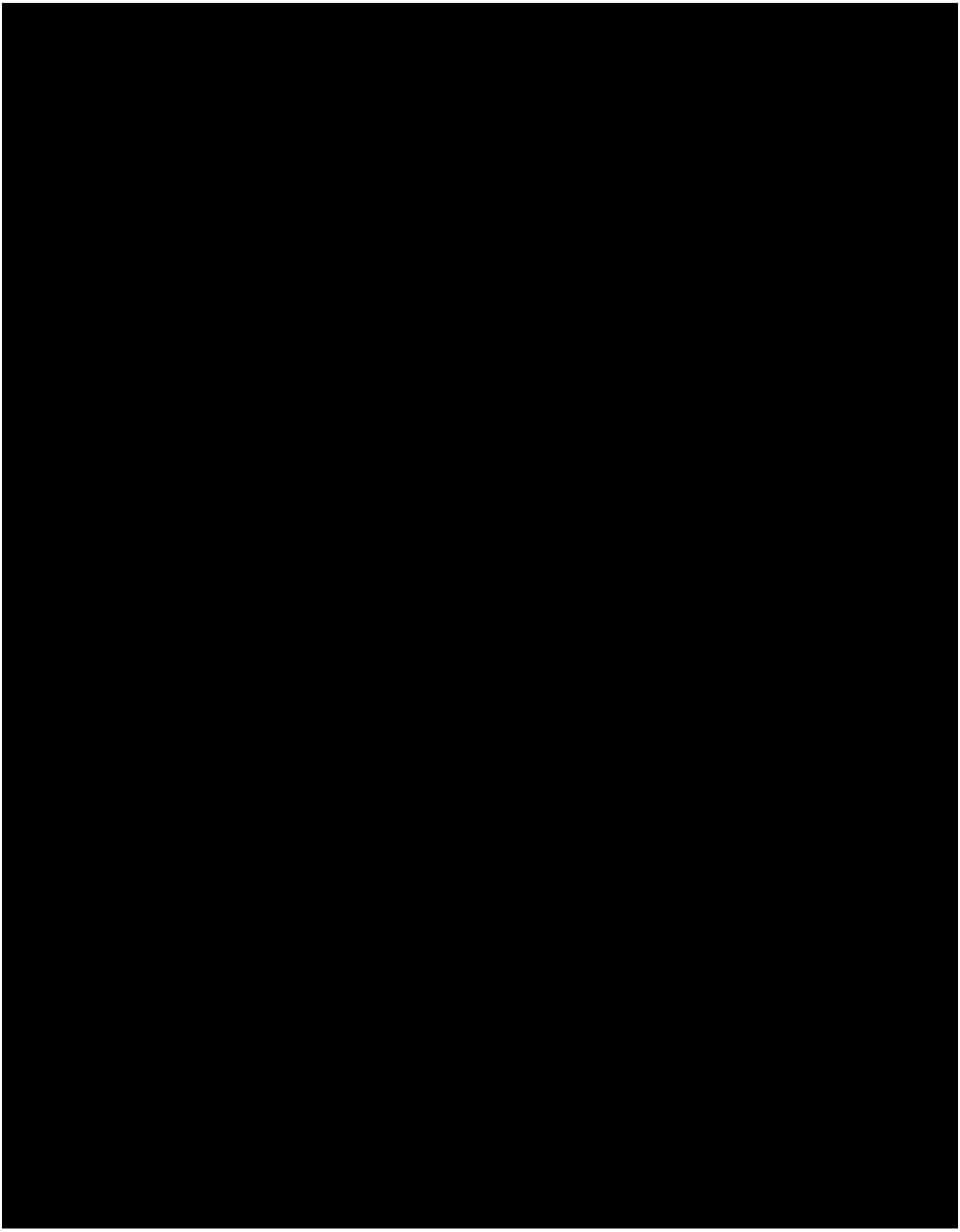


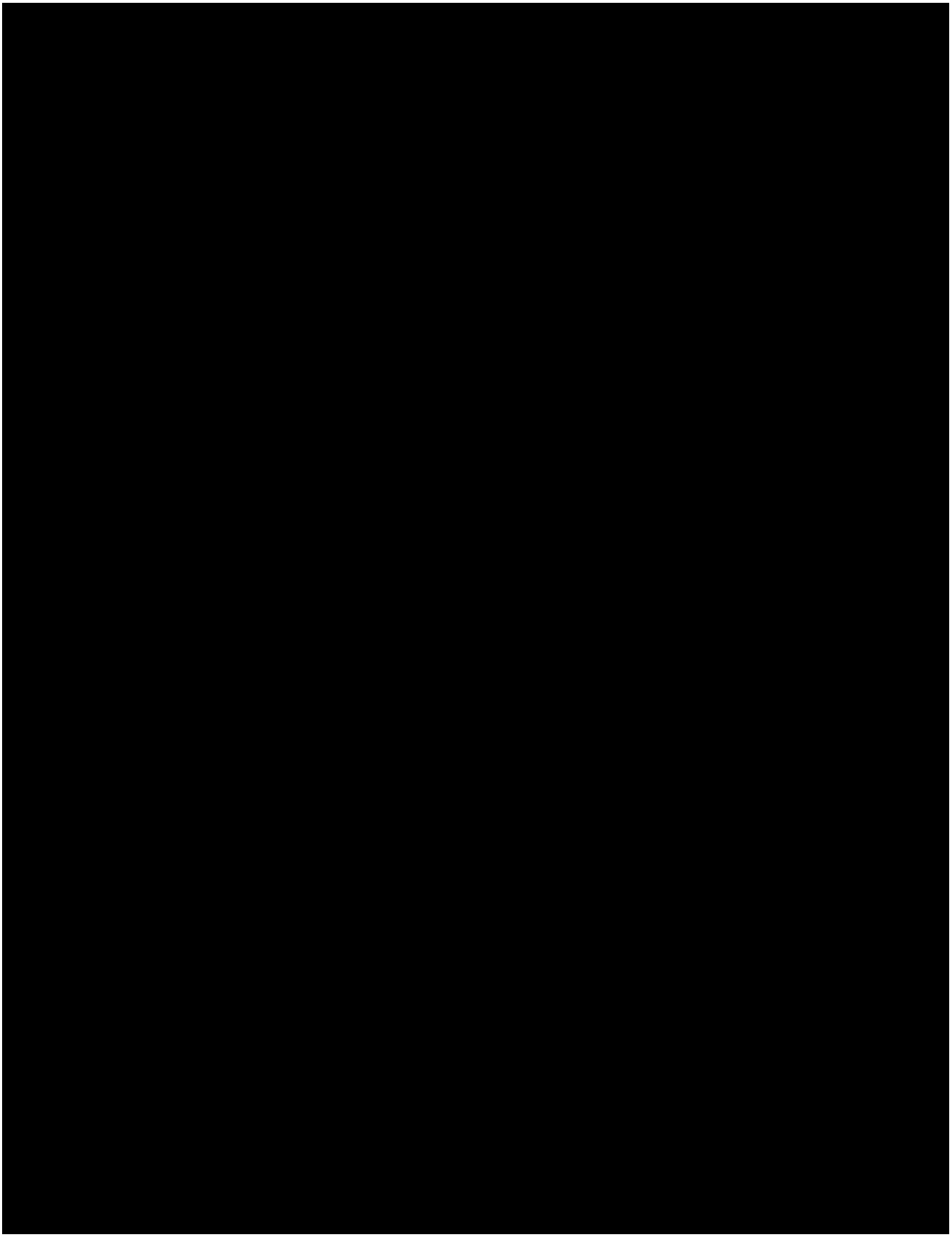


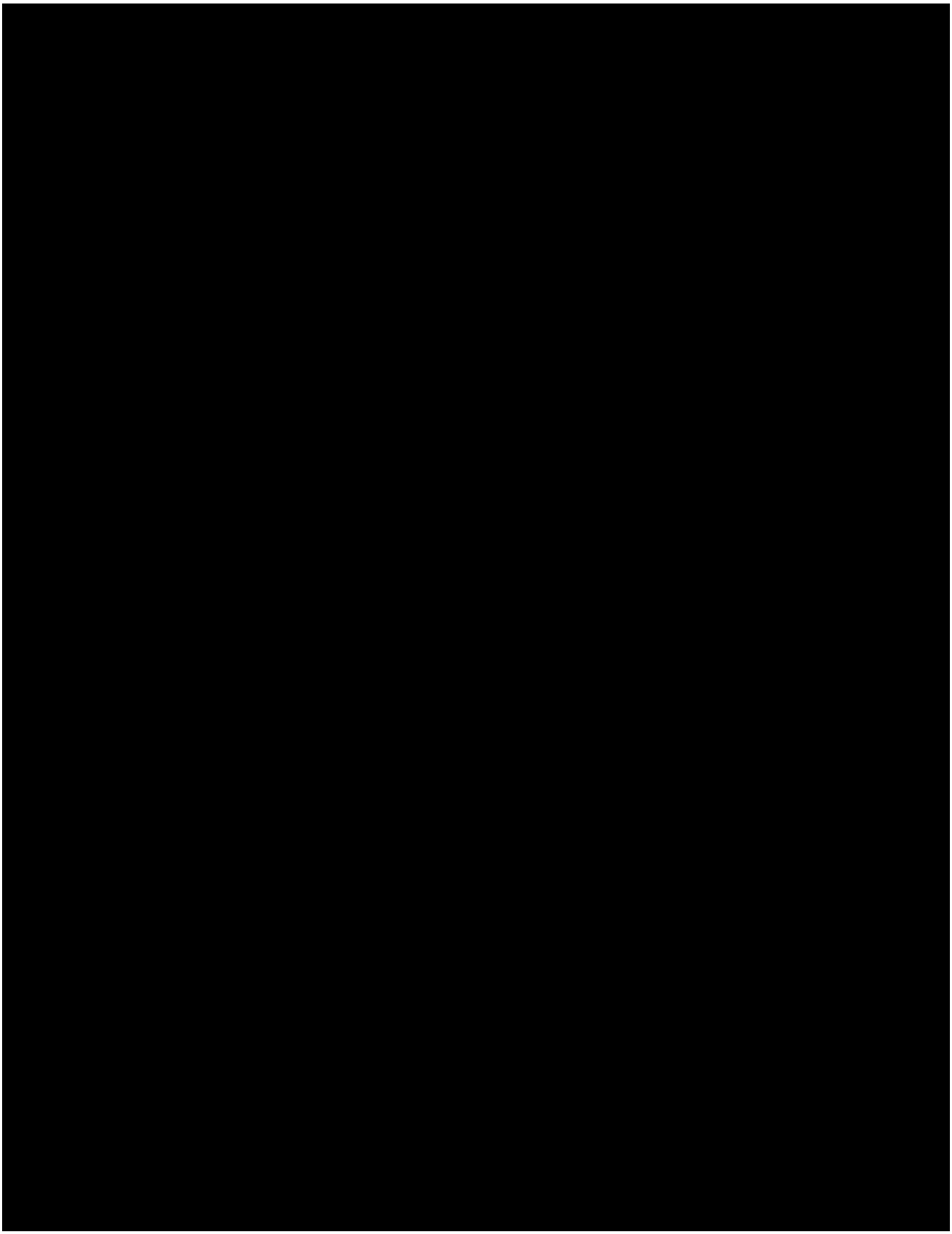


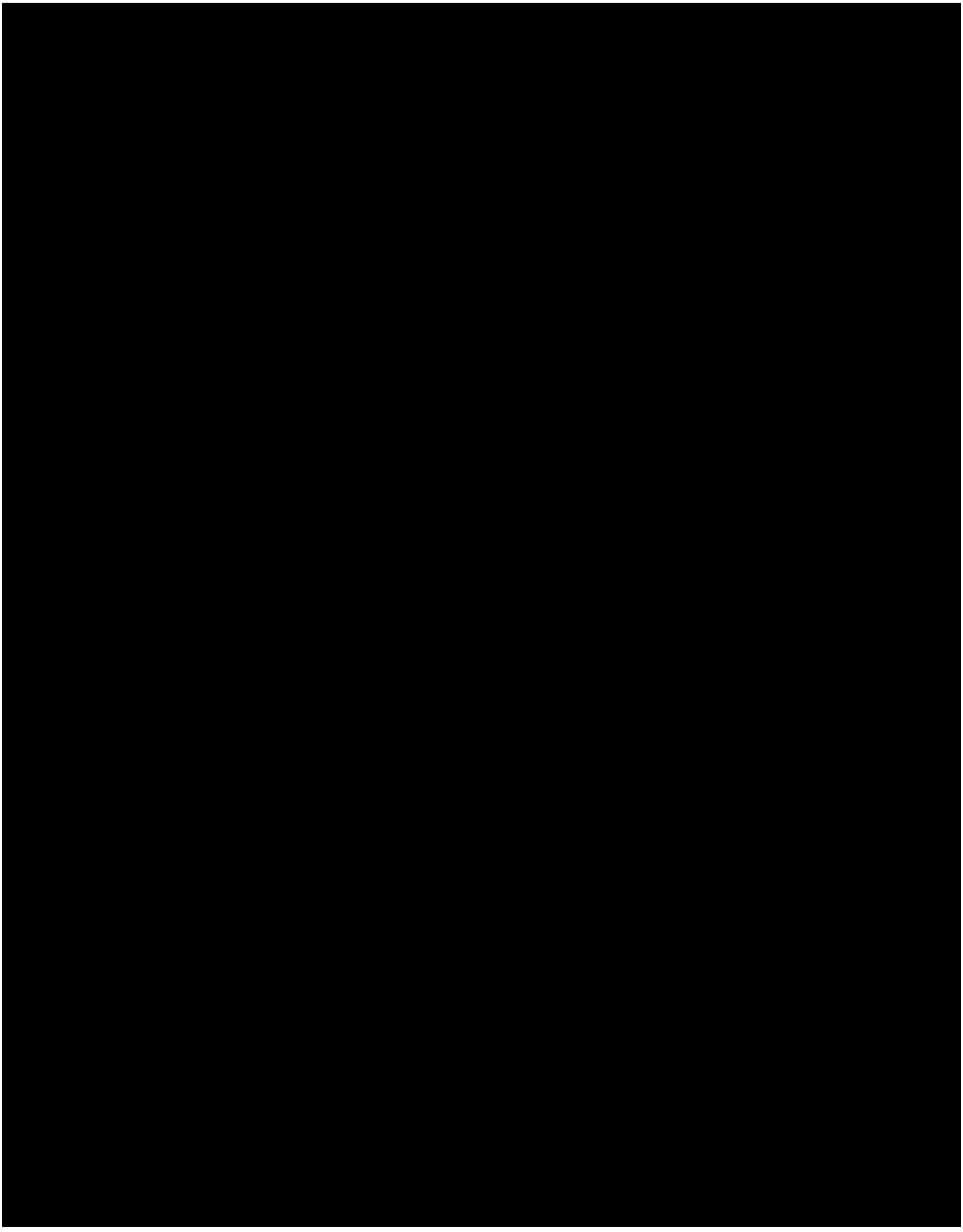


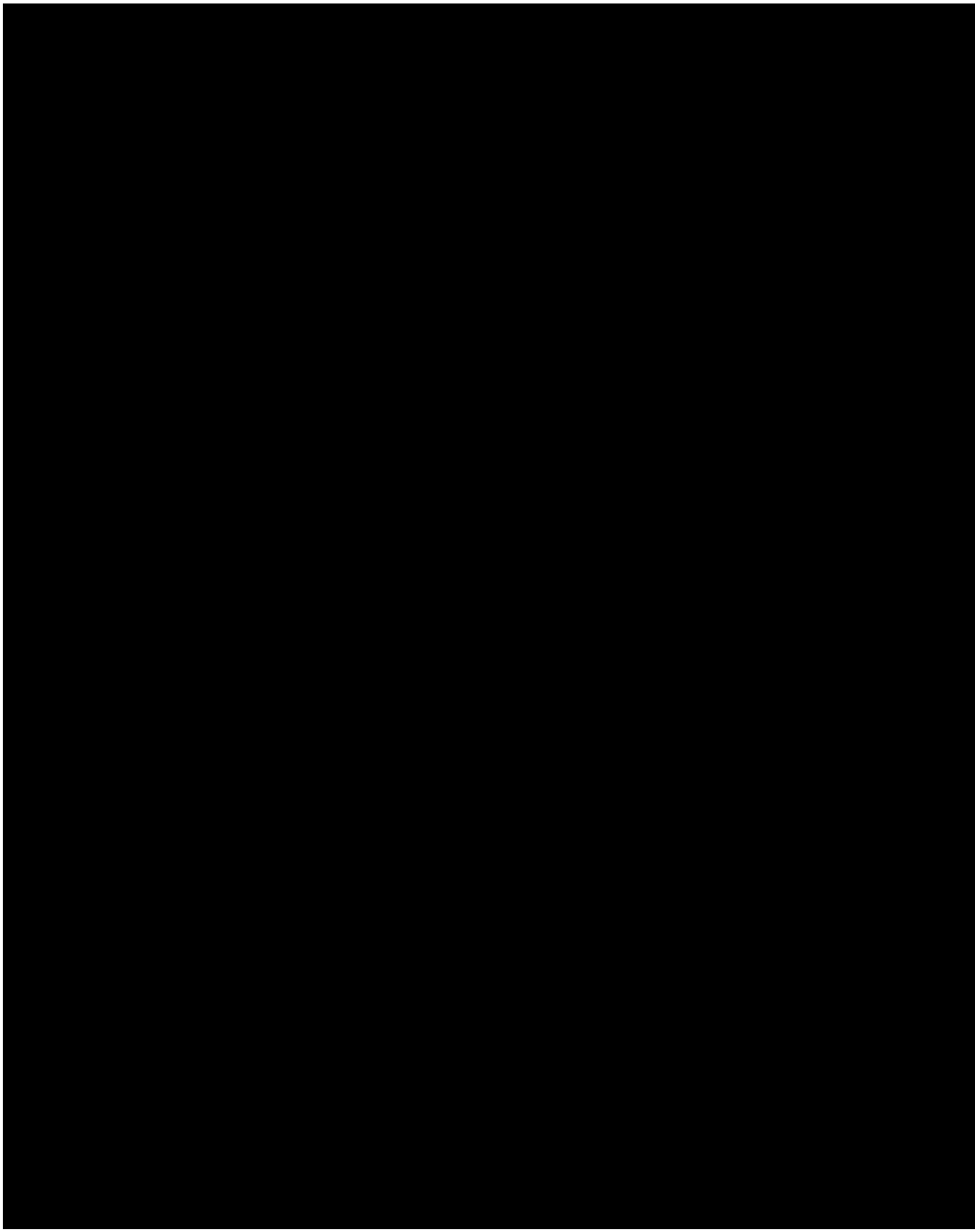


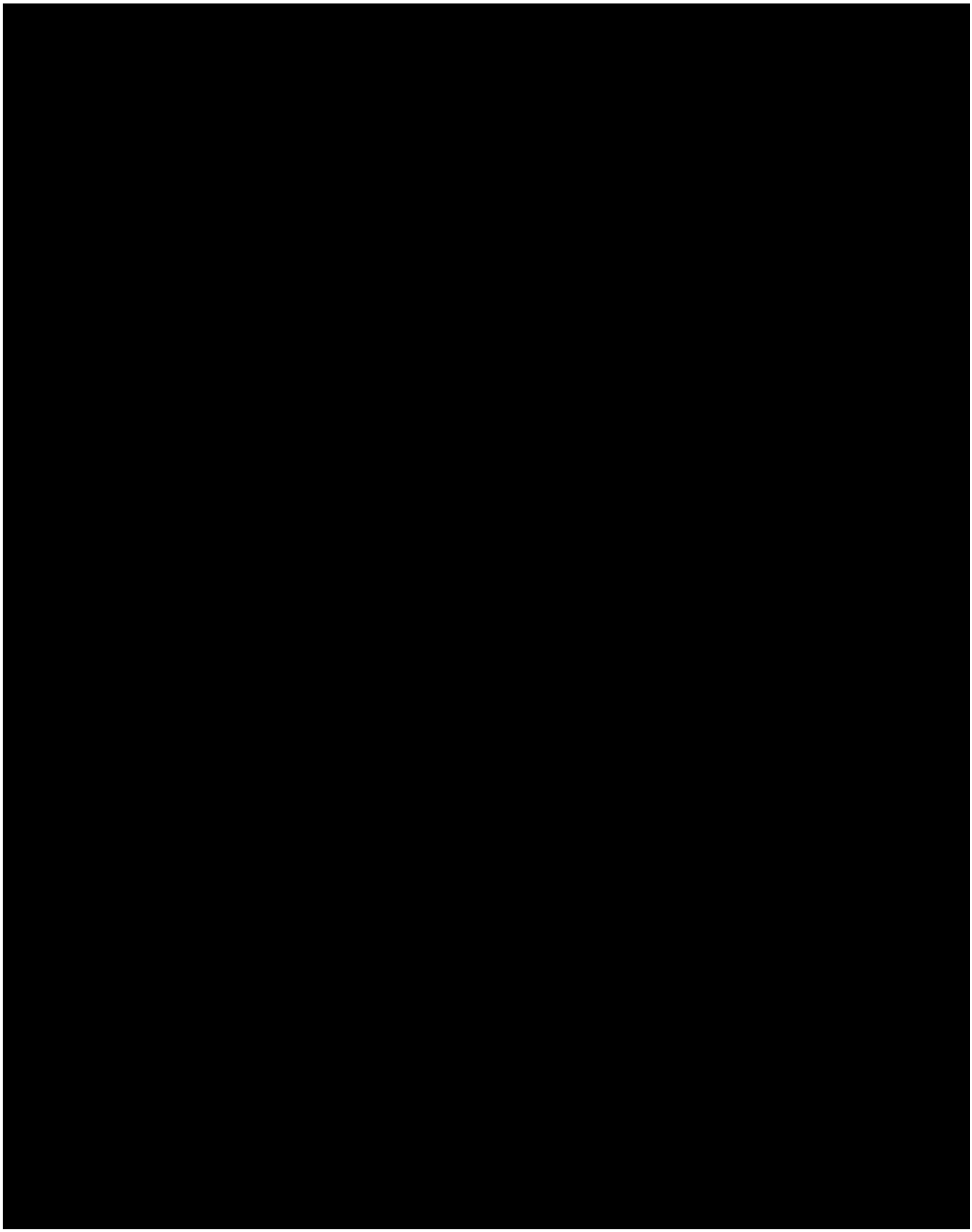








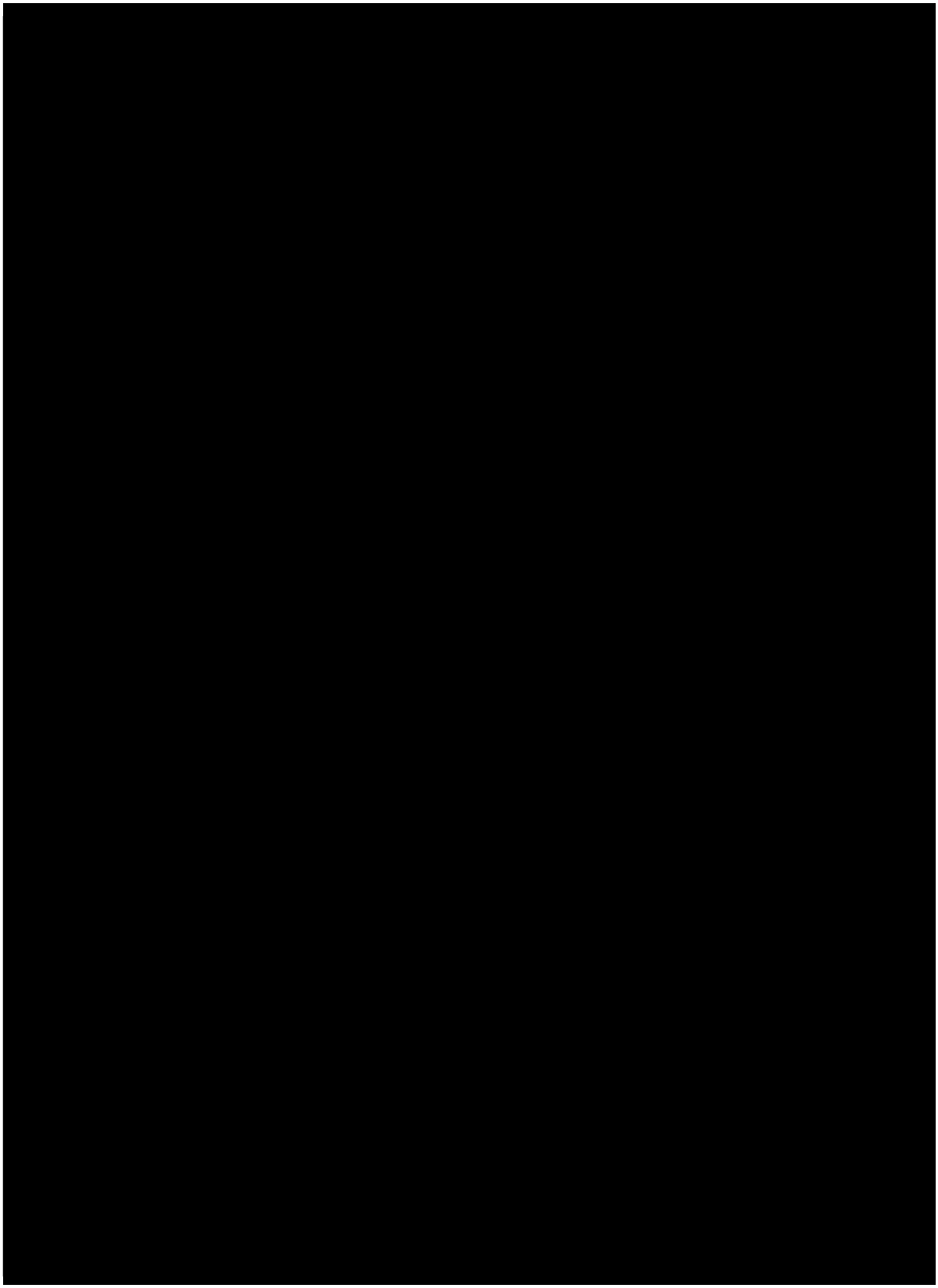


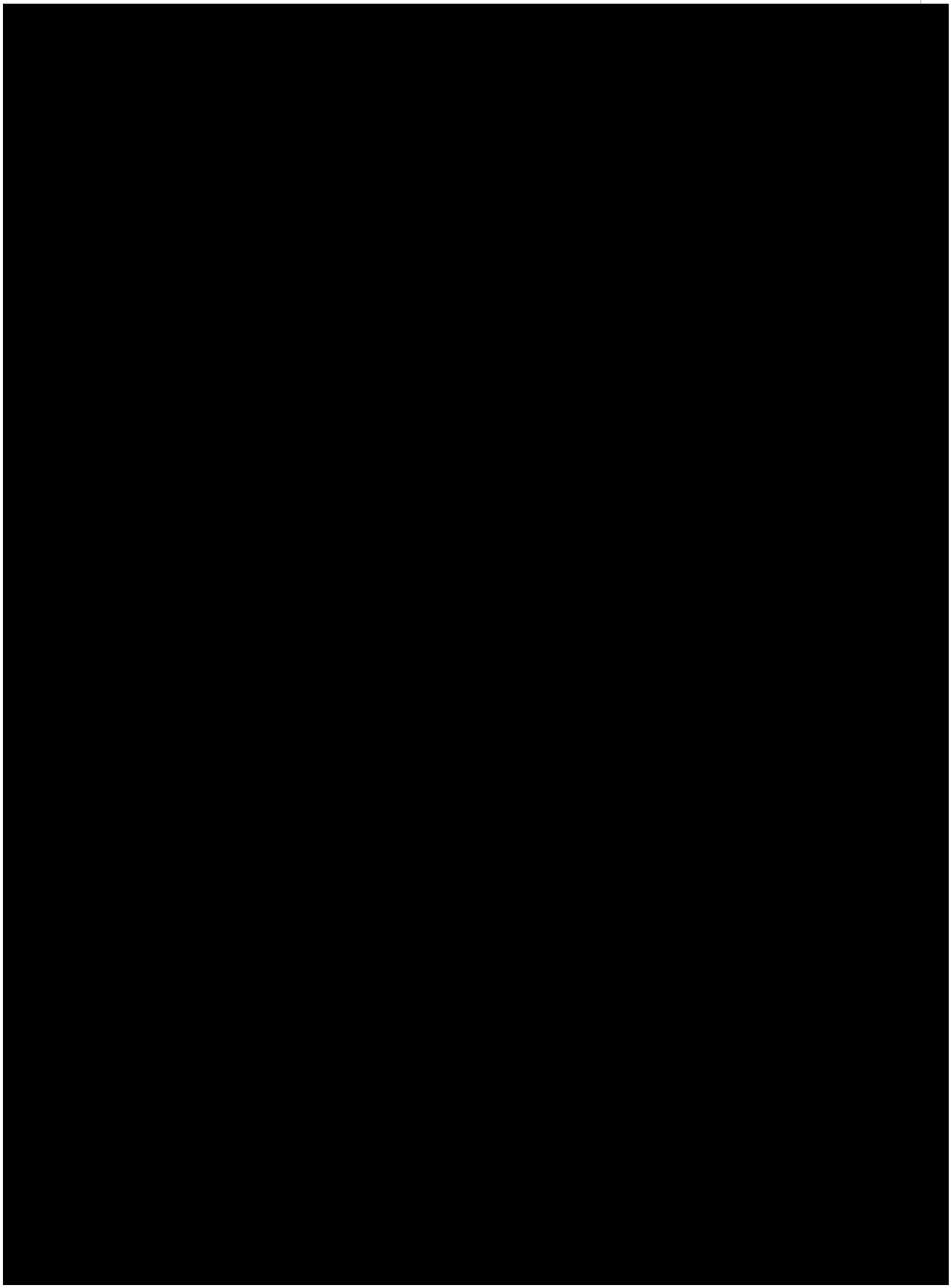


# APPENDIX 3. PERFORMANCE CRITERIA FOR BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3) DEVELOPMENTAL MILESTONES

| **Developmental Milestone** | [redacted] |
|---|---|
| Head Control – Gross Motor Subtest Item #4 | |
| Rolls from Back to Sides – Gross Motor Subtest Item #20 | |
| Sits Without Support – Gross Motor Subtest Item #26 | |
| Stands With Assistance - Gross Motor Subtest Item #33 | |
| Crawls – Gross Motor Subtest Item #34 | |
| Pulls to Stand – Gross Motor Subtest Item #35 | |
| Walks With Assistance – Gross Motor Subtest Item #37 | |
| Stands Alone – Gross Motor Subtest Item #40 | |
| Walks Alone – Gross Motor Subtest Item #43 | |

# APPENDIX 4. CHOP-INTEND





# APPENDIX 5. SCHEDULE OF ASSESSMENTS

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | X[s] | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | | |
| Echocardiogram | X | | | | | | | | | X[j] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| CK-MB | X | | | | | X | | | X | X[r] | X |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | | X | | X | | | | | | | |
| ELISA anti-AAV9/SMN Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISpot) | | | | | | X | | | X[l] | | |

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed every 6 months, starting at Month 6.
[k] Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
[r] CK-MB to be performed at Day 60, and Month 6, 9, 12, 15 months of age, 18 months of age/EOT).
[s] If a Day -1 CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Day 1 prior to dose administration.

# APPENDIX 6. COMPOUND MOTOR ACTION POTENTIAL MANUAL

**Phase 3 Gene Transfer Clinical Study for Spinal Muscular Atrophy Type 1 Delivering AVXS-101**

CMAP Manual
Compound Motor Action Potential (CMAP)

**Materials Needed for the Process**

- Carefusion Disposable Ring Electrode with Leads (order number 019-439300) (4 per visit)
- Carefusion Tab Electrodes 1.0 meter leads (order number 019-406600) (1 or 2 per visit)
- CMAP case report form
- Infrared temperature probe
- Electrode gel
- Warming packs or some other warming source
- Transpore adhesive tape
- Alcohol skin prep pads
- EMG machine

**Temperature and Warming**

As only the peroneal motor study will be performed, only lower extremity temperatures will need to be assessed. The temperature should be measured on the surface of the anterior calf distal to the recording electrodes and proximal to the ankle. As the protocol only refers to measurement of upper extremity temperatures, by convention a temperature threshold that is 2 degrees lower, i.e., ≥ 31 degrees Centigrade, should be sufficient. When the temperature is measured to be below 31 degrees, a warming procedure should be performed, either with heated towels or other authorized devices. Care must be taken not to apply towels or other devices at temperatures that would put the infants at risk of burns, the examiner must test the temperature of the warming device against his/her own skin and/or the skin of a parent prior to application. As a general rule, the warming device should feel lukewarm, not hot, against an adult's skin, and it should be expected that the warming procedure will take 3–5 minutes. Scheduling of this procedure should allow for both temperature recording and warming procedures.

**Preparation of Skin**

The skin should be cleaned with alcohol (or equivalent) as needed to improve contact with the electrodes.

**EMG machine settings**

For the peroneal CMAP measures the filter settings should be 10 Hz to 10 kHz.

**Tibialis Anterior (TA) CMAP Electrode Placement**

For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed over the tendon above the ankle in a standard "belly-tendon" arrangement. An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode. Adhesive tape may be used to secure any loose electrodes in place. Adhesive tape should not touch other electrodes or other pieces of adhesive tape.

**Supramaximal Nerve Stimulation for TA CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at or proximal to the fibular head. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. Maximum CMAP amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

**Alternate G1 Electrode Placements and Repetition of Motor Study**

As the motor point of the tibialis anterior does not have precise landmarks, there is a possibility that the G1 electrode will not be placed exactly over the motor point without testing multiple sites. Thus, as tolerated by the patient, the CMAP should be recorded at least three times, with a different placement of the G1 electrode each time. The CMAP with the highest amplitude among the trials should be reported.

# APPENDIX 7. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving Human subjects.
6. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or

healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.
    Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving Human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and

must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research patients should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without

informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

# APPENDIX 8. SUMMARY OF CHANGES

The section below highlights content changes represented in this version of the protocol. Language deleted from Protocol version 2.0 appears in ~~red strike through~~. Language added to Protocol version 3.0 appears in **bold**.

The Amendment 2 version of the protocol (Protocol version 3.0) is updated to clarify the datapoints which require review for the first three patients prior to continuing with enrollment. Additionally, a Day -1 CHOP-INTEND assessment is added and minor clarifications and corrections were included.

## Section 2 Synopsis

The synopsis was updated to reflect changes throughout the document.

## Section 7.1 Overall Study Design

There will be at least a 4 -week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (day~~s~~ 1, 2, 7, 14, 21, and 30 **visits**) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the ~~30 day~~ **4-week** interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

**Rationale for Change**

Language was updated to clarify the datapoints that will be required for the first three patients, prior to continuing with enrollment.

## Section 8.2 Patient Exclusion Criteria

**Exclusion #19:**

**Gestational age at birth < 35 weeks (<245 days)**

**Rationale for Change**

The use in premature infants may have additional, unknown risks and are excluded.

## Section 8.3 Patient Withdrawal Criteria

Patients may be discontinued from the study for the following reasons:

- Death
  - An autopsy will be requested for any patient who expires following participation in a gene replacement study ~~as per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25]~~ (see Autopsy Plan in Appendix 1)

**Rationale for Change**

The NIH Guidelines revised in 2016 no longer include language requiring autopsies for patients participating in gene therapy trials; however AveXis will continue to request autopsies/port-mortem tissue collection where applicable and allowed.

## Section 9.2.1 Prophylactic Administration of Prednisolone

In an attempt to dampen the host immune response to the AAV based- therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell response are ~~below the threshold~~ ≤ 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline:

- Until at least 30 days post-infusion: 1 mg/kg/day
- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/dayWeek 9: prednisolone discontinued

**Rationale for Change**

Removal of ambiguous language.

## Section 11.1 Developmental Milestones

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement in accordance with **Appendix 5**; this assessment must address all milestones/items noted on **Appendix 5** that are at or below the child's **expected** baseline function **for age**, and be rec~~orded on~~ video. The findings must be documented in the source. Items that are below the **expected function for age** baseline level of assessment that are ~~not successfully achiev~~ed during the baseline evaluation should be repeated at subsequent visits until successfully performed.

**Rationale for Change**

Language updated to clarify the expectations for baseline assessment of motor milestone achievements during the Screening visit.

**Section 11.2.2 CHOP-INTEND**

The CHOP-INTEND will be performed at screening**, Day -1,** and at each scheduled visit from Day 7 through the End of Study when the patient reaches 18 months of age (or early termination) (**Appendix 5**). **If Day -1 CHOP-INTEND assessment cannot be conducted, a CHOP-INTEND assessment must be completed on Day 1 prior to dose administration.**

**Rationale for Change**

A Day -1 CHOP-INTEND assessment has been added to ensure the lowest score for patient's motor function is documented prior to treatment, which will serve as the baseline value. If a Day -1 and Day 1 CHOP-INTEND score are not or cannot be conducted, the Screening visit CHOP-INTEND score will be considered the baseline value.

**Section 12.1.1 Demographic/Medical History**

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/**weight** ~~height~~/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any

**Reason for Change**

Correction to typographical error.

**Section 12.1.10.2 Blood Chemistry**

Creatine kinase (CK-MB) will be collected at Screening, Day 7, Day 30, Day 60, ~~and every 90 days~~ **Month 6, 9, 12**, **15 months of age, and at 18 months of age**/End of Study.

**Reason for Change**

Clarification for the CK-MD sample collection schedule.

**Section 13.2 Relationship to Study Product**

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related, Probably Related, or **Definitely Related**). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified

cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

**Reason for Change**

Template language updated to align with Section 13.1.1.1.

## Section 14.1.2.2 Efficacy Completers Population

The efficacy completers analysis population will consist of:

- **All treated patients who reach 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR**
- ~~All treated patients who reach 14 months of age, OR~~

All treated patients who meet discontinuation criteria, discontinue the study due to an AE or **experience** death.

**Reason for Change**

Updated to align with the analysis plan, in accord with the formal Statistical Analysis Plan (SAP).

## Section 14.4 CHOP-INTEND Comparison

A comparison will be performed of the first three patients CHOP-INTEND scores to the AVXS-101-CL-101 CHOP-INTEND scores. The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the **4-week** ~~30 day~~ interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

**Reason for Change**

Providing clarity that patient data will be reviewed/considered after four weeks, not specifically at Day 30.

## Section 21 List of References

Reference 25 was removed, as the NIH Guidelines are no longer cited as a reference in Section 8.3.

## Appendix 5 Schedule of Assessments

| Study Period | Screening | Gene Replacement Therapy (In-patient) | | | | Follow-up (Outpatient) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit # | 1 | 2 | | | | 3 | 4 | 5 | 6 | 7+ | End of Study[a] |
| # of Days in Study | –30 to –2 | -1 | 1[b] | 2 | 3 | 7 | 14 | 21 | 30 | Monthly[c] | 18 Months of Age (or ET) |
| Window | | | | | | ± 2 days | | | | ± 7 days (0–14 days at 14 Months of Age) | 0–14 days |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | X[s] | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | | |
| Echocardiogram | X | | | | | | | | | X[j] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| CK-MB | X | | | | | X | | | X | X[r] | X |

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | | X | | X | | | | | | | |
| ELISA anti-AAV9/SMN Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISpot) | | | | | | X | | | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed every 6 months, starting at Month 6.
[k] Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.

[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
[r] CK-MB to be performed at Day 60, ~~and every 90 days (~~Month 6, 9, 12~~ months of age~~, 15 months of age, 18 months of age/EOT).
[s] **If a Day -1 CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Day 1 prior to dose administration.**

**Rationale for Change**

CHOP-INTEND assessment was added at Day -1 to ensure the lowest functional ability of the patient is captured prior to treatment, to serve as the baseline value.

## Appendix 1 Autopsy Plan

An autopsy will be requested for any patient who receives gene replacement therapy and expires ~~as per the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25]~~. The autopsy and tissue collection will be performed by a contracted vendor who will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions will be used to perform the autopsy and pathology necessary to determine the cause of death.

**Rationale for Change**

The NIH Guidelines revised in 2016 no longer include language requiring autopsies for patients participating in gene therapy trials; however AveXis will continue to request autopsies/post-mortem tissue collection where applicable and allowed.

## Appendix 2 BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

[redacted]

**Rationale for Change**

Page 21 of the Bayley was accidentally omitted from the original protocol

## Appendix 6 Compound Motor Action Potential Manual

**EMG machine settings**

For ~~both~~ the ~~ulnar and~~ peroneal CMAP measures the filter settings should be 10 Hz to 10 kHz.

**Rationale for Change**

Removed references to ulnar CMAP from the standard manual, to alleviation confusion as only peroneal CMAP is required per protocol.

**Temperature and Warming**

**As only the peroneal motor study will be performed, only lower extremity temperatures will need to be assessed. The temperature should be measured on the surface of the anterior calf distal to the recording electrodes and proximal to the ankle. As the protocol only refers to measurement of upper extremity temperatures, by convention a temperature threshold that is 2 degrees lower, i.e., ≥ 31 degrees Centigrade, should be sufficient. When the temperature is measured to be below 31 degrees, a warming procedure should be performed, either with heated towels or other authorized devices. Care must be taken not to apply towels or other devices at temperatures that would put the infants at risk of burns, the examiner must test the temperature of the warming device against his/her own skin and/or the skin of a parent prior to application. As a general rule, the warming device should feel lukewarm, not hot, against an adult's skin, and it should be expected that the warming procedure will take 3-5 minutes. Scheduling of this procedure should allow for both temperature recording and warming procedures.**

~~**Assessment of Normal Limb Temperature**~~

~~Since temperature can affect maximum CMAP amplitude, temperature > 33 degrees centigrade should be noted prior to preparation of skin for electrode placement. Temperature should be measured using a surface probe on the lateral aspect of the hand just proximal to the fifth digit. If temperature is ≤ 33 degrees centigrade, a warming pack or other warming mechanism should be used to warm the hand to > 33 degrees centigrade prior to collecting data. Limb temperature does not need to be reassessed during the procedure.~~

**Rationale for Change**

As only peroneal CMAP will be performed, minor updates made to the CMAP recording procedures.

**Tibialis Anterior (TA) CMAP Electrode Placement**

**For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed over the tendon above the ankle in a standard "belly-tendon" arrangement. An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode , or at the patella. Adhesive tape may be used to secure any loose electrodes in place. Adhesive tape should not touch other electrodes or other pieces of adhesive tape.**

~~For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed on the patella.~~

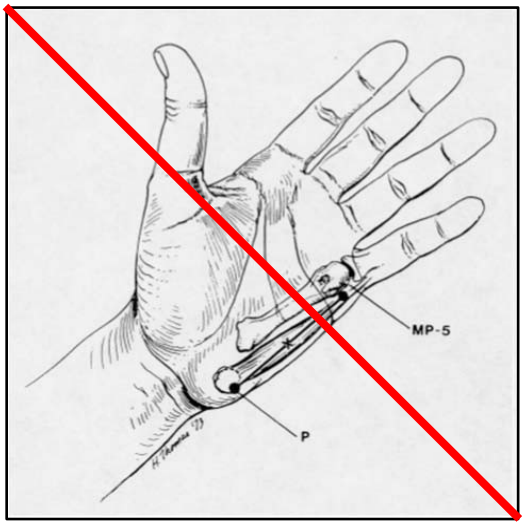
~~An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode. Tape should be placed over the electrodes to ensure they stay affixed during the procedure.~~

**Rationale for Change**

As only peroneal CMAP will be performed, minor updates made to the CMAP recording procedures.

~~**Abductor Digiti Minimi (ADM) CMAP Electrode Placement**~~

~~Electrodes used for recording will be *Carefusion Disposable Ring Electrode with Leads (order number 019-439300)*. For ADM CMAP, these have a longitudinal contact area of up to 106 mm, but should be cut so that they cover the body of the ADM, with position orthogonal to muscle fiber orientation. The distance between the ulnar aspect of the pisaform bone (P) and the ulnar aspect of the fifth metacarpophalangeal joint (MP-5) should be measured. The G1 electrode should be placed distal to P, 1/3 of the distance between P and MP-5, as defined above. The G2 reference electrode should be placed on the ulnar aspect of the MP-5 joint. See figure below for landmarks:~~




~~Modified figure from "Anatomic Guide for the Electromyographer" Charles C. Thomas, Publisher, 1980, p4.~~

~~**Supramaximal nerve stimulation for CMAP**~~

~~The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at the distal forearm just proximal to the wrist. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. CMAP maximum amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.~~

**Rationale for Change**

As only peroneal CMAP will be performed, minor updates made to the CMAP recording procedures.

**Alternate G1 electrode placements and repetition of motor study.**

**As the motor point of the tibialis anterior does not have precise landmarks, there is a possibility that the G1 electrode will not be placed exactly over the motor point without testing multiple sites. Thus, as tolerated by the patient, the CMAP should be recorded at least three times, with a different placement of the G1 electrode each time. The CMAP with the highest amplitude among the trials should be reported.**

**Rationale for Change**

As only peroneal CMAP will be performed, minor updates made to the CMAP recording procedures.

# AVXS-101

# AVXS-101-CL-303

| | |
|---|---|
| **IND Number:** | 15699 |
| **Protocol Title:** | Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion |
| **Indication Studied:** | Spinal Muscular Atrophy Type 1 |
| **Sponsor Address:** | AveXis, Inc.<br>2275 Half Day Road<br>Bannockburn, IL 60015 |
| **Protocol Version/Date:** | 2.0 / 15 October 2017 |

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

## Confidentiality Statement

# 1. ADMINISTRATIVE INFORMATION

## 1.1. Approval

**REPRESENTATIVES FROM AveXis:**

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization and the Harmonized Tripartite Guideline for Good Clinical Practice E6
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

**SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):**

[redacted] 10/16/2017

[redacted] Date (ddMmmyyyy)
Vice President Clinical Development
AveXis, Inc.

[redacted] 10/16/2017

[redacted] Date (ddMmmyyyy)
Chief Medical Officer
AveXis, Inc.

[redacted] 10/17/2017

[redacted] Date (ddMmmyyyy)
Senior Vice President, Chief Regulatory and Quality Officer
AveXis, Inc.

[redacted] 10/16/2017

[redacted] Date (ddMmmyyyy)
Sr. Director, Head of Clinical Operations
AveXis, Inc.

[redacted] 10/17/2017

[redacted] Date (ddMmmyyyy)
Sr. Director, Head of Biostatistics
AveXis, Inc.

## 1.2. Investigator's Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-CL-303 protocol and agree to conduct the study in accordance with the relevant current protocol(s). I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of study participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Informed Consent 21 CFR Part 56, Institutional Review Board Review in 21 CRF Part 56, Adverse Event Reporting as defined in Section 13.4 and in 21 CFR 312.64, Adequate/accurate and accessible records in accordance with 21CFR 312.62 and 312.68.
- Terms outlined in the study site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations) I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

**Confidentiality Statement**

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date (ddMmmyyyy)

## 1.3. Contact Information

**Table 1: Important Study Contact Information**

| Role in Study | Name/Address and Telephone Number |
|---|---|
| Clinical Study Leader | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Responsible Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Drug Safety Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Serious Adverse Event Reporting | Please see Project Management Plan in TMF or Study Contact list in ISF |
| 24-Hour Emergency Contact | Please see Study Contact List in ISF |

**Table 2: Study Vendor Listing**

| Role in Study | Name/Address |
|---|---|
| Clinical Research Organization | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Investigational Product Shipment | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Video | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Independent Video Review | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Holter Monitor and 12-lead Electrocardiogram | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-immunoassays | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-viral shedding studies | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Autopsy | Please see Project Management Plan in TMF or Study Contact list in ISF |

ISF = Investigator site file; TMF = trial master file

# 2. SYNOPSIS

**Name of Sponsor/Company:** AveXis, Inc.

**Name of Investigational Product:** AVXS-101

**Name of Active Ingredient:** Survival Motor Neuron Gene by Self-Complementary Adeno-Associated Virus Serotype 9 (AAV9)

**Title of Study:** Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

**Study Center(s):** 10 to 20 United States (US) Investigators

| **Studied Period (years):** | **Phase of Development:** 3 |
|---|---|
| Estimated date first patient enrolled: 2Q 2017<br>Estimated date last patient completed: 4Q 2019 | |

**Objectives:**

**Co-Primary**

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

**Co-Secondary**

- Determine effect of AVXS-101 on the ability to thrive defined as achieving all of the following at 18 months of age:
  - Does not receive nutrition through mechanical support (e.g., feeding tube) or other non-oral method
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age

[redacted]

**Safety**

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity

**Methodology:**

Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

The study includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of AVXS-101, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age. After the End of Study visit, eligible patients will be asked to rollover into the long-term follow up study.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (days 1, 2, 7, 14, 21, and 30) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient. The first three patients enrolled must meet the criteria for the Intent-to-Treat Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose $1.1 \times 10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 30-day interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to AVXS-101 infusion until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values, aspartate aminotransferase (AST) values, and T-cell response are below the threshold of 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline: 1 mg/kg/day until at least 30 days post-infusion, 0.5 mg/kg/day at Weeks 5 and 6, 0.25 mg/kg/day at Weeks 7 and 8, and discontinued at Week 9.

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age. The ability to thrive (as defined above) and the ability to remain independent of ventilatory support (as defined above) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development (Version 3). Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires

medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

**Number of Patients (planned):** Up to twenty (20) patients that meet the study enrollment criteria to enable at least fifteen (15) patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

1. Patients with SMA Type 1 as determined by the following features:
   a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))2.
2. The first three patients enrolled must meet the criteria for the Intent-To-Treat Population.
3. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27)
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

**Exclusion Criteria:**

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

   Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards[26]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)

7. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (international normalized ratio [INR] > 1.4, gamma-glutamyl transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)
16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form

**Investigational Product, Dosage and Mode of Administration:**
Patients will receive a one-time dose of AVXS-101 at 1.1 X $10^{14}$ vg/kg, a dose determined to be equivalent to the dose received by the Cohort 2 patients in the Phase 1 study (AVXS-101-CL-101) by direct testing using improved analytical methods.

**Duration of Treatment:**
AVXS-101 will be administered as a one-time IV infusion over approximately 30-60 minutes, dependent upon the volume required.

**Reference Therapy, Dosage and Mode of Administration:** Not Applicable

**Criteria for Evaluation:**

**Efficacy:**

**Co-Primary**

- Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 seconds
- Survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death

**Co-Secondary**

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [26] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)

- [redacted]

**Safety:**

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated liver function tests (LFTs) and/or unresolved liver function enzymes (LFEs)
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ Enzyme-linked ImmunoSpot (ELISpot) to detect T-cell responses to AAV9 and SMN

**Statistical Methods:**

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

Based upon widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patient meeting the study entrance criteria (*SMN2* copy number of 2 without the *SMN2* gene modifier mutation (c.859G>C)) would be expected to attain the ability to sit without support for at least 30 seconds at or before the 18 months of age study visit or other milestones (rolling over, standing, walking) assessed as part of the study.

Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis is

whether the AVXS-101 treated patients achieve a response rate greater than 0.1%. Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated patients in the ITT population are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age visit. With the assumption for the true response rate of AVXS-101 for the primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with $\alpha = 0.025$ using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint of survival at 14 months of age will be evaluated by comparing the results observed in the ITT population with the results from the age and gender-matched control patients selected from existing natural history data sets (PNCR) [*Neurol*. 2014; 83(9):810-817]. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. Based upon preliminary results from the ongoing Phase 1 clinical study (AVXS-101-CL-101), at least 80% of patients in the ITT population are expected to survive, as defined, through 14 months of age. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with $\alpha = 0.05$ using a 2-sided Fisher's Exact test.

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## TABLE OF CONTENTS

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AAV | Adeno-associated virus |
| AAV9 | Adeno-associated virus serotype 9 |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ASO | Antisense oligonucleotide |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CB | Chicken-β-actin-hybrid |
| CDC | Center for Disease Control |
| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| CI | CHOP-INTEND |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CK | Creatine kinase |
| CK-MB | Creatine kinase isoenzyme |
| CLIA | Clinical Laboratory Improvement Amendment |
| CMAP | Compound motor action potential |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Day 1 | First 24-hour interval after the start of gene replacement therapy infusion |
| Day –1 | 24-hour interval prior to the start of gene replacement therapy infusion |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-linked Immunosorbent Assay |
| ELISpot | Enzyme-linked ImmunoSpot |
| ET | Early termination |
| FVB | Friend Virus B-Type |
| GCP | Good Clinical Practice |
| GFP | Green fluorescent protein |
| GGT | Gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| HEENT | Head, eyes, ears, nose, and throat |
| HgB | Hemoglobin |
| HIV | Human Immunodeficiency Virus |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ICD-10 code | International Statistical Classification of Diseases and Related Health Problems |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon gamma |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| ITR | Inverted terminal repeat |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LFE | Liver function enzymes |
| LFT | Liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NHP | Non-human primates |
| NOAEL | No Observable Adverse Effect Level |
| OAE | Other significant Adverse Event |
| PBMC | Peripheral blood mononuclear cells |
| PICU | Pediatric intensive care unit |
| PNCR | Pediatric Neuromuscular Clinical Research Network |
| RNA | Ribonucleic acid |
| RSV | Respiratory syncytial virus |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | Self-complementary |
| scAAV | Self-complimentary adeno-associated virus |
| scAAV9.CB.SMN | Self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron |
| SMA | Spinal muscular atrophy |
| SMN | Survival motor neuron |
| *SMN1* | Survival motor neuron 1 gene |
| *SMN2* | Survival motor neuron 2 gene |
| SOC | System Organ Class |
| TMF | Trial master file |
| US | United States |
| vg/kg | Vector genome per kilogram |
| WBC | White blood cell |
| WHO | World Health Organization |
| WT | Wild type |

# 5. INTRODUCTION

Study AVXS-101-CL-303 is a pivotal Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* as well as 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The first three patients enrolled must meet the ITT criteria to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

In this study, the survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMNΔ7 mouse model for SMA from a median of 15.5 days to over 1 year, following IV delivery to a facial vein. Additionally, preliminary results from an ongoing Phase 1 clinical study (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function (Section 5.4).

## 5.1. Background

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births [1]. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*SMN2*). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis before 6 months of age and early death due to respiratory failure before 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the prenatal period), whereas motor neurons in SMA Type 2 and Type 3 patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of *SMN1* in hopes of rescuing neurons at this critical stage. The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [5,6]. However, clinical studies employing several of these agents, most notably phenylbutyrate, valproic acid, and hydroxyurea,

have not resulted in clinical benefit [7,8]. FDA recently approved Nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some modest promise in improving motor function; however the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring. A single-dose IV administration study of AVXS-101 will provide information on the potential gene transfer has in treating SMA Type 1 patients, and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose study that will include up to 20 Type 1 patients with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

## 5.2. Rationale for Gene Transfer to SMA Type 1 Patients

Patients with SMA Type 1 have been chosen as the target population for this gene therapy study based on studies of the natural history of this disease. The classification of SMA is shown below (Table 4) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

**Table 4: Spinal Muscular Atrophy Classification**

| Type | Age at Symptom Onset | | Maximum Motor Function | Life Expectancy | *SMN2* Copy No. |
|---|---|---|---|---|---|
| 0 | Fetal | | Nil | Days – Weeks | 1 |
| 1 | < 6 Months | 1A: B-2 Weeks<br>1B: < 3 Months<br>1C: > 3 Months | Never sits | < 2 years | 1, 2, 3 |
| 2 | 6 – 18 Months | | Never walks | 20 – 40 years | 2, 3, 4 |
| 3 | 1.5 – 10 Years | 3A: < 3 Years<br>3B: > 3 Years | Walks, regression | Normal | 3, 4, 5 |
| 4 | > 35 Years | | Slow decline | Normal | 4, 5 |

Source: Adapted from Kolb 2011 [10]
*SMN2* = survival motor neuron 2 gene

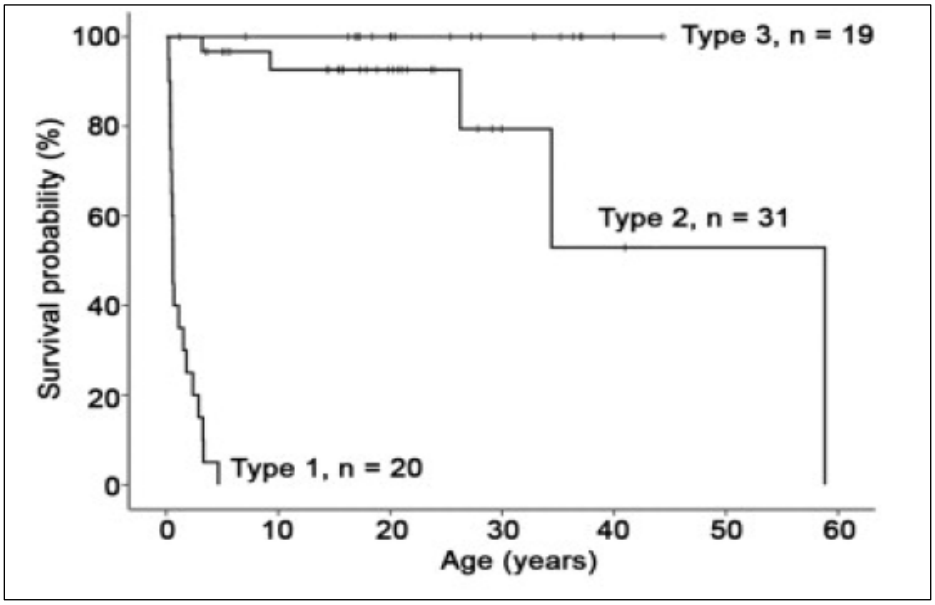
Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 months of age (Table 4). In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3 patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease.

The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [11]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10 to 15% of that produced by *SMN1* [11,12,13]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms of SMA generally have higher *SMN2* copy numbers [14,15]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, 2, or 3 SMA showed a significant correlation between *SMN2* copy number and SMA Type, as well as, duration of survival. In a large early study by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [16]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [17], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with two *SMN2* copies lived < 21 months, and 8/10 with three *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated, and has also influenced our choice of the study target group.

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

**Figure 1: Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3**




n = number of patients
Source: Farrar 2013 [18]

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the

growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the prenatal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [2,3,4].

There is reason to believe that there are few safety issues to be concerned about when targeting the SMA Type 1 group in this gene therapy clinical study. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans, a high copy number of *SMN2* poses no risk (as seen in Type 2, 3, and 4 patients who have high *SMN2* copy number), allowing for use of robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV can be employed for this study because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded adeno-associated virus (AAV) vectors.

Recent studies using self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron (scAAV9.CB.SMN) show a robust post-natal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology and survival after a one-time delivery of vector [19]. Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

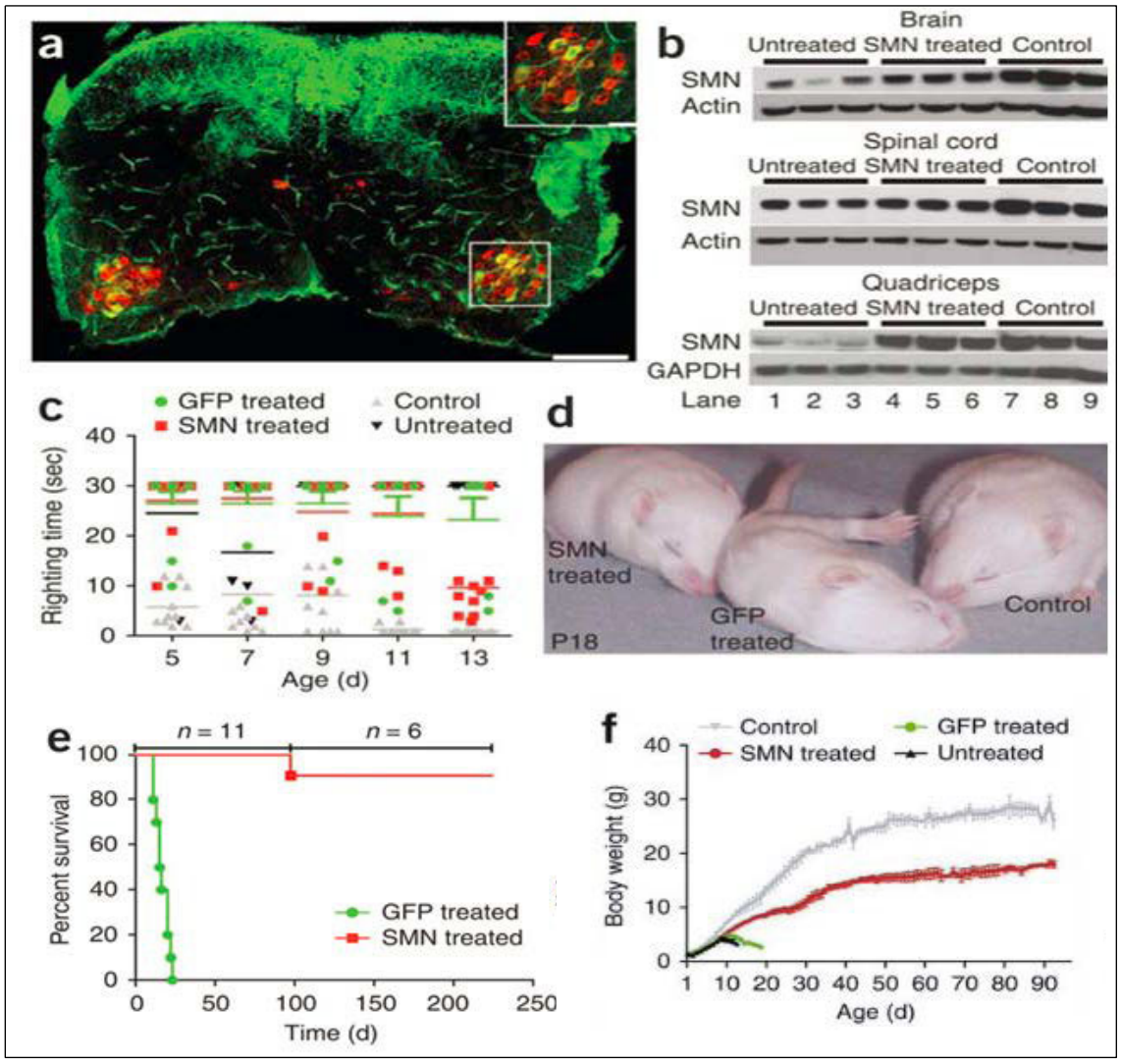
## 5.3. Non-clinical Studies

A mouse model was developed by the [redacted] after a generation of multiple variants. It was found that the double transgenic, referred to as the SMNΔ7 mouse, provided the most suitable model to study gene transfer [20]. Studies performed in the [redacted] have shown that injecting $5 \times 10^{11}$ viral genomes of scAAV9.CB.SMN into the facial vein on Day 1 old mice rescues the SMNΔ7 mouse model [19]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.GFP treated mice. SMN transduction was shown by real time polymerase chain reaction (RT-PCR) in the mice. GFP transduction was observed by microscopy. Both constructs were in AAV9 and had transduction of motor neurons. SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMNΔ7 mice (although lower than wild type [WT] controls). SMNΔ7 animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on post-natal Day 1 were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and green fluorescent protein (GFP)-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMNΔ7 animals compared with GFP-treated SMNΔ7 animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life

span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a 'chimeric' animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

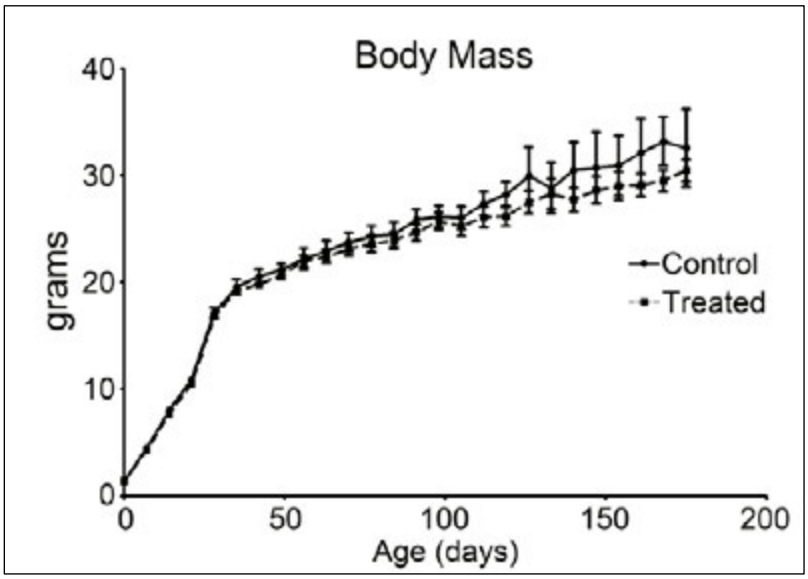
**Figure 2: Study Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves**




Source: Foust 2010 [19]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type
a) Shows transduced motor neurons in lumbar spinal cord
b) Western Blots of SMN expression in CNS and muscle
c) Improved righting ability of SMN-treated- similar to WT controls by P13
d) SMN-treated are larger than GFP-treated at P18
e) Survival of SMN-treated markedly improved compared to GFP- treated
f) Body weight increased in SMN-treated vs GFP

Toxicology biodistribution studies were generated by the [redacted] [data on file]. In the non-Good Laboratory Practice (GLP) studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with AVXS-101. To assess toxicity and safety, AVXS-101 was injected into P1 wild type Friend Virus B-Type (FVB) mice with either vehicle (3 males/6 females) or $3.3 \times 10^{14}$ vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the SMNΔ7 mouse model [19]. P1 mice were used in anticipation of simulating potential clinical studies in infants. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

**Figure 3 Body Mass of Treated and Control Mice Showed No Difference**




At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies including complete blood counts with differentials. At 90, 120 and 180 days post-injection, blood was collected for clinical chemistries assessment (alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase, creatinine, blood urea nitrogen [BUN], electrolytes, and creatine kinase [CK]). For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. There were no clinically significant results observed during from the hematology, clinical chemistry, and histopathology portions of the study and trends of both groups were comparable. Of note, no significant lesions were present in any brain or spinal cord sections, although, the sections were frozen and thicker than 5 microns which made cellular morphology obscure and subtle changes may not have been identified.

In the safety study for the 4 male Cynomolgus Macaques, animals were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The AVXS-101 vector was administered one time by catheterization of the saphenous vein with a dose of $6.7 \times 10^{13}$ vg/kg, which corresponds to the lowest dose tested for which SMNΔ7 mice showed a significant increase of survival. Animals were followed for six months until they were

sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using Enzyme-linked ImmunoSpot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

These mouse and monkey studies can be summarized as follows. The serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The NHP patients animals mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [data on file].

When newborn FVB mice were given a single IV injection of AVXS-101 at levels up to $3.3 \times 10^{14}$ vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of AVXS-101 was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given $3.3 \times 10^{14}$ vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses. Based on these results, the no observable adverse effect level (NOAEL) of AVXS-101 in newborn male and female mice is considered to be $3.3 \times 10^{14}$ vg/kg.

Intravenous administration of AAV9 has been shown to be safe and well tolerated when administered to mice and monkeys. The vector has also demonstrated the ability to cross the blood brain barrier in both species following IV administration. Body weight increased, righting behavior improved, survival was extended and cardiac deficits returned toward normal in treated SMNΔ7 mice when compared to untreated SMNΔ7 mice. Toxicology studies determined the NOAEL of AVXS-101 was $3.3 \times 10^{14}$ vg/kg and there was no test article mortality or toxicity observed up to 24 weeks following IV administration in mice. Biodistribution to the brain and spinal cord was reconfirmed and low levels of antibodies to the AAV9 capsid were observed at 12 and 24 weeks following the $3.3 \times 10^{14}$ vg/kg dose. No alteration was observed in clinical pathology and histopathology analyses.

