BEMPEDOIC ACID (ETC-1002)

1002-043

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF BEMPEDOIC ACID (ETC-1002) ON THE OCCURRENCE OF MAJOR CARDIOVASCULAR EVENTS IN PATIENTS WITH, OR AT HIGH RISK FOR, CARDIOVASCULAR DISEASE WHO ARE STATIN INTOLERANT

Study Phase: 3

IND Number: 106,654

EudraCT Number: 2016-003485-11

Indication: Reduction of cardiovascular disease risk

Investigators: Approximately 1200 sites located in 32 countries

Sponsor: Esperion Therapeutics, Inc.
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Version	Date
Original Protocol:	24 June 2016
Amendment 1:	08 February 2017
Amendment 2:	15 November 2017
Amendment 3*:	17 July 2018
Amendment 3.1*:	30 July 2018
Amendment 4	19 December 2019
Amendment 5	24 September 2020

* Amendments 3 and 3.1 are identical in content but are versioned separately for administrative reasons. Amendment 3 applies to all participating sites in all countries except the United States. Amendment 3.1 applies to sites from the United States.

NCT Number: NCT02993406
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Confidentiality Statement

APPENDIX 2. SPONSOR'S SIGNATURES

Study Title:	A Randomized, Double-blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at High Risk for, Cardiovascular Disease who are Statin Intolerant
Study Number:	1002-043
Final Date:	24 September 2020

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

Signed: [redacted] Date: [redacted]

[redacted] MS
Director, Clinical Development
Esperion Therapeutics, Inc.

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Signed: [redacted] Date [redacted]

[redacted] PhD
Director, Biostatistics
Esperion Therapeutics, Inc.

2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.

Name of Investigational Product: Bempedoic acid (ETC-1002) film coated tablets

Name of Active Ingredient: Bempedoic acid (ETC-1002)

Title of Study:

A Randomized, Double-blind, Placebo-controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerant

Study Number: 1002-043

Phase of Development: 3

Clinical Sites: Approximately 1200 sites located in 32 countries

Objectives:

Primary:

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease (CVD) who are statin intolerant. This will be assessed with a composite primary efficacy endpoint that includes time to first occurrence of cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization

Secondary:

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality
- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP)
- To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo
- To evaluate the 12-month efficacy of treatment with bempedoic acid 180 mg/day versus placebo on absolute change in hemoglobin A_{1C} (HbA_{1C}) in the Inadequately Controlled Diabetes Efficacy Population (patients with type 2 diabetes mellitus and having an HbA_{1C} of 7% or greater at baseline)
- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of new-onset diabetes

Tertiary:

- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-density-lipoprotein cholesterol (HDL-C), triglycerides (TG), HbA_{1C} and fasting glucose

Study Hypotheses:

This superiority study will test the hypothesis that bempedoic acid, compared to placebo, will reduce the risk of CV events in patients with, or at high risk for, CVD who are statin intolerant.

In addition, it will test the hypothesis that bempedoic acid, compared to placebo, will delay time to first occurrence of new-onset diabetes in patients in the prediabetes subpopulation. It will also test the hypothesis that bempedoic acid, compared to placebo, will reduce absolute change from baseline to Month 12 in HbA_{1C} in patients in the inadequately controlled diabetes subpopulation.

Endpoints:

The following endpoints will be used to evaluate the objectives of the study.

Primary efficacy endpoint:

- Time to first occurrence of MACE, where MACE is defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization

Key secondary efficacy time-to-event endpoints:

- Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke
- Time to first occurrence of (fatal + nonfatal) MI
- Time to first occurrence of coronary revascularization
- Time to first occurrence of (fatal + nonfatal) stroke
- Time to CV death
- Time to all-cause mortality

Secondary efficacy time-to-event endpoints:

- Time to first occurrence of the composite endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization
- Time to first occurrence of nonfatal MI
- Time to fatal MI
- Time to first occurrence of nonfatal stroke
- Time to fatal stroke
- Time to first occurrence of (fatal + nonfatal) hemorrhagic stroke
- Time to first occurrence of (fatal + nonfatal) nonhemorrhagic stroke
- Time to hospitalization for unstable angina
- Time to first occurrence of new-onset type 2 diabetes mellitus defined by one or more of the following criteria according to the current American Diabetes Association (ADA) guidelines (ADA, 2014):
  1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours;* or
  2. Two-hour post-prandial glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test as defined in the ADA guidelines;* or
  3. HbA_{1C} measurement ≥6.5% (48 mmol/mol);* or
  4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

  *Note: In the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in the 2 separate test results.

Secondary efficacy lipid and biomarker endpoints:

- Percent change from baseline to Month 6 in LDL-C
- Percent change from baseline to Month 6 in hs-CRP
- Absolute change from baseline to Month 12 in HbA_{1C} in patients in the inadequately controlled diabetes efficacy population (patients with type 2 diabetes mellitus and an HbA_{1C} of 7% or greater at baseline)

Tertiary lipid and biomarker endpoints:

- Percent change from baseline to Months 3, 12, 24, and end-of-study in LDL-C; percent change from baseline to Months 3, 6, 12, 24, and end-of-study in HDL-C, non-HDL-C, TC, and TG
- Absolute change from baseline to Months 3, 6, 12, 24, and end-of-study in LDL-C
- Percent change from baseline to Month 12 and end-of-study in hs-CRP
- Absolute change from baseline to Month 3, 6, every 6 months following Month 12, and end-of-study in HbA_{1C} in patients in the Inadequately Controlled Diabetes Efficacy Population (patients with type 2 diabetes mellitus and an HbA_{1C} of 7% or greater at baseline)
- Absolute change from baseline to Month 3, 6, 12, every 6 months following Month 12, and end-of-study in fasting glucose in patients in the Normoglycemia Efficacy Population, Prediabetes Efficacy Population, No Diabetes Efficacy Population, and Diabetes Efficacy Population

Safety endpoints:

- Adverse events (AEs; including adverse events of special interest [AESI]), vital signs (eg, heart rate, weight, blood pressure [BP]), and clinical laboratory measures

Study Design:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Screening (Visit S1) will occur approximately 5 weeks prior to Day 1 (Visit T1) but can be extended for an additional 5 weeks if needed to adjust background medical therapy or for other reasons. All eligible patients will return at Week -4 (Visit S2) to initiate a 4-week Run-in Period with single-blind (blinded to patient only) placebo once daily that will include assessment of tolerability and investigational medicinal product (IMP) adherence. On Day 1 (Visit T1), approximately 14,000 eligible patients will be randomized 1:1 to receive either double-blind bempedoic acid 180 mg (n = 7000) or placebo (n = 7000) once daily.

Randomized patients will return for clinic visits at Month 1 (Visit T2), Month 3 (Visit T3), and Month 6 (Visit T4). Following Month 6, patients will be contacted every 3 months (alternating with a phone visit and a clinic visit) for the remainder of the study. The study will continue until all of the

following have occurred: 1) at least 1620 patients have experienced an adjudicated primary 4-component MACE [CV death, nonfatal MI, nonfatal stroke, or coronary revascularization], 2) at least 810 patients have experienced an adjudicated 3-component MACE [CV death, nonfatal MI, or nonfatal stroke] and 3) 24 months have elapsed since the last patient was randomized. It is estimated that median treatment duration for all randomized patients will be approximately 3.5 years. For each patient, the last treatment visit will be a clinic visit, with a follow-up phone call approximately 30 days after study treatment completion. Patients who discontinue IMP for any reason will remain in the study to be evaluated for efficacy and safety endpoints and will be expected to continue study visits (preferred) or agree to some other form of contact with the site for the remainder of the study. For details of study assessments, see the Schedule of Events in Appendix 1.

This study will include several independent and expert committees. An Executive Committee (EC) will oversee the design and conduct of the study and the interpretation of study results. A Clinical Events Committee (CEC) will adjudicate blinded clinical endpoints, including MACE endpoints, as well as non-CV deaths using standardized definitions. An adjudicated clinical endpoint will not be reported as a serious adverse event (SAE). A Diabetes Committee (DC) will verify diagnosis of new-onset diabetes. A Tendon Rupture Adjudication Committee (TRAC) will adjudicate events of tendon rupture using standardized definitions. An independent Data Monitoring Committee (DMC) will review accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid approximately 4 times per year. Safety data reviewed by the DMC will include AEs, clinical endpoints, and lipids. Each of these committees has a charter that includes additional details.

Number of Patients (Planned): Approximately 14,000 adult male and female patients.

Duration of Treatment: It is estimated the median treatment duration will be approximately 42 months (3.5 years), with all patients remaining in the study for a minimum of 24 months (2 years) and some patients remaining in the study for up to approximately 72 months (6 years). For each patient, the actual duration of treatment will depend on time of randomization versus when the 'End of Study' conditions below have been met.

End of Study: The study will end when all of the following have occurred: 1) at least 1620 patients have experienced an adjudicated primary 4-component MACE, 2) at least 810 patients have experienced an adjudicated 3-component MACE (CV death, nonfatal MI, nonfatal stroke), and 3) at least 24 months (2 years) have elapsed since the last patient was randomized. The estimated overall duration of the study (first patient first visit to last patient last visit) is approximately up to 72 months (6 years).

Inclusion and Exclusion Criteria:

Each patient must meet the following criteria to be eligible for this study.

Subject Inclusion Criteria:

1. Provision of signed informed consent prior to any study-specific procedure.
2. Patient-reported statin intolerance (SI) due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued resulting in an inability to tolerate:
    - 2 or more statins at any dose, or
    - 1 statin at any dose and unwilling to attempt a second statin or advised by a physician to not attempt a second statin.

    Please note that patients currently tolerating very low dose statin therapy (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg) are considered to be intolerant to that low dose statin. Patients may continue taking very low dose statin therapy throughout

the study provided that it is stable (used for at least 4 weeks prior to screening) and well tolerated.

3. Written confirmation by both patient and investigator that the patient is statin intolerant as defined above, aware of the benefit of statin use to reduce the risk of MACE including death, and also aware that many other patients who are unable to tolerate a statin are able to tolerate a different statin or dose.
4. Age ≥18 years or legal age of majority based on regional law, whichever is greater, and ≤85 years at Week -5 (Visit S1).
5. Men and nonpregnant, nonlactating women. Women must be one of the following:
    - Naturally postmenopausal defined as ≥1 year without menses and:
        - ≥55 years, **or**
        - <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L, **or**
    - Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation, **or**
    - Women of childbearing potential willing to use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment, including:
        - oral, topical, injectable, or implantable birth control medications,
        - placement of an intrauterine device with or without hormones,
        - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly,
        - vasectomized male partner who is the sole partner for this patient,
        - true abstinence that is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of the study or withdrawal are not acceptable methods of true abstinence).

    There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
6. Fasting LDL-C ≥100 mg/dL (2.6 mmol/L) at Week -5 (Visit S1) while taking stable (4 weeks prior to Visit S1) and optimized background LDL-C-lowering therapies that may include very low dose statin (see definition above), ezetimibe, niacin, bile acid resins, fibrates, and/or proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors.

    Note: A single repeat of LDL-C may be completed prior to initiation of the single-blind Run-in Period. For those patients who have a repeat LDL-C, the repeat value will be used to determine eligibility.
7. History of, or at high risk for, CVD including documented evidence of one or more of the following:
    a. Documented history of CVD (ie, secondary prevention)
        - Coronary artery disease, defined by:
            - MI (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening, **or**
            - Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening, **or**
            - Angiographic stenosis of ≥50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or computed tomography angiography (CTA), **or**

- Symptomatic peripheral arterial disease (PAD), defined by:
  - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 or angiogram (including CTA) showing ≥50% stenosis (ankle brachial index will be measured after a period of rest and with the patient in the supine position using a Doppler device), **or**
  - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening, **or**
  - Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening, **or**
  - Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening, **or**
- Cerebrovascular atherosclerotic disease defined by:
  - Ischemic stroke occurring greater than 90 days prior to screening, **or**
  - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram (Note: If stenosis assessed by carotid ultrasound is reported as range between 60%-79%, patient may qualify only if internal carotid artery peak systolic velocity is ≥230 cm/sec), occurring greater than 90 days prior to screening, **or**

b. High risk for a CVD event (ie, high-risk primary prevention)

- Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years (see Appendix 3 and Appendix 4 for additional details), **or**
- Coronary artery calcium score >400 Agatston units (AU) at any time in the past, **or**
- Patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men).

Subject Exclusion Criteria:

Patients who meet any of the following criteria will not be eligible to participate:

1. Total fasting TG >500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1).

   Note: A single repeat of TG may be completed prior to initiation of the single-blind Run-in Period. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.

2. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

3. Forms of CVD that include any of the following:
   a. Recent (within 90 days prior to or during screening) acute CVD events including, but not only, transient ischemic attack (TIA), MI, coronary revascularization, peripheral arterial revascularization, ischemic stroke, carotid endarterectomy, carotid stenting.
   b. Recent (within 90 days of screening) unstable or symptomatic cardiac arrhythmia (including any associated medication changes). Patients with stable well-controlled atrial arrhythmias will be allowed to participate in the study.
   c. Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the investigator to be stable for greater than 90 days prior to screening,

d. New York Heart Association (NYHA) Functional Classification Class IV heart failure,

e. Uncontrolled hypertension, defined as mean sitting systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg,

Note: At the discretion of the investigator, BP medications can be adjusted and/or additional assessment of BP may be completed prior to randomization, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.

f. Planned coronary revascularization (patient may rescreen 3 months post-procedure).

4. HbA_{1C} ≥10% at Week -5 (Visit S1).
5. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Note: At the discretion of the Investigator, thyroid replacement therapy can be adjusted and/or additional measurement of TSH may be completed prior to randomization, with the repeat TSH value used to determine eligibility.
6. Liver disease or dysfunction, including:
   a) Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -4 (Visit S2), or
   b) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Week -5 (Visit S1).

   Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed prior to randomization. For those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for Hepatitis C antibody is positive, but optional reflexive test for Hepatitis C RNA is negative, patient can be enrolled.
7. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption.
8. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Week -5 (Visit S1).
9. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.
10. Unexplained creatine kinase (CK) >3 × ULN at Week -5 (Visit S1) (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
11. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator.
12. Blood transfusion for any reason within 30 days prior to randomization.
13. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer.
14. Randomization into another Phase 3 bempedoic acid clinical study.
15. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Week -5 [Visit S1]), lomitapide or apheresis therapy (must be stopped at least 3 months prior to Week -5 [Visit S1]),
    - Red yeast rice (must be stopped at least 2 weeks prior to Week -5 [Visit S1]),

- Statins are prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg.

16. Planned initiation or dose adjustments of these allowed drugs prior to screening and during the clinical trial (stable use of these drugs is permitted):
    - Statins are allowed only at average daily doses of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg (must be stable at least 4 weeks prior to Week -5 [Visit S1]),
    - Other lipid-regulating drugs or supplements (must be stable at least 4 weeks prior to Week -5 [Visit S1])
    - PCSK9 inhibitors (must be stable at least 12 weeks prior to Week -5 [Visit S1]).
17. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
18. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
19. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
20. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
21. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of IMP.

Investigational Medicinal Product, Dosage and Mode of Administration:

- Bempedoic acid 180 mg film-coated tablets
- Matching placebo tablets

All IMP will be ingested once daily at similar time with or without food.

Non-Investigational Medicinal Product

Background therapy for all patients will include a wide range of concomitant medications, according to local standard of care. Patients will be permitted to take any concomitant medications or therapies except mipomersen, lomitapide, apheresis therapy, red yeast rice, or any statin at a dose greater than those noted below. Background therapy to lower LDL-C may include nonstatin drugs and supplements such as ezetimibe, niacin, bile acid resins, fibrates, PCSK9 inhibitors, plant sterols, and plant stanols. Statin use will be limited to an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg. Additionally, patients may use any TG-lowering drugs and supplements.

Safety and Monitoring:

Monitoring and Management of Elevated LDL-C:

Postrandomization, LDL-C results will be masked in order to maintain the blind. Beginning at Month 6 (Visit T4) and for the remaining duration of the study, the central laboratory will notify the investigator if the patient's LDL-C level is ≥25% higher than baseline LDL-C. The patients will be counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria. If confirmed, the patient's LDL-C-lowering treatment regimen may be adjusted, if possible, per standard of care and local practice. Any initiation and/or dose change of LDL-C-lowering medications will be documented on the electronic case report form (eCRF) and will not be provided by the Sponsor.

Investigators will not measure LDL-C at a local lab during the study.

Monitoring and Managements of Elevated TG:

Postrandomization, TG results will be masked in order to maintain the blind. Beginning at Month 3 (Visit T3) and for the remaining duration of the study, the central laboratory will notify the investigator if a patient's TG level is >1000 mg/dL (11.3 mmol/L). The patient will be counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the TG value meets the threshold criteria. If confirmed, the patient's TG-lowering treatment regimen may be adjusted, if possible, per standard of care and local practice. Any initiation and/or dose change of TG medications will be documented on the eCRF and will not be provided by the Sponsor. If, despite adjustment of TG-lowering therapies, the TG level remains >1000 mg/dL (11.3 mmol/L), the patient will discontinue study medication but will remain in the study.

Statistical Methods:

Sample Size

This event-driven trial is designed to provide at least 90% power to detect an approximate 15% relative risk reduction in the primary 4-component MACE endpoint (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) at an overall study significance level (alpha) of 0.05. Assuming a 3.59% annual event rate in the placebo group, a minimum of 1620 patients experiencing an adjudicated primary MACE endpoint will be required. The median treatment duration for all patients was assumed to be approximately 42 months (3.5 years), with minimum treatment duration of 36 months (~3 years) and a lost-to-follow-up (LTFU) rate of 1% per year. In addition, the trial is designed to provide more than 95% power to detect an approximately 17% relative risk reduction in the primary 4-component MACE endpoint. A two-sided log-rank test (with the assumption of exponential distribution of survival times) was used to calculate the sample size.

Approximately 14,000 patients (approximately 7000 in the bempedoic acid group and 7000 in the placebo group) will be randomized into the study to achieve the 1620 patients experiencing an adjudicated primary endpoint event.

It is expected that 50% of the 1620 patients experiencing an adjudicated primary 4-component MACE (810 patients) will experience an adjudicated 3-component MACE (CV death, nonfatal MI, or nonfatal stroke). Additionally, the median treatment duration for the sample size calculation was assumed to be 42 months (~3.5 years) when the annual placebo event rate was 3.59%. Therefore, the study will not stop until at least 1620 patients have experienced an adjudicated primary MACE endpoint, with 50% of the patients experiencing an adjudicated 3-component MACE, and a minimum of 24 months (2 years) have elapsed since the last patient was randomized.

Interim Analyses

There will be no interim efficacy analyses in this study. The study may be altered or terminated based upon recommendations from the DMC as described in Section 14.2.

Statistical Adjustment for Testing Hypotheses Corresponding to the Primary and Key Secondary Efficacy Parameters

The following 7 hypotheses of no difference between bempedoic acid and placebo, based on the primary and key secondary efficacy endpoints, will be tested sequentially. This gatekeeping or stepdown testing approach will preserve the study-wise (family-wise) Type I error rate at 5%. The sequence for the stepdown procedure in this study is as follows:

1. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of MACE (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization; primary 4-component MACE)
2. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (3-component MACE)
3. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of fatal or nonfatal MI
4. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of coronary revascularization
5. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of fatal or nonfatal stroke
6. Testing the hypothesis of no difference between bempedoic acid and placebo in time to CV death
7. Testing the hypothesis of no difference between bempedoic acid and placebo in time to all-cause mortality

For the final analysis about the differences between bempedoic acid and placebo at the end of the study, each hypothesis in this hierarchical testing structure will be tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. For other efficacy endpoints, a significance level of 0.05 will be used.

Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses and summaries, is defined as all randomized patients and is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.

The Diabetes Efficacy Population, used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients in the FAS fulfilling one or more of the following criteria at baseline captured by information recorded as medical history, prior medication, and/or laboratory data:

- Medical history indicating type 2 diabetes
- Prior glucose-lowering medication with confirmation of diagnosis of diabetes by a DC (Section 14.4) if prior medication is the only criteria met for diagnosis of diabetes
- HbA_{1C} measurement $\geq$6.5%
- Two or more measurements of fasting glucose $\geq$126 mg/dL (7.0 mmol/L)

The Inadequately Controlled Diabetes Efficacy Population, is defined as the subset of patients in the Diabetes Efficacy Population with an HbA_{1C} of 7% or greater at baseline. This efficacy population will be used for the corresponding diabetes secondary and tertiary endpoints.

The Prediabetes Efficacy Population, used for efficacy analyses of time to new-onset diabetes and for efficacy analyses of HbA_{1C} and fasting glucose, is defined the subset of patients in the FAS fulfilling all of the following criteria captured at baseline by information recorded as medical history, prior medication, and/or laboratory data:

- Having no medical history indicating type 2 diabetes
- Having no prior glucose-lowering medication unless verified by the DC that there is no diagnosis of diabetes (Section 14.4) if prior medication is the only criteria assessed for the diagnosis of diabetes
- HbA_{1C} measurement of 5.7% to 6.4% or 1 or more measurements of fasting glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), but not more than 1 value of fasting glucose ≥126 mg/dL (7.0 mmol/L)

The Normoglycemia Efficacy Population, used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients not fulfilling the criteria at baseline for the Diabetes Population or Prediabetes Efficacy Population.

The No Diabetes Efficacy Population used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients not fulfilling the criteria at baseline for the Diabetes Efficacy Population.

The Safety Population (SP), used for all of the safety analyses, is defined as all randomized patients who received at least 1 dose of study medication (investigational product). Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

The Diabetes, Prediabetes, Normoglycemia and the Inadequately Controlled Diabetes Safety Populations are used for safety analyses as needed, and defined similarly as Diabetes, Prediabetes, Normoglycemia, and the Inadequately Controlled Diabetes Efficacy Populations but using patients from Safety Population instead.

Disposition and Baseline Characteristics:

Disposition, including reason for withdrawal from the study, will be summarized by treatment group. Demographic information and patient characteristics will also be summarized by treatment group.