## 5.4. Clinical Studies

First-in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received the low dose used in this study (equivalent to a dose that doubled mouse lifespan in the SMNΔ7 Mouse potency assay) and Cohort 2 (n = 12) received the high dose used in this study (equivalent to a dose that restored mouse lifespan to greater than 200 days or "full life" in the SMNΔ7 Mouse potency assay). The dose received by Cohort 2 patients in AVXS-101-CL-101 (proposed therapeutic dose) has been demonstrated to be equivalent to the dose to be used in the AVXS-101-CL-303 study by direct testing using improved analytical methods.

Preliminary data as of 15 September 2016 indicate that treatment with AVXS-101 results in broad improvements in survival, motor function, pulmonary function, and nutritional function.

All patients in Cohort 2 (proposed therapeutic dose) showed improvements in survival, as defined by Finkel et al 2014 [21], with no deaths or requirements for permanent ventilation ≥ 16 hours/day for ≥ 14 consecutive days through 15 September 2016. The median age at last follow-up for Cohort 2 was 17.3 months, with the oldest patient at 27.4 months of age. One patient in Cohort 1 (low-dose cohort) had a pulmonary event of increased use of bi-level positive airway pressure in advance of surgery related to hypersalivation, a condition experienced by some SMA patients. The event was determined by independent review to represent progression of disease and not related to AVXS-101.

As of September 15, 2016, improvements in motor function, as assessed by the CHOP-INTEND scores, were observed with mean increases of 9.0 points in Cohort 1 and 24.8 points in Cohort 2. The CHOP-INTEND scores in Cohort 2 were ≥ 40 points for 11/12 patients, ≥ 50 points for 9/12 patients, and ≥ 60 points (normal) for 3/12 patients.

As of September 15, 2016, patients in Cohort 2 consistently achieved and maintained key developmental motor milestones as summarized below:

- 11/12 patients achieved head control, 7/12 patients could roll, 11/12 patients could sit with support, and 8/12 patients could sit unassisted, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016
- 7 patients were able to feed themselves, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016, and 5 patients were speaking (1 bilingual)
- 2 patients were walking independently, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016. These 2 patients each achieved earlier and important developmental milestones such as crawling, standing with support, standing alone, and walking with support

As of September 15, 2016, AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in this study. A total of 118 treatment-related AEs were reported (34 serious adverse events [SAEs] and 84 non-serious adverse events [AEs]). Two SAEs were deemed treatment-related in 2 patients, and 3 AEs were deemed treatment-related in 2 patients. All treatment-related events consisted of clinically asymptomatic liver enzyme elevations that resolved with prednisolone treatment. There were no clinically significant elevations of gamma-glutamyl transferase (GGT), alkaline phosphatase or bilirubin, and as such, Hy's Law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

In summary, through September 15, 2016, the consistently positive clinical observations are remarkably different from that described in extensive natural history studies, clinical publications, the experience of seasoned clinicians, and concurrent SMA Type 1 studies with other therapies. These significant and clinically meaningful responses in patients treated with AVXS-101 indicate preliminary clinical evidence of a treatment effect that addresses an unmet need in this devastating pediatric disease.

A full understanding of all the risks associated with AVXS-101 is not known at this time. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 study, which is believed to be a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the study were accompanied by clinical sequelae. Patients could

experience an allergic response to AVXS-101. Patients could also develop an immune response to the AAV9 viral vector, which could prevent future use of gene transfers using this vector.

Taken together, results from the clinical and non-clinical studies support further clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objectives

The co-primary objectives are to:

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

## 6.2. Secondary Objective

The co-secondary objectives are to:

- Determine the effect of AVXS-101 on the on the ability to thrive defined as achieving all of the following at 18 months of age
  - Does not receive nutrition through mechanical support (e.g., feeding tube)
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device, for patients issued a Trilogy 100 BiPAP device

## 6.4. Safety Objectives

The safety objectives are to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) [9] Grade 3 or higher, unanticipated, treatment-related toxicity.

# 7. INVESTIGATIONAL PLAN

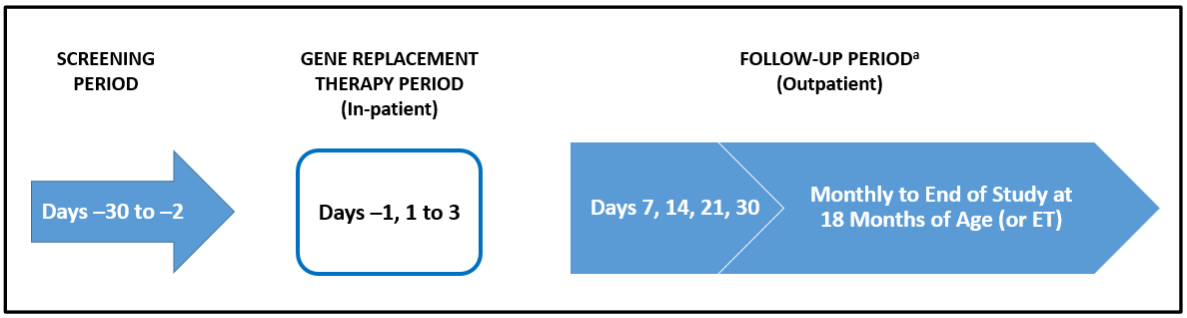
## 7.1. Overall Study Design

This is a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) that will enroll up to twenty (20) patients with SMA Type 1who may be either symptomatic or pre-symptomatic with no functional *SMN1* gene as well as 1 or 2 copies of *SMN2* and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).

The study includes 3 study periods: screening, gene replacement therapy, and follow-up (Figure 4). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time IV infusion of AVXS-101 at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study over approximately 60 minutes, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within 7 days.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days **after** the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients will be asked to roll over into the long-term follow-up study.

**Figure 4: Study Design**




Note: After the End of Study visit at 18 months of age, eligible patients will be asked to roll over into the long-term follow-up study.
ET = early termination
[a] All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 -week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (days 1, 2, 7, 14, 21, and 30) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 30-day interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion in accordance with the specified guidelines for tapering (Section 9.2.1).

A schedule of study assessments is provided in Appendix 1. Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined in Section 14.1.1.2) will also be assessed. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development© (Version 3) (Section 11). Safety will be assessed through monitoring AEs, concomitant

medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (Section 12). Additionally, a Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment (Section 13.1.1.1 and Section 15). This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

## 7.2. Number of Patients

Up to twenty (20) patients that meet the study ~~enrollment~~ entry criteria will be enrolled to enable enrollment of at least fifteen (15) patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.

## 7.3. Criteria for Study Termination

An independent DSMB will conduct quarterly and ad hoc reviews of the emerging safety data throughout the study as described in Section 15.

The study will be completed as planned but may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment
- DSMB can recommend early termination of the study for safety reasons
- Study is terminated by Sponsor
- Regulatory Authority recommendation

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients with SMA Type 1 who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) with proven bi-allelic mutations of the *SMN1* gene and 1 or 2 copies of the *SMN2* will be enrolled in this study. Patients may be of any racial, ethnic, or gender background.

## 8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Patients with SMA Type 1 as determined by the following features:
    a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))
2. The first three patients enrolled must meet the criteria for the Intent-To-Treat population
3. Patients must be < 6 months (< 180 days) of age at the time of AVXS-101 infusion
4. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
5. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27)
6. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

## 8.2. Patient Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

    Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours/day over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study

5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards [26]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non- respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for the treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (international normalized ratio [INR] > 1.4; GGT, ALT, and AST > 3 × ULN; bilirubin ≥ 3.0 mg/dL; creatinine ≥ 1.0 mg/dL; hemoglobin < 8 or > 18 g/dL; white blood cells [WBC] > 20,000/cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)

16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form

## 8.3. Patient Withdrawal Criteria

Patients may be discontinued from the study for the following reasons:

- Death

– An autopsy will be requested for any patient who expires following participation in a gene replacement study as per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25] (see Autopsy Plan in Appendix 2)

- Failure to comply with protocol-required visits or study procedures for 3 or more consecutive visits that are not rescheduled, unless due to hospitalization
- Parent(s)/legal guardian(s) withdraws consent
- Investigator discretion

Early termination procedures should be completed within 14 days for any patient who prematurely discontinues the study for any reason, as indicated in Appendix 1.

# 9. TREATMENT OF PATIENTS

It is the responsibility of the Investigator to ensure the safe storage and administration of gene replacement therapy.

## 9.1. Description of Product

The biological product is a non-replicating recombinant AAV9 containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed and the resulting protein is produced. The biological product, called AVXS-101 (formerly scAAV9.CB.hSMN), expresses the human SMN protein in transduced cells.

**Table 5: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name:** | AVXS-101 |
| **Dosage Form:** | Equivalent to the dose received by the second dosing cohort in the Phase 1 study |
| **Unit Dose** | 1.1 X $10^{14}$ vg/kg; Equivalent to the dose received by the Cohort 2 in the Phase 1 study (AVXS-101-CL-101) as determined by direct product testing with improved analytical methods. |
| **Route of Administration** | Intravenous infusion |
| **Physical Description** | AVXS-101 is a clear, colorless liquid. |

## 9.2. Prior and Concomitant Medications

Prior and concomitant medications will be captured in the electronic Case Report Form (eCRF) from 2 weeks prior to administration of gene replacement therapy through the last study visit.

### 9.2.1. Prophylactic Administration of Prednisolone

An antigen specific T-cell response to the AAV vector was observed in the ongoing Phase 1 clinical study (AVXS-101-CL-101) investigating AVXS-101 treatment via IV infusion. This is an expected response between 2 to 4 weeks following gene replacement therapy. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression.

In an attempt to dampen the host immune response to the AAV-based therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell response are below the threshold of ≤ 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline:

- Until at least 30 days post-infusion: 1 mg/kg/day
- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/day
- Week 9: prednisolone discontinued

If the AST or ALT values are > 2 X ULN, or if T-cell response is ≥ 100 SFC/$10^6$ PBMCs after 30 days of treatment, the dose of prednisolone will be maintained until the AST and ALT values decrease below threshold. If T-cell response continues past Day 60, Investigator discretion should be used considering risk benefit for maintaining prednisolone. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient.

### 9.2.2. Prohibited Medications

Concomitant use of any of the following medications is prohibited:

- Drugs for treatment of diabetes, myopathy or neuropathy
- Therapy received with the intent to treat SMA (e.g., nusinersen, valproic acid)
    - Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing.
    - Inhaled β-agonists may be used to treat respiratory complications of SMA provided such medications are dosed at clinically appropriate levels
- Any investigational medication other than AVXS-101 is prohibited during the study
- Ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of starting the study (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)

Corticosteroid usage following completion of the prednisolone taper is permissible as part of routine clinical management. The use of corticosteroids in such circumstances should be documented appropriately as a concomitant medication, and the event precipitating its usage should be appropriately documented as an adverse event.

Should the use of corticosteroids (aside from inhaled corticosteroids for bronchospasm) be considered as part of care during the course of the prednisolone taper, this medical management should be discussed with the medical monitor.

## 9.3. Treatment Compliance

AVXS-101 will be administered as a one-time IV injection.

## 9.4. Randomization and Blinding

This is an open-label study.

# 10. STUDY PRODUCT MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in accordance with current Good Manufacturing Practices (cGMP). Investigational product accountability logs will be maintained by the clinical pharmacy.

## 10.1. Study Product

AVXS-101

## 10.2. Study Product Dose and Dose Justification

Patients will receive a one-time dose of AVXS-101 at 1.1 X $10^{14}$ vg/kg, equivalent to the dose received by Cohort 2 in the Phase 1 study via IV infusion administered in the ongoing Phase 1 clinical study (AVXS-101-CL-101).

Two doses are being studied in the ongoing Phase 1 clinical study (AVXS-101-CL-101); the higher dose (dose received by the Cohort 2 patients) was chosen for the present study as preliminary data demonstrated both a dose response and significant clinical benefit thus identifying it as the proposed therapeutic dose. In the Phase 1 study, AVXS-101 demonstrated a dose response, with efficacy greater as observed by motor milestone achievement and CHOP-INTEND scores at the higher dose (received by Cohort 2) than the lower dose (received by Cohort 1). Direct testing of the actual lot of Investigational Medicinal Product (IMP) used in the AVXS-101-CL-101 study by an improved and more fully qualified analytical method has assigned a value of 1.1 x $10^{14}$ vg/kg to the actual dose received by Cohort 2 in this Phase 1 study. The same method has been used to establish an equivalent dose for the Phase 3 IMP. This vg/kg value has been further verified in an improved and more fully qualified SMNΔ7 Mouse Biopotency assay to support a similar extension of mouse life time in direct comparative assessment between the Phase 1 and Phase 3 IMP.

## 10.3. Study Product Packaging and Labeling

AVXS-101 kits are labeled with a specific kit number and batch/lot number assigned at the cGMP facility. The content of the labeling is in accordance with the local regulatory specifications and requirements.

## 10.4. Study Product Storage

AVXS-101 kits will be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared AVXS-101 should be managed in accordance with the Pharmacy Manual.

The vessel used for delivery of the vector should be resealed in the procedure room and processed for destruction and/or return to AveXis in accord with the Pharmacy manual and applicable biohazardous waste guidelines for disposal.

## 10.5. Study Product Preparation

Preparation of AVXS-101 will be done aseptically under sterile conditions by a pharmacist and will arrive at the clinical site ready for infusion.

AVXS-101 will be received diluted with normal saline, as outlined in the Pharmacy Manual.

The total vector genome dose will be calculated based on the patient's body weight.

The dose-delivery vessel will be delivered to the designated pediatric intensive care unit (PICU) patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. The vessel will be delivered in accord with the Pharmacy Manual.

## 10.6. Study Product Administration

AVXS-101 infusion will be administered under sterile conditions in a PICU or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study. AVXS-101 should be slowly infused over approximately 30-60 minutes, dependent upon total volume in accord with the Pharmacy Manual, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, patients should return to an appropriate designated setting to ensure close monitoring of vital signs and adverse events. Vital signs will be continuously monitored throughout the gene replacement therapy infusion as described in Section 12.1.3. Patients should be maintained in the PICU or other appropriate setting for 48 hours after the start of gene replacement therapy.

## 10.7. Dose Adjustment Criteria

The study investigates a one-time IV infusion of AVXS-101; no dose adjustments are possible.

## 10.8. Study Product Accountability

The pharmacist or designee will maintain accurate records of the quantities of AVXS-101 received, dispensed, destroyed, and/or returned to AveXis. The pharmacist or designee will document the date and time of delivery of the dose vessel to the dose procedure room as well as the time the used vessel was returned to AveXis or destroyed as per the Pharmacy Manual.

## 10.9. Study Product Handling and Disposal

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof containers. All waste must be sealed in bags bearing the biohazard symbol and disposed of in a biohazard waste container.

All transfers must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment, such as gloves.

Any quality issue noticed with the receipt or use of AVXS-101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accord with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply AVXS-101 to a third party, allow AVXS-101 to be used other than as directed by this clinical trial protocol, or dispose of AVXS-101 in any other manner.

# 11. ASSESSMENT OF EFFICACY

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined Section14.1.1.2) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using the Bayley Scales of Infant and Toddler Development (version 3©). Efficacy assessments will be performed at the times specified in the Table of Assessments (Appendix 1), and should be the first assessments performed at any scheduled visit. All post-treatment visits will be relative to the date on which gene replacement therapy is administered except the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

## 11.1. Developmental Milestones

Developmental milestones will be assessed using relevant definitions obtained from the Bayley Scales of Infant and Toddler Development (version 3), and will be analyzed to assess efficacy (Appendix 3 and Appendix 4). Achievement of each developmental milestone will be determined by the Physical Therapist and confirmed by the central reader (as may be necessary) based on an assessment of the submitted videos (Section 11.3). Developmental milestones will be determined at each monthly visit as listed in Section 11.2.1.

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement in accordance with Appendix 1; this assessment must address all milestones/items noted on Appendix 1 that are at or below the child's baseline function, and be recorded on video. The findings must be documented in the source. Items that are below the baseline level of assessment that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestones of sitting independently (items 22 and 26) should be assessed at every subsequent visit, until attainment of milestone, regardless of starting point on the scale. These milestones must also be assessed at the 18 months of age visit, regardless of previous attainment.

As the Bayley Scales do not necessarily require the child to repeat previously attained milestones, it is essential that each attained milestone be captured on video.

A milestone will be considered achieved when demonstrated by a patient and observed with video capture confirmation during a physical therapy assessment or observed with video as provided by the patient's family at the patient's visit at 18 months of age.

## 11.2. Motor Function Tests

### 11.2.1. Bayley Scales of Infant and Toddler Development/Developmental Milestones

The Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 3) is a standardized, norm-referenced infant assessment of developmental functioning across 5 domains of cognitive, language, motor, social-emotional, and adaptive behavior. The Bayley Scales will be administered by a qualified Physical Therapist.

The full Bayley Scales will be administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain will be administered at each monthly visit.

Each Bayley Scales/developmental milestone assessment will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and may be submitted to the vendor for review by a central reader (Section 11.3).

The following developmental milestones will be assessed:

- Ability to hold head erect without support
- Ability to roll from back to both sides
- Ability to sit with support
- Ability to sit independently, > 10 seconds; WHO [22]
- Ability to sit without support for at least 30 seconds
- Ability to crawl
- Ability to pull to stand
- Ability to stand with assistance
- Ability to stand alone
- Ability to walk with assistance
- Ability to walk alone

### 11.2.2. CHOP-INTEND

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA Type 1, and will be administered by a qualified Physical Therapist.[23,24] The CHOP-INTEND scale examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions (Appendix 5). Anti-gravity movements in assisted rolling, ventral suspension, and supported standing will also be measured.

The CHOP-INTEND will be performed at screening and at each scheduled visit from Day 7 through the End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not undergo any additional CHOP-INTEND examinations.

Each CHOP-INTEND exam will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and submitted to the vendor for review by a central reader as may be necessary (Section 11.3).

## 11.3. Video Evidence

Physical therapy assessments (Bayley Scales and CHOP-INTEND) required at each study visit will be video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

## 11.4. Compound Motor Action Potential

Peroneal nerve CMAP amplitude will be measured by a qualified electrophysiologist, at all clinical sites capable of performing this assessment, using the procedures as described in the CMAP Manual (Appendix 6). CMAP will be measured at screening, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

The CMAP data will be collected for centralized review and interpretation.

Sites that do not have equipment or appropriately experienced personnel required to perform CMAP measurements will not be required to perform these assessments.

# 12. ASSESSMENT OF SAFETY

## 12.1. Safety Parameters

Safety parameters include physical examinations, pulmonary examinations, vital signs, capillary blood gas assessments, weight and length measurements, 12-lead electrocardiograms (ECGs), 12-lead Holter monitor recordings, echocardiograms, swallowing tests, laboratory assessments, adverse event monitoring, and photographs of the infusion site. In general, safety assessments will be performed at the times specified in the Table of Assessments (Appendix 1). All post-treatment visits are relative to the date on which gene replacement therapy is administered until the patient reaches 14 months of age, at which point all visits are relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

### 12.1.1. Demographic/Medical History

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/height/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any
- Historical feeding support, if any

1. Patients are encouraged to follow all routinely scheduled immunizations, as recommended by the Center for Disease Control (CDC), throughout the study. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27).

### 12.1.2. Physical Examinations

Physical examinations will be conducted by the Investigator or Sub-Investigator at each scheduled visit, except Day –1 (Appendix 1). The Day 1 physical examination will be

performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

### 12.1.3. Vital Signs/Weight and Length

Vital sign parameters include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry. Vital signs will be obtained at each study visit (as specified in Appendix 1). On Day 1, vital signs will be continuously monitored throughout the gene replacement therapy infusion, and recorded pre-dose and every 15 (± 5) minutes for the first 4 hours after the start of infusion, and then every hour (± 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.

Weight and length will be measured at each study visit (as specified in Appendix 1). On Day 1, weight and length will be measured pre-dose.

### 12.1.4. Electrocardiogram

A 12-lead ECG will be performed at screening, Day –1, pre-dose on Day 1, Day 2, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1). Additional ECG monitoring will be at the discretion of the Investigator as per local institutional guidelines.

The ECG will be interpreted locally by a cardiologist. The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

### 12.1.5. 12-Lead Holter Monitor

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 72 hours from Day –1 (24 hours prior to the start of gene replacement therapy infusion) through 48 hours after the start of infusion. Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours
- 48 hours

Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist within 24 hours of data upload. The Sponsor physician or designee will be notified of any safety concerns from the centralized review, and the safety management plan will be followed for documenting and reporting of AEs/SAEs.

### 12.1.6. Echocardiogram

A standard transthoracic echocardiogram will be performed at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

### 12.1.7. Pulmonary Examinations

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit except Day 1 (Appendix 1). Prior to study entry, a pulmonologist or appropriate individual as per standard institutional practice will review and document ventilator usage in the 2 weeks prior to screening.

Patients may be fitted with non-invasive ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Non-invasive ventilatory support equipment will be provided by AveXis through a third-party vendor. Should the patient require non-invasive ventilatory support at any time during the study, the equipment provided by AveXis must be used.

Patients requiring non-invasive ventilatory support will be asked to bring their machine(s) to each study visit such that the study staff can remove an SD card which captures actual usage data. The hours per day usage data for each day between visits will be extracted with software provided by the device manufacturer into a format that will be transferred/transcribed to the clinical database.

### 12.1.8. Swallowing Test

A swallowing test will be performed at screening (at the Investigator site), every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1) to determine if the patient has signs of aspiration. If the test is positive for aspiration, there may be a recommendation for the patient to use an alternate method to oral feeding for the duration of the study at the determination of the Investigator and treating clinician.

### 12.1.9. Photographs of Infusion Site

Photographs will be taken of the infusion site at each scheduled visit from Day 1 (pre-dose) through Day 30 (Appendix 1) to monitor healing of the infusion site. AveXis will provide a secure and confidential upload process for transfer and storage of the photographs from the investigative sites to a contracted third-party vendor that will compile and arrange photographs as per AveXis requirements. Any/all photographs received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with

regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

### 12.1.10. Laboratory Assessments

Blood samples will be collected at each scheduled visit, except Day 1 and Day 3 (as specified in Appendix 1). On Day -1, blood and urine samples will be processed locally for receipt of results prior to the start of gene replacement therapy infusion. Any clinically significant laboratory value will be repeated at the discretion of the Investigator.

Blood samples will be collected and shipped to a central laboratory. Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's Clinical Laboratory Improvement Amendment (CLIA) CLIA-certified local laboratory to ensure receipt of results prior to dosing.

**Table 6: Total Blood Volume**

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Screening | Hematology, chemistry/CK-MB, virus serology, immunology sample (AAV9 Ab only), diagnostic confirmation sample | 16.9 |
| Day –1 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 2 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 7 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 14 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 21 | Hematology, chemistry, immunology sample (AAV9/SMN Ab only) | 3.3 |
| Day 30 | Hematology, chemistry/CK-MB, immunology sample (ELISA/ELISpot) | 7.6-9.6[b] |
| Day 60 | Hematology, chemistry/CK-MB, | 3.6 |
| Month 3/4/5/7/8/10/11/13/14/16/17 | Hematology, chemistry | 25.3 |
| Month 6/9/12/15 | Hematology, chemistry/CK-MB | 14.4 |
| End of Study/ET | Hematology, chemistry/CK-MB | 3.6 |
| | **Maximum Total Volume for Study[a]** | **96.2** |

ET = early termination

[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits, provided T-cell responses are not elevated at Day 30 requiring additional surveillance samples and virus serology is not positive at screening requiring additional testing

[b] Immunology sample for IFN-γ ELISpots requires 4-6 mL whole blood. Immunology sample for ELISA requires 1 mL whole blood. When drawn at the same visit, 4-6 mL is sufficient for both assays.

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety labs
    a. Chemistry
    b. Hematology
    c. CK-MB
2. Interferon gamma (IFN-γ) ELISpots to detect T-cell responses
3. Serum antibody to AAV9 and SMN
4. Genetic reconfirmation testing

If there is not sufficient blood volume to include the genetic reconfirmation testing sample at the screening visit, patient must return before Visit 2. All patients must have genetic reconfirmation testing completed.

#### 12.1.10.1. Hematology

Hematology analysis will include a complete blood count with differential and platelet count with smear. Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for hematology analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 1).

Immediate/same-day hematology analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory. Investigators will receive hematology results from all study visits from the central laboratory.

#### 12.1.10.2. Blood Chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 1).

Immediate/same-day chemistry analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory.

Chemistry analysis will include the following at all study visits:

- Serum GGT
- AST/ALT
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Total creatine kinase

- Creatinine
- BUN
- Electrolytes
- Alkaline phosphatase

Creatine kinase (CK-MB) will be collected at Screening, Day 7, Day 30, Day 60, every 90 days, and at End of Study.

Investigators will receive chemistry results from all study visits from the central laboratory (except Day -1).

#### 12.1.10.3. Urinalysis

Urine samples will be collected in accordance with the laboratory manual provided by the central laboratory at all study visits except Day 1 and Day 3 (Appendix 1). Day -1 urinalysis will be performed as per investigational site standard procedures at the local laboratory. Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin
- Blood
- Protein
- Red Blood Cell
- White Blood Cell
- Squamous epithelial cells
- Casts
- Crystals
- Bacteria
- Yeast

#### 12.1.10.4. Virus Serology

The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have HIV or positive serology for hepatitis B or C or Zika virus, administration of AAV vector may represent an unreasonable risk; therefore negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected at screening (Appendix 1) and shipped in accordance with the laboratory manual provided by the central laboratory.

#### 12.1.10.5. Capillary Blood Gas

Capillary blood gas will be completed locally at Day –1 and Day 2 (Appendix 1). A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

#### 12.1.10.6. Immunology Testing (ELISA and IFN-γ ELISpots)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA), and to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN. Blood samples will be collected at screening (ELISA anti-AAV9 only), Day 7, Day 14 (ELISA anti-AAV9/SMN only), Day 21 (ELISA anti-AAV9/SMN only), and Day 30 (Appendix 1). Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.

#### 12.1.10.7. AAV9 Antibody Screen in Mother

There is potential that the biological mother of the patient may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or, theoretically, via placental transfer in utero. Informed consent will be requested from the biological mother of the patient to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein at screening and shipped to the central laboratory for screening of anti-AAV9 antibodies. Mothers who test positive for antibodies to AAV9 will be asked to refrain from further feedings with breast milk.

If AAV9 antibodies are identified, the patient must desist in consuming breast milk from the biological mother.

Patients consuming banked breast milk from donor sources that cannot be test for anti-AAV9 antibodies must be transitioned to formula prior to participation.

#### 12.1.10.8. Blood for Diagnostic Confirmation Testing

A blood sample will be collected during the screening visit and shipped to the central laboratory in accordance with the laboratory manual for reconfirmation of *SMN1* deletions/mutations, *SMN2* copy number, and absence of exon 7 gene modifier mutation (c.859G>C). This will be done to ensure consistency in diagnostic testing practices.

#### 12.1.10.9. Saliva, Urine, and Stool Collection

Studies have shown that some vector can be excreted from the body for up to a few weeks after injection; this is called "viral shedding." Vector shedding can be found in the blood, urine, saliva, and stool for up to 1 week following infusion. The potential health risks associated with the shed vector are not fully known at this time; however the health risk is thought to be low as the vector cannot replicate. Regardless, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved instructions should be provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of 2 weeks (14 days) after gene replacement therapy. Additionally, patients are prohibited from donating blood for 2 years following the vector infusion.

Saliva, urine, and stool samples will be collected for viral shedding studies at screening, 24 hours post-dose, 48 hours post-dose, Day 7, Day 14, Day 21, and Day 30 (Appendix 1). Samples will be collected, prepared, and shipped as per the laboratory manual.

A subset of patients at sites opting to participate in the viral shedding sub-study will have 24-hour total volume urine and fecal samples collected through 24 hour post-dose and through 48 hours-post dose.

# 13. ADVERSE AND SERIOUS ADVERSE EVENTS

### 13.1.1. Definition of Adverse Events

#### 13.1.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur from the start of gene replacement therapy infusion through the last study visit will be collected and recorded in the eCRF.

All adverse events will be classified in accordance with the CTCAE version 4.03 outlined in Table 7.

**Table 7: Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 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: Common Terminology Criteria for Adverse Events (version 4.03) [9]

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

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

Study enrollment will be interrupted should any patient experience an unanticipated CTCAE Grade 3, or higher adverse event toxicity that is possibly, probably, or definitely related to the gene replacement therapy. The event will then be reviewed by the DSMB and an evaluation will be made as to whether the study should be terminated early following the discontinuation rules.

Unanticipated CTCAE Grade 3 or higher adverse events that are possibly, probably, or definitely related to the gene replacement therapy must be reported within 24 hours to Sponsor and/or designee as per study safety management plan to ensure timely escalation to the DSMB.

#### 13.1.1.2. Serious Adverse Event

A SAE is an AE occurring during any study phase (e.g., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or comparator that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after signing of the informed consent through the last study visit, whether or not they are related to the study product, must be collected and recorded on forms provided by the Contract Research Organization.

#### 13.1.1.3. Other Adverse Event

The following specific treatment-emergent AE of special interest, which may be searched using Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries, will be summarized:

- Elevated liver enzymes

Other adverse events (OAE) will be identified by the Drug Safety Physician and, if applicable, also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

## 13.2. Relationship to Study Product

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” then the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 13.3. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the time of vector infusion until the end of the study. Serious Adverse Event information will be collected from signing of consent form until the last study visit. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date (and time if during Visit 2)), resolution (date (and time if start date during Visit 2)), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.1.2. An AE of severe intensity may not be considered serious.

## 13.4. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of consent form until the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or e-mail to AveXis or designee.

Additional follow-up information, if required or available, should all be faxed or e-mailed to AveXis or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

AveXis is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, product-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

# 14. STATISTICS

This section summarizes key aspects of the analysis plan including definitions of co-primary, co-secondary, and [redacted] and safety endpoints, and the methods to be used to test the primary effectiveness hypothesis. Additional details regarding methods for the final data analysis will be provided in a separate Statistical Analysis Plan (SAP) which will be finalized and submitted to the Investigational New Drug application prior to the enrollment of the first patient. The SAP will detail all analyses and data displays, and will be executed according to Standard Operating Procedures in a controlled environment.

## 14.1. Study Endpoints and Populations

### 14.1.1. Study Endpoints

The primary and efficacy endpoint will be compared to the null. The survival co-primary efficacy variable will be evaluated relative to literature-based historical controls (such as the Pediatric Neuromuscular Clinical Research Network [PNCR] [21]. These were selected on the basis of comparability to the target population and similarity to the investigational device.

#### 14.1.1.1. Co-Primary Efficacy Endpoint

The co-primary efficacy endpoints are:

- The proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 3), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds.
- The survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

An “acute reversible illness” is defined as any condition other than SMA that results in increased medical intervention (e.g., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (e.g., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (e.g., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of “acute.” The date of “definitive intervention” shall be defined as the date of provision of a procedure (e.g., surgery, etc.) or medication (e.g., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of “definitive intervention” shall be considered the date of hospitalization or substantial escalation of care.

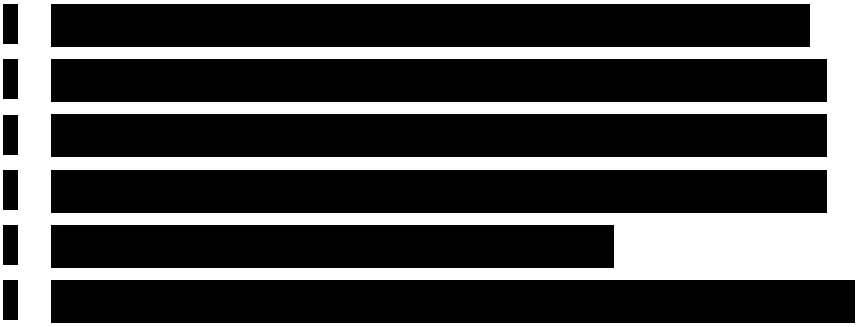
"Perioperative" use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.

For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

#### 14.1.1.2. Co-Secondary Efficacy Endpoint

The co-secondary efficacy endpoints are:

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [26] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy).



#### 14.1.1.4. Safety Endpoints

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated LFTs and/or unresolved LFEs
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ ELISpot to detect T cell responses to AAV9 and SMN

### 14.1.2. Statistical Analysis Populations

#### 14.1.2.1. Intent-to-Treat Population (ITT)

The ITT population will consist of symptomatic patients with bi-allelic deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at less than 180 days of age. The first three patients enrolled must meet the criteria for the Intent-to-Treat Population.

#### 14.1.2.2. Efficacy Completers Population

The efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE or death

#### 14.1.2.3. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101. Analyses of endpoints in this population are considered descriptive.

#### 14.1.2.4. Safety Population

The safety analysis population will consist of all patients who receive an IV infusion of AVXS-101. All safety analyses will be conducted on the safety analysis population.

## 14.2. Sample Size Calculation

This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.

The two co-primary efficacy endpoints will be assessed in sequence: The endpoint of functional independent sitting will be assessed first and, only if this assessment meets statistical significance will the endpoint of survival be assessed.

Based upon the widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patients in this population would be expected to attain the ability to sit without support or accomplish other milestones (rolling over, standing, walking) prior to 18 months of age. Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age study visit. With the assumption for the true response rate of AVXS-101 for the

primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of > 90% to detect a significant difference from 0.1% with α = 0.025 using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion of patients surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with α = 0.05 using a 2-sided Fisher's Exact test, comparing to the 26 age and gender matched patients from a published natural history observational study performed at 3 large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

## 14.3. Efficacy Analysis

### 14.3.1. General Considerations

This study will compare the activity of AVXS-101 administered IV versus the natural observational results from PNCR [21] in terms of functional independent sitting and survival rate. The ability to thrive and the ability remain independent of ventilatory support will also be assessed.

The analysis of the co-primary and co-secondary efficacy endpoints will be performed for the ITT and efficacy completers population. The analysis based on the ITT population will be considered as the primary analysis. In the case of missing data, observed data will be used for the analyses.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (e.g., on or before Day 1 visit).

### 14.3.2. Primary and Secondary Efficacy Analysis

Primary and secondary efficacy analyses will be based on the ITT population, those patients that are symptomatic with bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 to the results from natural observation study (PNCR) [21].

The first co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion surviving at 14 months of age.

Primary efficacy endpoints will be examined on the ITT population. Testing for the first co-primary endpoint, functional independent sitting will first be performed using 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at $p<0.025$, will the co-primary endpoint survival improvement be tested using 2-sided Fisher's Exact test on the ITT population, comparing to matched patients from natural observational study (PNCR). This hierarchy approach strongly protects the Type I error rate.

The hypothesis for both co-secondary efficacy endpoints to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of patients maintaining the ability to thrive/are independent of ventilatory support.

One-sided exact binomial tests will be executed for secondary efficacy analyses on the ITT population.

A sensitivity analysis will be conducted by repeating the primary efficacy analysis on the efficacy completers analysis population.

## 14.4. CHOP-INTEND Comparison

A comparison will be performed of the first three patients CHOP-INTEND scores to the AVXS-101-CL-101 CHOP-INTEND scores. The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 30-day interval between patients and proceed

to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.

## 14.5. Safety Analysis

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, urinalysis, immunology), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary.

Safety analyses will be conducted on safety population, and summarized by subgroup and overall.

# 15. DATA SAFETY MONITORING BOARD

The DSMB is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, have experience in the management of patients with SMA Type 1 and other diseases, and in the conduct and monitoring of randomized clinical studies with interim analyses. The DSMB will be chartered to oversee the safety of patients during the conduct of the study, and will act in an advisory capacity to AveXis. A detailed description of the DSMB, its role in this study, and the timing of the scheduled reviews will be described in a DSMB Charter.

The DSMB will routinely convene on a quarterly basis to review emerging safety data from the study. All available safety data from all enrolled patients will be included in such reviews, which include, but are not limited to, screen failures, enrollment status, data from safety parameters, all SAEs, and other AEs. Following each meeting, the DSMB will make a recommendation as to whether or not the accumulated safety data warrants a suspension or discontinuation of the study, a modification to the study, or any additional comments or recommendations related to safety. The DSMB will prepare and provide minutes of their meetings to AveXis who will provide copies to the regulatory authorities as appropriate.

The DSMB will also convene on an ad hoc basis within 48 hours should any patient experience an unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation.

# 16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 16.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of AveXis will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AveXis or its representatives. This will be documented in a Clinical Study Agreement between AveXis and the Investigator.

During the study, a monitor from AveXis or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts, electronic medical records)
- Record and report any protocol deviations not previously sent to AveXis
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to AveXis and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

## 16.2. Audits and Inspections

Authorized representatives of AveXis, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact AveXis immediately if contacted by a regulatory agency about an inspection.

### 16.3. Institutional Biosafety Committee

As this study involves gene therapy, the Principal Investigator must obtain approval/favorable opinion for the investigation from a designated institutional or independent biosafety committee in accordance with institutional requirements and/or guidelines.

### 16.4. Institutional Review Board/Institutional Ethics Committee

The Principal Investigator must obtain IRB/IEC approval for the investigation (Section 18.1). Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

# 17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. AveXis may also conduct a quality assurance audit any time during or after the completion of the study. Please see Section 16.2 for more details regarding the audit process.

The Investigator agrees to allow these Sponsor representatives direct access to the clinical data and supplies, dispensing and storage areas and if requested, agrees to cooperate fully or assist the Sponsor representative. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, site staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/IEC and relevant regulatory authority will also be informed.

# 18. ETHICS

## 18.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to AveXis before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## 18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 7) and are consistent with ICH/GCP, applicable regulatory requirements and the AveXis' policy on Bioethics.

## 18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the parent(s)/legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent(s)/legal guardian(s) must also be notified that they are free to discontinue the patient from the study at any time. The parent(s)/legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the parent(s)/legal guardian(s).

There will be 3 informed consent forms:

- Parent(s)/legal guardian(s) informed consent form
- Biological mother baseline AAV9 antibody screening informed consent form
- Autopsy informed consent form (Appendix 2; if the parent(s)/legal guardian(s) decline an autopsy, it will not prevent the patient from participating in the study)

# 19. DATA HANDLING AND RECORDKEEPING

## 19.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion criteria, product administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

## 19.2. Inspection of Records

AveXis or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the product storage area, study product stocks, product accountability records, patient charts and study source documents, and other records relative to study conduct.

## 19.3. Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years included in ICH shall be followed.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, patient / subject screening records, patient / subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB/IEC documentation, an approved sample ICF, drug / product accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

# 20. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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# 22. APPENDICES

# APPENDIX 1. SCHEDULE OF ASSESSMENTS

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | | |
| Echocardiogram | X | | | | | | | | | X[j] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| CK-MB | X | | | | | X | | | X | X[r] | X |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | | X | | X | | | | | | | |
| ELISA anti-AAV9/SMN Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISpot) | | | | | | X | | | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed every 6 months, starting at Month 6.
[k] Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
[r] CK-MB to be performed at Day 60, and every 90 days (Month 6, 9, 12 months of age, 15 months of age, 18 months of age/EOT).

# APPENDIX 2. AUTOPSY PLAN

An autopsy will be requested for any patient who receives gene replacement therapy and expires as per the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25]. The autopsy and tissue collection will be performed by a contracted vendor who will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions will be used to perform the autopsy and pathology necessary to determine the cause of death.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes, including up to 7 sections or pieces from each organ and each region of the spinal cord. Upon collection, these tissue samples will be provided to AveXis for analysis. Tissue analysis will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results will demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

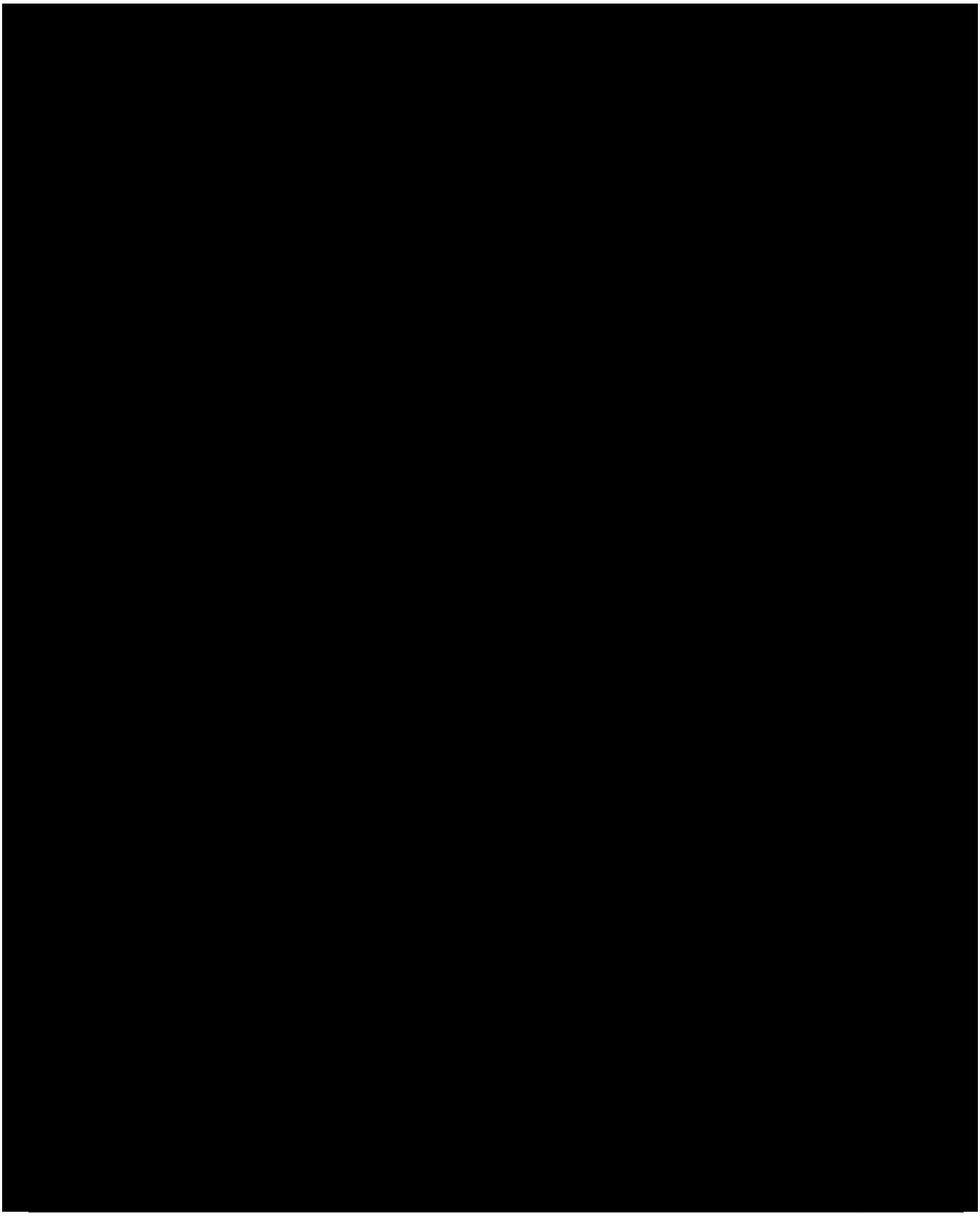
Specifically, tissue samples from the spinal cord, muscles, and organs will be collected as indicated in Table 8. Tissue samples will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

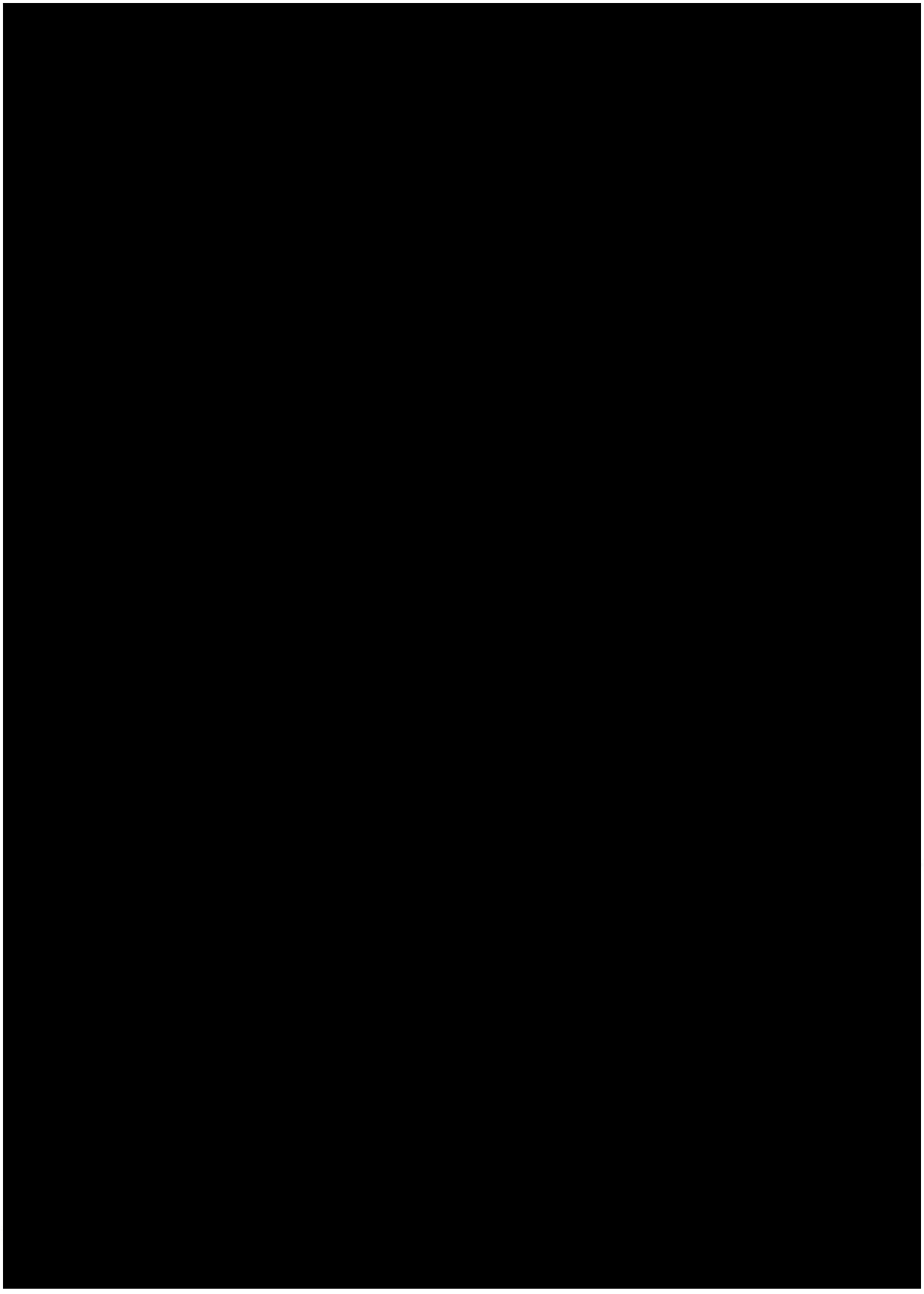
Families will be asked to consent to the autopsy and authorize tissue collection prior to any sign of moribund or death by the clinical team conducting the study. There are distinct forms for the formal autopsy and for the research tissue collection. This will allow families the flexibility to participate in one or both of the research activities. Declining an autopsy will not prevent patients from participating in the study.

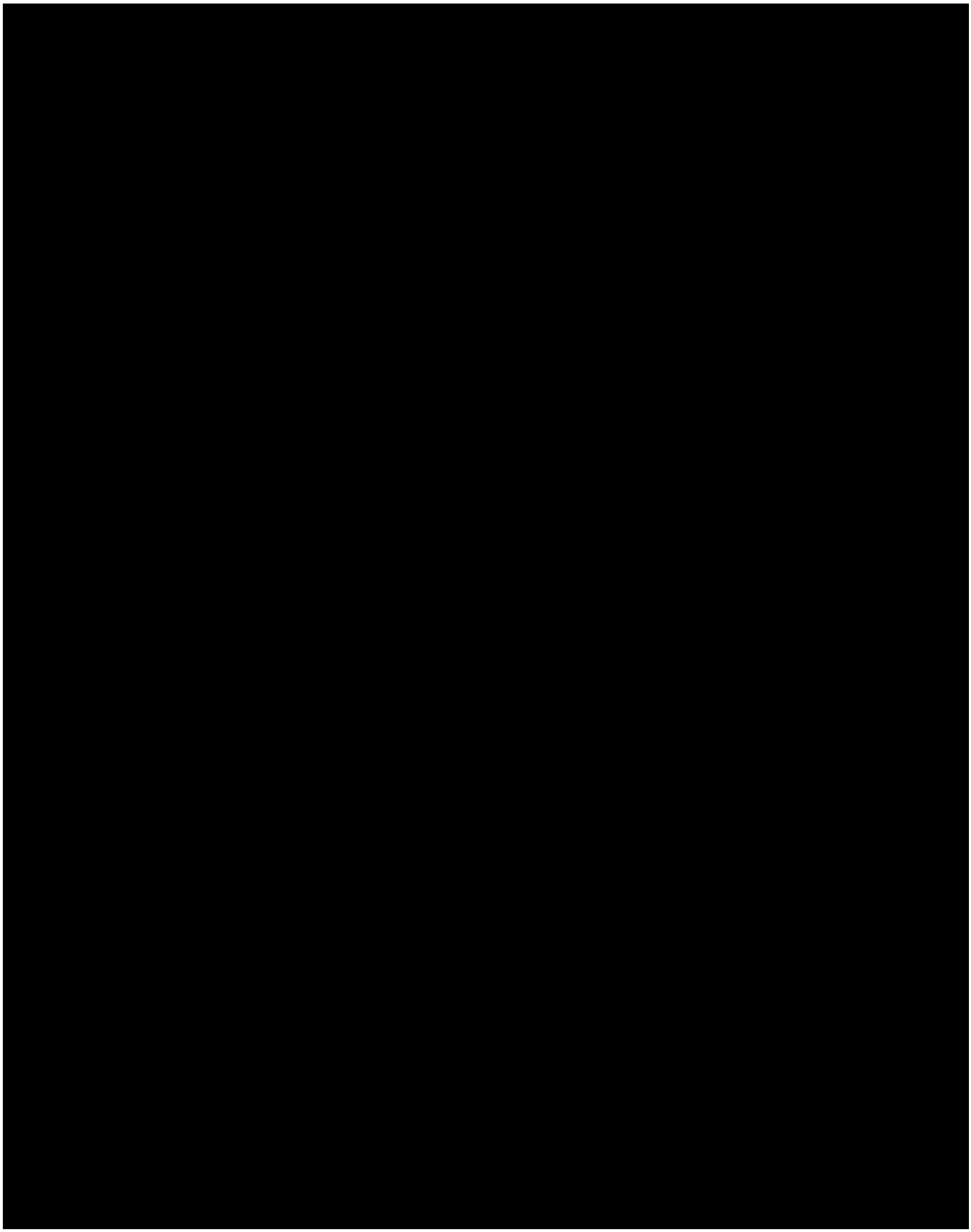
**Table 8: Tissue Sample for Analysis**

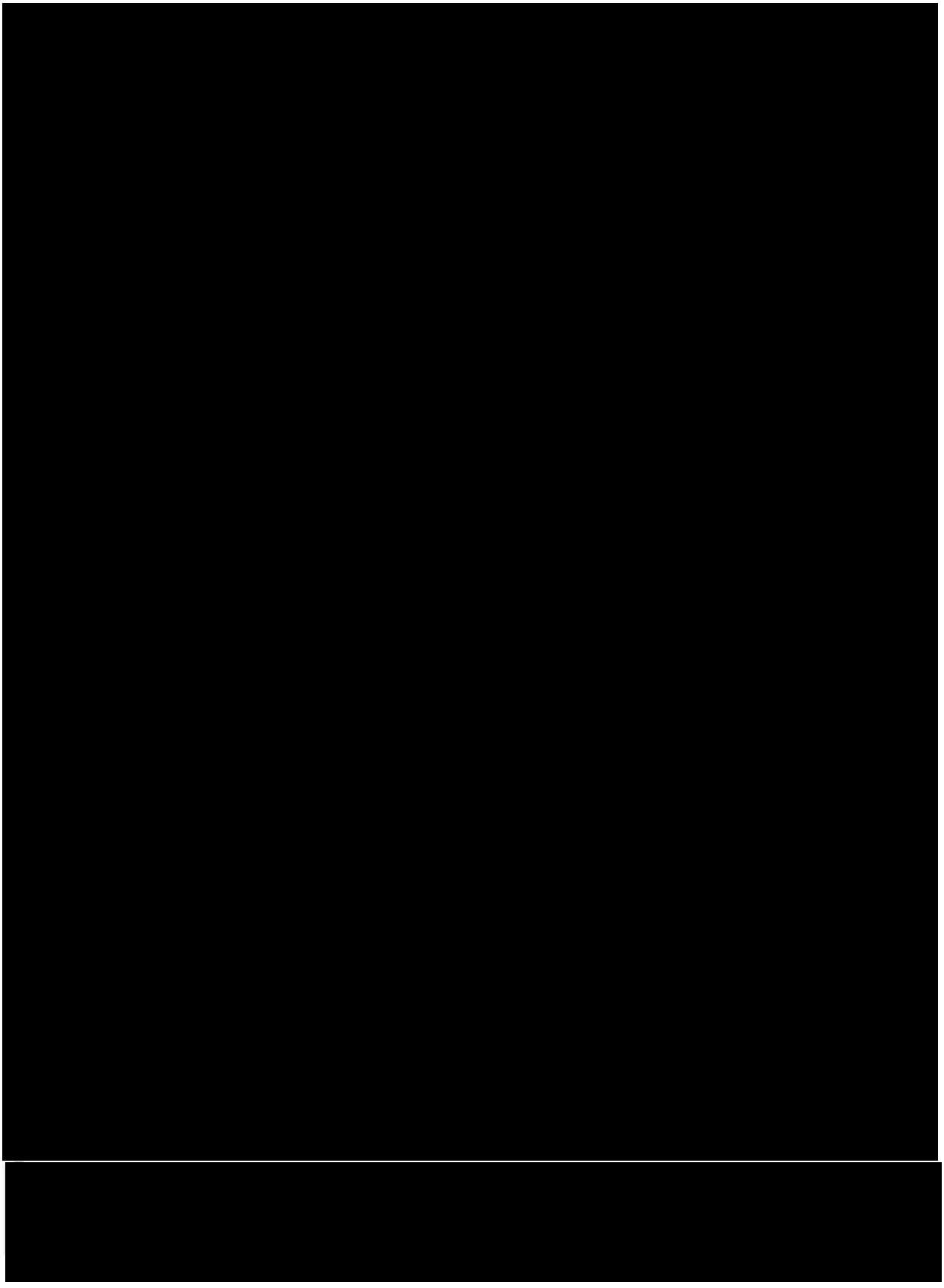
| Brain | Spinal Cord | Muscles | Organs |
|---|---|---|---|
| Motor cortex | Cervical spinal cord | Diaphragm | Spleen |
| Layer 5 motor cortex | Thoracic spinal cord | #6/#7 Rib with intercostal muscle and nerve | Kidney |
| Brain stem | Lumbar spinal cord | Psoas muscle | Small intestine |
| | Sacral spinal cord | | Large intestine |
| | Dorsal root | | Pancreas |
| | Cervical level | | Stomach |
| | Ventral root | | Lung |
| | Cervical level | | Heart |
| | DRG root | | Liver |
| | Cervical level | | Inguinal lymph node |
| | Cerebrospinal fluid | | Gonads |

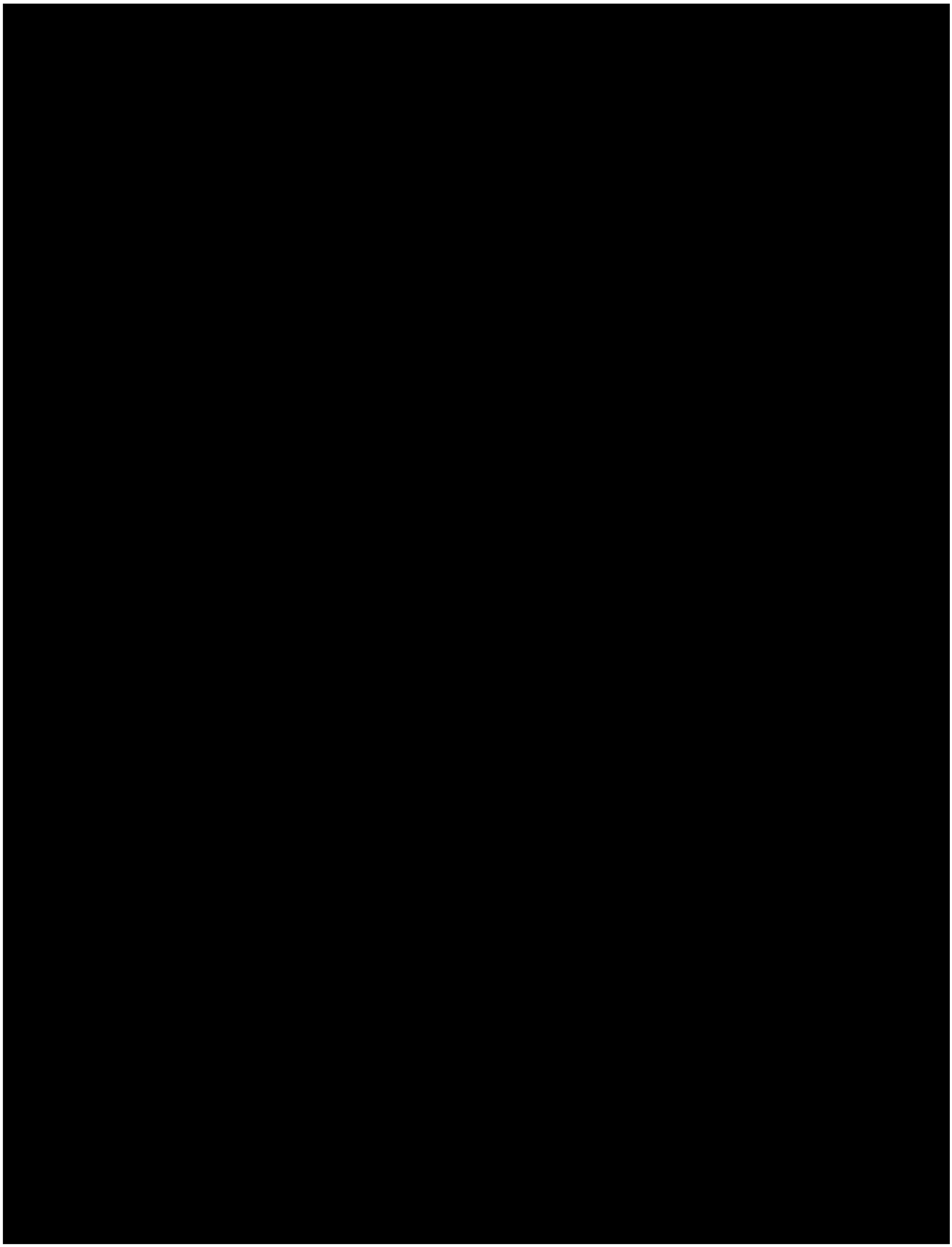
# APPENDIX 3. BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