Primary Endpoint:

The primary endpoint of this study is time to first occurrence of a confirmed (adjudicated) MACE, where MACE is defined as a composite primary efficacy endpoint that includes CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

The primary efficacy endpoint will be analyzed using Cox proportional hazards (PH) model with treatment as a factor. The Cox PH analysis will be performed using the FAS, with patients included in their randomized treatment group, regardless of the treatment they actually received. Note that the FAS includes patients who permanently discontinue treatment but remain in the study (patients are included regardless of their adherence to treatment). For this analysis, patients who are LTFU without experiencing a MACE will be censored at the time they are last known to be event-free. Patients who withdraw consent (withdraw from the study and refuse further contact) without experiencing a MACE will be censored at the time of consent withdrawal. Additionally, taking into account the period for CV event monitoring is every 3 months, when a patient who is LTFU or withdraws consent without experiencing a MACE is known to have later experienced a non-CV death, if the death was within 3 months of last contact, the patient will be censored at the time of death. If the death occurs more than 3 months after last contact, then the patient will be censored at the time of last contact. The hazard ratio (HR) and its 95% confidence interval (CI) and associated p-value will be provided.

In addition, Kaplan-Meier (K-M) curves will be provided, to provide a graphical description of the time to first occurrence of MACE.

Each individual component of the primary efficacy endpoint (CV death, nonfatal MI, nonfatal stroke, and coronary revascularization; each of the individual components are secondary time-to-event endpoints) will also be analyzed using Cox PH model, to ensure consistency of the treatment effect across the components that comprise the composite endpoint. Each Cox PH model will include treatment as a factor and will be performed on the FAS with patients included in their randomized treatment group. The HR and its 95% CI will be provided for each individual component of the primary efficacy endpoint.

Secondary Efficacy Time-to-Event Endpoints:

Secondary efficacy MACE endpoints related to time-to-events will be analyzed in a manner analogous to that used for the primary efficacy analysis, using Cox PH model and with similar censoring definitions. K-M curves will also be provided for each endpoint.

The time to first occurrence of new onset of diabetes during the treatment period will be analyzed by a Cox model in the Prediabetes Efficacy Population. The date of new onset of diabetes will be the earliest date of the event observed during the treatment period. For this analysis, patients who are LTFU and discontinue the study drug early without experiencing a new onset of diabetes will be censored at 30 days after the last date of the treatment.

Secondary Efficacy Lipid and Other Biomarker Endpoints:

Percent change from baseline to Month 6 in LDL-C and change from baseline to Month 12 in HbA_{1C} will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and the relevant baseline as a covariate. The ANCOVA for LDL-C will be performed using the FAS. The ANCOVA for HbA_{1C} will be performed in the Inadequately Controlled Diabetes Efficacy Population. Two methods for data handling will be used: the first (primary) will involve specification of the missing data mechanism using a pattern mixture model (PMM), while the second (supportive) will be observed case data only. For each analysis, the least squares mean (LSM) and standard error (SE) will be provided for each treatment group, along with the placebo-corrected LSM, its 95% CI, and associated p-value.

A nonparametric analysis based on Wilcoxon rank sum test and Hodges-Lehmann (H-L) estimate of location shift will be performed in the FAS for percent change from baseline to Month 6 in hs-CRP. No imputation will be performed for the hs-CRP endpoint due to the extreme skewed distribution.

Tertiary Lipid and Biomarker Endpoints:

Tertiary lipid and HbA_{1C}-related endpoints will be summarized and analyzed as needed. For each parameter at each time point, the value of the parameter, change and the percent change from baseline will be summarized by treatment group. The Mixed Model Repeated Measure (MMRM) analysis including factors of treatment group, time point (as a categorical variable), baseline value, and treatment group-by-time point interaction will be performed in the observed FAS data. The LSM and SE will be provided for each treatment group, along with the placebo-corrected LSM, its 95% CI, and associated p-value, as needed. A nonparametric analysis based on Wilcoxon rank sum test and H-L estimate of location shift will be performed in observed FAS data for percent change from baseline to Month 12 and end-of study in hs-CRP.

Safety Endpoints:

General safety data in this study include AEs, clinical safety laboratories, physical examinations (PEs), vital signs, and electrocardiograms (ECGs). The summarization of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after randomization and ingestion of the first dose of randomized IMP. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to IMP for each treatment group. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, and urinalysis; PE findings; vital signs; ECG readings; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each postbaseline time point.

AESI:

All AESI will be identified and evaluated by routine safety monitoring of AEs and laboratory values (where appropriate) and will be summarized by severity and relationship to IMP for each treatment group

The following are considered AESI categories for this study:

- Hepatic Safety, including liver-associated enzymes, total bilirubin (TB), and any Hy's law cases (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the setting of no known other cause)
- Musculoskeletal Safety, including creatinine phosphokinase (CK)
- Diabetes and Glycemia, including new onset of diabetes and worsening of diabetes
- Hypoglycemia Associated with Metabolic Acidosis
- Renal Impairment, including lab measures of renal function
- Neurocognitive Events
- Atrial Fibrillation
- Tendon Rupture/Tendinopathy. The TRAC will adjudicate events of tendon rupture per the Tendon Rupture Independent Adjudicator Charter (TRIAC), and adjudicated events will be summarized.
- Malignancies

Additional postrandomization adjunctive lipid-modifying therapy:

The number and percent of patients in each treatment group requiring additional (postrandomization) adjunctive lipid-modifying therapy will be summarized by treatment and by lipid-lowering therapy class. The reasons for their additional treatment (hyperlipidemia versus hypertriglyceridemia) will be summarized. Medications will be summarized by treatment group.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-CoA synthetase
ACSVL1	very long-chain acyl-CoA synthetase 1
ADA	American Diabetes Association
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AESI	adverse events of special interest
Alb	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AU	Agatston units
AUC_{0-24}	area under the curve during 24 hours
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C5Research	Cleveland Clinic Coordinating Center for Clinical Research
Ca	calcium
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI(s)	confidence interval(s)
CK	creatine kinase
COVID-19	Coronavirus disease of 2019
CPK	creatine phosphokinase
Cl	chloride
CNS	central nervous system
CoA	acetyl-coenzyme A
CO_2	carbon dioxide
CRO(s)	contract research organization(s)
CTA	computed tomography angiography
CV	cardiovascular

Abbreviation or Specialist Term	Explanation
CVD	cardiovascular disease
CYP	cytochrome P450
DBP	diastolic blood pressure
DC	Diabetes Committee
DHA	docosahexaenoic acid
DMC	Data Monitoring Committee
EC	Executive Committee
ECG(s)	electrocardiogram(s)
eCRF	electronic case report form
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
EPA	eicosapentaenoic acid
ESP15228	metabolite of bempedoic acid
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA_{1C}	glycosylated hemoglobin, Type A_{1C}
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HCV-Ab	hepatitis C antibodies
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
H-L	Hodges-Lehmann
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
INR	international normalized ratio

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
ITT	intention-to-treat
IWRS	interactive web response system
K	potassium
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LS	least square
LSM	least squares mean
LTFU	lost-to-follow-up
MACE	major adverse cardiovascular event
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MED ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model repeated measure
MRI	magnetic resonance imaging
Na	sodium
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCSK9	proprotein convertase subtilisin kexin type 9
PE	physical exam
PH	proportional hazards
PK	pharmacokinetic(s)
PMM	pattern mixture model
PT	prothrombin time
RBC	red blood cell
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	systolic blood pressure

Abbreviation or Specialist Term	Explanation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SI	statin intolerance
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP(s)	standard operating procedure(s)
SP	Safety Population
SUSAR(s)	suspected and unexpected serious adverse reaction(s)
TB	total bilirubin
TC	total cholesterol
TEAE(s)	treatment-emergent adverse event(s)
TG(s)	triglyceride(s)
TIA(s)	transient ischemic attack(s)
TRAC	Tendon Rupture Adjudication Committee
TRIAC	Tendon Rupture Independent Adjudicator Charter
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	white blood cell
WHO	World Health Organization

4. INTRODUCTION

Bempedoic acid (ETC-1002) is an oral, first-in class, small molecule designed to lower low-density lipoprotein cholesterol (LDL-C). It inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid, like statins, inhibits cholesterol synthesis and up-regulates LDL-C receptors. However, unlike statins, bempedoic acid does not inhibit cholesterol synthesis in muscle tissue, therefore it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of bempedoic acid.

Bempedoic acid and bempedoic acid and ezetimibe, under the marketed names of Nexletol® and Nexlizet™ respectively, have been approved by the United States (US) Food and Drug Administration (FDA) as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease in adults who require additional lowering of LDL-C (Nexletol, 2020; Nexlizet, 2020). In the European Union (EU) bempedoic acid and bempedoic acid and ezetimibe have been approved by the European Commission and are marketed under the names Nilemdo® and Nustendi®, respectively, for the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in adults unable to reach LDL-C goals with the maximum tolerated dose of statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated. Additionally, Nustendi® is indicated in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin (Nilemdo, 2020; Nustendi, 2020).

Patients who are statin intolerant have an unmet medical need for therapeutic options to lower LDL-C and reduce their risk of cardiovascular disease (CVD). Recent mechanistic and clinical data suggest that bempedoic acid may meet this medical need with a once-daily, nonstatin alternative. This Phase 3 study is being conducted as a part of a comprehensive Phase 3 program to determine whether bempedoic acid will reduce the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, CVD who are unable to tolerate statins.

4.1. Cardiovascular Disease, LDL-C-Lowering Drugs, and Statin Intolerance

Despite aggressive interventional and pharmacologic therapies, CVD is the number 1 cause of death globally (World Health Organization [WHO], 2015). The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (approximately 15.6 million deaths) were caused by CVD in 2010, more than all communicable, maternal, neonatal, and nutritional disorders combined, and double the number of deaths caused by cancers (Nichols, 2014). In the US, based on 2011 death rate data, more than 2150 Americans die from CVD daily, an average of 1 death every 40 seconds (Mozffarian, 2015). Of great concern, approximately 155,000 Americans dying from CVD are less than 65 years of age (Mozffarian, 2015). In Europe, CVD remains the most common cause of deaths, resulting in almost 2 times as many deaths as cancer (Townsend, 2015).

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and CVD (Sharrett, 2001). Evidence supporting LDL-C as a therapeutic target and surrogate for

cardiovascular (CV) outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, and genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent, log-linear relationship between LDL-C reduction and CV risk reduction, independent of the mechanism for LDL-C lowering (Kathiresan, 2008; Baigent, 2010; Robinson, 2005; Stamler, 1986). A published patient-level meta-analysis including 26 trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes (Baigent, 2010). This analysis showed that a 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Thus, LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities (Stone, 2013).

Statins are central to the LDL-C-lowering strategy and are supported by a large body of data demonstrating robust effectiveness in lowering LDL-C and reducing the risk of CVD (Waters, 2006; Grundy, 2004). However, there is increasing awareness of the limitations and risks of statin use. Many individuals at risk for CVD fail to achieve LDL-C goals (Martin, 2013; Virani, 2011). In 2011, the FDA mandated safety-labeling changes limiting the use of high dose (80 mg) simvastatin due to safety concerns of muscle injury or myopathy (Egan, 2011). Although myopathy events are rare, a more widespread problem is various muscle side effects such as pain and weakness, particularly at high doses, leading to poor tolerability and lack of persistence on statin therapy (Cohen, 2012). It is estimated that approximately 10% of patients who are prescribed statins are considered statin intolerant (Bruckert, 2005). Statin intolerance (SI) in patients most frequently manifests as muscle soreness and aching, but a range of signs and symptoms may be present, including elevated liver enzymes, gastric upset, diarrhea, constipation, rash, headache, dizziness, mental confusion, forgetfulness, or erectile dysfunction (Eckel, 2010). Given the importance of statin treatment for lowering CVD risk, statin discontinuation can have a marked adverse impact on CV outcomes in this population (Stroes, 2015). A study found that SI patients who discontinued therapy demonstrated a nonsignificant trend toward increased 8-year all-cause mortality compared with those who remained on statin therapy (Mampuya, 2013).

Other than statins, only a few drugs are approved to lower LDL-C, none of which are approved in the US to treat patients with SI. Currently, there are no approved drugs or studies that demonstrate CV risk reduction in the SI population. In the EU there are lipid-lowering therapies approved for SI patients such as the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, ezetimibe, bempedoic acid, and bempedoic acid and ezetimibe. Although LDL-C lowering is robust with PCSK9 inhibitors, use of these drugs is limited by mode of administration and other accessibility issues. Ezetimibe is an intestinal cholesterol absorption inhibitor that lowers LDL-C by 18% in patients with primary hyperlipidemia (Knopp, 2003). Other LDL-C-lowering therapies include colesevelam, a bile acid sequestrant that lowers LDL-C by up to 18% but is limited by considerable gastrointestinal side effects (Insull, 2001), while extended-release niacin in doses up to 2 g lowers LDL-C by up to 17% (Goldberg, 1998). Finally, fenofibrate, an activator of peroxisome proliferator-activated receptor alpha, lowers LDL-C by approximately 20% in patients with hypercholesterolemia (Knopp, 1987), but may substantially increase LDL-C in patients with hypertriglyceridemia.

Statin intolerance is a significant barrier to successful cholesterol management, particularly in CVD patients (Harris, 2011). Therefore, a once-daily oral therapy demonstrated to reduce CV events in patients who are statin intolerant can fulfill an unmet medical need.

4.2. Background on Bempedoic Acid

4.2.1. Mechanism of Action

Bempedoic acid is a first-in-class small molecule that decreases cholesterol synthesis in the liver. Bempedoic acid is a prodrug that requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA. ETC-1002-CoA inhibits ACL, an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Like statins, bempedoic acid decreases liver cholesterol synthesis which results in increased LDL receptor activity and LDL particle clearance from the blood.

Both ETC-1002-CoA (via ACL inhibition) and statins (via HMG-CoA reductase inhibition) inhibit cholesterol synthesis in the liver, but an important differentiating feature is that unlike statins, bempedoic acid is inactive in skeletal muscle. This is consistent with the absence of ACSVL1 (the synthetase required to activate bempedoic acid to ETC-1002-CoA and inhibit ACL) expression in muscle tissue. Evidence suggests that muscle-related adverse effects associated with statin use is a result of HMG-CoA reductase inhibition directly in skeletal muscle leading to a reduction of several downstream biological intermediates within the cholesterol synthesis pathway important for muscle cell function. Since bempedoic acid is not activated to ETC-1002-CoA and does not inhibit cholesterol synthesis in muscle tissue, it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of bempedoic acid.

Due to the position of ATP-ACL in the lipid biosynthesis pathway upstream of HMG-CoA reductase, its inhibition also results in concomitant suppression of fatty acid synthesis and potential improvement in glycemic control (Ference, 2019). In nonclinical disease models where elevated hepatic fatty acid synthesis promotes the accumulation of lipotoxic metabolites, inflammatory signaling, and insulin resistance; treatment with bempedoic acid improves inflammatory status and insulin sensitivity (Pinkosky, 2013; Samsoondar, 2017). Therefore, the impact of bempedoic acid on fatty acid synthesis in the liver provides a mechanistic basis for improvements in glycemic control.

4.2.2. Nonclinical Experience

The primary pharmacology of bempedoic acid was evaluated in several well-characterized and predictive rodent models of dyslipidemia. In these studies, bempedoic acid lowered LDL-C and triglycerides (TGs) and increased high-density lipoprotein cholesterol (HDL-C). In a study of cholesterol-fed LDL receptor-deficient mice, bempedoic acid substantially slowed the progression of atherosclerosis in a dose-related manner.

Results of the nonclinical safety pharmacology studies did not identify any significant risks for subjects over the mean range of bempedoic acid exposures in clinical studies.

In toxicology studies, evaluations of bempedoic acid in mice, rats, and monkeys in oral studies up to 52 weeks in duration have been completed. No significant central nervous system (CNS),

respiratory, or CV liabilities were identified. Target organs identified in repeat-dose studies were liver in rats, and liver and kidney in monkeys, and changes were reversible following cessation of treatment. Changes in clinical laboratory parameters indicative of hepatic and renal function were observed in animals at doses lower than those associated with frank toxicity.

Bempedoic acid is nonmutagenic and nonclastogenic in both in vitro and in vivo genetic toxicology assays.

In the pivotal 26-week rat study, the no-observed-adverse-effect level (NOAEL) dose was 30 mg/kg/day in rats and the corresponding area under the curve during 24 hours (AUC_{0-24}) values of the sum of bempedoic acid and its metabolite ESP15228 were up to 528 µg·hr/mL. In the pivotal 52-week monkey study, the NOAEL dose was 60 mg/kg/day and the corresponding AUC_{0-24} values of the sum of bempedoic acid and ESP15228 were up to 4760 µg·hr/mL.

In vitro studies indicated that bempedoic acid is neither an inhibitor nor inducer of major cytochrome P450 (CYP) enzymes at clinically relevant plasma concentrations. In addition, bempedoic acid does not appear to inhibit major drug transporters.

Please refer to the most recent Investigator's Brochure (IB) for additional information regarding pharmacology, pharmacokinetics (PK), and nonclinical safety studies.

4.2.3. Previous Human Experience

Detailed information on the clinical effects of bempedoic acid in indicated patient populations are provided in the country-specific prescribing information within the current United States Prescribing Information (USPI) and the EU Summary of Product Characteristics (SmPC).

Please refer to the most recent IB for information regarding previous human experience.

4.2.4. Dose Selection

Doses of bempedoic acid ranging from 40 to 240 mg/day have been evaluated in the Phase 2 program. Based on data from the integrated analysis of safety and efficacy, observed values and percent change from baseline in the primary efficacy endpoint, LDL-C, together with a positive safety profile, support the choice of the 180 mg dose for the Phase 3 studies. An integrated analysis of six Phase 2 studies resulted in placebo-adjusted LS means for percent change from baseline of approximately 32% with bempedoic acid 180 mg monotherapy, 50% with bempedoic acid 180 mg + ezetimibe 10 mg, and 22% for 180 mg on top of stable statin therapy. The 180 mg dose was noted to have an excellent safety profile. Overall, balancing efficacy and safety the 180 mg dose was chosen for the Phase 3 program.

4.3. Risk Benefit Summary

To date, the nonclinical and clinical data indicate that bempedoic acid 180 mg has a favorable risk-benefit profile. The ability of bempedoic acid to achieve clinically meaningful LDL-C lowering while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of bempedoic acid.

Two Phase 2 clinical studies have assessed bempedoic acid in patients unable to tolerate statins due to muscle related side effects (1002-006 and 1002-008). These studies have demonstrated that the magnitude of LDL-C lowering due to bempedoic acid treatment in patients with SI is

similar to that occurring in patients who tolerate statins. Additionally, in patients with SI, the safety and tolerability profile of bempedoic acid was similar to either ezetimibe (1002-008) or placebo (1002-006).

Although a large body of data has shown that LDL-C lowering, particularly via inhibition of cholesterol synthesis and up-regulation of LDL receptors, results in reduced CV risk, the direct effect of bempedoic acid on reducing CV risk has not previously been assessed. That is the purpose of this study.

Please refer to the most recent IB for additional information regarding previous human experience.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objectives

5.1.1. Primary Objective

The primary objective is to evaluate whether administration of bempedoic acid 180 mg/day versus placebo reduces the risk of MACE in patients with, or at high risk for, CVD who are statin intolerant. This will be assessed with a composite primary efficacy endpoint that includes time to first occurrence of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization.

5.1.2. Secondary Objectives

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality
- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on LDL-C and high-sensitivity C-reactive protein (hs-CRP)
- To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo
- To evaluate the 12-month efficacy of treatment with bempedoic acid 180 mg/day versus placebo on absolute change in hemoglobin A_{1C} (HbA_{1C}) in the Inadequately Controlled Diabetes Efficacy Population (patients with type 2 diabetes mellitus and having an HbA_{1C} of 7% or greater at baseline)
- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of new-onset diabetes

5.1.3. Tertiary Objective

- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), HDL-C, TG, HbA_{1C}, and fasting glucose

5.2. Study Endpoints

The following endpoints will be used to evaluate the objectives of the study.

5.2.1. Primary Efficacy Endpoint

- Time to first occurrence of a MACE, where MACE is defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization

5.2.2. Secondary Efficacy Time-to-Event Endpoints

Key secondary efficacy time-to-event endpoints:

- Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke
- Time to first occurrence of (fatal + nonfatal) MI
- Time to first occurrence of coronary revascularization
- Time to first occurrence of (fatal + nonfatal) stroke
- Time to CV death
- Time to all-cause mortality

Secondary efficacy time-to-event endpoints:

- Time to first occurrence of the composite endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization
- Time to first occurrence of nonfatal MI
- Time to fatal MI
- Time to first occurrence of nonfatal stroke
- Time to fatal stroke
- Time to first occurrence of (fatal + nonfatal) hemorrhagic stroke
- Time to first occurrence of (fatal + nonfatal) nonhemorrhagic stroke
- Time to hospitalization for unstable angina
- Time to first occurrence of new-onset type 2 diabetes mellitus defined by one or more of the following criteria according to the current American Diabetes Association (ADA) guidelines (ADA, 2014):

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours;* or
2. Two-hour post-prandial glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test as defined in the ADA guidelines;* or
3. HbA_{1C} measurement ≥6.5% (48 mmol/mol);* or
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*Note: In the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test results.

5.2.3. Secondary Efficacy Lipid and Biomarker Endpoints

- Percent change from baseline to Month 6 in LDL-C
- Percent change from baseline to Month 6 in hs-CRP
- Absolute change from baseline to Month 12 in HbA_{1C} in patients in the inadequately controlled diabetes efficacy population (patients with type 2 diabetes mellitus and an HbA_{1C} of 7% or greater at baseline)

5.2.4. Tertiary Efficacy Lipid and Other Biomarker Endpoints

- Percent change from baseline to Months 3, 12, 24, and end-of-study in LDL-C; percent change from baseline to Months 3, 6, 12, 24, and end-of-study in HDL-C, non-HDL-C, TC, and TG
- Absolute change from baseline to Months 3, 6, 12, 24, and end-of-study in LDL-C
- Percent change from baseline to Month 12 and end-of-study in hs-CRP
- Absolute change from baseline to Month 3, 6, every 6 months following Month 12, and end-of-study in HbA_{1C} in patients in the Inadequately Controlled Diabetes Efficacy Population (patients with type 2 diabetes mellitus and HbA_{1C} of 7% or greater at baseline)
- Absolute change from baseline to Month 3, 6, 12, every 6 months following Month 12, and end-of-study in fasting glucose in patients in the Normoglycemia Efficacy Population, Prediabetes Efficacy Population, No Diabetes Efficacy Population, and Diabetes Efficacy Population

5.2.5. Safety Endpoints

- Adverse events (AEs including adverse events of special interest [AESI]), vital signs (eg, heart rate, weight, blood pressure [BP]), and clinical laboratory measures

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessing the occurrence of MACE in patients with, or at high risk for, CVD who are unable to tolerate statin therapy. The study will be conducted at approximately 1200 clinical sites in 32 countries.