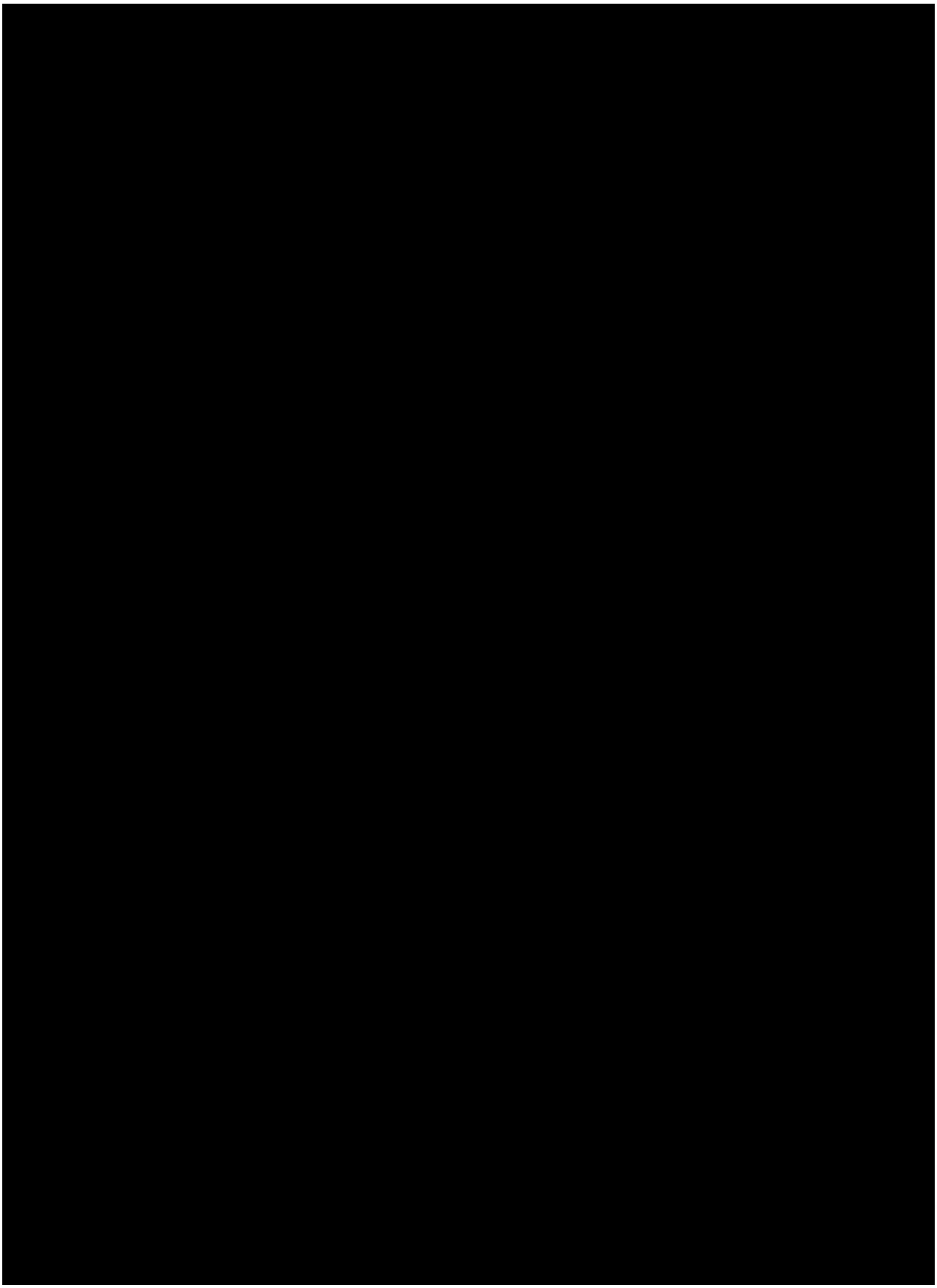


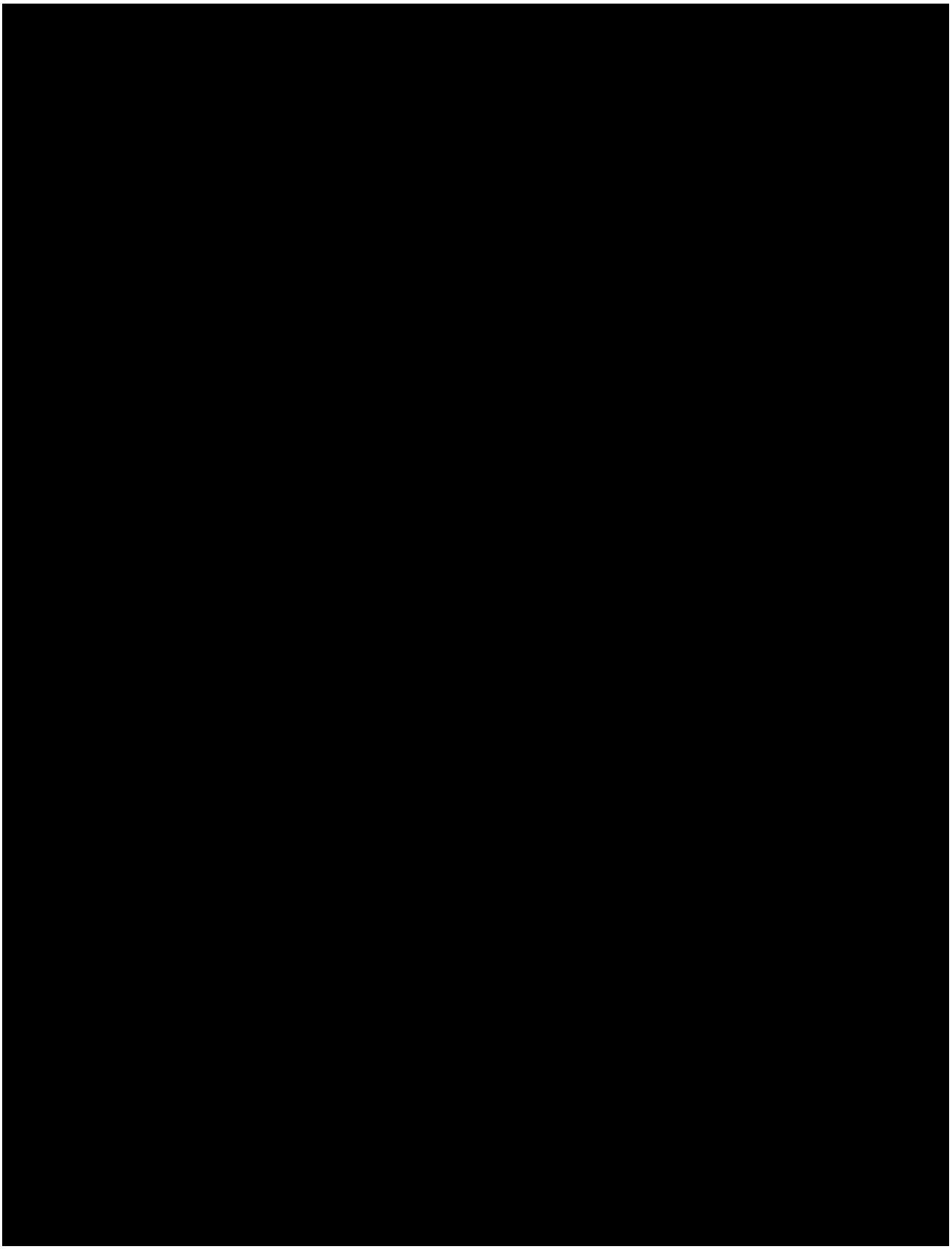


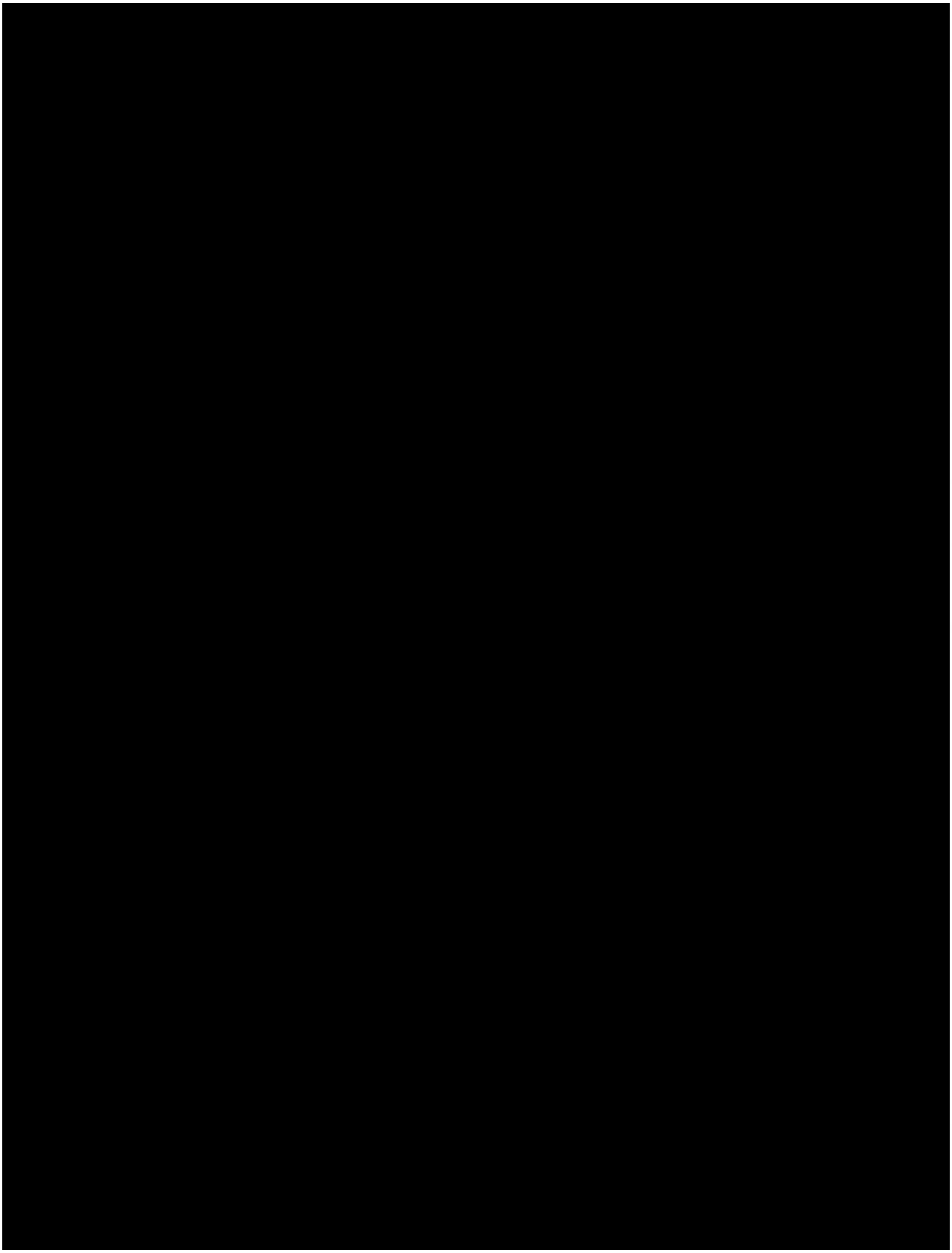


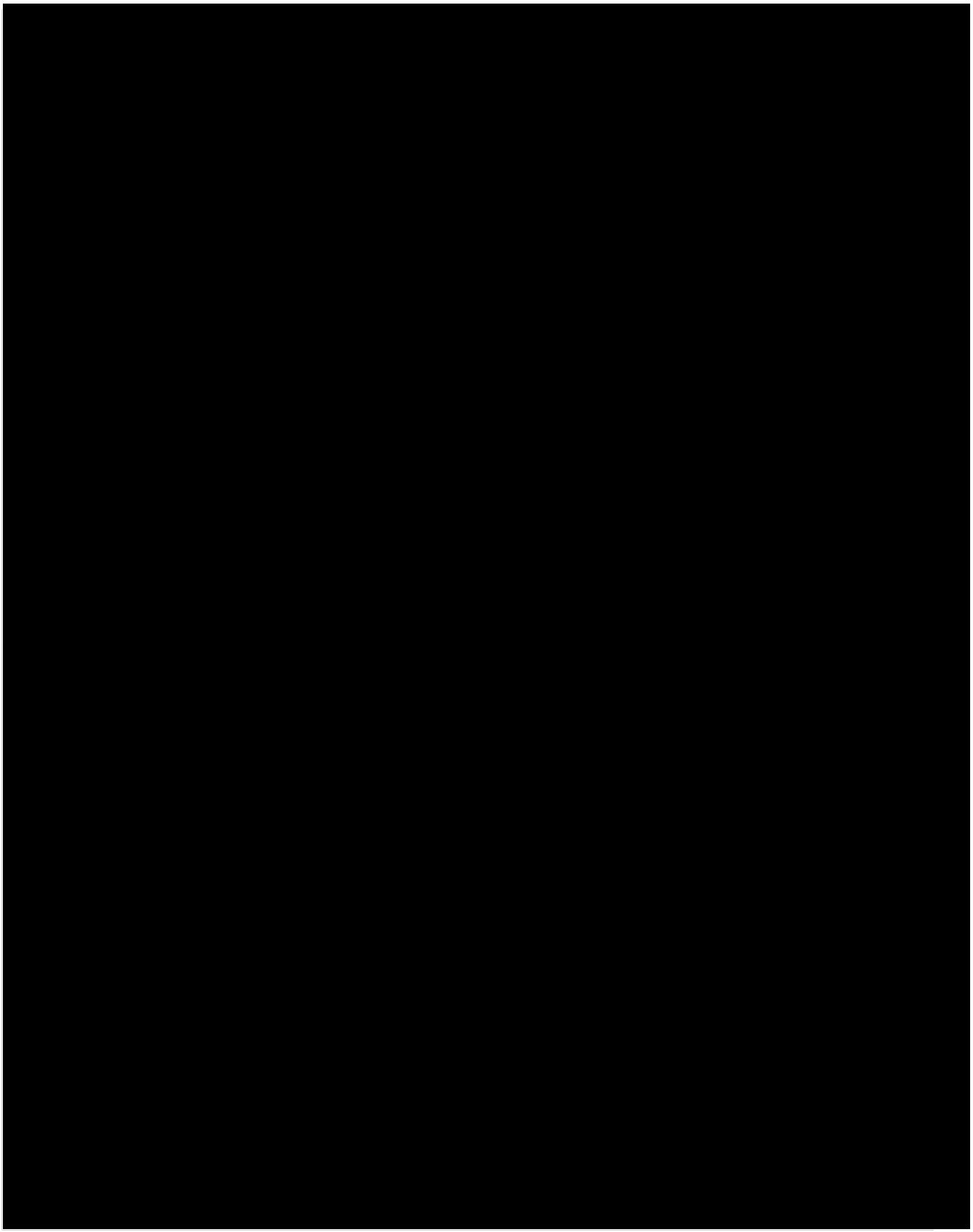


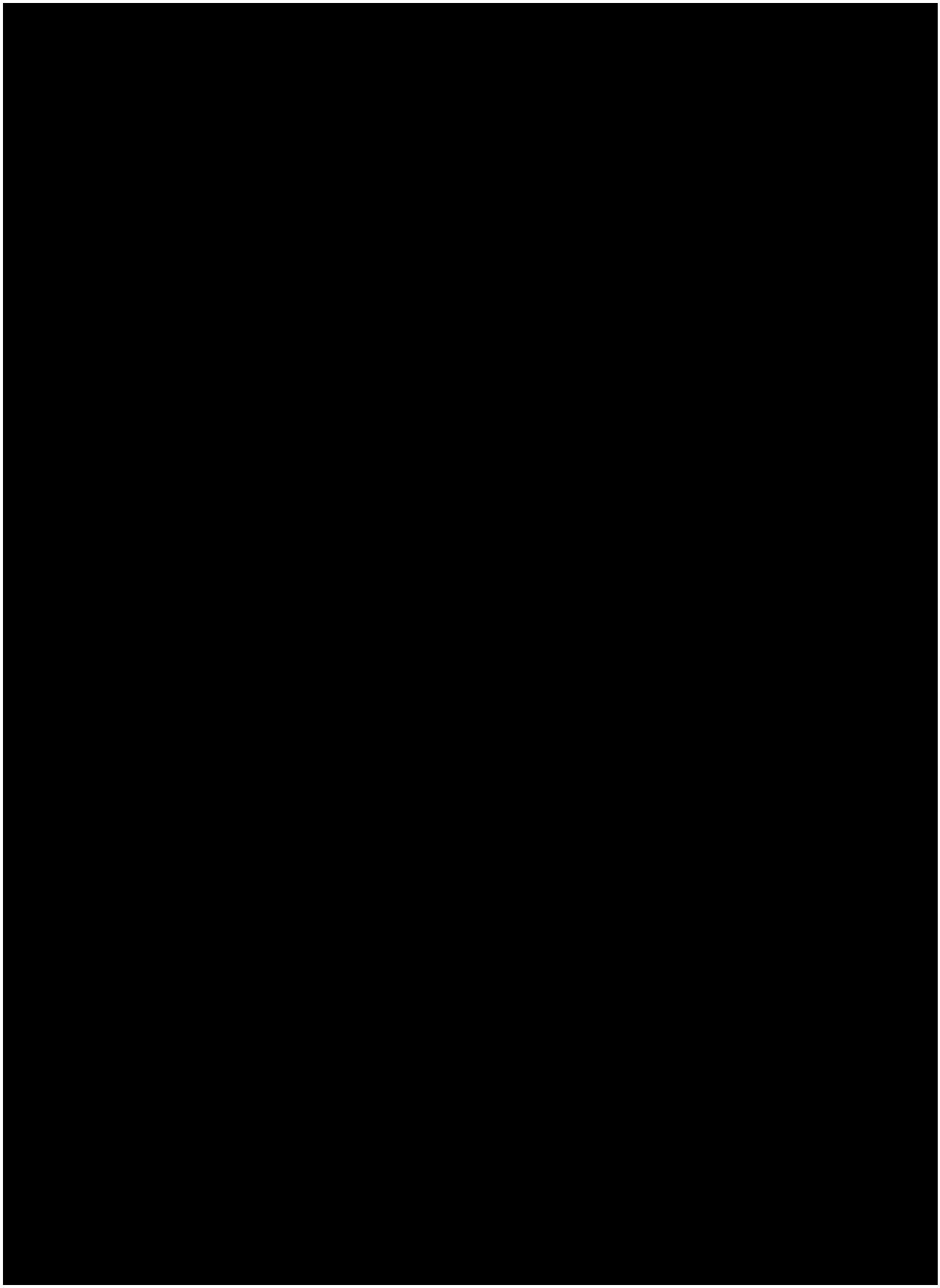


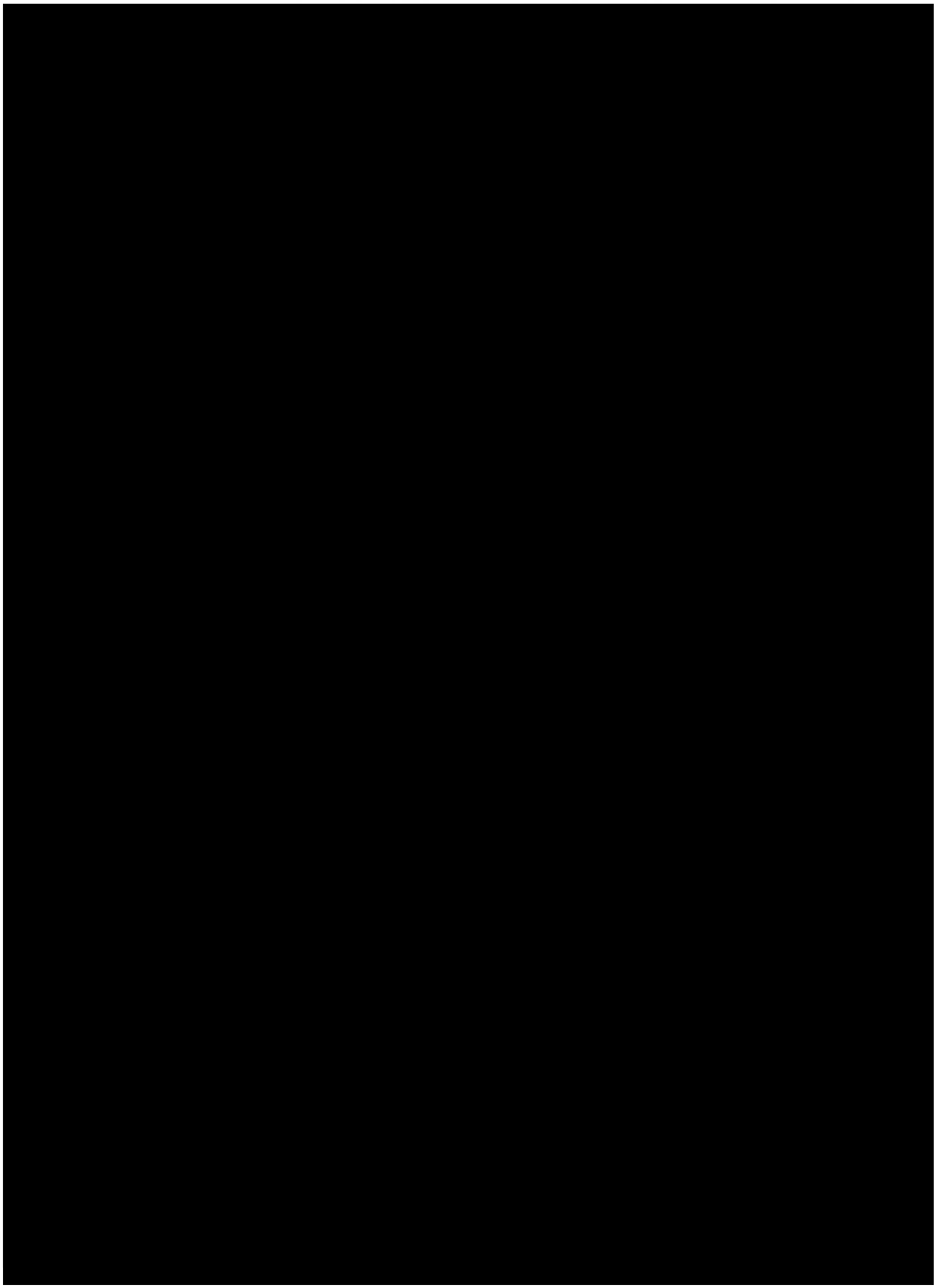


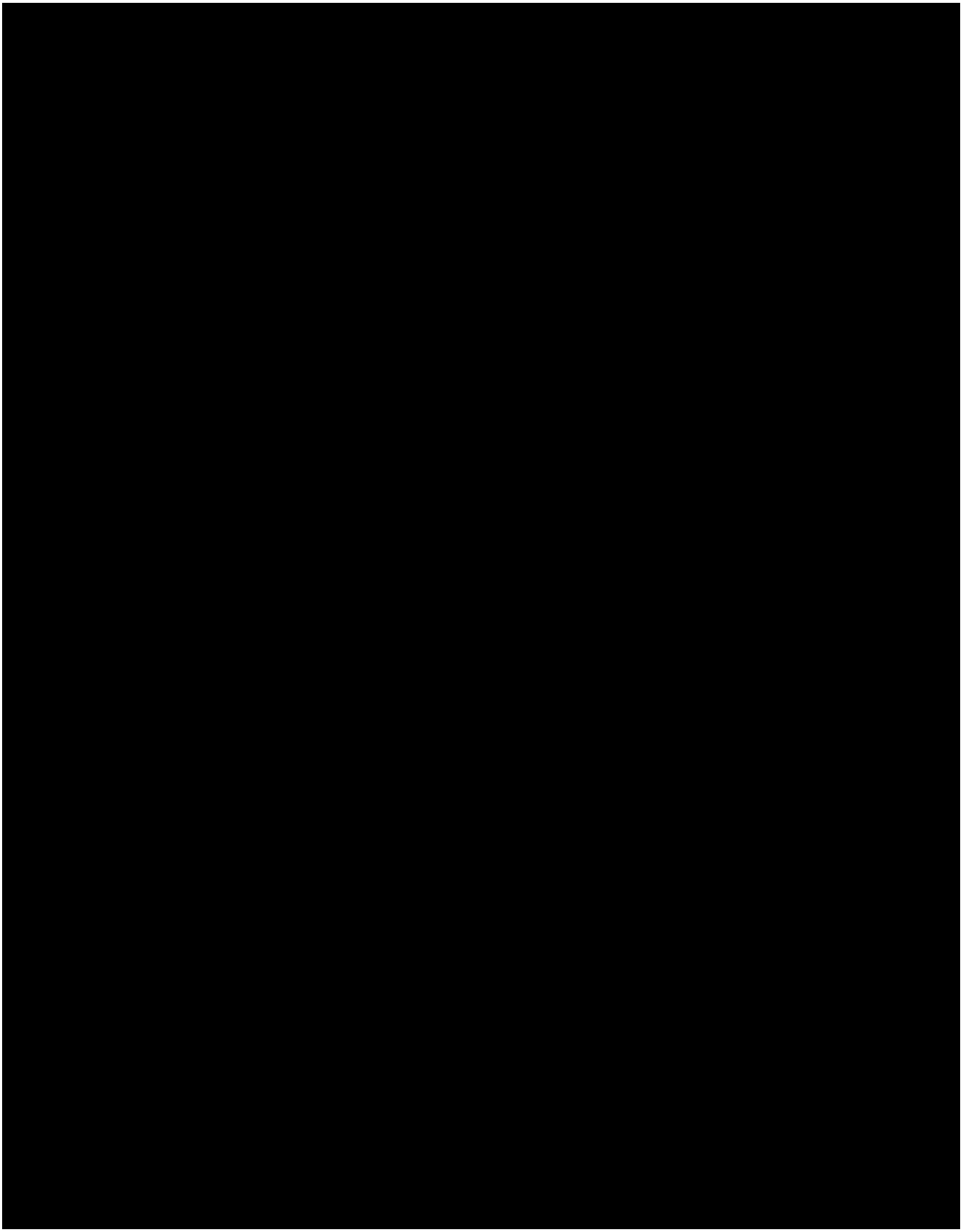


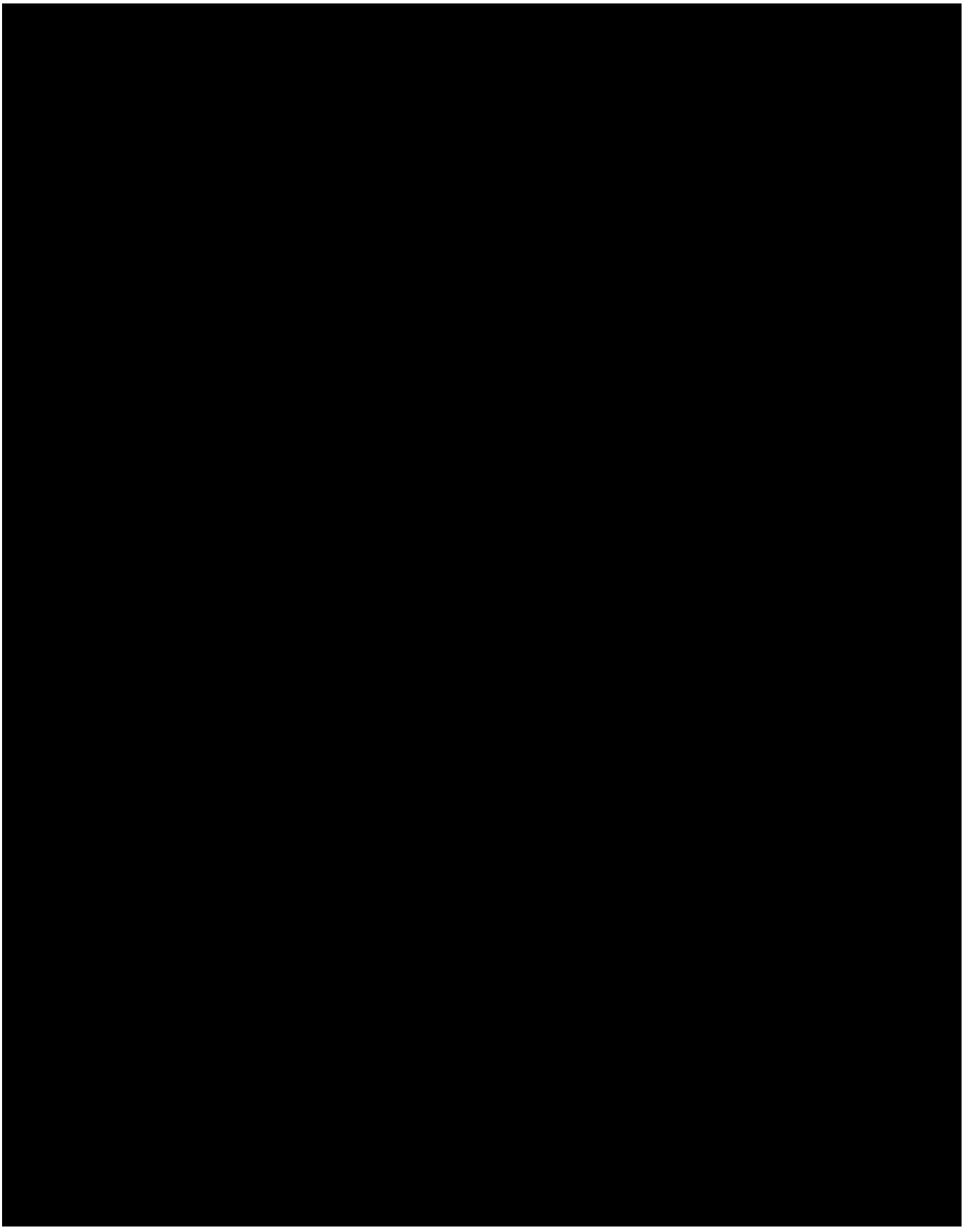


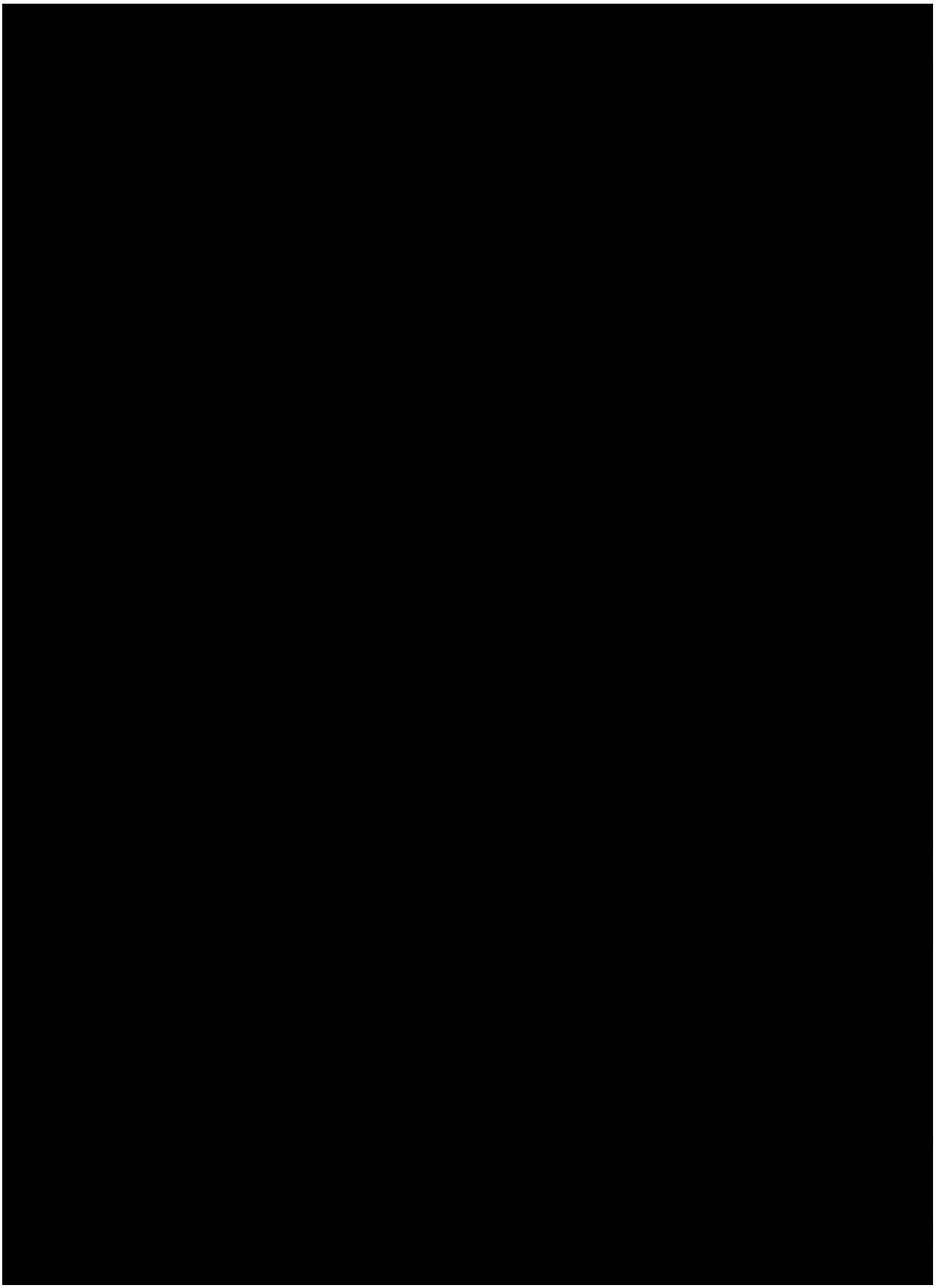


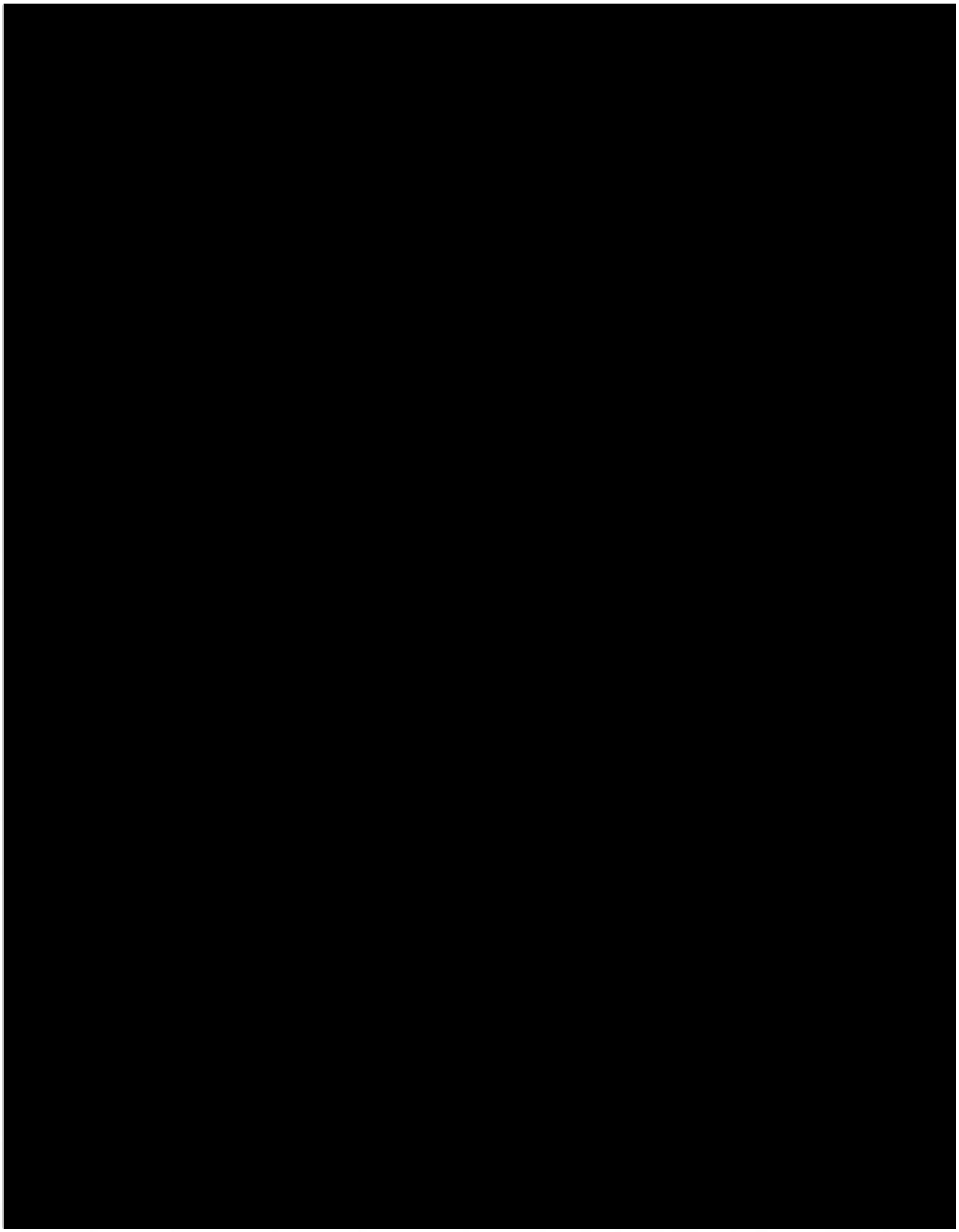


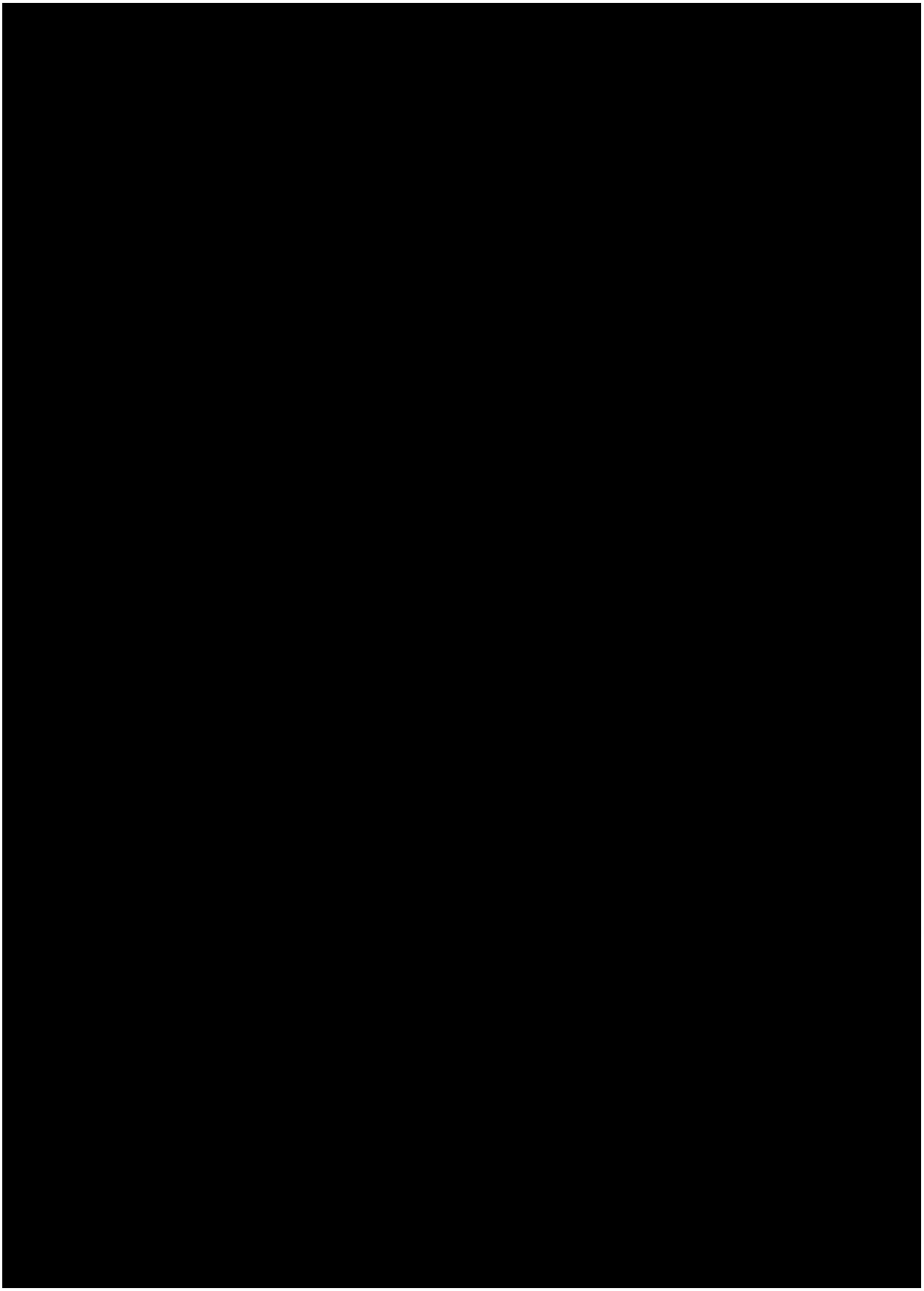


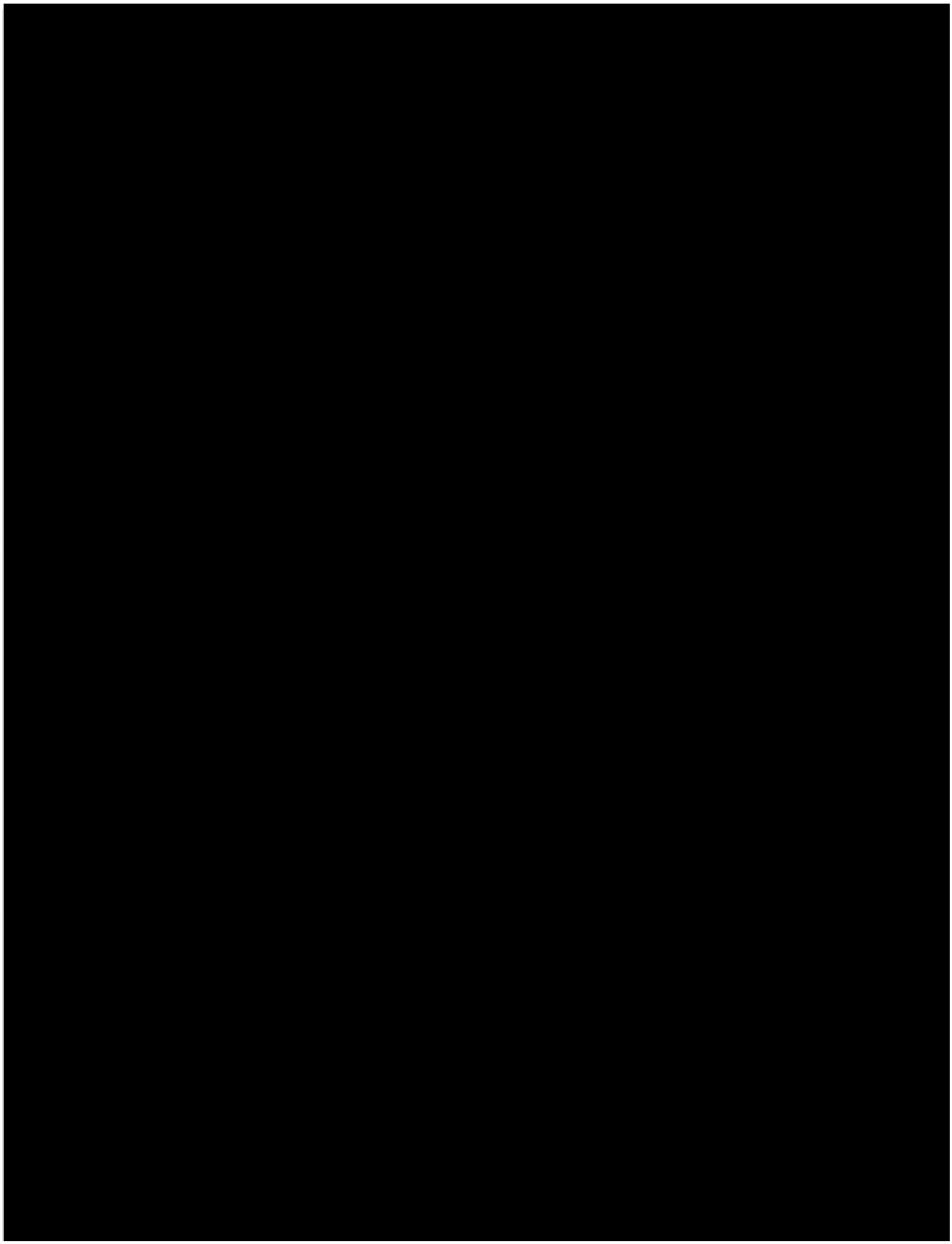


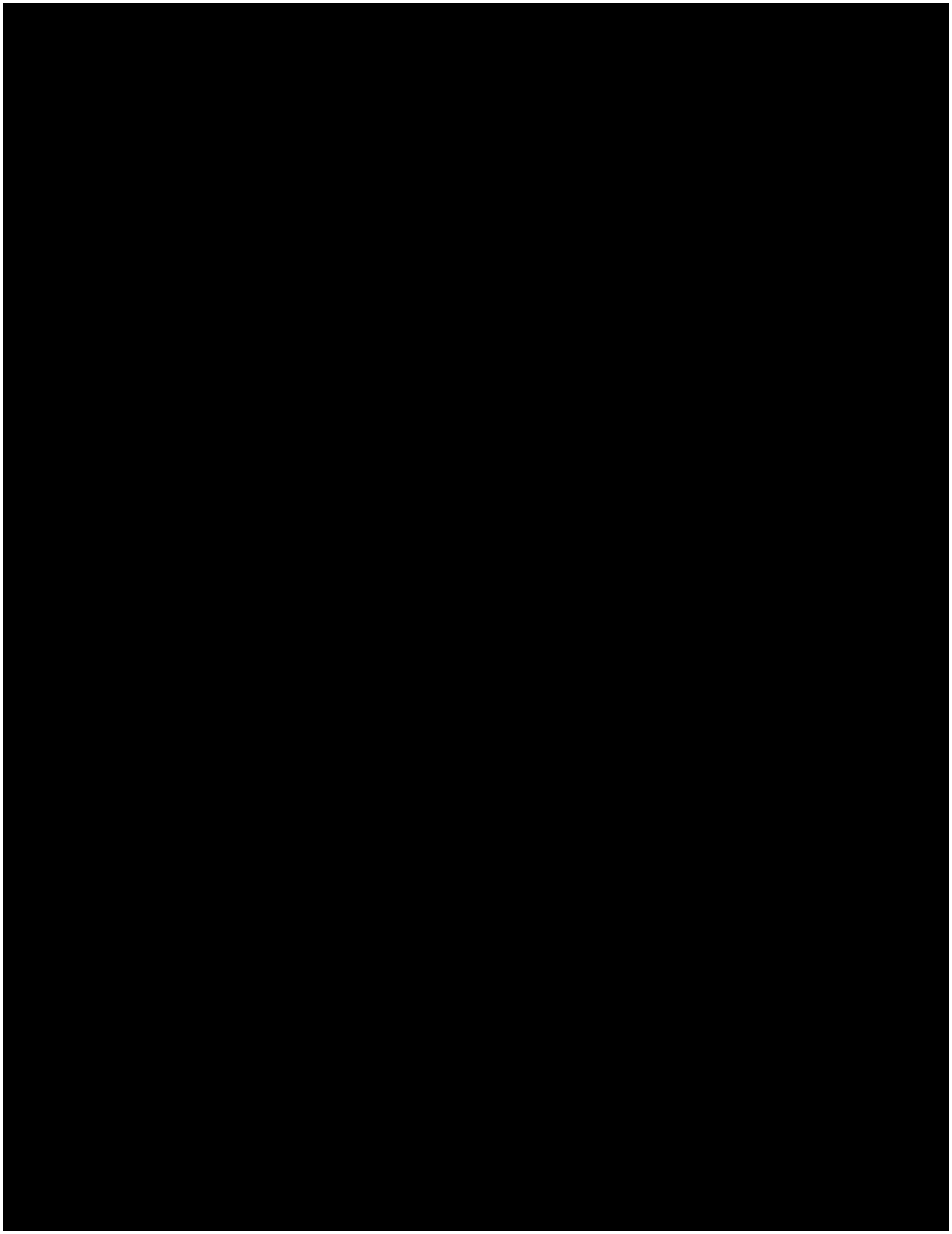


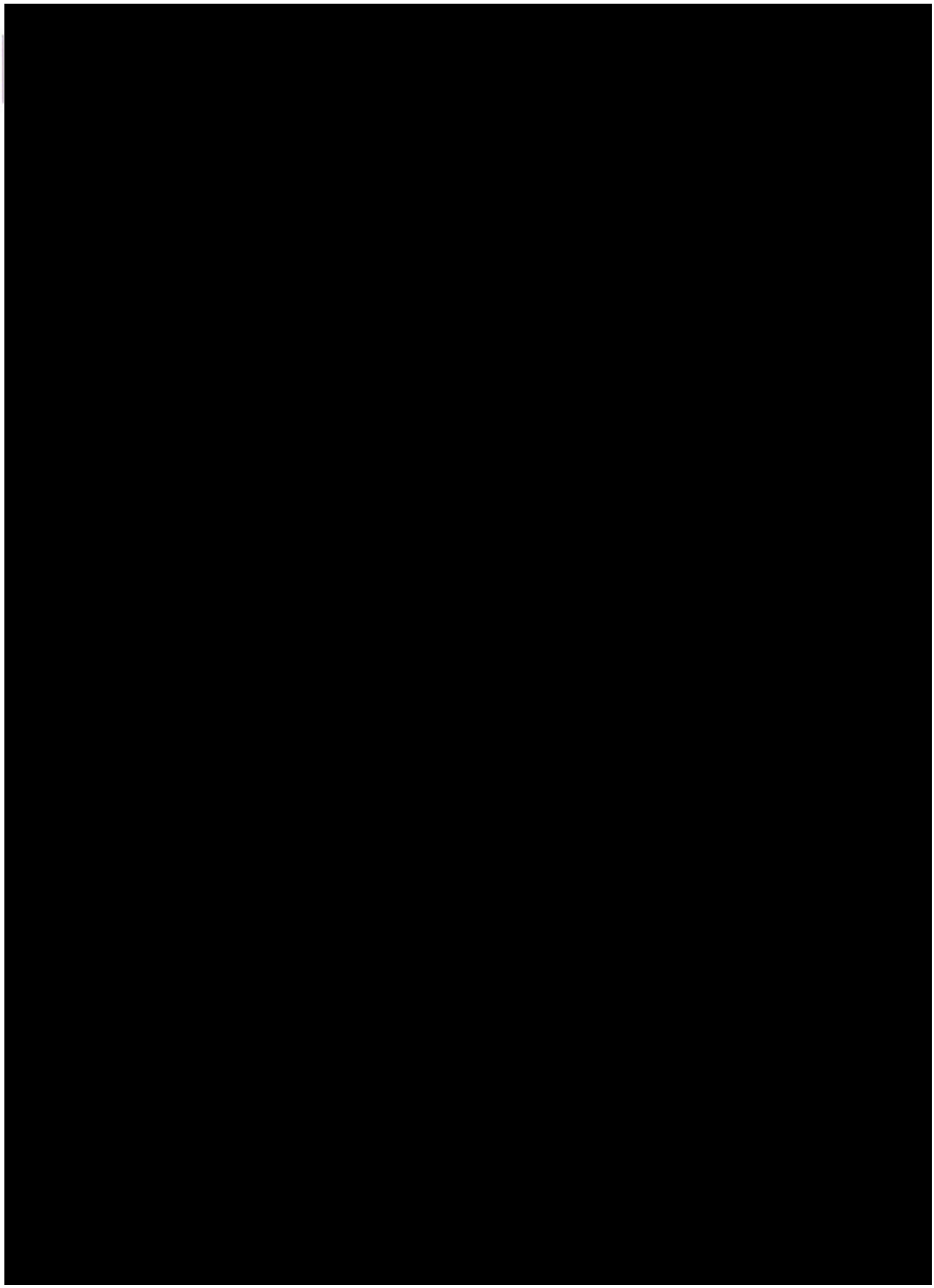


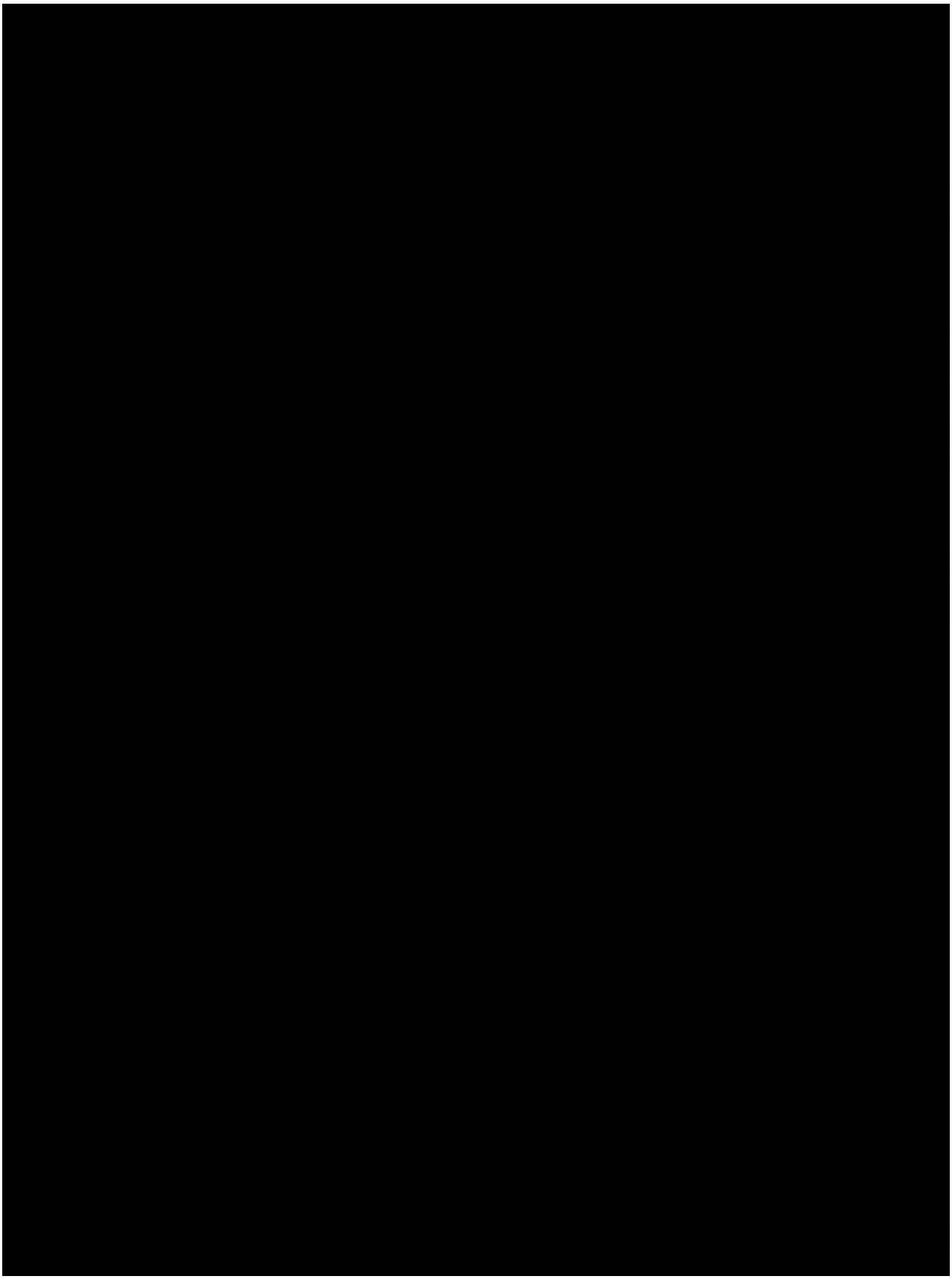


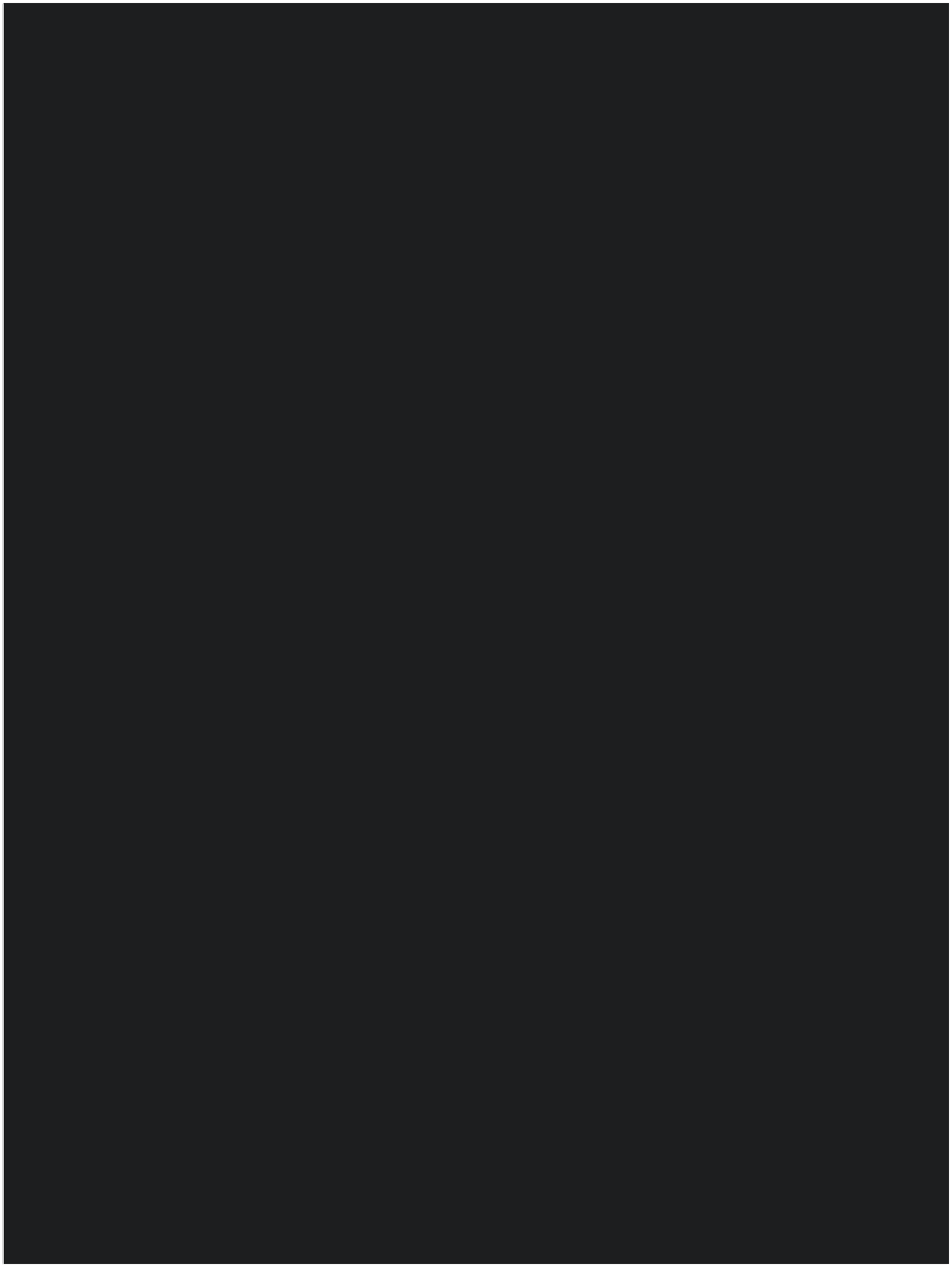


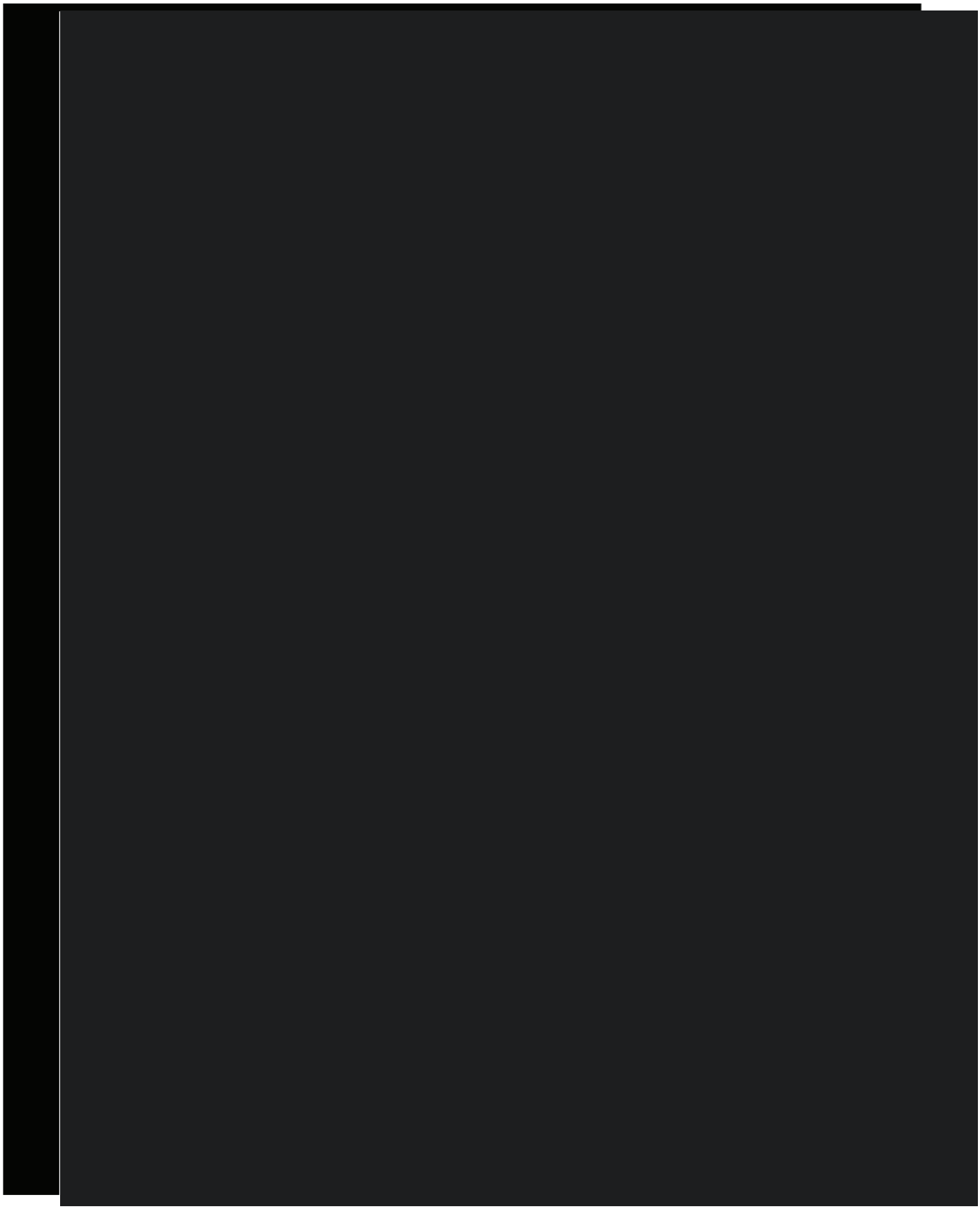


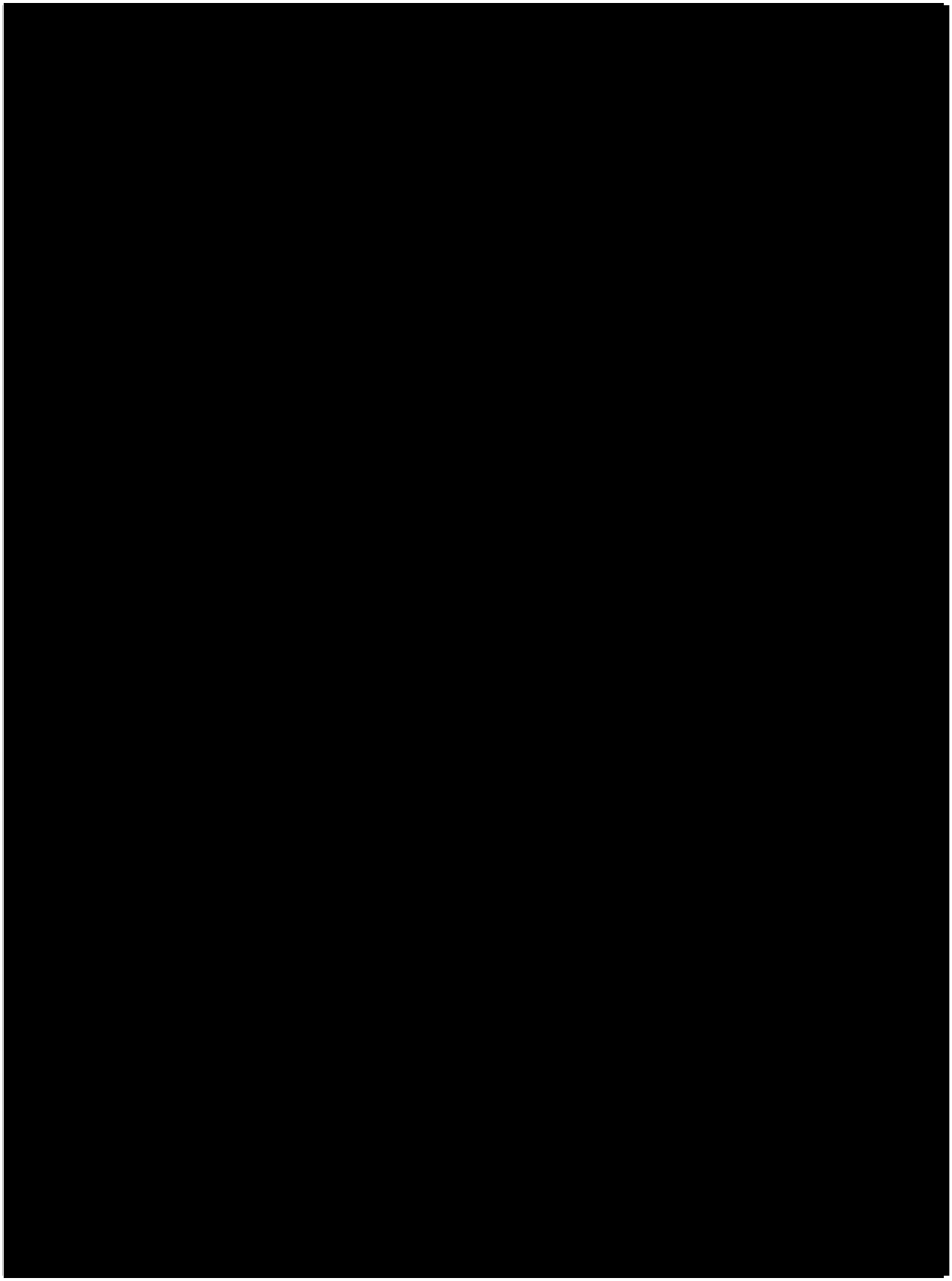


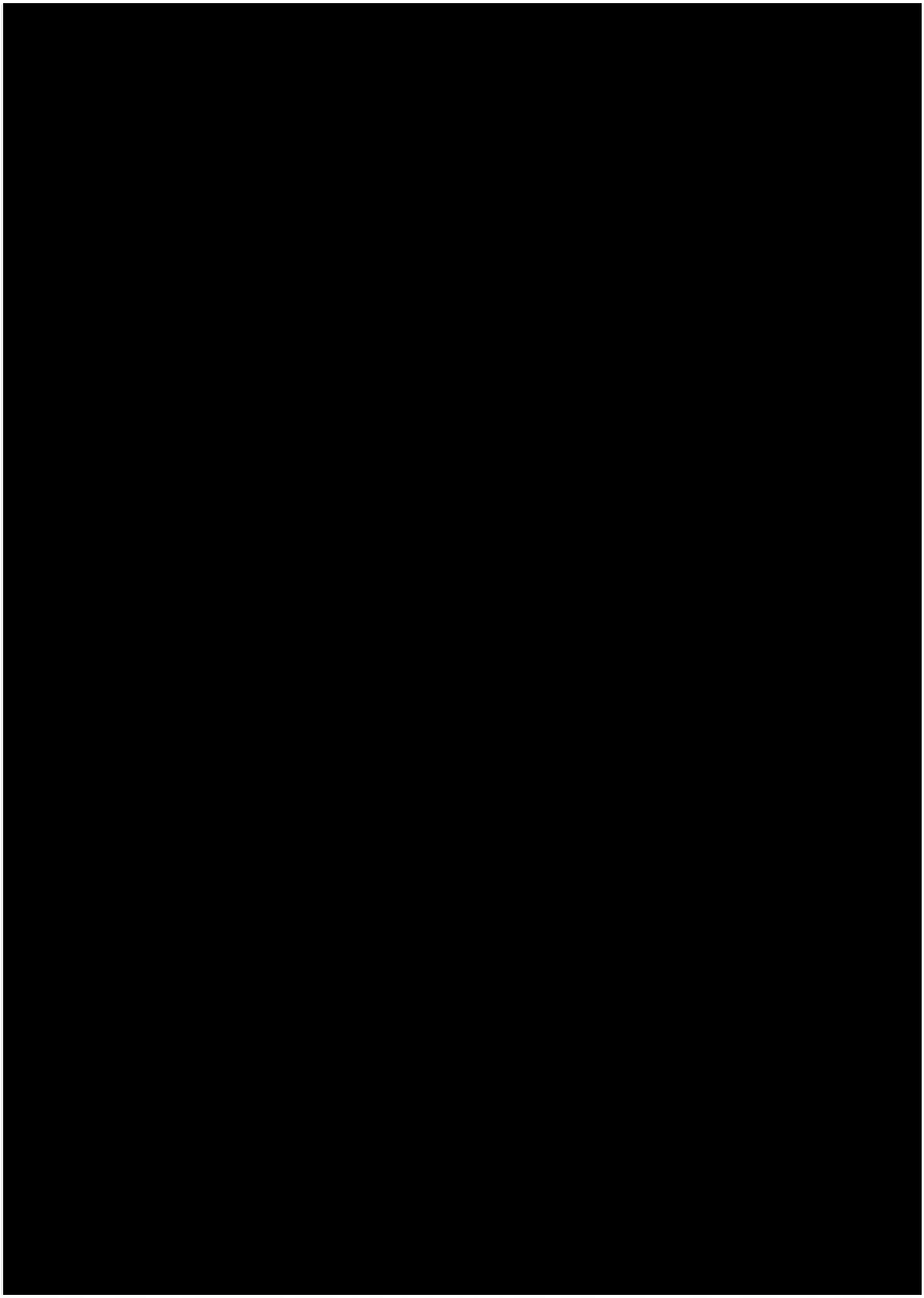


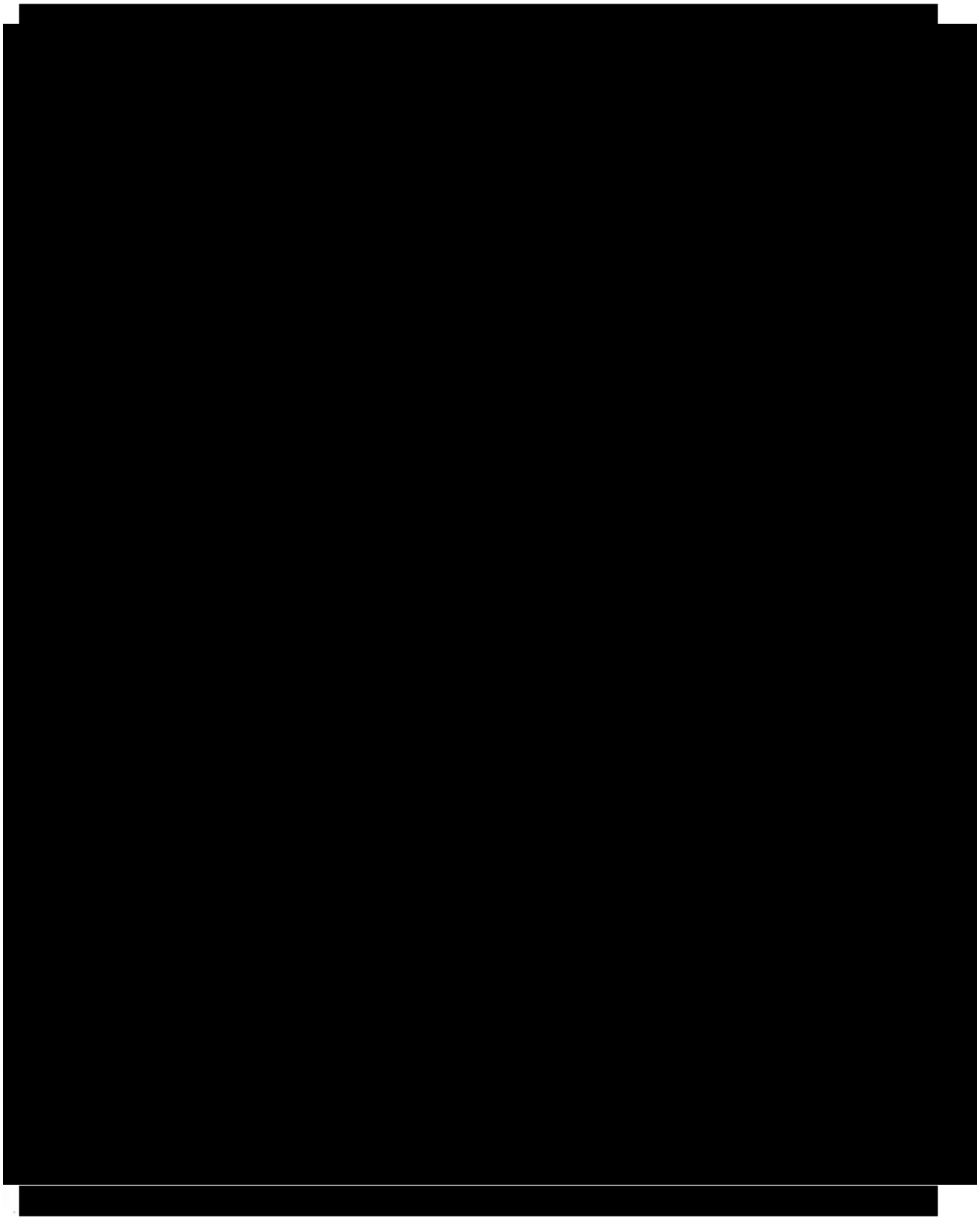


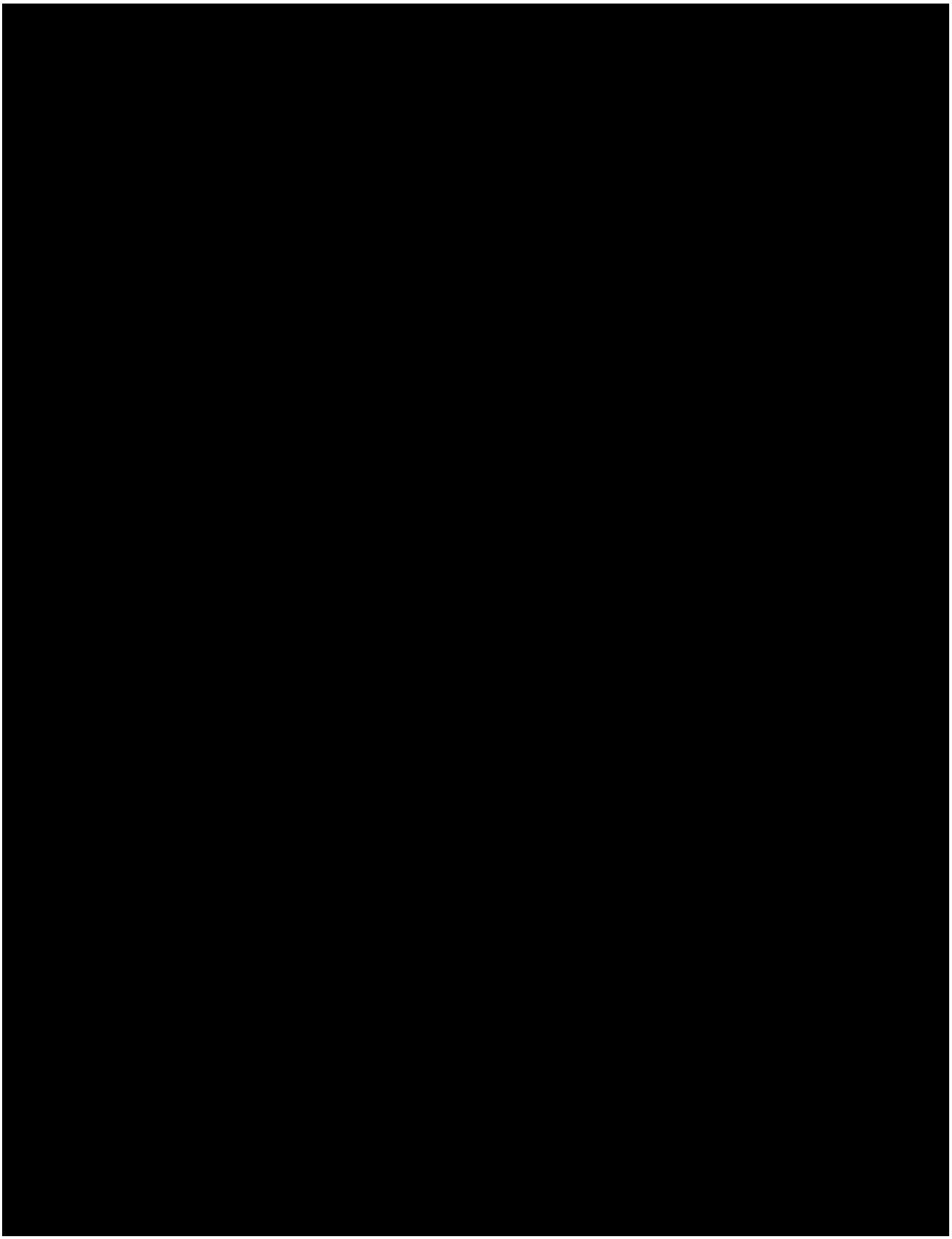


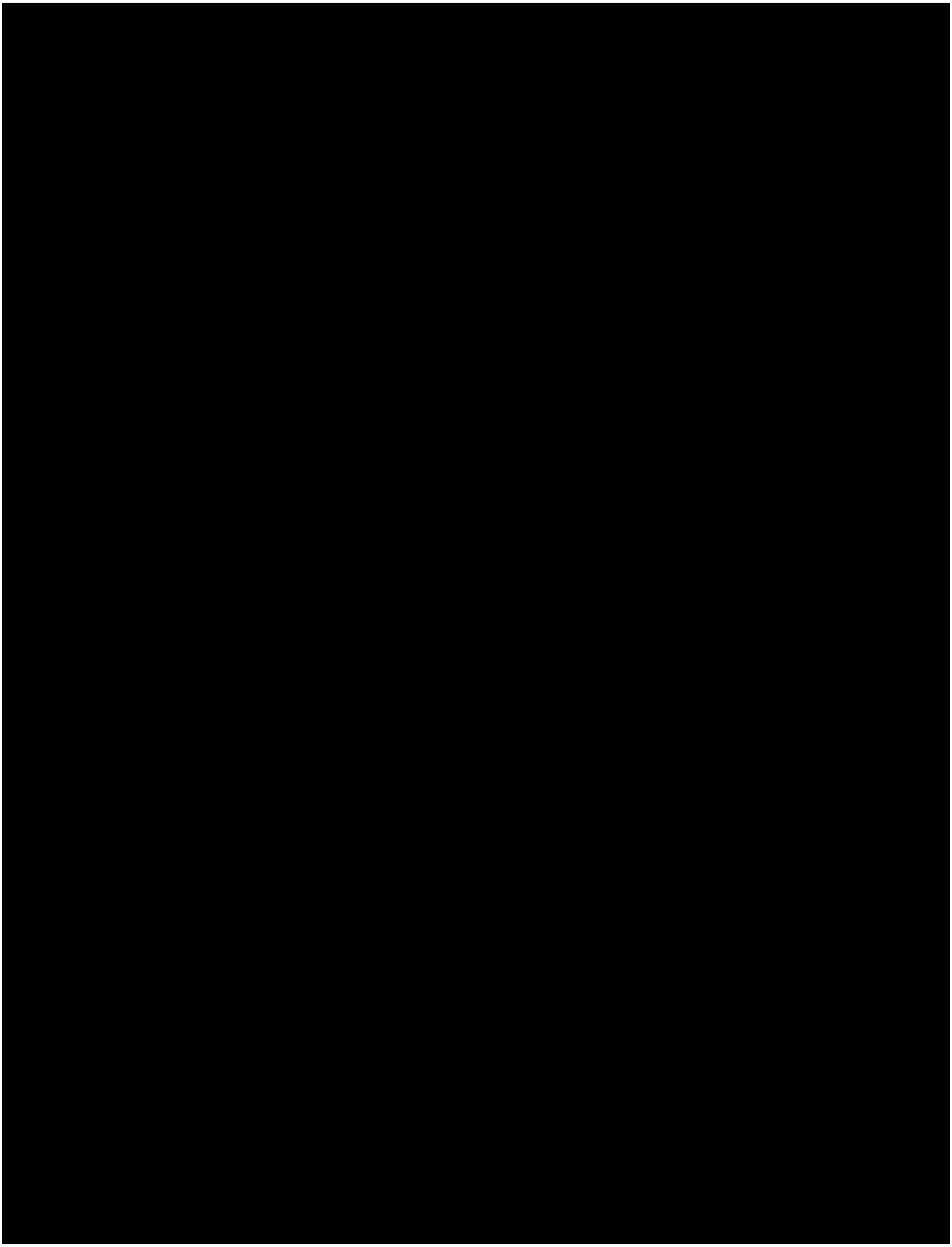


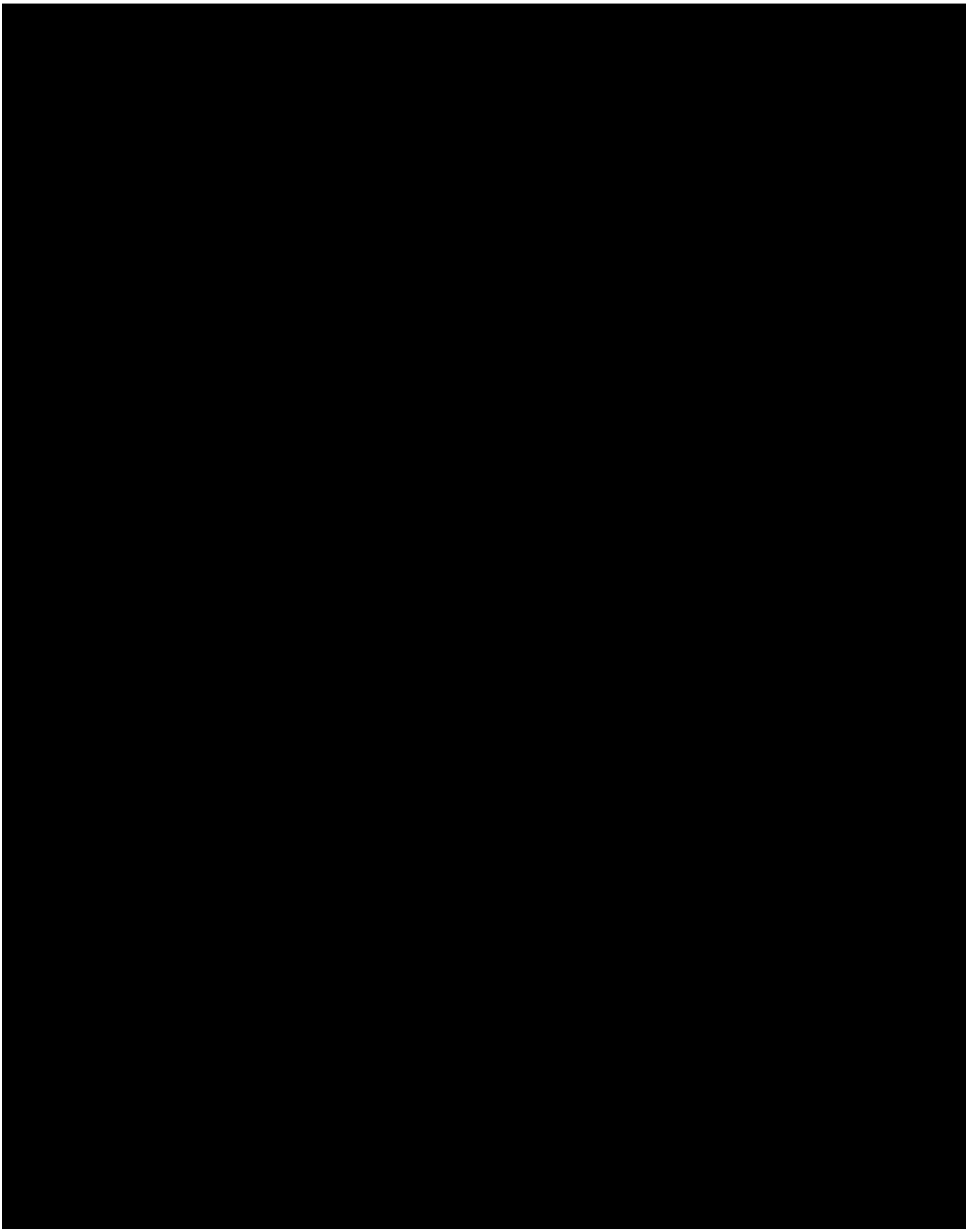


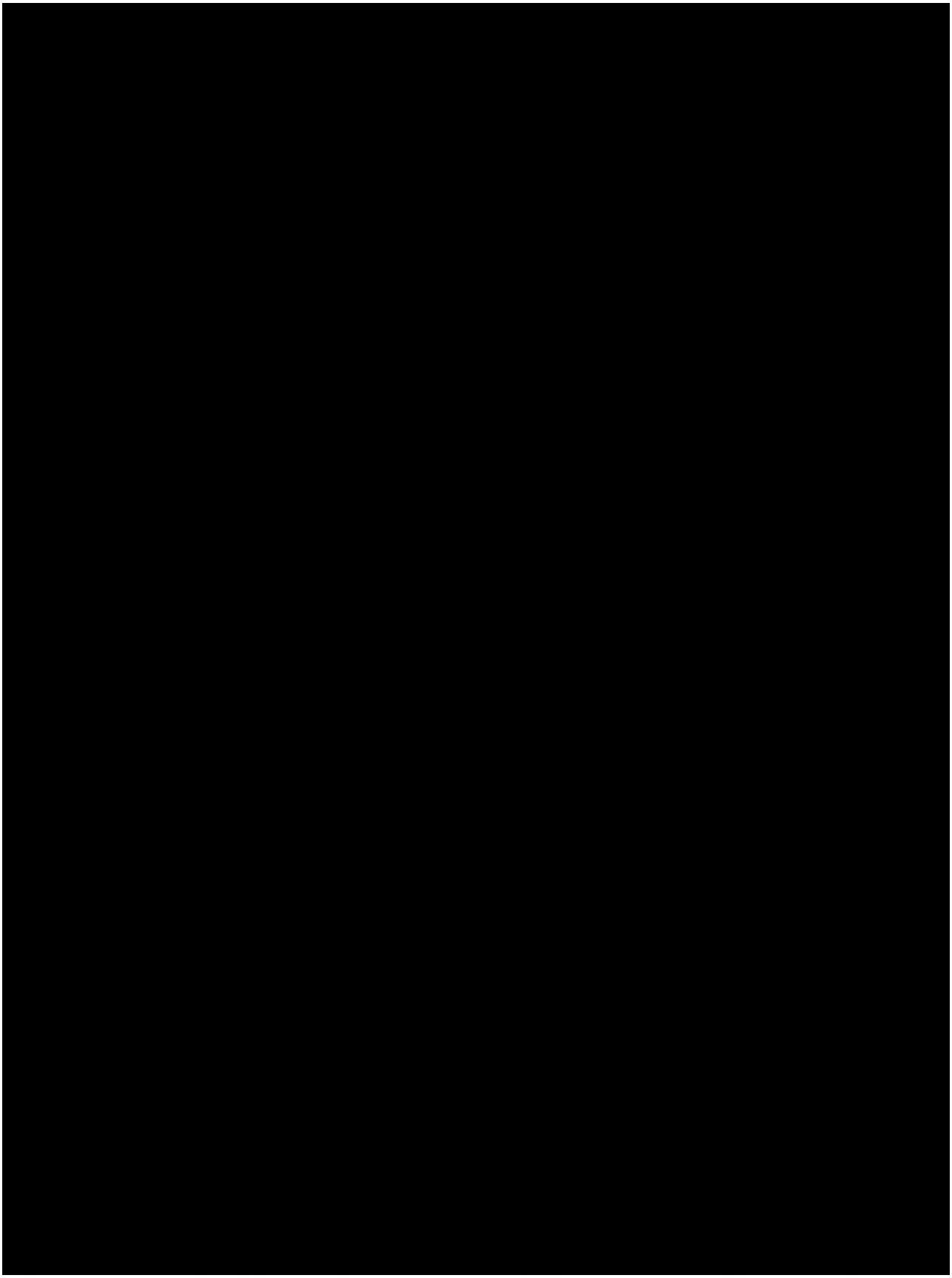


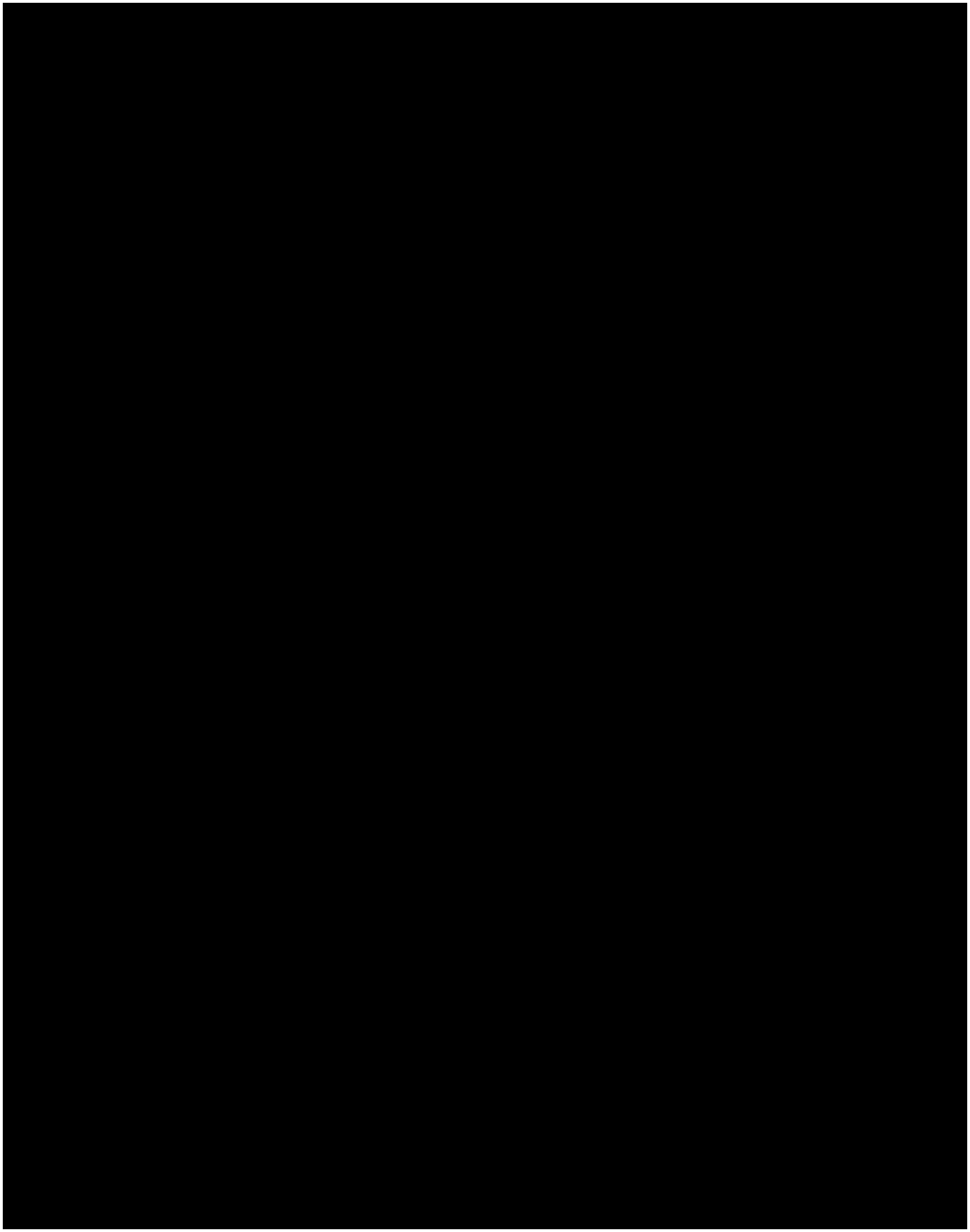


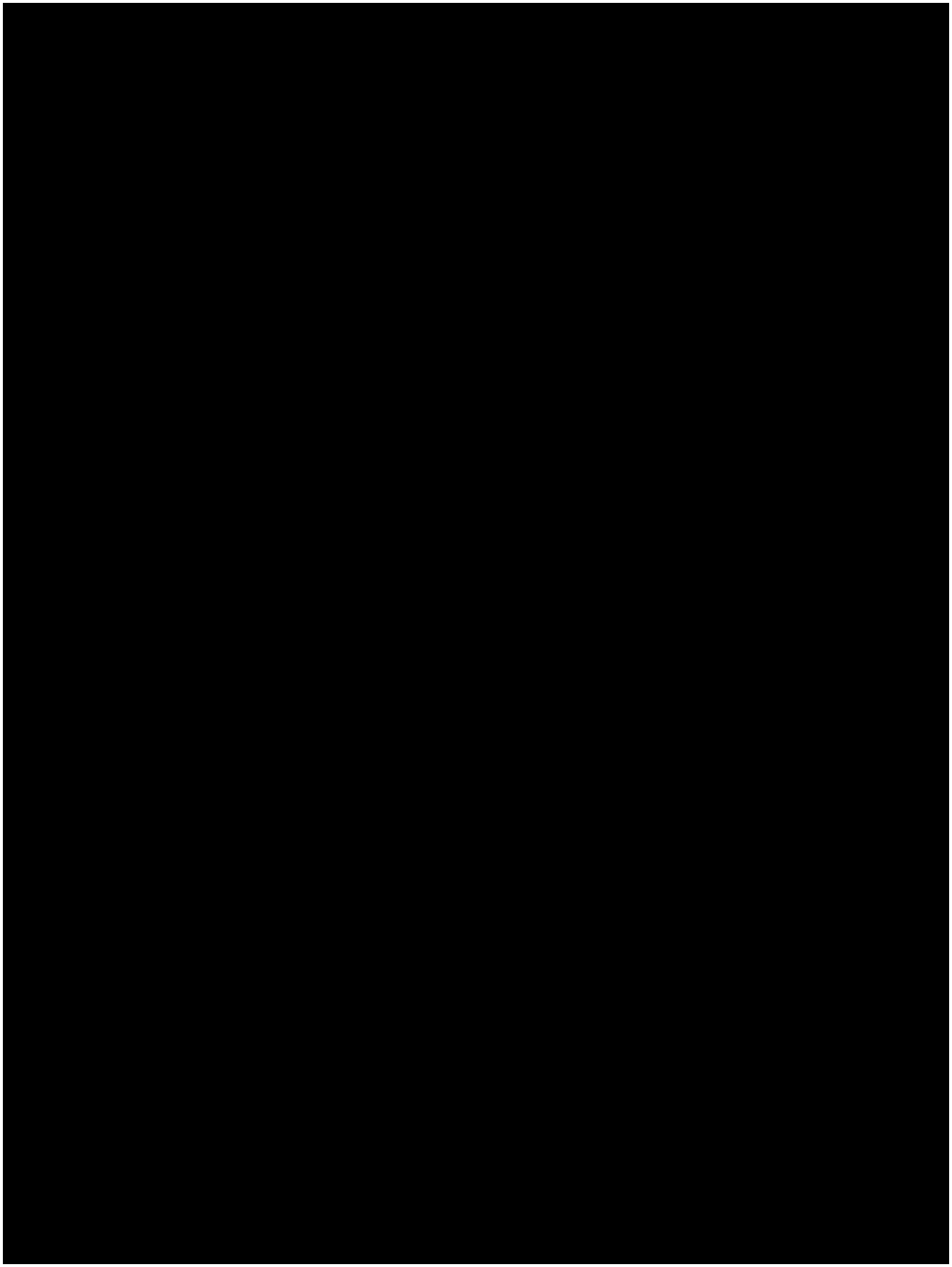


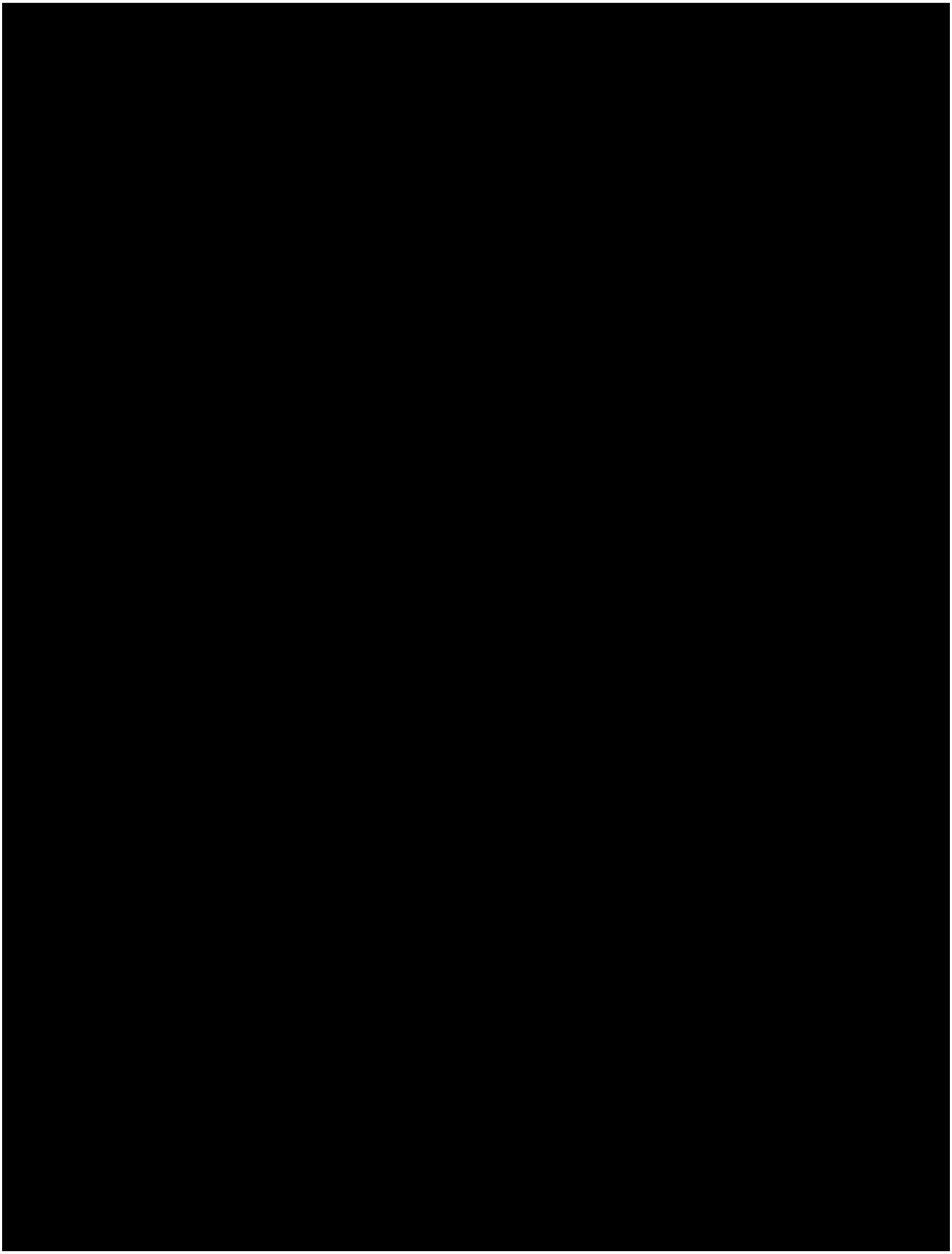


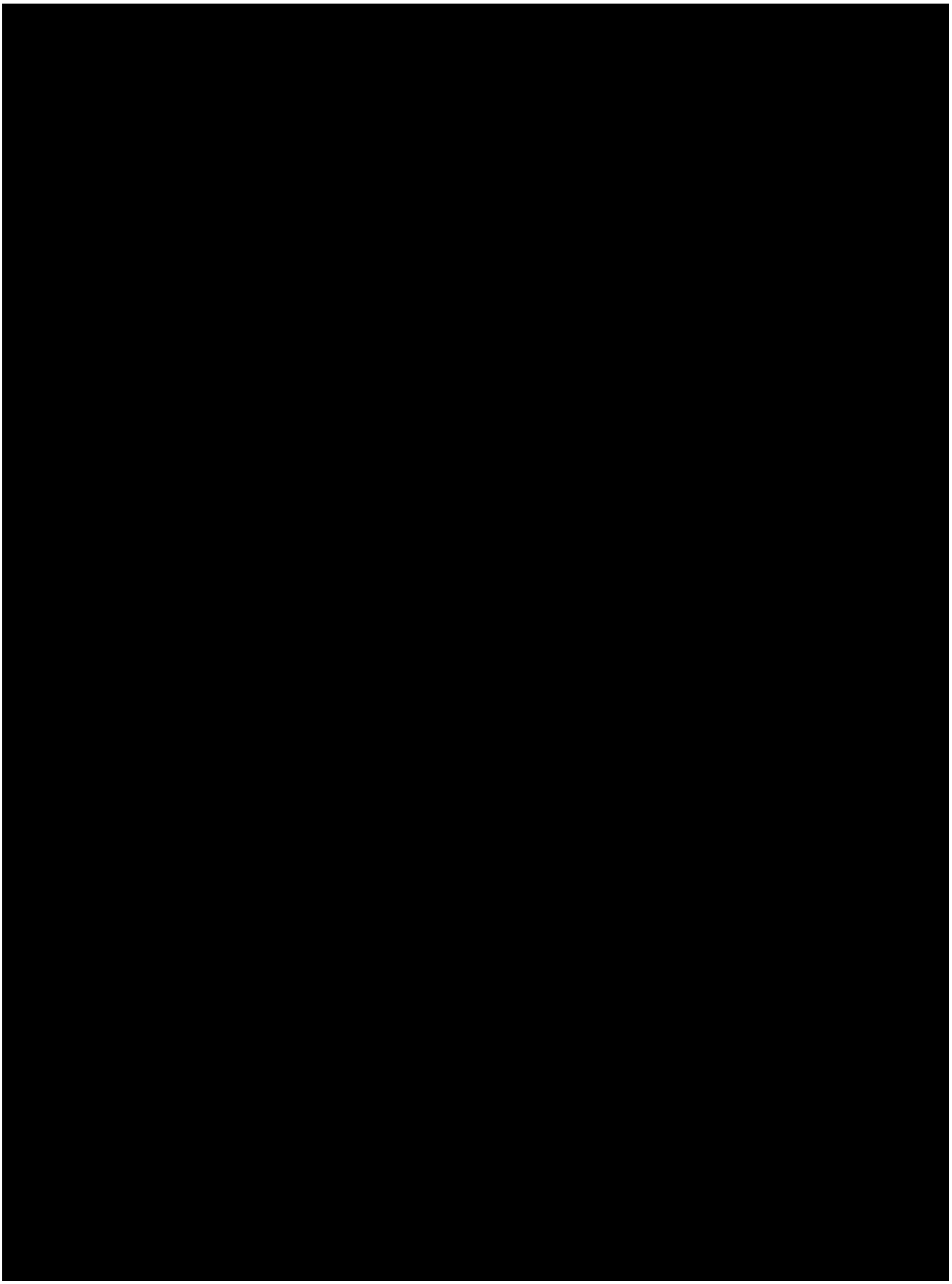


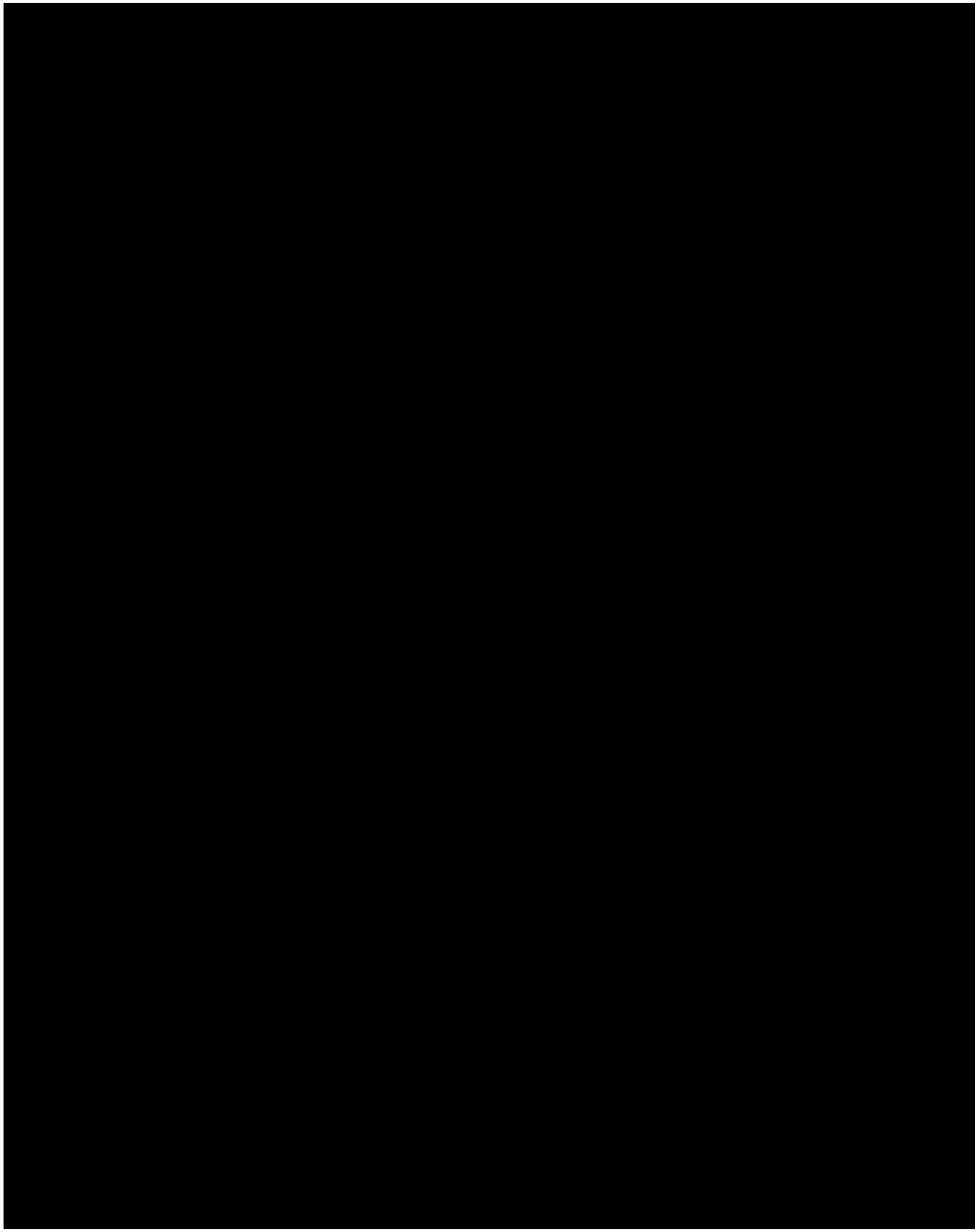


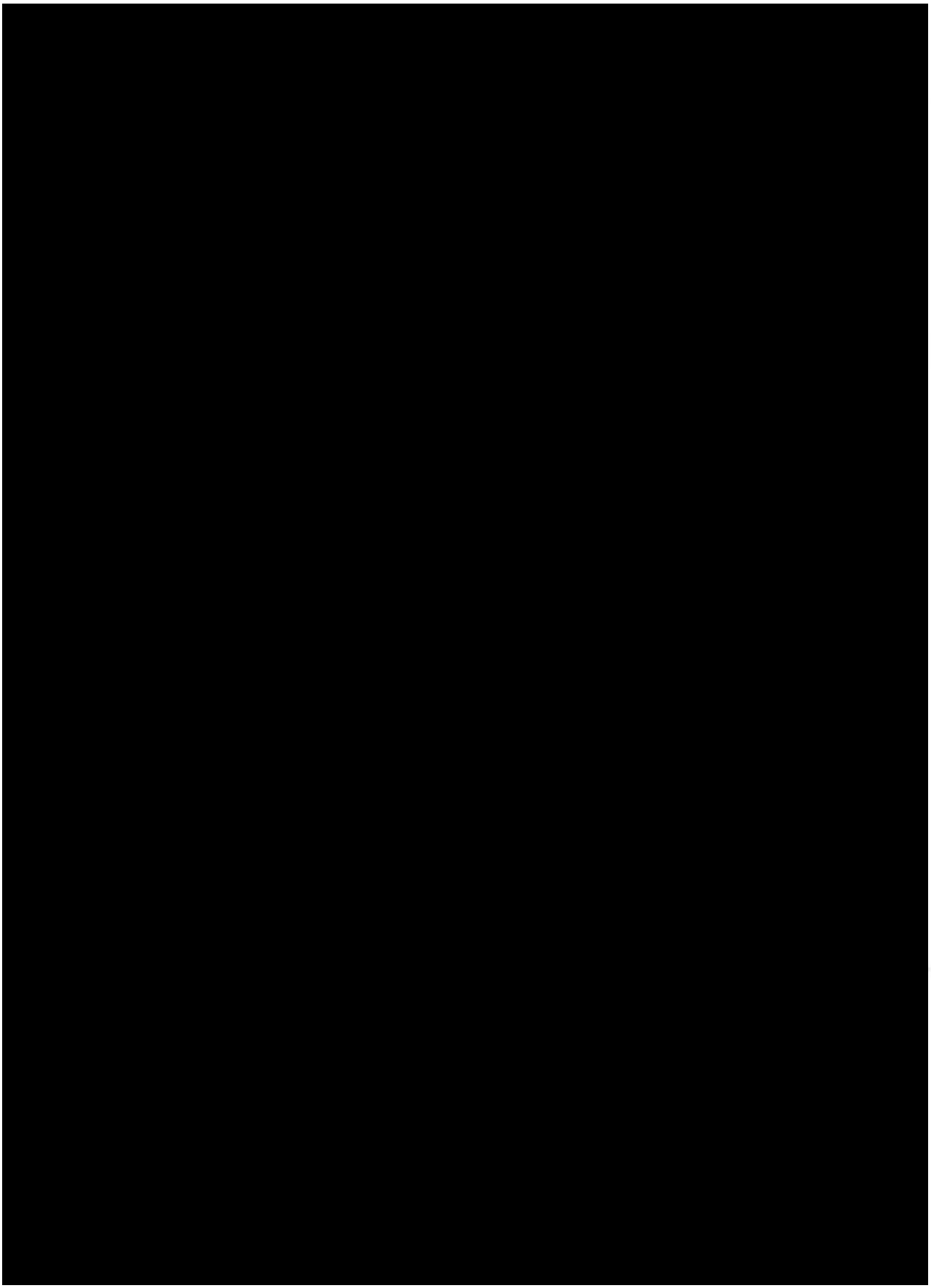


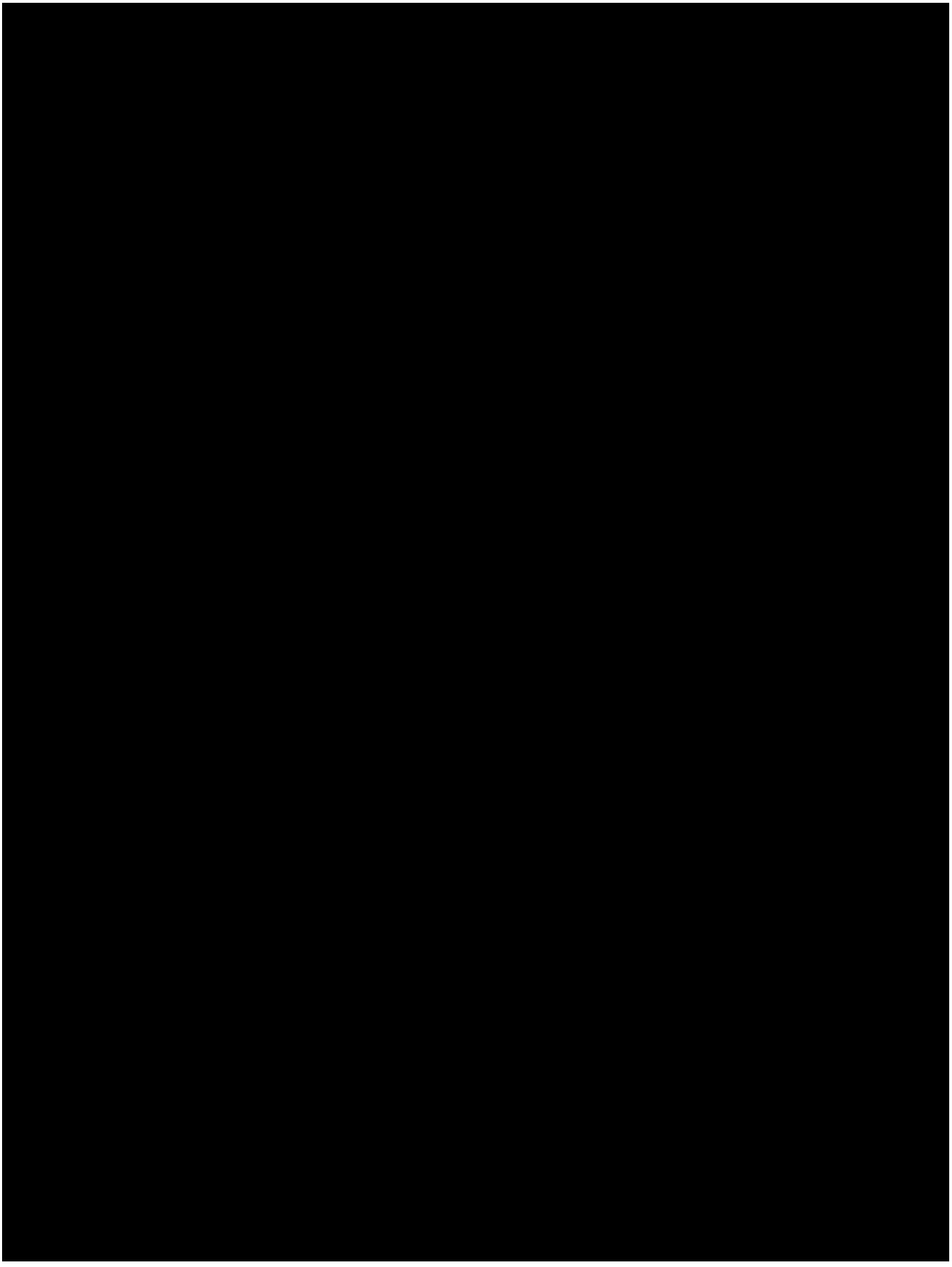


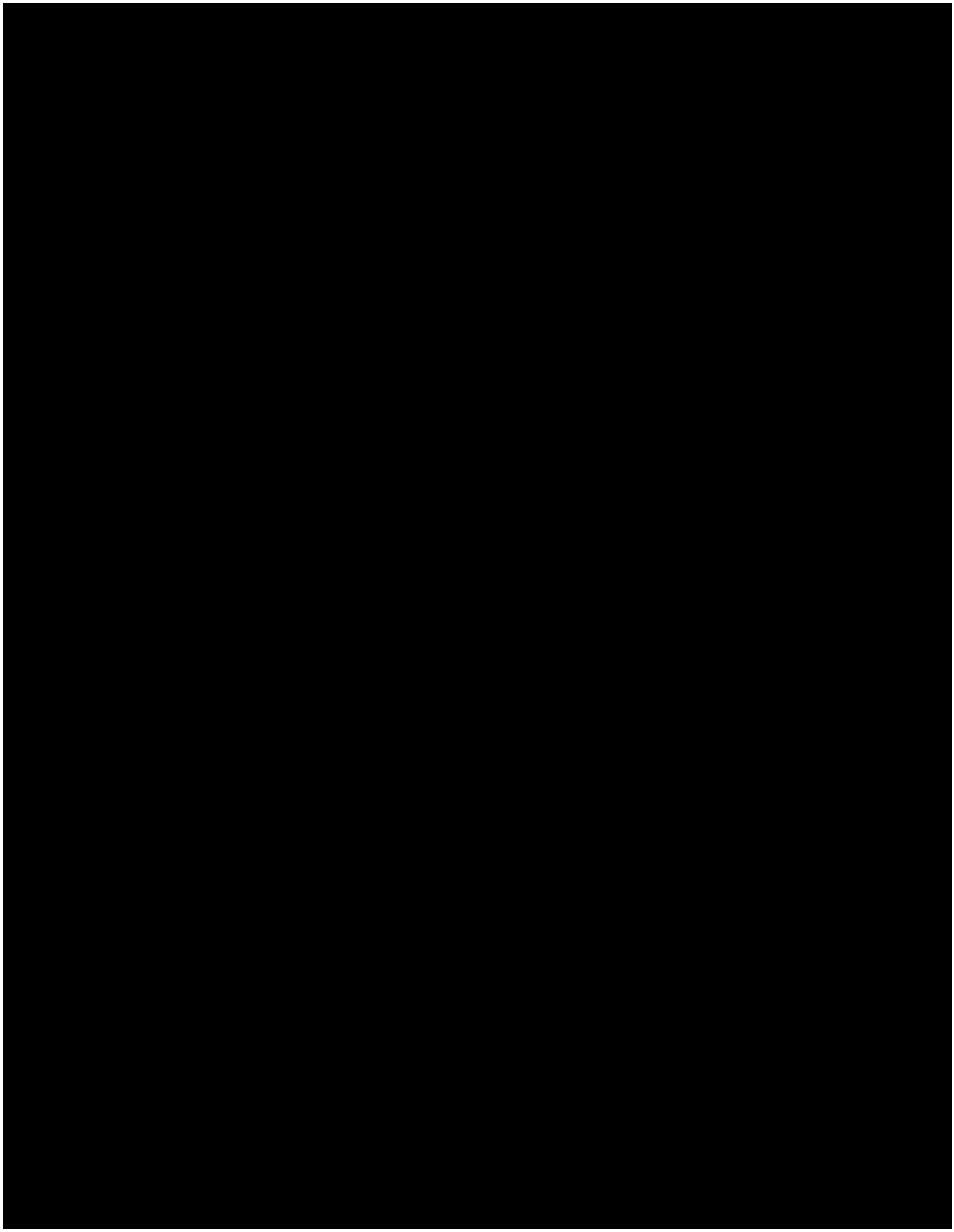


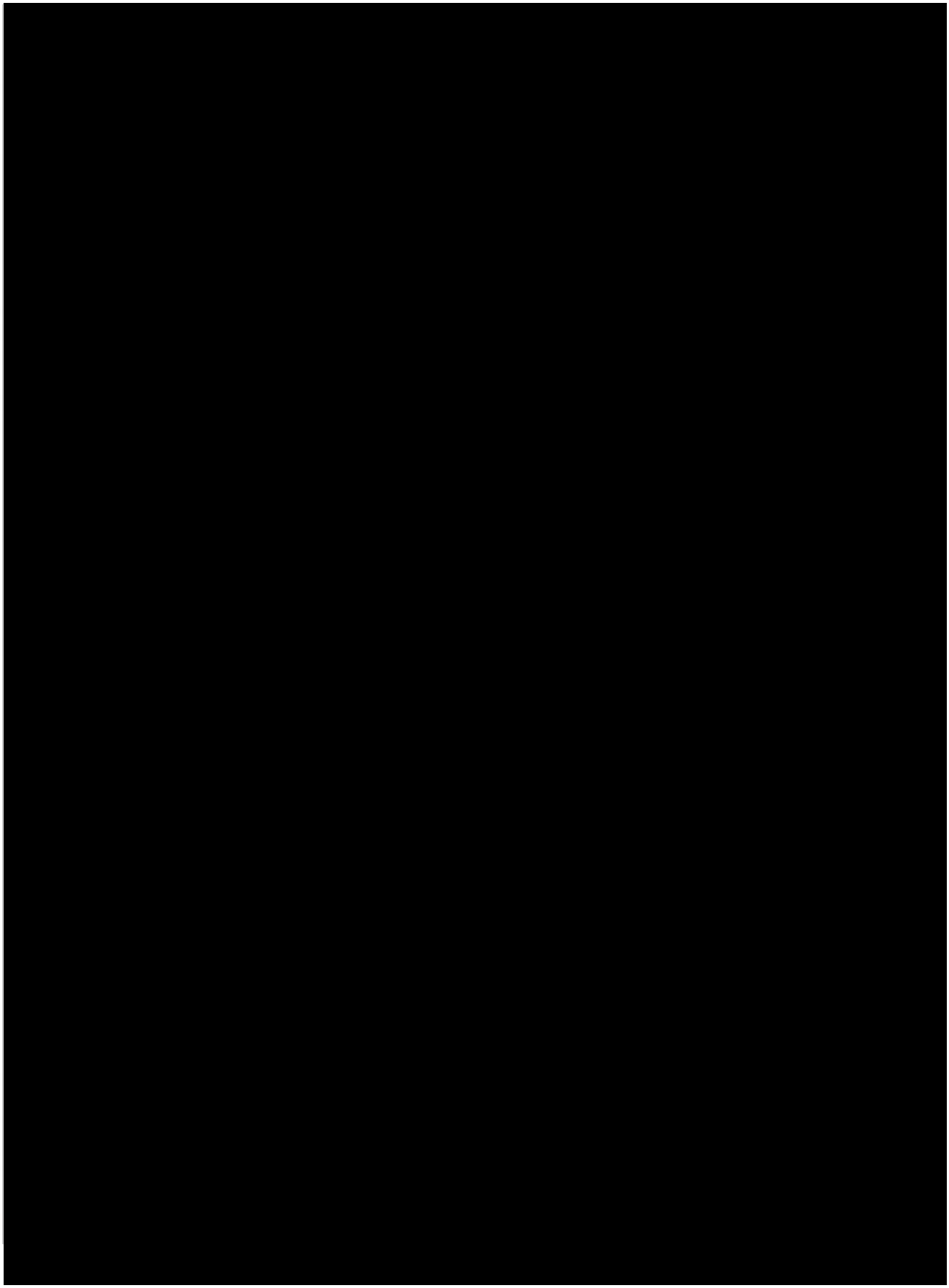


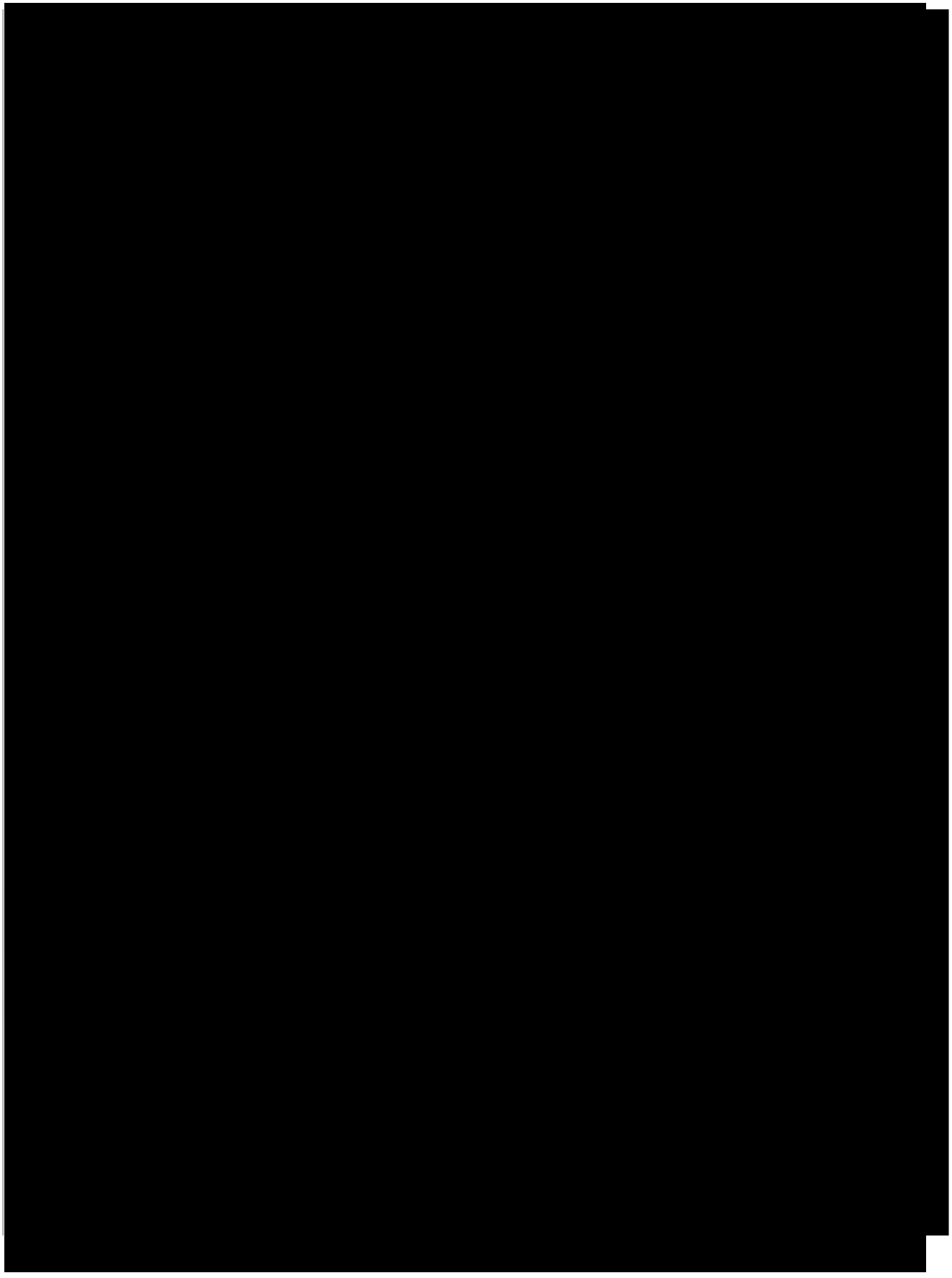


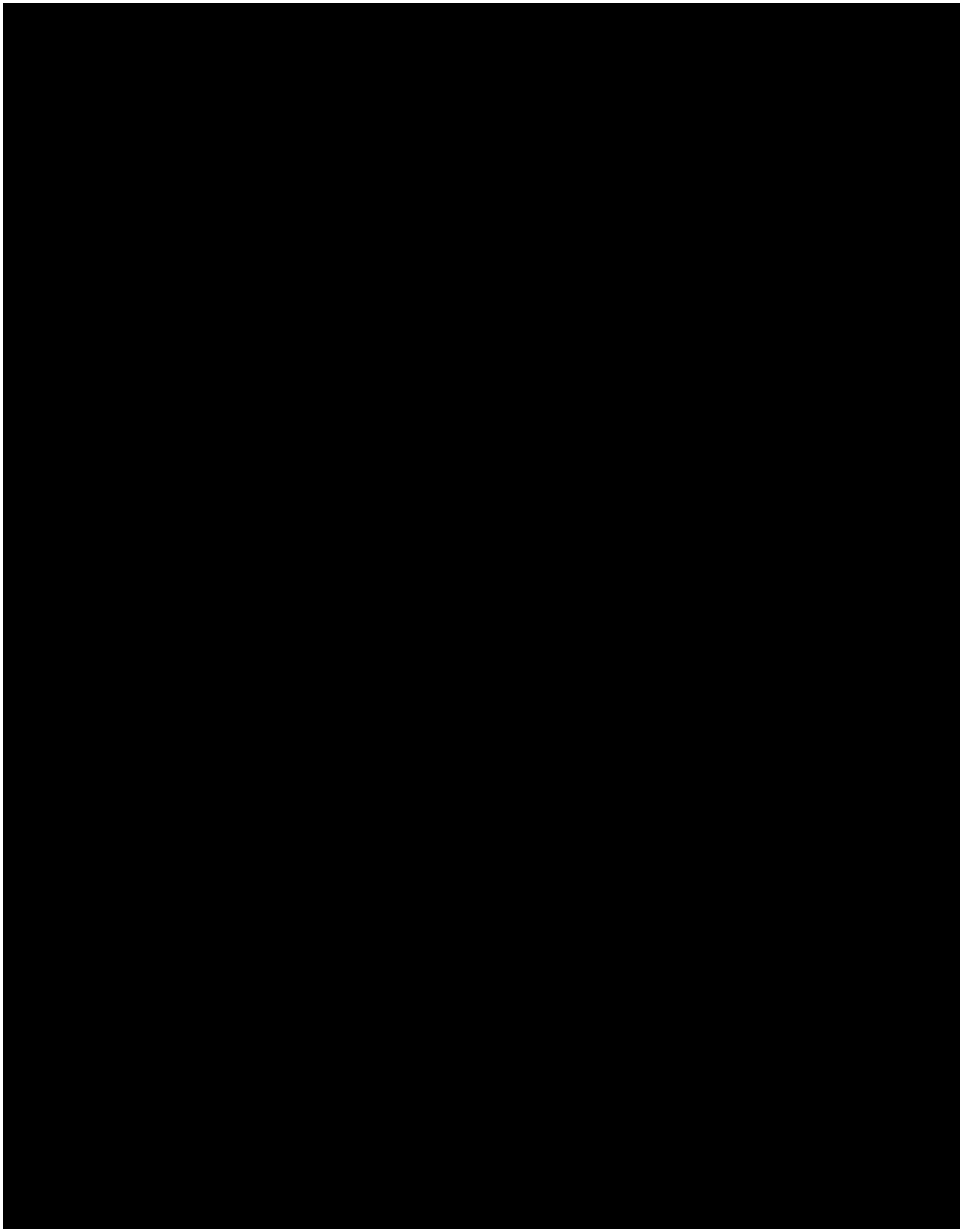


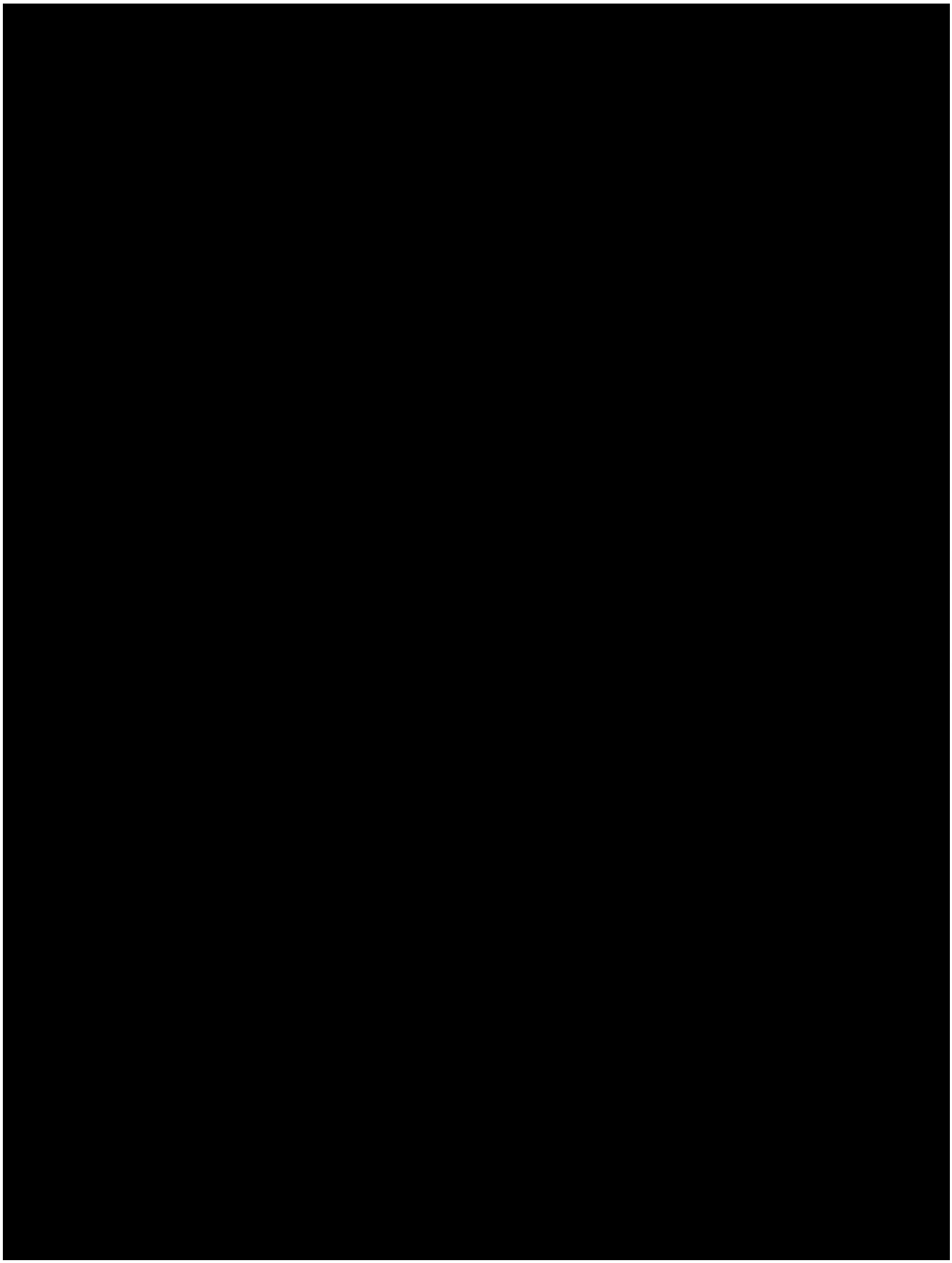


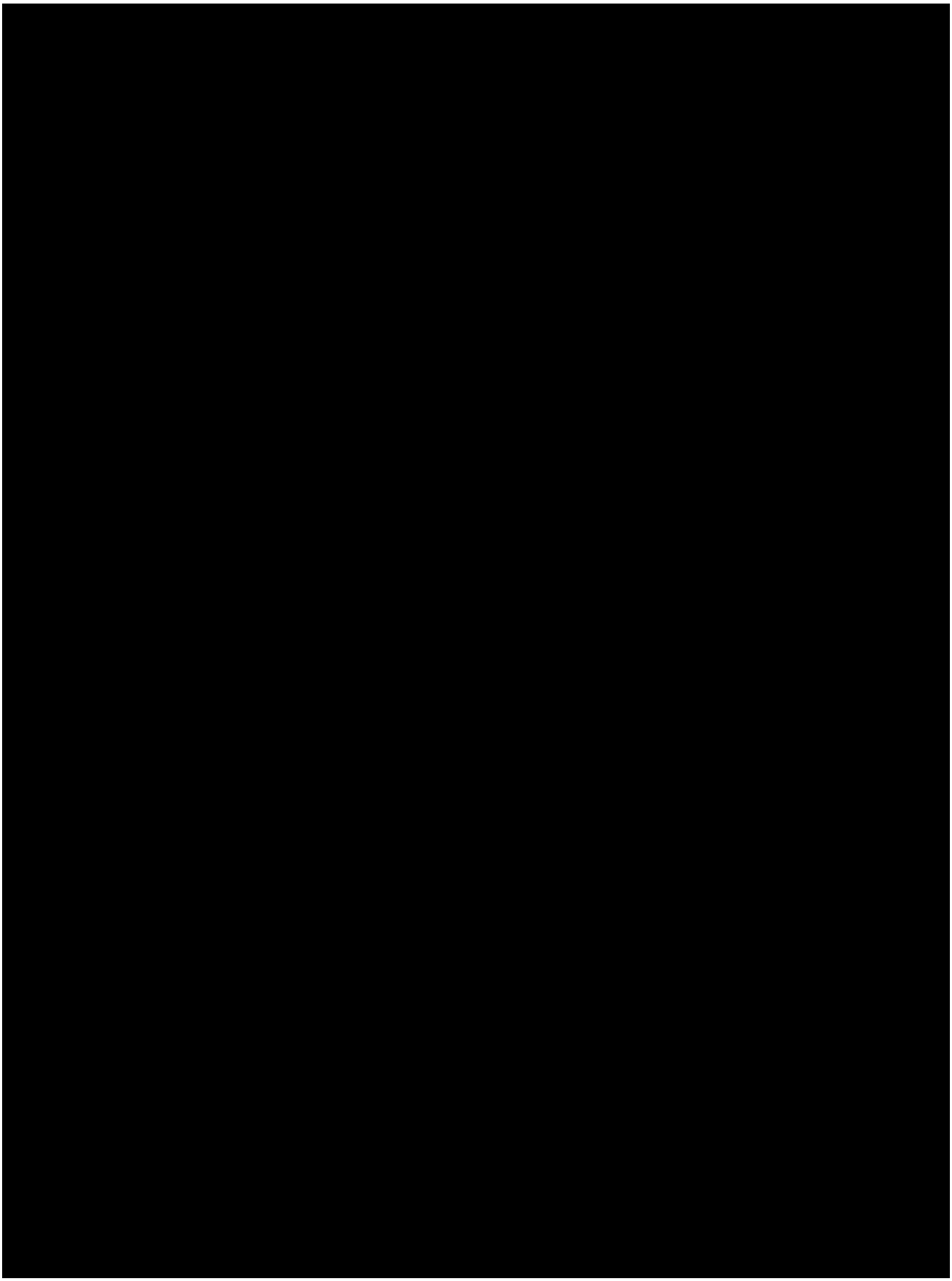


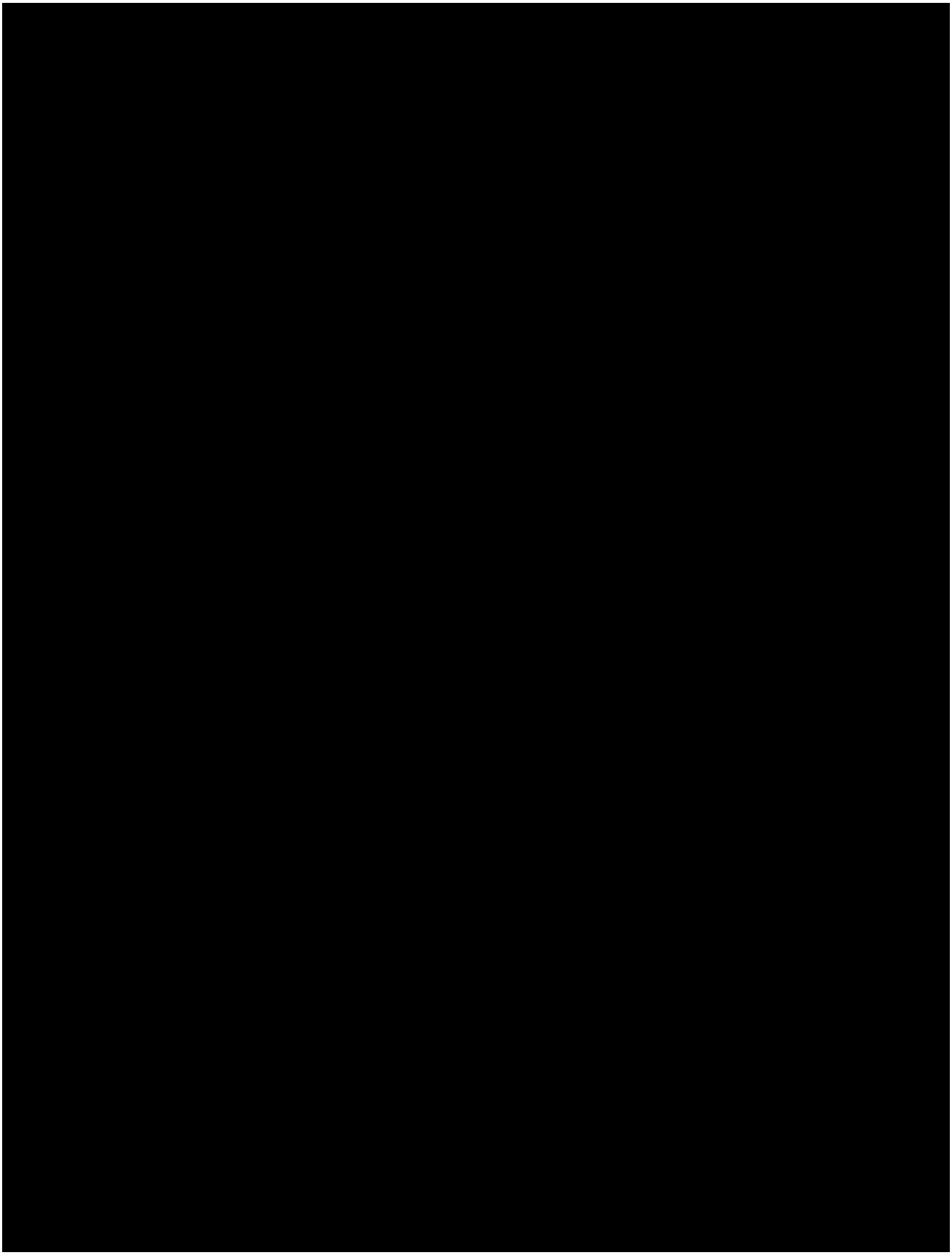








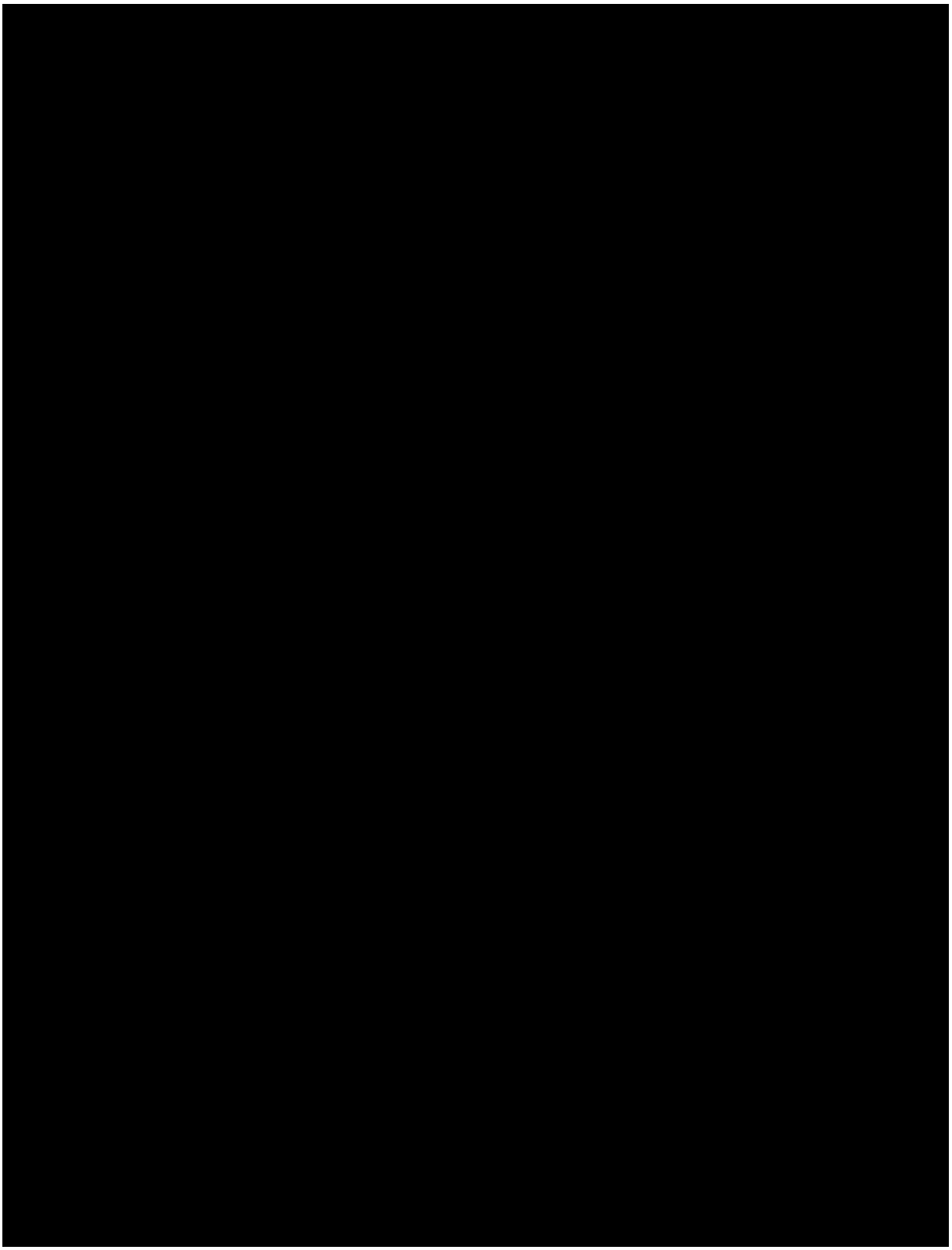


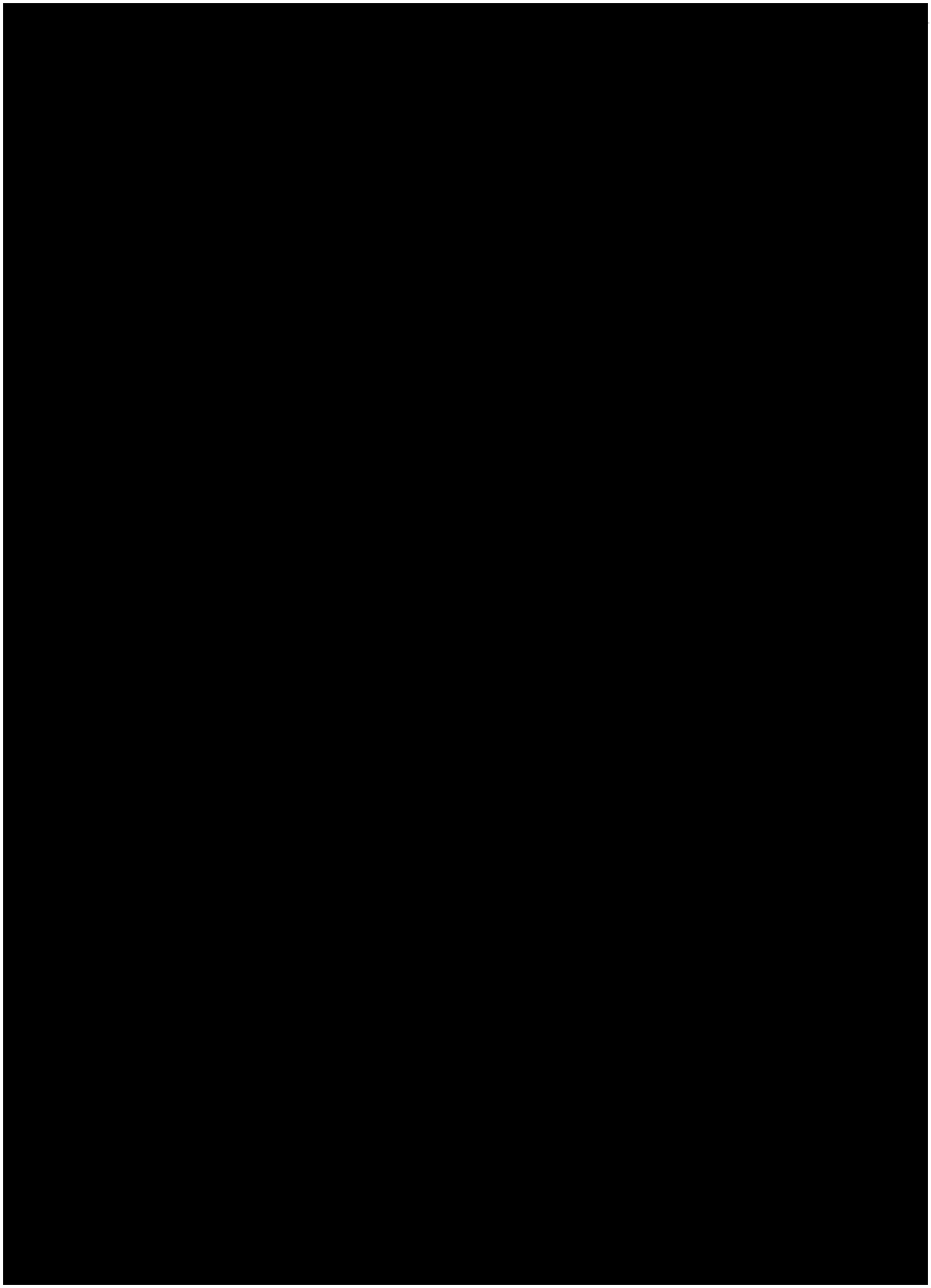


# APPENDIX 4. PERFORMANCE CRITERIA FOR BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3) DEVELOPMENTAL MILESTONES

| **Developmental Milestone** | [redacted] |
|---|---|
| Head Control – Gross Motor Subtest Item #4 | |
| Rolls from Back to Sides – Gross Motor Subtest Item #20 | |
| Sits Without Support – Gross Motor Subtest Item #26 | |
| Stands With Assistance - Gross Motor Subtest Item #33 | |
| Crawls – Gross Motor Subtest Item #34 | |
| Pulls to Stand – Gross Motor Subtest Item #35 | |
| Walks With Assistance – Gross Motor Subtest Item #37 | |
| Stands Alone – Gross Motor Subtest Item #40 | |
| Walks Alone – Gross Motor Subtest Item #43 | |

# APPENDIX 5. CHOP-INTEND





# APPENDIX 6. COMPOUND MOTOR ACTION POTENTIAL MANUAL

**Phase 3 Gene Transfer Clinical Study for Spinal Muscular Atrophy Type 1 Delivering AVXS-101**

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CMAP Manual
Compound Motor Action Potential (CMAP)

**Materials Needed for the Process**

- Carefusion Disposable Ring Electrode with Leads (order number 019-439300) (4 per visit)
- Carefusion Tab Electrodes 1.0 meter leads (order number 019-406600) (1 or 2 per visit)
- CMAP case report form
- Infrared temperature probe
- Electrode gel
- Warming packs or some other warming source
- Transpore adhesive tape
- Alcohol skin prep pads
- EMG machine

**Assessment of Normal Limb Temperature**

Since temperature can affect maximum CMAP amplitude, temperature > 33 degrees centigrade should be noted prior to preparation of skin for electrode placement. Temperature should be measured using a surface probe on the lateral aspect of the hand just proximal to the fifth digit. If temperature is ≤ 33 degrees centigrade, a warming pack or other warming mechanism should be used to warm the hand to > 33 degrees centigrade prior to collecting data. Limb temperature does not need to be reassessed during the procedure.