Following signing of an informed consent document (ICD) prior to any study procedures, screening (Visit S1) will occur approximately 5 weeks prior to Day 1 (Visit T1) (Note: the screening period can be extended for an additional 5 weeks if needed to adjust background therapy or for other reasons). All eligible patients in stable condition and who meet all the entry criteria will return for Week -4 (Visit S2) to initiate a 4-week Run-in Period with single-blind (blinded to patient only) daily placebo treatment. At Day 1 (Visit T1), assessment of tolerability and adherence to IMP (single-blind placebo) during run-in, laboratory results, and other screening assessments will be reviewed to confirm eligibility prior to randomization. Patients who meet all entry criteria will be eligible for randomization into the study.

Randomization numbers will be assigned via interactive web response system (IWRS) at Day 1 (Visit T1). Approximately 14,000 eligible patients will be randomized in a ratio of 1:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- Bempedoic acid 180 mg tablet once daily (n = 7000)
- Matching placebo tablet once daily (n = 7000)

Please note that among other qualifying events, patients may meet the CVD inclusion criterion by being part of the group identified as “at high risk for a CVD event” based on Reynolds risk, SCORE risk, or coronary artery calcium score. It is anticipated that less than 30% of total patients will fall into this group by meeting the CVD inclusion criterion based solely on the events listed above. If, during the randomization period, more than 30% of the overall 14,000 patients are part of this group (more than 4200 randomized patients), then recruitment into this group may be capped.

Treatment with randomized, double-blind IMP will begin at Visit T1 and continue daily. Randomized patients will return for clinic visits at Month 1 (Visit T2), Month 3 (Visit T3), and Month 6 (Visit T4). Following Month 6, patients will be contacted every 3 months (alternating phone visits and clinic visits) for the remainder of the study. The study will continue until the following 3 conditions are met: 1) at least 1620 patients have experienced an adjudicated primary 4-component MACE (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization), 2) at least 810 patients have experienced an adjudicated 3-component MACE (CV death, nonfatal MI, or nonfatal stroke), and 3) 24 months (2 years) have elapsed since the last patient was randomized. It is estimated that average treatment duration for all randomized patients will be approximately 3.5 years. For each patient, the last treatment visit will be a clinic visit, with a follow-up phone call approximately 30 days after study treatment completion. Patients who discontinue IMP for any reason will remain in the study to be evaluated for efficacy and safety endpoints and will be expected to continue study visits (preferred) or agree to some

other form of contact with the site for the remainder of the study. For details of study assessments, see the Schedule of Events in Appendix 1.

This study will include several independent and expert committees. An Executive Committee (EC) will oversee the design and conduct of the study and the interpretation of study results. A Clinical Events Committee (CEC) will adjudicate blinded clinical endpoints, including MACE endpoints, as well as non-CV deaths using standardized definitions. An adjudicated clinical endpoint will not be reported as a serious adverse event (SAE). A Diabetes Committee (DC) will verify diagnosis of new onset diabetes. A Tendon Rupture Adjudication Committee (TRAC) will adjudicate AEs of tendon rupture using standardized definitions. An independent Data Monitoring Committee (DMC) will review accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid approximately 4 times per year. Safety data reviewed by the DMC will include AEs, clinical endpoints, and lipids. Each of these committees has a charter that includes additional details.

6.2. Study Hypotheses

This superiority study will test the hypothesis that bempedoic acid, compared to placebo, will reduce the risk of CV events in patients with, or at high risk for, CVD who are statin intolerant.

In addition, it will test the hypothesis that bempedoic acid, compared to placebo, will delay time to first occurrence of new-onset diabetes in patients in the prediabetes subpopulation. It will also test the hypothesis that bempedoic acid, compared to placebo, will reduce absolute change from baseline to Month 12 in HbA_{1C} in patients in the inadequately controlled diabetes subpopulation.

6.3. Estimated Study Duration and Period

The estimated enrollment period is approximately 33 months. It is estimated the median treatment duration will be approximately 42 months (3.5 years), with all patients remaining in the study for a minimum of 24 months (2 years) and some patients remaining in the study for up to approximately up to 72 months (6 years). The study will continue until all 3 criteria for study end described in Section 6.5 have been met. Depending on the rates of accumulating endpoints in this study, the study duration may be shorter or longer. The estimated overall duration of the study (first patient first visit to last patient last visit) is approximately 72 months (6 years).

For each patient, the actual duration of treatment will depend on time of randomization versus when the 'End of Study' conditions have been met. All patients will be followed from randomization through the date of study termination unless the patient has withdrawn consent, irrespective of whether the patient is continuing to receive study treatment.

6.4. Number of Centers

Up to approximately 1200 centers will participate in this study worldwide. Additional sites may be invited to participate to ensure study timelines are met. Sites that do not enroll patients within 3 to 6 months of being open for enrollment may be closed.

6.5. End of Study

This study is event-driven. The study will end when all of the following have occurred: 1) at least 1620 patients have experienced an adjudicated primary 4-component MACE, 2) at least 810 patients have experienced an adjudicated 3-component MACE (CV death, nonfatal MI, nonfatal stroke), and 3) at least 24 months (2 years) have elapsed since the last patient was randomized.

6.6. Number of Patients

The study will enroll approximately 14,000 adult male and female patients.

7. SELECTION OF PATIENTS

Please note that among other qualifying events, patients may meet the CVD inclusion criterion by being part of the group identified as "at high risk for a CVD event" based on Reynolds risk, SCORE risk, or coronary artery calcium score. It is anticipated that less than 30% of total patients will meet the CVD inclusion criterion based solely on Reynolds risk, SCORE risk, or coronary artery calcium score. If, during the randomization period, more than 30% of the overall 14,000 patients are part of this group (more than 4200 randomized patients), then recruitment into this group may be capped.

7.1. Subject Inclusion Criteria

Each patient must meet the following criteria to be eligible for this study.

1. Provision of signed informed consent prior to any study-specific procedure.
2. Patient-reported SI due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued resulting in an inability to tolerate:

   - 2 or more statins at any dose, or
   - 1 statin at any dose and unwilling to attempt a second statin or advised by a physician to not attempt a second statin.

   Please note that patients currently tolerating very low dose statin therapy (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg) are considered to be intolerant to that low dose statin. Patients may continue taking very low dose statin therapy throughout the study provided that it is stable (used for at least 4 weeks prior to screening) and well tolerated.
3. Written confirmation by both patient and investigator that the patient is statin intolerant as defined above, aware of the benefit of statin use to reduce the risk of MACE including death, and also aware that many other patients who are unable to tolerate a statin are able to tolerate a different statin or dose.
4. Age ≥18 years or legal age of majority based on regional law, whichever is greater, and ≤85 years at Week -5 (Visit S1).
5. Men and nonpregnant, nonlactating women. Women must be one of the following:

   - Naturally postmenopausal defined as ≥1 year without menses and:
     - ≥55 years, **or**
     - <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L, **or**
   - Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation, **or**

- Women of childbearing potential willing to use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment, including:
  - oral, topical, injectable, or implantable birth control medications,
  - placement of an intrauterine device with or without hormones,
  - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly,
  - vasectomized male partner who is the sole partner for this patient,
  - true abstinence that is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of the study or withdrawal are not acceptable methods of true abstinence).

There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

6. Fasting LDL-C ≥100 mg/dL (2.6 mmol/L) at Week -5 (Visit S1) while taking stable (4 weeks prior to Visit S1) and optimized background LDL-C-lowering therapies that may include very low dose statin (see definition above), ezetimibe, niacin, bile acid resins, fibrates, and/or PCSK9 inhibitors.

   Note: A single repeat of LDL-C may be completed prior to initiation of the single-blind Run–in Period. For those patients who have a repeat LDL-C, the repeat value will be used to determine eligibility.

7. History of, or at high risk for, CVD including documented evidence of one or more of the following:
   a. Documented history of CVD (ie, secondary prevention)
      - Coronary artery disease, defined by:
        - MI (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening, **or**
        - Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening, **or**
        - Angiographic stenosis of ≥50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or computed tomography angiography (CTA), **or**
      - Symptomatic peripheral arterial disease (PAD), defined by:
        - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 or angiogram (including CTA) showing ≥50% stenosis (ankle brachial index will be measured after a period of rest and with the patient in the supine position using a Doppler device), **or**
        - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening, **or**

- Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening, **or**
- Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening, **or**

– Cerebrovascular atherosclerotic disease defined by:

- Ischemic stroke occurring greater than 90 days prior to screening, **or**
- Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram (Note: If stenosis assessed by carotid ultrasound is reported as range between 60%-79%, patient may qualify only if internal carotid artery peak systolic velocity is >230 cm/sec), occurring greater than 90 days prior to screening, **or**

b. High risk for a CVD event (ie, high-risk primary prevention)

– Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years (see Appendix 3 and Appendix 4 for additional details), **or**

– Coronary artery calcium score >400 Agatston units (AU) at any time in the past, **or**

– Patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men).

7.2. Subject Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate:

1. Total fasting TG >500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1).

   Note: A single repeat of TG may be completed prior to initiation of the single-blind Run-in Period. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.

2. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

3. Forms of CVD that include any of the following:

   a. Recent (within 90 days prior to or during screening) acute CVD events including, but not only transient ischemic attack (TIA), MI, coronary revascularization, peripheral arterial revascularization, ischemic stroke, carotid endarterectomy, carotid stenting,
   b. Recent (within 90 days of screening) unstable or symptomatic cardiac arrhythmia (including any associated medication changes). Patients with stable well-controlled atrial arrhythmias will be allowed to participate in the study.

c. Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the investigator to be stable for greater than 90 days prior to screening,
d. New York Heart Association (NYHA) Functional Classification Class IV heart failure,
e. Uncontrolled hypertension, defined as mean sitting systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg,

   Note: At the discretion of the investigator, BP medications can be adjusted and/or additional assessment of BP may be completed prior to randomization, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.

f. Planned coronary revascularization (patient may rescreen 3 months post-procedure).

4. HbA_{1C} ≥10% at Week -5 (Visit S1).
5. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Note: At the discretion of the investigator, thyroid replacement therapy can be adjusted and/or additional measurement of TSH may be completed prior to randomization, with the repeat TSH value used to determine eligibility.
6. Liver disease or dysfunction, including:
   a. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -4 (Visit S2), or
   b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Week -5 (Visit S1).

   Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed prior to randomization. For those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for Hepatitis C antibody is positive, but optional reflexive test for Hepatitis C RNA is negative, patient can be enrolled.
7. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption.
8. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Week -5 (Visit S1).
9. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.
10. Unexplained creatine kinase (CK) >3 × ULN at Week -5 (Visit S1) (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.

11. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator.
12. Blood transfusion for any reason within 30 days prior to randomization.
13. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer.
14. Randomization into another Phase 3 bempedoic acid clinical study.
15. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Week -5 [Visit S1]), lomitapide or apheresis therapy (must be stopped at least 3 months prior to Week -5 [Visit S1]),
    - Red yeast rice (must be stopped at least 2 weeks prior to Week -5 [Visit S1]),
    - Statins are prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg.
16. Planned initiation or dose adjustments of these allowed drugs prior to screening and during the clinical trial (stable use of these drugs is permitted):
    - Statins are allowed only at average daily doses of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg (must be stable at least 4 weeks prior to Week -5 [Visit S1]) ,
    - Other lipid-regulating drugs or supplements must be stable at least 4 weeks prior to Week -5 [Visit S1]),
    - PCSK9 inhibitors (must be stable at least 12 weeks prior to Week -5 [Visit S1]).
17. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
18. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
19. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
20. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
21. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of IMP.

7.3. Patient Lifestyle and Dietary Guidelines

Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples (water and concomitant medications are permitted).

Patients will be counseled to follow a heart-healthy diet as per local or regional guidelines and should be encouraged (as able) to participate in a regular exercise program throughout the study.

Women of childbearing potential must use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment. Acceptable method(s) of birth control are defined in Section 7.1.

8. TREATMENT OF PATIENTS

8.1. Administration of Investigational Medicinal Product

During the Run-in Period, all patients will receive single-blind placebo (once daily tablets). During the Treatment Period, patients will be randomized to receive IMP of either bempedoic acid 180 mg or placebo once daily. Each dose of IMP is comprised of 1 tablet from 1 bottle. The IMP will be dispensed at most, but not all, scheduled clinic visits. Patients will be instructed to ingest IMP orally once daily at a similar time with or without food.

If the patient forgets to take IMP on nonclinic visit days, it may be taken up to 12 hours later the same day. After that time, the patient should not take IMP that day and should resume ingestion of IMP the following day. Details describing the reasons for nondosing should be documented in the patient's medical records and electronic case report form (eCRF). Extra IMP is provided and can be used, if needed, prior to the next visit or to replace a dose of IMP that cannot be used because it is lost or damaged.

Other details regarding IMP, including description, supply and control, accountability, handling, and disposal are provided in Section 9.

8.2. Prior and Concomitant Medications

Patients will be questioned about their concomitant medication use at each clinic visit.

Patients in this study may be using a wide range of concomitant medications, according to local standard of care for their medical conditions. Patients will be permitted to take any concomitant medications required except those listed in Section 8.2.1. Therapies to lower LDL-C may include nonstatin drugs and supplements such as ezetimibe, niacin, bile acid resins, fibrates, PCSK9 inhibitors, plant sterols, and plant stanols, but not red yeast rice. Statin use will be limited to the doses listed below and must be currently well tolerated. Additionally, patients may use any TG-lowering drugs and supplements.

All concomitant medication taken chronically or intermittently during the study must be recorded with indication, total daily dose, and start and stop dates of administration.

The Prior/Concomitant Nonstatin Medications eCRF will be used to record nonstatin medications, herbal remedies, vitamins, other supplements, and over-the-counter medications taken within 3 months prior to screening and during the study.

The Prior and Concomitant Statin Therapy for Dyslipidemia eCRF will be used to record statin medications taken at any point in the past in order to document patient's efforts to utilize statins. In addition to statin type, dose, and frequency of use, information about start dates, stop dates, and reason for discontinuation will be collected when available.

8.2.1. Prohibited Medications and Dietary Supplement

Patients may not have used medications (monotherapies or combination therapies) listed below within the time periods indicated, and may not use these drugs during the study:

- Mipomersen (within the last 6 months prior to Week -5 [Visit S1]), lomitapide, or apheresis therapy (within the last 3 months prior to Week -5 [Visit S1])

- Red yeast rice, also known as monascus purpureus extract or Cholestin, (within the last 2 weeks prior to Week -5 [Visit S1])
- If approved and commercially available, bempedoic acid or the fixed dose combination of bempedoic acid and ezetimibe
- Any statin taken within the first 6 months at average daily doses greater than those listed in Section 8.2.2 below. However, beginning at Month 6, if the threshold for elevated LDL-C levels has been met and confirmed as described in the monitoring and management section of the protocol (Section 12.1.6.3.3), average daily doses of statins greater than those listed in Section 8.2.2 below may be used in accordance with the standard of care and local practice. Simvastatin at average daily doses greater than or equal to 40 mg and pravastatin at average daily doses greater than or equal to 80 mg may not be used while the patient is taking IMP.

8.2.2. Permitted Medications

Permitted medications must be stable for at least 2 weeks prior to Visit S1 (Week -5) with the exception of PCSK9 inhibitors, which must be stable for 12 weeks prior to screening and other lipid-regulating medications that must be stable for 4 weeks prior to screening and during the study. Stable is defined as no addition or cessation of a drug or change in the dose of a drug.

Lipid-regulating medications and dietary supplements including but not limited to:

Statins – permitted only at average daily doses defined below provided these statin/doses are currently well tolerated. However, beginning at Month 6, if the threshold for elevated LDL-C levels has been met and confirmed as described in the monitoring and management section of the protocol (Section 12.1.6.3.3), average daily doses of statins greater than those listed below may be used in accordance with the standard of care and local practice. Simvastatin at average daily doses greater than or equal to 40 mg and pravastatin at average daily doses greater than or equal to 80 mg may not be used while the patient is taking IMP.

- Atorvastatin <10 mg
- Fluvastatin <40 mg
- Lovastatin <20 mg
- Pravastatin <40 mg
- Pitavastatin <2 mg
- Rosuvastatin <5 mg
- Simvastatin <10 mg

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestipol/Colesevelam hydrochloride
- Ezetimibe

Fibrates

- Fenofibrate
- Bezafibrate
- Ciprofibrate
- Gemfibrozil

PCSK9 inhibitors

- Evolocumab
- Alirocumab
- Other PCSK9 inhibitors that may become commercially available

Niacin derivatives

Other TG-lowering agents containing

- Eicosapentaenoic acid (EPA) and/or
- Docosahexaenoic acid (DHA)

8.3. Treatment Assignment, Randomization, and Blinding

During the Run-in Period, all patients will receive single-blind (blinded to patient only) daily placebo. Sponsor and site personnel will be aware that this single-blind IMP is placebo, and will ensure that this information is not in any manner provided to the patient.

During the Treatment Period, patients will receive double-blind IMP. At Day 1 (Visit T1), patients will be randomized to receive either bempedoic acid 180 mg/day or placebo. The investigator or designee will utilize IWRS during the visit to obtain a randomization number and the appropriate IMP container via medication identification numbers (MED ID). A patient is considered to be randomized when they have been assigned a randomization number by IWRS.

The randomization number will be determined by a computer-generated random code and will correspond to a treatment group according to patient's sequential entrance into the study. The randomization schedule for blinding of treatment assignment will be generated by the contract research organization (CRO), provided to IWRS, and released only after the study is complete and the database is locked.

During the Treatment Period, Sponsor, site personnel, CRO, and patient will all be unaware of patient's treatment assignment.

Blinding of treatment must be maintained for all patients unless, in the opinion of the investigator, the safety of the patient may be at risk. Only under the rarest of circumstances should the investigator consider breaking the blind and only when medical/supportive care cannot be provided without determining if the patient is receiving active drug treatment. In the event that the blind needs to be broken prior to completion of the study, the investigator should contact the appropriate Medical Monitor by telephone. If the blind must be broken prior to consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind.

At the initiation of the study, the clinical site will be instructed on procedures for breaking the blind via the IWRS. In all cases of breaking the blind, the investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved. Unblinding of IMP will NOT automatically discontinue the patient from the study. Any patient for whom the blind is broken will be permanently discontinued from IMP but should continue in the study per Section 10.7.3.

Postrandomization values for individual laboratory measures for LDL-C, non-HDL-C, TC, TG, and hs-CRP that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, or the CRO. While knowledge of these values does not truly 'unblind,' the completion of these lab assessments by the investigator, all collaborating physicians, or the patients locally (outside the study visits) is strongly discouraged. Investigators should not perform testing of these analytes at the local lab during the conduct of the study, except for TG levels that may be measured for some safety reasons.

During the study, an independent DMC will monitor accumulating unblinded patient safety data summaries and an unblinded independent CRO programmer and statistician will provide data to the DMC. Additional details will be provided in a DMC Charter.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Description of Investigational Medicinal Product

Table 2: Investigational Medicinal Products

	Investigational Medicinal Product	
Product Name:	**Bempedoic acid**	**Placebo**
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure:	100-count bottle with screw-on, non-childproof cap	35- and 100-count bottle (depending upon visit) with screw-on, non-childproof cap
Route of Administration:	Oral, daily at similar time, with or without food	Oral, daily at similar time, with or without food
Physical Description:	Oval, white to off-white film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face	Oval, white to off-white film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face

Please see Pharmacy Manual for detailed storage requirements and instructions.

9.2. Investigational Medicinal Product Supply and Control

The Sponsor will supply the IMP for this study. The IMP for this study includes bempedoic acid (180 mg film-coated tablets) and matching placebo (film-coated tablets). IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study.

The MED ID number (an identifier on the IMP packaging) will be obtained via IWRS and used to select single- and double-blind IMP from available clinical supplies at the clinical site.

IMP will be dispensed by the investigator or other qualified site personnel only to appropriate patients who have provided written informed consent.

9.3. Packaging and Labeling

Single-blind IMP will be packaged in bottles containing 35 tablets. Double-blind IMP will be packaged in bottles containing 100 tablets.

The IMP bottle labels will include protocol number, MED ID number, patient identification number, lot number, site number, and investigator name in addition to standard language regarding warnings and regulations, administration, and storage of the product.

9.4. Investigational Medicinal Product Adherence

IMP Adherence during the Run-in Period

In order to reduce the burden of unnecessary procedures on patients who may not be appropriate for this study, all patients will receive daily placebo during the 4-week Run-in Period to assess their adherence and ability to tolerate the single-blind treatment. IMP (placebo) will be dispensed at Week -4 (Visit S2). At Day 1 (Visit T1), designated clinical site staff will assess patient IMP intake adherence by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If the patient has not taken all doses of IMP as instructed, the patient will be queried for a reason and findings will be documented. Patients with adherence <80% will not be eligible for randomization.

IMP Adherence during the Randomization Period

At each clinic visit during the Treatment Period, designated clinical site staff will assess patient IMP intake adherence by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If the patient has not taken multiple consecutive doses (ie, more than 5 consecutive doses) of IMP as instructed, the patient will be queried for a reason, findings will be documented, and the patient will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. Patients demonstrating poor adherence during the Treatment Period will continue to be counseled on the importance of carefully following all dosing instructions but will not be removed from the study.

9.5. Investigational Medicinal Product Accountability

Patients will be instructed to return all packaging and unused IMP at every visit for assessment of adherence and drug accountability.

Accurate records of the receipt of all IMP shipped by the Sponsor (or designee) and the disposition of that IMP must be maintained.