**Preparation of Skin**

The skin should be cleaned with alcohol (or equivalent) as needed to improve contact with the electrodes.

**EMG machine settings**

For both the ulnar and peroneal CMAP measures the filter settings should be 10 Hz to 10 kHz.

**Tibialis Anterior (TA) CMAP Electrode Placement**

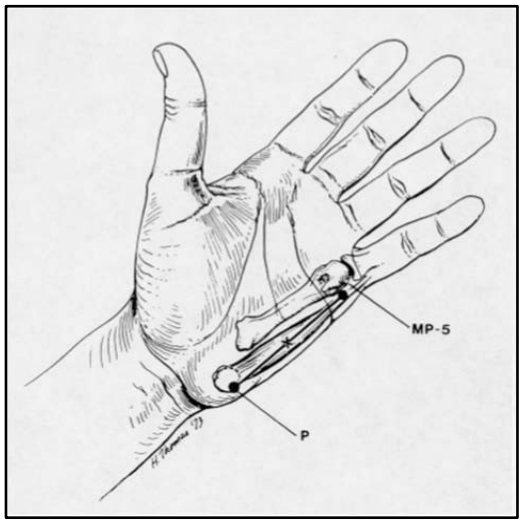
For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed on the patella. An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode. Tape should be placed over the electrodes to ensure they stay affixed during the procedure.

**Supramaximal nerve stimulation for TA CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at or proximal to the fibular head. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. Maximum CMAP amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

**Abductor Digiti Minimi (ADM) CMAP Electrode Placement**

Electrodes used for recording will be *Carefusion Disposable Ring Electrode with Leads (order number 019-439300)*. For ADM CMAP, these have a longitudinal contact area of up to 106 mm, but should be cut so that they cover the body of the ADM, with position orthogonal to muscle fiber orientation. The distance between the ulnar aspect of the pisaform bone (P) and the ulnar aspect of the fifth metacarpophalangeal joint (MP-5) should be measured. The G1 electrode should be placed distal to P, 1/3 of the distance between P and MP-5, as defined above. The G2 reference electrode should be placed on the ulnar aspect of the MP-5 joint. See figure below for landmarks:




Modified figure from "Anatomic Guide for the Electromyographer" Charles C. Thomas, Publisher, 1980, p4.

**Supramaximal nerve stimulation for CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at the distal forearm just proximal to the wrist. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. CMAP maximum amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

# APPENDIX 7. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving Human subjects.

6. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician

or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving Human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the

study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

# APPENDIX 8. SUMMARY OF CHANGES

The section below highlights content changes represented in this version of the protocol. Language deleted from Protocol version 1.0 appears in ~~red strike through~~. Language added to Protocol version 2.0 appears in **bold**.

The Amendment 1 version of the protocol (Protocol version 2.0) is updated to include cardiac enzyme monitoring (CK-MB) and to require a total of 15 patients meeting the intent-to-treat criteria to be enrolled.

## Section 2 Synopsis

Section was updated as per changes throughout the document; however one area reflects information that is not captured elsewhere in the document:

## Section 5.1 Background

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [5,6]. However, clinical studies employing several of these agents, most notably phenylbutyrate, **valproic** ~~valporic~~ acid, and hydroxyurea, have not resulted in clinical benefit [7,8]. FDA recently approved Nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some modest promise in improving motor function; however the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring. A single-dose IV administration study of AVXS-101 will provide information on the potential gene transfer has in treating SMA Type 1 patients, and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose study that will include up to **20** ~~15~~ Type 1 patients with **no functional *SMN1* gene as well as** 1 or 2 copies of *SMN2* **and who are < 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1)**. The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

Rationale for Change

Corrected typographical error in first paragraph. Second paragraph reflects revision in study design, which requires enrollment of 15 patients meeting the ITT criteria.

## Section 5.4 Clinical Studies

First-in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received **the low dose**

**used in this study (equivalent to a dose that doubled mouse lifespan in the SMNΔ ~~6X10$^{13}$ vg/kg~~7 Mouse potency assay)** and Cohort 2 (n = 12) received **the high dose used in this study (equivalent to a dose that restored mouse lifespan to greater than 200 days or "full life" in the SMNΔ7 Mouse potency assay). The dose received by Cohort 2 patients in AVXS-101-CL-101 ~~2.0 X 10$^{14}$ vg/kg~~** (proposed therapeutic dose) **has been demonstrated to be equivalent to the dose to be used in the AVXS-101-CL-303 study by direct testing using improved analytical methods.**

Rationale for Change

Removed references to doses measured by qPCR, for clarity, and provided further information as to the method by which it has been determined that the AVXS-101-CL-303 is equivalent to the phase 1 study cohort 2 dose.

[redacted]

Section 7.1 Overall Study Design

This is a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) **that will enroll up to twenty (20)** ~~in~~ patients with SMA Type 1**who may be either symptomatic or pre-symptomatic** with **no functional *SMN1* gene as well as** 1 or 2 copies of *SMN2* **and who are**~~. Fifteen (15) patients~~< 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). **Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101).**

**The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND-one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x 10$^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 30-day interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol**

**(AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.**

Rationale for Change

Comparability of the AVXS-101 GMP product to the AVXS-101 product utilized in the Phase 1 study (AVXS-101-CL-101) will be assessed by reviewing data from the first three patients, ensuring the clinical response is similar to what was observed in the previous study.

Section 7.2 Number of Patients

**Up to twenty (20) patients that meet the study entry criteria will be enrolled to enable enrollment of at least fifteen (15) patients that meet ITT criteria. Study enrollment will stop as soon as practical following enrollment of the fifteenth patient that meets the ITT criteria.**

~~A total of 15 patients will be enrolled.~~

Rationale for Change

Protocol revisions reflect alignment with agency request for analysis of at least 15 patients meeting the intent-to-treat population criteria.

Section 8.1 Patient Inclusion Criteria

Inclusion criteria have been re-numbered to accommodate inclusion of an additional criterion.

**Criterion #2: The first thee patients enrolled must meet the criteria for the Intent-To-Treat population**

Rationale for Change

The Intent-to-Treat Population matches the patient population enrolled in Cohort 2 of the Phase 1 study (AVXS-101-CL-101). Ensuring the first three patients enrolled match these criteria will ensure appropriate assessment of the expected efficacy, based on Chop-Intend improvements.

Section 9.1 Description of Product

**Table 5: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name:** | AVXS-101 |
| **Dosage Form:** | **Equivalent to the dose received by the second dosing cohort in the Phase 1 study** |
| **Unit Dose** | **1.1 X $10^{14}$ vg/kg;** Equivalent to the dose received by **Cohort 1** ~~the second dosing cohort~~ in the Phase 1 study **(AVXS-101-CL-101) as determined by direct product testing with improved analytical methods.** |
| **Route of Administration** | Intravenous infusion |
| **Physical Description** | AVXS-101 is a clear, colorless liquid. |

Rationale for Change

The unit dose was updated to reflect the AVXS-101 dose determined through ddPCR with AveXis GMP product.

Section 10.2 Study Product Dose and Dose Justification

Patients will receive a one-time dose of AVXS-101 **at 1.1 X $10^{14}$ vg/kg,** equivalent to the dose received by **Cohort 2** ~~the second dosing cohort~~ in the Phase 1 study via IV infusion administered in the ongoing Phase 1 clinical study (AVXS-101-CL-101).

Two doses ~~(2.0 x $10^{14}$ vg/kg and 6.7 x $10^{13}$ vg/kg)~~ are being studied in the ongoing Phase 1 clinical study (AVXS-101-CL-101); the higher dose (**dose received by the Cohort 2 patients** ~~2.0 x $10^{14}$ vg/kg~~) was chosen for the present study as preliminary data demonstrated both a dose response and significant clinical benefit thus identifying **it** ~~2.0 x $10^{14}$ vg/kg~~ as the **proposed therapeutic dose. In the Phase 1 study, AVXS-101 demonstrated a dose response, with efficacy greater as observed by motor milestone achievement and CHOP-INTEND scores at the higher dose (received by Cohort 2) than the lower dose (received by Cohort 1). Direct testing of the actual lot of Investigational Medicinal Product (IMP) used in the AVXS-101-CL-101 study by an improved and more fully qualified analytical method has assigned a value of 1.1 x $10^{14}$ vg/kg to the actual dose received by Cohort 2 in this Phase 1 study. The same method has been used to establish an equivalent dose for the Phase 3 IMP. This vg/kg value has been further verified in an improved and more fully qualified SMNΔ7 Mouse Biopotency assay to support a similar extension of mouse life time in direct comparative assessment between the Phase 1 and Phase 3 IMP** ~~minimum dose that is clinically effective~~.

Rationale for Change

The dose was updated to reflect the AVXS-101 dose determined through ddPCR with AveXis GMP product. Language was added to clarify that the higher dose studied in the Phase 1 AVXS-101-CL-101 is considered the therapeutic dose, and to explain the reason the dose used in this study has a different numerical value. The dose used in the AVXS-101-CL-101 study was measured by qPCR; the AveXis GMP AVXS-101 is measured by ddPCR.

Section 12.1.10 Laboratory Assessments

**Table 6: Total Blood Volume**

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Screening | Hematology, chemistry/**CK-MB**, virus serology, ~~capillary blood gas,~~, immunology sample (AAV9 Ab only), diagnostic confirmation sample | 16.9~~6~~ |
| Day –1 | Hematology, chemistry, capillary blood gas | 3.3 |
| ~~Day –1~~ | ~~Capillary blood gas~~ | ~~1~~ |
| Day 2 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 7 | Hematology, chemistry/**CK-MB**, immunology sample **(ELISA/ELISpot)** | 7.6-9.6~~6.3-8.3~~[b] |

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Day 14 | Hematology, chemistry, immunology sample **(AAV9 Ab/SMN only)** | 3.3~~6.3-8.3~~[b] |
| Day 21 | Hematology, chemistry, immunology sample **(AAV9 Ab/SMN only)** | 3.3~~6.3-8.3~~[b] |
| Day 30 | Hematology, chemistry/**CK-MB**, immunology sample **(ELISA/ELISpot)** | 7.6-9.6~~6.3-8.3~~[b] |
| **Day 60** | **Hematology, chemistry/CK-MB** | **3.6** |
| **Month 3/4/5/7/8/10/11/ 13/14/16/17** | **Hematology, chemistry** | **25.3** |
| **Month 6/9/12/15** ~~Monthly~~ | Hematology, chemistry/**CK-MB** | 14.4~~36.8~~ |
| End of Study/ET | Hematology, chemistry/**CK-MB** | 3.6~~2.3~~ |
| | **Maximum Total Volume for Study**[a] | **96.2**~~96.5~~ |

ET = early termination

[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits, provided T-cell responses are not elevated at Day 30 requiring additional surveillance samples and virus serology is not positive at screening requiring additional testing

[b] Immunology sample **for IFN-γ ELISpots** requires 4-6 mL whole blood. **Immunology sample for ELISA requires 1 mL whole blood. When drawn at the same visit, 4-6 mL is sufficient for both assays.**

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

5. Safety labs
    a. **Chemistry**
    b. **Hematology**
    c. **CK-MB**
6. Interferon gamma (IFN-γ) ELISpots to detect T-cell responses
7. Serum antibody to AAV9 and SMN
8. Genetic reconfirmation testing

Rationale for Change

Additional cardiac enzyme monitoring was added to the schedule of assessments; to accommodate these additional blood samples, the capillary blood gas and IFN-γ ELISpot collect schedules were reduced to comply with maximum total blood volume allowances. Additionally, further detail was added to the laboratory sample prioritization schedule.

Section 12.1.10.2 Blood Chemistry

**Creatine kinase (CK-MB) will be collected at Screening, Day 7, Day 30, Day 60, every 90 days, and at End of Study.**

Rational for Change

Additional cardiac enzyme monitoring was added to ensure patient safety. Recent toxicology studies performed in mice affected with SMA Type 1 demonstrated microscopic degeneration/generation of tissues in the heart.

Section 12.1.10.5 Capillary Blood Gas

Capillary blood gas will be completed locally at ~~screening~~ Day –1~~, pre-dose on Day 1,~~ and Day 2 (). A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

Rationale for Change

Additional cardiac enzyme monitoring was added to the schedule of assessments; to accommodate these additional blood samples, the capillary blood gas and IFN-γ ELISpot collect schedules were reduced to comply with maximum total blood volume allowances.

Section 12.1.10.6 Immunology Testing (ELISA and IFN-γ ELISpots)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA), and to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN. Blood samples will be collected at screening (ELISA anti-AAV9 only), Day 7, Day 14 **(ELISA anti-AAV9/SMN only)**, Day 21 **(ELISA anti-AAV9/SMN only)**, and Day 30 (). Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.

Rationale for Change

Additional cardiac enzyme monitoring was added to the schedule of assessments; to accommodate these additional blood samples, the capillary blood gas and IFN-γ ELISpot collect schedules were reduced to comply with maximum total blood volume allowances.

[redacted]

Section 14.1.2.1 Intent-to-Treat Population

The ITT population will consist of symptomatic patients with bi-allelic deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at less than 180 days of age. ~~All primary and secondary efficacy analyses and subgroup analyses will be conducted on the ITT population.~~ **The first three patients enrolled must meet the criteria for the Intent-to-Treat Population.**

Rationale for Change

The Intent-to-Treat Population matches the patient population enrolled in Cohort 2 of the Phase 1 study (AVXS-101-CL-101). Ensuring the first three patients enrolled match these criteria will ensure appropriate assessment of the expected efficacy, based on CHOP-INTEND improvements.

Section 14.2 Sample Size Calculation

**This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within the Statistical Analysis Plan.**

~~The current study will enroll 15 patients. Only those patients with baseline symptoms, bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C), ITT population will be assessed for the primary and secondary efficacy analyses. The study power is based upon efficacy analysis of the ITT population.~~

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age study visit. With the assumption for the true response rate of AVXS-101 **for the primary endpoint** being in the range of 30% - 40%, a sample size of 15 patients **that meet ITT criteria will be enrolled and** ~~(~~assuming **approximately** 30% of patients ~~do not qualify for the ITT population or~~ are ~~otherwise~~ excluded from ~~the~~ analysis**, would yield an ITT population that**~~)~~ would provide power of > 90% to detect a significant difference **from 0.1%** with α = 0.**025**~~05~~ using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion of patients surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, **an enrolled** ~~a~~ sample size of 15 patients **that meet ITT criteria** (assuming 30% of patients ~~do not qualify for the ITT or~~ are ~~otherwise~~ excluded from the analysis) would **yield an ITT population that would** provide power of > 80% to detect a significant difference **from the historical control** with α = 0.05 using a ~~two sample~~ 2-sided Fisher's **Exact** test, comparing to the 26 age and gender matched patients from a published natural history observational study performed at 3 large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

Rationale for Change

The Intent-to-Treat Population matches the patient population enrolled in Cohort 2 of the Phase 1 study (AVXS-101-CL-101). Ensuring the first three patients enrolled match these criteria will ensure appropriate assessment of the expected efficacy, based on CHOP-INTEND improvements. The change in alpha for the exact binomial test is due to agreement with the agency that a 1-sided test for bionomial proportion should be utilized with an alpha = 0.025.

Section 14.3.2 Primary and Secondary Efficacy Analysis

Primary and secondary efficacy analyses will be based on the ITT population, those patients **that are symptomatic** with bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 to the results from natural observation study (PNCR) [21].

The first co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion surviving at 14 months of age.

Primary efficacy endpoints will be examined on **the** ITT population. Testing for the first co-primary endpoint, functional independent sitting will first be performed using 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at p<0.**025**~~05~~, will the co-primary endpoint survival improvement be tested using 2-sided Fisher's Exact test on **the** ITT population, comparing to matched patients from natural observational study (PNCR). This hierarchy approach strongly protects the Type I error rate.

Rationale for Change

Correction to the definition for the intent-to-treat population; clarification that this must include patients that are symptomatic at baseline.

Section 14.4 CHOP-INTEND Comparison

**A comparison will be performed of the first three patients CHOP-INTEND scores to the AVXS-101-CL-101 CHOP-INTEND scores. The first three patients enrolled must meet the criteria for the Intent-to-Treat (ITT) Population. AveXis will compare the CHOP-INTEND one month improvement for the AVXS-101-CL-303 patients that meet the ITT criteria to assess the clinical response to the dose 1.1 x $10^{14}$ vg/kg as being what was expected from the Cohort 2 patients in the Phase 1 trial (AVXS-101-CL-101). This comparison will be performed as a per patient assessment for the first three patients. The individual patients who receive their gene therapy at 0-3 months of age will be compared to a value of 10 CI points, while patients who receive their gene therapy at >3 but <6 months of age will be compared to a value of 5 CI points. Furthermore, patients from either age group are expected to maintain the improvement in the absence of an acute illness or perioperatively. If the expected CI improvements are observed for the first three ITT patients, AveXis will remove the 30-day interval between patients and proceed to dose at least 12 additional patients that meet the ITT criteria and perform safety and efficacy assessments as described elsewhere in the clinical protocol (AVXS-101-CL-303) and corresponding Statistical Analysis Plan. If the expected CI improvements are not observed for the first three ITT patients, AveXis will discuss next steps with the FDA before continuing study enrollment.**

Rationale for Change

Language added because this comparison is now planned.

## Appendix 1 Schedule of Assessments

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | | |
| Echocardiogram | X | | | | | | | | | X[j] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| **CK-MB** | **X** | | | | | **X** | | | **X** | **X[r]** | **X** |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | ~~X~~ | X | ~~X~~ | X | | | | | | | |
| ELISA anti-AAV9/**SMN** Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (~~ELISA anti-SMN Ab and~~ ELISpot) | | | | | | X | ~~X~~ | ~~X~~ | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed every 6 months, starting at Month 6.
[k] Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day -1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
[r] **CK-MB to be performed at Day 60, and every 90 days (Month 6, 9, 12 months of age, 15 months of age, 18 months of age/EOT).**

## Rationale for Change

Additional cardiac enzyme monitoring was added to the schedule of assessments; to accommodate these additional blood samples, the capillary blood gas and IFN-γ ELISpot collect schedules were reduced to comply with maximum total blood volume allowances. Additionally, further detail was added to the laboratory sample prioritization schedule.

# AVXS-101

# AVXS-101-CL-303

| | |
|---|---|
| **IND Number:** | 15699 |
| **Protocol Title:** | Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion |
| **Indication Studied:** | Spinal Muscular Atrophy Type 1 |
| **Sponsor Address:** | AveXis, Inc.<br>2275 Half Day Road<br>Bannockburn, IL 60015 |
| **Protocol Version/Date:** | 1.0/ 29 Mar 2017 |

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

## Confidentiality Statement

# 1. ADMINISTRATIVE INFORMATION

## 1.1. Approval

**REPRESENTATIVES FROM AveXis:**

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization and the Harmonized Tripartite Guideline for Good Clinical Practice E6
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

**SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):**

[redacted]
Vice President Clinical Development and Medical Affairs
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Chief Medical Officer
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Senior Vice President, Chief Regulatory and Quality Officer
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Sr. Director, Head of Clinical Operations
AveXis, Inc.

Date (ddMmmyyyy)

[redacted]
Biostatistician
AveXis, Inc.

Date (ddMmmyyyy)

## 1.2. Investigator's Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-CL-303 protocol and agree to conduct the study in accordance with the relevant current protocol(s). I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of study participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Informed Consent 21 CFR Part 56, Institutional Review Board Review in 21 CRF Part 56, Adverse Event Reporting as defined in Section 13.4 and in 21 CFR 312.64, Adequate/accurate and accessible records in accordance with 21CFR 312.62 and 312.68.
- Terms outlined in the study site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations) I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

**Confidentiality Statement**

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date (ddMmmyyyy)

## 1.3. Contact Information

**Table 1: Important Study Contact Information**

| Role in Study | Name/<br>Address and Telephone Number |
|---|---|
| Clinical Study Leader | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Responsible Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Drug Safety Physician | Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF) |
| Serious Adverse Event Reporting | Please see Project Management Plan in TMF or Study Contact list in ISF |
| 24-Hour Emergency Contact | Please see Study Contact List in ISF |

**Table 2: Study Vendor Listing**

| Role in Study | Name/Address |
|---|---|
| Clinical Research Organization | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Investigational Product Shipment | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Video | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Independent Video Review | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Holter Monitor and 12-lead Electrocardiogram | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-immunoassays | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Central Laboratory-viral shedding studies | Please see Project Management Plan in TMF or Study Contact list in ISF |
| Autopsy | Please see Project Management Plan in TMF or Study Contact list in ISF |

ISF = Investigator site file; TMF = trial master file

# 2. SYNOPSIS

**Name of Sponsor/Company:** AveXis, Inc.

**Name of Investigational Product:** AVXS-101

**Name of Active Ingredient:** Survival Motor Neuron Gene by Self-Complementary Adeno-Associated Virus Serotype 9 (AAV9)

**Title of Study:** Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

**Study Center(s):** 10 to 20 United States (US) Investigators

| **Studied Period (years):** | **Phase of Development:** 3 |
|---|---|
| Estimated date first patient enrolled: 2Q 2017<br>Estimated date last patient completed: 4Q 2019 | |

**Objectives:**

**Co-Primary**

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

**Co-Secondary**

- Determine effect of AVXS-101 on the ability to thrive defined as achieving all of the following at 18 months of age:
  - Does not receive nutrition through mechanical support (e.g., feeding tube) or other non-oral method
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age

[redacted]

**Safety**

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity

**Methodology:**

Phase 3, open-label, single-arm, single-dose, study of AVXS-101 (gene replacement therapy) in patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria and are genetically defined by nonfunctional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*). Fifteen (15) patients < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) will be enrolled.

The study includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of AVXS-101, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety

assessments until the End of Study when the patient reaches 18 months of age. After the End of Study visit, eligible patients will be asked to rollover into the long-term follow up study.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (days 1, 2, 7, 14, 21, and 30) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to AVXS-101 infusion until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values, aspartate aminotransferase (AST) values, and T-cell response are below the threshold of 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline: 1 mg/kg/day until at least 30 days post-infusion, 0.5 mg/kg/day at Weeks 5 and 6, 0.25 mg/kg/day at Weeks 7 and 8, and discontinued at Week 9.

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age. The ability to thrive (as defined above) and the ability to remain independent of ventilatory support (as defined above) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development (Version 3). Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

**Number of Patients (planned):** 15

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

1. Patients with SMA Type 1 as determined by the following features:
   a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))
2. Patients must be < 6 months (< 180 days) of age **at the time** of AVXS-101 infusion
3. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
4. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27)
5. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

**Exclusion Criteria:**

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

   Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study
5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards[26]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
   a. Major renal or hepatic impairment
   b. Known seizure disorder
   c. Diabetes mellitus
   d. Idiopathic hypocalcuria
   e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (international normalized ratio [INR] > 1.4, gamma-glutamyl transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy

14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)
16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form

**Investigational Product, Dosage and Mode of Administration:**

Patients will receive a one-time dose of AVXS-101 at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study, as administered in AVXS-101-CL-101.

**Duration of Treatment:**

AVXS-101 will be administered as a one-time IV infusion over approximately 30-60 minutes, dependent upon the volume required.

**Reference Therapy, Dosage and Mode of Administration:** Not Applicable

**Criteria for Evaluation:**

**Efficacy:**

**Co-Primary**

- Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 seconds
- Survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death

**Co-Secondary**

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [26] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative

ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)

**Safety:**

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated liver function tests (LFTs) and/or unresolved liver function enzymes (LFEs)
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ Enzyme-linked ImmunoSpot (ELISpot) to detect T-cell responses to AAV9 and SMN

**Statistical Methods:**

This is a pivotal Phase 3 study assessing the efficacy and safety of AVXS-101. Details of all analysis will be contained within the Statistical Analysis Plan.

The primary and secondary efficacy analyses will be performed on the population of symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). While the study may enroll a small number of additional patients, the above will comprise the population for evaluation of the primary and secondary endpoints and will be referred to as the Intent-To-Treat (ITT) population hereafter. Study power is based upon efficacy analysis of this subpopulation. Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) will be evaluated separately as part of additional subgroup analyses. Fifteen (15) patients will be enrolled to ensure a reasonably robust safety database at the time of the Biologics License Application submission.

Based upon widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patient meeting the study entrance criteria (*SMN2* copy number of 2 without the *SMN2* gene modifier mutation (c.859G>C)) would be expected to attain the ability to sit without support for at least 30 seconds at or before the 18 months of age study visit or other milestones (rolling over, standing, walking) assessed as part of the study.

Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis is whether the AVXS-101 treated patients achieve a response rate greater than 0.1%. Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated patients in the ITT population are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age visit. With the assumption for the true response rate of AVXS-101 for the primary endpoint being in the range of 30% - 40%, an evaluable sample size of 15 patients (assuming 30% of patients do not qualify for the ITT population or are otherwise excluded from analysis) would provide power of > 90% to detect a significant difference from 0.1% with $\alpha = 0.05$ using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint of survival at 14 months of age will be evaluated by comparing the results observed in the ITT population with the results from the age and gender-matched control patients selected from existing natural history data sets (PNCR) [*Neurol*. 2014; 83(9):810-817]. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. Based upon preliminary results from the ongoing Phase 1 clinical study (AVXS-101-CL-101), at least 80% of patients in the ITT population are expected to survive, as defined, through 14 months of age. With this efficacy, an evaluable sample size of 15 patients (assuming 30% of patients do not qualify for the ITT or are otherwise excluded from the analysis) would provide power of > 80% to detect a significant difference from the historical control with $\alpha = 0.05$ using a 2-sided Fisher's Exact test.

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

## TABLE OF CONTENTS

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AAV | Adeno-associated virus |
| AAV9 | Adeno-associated virus serotype 9 |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ASO | Antisense oligonucleotide |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CB | Chicken-β-actin-hybrid |
| CDC | Center for Disease Control |
| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CK | Creatine kinase |
| CLIA | Clinical Laboratory Improvement Amendment |
| CMAP | Compound motor action potential |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Day 1 | First 24-hour interval after the start of gene replacement therapy infusion |
| Day –1 | 24-hour interval prior to the start of gene replacement therapy infusion |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-linked Immunosorbent Assay |
| ELISpot | Enzyme-linked ImmunoSpot |
| ET | Early termination |
| FVB | Friend Virus B-Type |
| GCP | Good Clinical Practice |
| GFP | Green fluorescent protein |
| GGT | Gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| HEENT | Head, eyes, ears, nose, and throat |
| HgB | Hemoglobin |
| HIV | Human Immunodeficiency Virus |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ICD-10 code | International Statistical Classification of Diseases and Related Health Problems |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon gamma |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| ITR | Inverted terminal repeat |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LFE | Liver function enzymes |
| LFT | Liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NHP | Non-human primates |
| NOAEL | No Observable Adverse Effect Level |
| OAE | Other significant Adverse Event |
| PBMC | Peripheral blood mononuclear cells |
| PICU | Pediatric intensive care unit |
| PNCR | Pediatric Neuromuscular Clinical Research Network |
| RNA | Ribonucleic acid |
| RSV | Respiratory syncytial virus |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | Self-complementary |
| scAAV | Self-complimentary adeno-associated virus |
| scAAV9.CB.SMN | Self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron |
| SMA | Spinal muscular atrophy |
| SMN | Survival motor neuron |
| *SMN1* | Survival motor neuron 1 gene |
| *SMN2* | Survival motor neuron 2 gene |
| SOC | System Organ Class |
| TMF | Trial master file |
| US | United States |
| vg/kg | Vector genome per kilogram |
| WBC | White blood cell |
| WHO | World Health Organization |
| WT | Wild type |

# 5. INTRODUCTION

Study AVXS-101-CL-303 is a pivotal Phase 3 clinical gene therapy study investigating the efficacy and safety of a single intravenous (IV) infusion of AVXS-101 in up to 15 patients with Type 1 spinal muscular atrophy (SMA) with 1 or 2 copies of *SMN2*. The survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMNΔ7 mouse model for SMA from a median of 15.5 days to over 1 year, following IV delivery to a facial vein. Additionally, preliminary results from an ongoing Phase 1 clinical study (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function (Section 5.4).

## 5.1. Background

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births [1]. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*SMN2*). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis before 6 months of age and early death due to respiratory failure before 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the prenatal period), whereas motor neurons in SMA Type 2 and Type 3 patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of *SMN2* in hopes of rescuing neurons at this critical stage. The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [5,6]. However, clinical studies employing several of these agents, most notably phenylbutyrate, valporic acid, and hydroxyurea, have not resulted in clinical benefit [7,8]. FDA recently approved Nusinersen, an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Clinical studies have shown some modest promise in improving motor function; however the treatment must be administered indefinitely on a quarterly basis via intrathecal injection, requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring. A single-dose IV administration study of AVXS-101 will provide

information on the potential gene transfer has in treating SMA Type 1 patients, and will hopefully show promise for success in modifying the disease prognosis.

This is a single-dose study that will include up to 15 Type 1 patients with 1 or 2 copies of *SMN2*. The rationale for IV dosing is based upon the need for rapid, systemic impact given the severity of the disease in SMA Type 1 and its potential impact on systems outside of the central nervous system (CNS) such as the peripheral and autonomic nervous systems, heart, pancreas and gastrointestinal tract.

## 5.2. Rationale for Gene Transfer to SMA Type 1 Patients

Patients with SMA Type 1 have been chosen as the target population for this gene therapy study based on studies of the natural history of this disease. The classification of SMA is shown below (Table 4) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

**Table 4: Spinal Muscular Atrophy Classification**

| Type | Age at Symptom Onset | | Maximum Motor Function | Life Expectancy | *SMN2* Copy No. |
|---|---|---|---|---|---|
| 0 | Fetal | | Nil | Days – Weeks | 1 |
| 1 | < 6 Months | 1A: B-2 Weeks<br>1B: < 3 Months<br>1C: > 3 Months | Never sits | < 2 years | 1, 2, 3 |
| 2 | 6 – 18 Months | | Never walks | 20 – 40 years | 2, 3, 4 |
| 3 | 1.5 – 10 Years | 3A: < 3 Years<br>3B: > 3 Years | Walks, regression | Normal | 3, 4, 5 |
| 4 | > 35 Years | | Slow decline | Normal | 4, 5 |

Source: Adapted from Kolb 2011 [10]
*SMN2* = survival motor neuron 2 gene

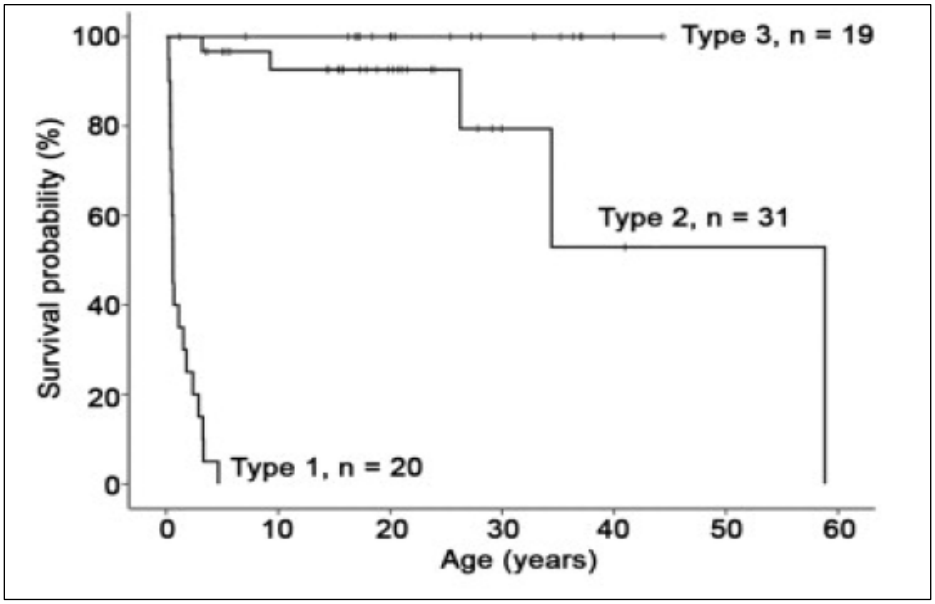
Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 months of age (Table 4). In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3 patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [11]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10 to 15% of that produced by *SMN1* [11,12,13]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms

of SMA generally have higher *SMN2* copy numbers [14,15]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, 2, or 3 SMA showed a significant correlation between *SMN2* copy number and SMA Type, as well as, duration of survival. In a large early study by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [16]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [17], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with two *SMN2* copies lived < 21 months, and 8/10 with three *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated, and has also influenced our choice of the study target group.

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

**Figure 1: Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3**




n = number of patients
Source: Farrar 2013 [18]

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the prenatal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [2,3,4].

There is reason to believe that there are few safety issues to be concerned about when targeting the SMA Type 1 group in this gene therapy clinical study. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans, a high copy number of *SMN2* poses no risk (as seen in Type 2, 3, and 4 patients who have high *SMN2* copy number), allowing for use of robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV can be employed for this study because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded adeno-associated virus (AAV) vectors.

Recent studies using self-complimentary adeno-associated virus serotype 9 chicken-β-actin-hybrid survival motor neuron (scAAV9.CB.SMN) show a robust post-natal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology and survival after a one-time delivery of vector [19]. Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

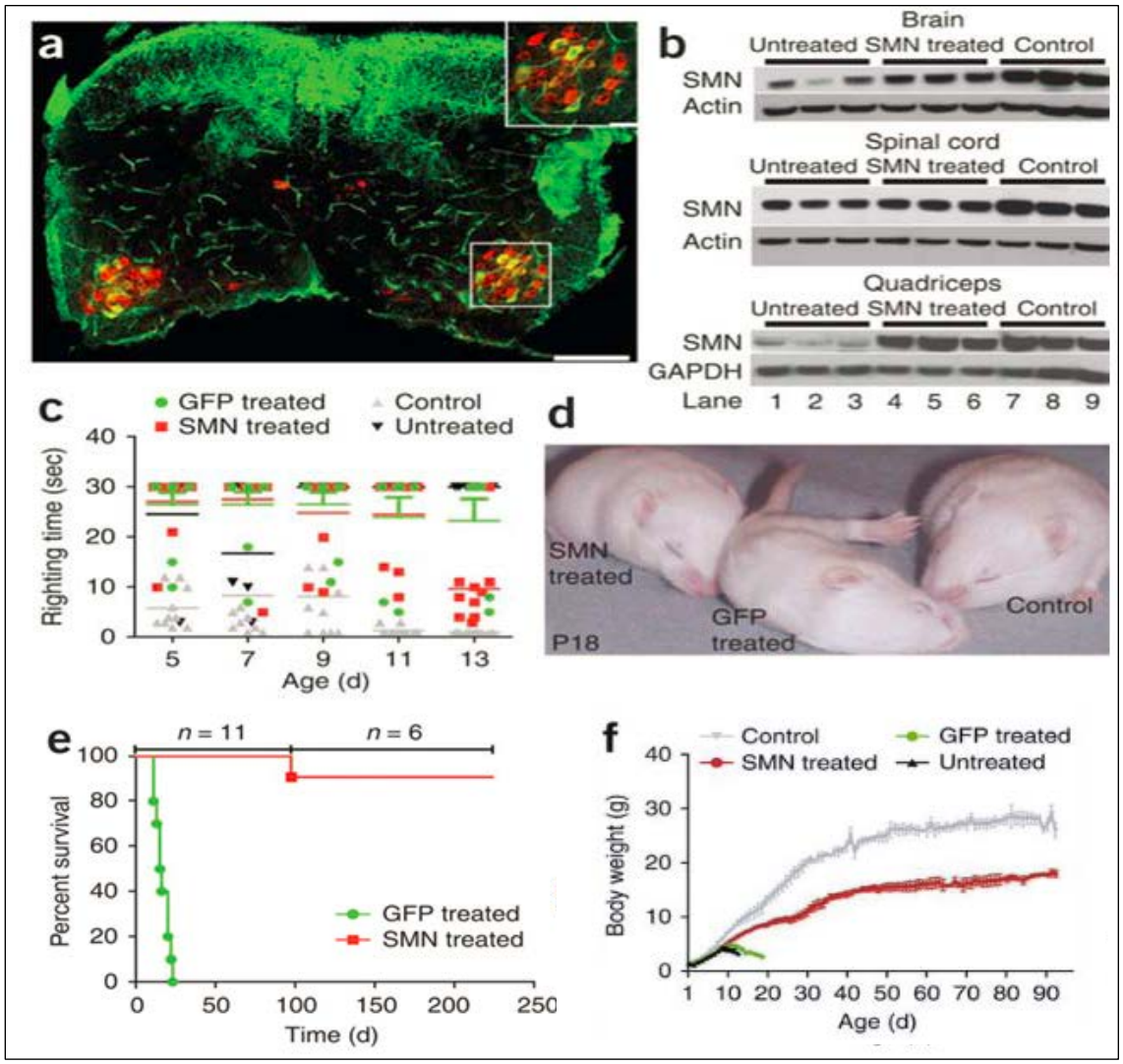
## 5.3. Non-clinical Studies

A mouse model was developed by the [redacted] after a generation of multiple variants. It was found that the double transgenic, referred to as the SMNΔ7 mouse, provided the most suitable model to study gene transfer [20]. Studies performed in the [redacted] have shown that injecting $5 \times 10^{11}$ viral genomes of scAAV9.CB.SMN into the facial vein on Day 1 old mice rescues the SMNΔ7 mouse model [19]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.GFP treated mice. SMN transduction was shown by real time polymerase chain reaction (RT-PCR) in the mice. GFP transduction was observed by microscopy. Both constructs were in AAV9 and had transduction of motor neurons. SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMNΔ7 mice (although lower than wild type [WT] controls). SMNΔ7 animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on post-natal Day 1 were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and green fluorescent protein (GFP)-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMNΔ7 animals compared with GFP-treated SMNΔ7 animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a ‘chimeric’ animal in which

some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

**Figure 2: Study Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves**

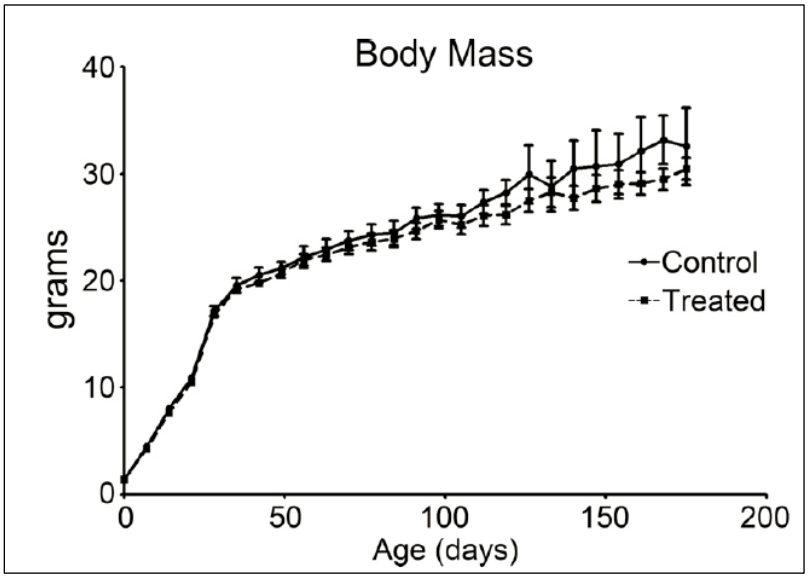



Source: Foust 2010 [19]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type
a)Shows transduced motor neurons in lumbar spinal cord
b) Western Blots of SMN expression in CNS and muscle
c)Improved righting ability of SMN-treated- similar to WT controls by P13
d) SMN-treated are larger than GFP-treated at P18
e)Survival of SMN-treated markedly improved compared to GFP- treated
f) Body weight increased in SMN-treated vs GFP

Toxicology biodistribution studies were generated by the [redacted] [data on file]. In the non-Good Laboratory Practice (GLP) studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with AVXS-101. To assess toxicity and safety, AVXS-101 was injected into P1 wild type Friend Virus B-Type (FVB) mice with either vehicle

(3 males/6 females) or $3.3 \times 10^{14}$ vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the SMNΔ7 mouse model [19]. P1 mice were used in anticipation of simulating potential clinical studies in infants. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

**Figure 3 Body Mass of Treated and Control Mice Showed No Difference**




At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies including complete blood counts with differentials. At 90, 120 and 180 days post-injection, blood was collected for clinical chemistries assessment (alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase, creatinine, blood urea nitrogen [BUN], electrolytes, and creatine kinase [CK]). For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. There were no clinically significant results observed during from the hematology, clinical chemistry, and histopathology portions of the study and trends of both groups were comparable. Of note, no significant lesions were present in any brain or spinal cord sections, although, the sections were frozen and thicker than 5 microns which made cellular morphology obscure and subtle changes may not have been identified.

In the safety study for the 4 male Cynomolgus Macaques, animals were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The AVXS-101 vector was administered one time by catheterization of the saphenous vein with a dose of $6.7 \times 10^{13}$ vg/kg, which corresponds to the lowest dose tested for which SMNΔ7 mice showed a significant increase of survival. Animals were followed for six months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using Enzyme-linked ImmunoSpot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

These mouse and monkey studies can be summarized as follows. The serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The NHP patients animals mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [data on file].

When newborn FVB mice were given a single IV injection of AVXS-101 at levels up to $3.3 \times 10^{14}$ vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of AVXS-101 was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given $3.3 \times 10^{14}$ vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses. Based on these results, the no observable adverse effect level (NOAEL) of AVXS-101 in newborn male and female mice is considered to be $3.3 \times 10^{14}$ vg/kg.

Intravenous administration of AAV9 has been shown to be safe and well tolerated when administered to mice and monkeys. The vector has also demonstrated the ability to cross the blood brain barrier in both species following IV administration. Body weight increased, righting behavior improved, survival was extended and cardiac deficits returned toward normal in treated SMNΔ7 mice when compared to untreated SMNΔ7 mice. Toxicology studies determined the NOAEL of AVXS-101 was $3.3 \times 10^{14}$ vg/kg and there was no test article mortality or toxicity observed up to 24 weeks following IV administration in mice. Biodistribution to the brain and spinal cord was reconfirmed and low levels of antibodies to the AAV9 capsid were observed at 12 and 24 weeks following the $3.3 \times 10^{14}$ vg/kg dose. No alteration was observed in clinical pathology and histopathology analyses.

## 5.4. Clinical Studies

First-in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the efficacy and safety of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received $6.7 \times 10^{13}$ vg/kg and Cohort 2 (n = 12) received $2.0 \times 10^{14}$ vg/kg (proposed therapeutic dose).

Preliminary data as of 15 September 2016 indicate that treatment with AVXS-101 results in broad improvements in survival, motor function, pulmonary function, and nutritional function. All patients in Cohort 2 (proposed therapeutic dose) showed improvements in survival, as defined by Finkel et al 2014 [21], with no deaths or requirements for permanent ventilation ≥ 16 hours/day for ≥ 14 consecutive days through 15 September 2016. The median age at last follow-up for Cohort 2 was 17.3 months, with the oldest patient at 27.4 months of age. One patient in Cohort 1 (low-dose cohort) had a pulmonary event of increased use of bi-level positive airway pressure in advance of surgery related to hypersalivation, a condition experienced by some SMA patients. The event was determined by independent review to represent progression of disease and not related to AVXS-101.

As of September 15, 2016, improvements in motor function, as assessed by the CHOP-INTEND scores, were observed with mean increases of 9.0 points in Cohort 1 and 24.8 points in Cohort 2. The CHOP-INTEND scores in Cohort 2 were ≥ 40 points for 11/12 patients, ≥ 50 points for 9/12 patients, and ≥ 60 points (normal) for 3/12 patients.

As of September 15, 2016, patients in Cohort 2 consistently achieved and maintained key developmental motor milestones as summarized below:

- 11/12 patients achieved head control, 7/12 patients could roll, 11/12 patients could sit with support, and 8/12 patients could sit unassisted, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016
- 7 patients were able to feed themselves, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016, and 5 patients were speaking (1 bilingual)
- 2 patients were walking independently, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016. These 2 patients each achieved earlier and important developmental milestones such as crawling, standing with support, standing alone, and walking with support

As of September 15, 2016, AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in this study. A total of 118 treatment-related AEs were reported (34 serious adverse events [SAEs] and 84 non-serious adverse events [AEs]). Two SAEs were deemed treatment-related in 2 patients, and 3 AEs were deemed treatment-related in 2 patients. All treatment-related events consisted of clinically asymptomatic liver enzyme elevations that resolved with prednisolone treatment. There were no clinically significant elevations of gamma-glutamyl transferase (GGT), alkaline phosphatase or bilirubin, and as such, Hy's Law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

In summary, through September 15, 2016, the consistently positive clinical observations are remarkably different from that described in extensive natural history studies, clinical publications, the experience of seasoned clinicians, and concurrent SMA Type 1 studies with other therapies. These significant and clinically meaningful responses in patients treated with AVXS-101 indicate preliminary clinical evidence of a treatment effect that addresses an unmet need in this devastating pediatric disease.

A full understanding of all the risks associated with AVXS-101 is not known at this time. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 study, which is believed to be a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the study were accompanied by clinical sequelae. Patients could experience an allergic response to AVXS-101. Patients could also develop an immune response to the AAV9 viral vector, which could prevent future use of gene transfers using this vector.

Taken together, results from the clinical and non-clinical studies support further clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objectives

The co-primary objectives are to:

- Determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit.
- Determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

## 6.2. Secondary Objective

The co-secondary objectives are to:

- Determine the effect of AVXS-101 on the on the ability to thrive defined as achieving all of the following at 18 months of age
  - Does not receive nutrition through mechanical support (e.g., feeding tube)
  - Ability to tolerate thin liquids as demonstrated through a formal swallowing test
  - Maintains weight (> third percentile for age and gender)
- Determine the effect of AVXS-101 on the ability to remain independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device, for patients issued a Trilogy 100 BiPAP device

## 6.4. Safety Objectives

The safety objectives are to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) [9] Grade 3 or higher, unanticipated, treatment-related toxicity.

# 7. INVESTIGATIONAL PLAN

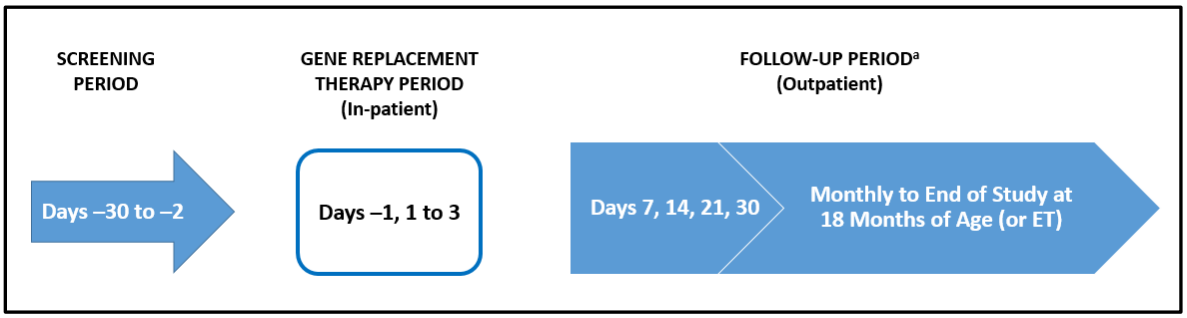
## 7.1. Overall Study Design

This is a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) in patients with SMA Type 1 with 1 or 2 copies of *SMN2*. Fifteen (15) patients < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) will be enrolled.

The study includes 3 study periods: screening, gene replacement therapy, and follow-up (Figure 4). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time IV infusion of AVXS-101 at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study over approximately 60 minutes, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within 7 days.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days **after** the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients will be asked to roll over into the long-term follow-up study.

**Figure 4: Study Design**




Note: After the End of Study visit at 18 months of age, eligible patients will be asked to roll over into the long-term follow-up study.
ET = early termination
[a] All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

There will be at least a 4 week dosing interval between dosing of the first three patients to allow review of the safety analysis from six time points (days 1, 2, 7, 14, 21, and 30) as well as early signals of efficacy including CHOP-INTEND score prior to dosing of the next patient.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion in accordance with the specified guidelines for tapering (Section 9.2.1).

A schedule of study assessments is provided in Appendix 1. Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined in Section 14.1.1.2) will also be assessed. Additional developmental milestones will be assessed using Bayley Scales of Infant and Toddler Development© (Version 3) (Section 11). Safety will be assessed through monitoring AEs, concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (Section 12). Additionally, a Data Safety Monitoring Board (DSMB) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment (Section 13.1.1.1 and Section 15). This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation. The DSMB can recommend early termination of the study for safety reasons.

## 7.2. Number of Patients

A total of 15 patients will be enrolled.

## 7.3. Criteria for Study Termination

An independent DSMB will conduct quarterly and ad hoc reviews of the emerging safety data throughout the study as described in Section 15.

The study will be completed as planned but may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment
- DSMB can recommend early termination of the study for safety reasons
- Study is terminated by Sponsor
- Regulatory Authority recommendation

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients with SMA Type 1 who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1) with proven bi-allelic mutations of the *SMN1* gene and 1 or 2 copies of the *SMN2* will be enrolled in this study. Patients may be of any racial, ethnic, or gender background.

## 8.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Patients with SMA Type 1 as determined by the following features:
    a. Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation (c.859G>C))
2. Patients must be < 6 months (< 180 days) of age at the time of AVXS-101 infusion
3. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy
4. Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27)
5. Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule

## 8.2. Patient Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period
2. Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support

    Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points
3. Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours/day over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing
4. Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study

5. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards [26]
6. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
7. Serious non- respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening
8. Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening
9. Severe non-pulmonary/respiratory tract infection (e.g., pyelonephritis or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy such as:
    a. Major renal or hepatic impairment
    b. Known seizure disorder
    c. Diabetes mellitus
    d. Idiopathic hypocalcuria
    e. Symptomatic cardiomyopathy
10. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
11. Concomitant use of any of the following: drugs for the treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
12. Anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential patient demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50
13. Clinically significant abnormal laboratory values (international normalized ratio [INR] > 1.4; GGT, ALT, and AST > 3 × ULN; bilirubin ≥ 3.0 mg/dL; creatinine ≥ 1.0 mg/dL; hemoglobin < 8 or > 18 g/dL; white blood cells [WBC] > 20,000/cmm) prior to gene replacement therapy
14. Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (e.g., nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study
15. Expectation of major surgical procedures during the study assessment period (e.g., spinal surgery or tracheostomy)

16. Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits
17. Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
18. Parent(s)/legal guardian(s) refuses to sign consent form

## 8.3. Patient Withdrawal Criteria

Patients may be discontinued from the study for the following reasons:

- Death

– An autopsy will be requested for any patient who expires following participation in a gene replacement study as per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25] (see Autopsy Plan in Appendix 2)

- Failure to comply with protocol-required visits or study procedures for 3 or more consecutive visits that are not rescheduled, unless due to hospitalization
- Parent(s)/legal guardian(s) withdraws consent
- Investigator discretion

Early termination procedures should be completed within 14 days for any patient who prematurely discontinues the study for any reason, as indicated in Appendix 1.

# 9. TREATMENT OF PATIENTS

It is the responsibility of the Investigator to ensure the safe storage and administration of gene replacement therapy.

## 9.1. Description of Product

The biological product is a non-replicating recombinant AAV9 containing the complimentary deoxyribonucleic acid (cDNA) of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed and the resulting protein is produced. The biological product, called AVXS-101 (formerly scAAV9.CB.hSMN), expresses the human SMN protein in transduced cells.

**Table 5: Investigational Product**

| | **Investigational Product** |
|---|---|
| **Product Name:** | AVXS-101 |
| **Dosage Form:** | Equivalent to the dose received by the second dosing cohort in the Phase 1 study |
| **Unit Dose** | Equivalent to the dose received by the second dosing cohort in the Phase 1 study |
| **Route of Administration** | Intravenous infusion |
| **Physical Description** | AVXS-101 is a clear, colorless liquid. |

## 9.2. Prior and Concomitant Medications

Prior and concomitant medications will be captured in the electronic Case Report Form (eCRF) from 2 weeks prior to administration of gene replacement therapy through the last study visit.

### 9.2.1. Prophylactic Administration of Prednisolone

An antigen specific T-cell response to the AAV vector was observed in the ongoing Phase 1 clinical study (AVXS-101-CL-101) investigating AVXS-101 treatment via IV infusion. This is an expected response between 2 to 4 weeks following gene replacement therapy. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression.

In an attempt to dampen the host immune response to the AAV-based therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to gene replacement therapy until at least 30 days post-infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell response are below the threshold of ≤ 2 X ULN for ALT and AST, and < 100 SFC/$10^6$ PBMCs in accordance with the following treatment guideline:

- Until at least 30 days post-infusion: 1 mg/kg/day

- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/day
- Week 9: prednisolone discontinued

If the AST or ALT values are > 2 X ULN, or if T-cell response is ≥ 100 SFC/$10^6$ PBMCs after 30 days of treatment, the dose of prednisolone will be maintained until the AST and ALT values decrease below threshold. If T-cell response continues past Day 60, Investigator discretion should be used considering risk benefit for maintaining prednisolone. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient.

### 9.2.2. Prohibited Medications

Concomitant use of any of the following medications is prohibited:

- Drugs for treatment of diabetes, myopathy or neuropathy
- Therapy received with the intent to treat SMA (e.g., nusinersen, valproic acid)
    - Oral β-agonists must be discontinued at least 30 days prior to gene therapy dosing.
    - Inhaled β-agonists may be used to treat respiratory complications of SMA provided such medications are dosed at clinically appropriate levels
- Any investigational medication other than AVXS-101 is prohibited during the study
- Ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of starting the study (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)

Corticosteroid usage following completion of the prednisolone taper is permissible as part of routine clinical management. The use of corticosteroids in such circumstances should be documented appropriately as a concomitant medication, and the event precipitating its usage should be appropriately documented as an adverse event.

Should the use of corticosteroids (aside from inhaled corticosteroids for bronchospasm) be considered as part of care during the course of the prednisolone taper, this medical management should be discussed with the medical monitor.

## 9.3. Treatment Compliance

AVXS-101 will be administered as a one-time IV injection.

## 9.4. Randomization and Blinding

This is an open-label study.

# 10. STUDY PRODUCT MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in accordance with current Good Manufacturing Practices (cGMP). Investigational product accountability logs will be maintained by the clinical pharmacy.

## 10.1. Study Product

AVXS-101

## 10.2. Study Product Dose and Dose Justification

Patients will receive a one-time dose of AVXS-101 equivalent to the dose received by the second dosing cohort in the Phase 1 study via IV infusion administered in the ongoing Phase 1 clinical study (AVXS-101-CL-101).

Two doses ($2.0 \times 10^{14}$ vg/kg and $6.7 \times 10^{13}$ vg/kg) are being studied in the ongoing Phase 1 clinical study (AVXS-101-CL-101); the higher dose ($2.0 \times 10^{14}$ vg/kg) was chosen for the present study as preliminary data demonstrated both a dose response and significant clinical benefit thus identifying $2.0 \times 10^{14}$ vg/kg, as the minimum dose that is clinically effective.

## 10.3. Study Product Packaging and Labeling

AVXS-101 kits are labeled with a specific kit number and batch/lot number assigned at the cGMP facility. The content of the labeling is in accordance with the local regulatory specifications and requirements.

## 10.4. Study Product Storage

AVXS-101 kits will be stored in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared AVXS-101 should be managed in accordance with the Pharmacy Manual.

The vessel used for delivery of the vector should be resealed in the procedure room and processed for destruction and/or return to AveXis in accord with the Pharmacy manual and applicable biohazardous waste guidelines for disposal.

## 10.5. Study Product Preparation

Preparation of AVXS-101 will be done aseptically under sterile conditions by a pharmacist and will arrive at the clinical site ready for infusion.

AVXS-101 will be received diluted with normal saline, as outlined in the Pharmacy Manual.

The total vector genome dose will be calculated based on the patient's body weight.

The dose-delivery vessel will be delivered to the designated pediatric intensive care unit (PICU) patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. The vessel will be delivered in accord with the Pharmacy Manual.

## 10.6. Study Product Administration

AVXS-101 infusion will be administered under sterile conditions in a PICU or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose equivalent to the dose received by the second dosing cohort in the Phase 1 study. AVXS-101 should be slowly infused over approximately 30-60 minutes, dependent upon total volume in accord with the Pharmacy Manual, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, patients should return to an appropriate designated setting to ensure close monitoring of vital signs and adverse events. Vital signs will be continuously monitored throughout the gene replacement therapy infusion as described in Section 12.1.3. Patients should be maintained in the PICU or other appropriate setting for 48 hours after the start of gene replacement therapy.

## 10.7. Dose Adjustment Criteria

The study investigates a one-time IV infusion of AVXS-101; no dose adjustments are possible.

## 10.8. Study Product Accountability

The pharmacist or designee will maintain accurate records of the quantities of AVXS-101 received, dispensed, destroyed, and/or returned to AveXis. The pharmacist or designee will document the date and time of delivery of the dose vessel to the dose procedure room as well as the time the used vessel was returned to AveXis or destroyed as per the Pharmacy Manual.

## 10.9. Study Product Handling and Disposal

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof containers. All waste must be sealed in bags bearing the biohazard symbol and disposed of in a biohazard waste container.

All transfers must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment, such as gloves.

Any quality issue noticed with the receipt or use of AVXS-101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accord with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply AVXS-101 to a third party, allow AVXS-101 to be used other than as directed by this clinical trial protocol, or dispose of AVXS-101 in any other manner.

# 11. ASSESSMENT OF EFFICACY

Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age (as defined in Section 14.1.1.1). The ability to thrive and the ability to remain independent of ventilatory support (as defined Section14.1.1.2) will also be assessed at 18 months of age. Additional developmental milestones will be assessed using the Bayley Scales of Infant and Toddler Development (version 3©). Efficacy assessments will be performed at the times specified in the Table of Assessments (Appendix 1), and should be the first assessments performed at any scheduled visit. All post-treatment visits will be relative to the date on which gene replacement therapy is administered except the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

## 11.1. Developmental Milestones

Developmental milestones will be assessed using relevant definitions obtained from the Bayley Scales of Infant and Toddler Development (version 3), and will be analyzed to assess efficacy (Appendix 3 and Appendix 4). Achievement of each developmental milestone will be determined by the Physical Therapist and confirmed by the central reader (as may be necessary) based on an assessment of the submitted videos (Section 11.3). Developmental milestones will be determined at each monthly visit as listed in Section 11.2.1.

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement in accordance with Appendix 1; this assessment must address all milestones/items noted on Appendix 1 that are at or below the child's baseline function, and be recorded on video. The findings must be documented in the source. Items that are below the baseline level of assessment that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestones of sitting independently (items 22 and 26) should be assessed at every subsequent visit, until attainment of milestone, regardless of starting point on the scale. These milestones must also be assessed at the 18 months of age visit, regardless of previous attainment.

As the Bayley Scales do not necessarily require the child to repeat previously attained milestones, it is essential that each attained milestone be captured on video.

A milestone will be considered achieved when demonstrated by a patient and observed with video capture confirmation during a physical therapy assessment or observed with video as provided by the patient's family at the patient's visit at 18 months of age.

## 11.2. Motor Function Tests

### 11.2.1. Bayley Scales of Infant and Toddler Development/Developmental Milestones

The Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 3) is a standardized, norm-referenced infant assessment of developmental functioning across 5 domains of cognitive, language, motor, social-emotional, and adaptive behavior. The Bayley Scales will be administered by a qualified Physical Therapist.

The full Bayley Scales will be administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain will be administered at each monthly visit.

Each Bayley Scales/developmental milestone assessment will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and may be submitted to the vendor for review by a central reader (Section 11.3).

The following developmental milestones will be assessed:

- Ability to hold head erect without support
- Ability to roll from back to both sides
- Ability to sit with support
- Ability to sit independently, > 10 seconds; WHO [22]
- Ability to sit without support for at least 30 seconds
- Ability to crawl
- Ability to pull to stand
- Ability to stand with assistance
- Ability to stand alone
- Ability to walk with assistance
- Ability to walk alone

### 11.2.2. CHOP-INTEND

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA Type 1, and will be administered by a qualified Physical Therapist.[23,24] The CHOP-INTEND scale examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions (Appendix 5). Anti-gravity movements in assisted rolling, ventral suspension, and supported standing will also be measured.

The CHOP-INTEND will be performed at screening and at each scheduled visit from Day 7 through the End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not undergo any additional CHOP-INTEND examinations.

Each CHOP-INTEND exam will be video recorded in accordance with the AVXS-101-CL-303 Video Manual and submitted to the vendor for review by a central reader as may be necessary (Section 11.3).

## 11.3. Video Evidence

Physical therapy assessments (Bayley Scales and CHOP-INTEND) required at each study visit will be video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

## 11.4. Compound Motor Action Potential

Peroneal nerve CMAP amplitude will be measured by a qualified electrophysiologist, at all clinical sites capable of performing this assessment, using the procedures as described in the CMAP Manual (Appendix 6). CMAP will be measured at screening, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

The CMAP data will be collected for centralized review and interpretation.

Sites that do not have equipment or appropriately experienced personnel required to perform CMAP measurements will not be required to perform these assessments.

# 12. ASSESSMENT OF SAFETY

## 12.1. Safety Parameters

Safety parameters include physical examinations, pulmonary examinations, vital signs, capillary blood gas assessments, weight and length measurements, 12-lead electrocardiograms (ECGs), 12-lead Holter monitor recordings, echocardiograms, swallowing tests, laboratory assessments, adverse event monitoring, and photographs of the infusion site. In general, safety assessments will be performed at the times specified in the Table of Assessments (Appendix 1). All post-treatment visits are relative to the date on which gene replacement therapy is administered until the patient reaches 14 months of age, at which point all visits are relative to the patient's date of birth.

Unless otherwise noted, visit windows for the outpatient follow-up visits are as follows:

- Days 7, 14, 21, and 30: ± 2 days
- Monthly visits starting at Month 2: ± 7 days
- 14 months of age visit: 0 to 14 days **after** the patient reaches 14 months of age
- 18 months of age/End of Study visit: 0 to 14 days **after** the patient reaches 18 months of age

### 12.1.1. Demographic/Medical History

Demographic/medical history information will be collected at screening and captured in the eCRF. Information that will be collected includes:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/height/head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including International Statistical Classification of Diseases and Related Health Problems (ICD-10 codes), if available
- Historical ventilatory support, if any
- Historical feeding support, if any

1. Patients are encouraged to follow all routinely scheduled immunizations, as recommended by the Center for Disease Control (CDC), throughout the study. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics (27).

### 12.1.2. Physical Examinations

Physical examinations will be conducted by the Investigator or Sub-Investigator at each scheduled visit, except Day –1 (Appendix 1). The Day 1 physical examination will be

performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

### 12.1.3. Vital Signs/Weight and Length

Vital sign parameters include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry. Vital signs will be obtained at each study visit (as specified in Appendix 1). On Day 1, vital signs will be continuously monitored throughout the gene replacement therapy infusion, and recorded pre-dose and every 15 (± 5) minutes for the first 4 hours after the start of infusion, and then every hour (± 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.

Weight and length will be measured at each study visit (as specified in Appendix 1). On Day 1, weight and length will be measured pre-dose.

### 12.1.4. Electrocardiogram

A 12-lead ECG will be performed at screening, Day –1, pre-dose on Day 1, Day 2, every 6 months starting at Month 6, and End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1). Additional ECG monitoring will be at the discretion of the Investigator as per local institutional guidelines.

The ECG will be interpreted locally by a cardiologist. The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

### 12.1.5. 12-Lead Holter Monitor

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 72 hours from Day –1 (24 hours prior to the start of gene replacement therapy infusion) through 48 hours after the start of infusion. Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours
- 48 hours

Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist within 24 hours of data upload. The Sponsor physician or designee will be notified of any safety concerns from the centralized review, and the safety management plan will be followed for documenting and reporting of AEs/SAEs.

### 12.1.6. Echocardiogram

A standard transthoracic echocardiogram will be performed at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1).

### 12.1.7. Pulmonary Examinations

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit except Day 1 (Appendix 1). Prior to study entry, a pulmonologist or appropriate individual as per standard institutional practice will review and document ventilator usage in the 2 weeks prior to screening.

Patients may be fitted with non-invasive ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Non-invasive ventilatory support equipment will be provided by AveXis through a third-party vendor. Should the patient require non-invasive ventilatory support at any time during the study, the equipment provided by AveXis must be used.

Patients requiring non-invasive ventilatory support will be asked to bring their machine(s) to each study visit such that the study staff can remove an SD card which captures actual usage data. The hours per day usage data for each day between visits will be extracted with software provided by the device manufacturer into a format that will be transferred/transcribed to the clinical database.

### 12.1.8. Swallowing Test

A swallowing test will be performed at screening (at the Investigator site), every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination) (Appendix 1) to determine if the patient has signs of aspiration. If the test is positive for aspiration, there may be a recommendation for the patient to use an alternate method to oral feeding for the duration of the study at the determination of the Investigator and treating clinician.

### 12.1.9. Photographs of Infusion Site

Photographs will be taken of the infusion site at each scheduled visit from Day 1 (pre-dose) through Day 30 (Appendix 1) to monitor healing of the infusion site. AveXis will provide a secure and confidential upload process for transfer and storage of the photographs from the investigative sites to a contracted third-party vendor that will compile and arrange photographs as per AveXis requirements. Any/all photographs received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with

regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

### 12.1.10. Laboratory Assessments

Blood samples will be collected at each scheduled visit, except Day 1 and Day 3 (as specified in Appendix 1). On Day -1, blood and urine samples will be processed locally for receipt of results prior to the start of gene replacement therapy infusion. Any clinically significant laboratory value will be repeated at the discretion of the Investigator.

Blood samples will be collected and shipped to a central laboratory. Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's Clinical Laboratory Improvement Amendment (CLIA) CLIA-certified local laboratory to ensure receipt of results prior to dosing.

**Table 6: Total Blood Volume**

| Visit | Tests | Total Volume (mL) |
|---|---|---|
| Screening | Hematology, chemistry, virus serology, capillary blood gas, immunology sample (AAV9 Ab only), diagnostic confirmation sample | 16.6 |
| Day –1 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 1 | Capillary blood gas | 1 |
| Day 2 | Hematology, chemistry, capillary blood gas | 3.3 |
| Day 7 | Hematology, chemistry, immunology sample | 6.3-8.3[b] |
| Day 14 | Hematology, chemistry, immunology sample | 6.3-8.3[b] |
| Day 21 | Hematology, chemistry, immunology sample | 6.3-8.3[b] |
| Day 30 | Hematology, chemistry, immunology sample | 6.3-8.3[b] |
| Monthly | Hematology, chemistry | 36.8 |
| End of Study/ET | Hematology, chemistry | 2.3 |
| | **Maximum Total Volume for Study[a]** | **96.5** |

ET = early termination
[a] Patients will have different numbers of monthly visits, depending on their age at dosing. Maximum total volume based on a maximum of 16 monthly visits, provided T-cell responses are not elevated at Day 30 requiring additional surveillance samples and virus serology is not positive at screening requiring additional testing
[b] Immunology sample requires 4-6 mL whole blood

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety labs
2. Interferon gamma (IFN-γ) ELISpots to detect T-cell responses
3. Serum antibody to AAV9 and SMN
4. Genetic reconfirmation testing

If there is not sufficient blood volume to include the genetic reconfirmation testing sample at the screening visit, patient must return before Visit 2. All patients must have genetic reconfirmation testing completed.

#### 12.1.10.1. Hematology

Hematology analysis will include a complete blood count with differential and platelet count with smear. Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for hematology analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 1).

Immediate/same-day hematology analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory. Investigators will receive hematology results from all study visits from the central laboratory.

#### 12.1.10.2. Blood Chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected at all scheduled visits except Day 1 and Day 3 (Appendix 1).

Immediate/same-day chemistry analyses required during in-patient dosing, as determined by the Investigator, will be performed as per investigational site standard procedures at the local laboratory.

Chemistry analysis will include the following at all study visits:

- Serum GGT
- AST/ALT
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Total creatine kinase
- Creatinine
- BUN
- Electrolytes
- Alkaline phosphatase

Investigators will receive chemistry results from all study visits from the central laboratory (except Day -1).

#### 12.1.10.3. Urinalysis

Urine samples will be collected in accordance with the laboratory manual provided by the central laboratory at all study visits except Day 1 and Day 3 (Appendix 1). Day -1 urinalysis will be performed as per investigational site standard procedures at the local laboratory. Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin
- Blood
- Protein
- Red Blood Cell
- White Blood Cell
- Squamous epithelial cells
- Casts
- Crystals
- Bacteria
- Yeast

#### 12.1.10.4. Virus Serology

The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have HIV or positive serology for hepatitis B or C or Zika virus, administration of AAV vector may represent an unreasonable risk; therefore negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected at screening (Appendix 1) and shipped in accordance with the laboratory manual provided by the central laboratory.

#### 12.1.10.5. Capillary Blood Gas

Capillary blood gas will be completed locally at screening, Day –1, pre-dose on Day 1, and Day 2 (Appendix 1). A puncture or small incision will be made with a lancet or similar device

into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

#### 12.1.10.6. Immunology Testing (ELISA and IFN-γ ELISpots)

Blood samples for immunology testing will be collected and shipped to the central laboratory in accordance with the laboratory manual to test for serum antibodies to AAV9 and SMN (ELISA), and to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN. Blood samples will be collected at screening (ELISA anti-AAV9 only), Day 7, Day 14, Day 21, and Day 30 (Appendix 1). Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.

#### 12.1.10.7. AAV9 Antibody Screen in Mother

There is potential that the biological mother of the patient may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or, theoretically, via placental transfer in utero. Informed consent will be requested from the biological mother of the patient to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein at screening and shipped to the central laboratory for screening of anti-AAV9 antibodies. Mothers who test positive for antibodies to AAV9 will be asked to refrain from further feedings with breast milk.

If AAV9 antibodies are identified, the patient must desist in consuming breast milk from the biological mother.

Patients consuming banked breast milk from donor sources that cannot be test for anti-AAV9 antibodies must be transitioned to formula prior to participation.

#### 12.1.10.8. Blood for Diagnostic Confirmation Testing

A blood sample will be collected during the screening visit and shipped to the central laboratory in accordance with the laboratory manual for reconfirmation of *SMN1* deletions/mutations, *SMN2* copy number, and absence of exon 7 gene modifier mutation (c.859G>C). This will be done to ensure consistency in diagnostic testing practices.

#### 12.1.10.9. Saliva, Urine, and Stool Collection

Studies have shown that some vector can be excreted from the body for up to a few weeks after injection; this is called "viral shedding." Vector shedding can be found in the blood, urine, saliva, and stool for up to 1 week following infusion. The potential health risks associated with the shed vector are not fully known at this time; however the health risk is thought to be low as the vector cannot replicate. Regardless, Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved instructions should be provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of 2 weeks (14 days) after gene replacement therapy. Additionally, patients are prohibited from donating blood for 2 years following the vector infusion.

Saliva, urine, and stool samples will be collected for viral shedding studies at screening, 24 hours post-dose, 48 hours post-dose, Day 7, Day 14, Day 21, and Day 30 (Appendix 1). Samples will be collected, prepared, and shipped as per the laboratory manual.

A subset of patients at sites opting to participate in the viral shedding sub-study will have 24-hour total volume urine and fecal samples collected through 24 hour post-dose and through 48 hours-post dose.

# 13. ADVERSE AND SERIOUS ADVERSE EVENTS

### 13.1.1. Definition of Adverse Events

#### 13.1.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur from the start of gene replacement therapy infusion through the last study visit will be collected and recorded in the eCRF.

All adverse events will be classified in accordance with the CTCAE version 4.03 outlined in Table 7.

**Table 7: Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 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: Common Terminology Criteria for Adverse Events (version 4.03) [9]

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

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

Study enrollment will be interrupted should any patient experience an unanticipated CTCAE Grade 3, or higher adverse event toxicity that is possibly, probably, or definitely related to the gene replacement therapy. The event will then be reviewed by the DSMB and an evaluation will be made as to whether the study should be terminated early following the discontinuation rules.

Unanticipated CTCAE Grade 3 or higher adverse events that are possibly, probably, or definitely related to the gene replacement therapy must be reported within 24 hours to Sponsor and/or designee as per study safety management plan to ensure timely escalation to the DSMB.

#### 13.1.1.2. Serious Adverse Event

A SAE is an AE occurring during any study phase (e.g., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or comparator that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after signing of the informed consent through the last study visit, whether or not they are related to the study product, must be collected and recorded on forms provided by the Contract Research Organization.

#### 13.1.1.3. Other Adverse Event

The following specific treatment-emergent AE of special interest, which may be searched using Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries, will be summarized:

- Elevated liver enzymes

Other adverse events (OAE) will be identified by the Drug Safety Physician and, if applicable, also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

## 13.2. Relationship to Study Product

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" then the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

## 13.3. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs will be collected from the time of vector infusion until the end of the study. Serious Adverse Event information will be collected from signing of consent form until the last study visit. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date (and time if during Visit 2)), resolution (date (and time if start date during Visit 2)), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.1.2. An AE of severe intensity may not be considered serious.

## 13.4. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of consent form until the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or e-mail to AveXis or designee.

Additional follow-up information, if required or available, should all be faxed or e-mailed to AveXis or designee within 24 hours of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

AveXis is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, product-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

# 14. STATISTICS

This section summarizes key aspects of the analysis plan including definitions of co-primary, co-secondary, and [redacted] and safety endpoints, and the methods to be used to test the primary effectiveness hypothesis. Additional details regarding methods for the final data analysis will be provided in a separate Statistical Analysis Plan (SAP) which will be finalized and submitted to the Investigational New Drug application prior to the enrollment of the first patient. The SAP will detail all analyses and data displays, and will be executed according to Standard Operating Procedures in a controlled environment.

## 14.1. Study Endpoints and Populations

### 14.1.1. Study Endpoints

The primary and efficacy endpoint will be compared to the null. The survival co-primary efficacy variable will be evaluated relative to literature-based historical controls (such as the Pediatric Neuromuscular Clinical Research Network [PNCR] [21]. These were selected on the basis of comparability to the target population and similarity to the investigational device.

#### 14.1.1.1. Co-Primary Efficacy Endpoint

The co-primary efficacy endpoints are:

- The proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3) (Appendix 3), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds.
- The survival at 14 months of age. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

An “acute reversible illness” is defined as any condition other than SMA that results in increased medical intervention (e.g., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (e.g., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (e.g., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of “acute.” The date of “definitive intervention” shall be defined as the date of provision of a procedure (e.g., surgery, etc.) or medication (e.g., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of “definitive intervention” shall be considered the date of hospitalization or substantial escalation of care.

"Perioperative" use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.

For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

#### 14.1.1.2. Co-Secondary Efficacy Endpoint

The co-secondary efficacy endpoints are:

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (> third percentile based on World Health Organization [WHO] Child Growth Standards [26] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy).

#### 14.1.1.3. [redacted]

[redacted]

- [redacted]

#### 14.1.1.4. Safety Endpoints

Assessment of the safety and tolerability of AVXS-101 treatment, including:

- Incidence of elevated LFTs and/or unresolved LFEs
- Incidence of CTCAE Grade 3 or higher toxicity, treatment-emergent adverse events
- Clinically significant changes in laboratory values, physical exams, cardiac assessments or vital signs
- Research Immunology Blood Labs including serum antibody to AAV9 and SMN as well as IFN-γ ELISpot to detect T cell responses to AAV9 and SMN

### 14.1.2. Statistical Analysis Populations

#### 14.1.2.1. Intent-to-Treat Population (ITT)

The ITT population will consist of symptomatic patients with bi-allelic deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of AVXS-101 at less than 180 days of age. All primary and secondary efficacy analyses and subgroup analyses will be conducted on the ITT population.

#### 14.1.2.2. Efficacy Completers Population

The efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE or death

#### 14.1.2.3. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101. Analyses of endpoints in this population are considered descriptive.

#### 14.1.2.4. Safety Population

The safety analysis population will consist of all patients who receive an IV infusion of AVXS-101. All safety analyses will be conducted on the safety analysis population.

## 14.2. Sample Size Calculation

The current study will enroll 15 patients. Only those patients with baseline symptoms, bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C), ITT population will be assessed for the primary and secondary efficacy analyses. The study power is based upon efficacy analysis of the ITT population.

The two co-primary efficacy endpoints will be assessed in sequence: The endpoint of functional independent sitting will be assessed first and, only if this assessment meets statistical significance will the endpoint of survival be assessed.

Based upon widely cited natural history of the disease (Pediatric Neuromuscular Clinical Research Network [PNCR]) [*Neurol*. 2014; 83(9):810-817], it is expected that no patients in this population would be expected to attain the ability to sit without support or accomplish other milestones (rolling over, standing, walking) prior to 18 months of age. Assuming that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of interest of the historical control, the first co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at the 18 months of age study visit. With the assumption for the true response rate of AVXS-101 being in the range of 30% - 40%, a sample size of 15 patients (assuming 30% of patients do not qualify for the ITT population or are otherwise excluded from the analysis) would provide power of > 90% to detect a significant difference with α 0.05 using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion of patients surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, a sample size of 15 patients (assuming 30% of patients do not qualify for the ITT or are otherwise excluded from the analysis) would provide power of > 80% to detect a

significant difference with α 0.05 using a two sample 2-sided Fisher's exact test, comparing to the 26 age and gender matched patients from a published natural history observational study performed at 3 large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

## 14.3. Efficacy Analysis

### 14.3.1. General Considerations

This study will compare the activity of AVXS-101 administered IV versus the natural observational results from PNCR [21] in terms of functional independent sitting and survival rate. The ability to thrive and the ability remain independent of ventilatory support will also be assessed.

The analysis of the co-primary and co-secondary efficacy endpoints will be performed for the ITT and efficacy completers populations. The analysis based on the ITT population will be considered as the primary analysis. In the case of missing data, observed data will be used for the analyses.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to or on the day of gene replacement therapy infusion (e.g., on or before Day 1 visit).

### 14.3.2. Primary and Secondary Efficacy Analysis

Primary and secondary efficacy analyses will be based on the ITT population, those patients with bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 to the results from natural observation study (PNCR) [21].

The first co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where $p$ is the proportion of functional independent sitting for at least 30 seconds at the 18 months of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where $p$ is the proportion surviving at 14 months of age.

Primary efficacy endpoints will be examined on ITT population. Testing for the first co-primary endpoint, functional independent sitting will first be performed using 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at $p<0.05$, will the co-primary endpoint survival improvement be tested using 2-sided Fisher's Exact

test on ITT population, comparing to matched patients from natural observational study (PNCR). This hierarchy approach strongly protects the Type I error rate.

The hypothesis for both co-secondary efficacy endpoints to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$
$$versus\ the\ alternative$$
$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%\ ,$$

where *p* is the proportion of patients maintaining the ability to thrive/are independent of ventilatory support.

One-sided exact binomial tests will be executed for secondary efficacy analyses in ITT population.

A sensitivity analysis will be conducted by repeating the primary efficacy analysis on the efficacy completers analysis population.

## 14.4. Safety Analysis

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, urinalysis, immunology), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary.

Safety analyses will be conducted on safety population, and summarized by subgroup and overall.

# 15. DATA SAFETY MONITORING BOARD

The DSMB is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, have experience in the management of patients with SMA Type 1 and other diseases, and in the conduct and monitoring of randomized clinical studies with interim analyses. The DSMB will be chartered to oversee the safety of patients during the conduct of the study, and will act in an advisory capacity to AveXis A detailed description of the DSMB, its role in this study, and the timing of the scheduled reviews will be described in a DSMB Charter.

The DSMB will routinely convene on a quarterly basis to review emerging safety data from the study. All available safety data from all enrolled patients will be included in such reviews, which include, but are not limited to, screen failures, enrollment status, data from safety parameters, all SAEs, and other AEs. Following each meeting, the DSMB will make a recommendation as to whether or not the accumulated safety data warrants a suspension or discontinuation of the study, a modification to the study, or any additional comments or recommendations related to safety. The DSMB will prepare and provide minutes of their meetings to AveXis who will provide copies to the regulatory authorities as appropriate.

The DSMB will also convene on an ad hoc basis within 48 hours should any patient experience an unanticipated CTCAE Grade 3 or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB will review the safety information and provide its recommendation.

# 16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 16.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of AveXis will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of AveXis or its representatives. This will be documented in a Clinical Study Agreement between AveXis and the Investigator.

During the study, a monitor from AveXis or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts, electronic medical records)
- Record and report any protocol deviations not previously sent to AveXis
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to AveXis and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

## 16.2. Audits and Inspections

Authorized representatives of AveXis, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact AveXis immediately if contacted by a regulatory agency about an inspection.

### 16.3. Institutional Biosafety Committee

As this study involves gene therapy, the Principal Investigator must obtain approval/favorable opinion for the investigation from a designated institutional or independent biosafety committee in accordance with institutional requirements and/or guidelines.

### 16.4. Institutional Review Board/Institutional Ethics Committee

The Principal Investigator must obtain IRB/IEC approval for the investigation (Section 18.1). Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

# 17. QUALITY CONTROL AND QUALITY ASSURANCE

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. AveXis may also conduct a quality assurance audit any time during or after the completion of the study. Please see Section 16.2 for more details regarding the audit process.

The Investigator agrees to allow these Sponsor representatives direct access to the clinical data and supplies, dispensing and storage areas and if requested, agrees to cooperate fully or assist the Sponsor representative. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, site staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/IEC and relevant regulatory authority will also be informed.

# 18. ETHICS

## 18.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to AveXis before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## 18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 7) and are consistent with ICH/GCP, applicable regulatory requirements and the AveXis' policy on Bioethics.

## 18.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the parent(s)/legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent(s)/legal guardian(s) must also be notified that they are free to discontinue the patient from the study at any time. The parent(s)/legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the parent(s)/legal guardian(s).

There will be 3 informed consent forms:

- Parent(s)/legal guardian(s) informed consent form
- Biological mother baseline AAV9 antibody screening informed consent form
- Autopsy informed consent form (Appendix 2; if the parent(s)/legal guardian(s) decline an autopsy, it will not prevent the patient from participating in the study)

# 19. DATA HANDLING AND RECORDKEEPING

## 19.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion criteria, product administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

## 19.2. Inspection of Records

AveXis or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the product storage area, study product stocks, product accountability records, patient charts and study source documents, and other records relative to study conduct.

## 19.3. Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years included in ICH shall be followed.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, patient / subject screening records, patient / subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB/IEC documentation, an approved sample ICF, drug / product accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

# 20. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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# 22. APPENDICES

# APPENDIX 1. SCHEDULE OF ASSESSMENTS

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Informed Consent | X | | | | | | | | | | |
| Prophylactic Prednisolone | | X[q] | X | X | X | X | X | X | X[q] | | |
| AVXS-101 Infusion | | | X | | | | | | | | |
| Bayley Scales/ Developmental Milestones[d] (with video)[e] | X | | | | | | | | X[f] | X[f] | X |
| CHOP-INTEND[g] (with video)[e] | X | | | | | X | X | X | X | X | X |
| CMAP | X | | | | | | | | | X[j] | X |
| Demographic/Medical History | X | | | | | | | | | | |
| Physical Exam | X | | X | X | X | X | X | X | X | X | X |
| Vital Signs[h]/Weight & Length | X | X | X[i] | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | | | | | | X[j] | X |
| 12-Lead Holter Monitoring[k] | | X | X | X | X | | | | | | |
| Echocardiogram | X | | | | | | | | | X[j] | X |
| Pulmonary Examination | X | X | | X | X | X | X | X | X | X | X |
| Swallowing Test | X | | | | | | | | | X[j] | X |
| Photograph of Infusion Site | | | X | X | X | X | X | X | X | | |
| Hematology/Chemistry/ Urinalysis | X | X[o] | | X | | X | X | X | X | X | X |
| Virus Serology | X | | | | | | | | | | |
| Capillary Blood Gas | X | X | X | X | | | | | | | |
| ELISA anti-AAV9 Ab | X | | | | | X | X | X | X[l] | | |
| Immunology Testing (ELISA anti-SMN Ab and ELISpot) | | | | | | X | X | X | X[l] | | |
| Anti-AAV9 Ab Screen in Mother | X | | | | | | | | | | |
| Blood for Diagnostic Confirmation Testing | X | | | | | | | | | | |
| Saliva, Urine, and Stool Samples (for viral shedding)[p] | X | | | X[m] | X[m] | X | X | X | X | | |
| Adverse Events[n] | X | X | X | X | X | X | X | X | X | X | X |

| **Study Period** | **Screening** | **Gene Replacement Therapy (In-patient)** | | | | **Follow-up (Outpatient)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit #** | **1** | **2** | | | | **3** | **4** | **5** | **6** | **7+** | **End of Study[a]** |
| **# of Days in Study** | **–30 to –2** | **-1** | **1[b]** | **2** | **3** | **7** | **14** | **21** | **30** | **Monthly[c]** | **18 Months of Age (or ET)** |
| **Window** | | | | | | **± 2 days** | | | | **± 7 days (0–14 days at 14 Months of Age)** | **0–14 days** |
| Prior and Concomitant Medications | Collected from 2 weeks before gene replacement therapy until End of Study visit | | | | | | | | | | |

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization

[a] The End of Study visit must occur within 0 to 14 days **after** the date on which the patient reaches 18 months of age (or ET).
[b] Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
[c] The 14 months of age visit must occur within 0 to 14 days **after** the date on which the patient reaches 14 months of age.
[d] Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
[e] Videos may be submitted for review by a central reader.
[f] The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
[g] Patients who achieve 3 consecutive CHOP-INTEND scores ≥ 58 will not continue CHOP-INTEND assessments.
[h] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
[i] Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
[j] Completed every 6 months, starting at Month 6.
[k] Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
[l] Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
[m] Collected at 24 and 48 hours post-dose.
[n] Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.
[o] Laboratory samples collected on Day 1 to be processed locally, prior to dosing.
[p] Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
[q] Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.

# APPENDIX 2. AUTOPSY PLAN

An autopsy will be requested for any patient who receives gene replacement therapy and expires as per the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [25]. The autopsy and tissue collection will be performed by a contracted vendor who will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions will be used to perform the autopsy and pathology necessary to determine the cause of death.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes, including up to 7 sections or pieces from each organ and each region of the spinal cord. Upon collection, these tissue samples will be provided to AveXis for analysis. Tissue analysis will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results will demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

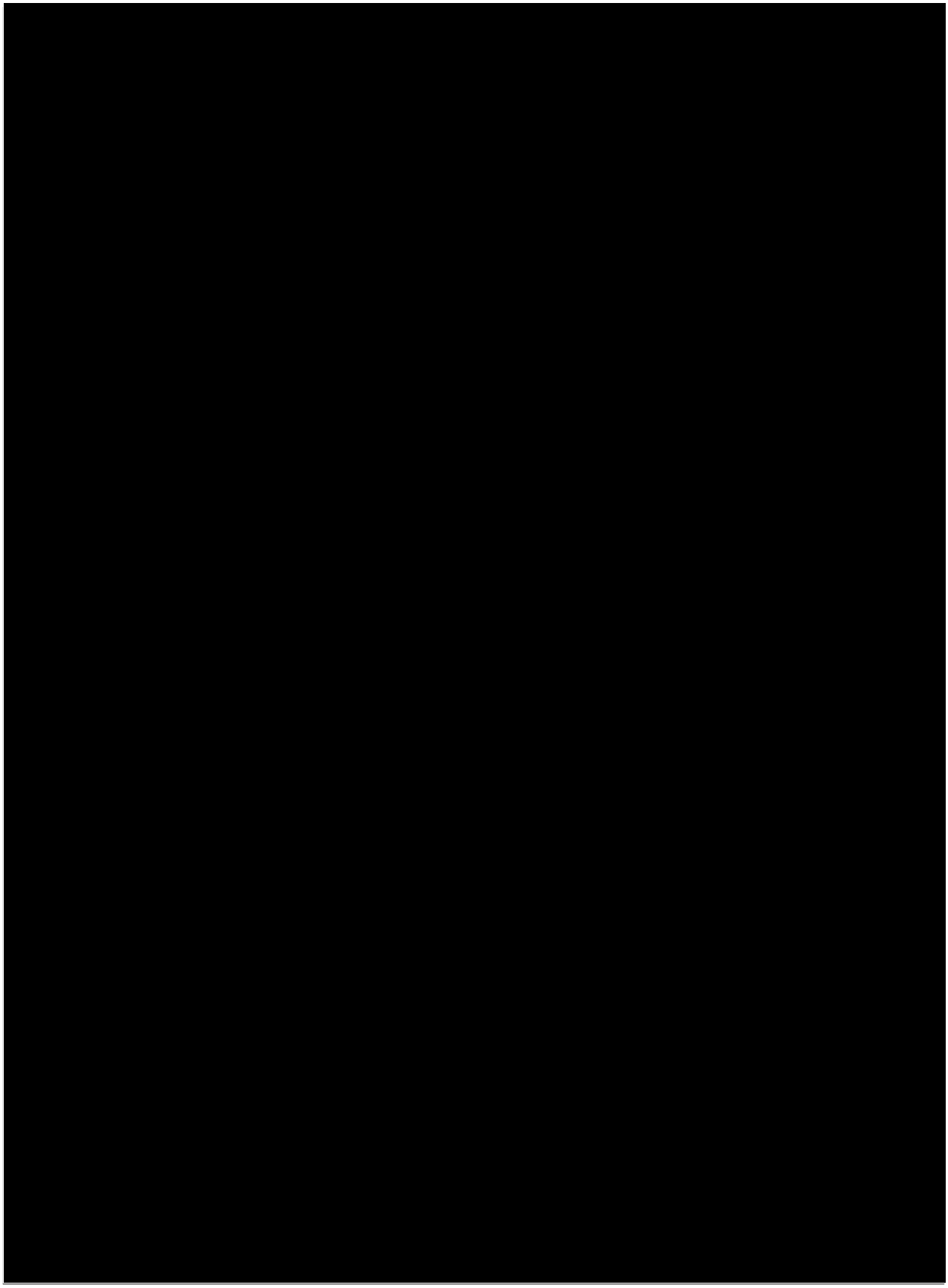
Specifically, tissue samples from the spinal cord, muscles, and organs will be collected as indicated in Table 9. Tissue samples will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

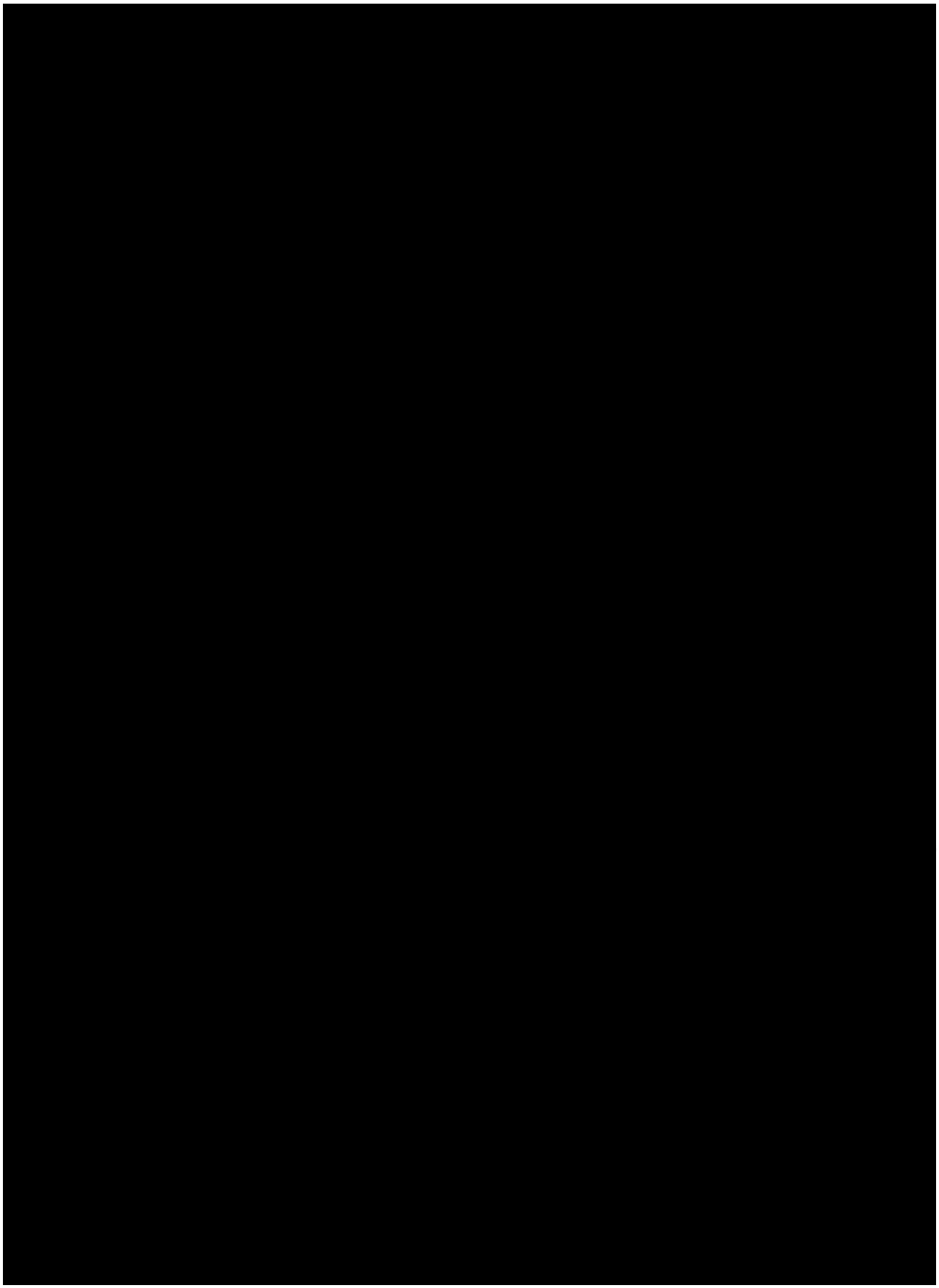
Families will be asked to consent to the autopsy and authorize tissue collection prior to any sign of moribund or death by the clinical team conducting the study. There are distinct forms for the formal autopsy and for the research tissue collection. This will allow families the flexibility to participate in one or both of the research activities. Declining an autopsy will not prevent patients from participating in the study.

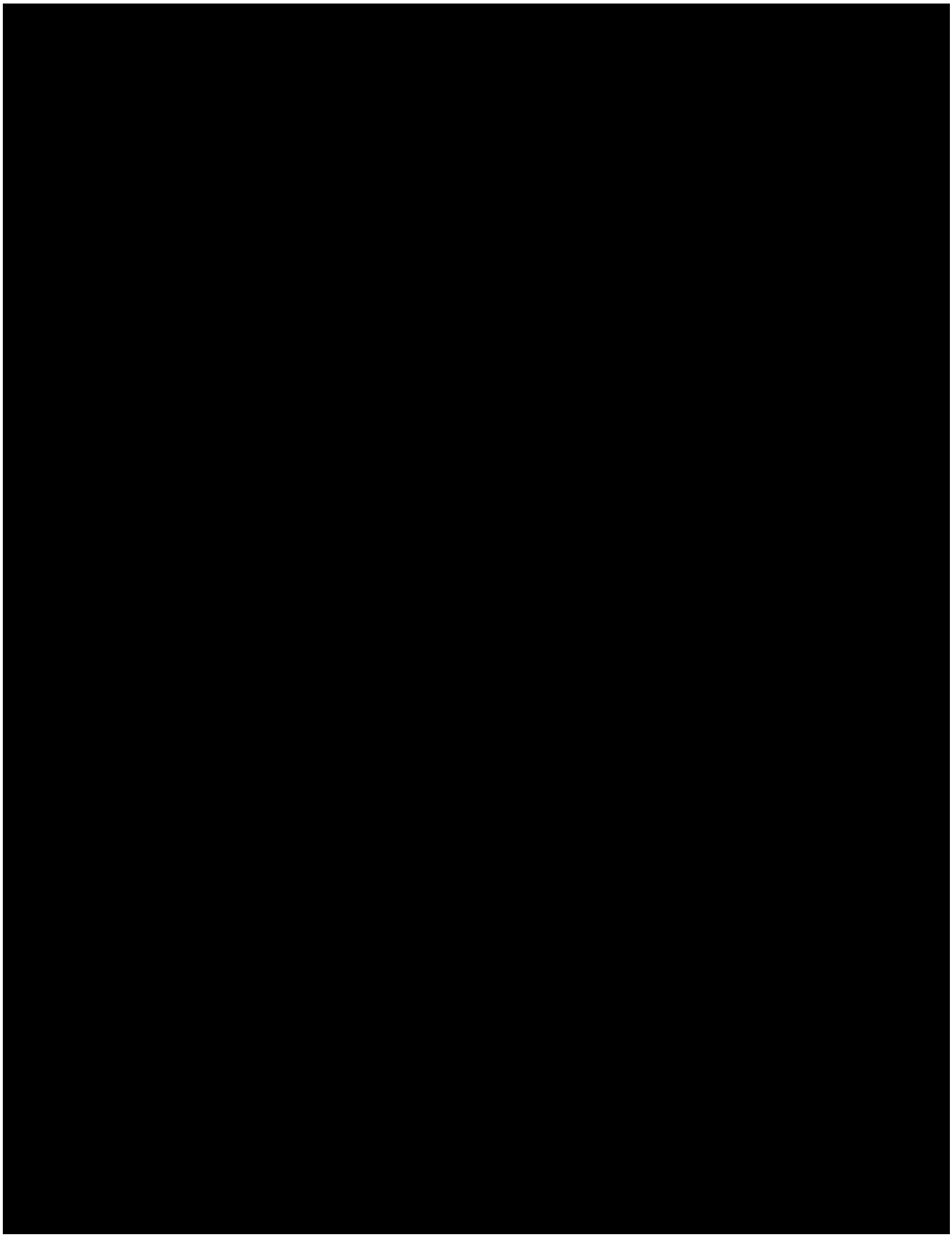
**Table 8: Tissue Sample for Analysis**

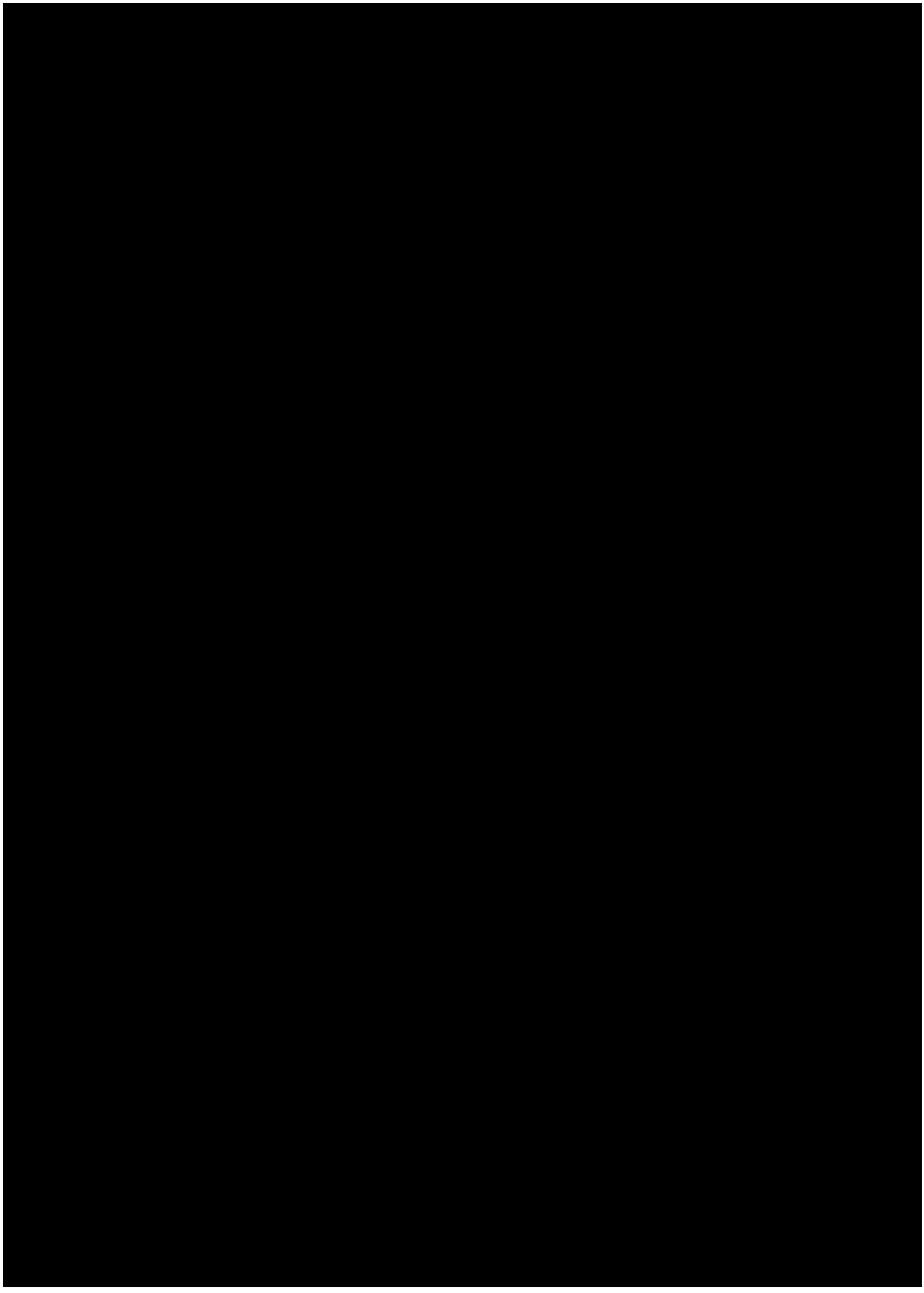
| Brain | Spinal Cord | Muscles | Organs |
|---|---|---|---|
| Motor cortex | Cervical spinal cord | Diaphragm | Spleen |
| Layer 5 motor cortex | Thoracic spinal cord | #6/#7 Rib with intercostal muscle and nerve | Kidney |
| Brain stem | Lumbar spinal cord | Psoas muscle | Small intestine |
| | Sacral spinal cord | | Large intestine |
| | Dorsal root | | Pancreas |
| | Cervical level | | Stomach |
| | Ventral root | | Lung |
| | Cervical level | | Heart |
| | DRG root | | Liver |
| | Cervical level | | Inguinal lymph node |
| | Cerebrospinal fluid | | Gonads |

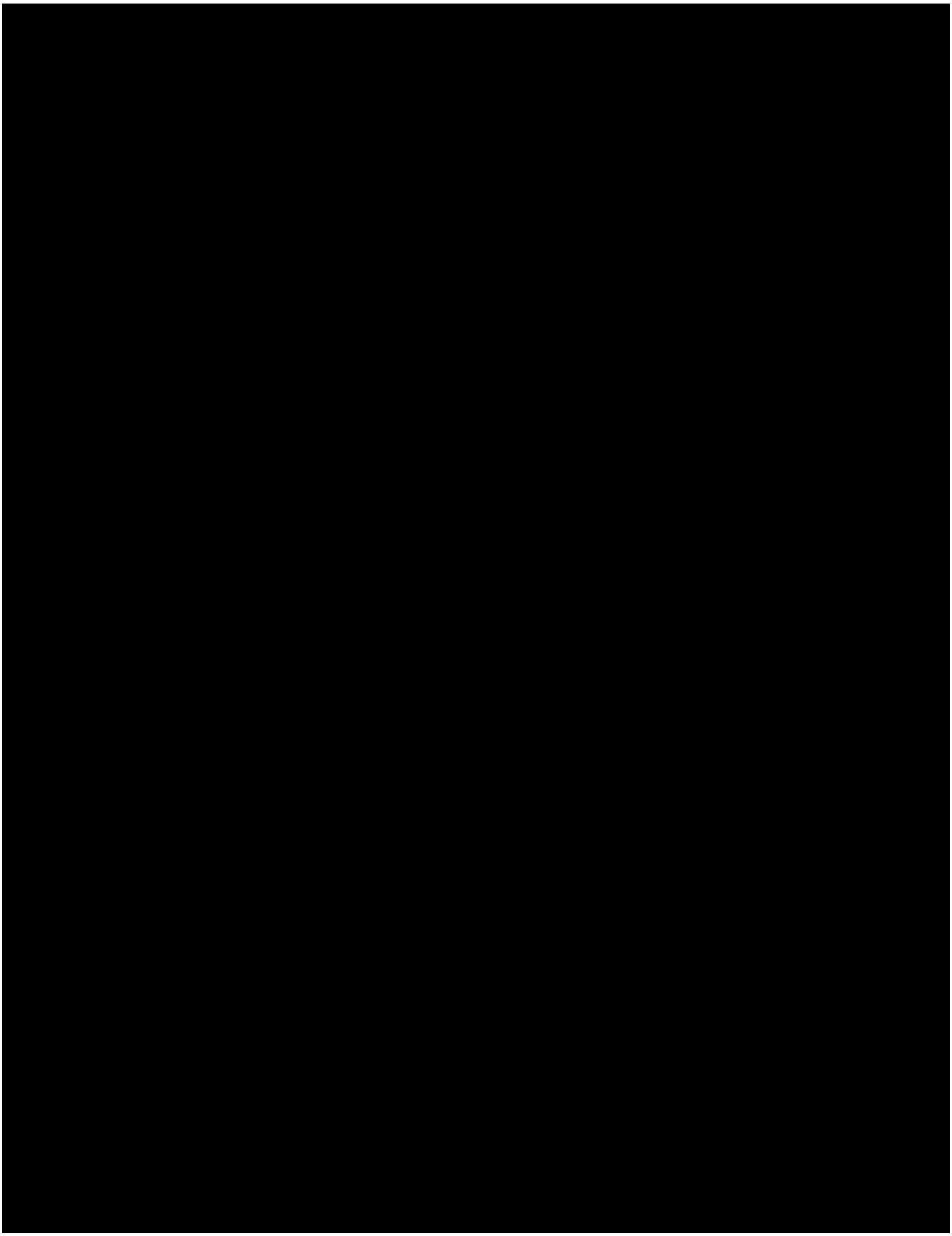
# APPENDIX 3. BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3)