IMP records or logs must comply with applicable regulations, local law, and guidelines, and should include:

- Amount received/placed in storage area
- Amount currently in storage area
- MED ID number for all IMP
- Dates and initials of person(s) responsible for IMP inventory (including entry/movement/disposition)
- Date and amount of IMP dispensed to each patient, including unique patient identifiers
- Date that IMP was returned by patient, assessment of adherence, and relevant documentation of discrepancies
- Nonstudy disposition (eg, lost, broken, wasted)

- Amount returned to Sponsor (or designee)/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.6. Investigational Medicinal Product Handling, Storage, and Disposal

The Principal Investigator will ensure that all IMP is stored in a secured area, under recommended storage conditions (at room temperature [15°C/59°F to 30°C/86°F] protected from any extreme conditions of temperature, light, or humidity) in accordance with applicable regulatory requirements for investigational drugs. Access to IMP will be limited to those clinical site personnel authorized by the investigator. Upon completion or termination of the study, all IMP and used and unused IMP packaging must be returned to the Sponsor (or designee) for eventual destruction unless otherwise authorized by the Sponsor. All IMP returns must be accompanied by the appropriate documentation.

10. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

10.1. Informed Consent

The patient must be adequately informed of the nature and risks of the study and understand the ICD. It is the investigator's responsibility that no study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The written ICD should be prepared in the local language(s) of the potential patient population.

10.2. Confirmation of Statin Intolerance

The investigator is responsible for reviewing the patient's available medical records and assessing the patient for SI. This will include a review of statin use history and a discussion with the patient about the patient's high risk of experiencing MACE, the ability of a statin to reduce that risk, and the patient's experience using a statin. For patients who are unwilling to attempt a second statin or a low dose despite physician encouragement, the investigator will explain that many patients unable to tolerate a single statin are able to tolerate a different statin or a lower dose.

Both the patient and the investigator will sign a form confirming that the patient is statin intolerant. Within this form, the patient will confirm an understanding that he/she is at high risk for experiencing a heart attack, stroke, or death and that using a statin would reduce that risk and also that many other patients who are unable to tolerate a single statin are able to tolerate a different statin or dose; however, he/she is not taking a statin because of intolerable side effects that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. Within the same form, the investigator will confirm that the patient is unable to tolerate statin therapy (except possibly at very low average daily doses of atorvastatin <10 mg, fluvastatin <40 mg, lovastatin <20 mg, pravastatin <40 mg, pitavastatin <2 mg, rosuvastatin <5 mg, or simvastatin <10 mg) based on review of the medical history and discussion with the patient.

Documentation of prior statin use will be based on patient recall and copies of relevant medical records if readily available. If investigator is unable to assess prior statin use due to poor patient recall and/or lack of relevant medical records, and if appropriate according to local medical practice, documentation of contact with primary care physician regarding prior statin use should be obtained. All available prior statin use history will be recorded in the eCRF. Additionally, the basis for the investigator's confirmation of the patient's SI will be noted in the eCRF.

10.3. Interactive Web Response System and eCRFs

Data will be captured on eCRFs. Randomization, IMP (re)ordering, IMP distribution, and patient status tracking will occur via IWRS. Instructions for these systems and additional contact time points for IWRS will be provided separately.

10.4. Patient Identification Numbers

A unique patient identification number will be assigned to each patient to identify each patient throughout the study. Patient identification numbers will be assigned sequentially by IWRS at the time of informed consent during the screening module transaction. The 10-digit number is comprised of protocol, country, site, and patient-specific numbers (ie, 43 01 002 003 identifies Protocol 43, Country 01, Site 002, and Patient 003).

10.5. Rescreening

Patients who are screen or run-in failures due to stability requirements for a condition or concurrent medication or other reason may be considered for rescreening after consultation with the Sponsor (or designee). If rescreened, these patients must also be re-consented and screening procedures must be repeated. If a patient is a screen failure or a run-in failure, or if a patient discontinues from the study, their patient ID number will not be assigned to another patient.

10.6. Procedures and Schedule of Assessments

The study is comprised of 3 distinct periods: screening, run-in, and double-blind treatment.

The schedule of study events is provided in Appendix 1. However, a patient can be seen at any time for reasons of safety.

Note: If the patient discontinues IMP at any time after T1, please proceed to Section 10.7 for detailed instructions.

- If the patient agrees to clinical visits after withdrawing from IMP at any time after Visit T1, the visit will include all procedures and assessments except for those pertaining to IMP management (IMP dispensing, adherence, and accountability).
- If the patient agrees to telephone or other form of contact after withdrawing from IMP at any time after Visit T1, the contact will include collection of patient-reported information to complete the eCRF including concomitant medication use, AEs, SAEs, and potential clinical endpoints.
- Patient is expected to continue to receive IMP and complete study visits following a clinical endpoint unless, for some reason, this is no longer clinically appropriate.

10.6.1. Screening Week -5 (Visit S1; Day -35)

The screening period will begin with a screening visit that will occur 5 weeks prior to randomization. Visit S1 will allow the investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Assess AEs, SAEs, and potential clinical endpoints (starting from signing the informed consent document)
- Demographics
- Clinically relevant medical history

- Prior and concomitant medication review
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Height (cm), and weight (kg)
- Vital signs
- Central clinical laboratory evaluations:
  - TSH
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs)
  - hs-CRP (optional assessment to be completed only if patient qualifies based on Reynolds Risk Score and local hs-CRP value is not available)
  - HbA_{1C}
  - Serum pregnancy test (in female patients of childbearing potential) or FSH (on postmenopausal women <55 years of age)
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their allowed therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Note:

- The number of days between Week -5 (Visit S1) and Week -4 (Visit S2) may be less than 7, and the number of days between Week -5 (Visit S1) and randomization may be less than 35 as long as eligibility can be determined.
- The screening period can be extended for an additional 5 weeks without repeat of all screening procedures if needed to adjust background therapy or for other reason.
- An additional visit prior to Visit S2 MAY be completed if patient fails to meet LDL-C and/or TG entry criterion. If this optional visit is completed, the value from the repeat visit will be used to determine eligibility.
- An additional visit and/or assessment between Visits S1 and T1 MAY be completed if the patient fails to meet DBP, SBP, TSH, eGFR, ALT, AST, and CK entry criteria. Patients may qualify for randomization after any associated medications have been adjusted, they have been on stable doses for at least 2 weeks, and the repeat assessment meets entry criteria.

10.6.2. Screening Week -4 (Visit S2; Day -31 to -25)

- The single-blind Run-in Period for placebo begins at this visit. The patient will undergo the following assessments and procedures at Visit S2:Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Physical examination (PE)
- 12-lead electrocardiogram (ECG)
- Central clinical laboratory evaluations:
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Serology (including HBsAg, hepatitis C virus [HCV] antibody)
- Dispense single-blind IMP (placebo) and dosing and storage instructions
- Diet and exercise counselling

10.6.3. Treatment Week 0 (Visit T1; Day 1)

Prior to scheduling Visit T1, screening clinical results will be reviewed to determine whether the patient continues to meet lab eligibility criteria. At Visit T1, adherence to and tolerability with placebo IMP during the Run-in Period (≥80% adherence required) will be assessed. Patients with intolerable side effects, including but not limited to muscular skeletal pain, will be run-in failures.

If the patient has met all inclusion criteria and none of the exclusion criteria, the patient may be randomized into the double-blind Treatment Period. Patients who fail to meet all entry criteria after initiation of single-blind run-in IMP are considered to be run-in failures and will not be randomized.

Patients are considered randomized once all eligibility criteria are confirmed and a randomization number is obtained by the IWRS on the day of first dose.

The patient will undergo the following assessments and procedures at Day 1 (Visit T1):

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Return of unused single-blind IMP and assessment of IMP dosing adherence
- Assessment of tolerability of IMP and continued interest in study participation
- Review inclusion/exclusion criteria to establish patient eligibility
- Weight
- Vital signs

- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG) and hs-CRP
- Urine pregnancy test (in female patients of childbearing potential)
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind IMP
- Dispense double-blind IMP and provide dosing and storage instructions
- Diet and exercise counselling
- Schedule next visit

10.6.4. Treatment Month 1 (Visit T2; ± 3 days)

Patients will undergo the following assessments and procedures at Month 1 (Visit T2):

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Central clinical laboratory evaluations:
  - Limited blood chemistry safety panel (ALT, AST, total bilirubin [TB], and CK)
- Return of IMP; assessment and recording of IMP dosing adherence
- Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing and storage instruction
- Diet and exercise counselling
- Schedule next visit

Note: If the patient discontinues at any scheduled visit after T1, or between study visits, please proceed to Section 10.7 for detailed instructions.

10.6.5. Treatment Month 3 (Visit T3; ± 5 days)

Patients will undergo the following assessments and procedures at Month 3 (Visit T3):

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs

- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs)
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP adherence
- IWRS contact to obtain new MED ID number for double-blind IMP
- Dispense double-blind IMP and provide dosing and storage instruction
- Diet and exercise counselling
- Schedule next visit

Note: If the patient discontinues at or between study visits, please proceed to Section 10.7 for detailed instructions.

10.6.6. Treatment Month 6 (Visit T4; ± 5 days)

Patients will undergo the following assessments and procedures at Month 6 (Visit T4):

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints (ongoing)
- Weight
- Vital signs
- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs) and hs-CRP
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP adherence
- IWRS contact to obtain new MED ID numbers for double-blind IMP
- Dispense double-blind IMP (with amount sufficient until next clinic visit, typically 2 bottles) and provide dosing instruction
- Diet and exercise counselling
- Schedule next visit

Note: If the patient discontinues at any scheduled visit after T1, or between study visits, please proceed to Section 10.7 for detailed instructions.

The conduct of this visit may be altered to ensure patient safety during the global coronavirus disease of 2019 (COVID-19) pandemic. If permitted and approved by regional regulatory authorities and the appropriate IRB/IEC, this visit may be converted to a remote visit (telephone,

telemedicine, etc.) or conducted within the patient's home by a qualified visiting nurse. After obtaining either written or verbal consent from the patient, verifying the correct shipping address and patient availability to receive the shipment, IMP dispensation may be completed by utilizing an appropriate courier service. IMP may also be dispensed utilizing curbside pick-up at the site by the patient or patient representative. The procedures and data collected will be dependent upon the type of visit that is conducted. However, at a minimum, it is expected that the following data be collected regardless of whether the visit is conducted by phone or by visiting nurse: concomitant medications, assessment of AEs, SAEs, and clinical endpoints, and IMP adherence. When visits are conducted in the patient's home by a qualified visiting nurse, it is also expected, if logistically possible, that weight, vital signs, and samples for central laboratory evaluations will also be collected. Alterations to study visits and procedures during the pandemic will be recorded on a COVID-19-specific case report form.

Local laboratories may be utilized during the pandemic at the investigator's discretion with the following requirements:

- Lipids should not be assessed by local laboratories during the study. However, if lipids are included in a local laboratory report, care must be taken to ensure that the values remain masked for study site personnel, the patient, CRO, and Sponsor.
- A copy of the lab results and reference ranges, with lipid results redacted, must be filed within the patient records.

10.6.7. Treatment Month 9 (Phone Visit; Visit T5 ± 10 days), Month 15 (Phone Visit; Visit T7 ± 10 days), Month 21 (Phone Visit; Visit T9 ± 10 days), and Additional Telephone Visits Until Study Conclusion Every 6 Months Thereafter

Patients will undergo the following assessments via telephone at Month 9 (Visit T5), and every 6 months thereafter as long as the patient remains on study:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Diet and exercise counselling

Note: If the patient discontinues at or between study visits, please proceed to Section 10.7 for detailed instructions.