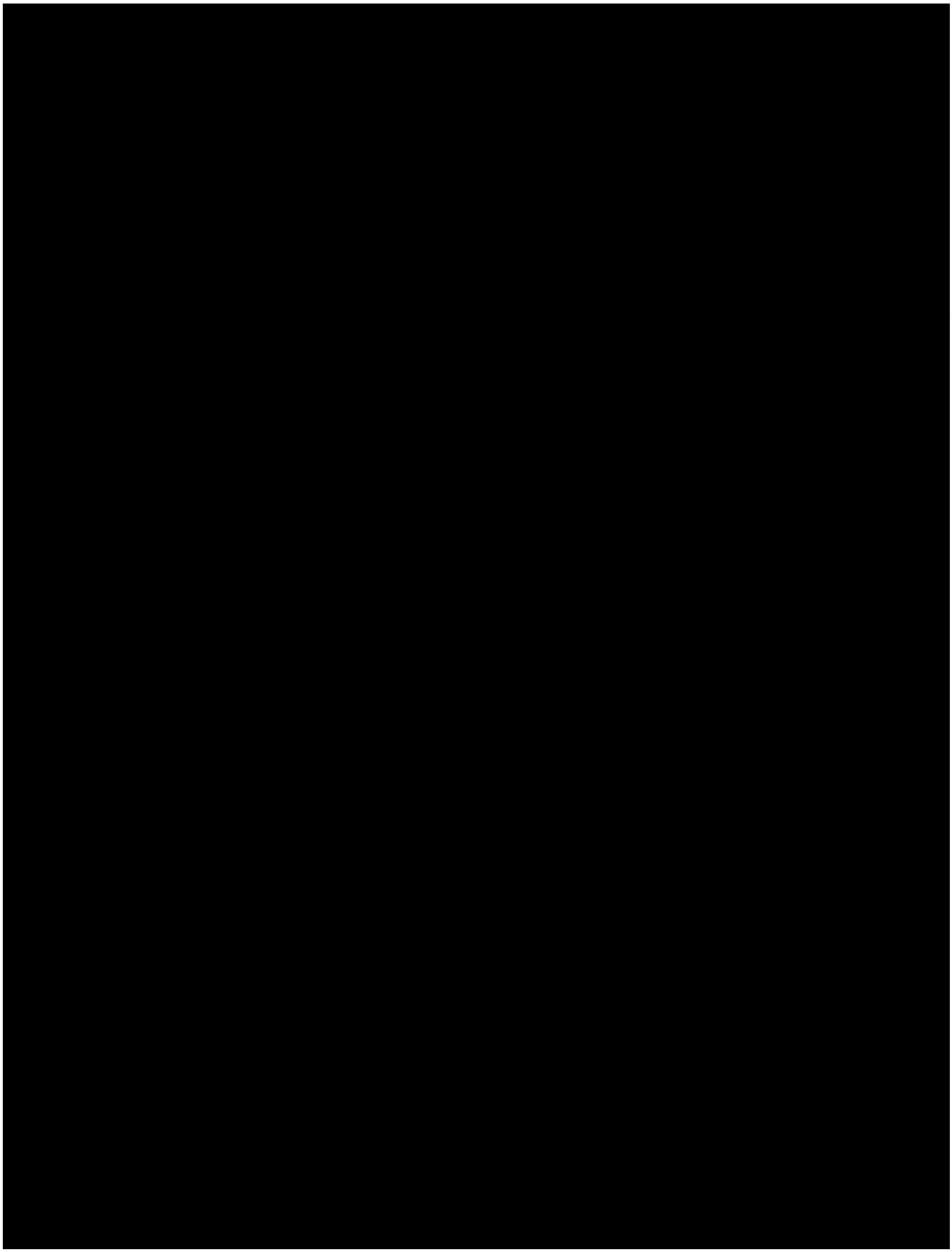


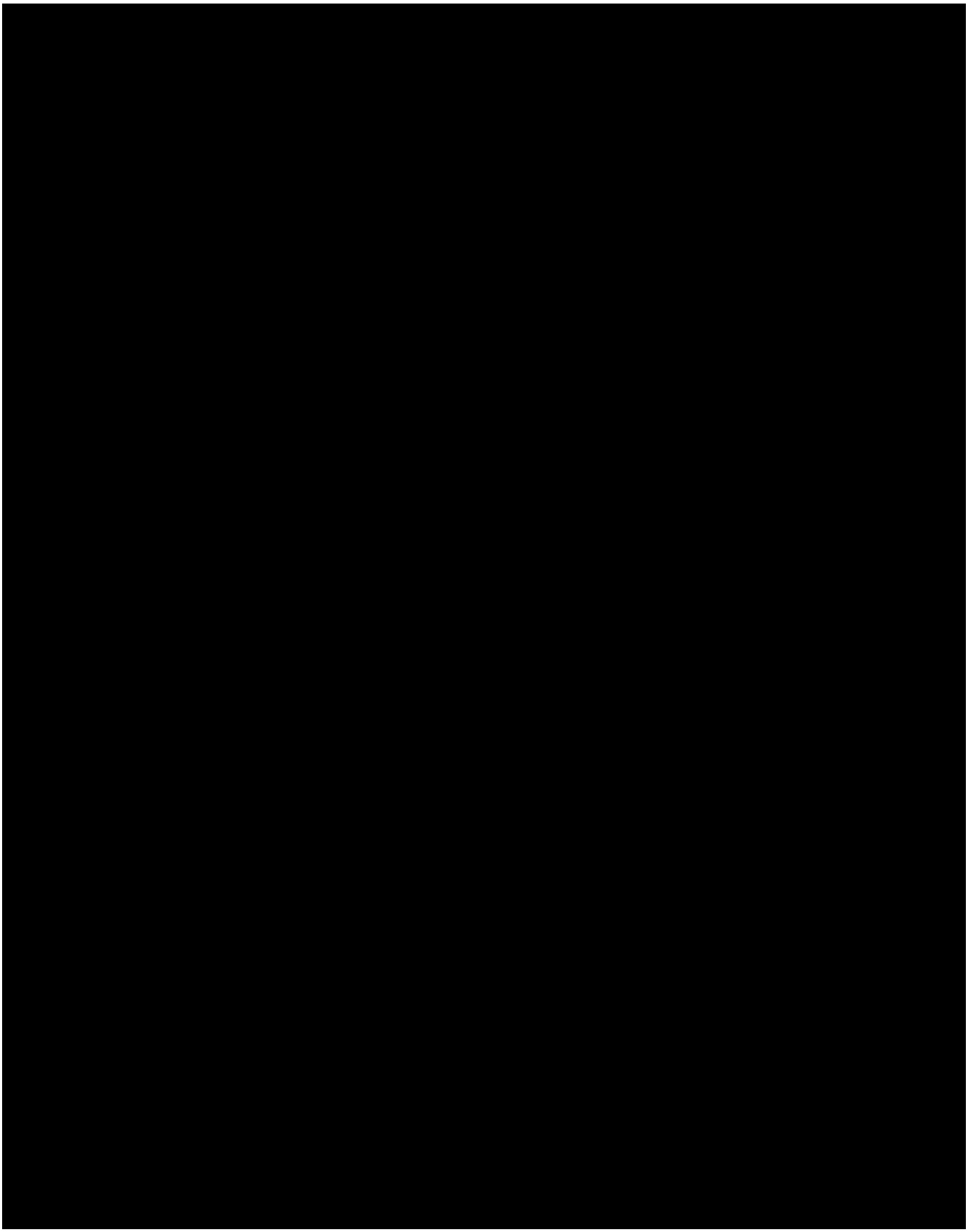


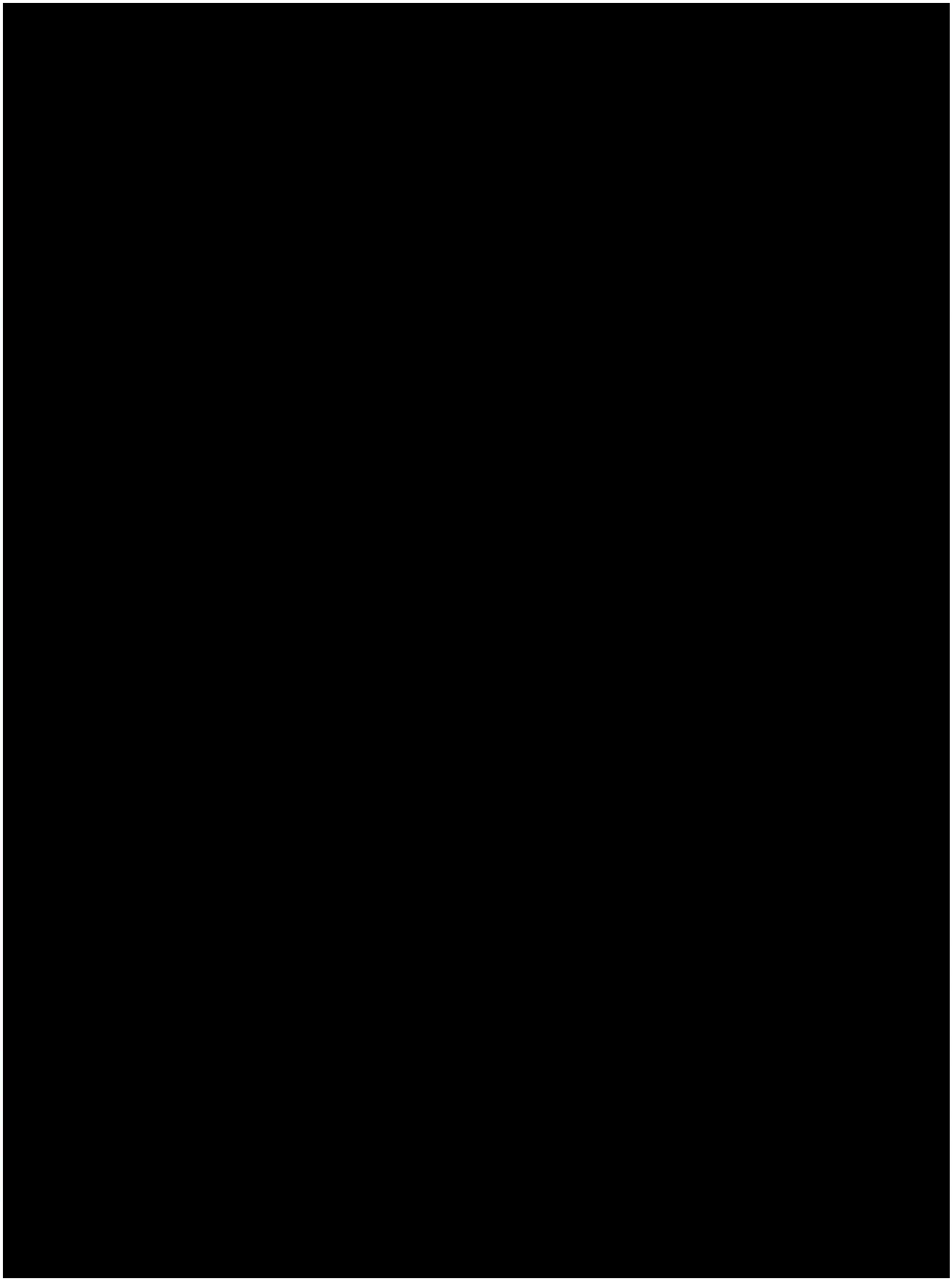


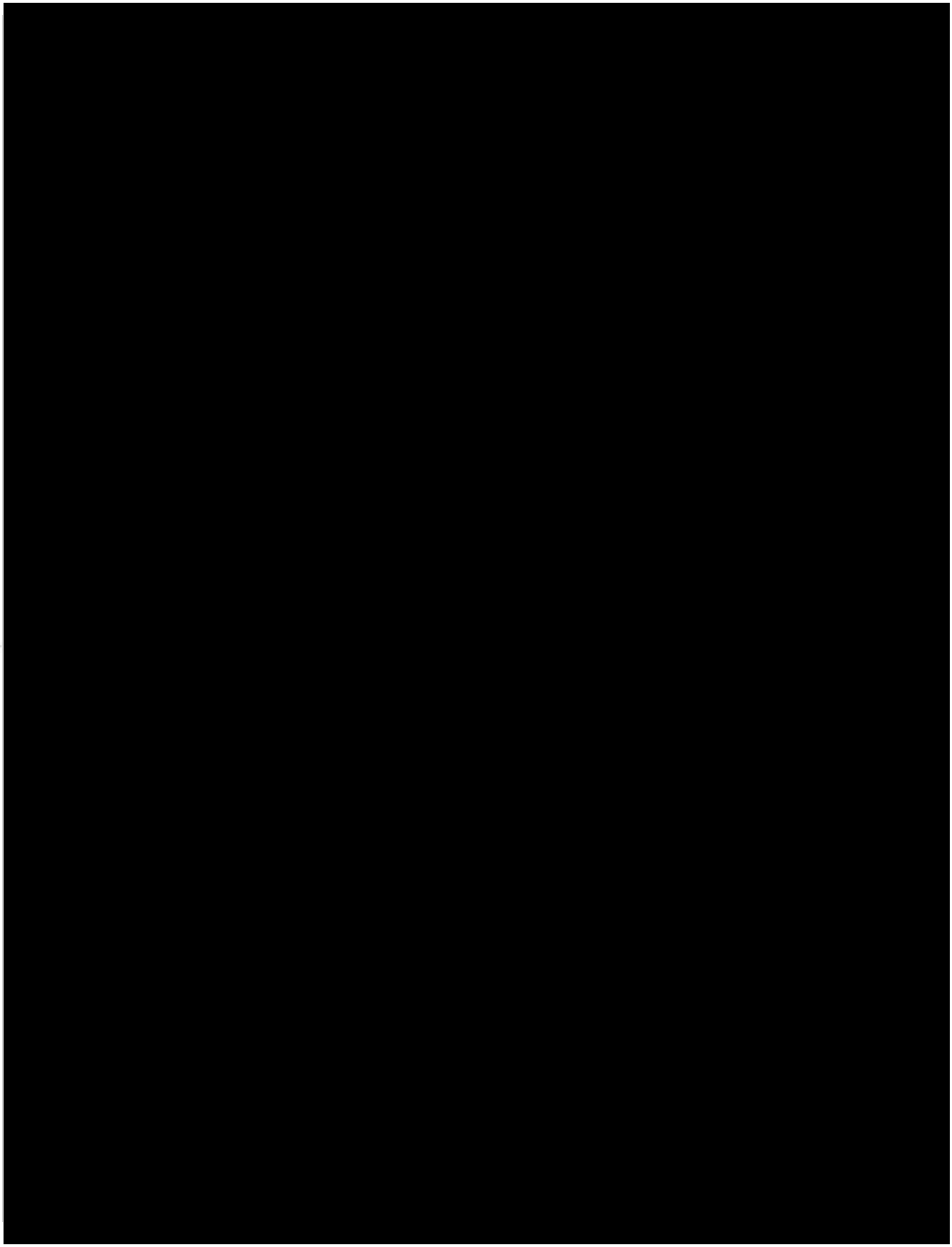


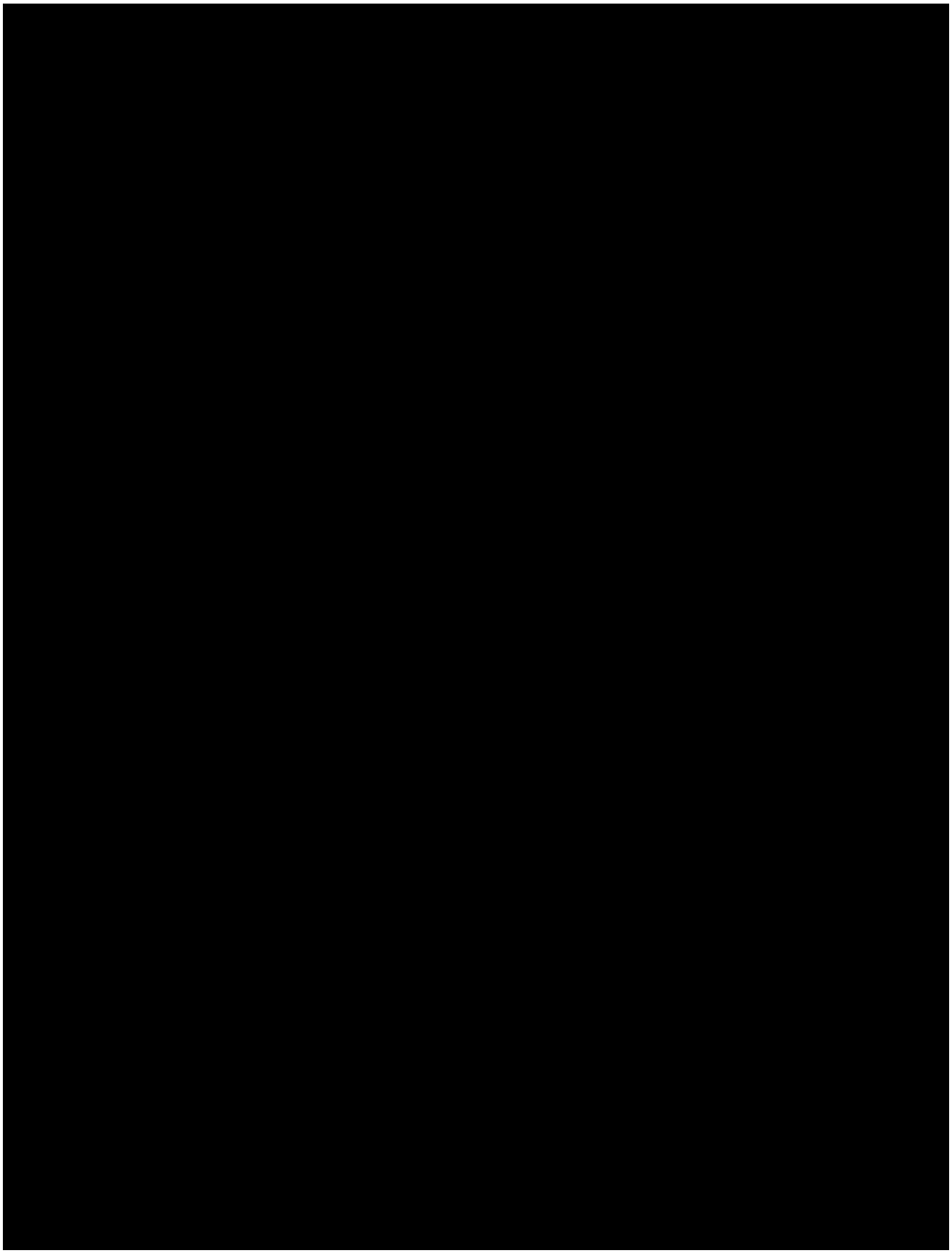


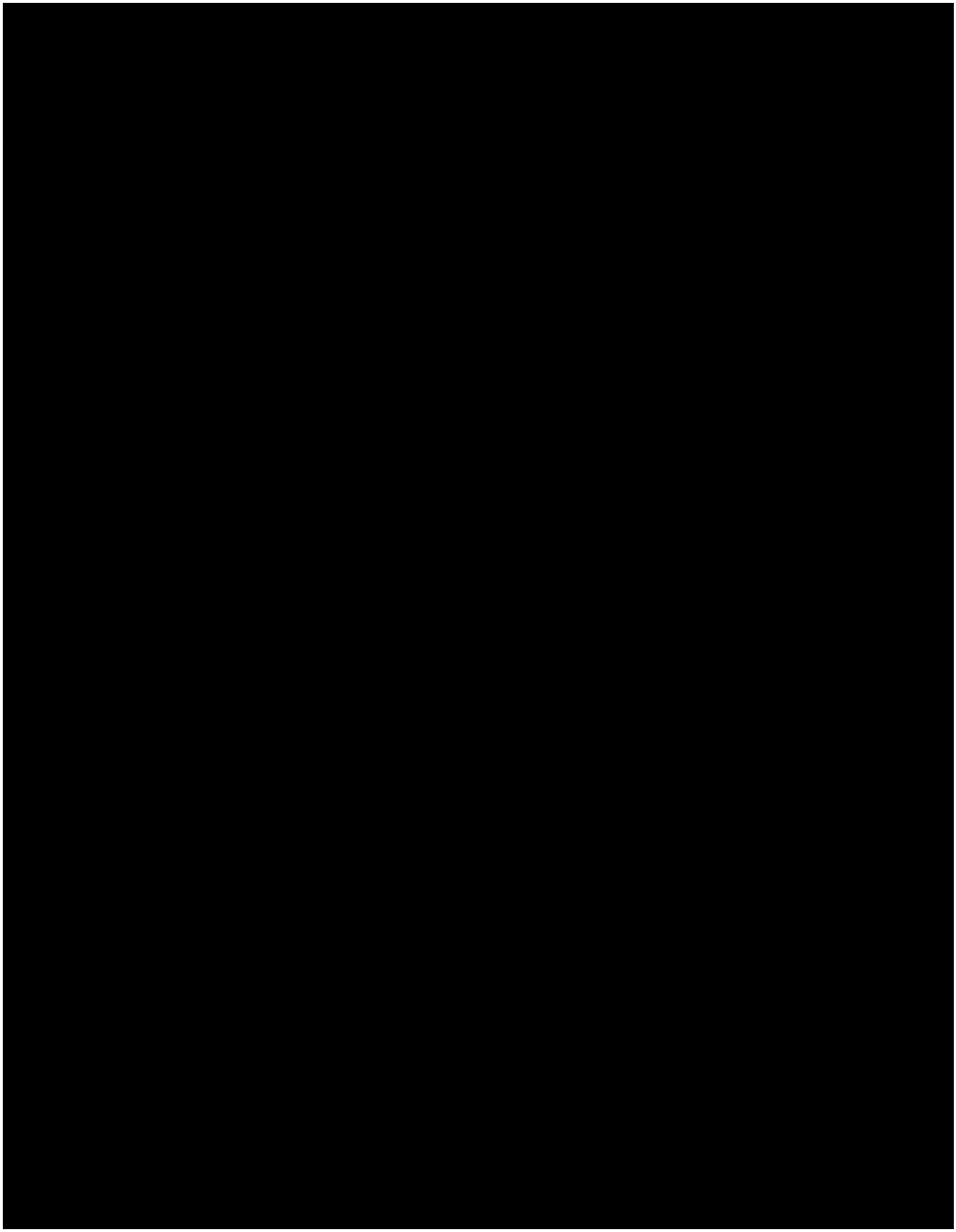


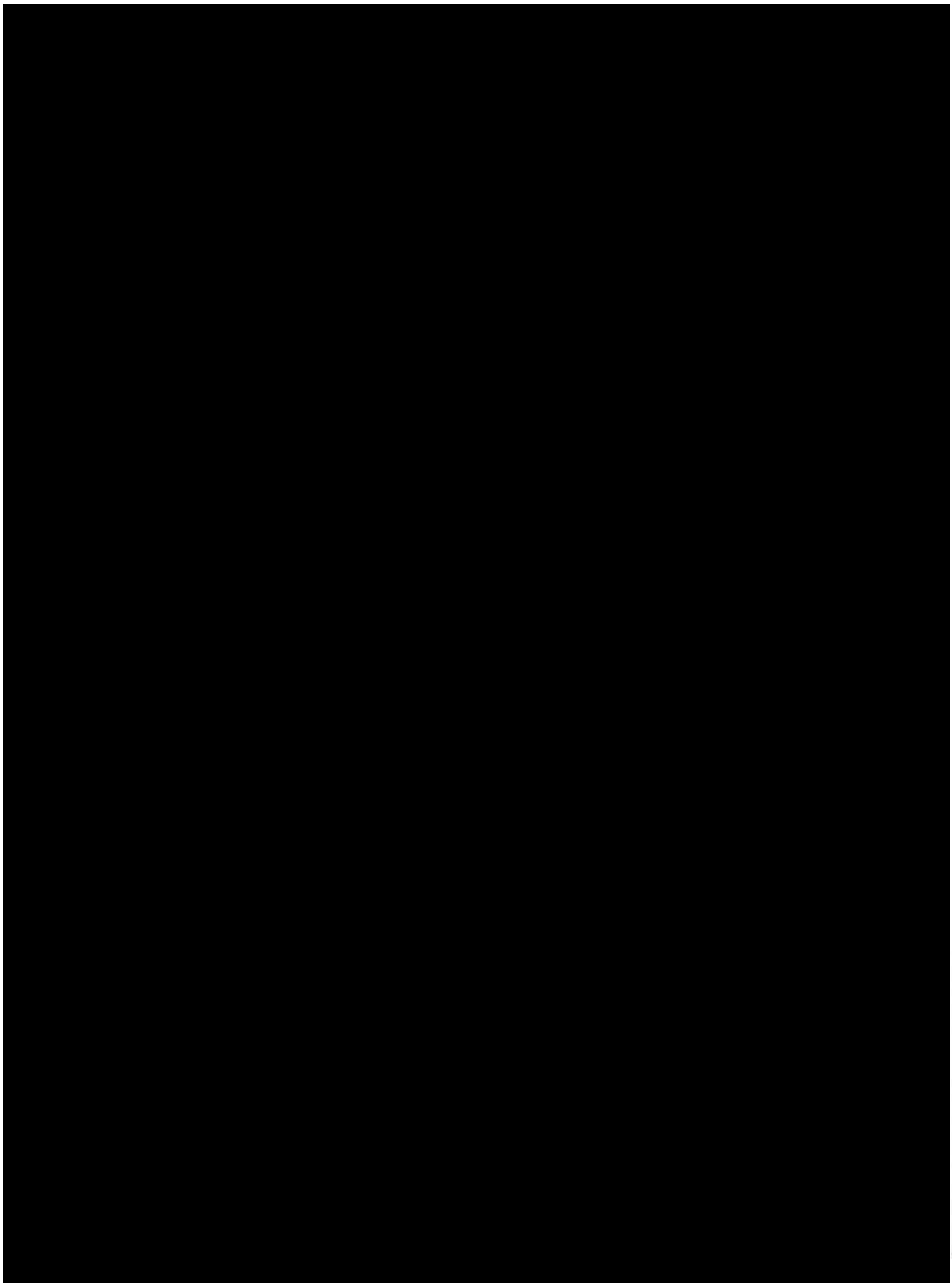


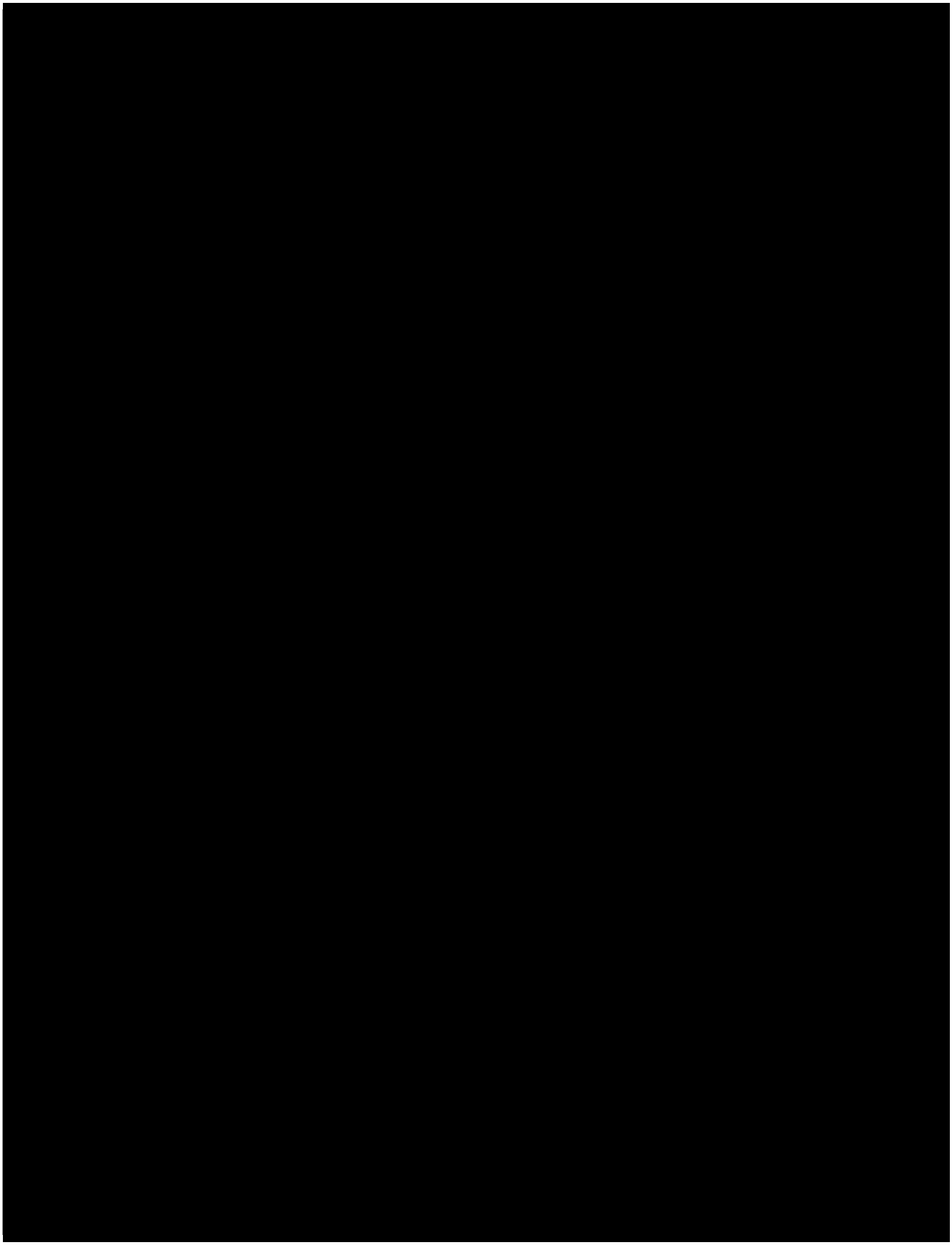


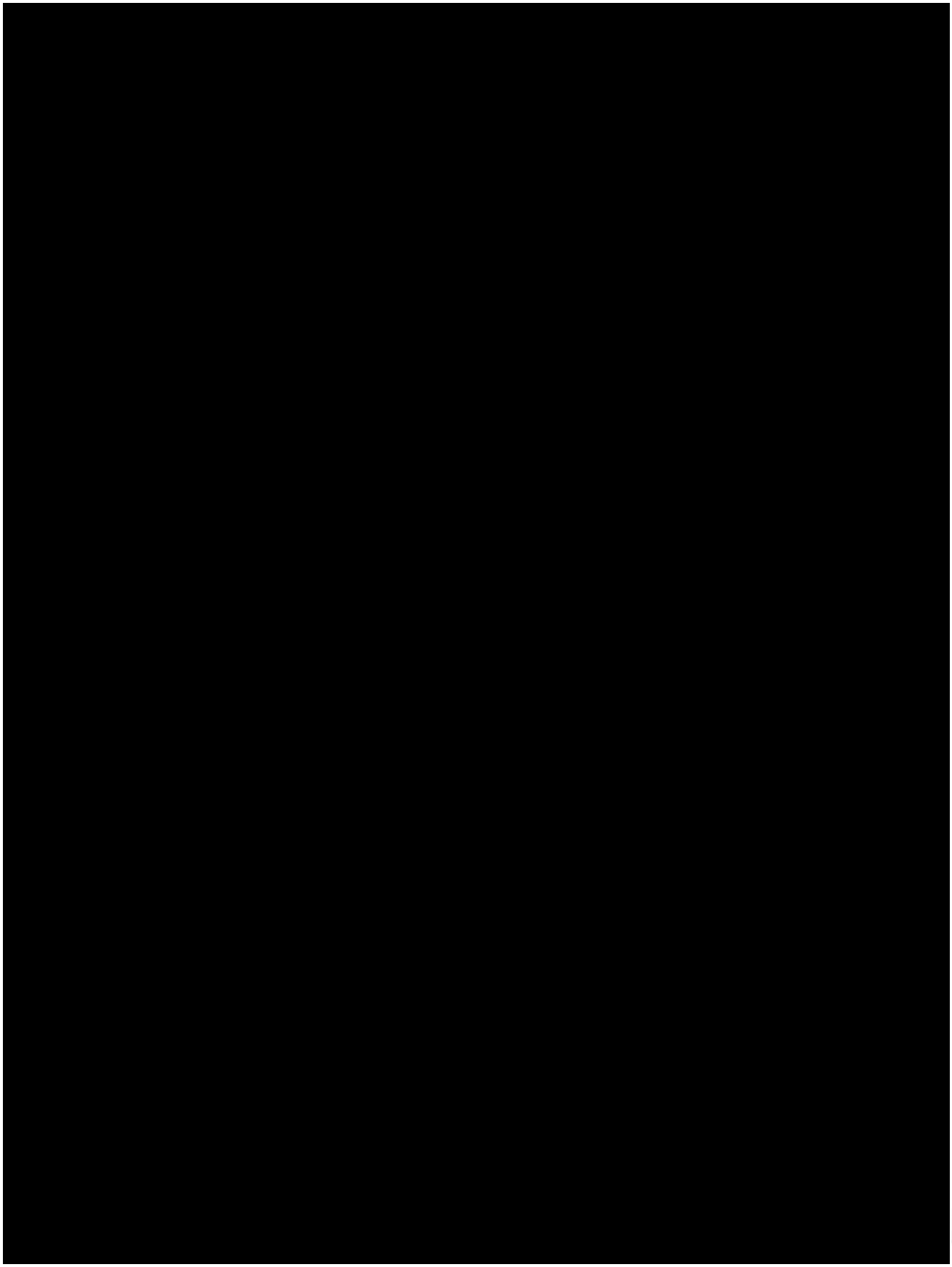


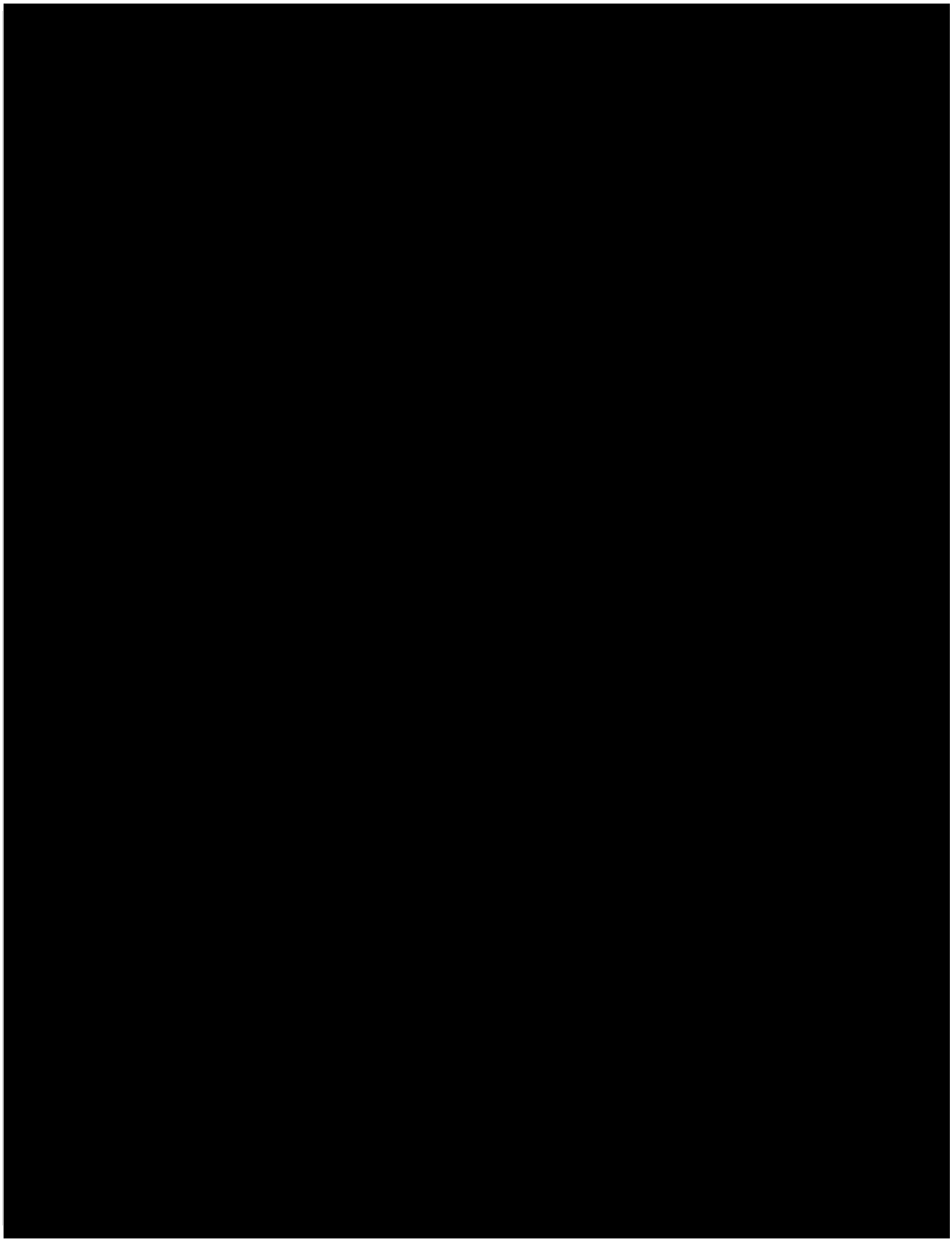


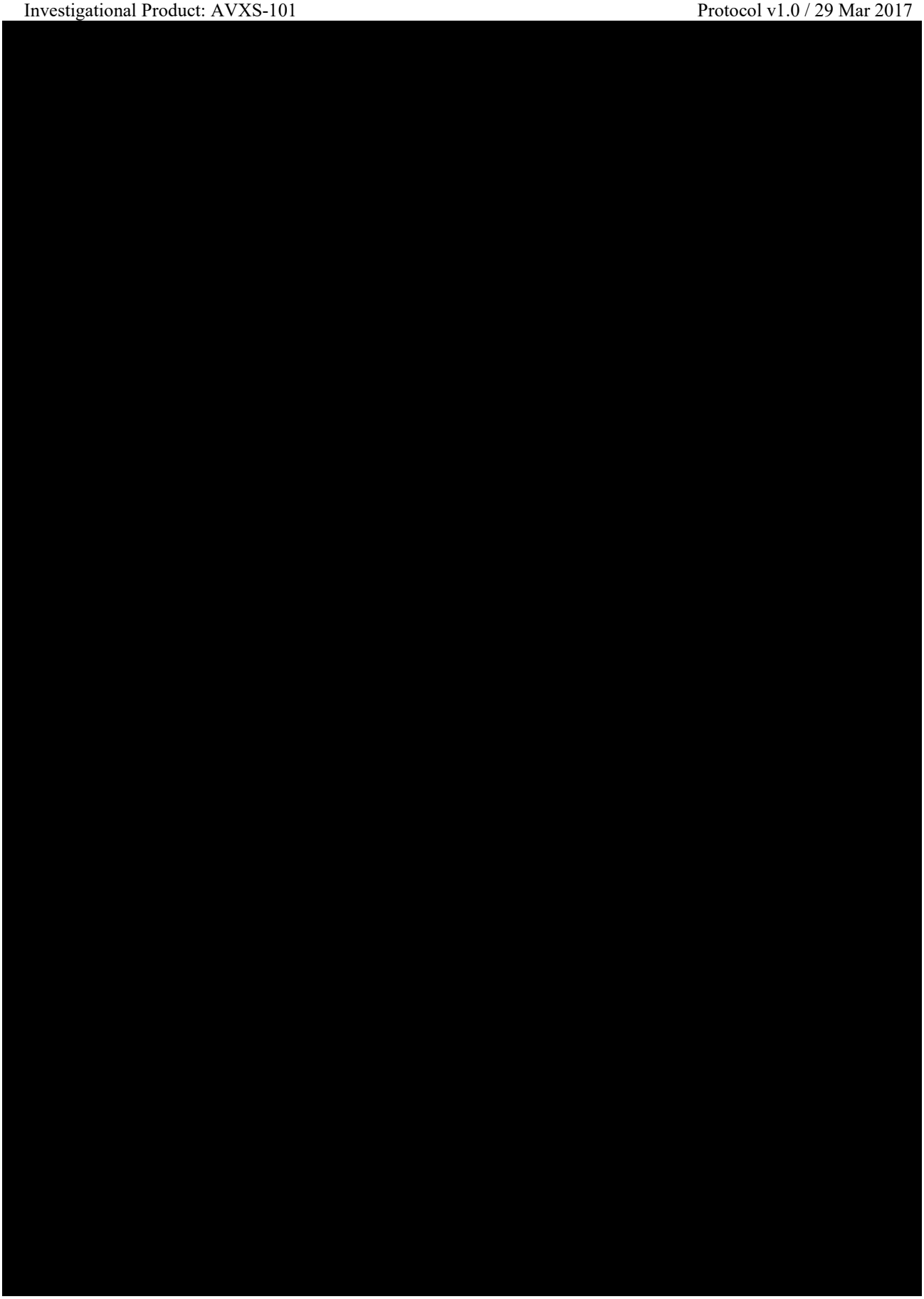


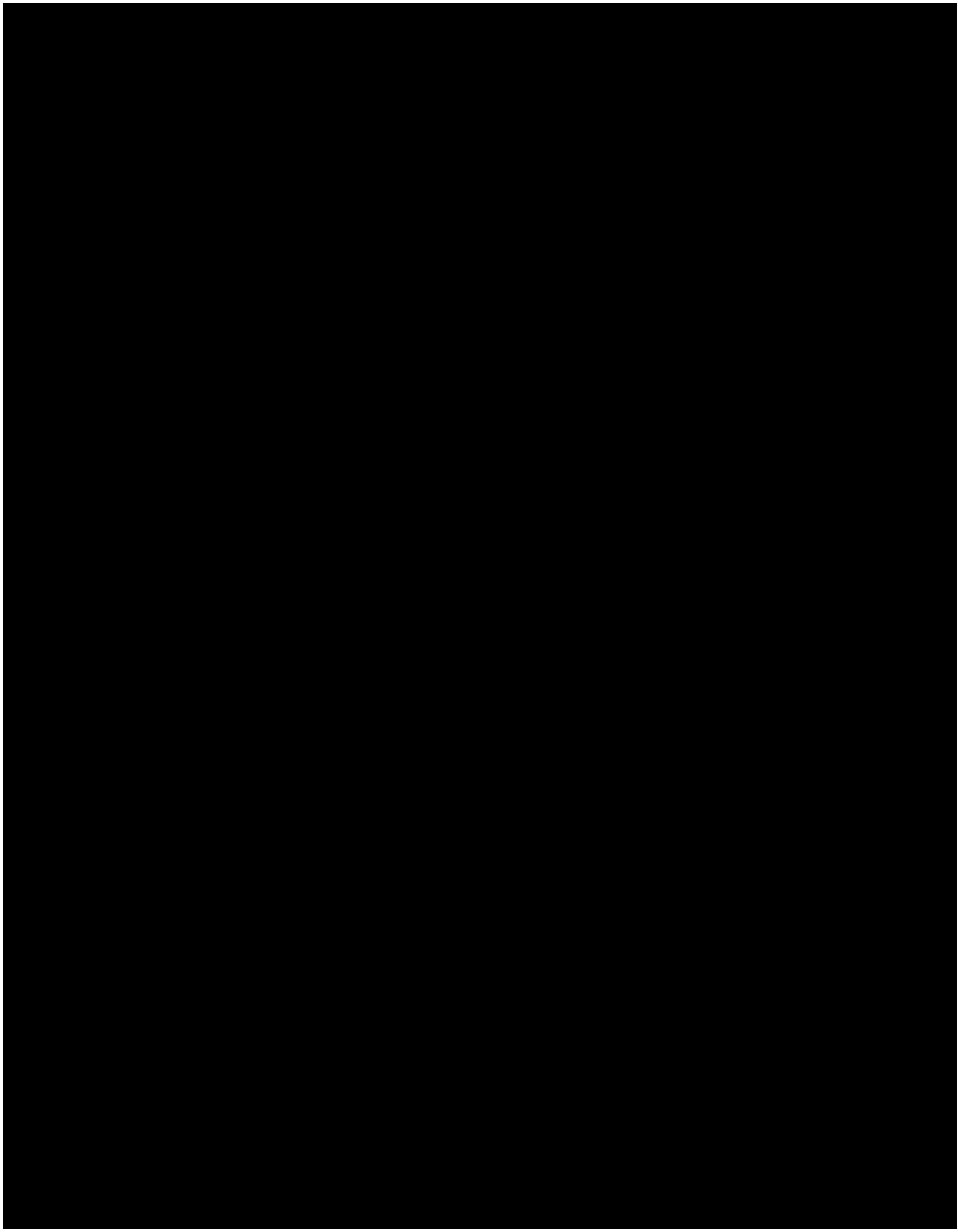


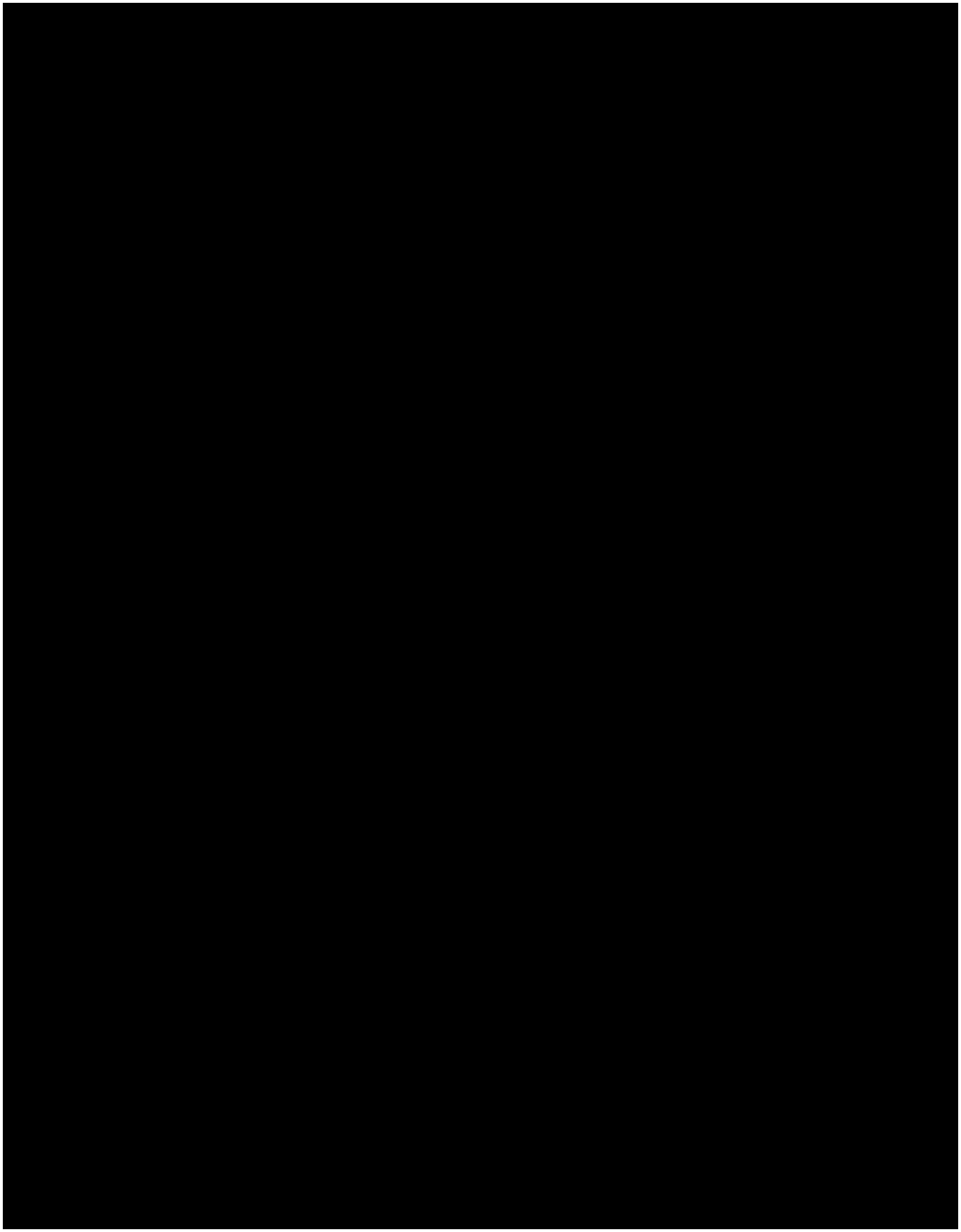


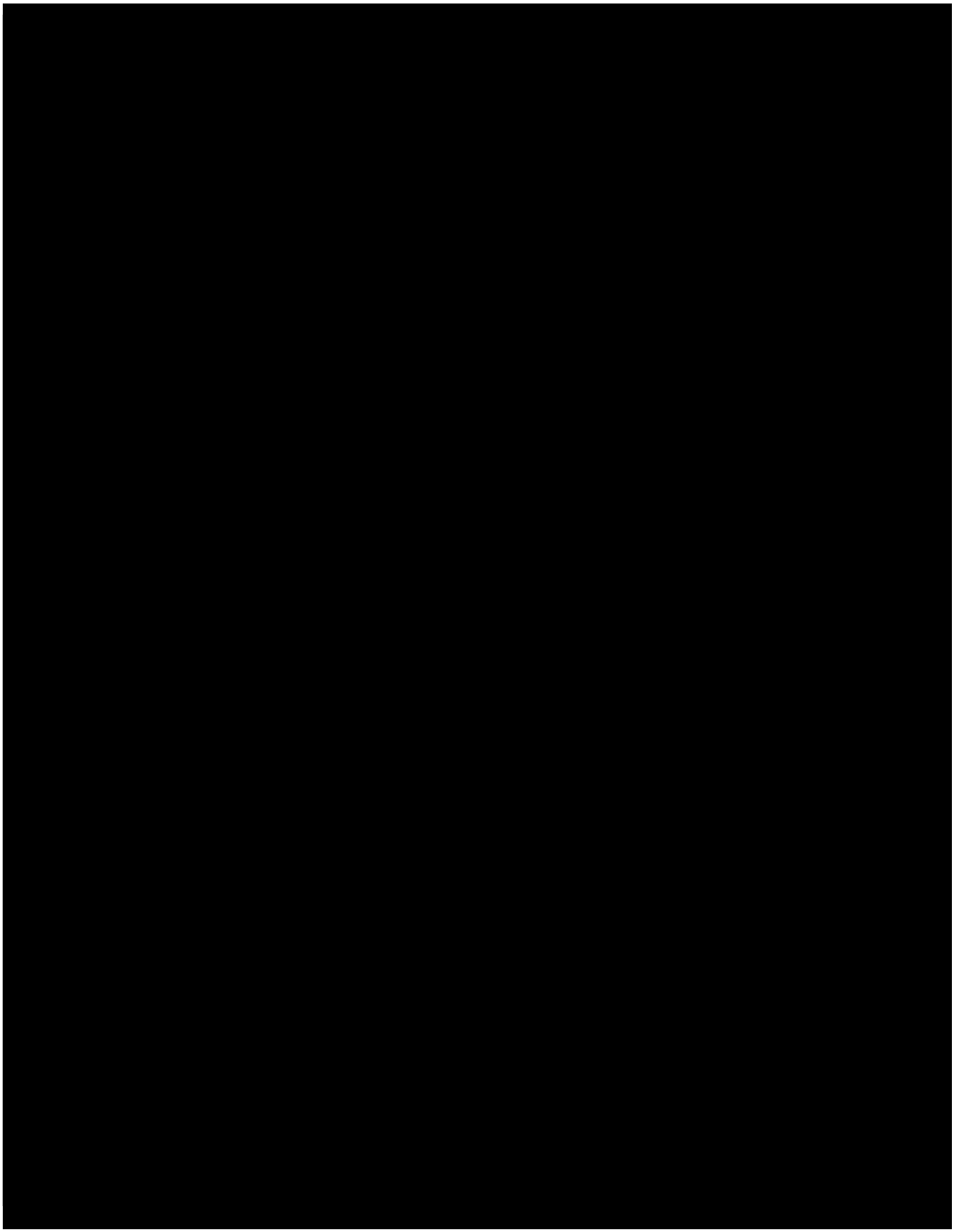


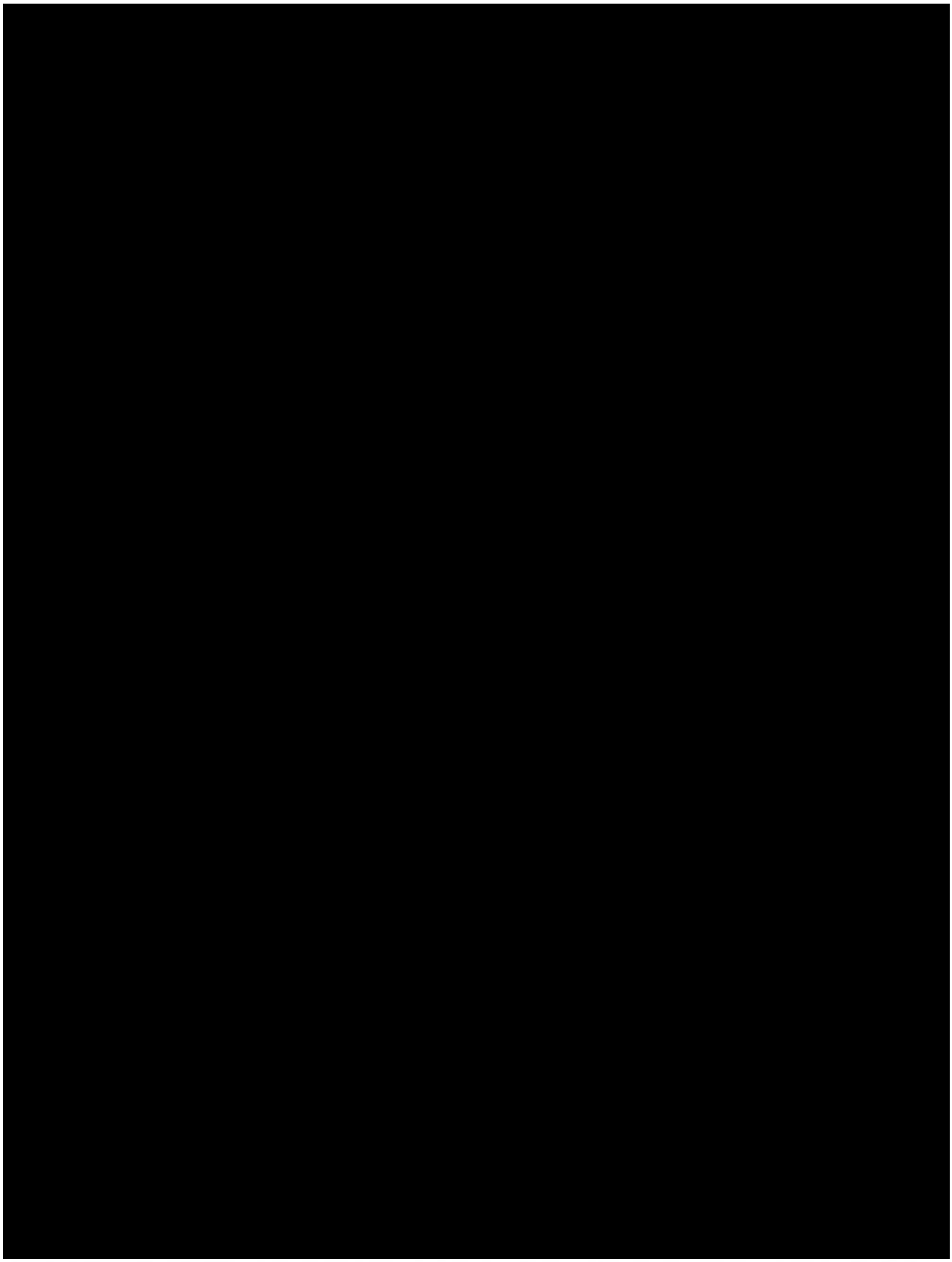


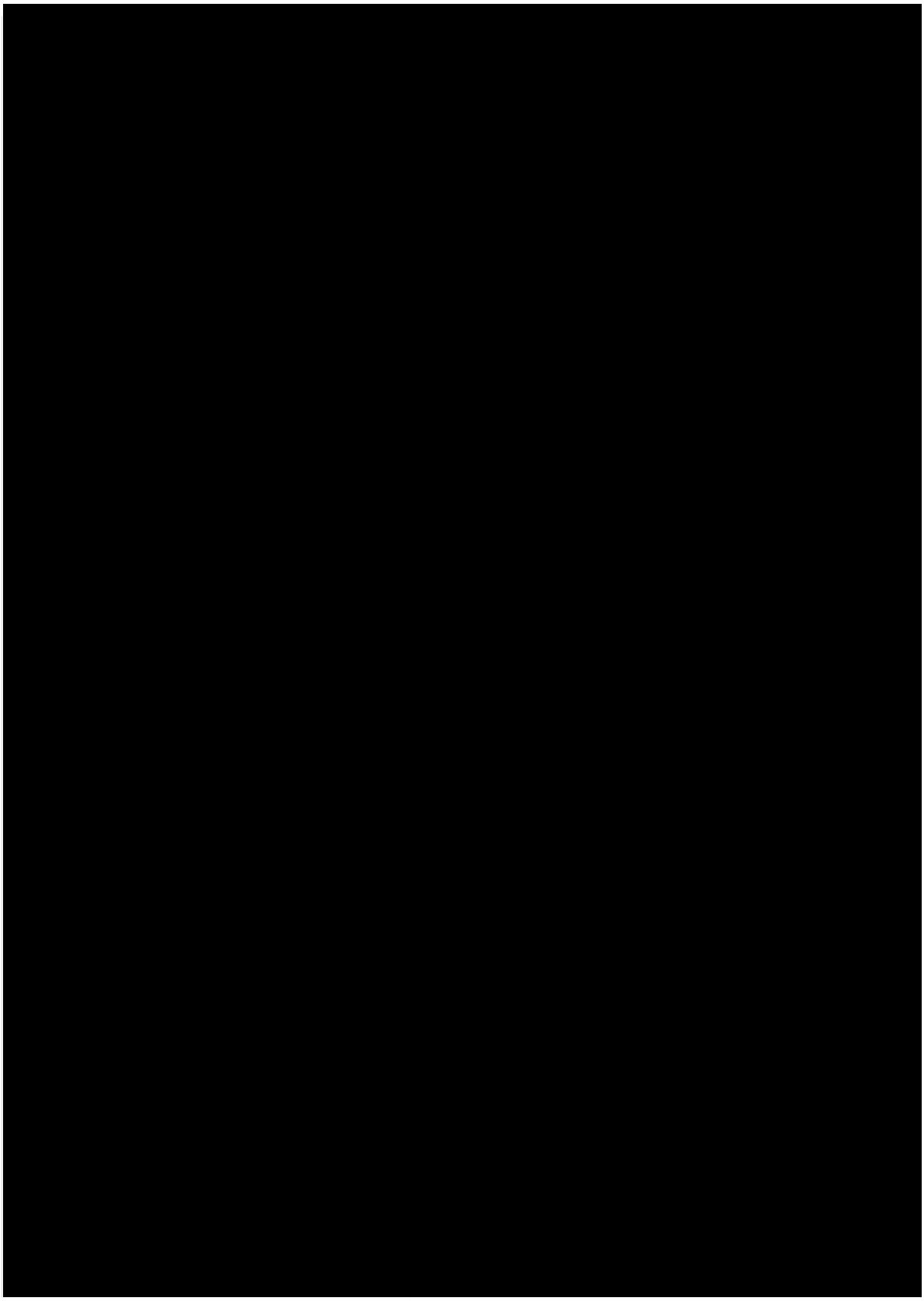


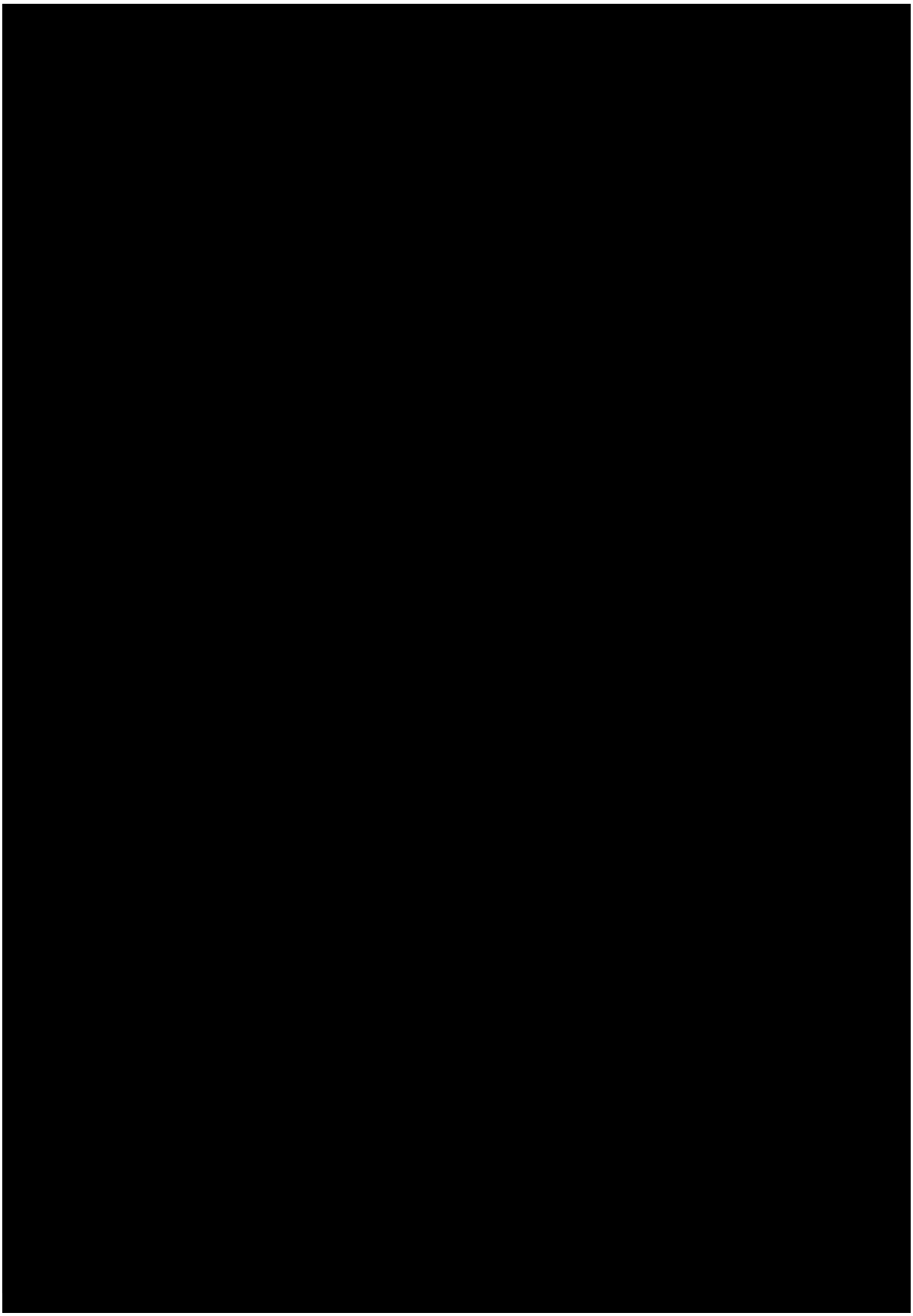


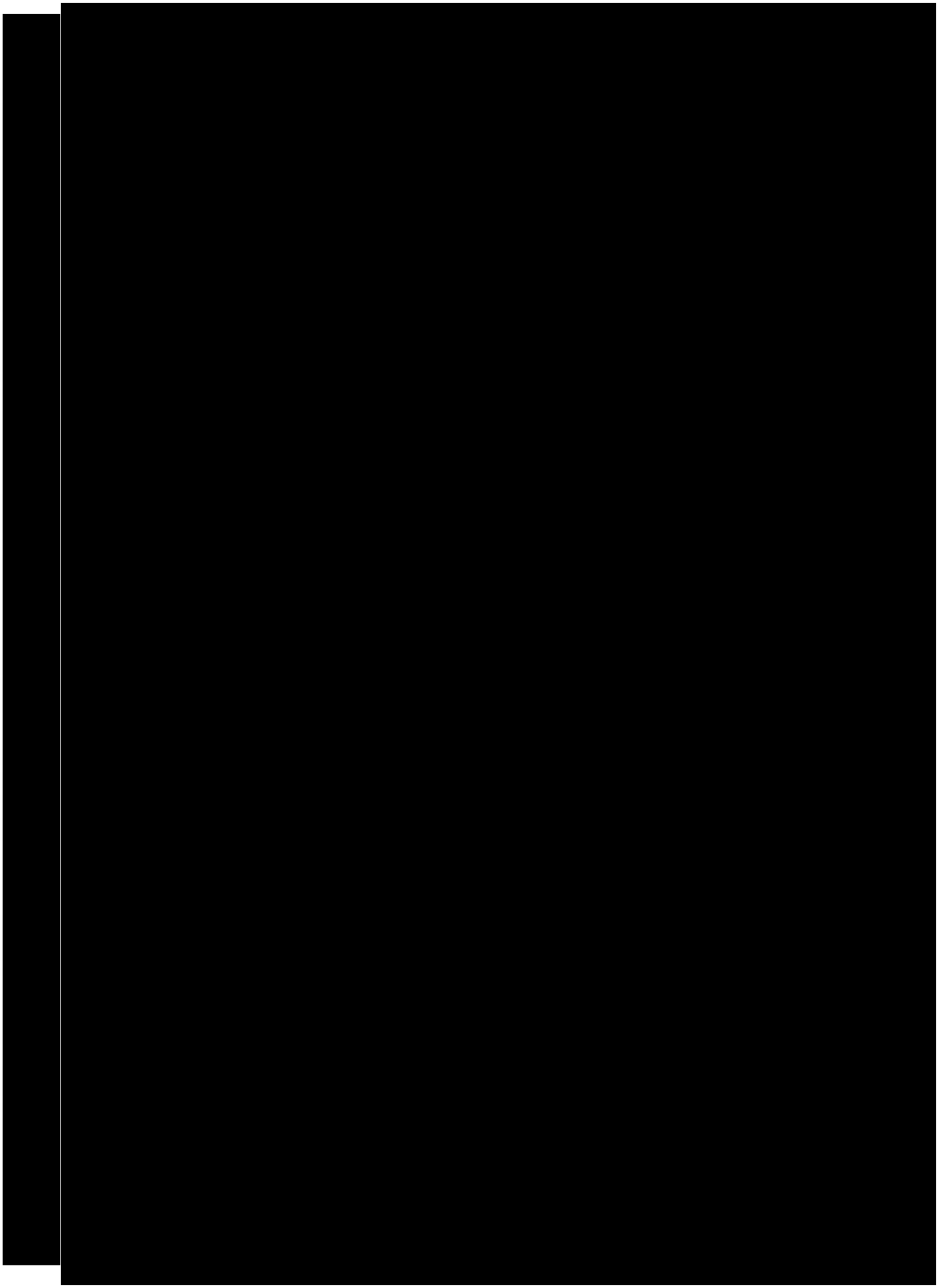


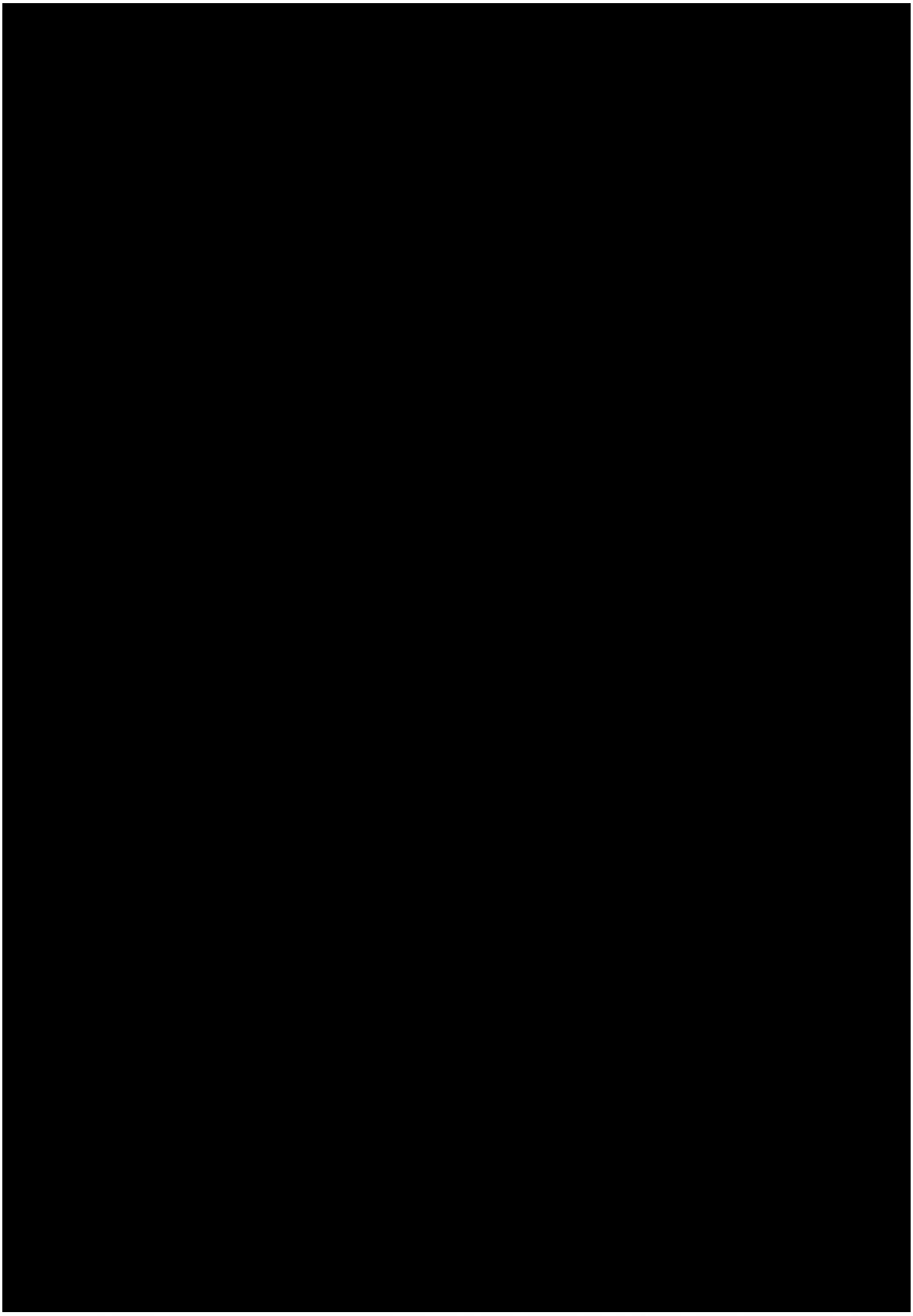


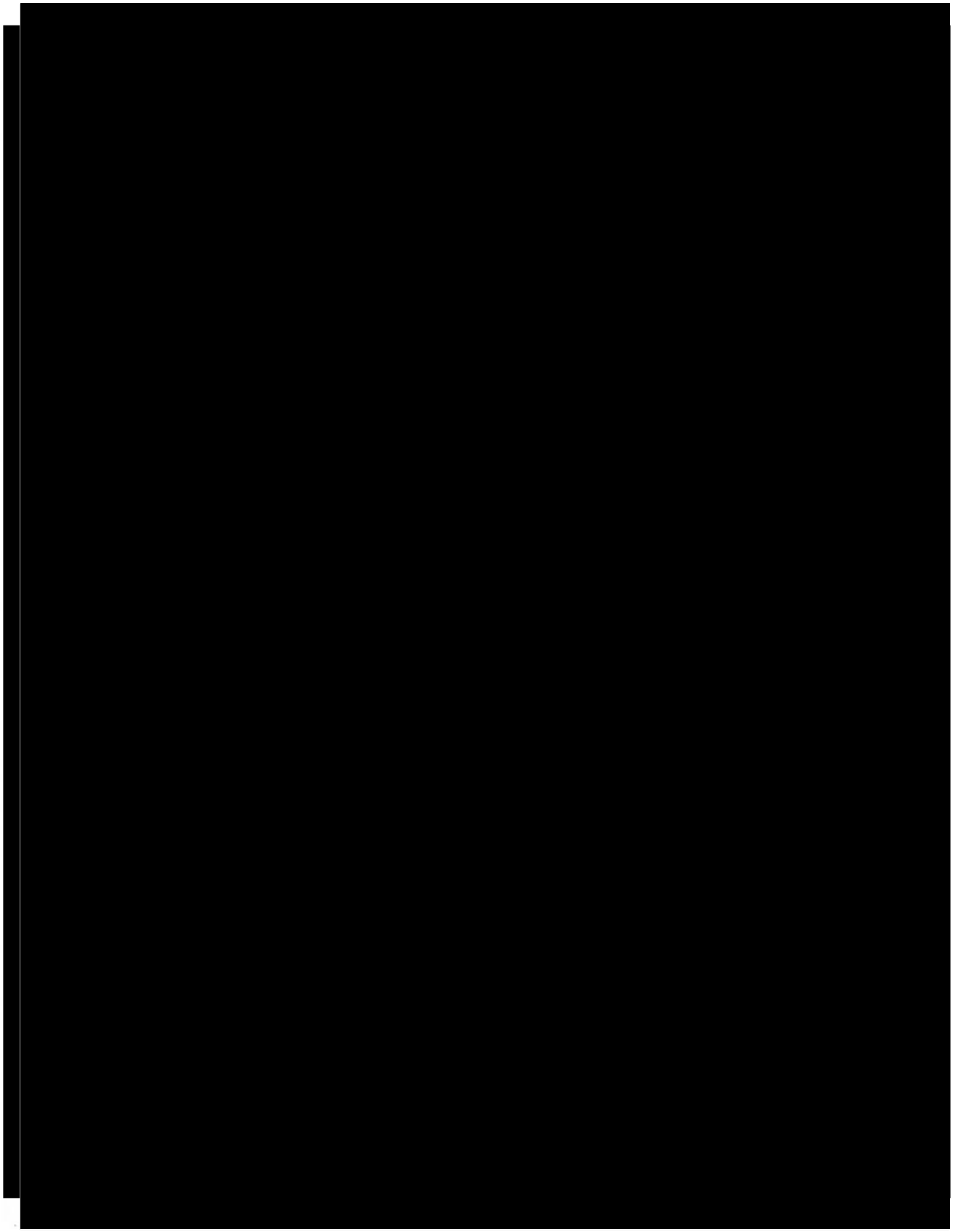


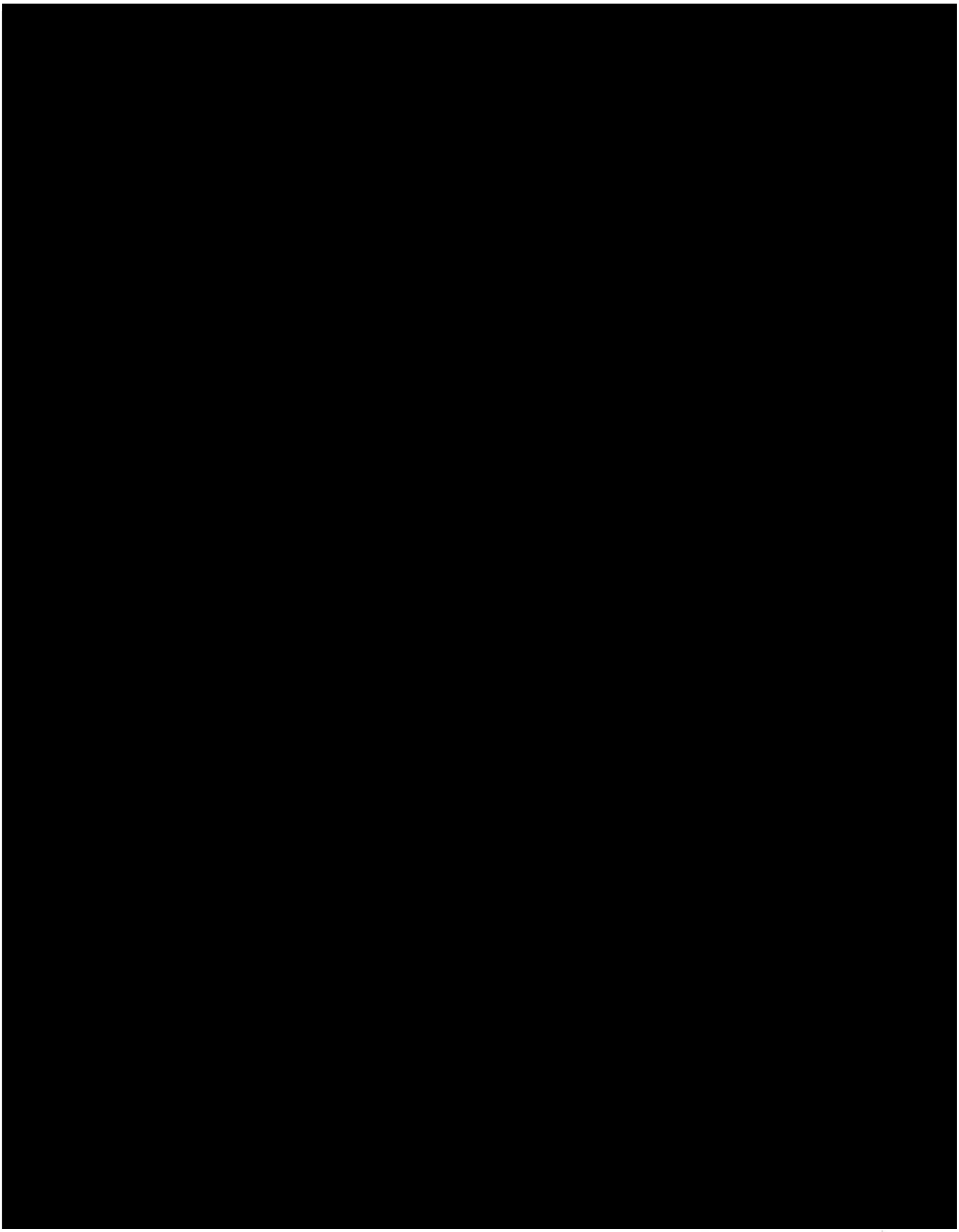


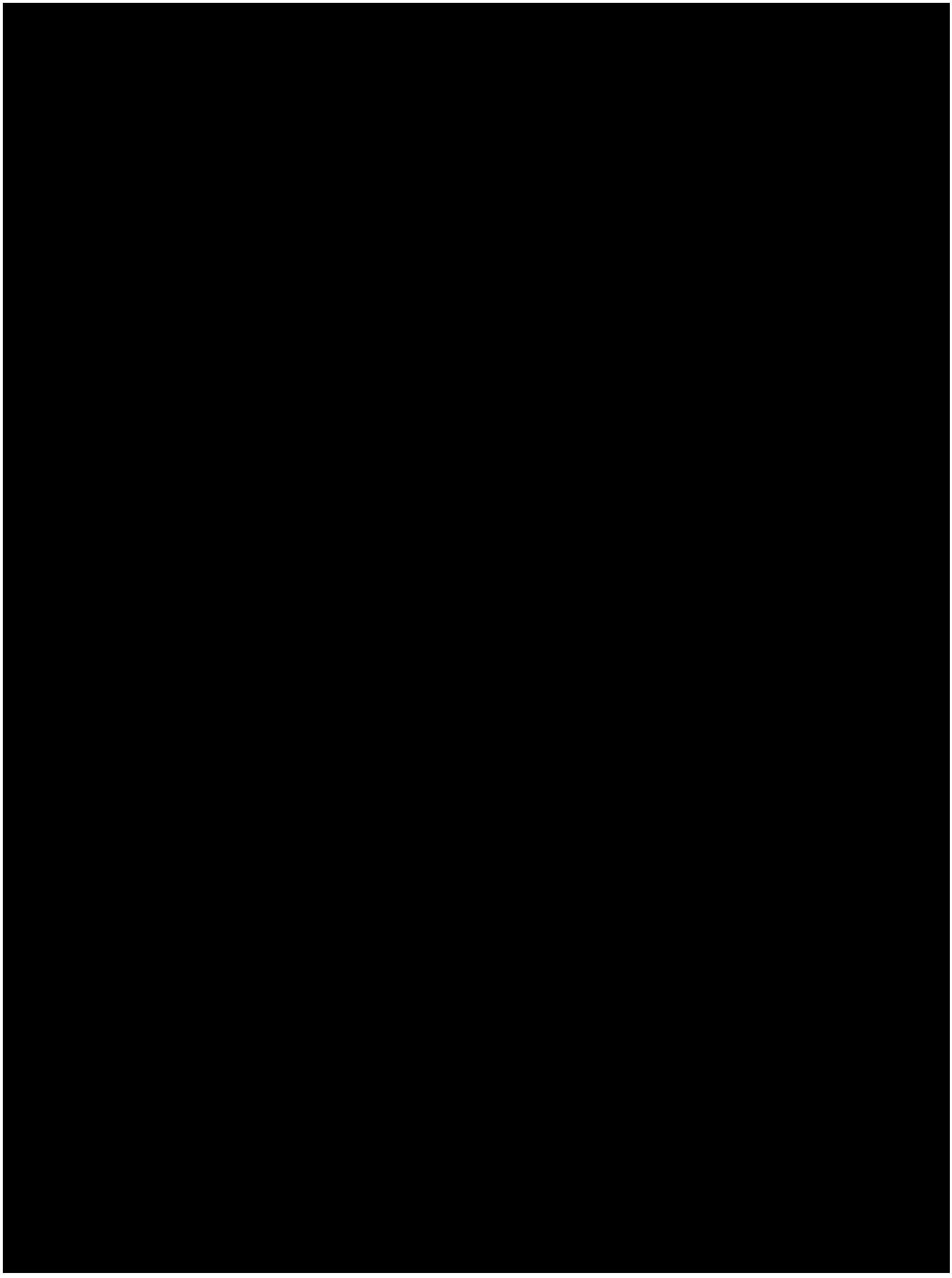


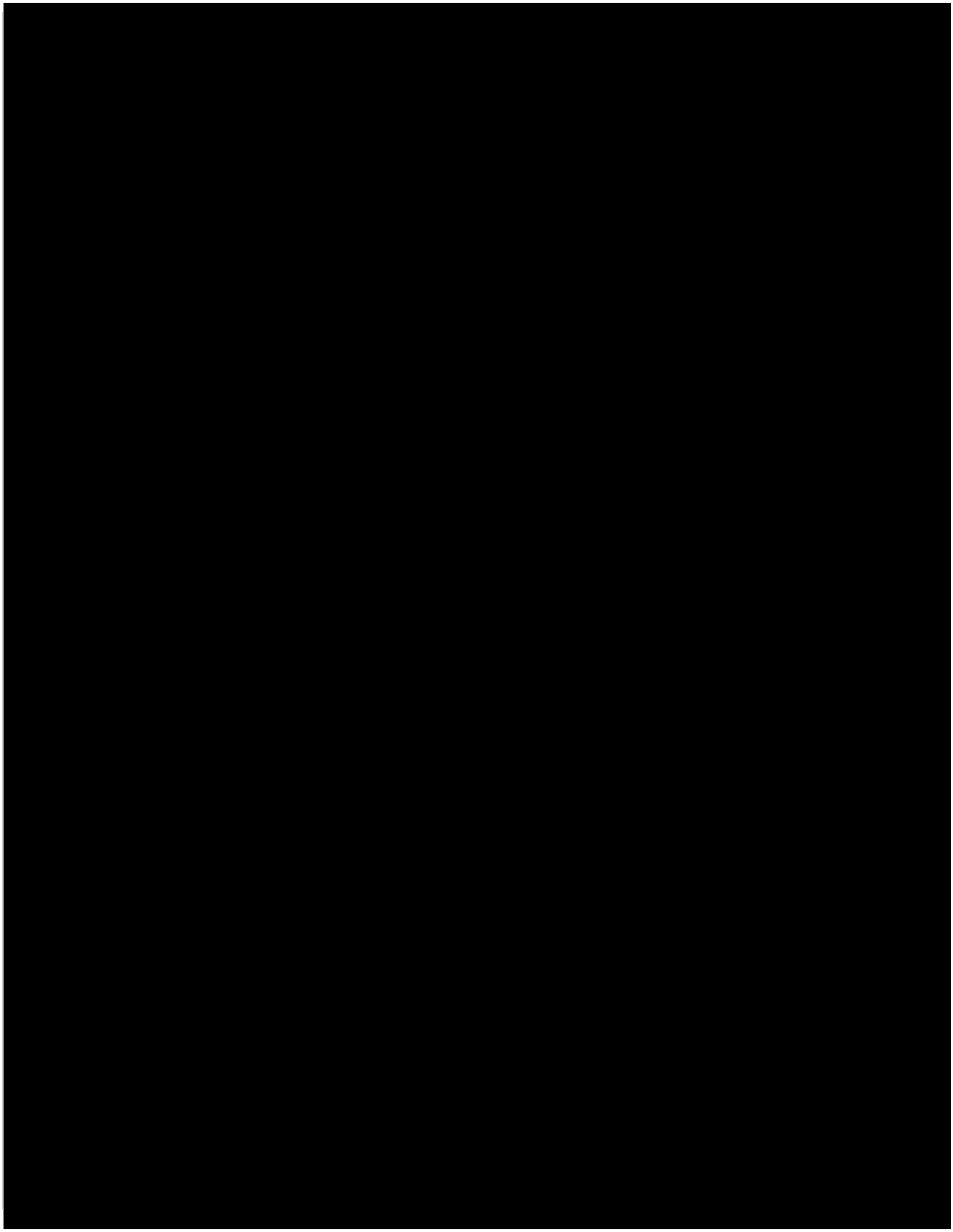


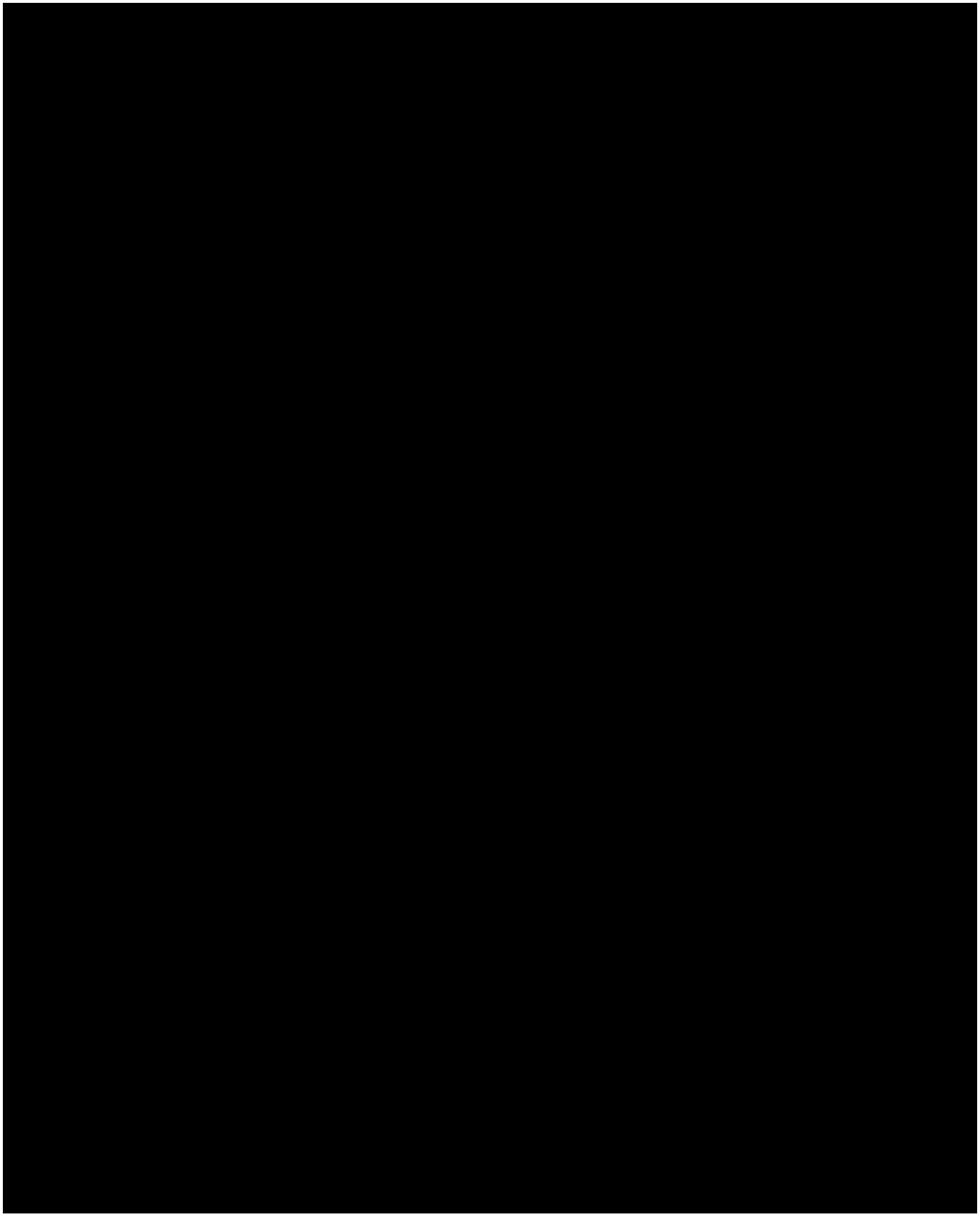


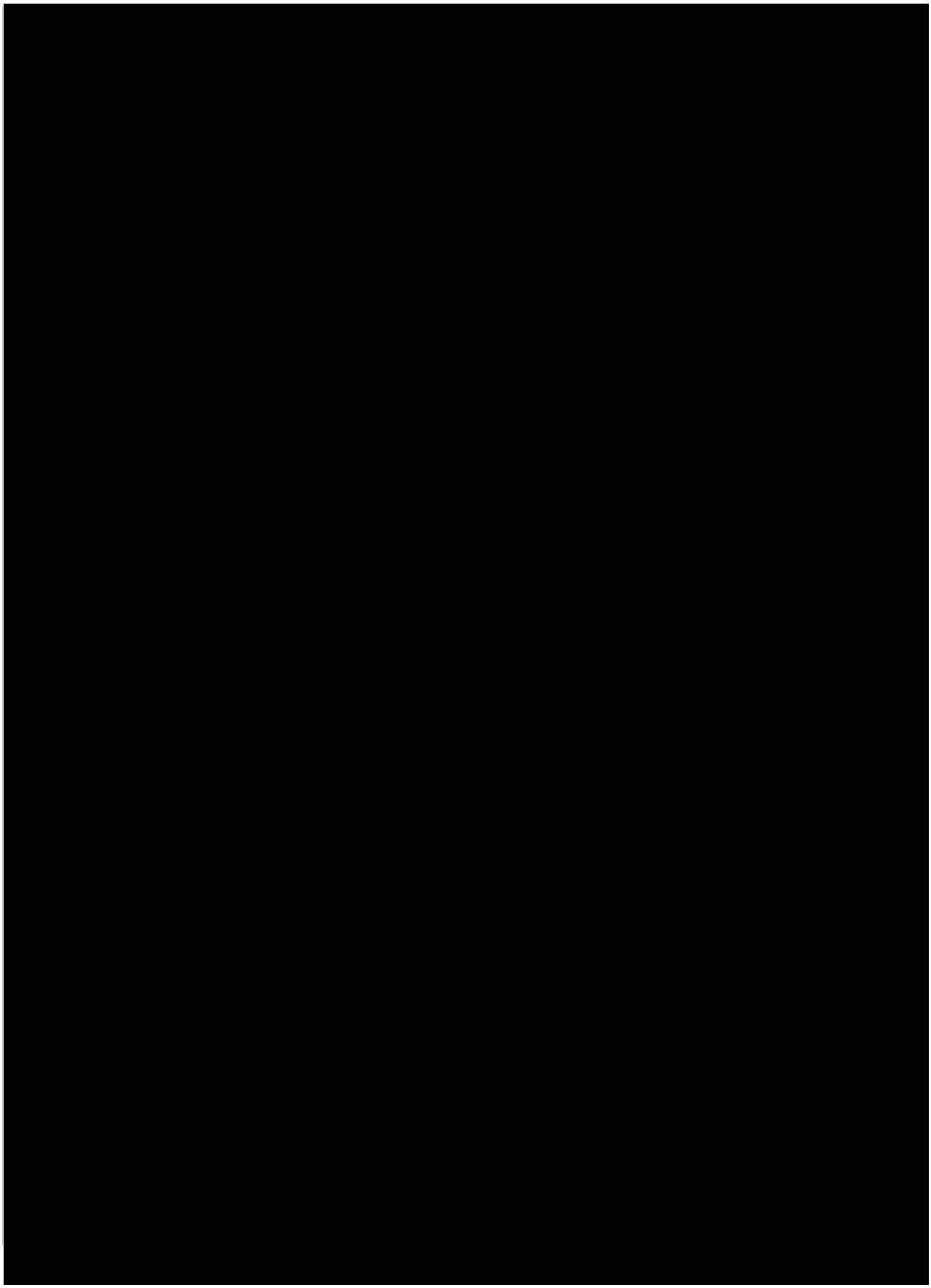


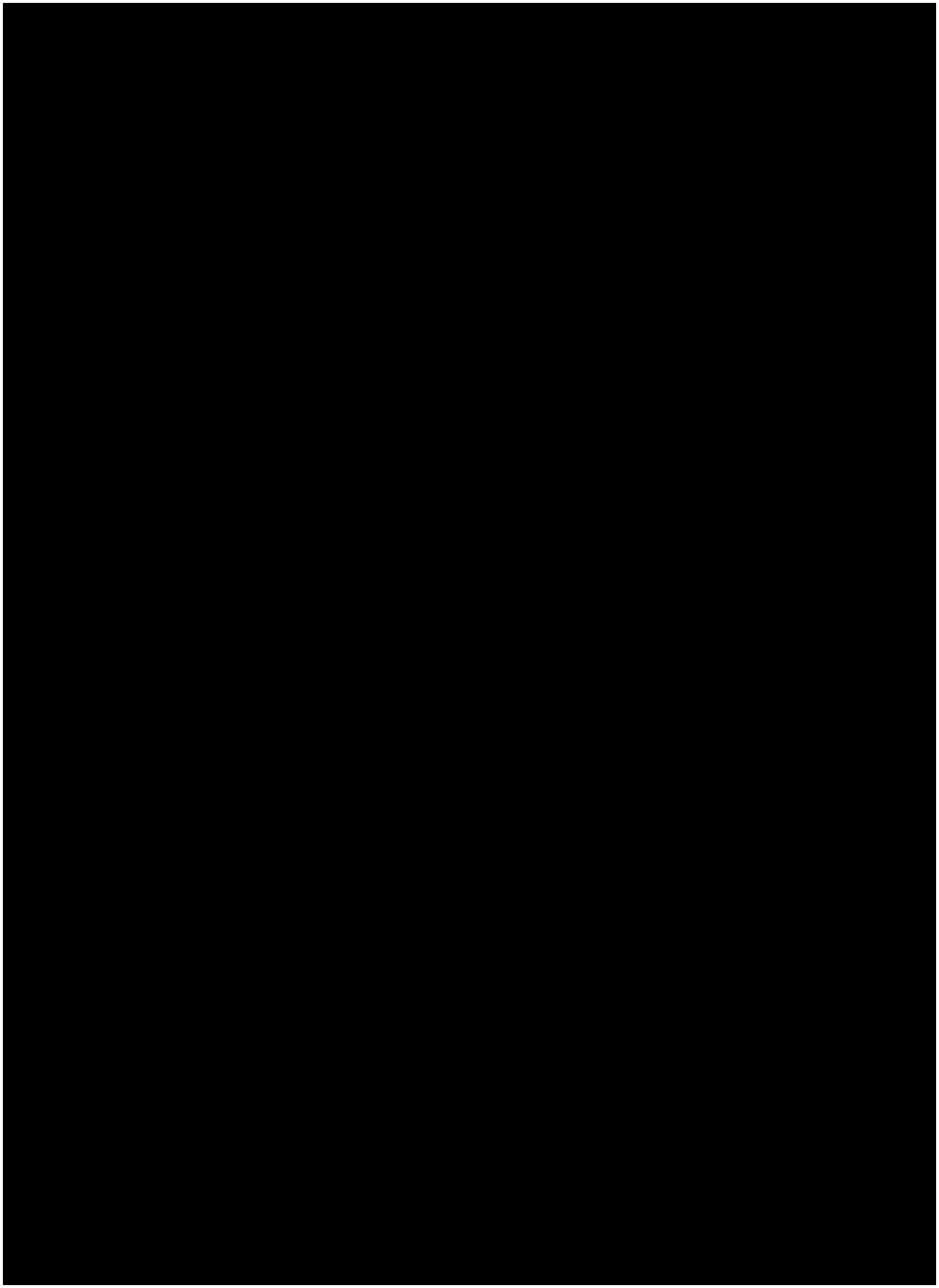


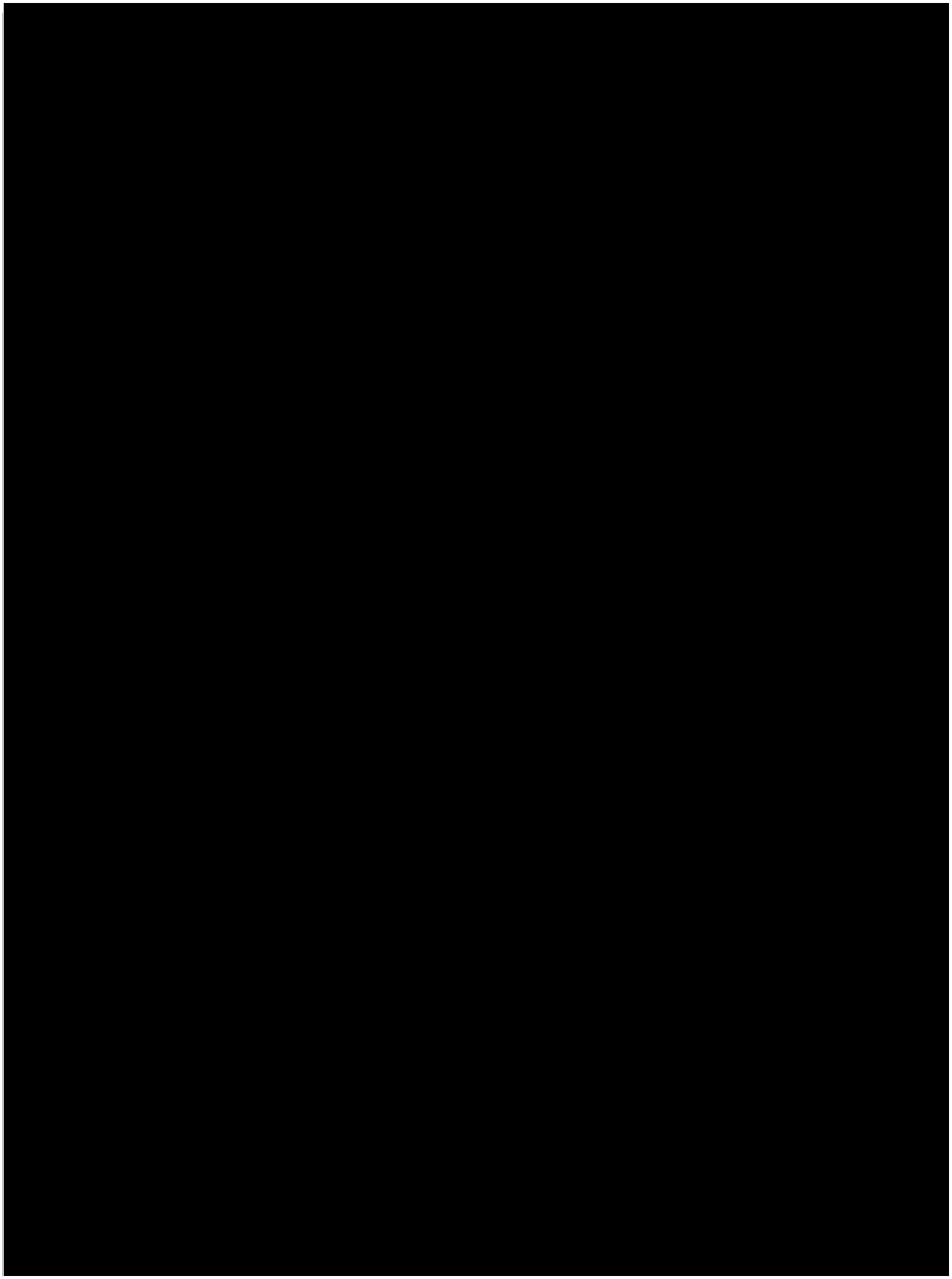


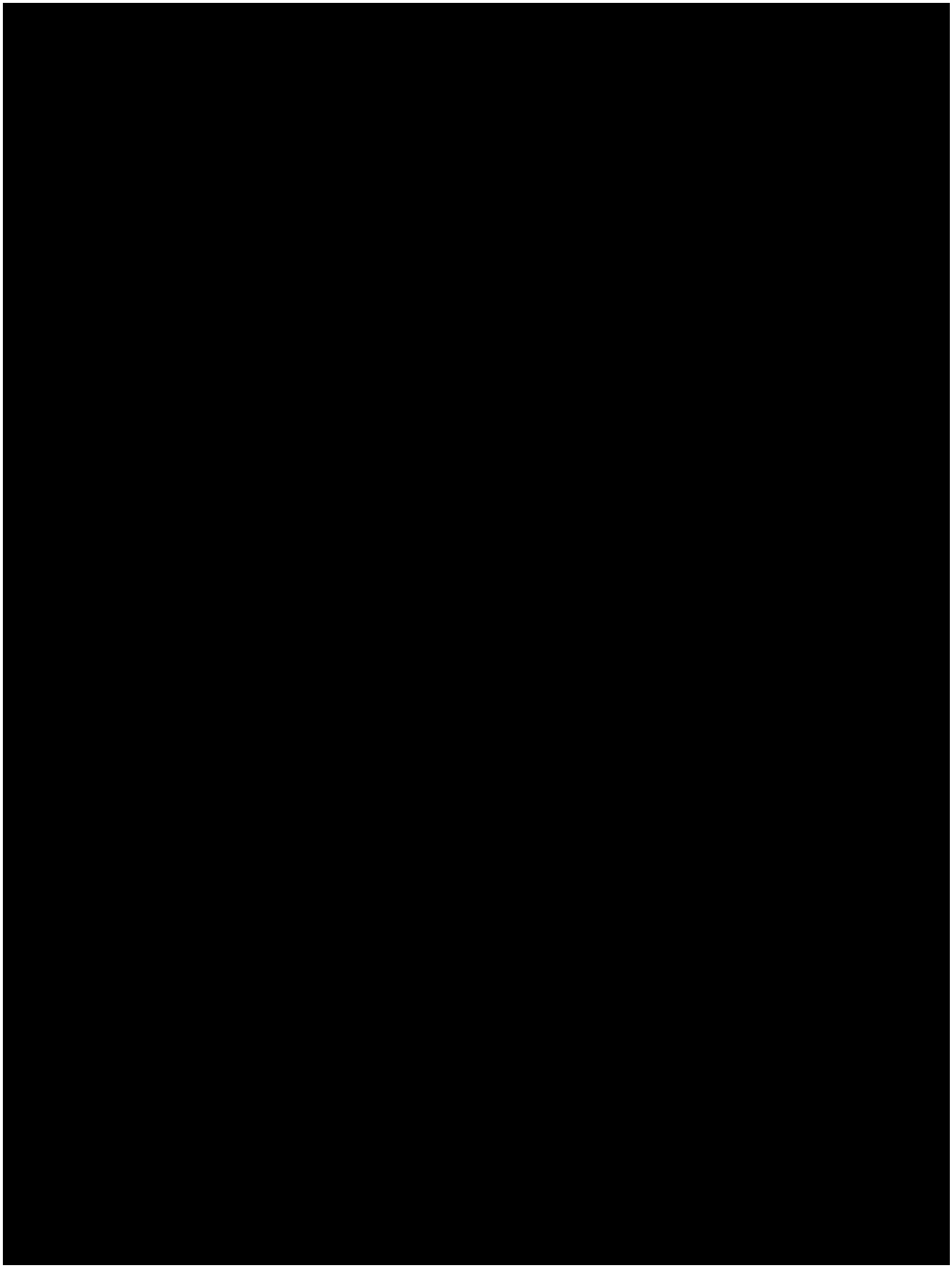


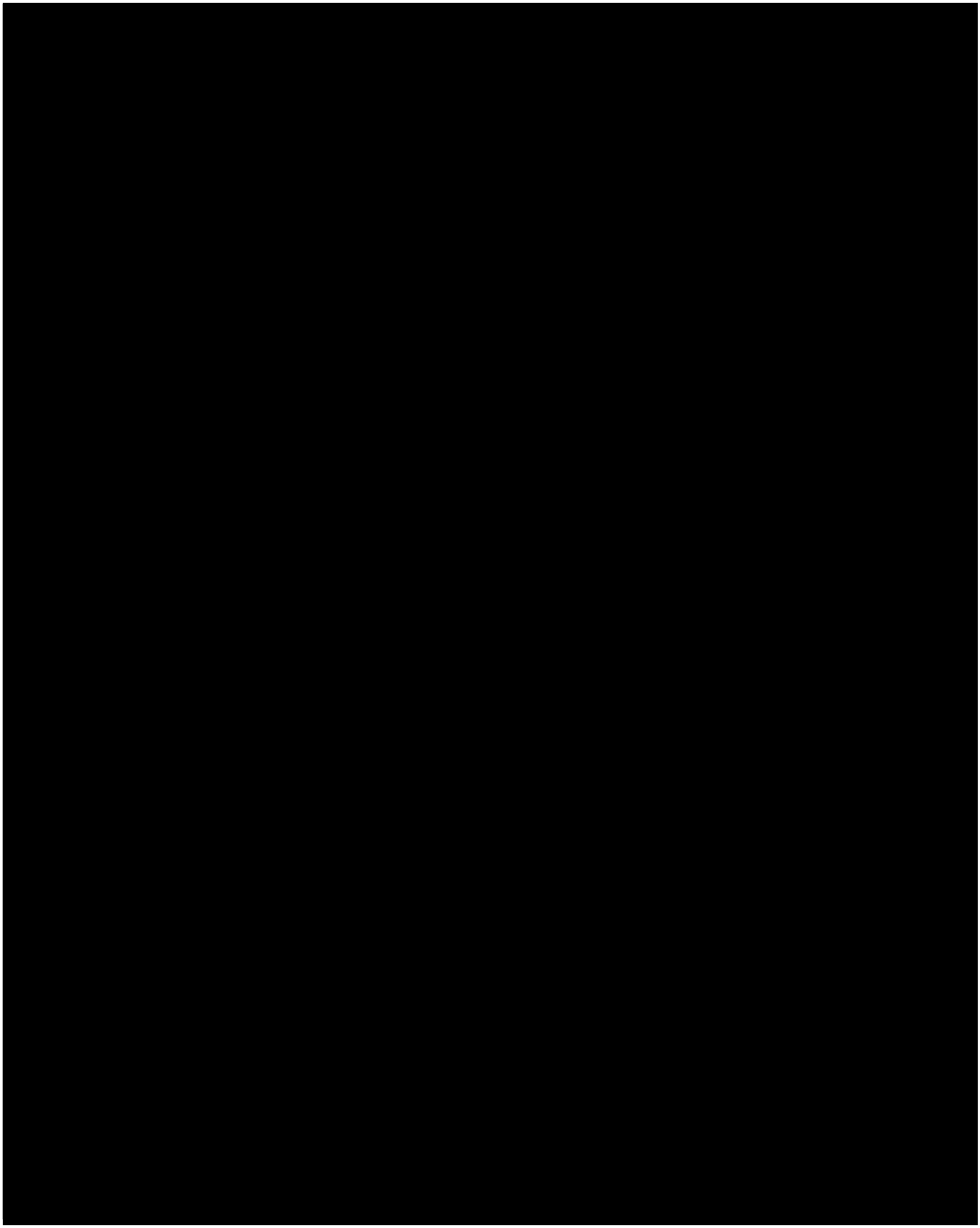


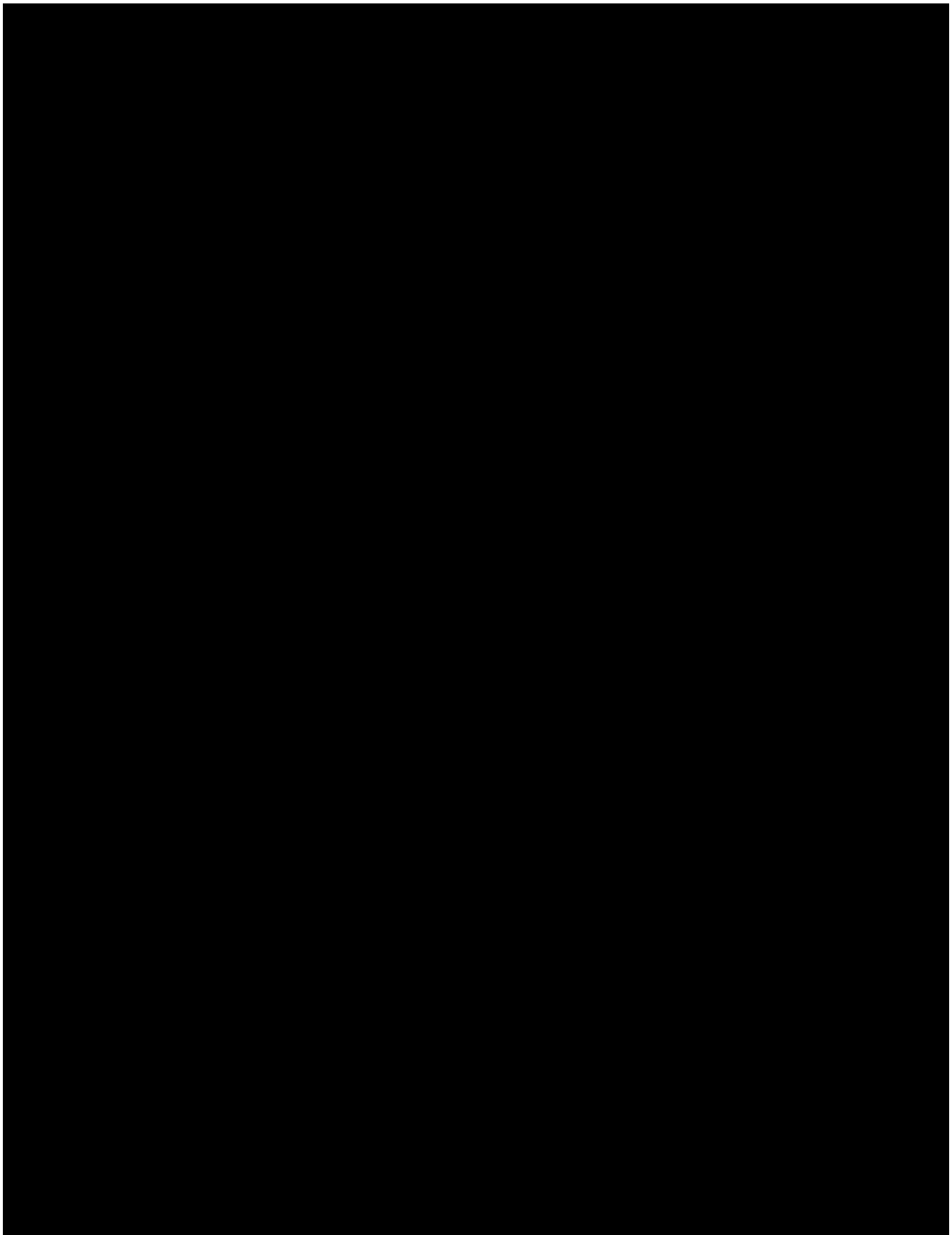


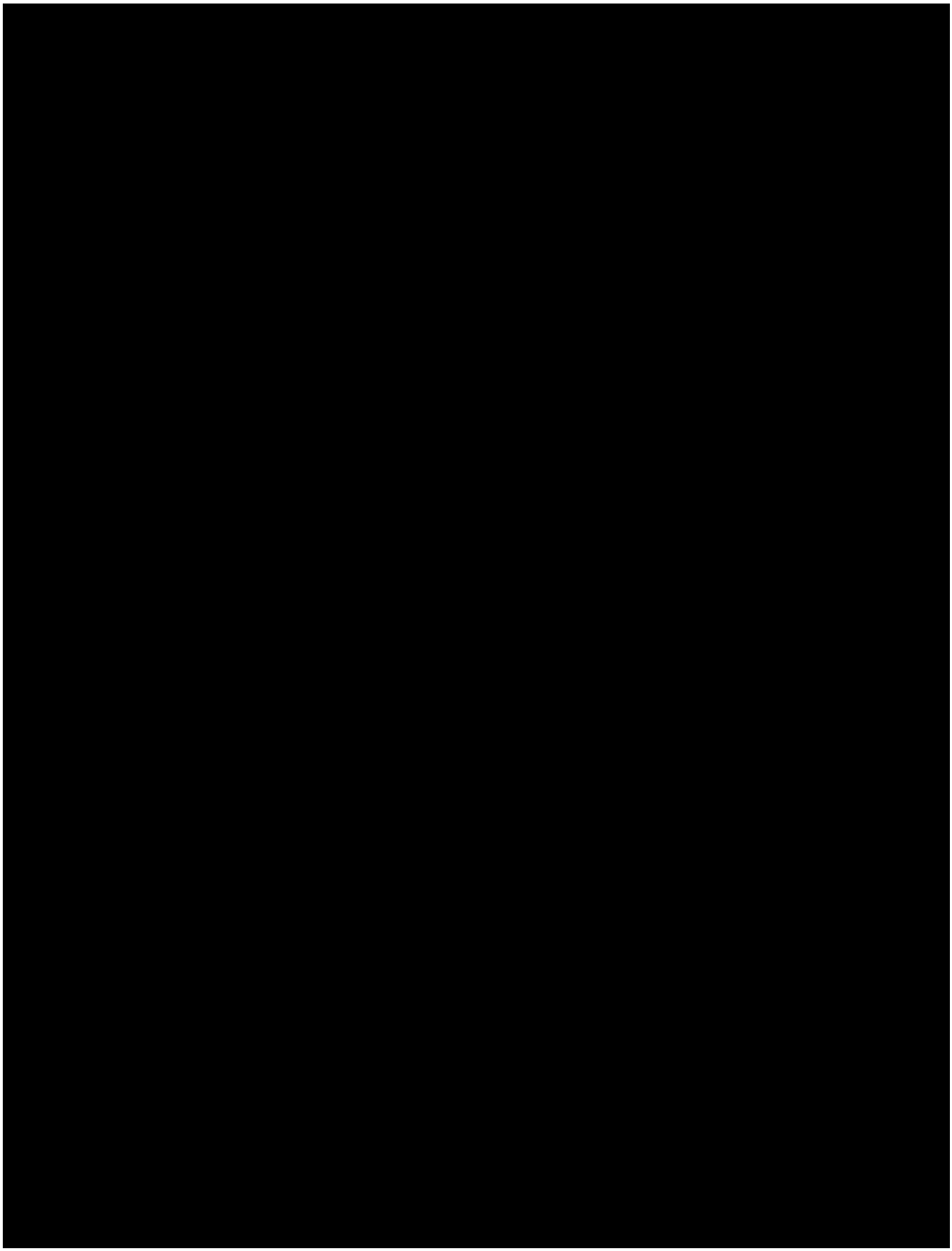


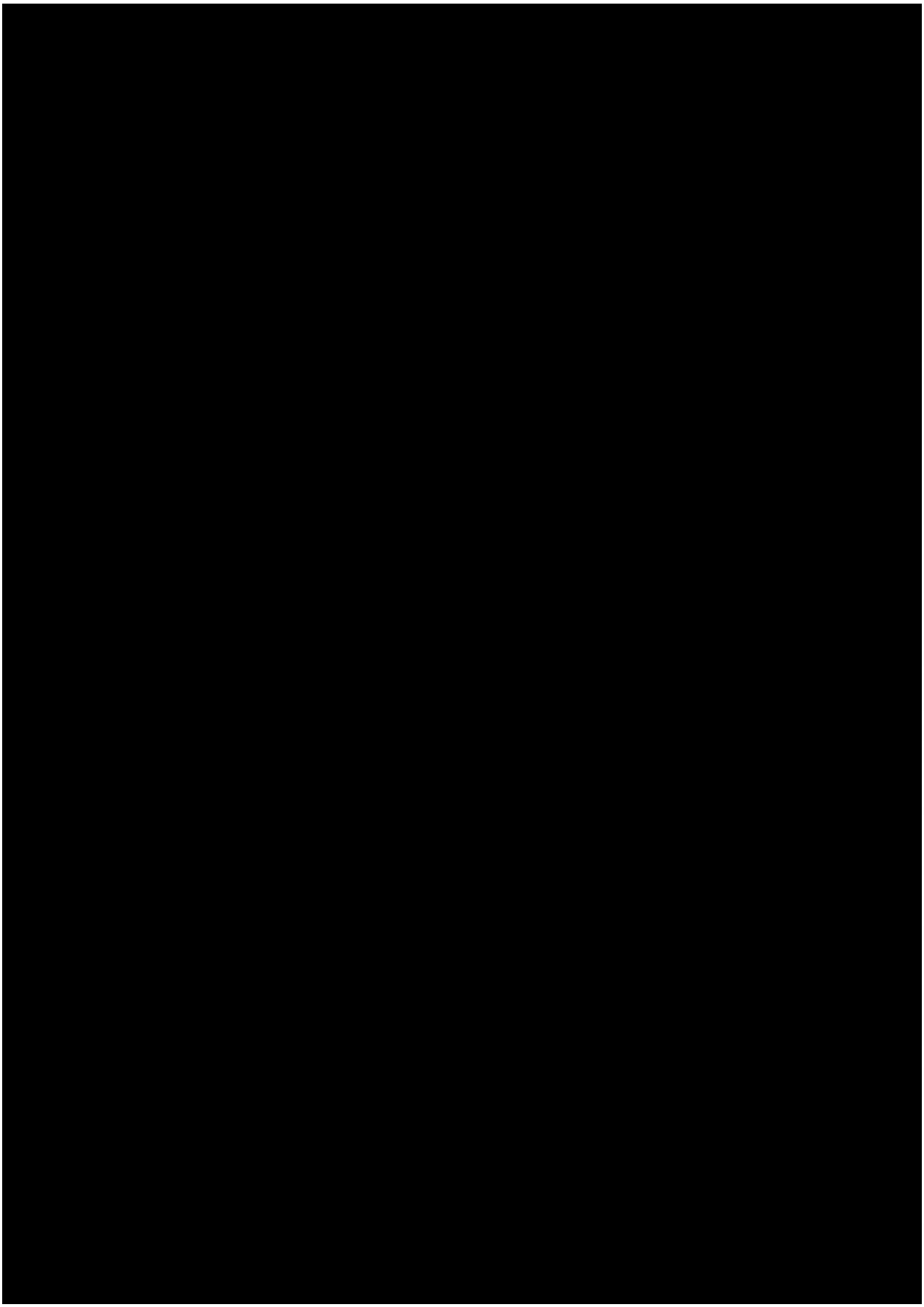


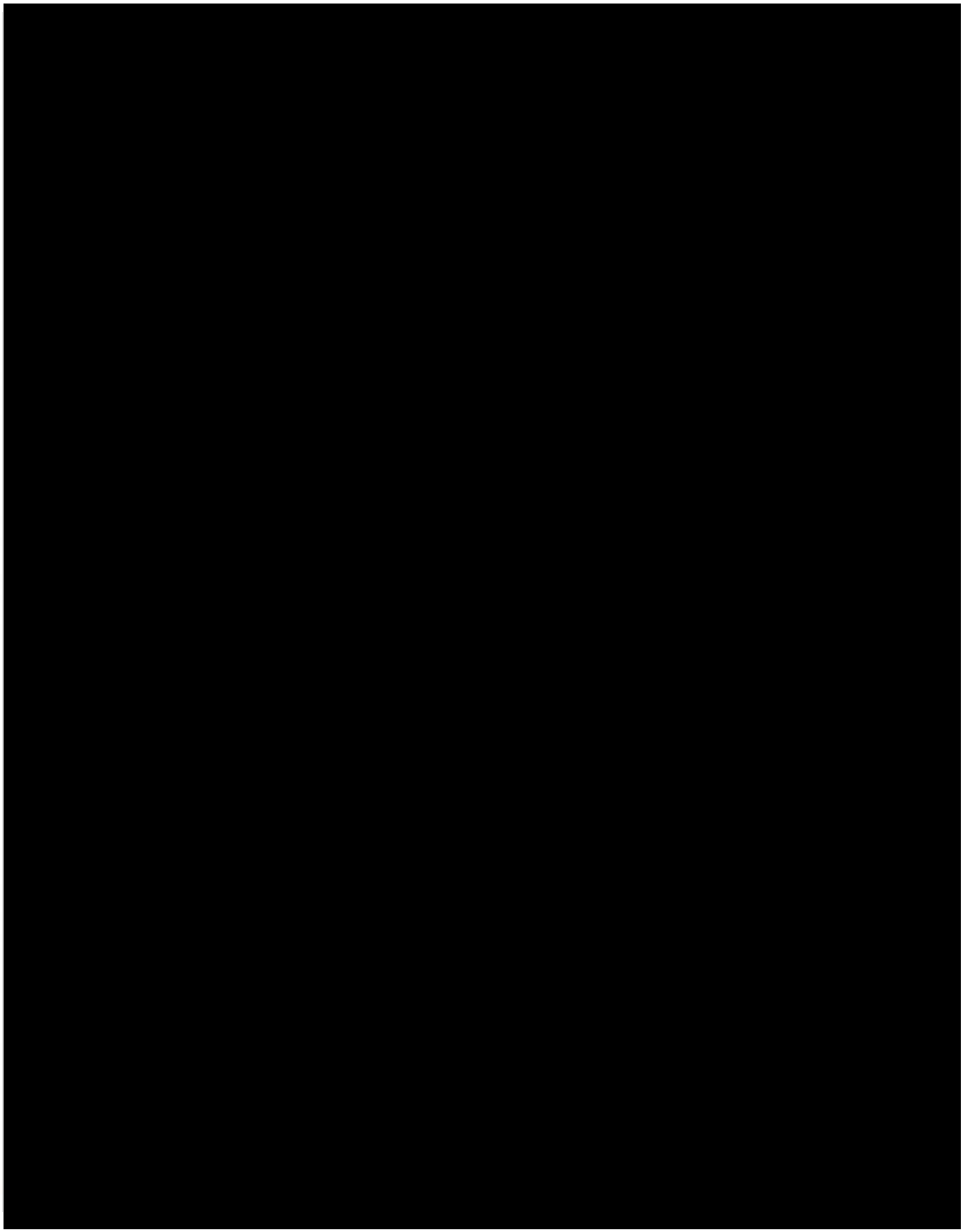


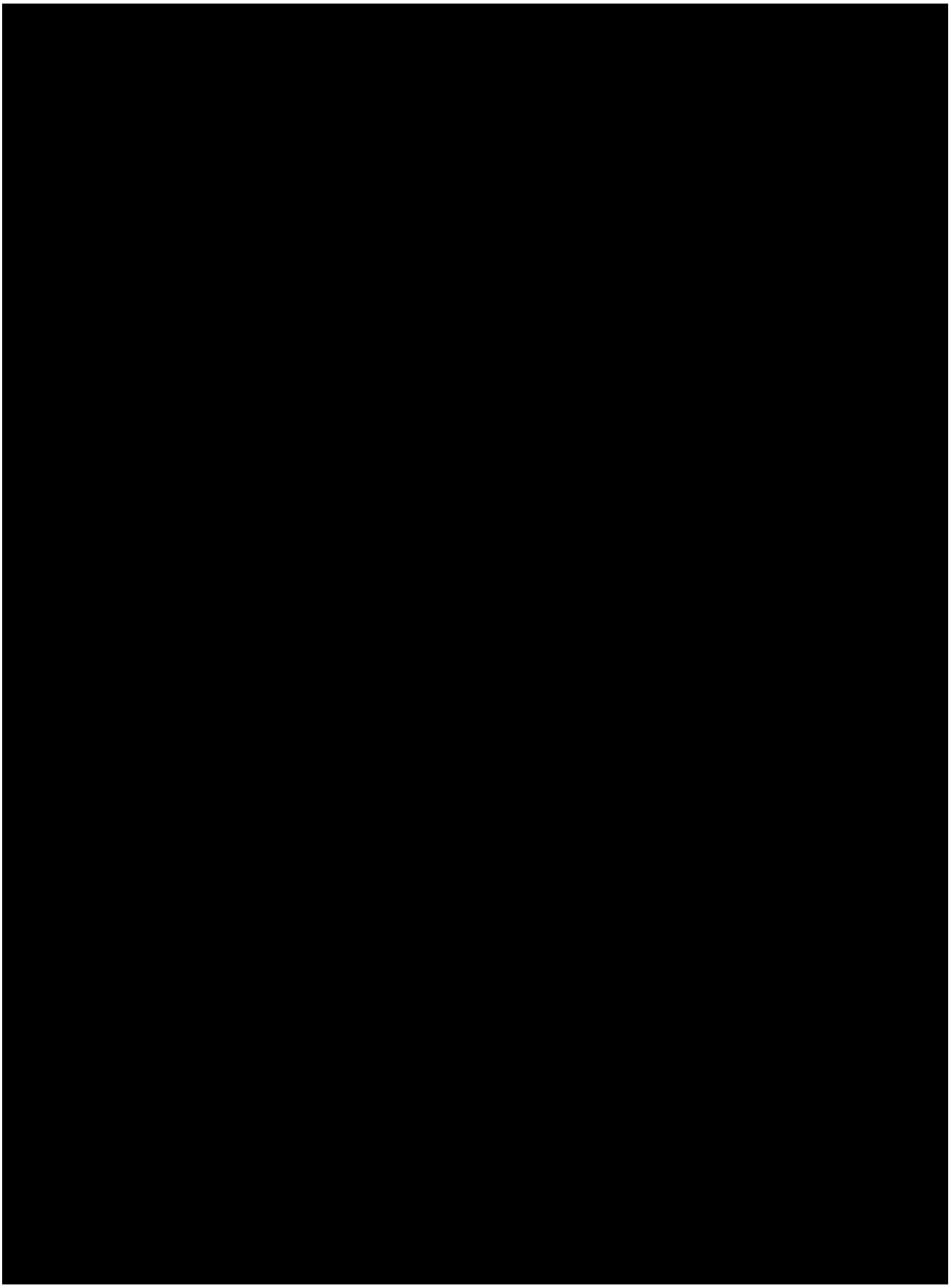


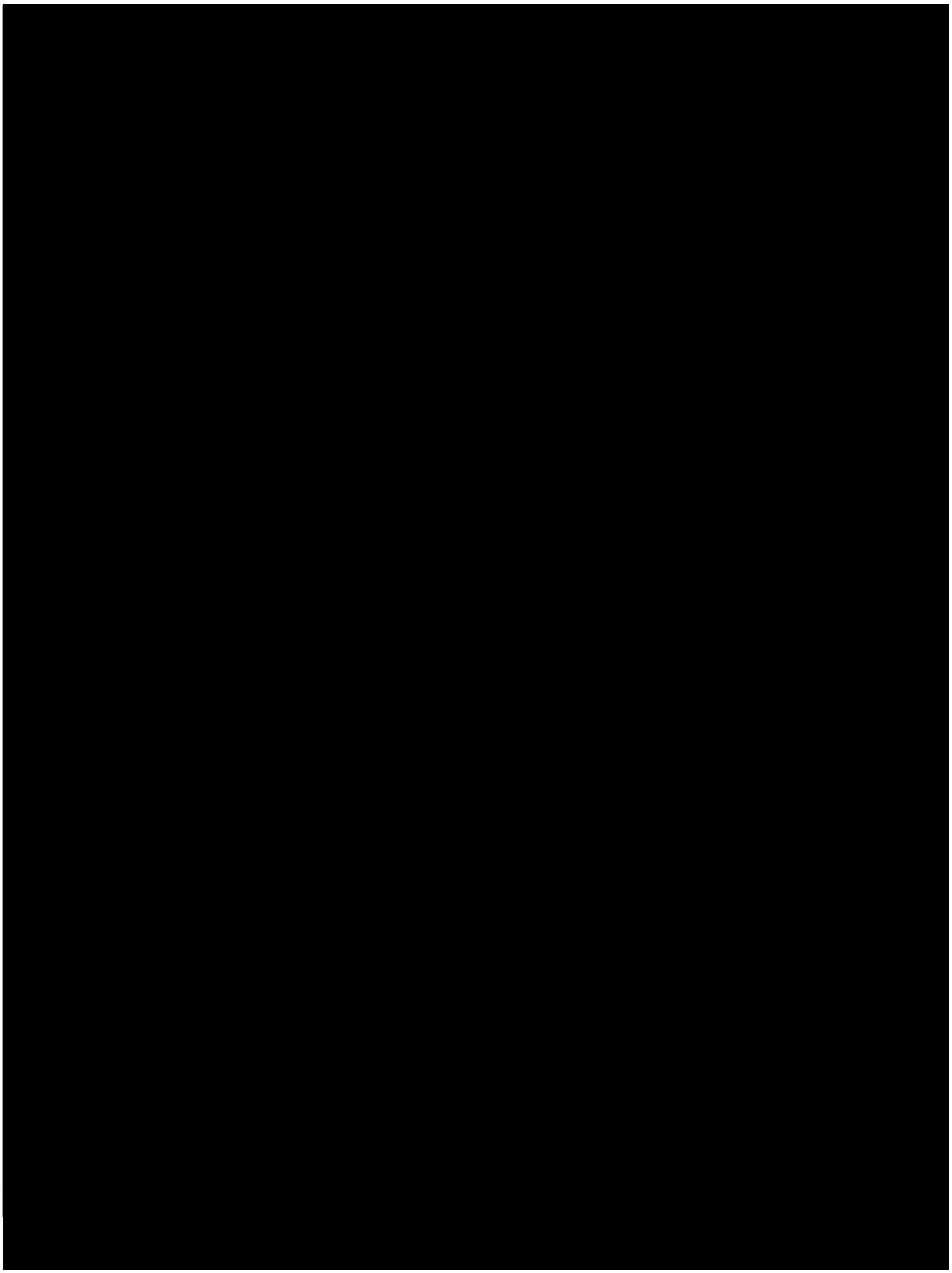


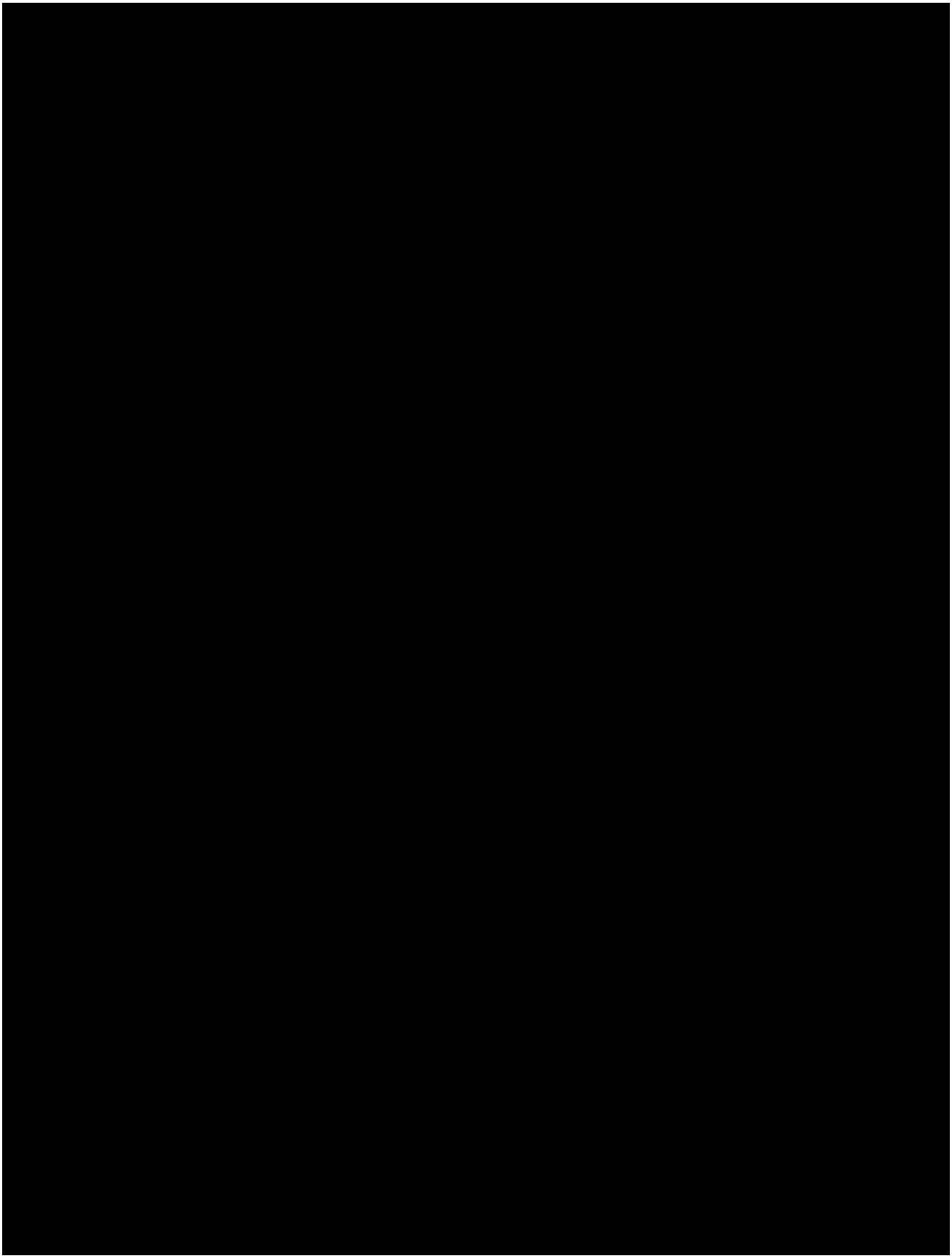


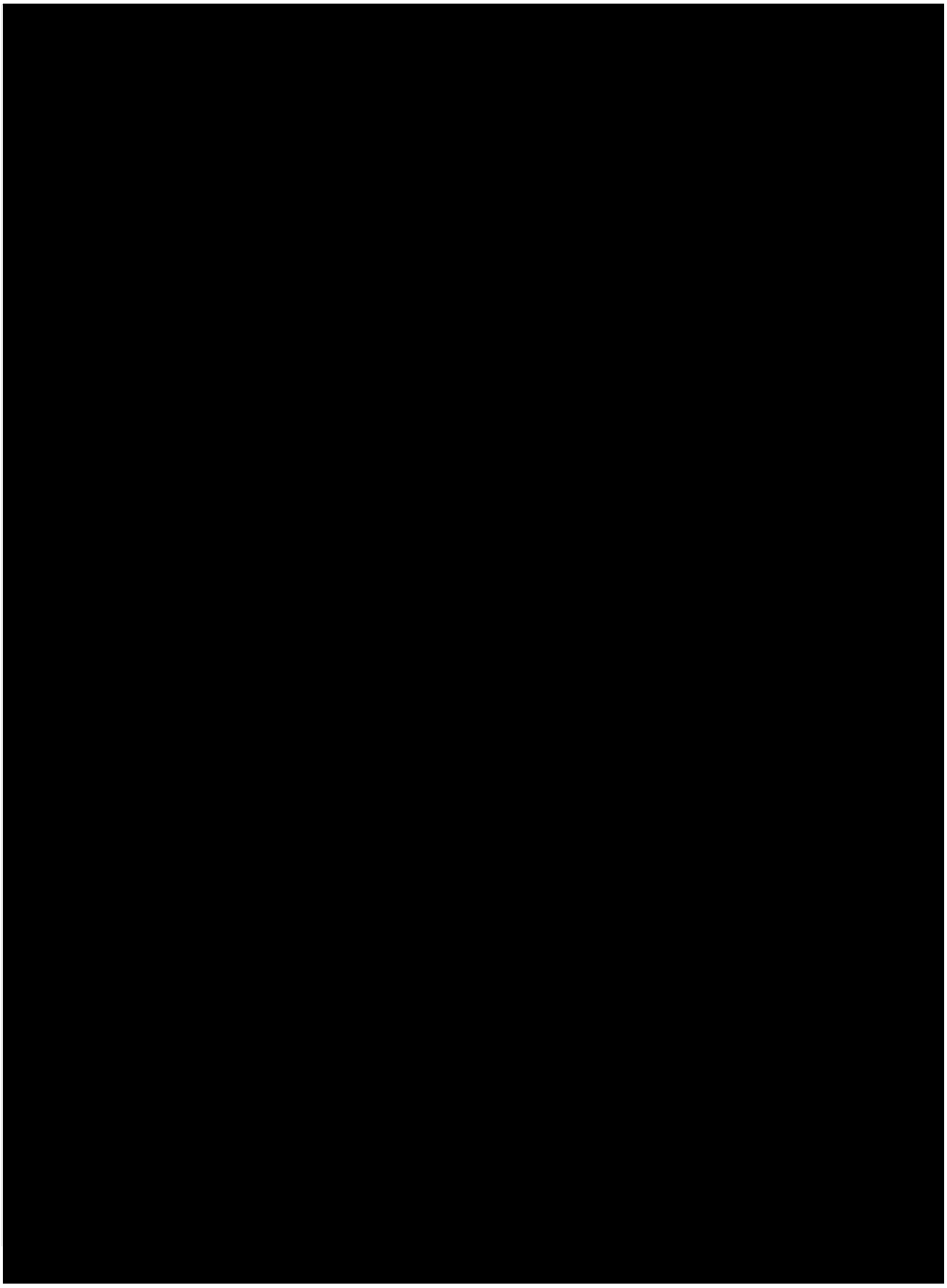


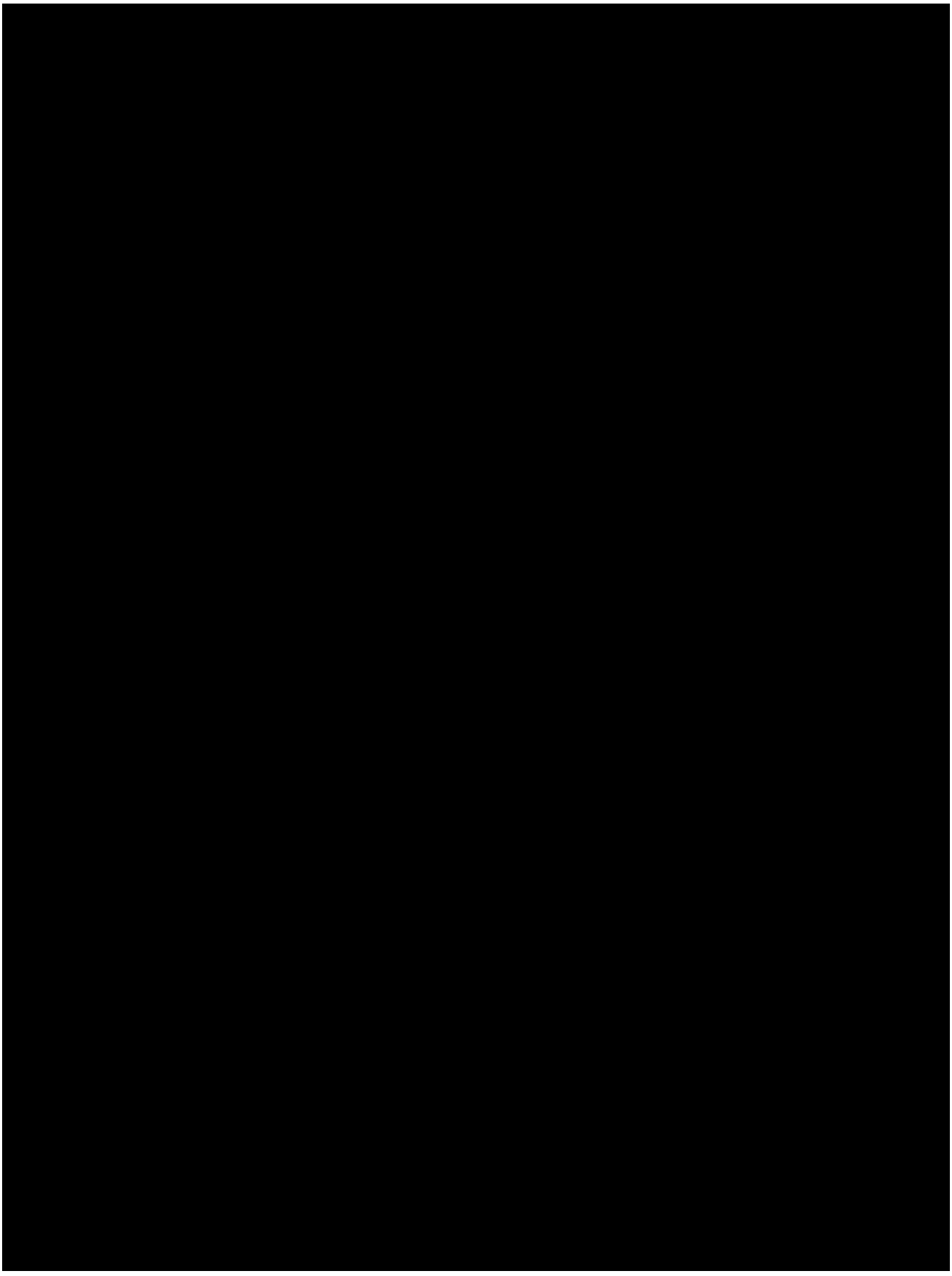






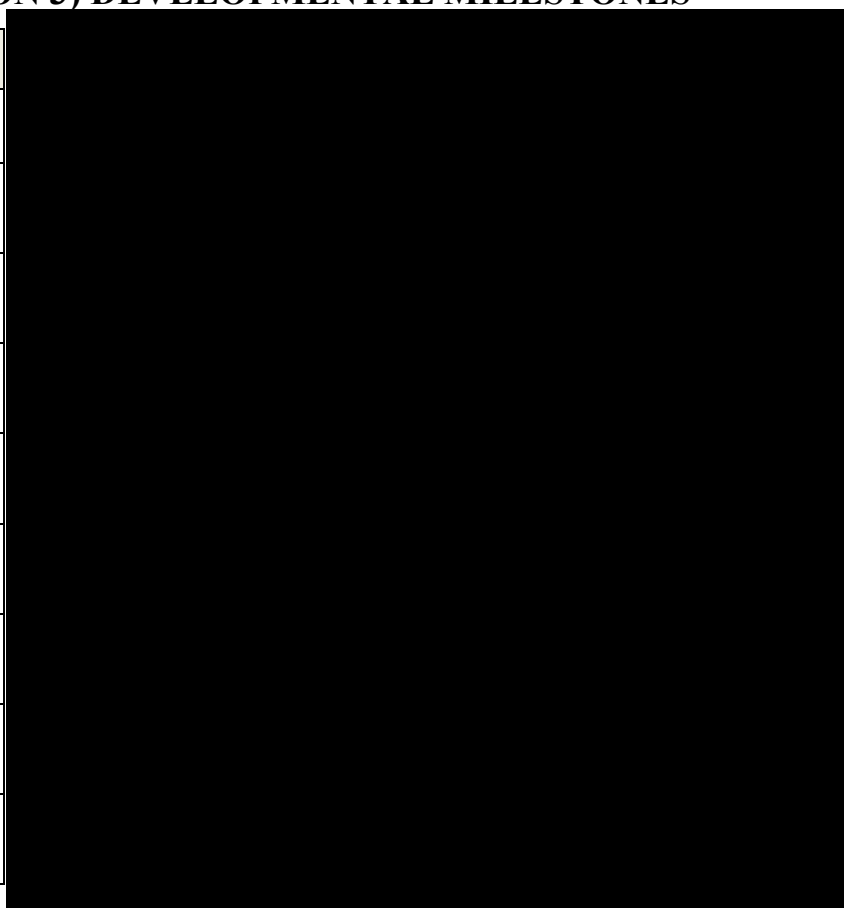




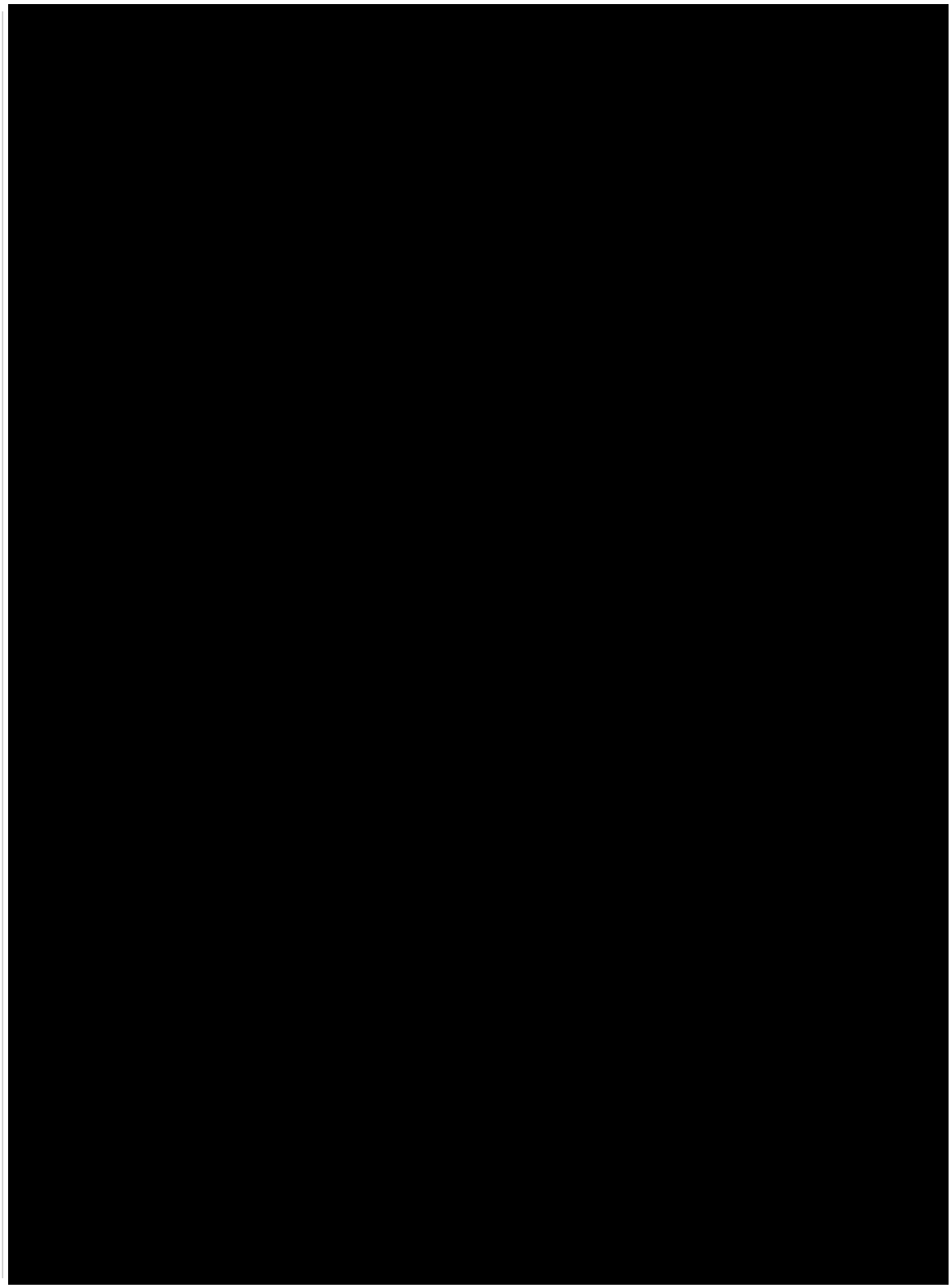


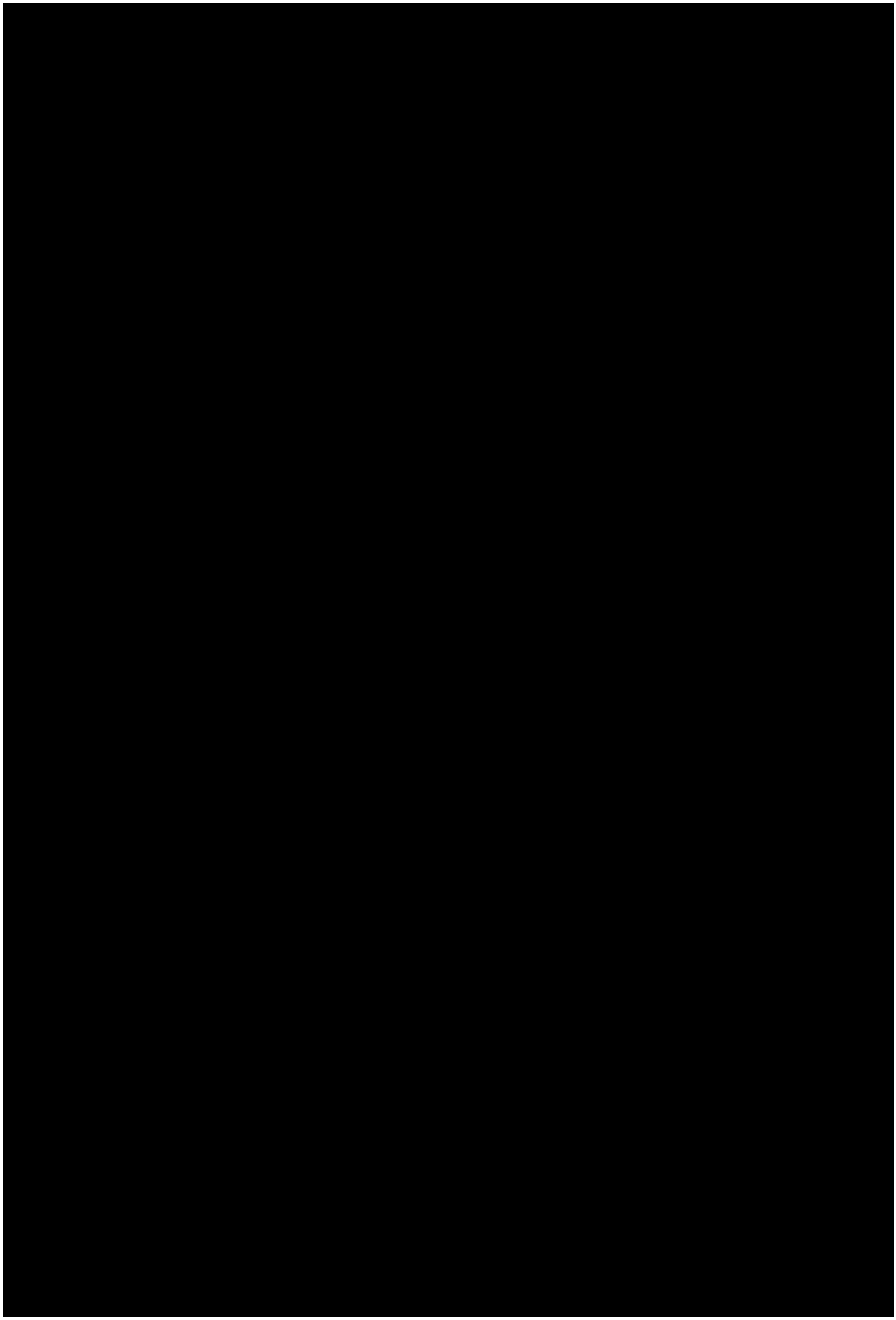
# APPENDIX 4. PERFORMANCE CRITERIA FOR BAYLEY SCALES OF INFANT AND TODDLER DEVELOPMENT (VERSION 3) DEVELOPMENTAL MILESTONES

| **Developmental Milestone** |
|---|
| Head Control – Gross Motor Subtest Item #4 |
| Rolls from Back to Sides – Gross Motor Subtest Item #20 |
| Sits Without Support – Gross Motor Subtest Item #26 |
| Stands With Assistance - Gross Motor Subtest Item #33 |
| Crawls – Gross Motor Subtest Item #34 |
| Pulls to Stand – Gross Motor Subtest Item #35 |
| Walks With Assistance – Gross Motor Subtest Item #37 |
| Stands Alone – Gross Motor Subtest Item #40 |
| Walks Alone – Gross Motor Subtest Item #43 |



# APPENDIX 5. CHOP-INTEND





# APPENDIX 6. COMPOUND MOTOR ACTION POTENTIAL MANUAL

**Phase 3 Gene Transfer Clinical Study for Spinal Muscular Atrophy Type 1 Delivering AVXS-101**

CMAP Manual
Compound Motor Action Potential (CMAP)

**Materials Needed for the Process**

- Carefusion Disposable Ring Electrode with Leads (order number 019-439300) (4 per visit)
- Carefusion Tab Electrodes 1.0 meter leads (order number 019-406600) (1 or 2 per visit)
- CMAP case report form
- Infrared temperature probe
- Electrode gel
- Warming packs or some other warming source
- Transpore adhesive tape
- Alcohol skin prep pads
- EMG machine

**Assessment of Normal Limb Temperature**

Since temperature can affect maximum CMAP amplitude, temperature > 33 degrees centigrade should be noted prior to preparation of skin for electrode placement. Temperature should be measured using a surface probe on the lateral aspect of the hand just proximal to the fifth digit. If temperature is ≤ 33 degrees centigrade, a warming pack or other warming mechanism should be used to warm the hand to > 33 degrees centigrade prior to collecting data. Limb temperature does not need to be reassessed during the procedure.

**Preparation of Skin**

The skin should be cleaned with alcohol (or equivalent) as needed to improve contact with the electrodes.

**EMG machine settings**

For both the ulnar and peroneal CMAP measures the filter settings should be 10 Hz to 10 kHz.

**Tibialis Anterior (TA) CMAP Electrode Placement**

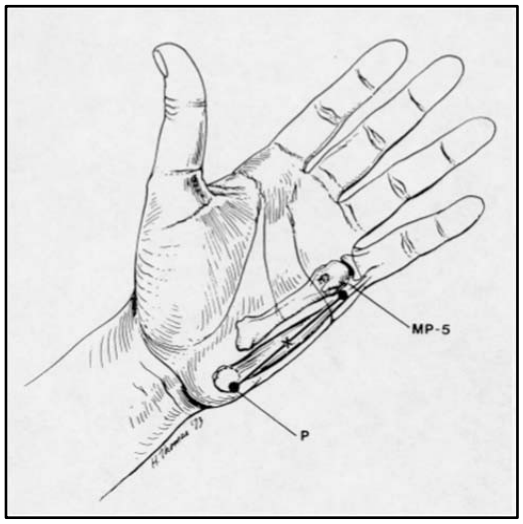
For the TA CMAP, the G1 electrode should be placed below the fibular head on the bulk of the Tibialis Anterior (TA) muscle belly. The G2 reference electrode should be placed on the patella. An adhesive ground electrode (Carefusion Tab Electrodes 1.0 meter leads (DIN Style) order number 019-406600) is placed between the stimulating electrodes and the G1 electrode. Tape should be placed over the electrodes to ensure they stay affixed during the procedure.

**Supramaximal nerve stimulation for TA CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at or proximal to the fibular head. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. Maximum CMAP amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

**Abductor Digiti Minimi (ADM) CMAP Electrode Placement**

Electrodes used for recording will be *Carefusion Disposable Ring Electrode with Leads (order number 019-439300)*. For ADM CMAP, these have a longitudinal contact area of up to 106 mm, but should be cut so that they cover the body of the ADM, with position orthogonal to muscle fiber orientation. The distance between the ulnar aspect of the pisaform bone (P) and the ulnar aspect of the fifth metacarpophalangeal joint (MP-5) should be measured. The G1 electrode should be placed distal to P, 1/3 of the distance between P and MP-5, as defined above. The G2 reference electrode should be placed on the ulnar aspect of the MP-5 joint. See figure below for landmarks:




Modified figure from "Anatomic Guide for the Electromyographer" Charles C. Thomas, Publisher, 1980, p4.

**Supramaximal nerve stimulation for CMAP**

The stimulator should be a pediatric sized bipolar probe. The stimulation site should be at the distal forearm just proximal to the wrist. A maximal response should be obtained (CMAP), using a stimulus 120% of that producing the maximal response and a stimulus duration of 0.2 msec. CMAP maximum amplitude and area should be recorded on the Source Document and a printout of the CMAP tracing made. Area is measured only for the initial negative peak. Subsequent negative peaks are not included.

# APPENDIX 7. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving Human subjects.

6. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician

or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving Human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the

study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.