10.6.8. Treatment Month 12 (Visit T6 ± 10 days), Month 18 (Visit T8 ± 10 days), and Additional Clinic Visits Until Study Conclusion Every 6 Month Thereafter

Patients will undergo the following assessments and procedures at Month 12 (Visit T6), and every 6 months thereafter as long as the patient remains on study:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs

- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs)
  - hs-CRP (Month 12 only)
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP adherence
- IWRS contact to obtain new MED ID numbers for double-blind IMP
- Dispense double-blind IMP (with amount sufficient until next clinic visit, typically 2 bottles) and provide dosing instruction
- Diet and exercise counselling
- Schedule next visit

Note: If the patient discontinues at or between study visits, please proceed to Section 10.7 for detailed instructions.

The conduct of this visit may be altered to ensure patient safety during the global COVID-19 pandemic. If permitted and approved by regional regulatory authorities and the appropriate IRB/IEC, this visit may be converted to a remote visit (telephone, telemedicine, etc.) or conducted within the patient's home by a qualified visiting nurse. After obtaining either written or verbal consent from the patient, verifying the correct shipping address and patient availability to receive the shipment, IMP dispensation may be completed by utilizing an appropriate courier service. IMP may also be dispensed utilizing curbside pick-up at the site by the patient or patient representative. The procedures and data collected will be dependent upon the type of visit that is conducted. However, at a minimum, it is expected that the following data be collected regardless of whether the visits is conducted by phone or by visiting nurse: concomitant medications, assessment of AEs, SAEs, and clinical endpoints, and IMP adherence. When visits are conducted in the patient's home by a qualified visiting nurse, it is also expected, if logistically possible, that weight, vital signs, and samples for central laboratory evaluations will also be collected. Alterations to study visits and procedures during the pandemic will be recorded on a COVID-19-specific case report form.

Local laboratories may be utilized during the pandemic at the investigator's discretion with the following requirements:

- Lipids should not be assessed by local laboratories during the study. However, if lipids are included in a local laboratory report, care must be taken to ensure that the values remain masked for study site personnel, the patient, CRO, and Sponsor.
- A copy of the lab results and reference ranges, with lipid results redacted, must be filed within the patient records.

In individual cases after the pandemic has been determined to be over and if permitted and approved by regional regulatory authorities and the appropriate IRB/IEC, these visits may continue to be conducted within the patient's home by a qualified visiting nurse. In instances

where it is identified as necessary, IMP dispensation may be completed utilizing either an appropriate courier service (after obtaining consent and verification of shipping address and patient availability) or curbside pick-up at the site.

10.6.9. End of Study

Patients will undergo the following assessments and procedures at End of Study:

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints (ongoing)
- Weight
- Vital signs
- 12-lead ECG
- PE
- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs)
  - hs-CRP
  - HbA_{1C}
- Return of IMP; assessment and recording of IMP adherence
- Diet and exercise counselling

Note: The conduct of this visit may be altered to ensure patient safety during the global COVID-19 pandemic. If permitted and approved by regional regulatory authorities and the appropriate IRB/IEC, this visit may be converted to a remote visit (telephone, telemedicine, etc.) or conducted within the patient's home by a qualified visiting nurse. However, at a minimum, it is expected that the following data be collected regardless of whether the visits is conducted by phone or by visiting nurse: concomitant medications, assessment of AEs, SAEs, and clinical endpoints, and IMP adherence. When visits are conducted in the patient's home by a qualified visiting nurse, it is also expected, if logistically possible, that weight, vital signs, and samples for central laboratory evaluations will also be collected. Alterations to study visits and procedures during the pandemic will be recorded on a COVID-19-specific case report form.

Local laboratories may be utilized during the pandemic at the investigator's discretion with the following requirements:

- Lipids should not be assessed by local laboratories during the study. However, if lipids are included in a local laboratory report, care must be taken to ensure that the values remain masked for study site personnel, the patient, CRO, and Sponsor.
- A copy of the lab results and reference ranges, with lipid results redacted, must be filed within the patient records.

In individual cases after the pandemic has been determined to be over and if permitted and approved by regional regulatory authorities and the appropriate IRB/IEC, this visit may be conducted within the patient's home by a qualified visiting nurse.

10.6.10. Post-treatment Visit (Phone Visit; Visit PT1, 30 days ± 10 days After End of Study)

Patients will undergo the following assessments via telephone 30 days after the end of study:

- Assess AEs, SAEs, and potential clinical endpoints

10.7. Discontinuations

10.7.1. Patients Inadvertently Enrolled

The inclusion and exclusion criteria for enrollment must be followed exactly and completely. If a patient who does not meet enrollment criteria is inadvertently enrolled, the Medical Monitor should be contacted within 24 hours of identification. If it is determined after discussion with the Medical Monitor that, in considering patient safety, it is appropriate to continue IMP (documentation of this is necessary), the patient will continue on IMP and be monitored for all visits and testing (including laboratory measures) for the duration of the study. If, after discussion with the Medical Monitor, it is determined that the patient should not continue IMP, IMP will be discontinued, but the patient will remain in the study to be evaluated for concomitant medications, and efficacy and safety endpoints until the end of the study visit.

Patients inadvertently enrolled under the following criteria should be discontinued from IMP (but remain in the study):

- Female patients who are pregnant or are breastfeeding or who do not agree to use an acceptable method(s) of birth control during the study
- Any clinically significant medical condition that according to the investigator could interfere with participation in the study
- Unable or unwilling to comply with protocol requirements, or deemed by the investigator to be unfit for the study
- Have a history of drug, alcohol, or substance abuse within the past 6 months, as assessed by the investigator

If a patient stops IMP for any of the above exclusion criteria following discussion with the Medical Monitor, then investigators should notify the Sponsor (or designee). The reason for the patient's inadvertent enrollment should be documented in the patient's record.

10.7.2. Temporary Discontinuation of Investigational Medicinal Product

There may be situations in which IMP is temporarily discontinued at the discretion of the investigator. IMP should be restarted as soon as possible based on investigator judgment. The number of days the IMP was not taken and the reason for temporary discontinuation should be documented in the patient's record. There is no limit to the amount of time patient can be off IMP prior to restarting.

Investigators should contact the Medical Monitor if IMP is temporarily discontinued and this should occur prior to IMP discontinuation if possible.

10.7.3. Permanent Discontinuation of Investigational Medicinal Product

There may be situations where it may be necessary for a patient to permanently discontinue IMP.

Investigators should contact the Medical Monitor prior to permanent IMP discontinuation to discuss the situation. **If IMP is permanently discontinued, the patient will remain in the study to be evaluated for concomitant medications, efficacy and safety endpoints until the final study visit.** If the patient is unwilling or unable to return for follow-up visits in person, alternatives such as telephone contact visits per the Schedule of Events, or telephone follow up bi-annually, annually or at the end of the study will be offered. The follow-up frequency will be documented in the eCRF.

The reason for permanent discontinuation of IMP should be documented in the eCRF. If the discontinuation of IMP is due to an AE, the event should be documented in the eCRF. Some possible reasons that must lead to permanent early IMP discontinuation include:

- Female patients who become pregnant or are breastfeeding or who do not agree to use an acceptable method(s) of birth control during the study will be permanently discontinued from IMP
- The patient requests to stop IMP permanently
- The patient study blind is broken
- Patient moves away and it is impossible to come to this or any other trial site for visits as required by protocol.

Some possible reasons that may lead to permanent early IMP discontinuation include:

- In the opinion of the investigator, any AE or a significant change in a laboratory value that warrants permanent discontinuation of IMP therapy. Investigators are advised to call the Medical Monitor prior to making such a decision.
- Illness, condition, or procedural complication (including AEs) affecting the patient's ability to participate or requiring prohibited medication. Investigators are advised to call the Medical Monitor prior to making such a decision.
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study. If, after discussion with the study Medical Monitor, it is determined that the patient should not continue IMP, IMP will be discontinued.

10.7.4. Patient Discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be uncommon, occurring only if the patient explicitly withdraws consent. At the time of discontinuing from the study, the Medical Monitor should be contacted, and, if possible, an early discontinuation visit should be conducted, per the Study Schedule. The patient will be

permanently discontinued both from the IMP and from the study at that time. During the study closeout period, survival (vital) status will be collected within legal and ethical boundaries for all patients randomized who withdrew their participation from the study.

10.7.5. Patients Lost to Follow-Up

A patient would be considered potentially lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Refer to the Retention Guide for additional details. Vital status will be collected within legal and ethical boundaries during the study closeout period. If vital status is determined, the patient will not be considered lost to follow-up.

10.7.6. Discontinuation of Study Sites or the Study

The Sponsor may suspend enrollment or discontinue a site at any time. A written statement will be provided to the investigator, the IRB or IEC, and regulatory authorities, if required.

Possible reasons for site discontinuation include, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection on a chronic basis
- Falsification of records
- Failure to adhere to the protocol
- Lack of study oversight by the Principal Investigator and/or designee

If any serious or nonserious AEs have occurred at such a clinical site, all documentation relating to the event(s) must be obtained.

The Sponsor in consultation with the EC Chair will retain responsibility for discontinuation of the study. The study will be discontinued if necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

Discontinuation of the study may be based on a recommendation from the DMC. The criteria that the DMC will follow to recommend early termination the study will be described in the DMC Charter.

11. ASSESSMENT OF EFFICACY

11.1. Reporting of Clinical Endpoints

All clinical endpoints occurring at any point from signing the ICD until 30 days after completion of the study will be reported by the site and adjudicated by the CEC according to guidelines detailed in the CEC Charter. Study sites will complete the relevant clinical endpoint eCRFs and obtain other required source documents in a timely fashion as per study-specific instructions contained in the Endpoint Manual.

Clinical endpoints include any of the following:

- CV Death (MACE)
- Non-CV Death (non-MACE clinical endpoint)
- Nonfatal MI (MACE)
- Nonfatal stroke (MACE)
- Hospitalization for unstable angina (non-MACE clinical endpoint)
- Coronary revascularization (MACE)

Detailed definitions of these clinical endpoints are included in the CEC Charter and the Endpoint Manual. Please note that the Sponsor will also review blinded AE and SAE reports on a routine basis in order to identify potential additional clinical endpoints. AEs and SAEs that are identified by the Sponsor as potential clinical endpoints will be reviewed by the CEC and may result in a request to the site that additional source documentation be obtained or adjustments to reporting in the eCRF be completed.

An adjudicated clinical endpoint will not be reported as an AE nor, if appropriate, as an SAE in the eCRF. Additionally, it will NOT be reported in an expedited manner as an SAE since these events are expected to occur in this patient population.

A clinical endpoint that is reported by the site but, upon subsequent review by the CEC is adjudicated to NOT meet all of the clinical endpoint criteria as defined by the CEC Charter, will be reclassified as an AE, SAE, or procedure as appropriate. If that reclassified event meets one or more of the seriousness criteria for AEs, the event must be reported (within 24 hours of notification of investigator) as an SAE in the same manner as other SAEs. In this instance, Day 1 for SAE reporting purposes will be the day that the investigator is informed that the reported clinical endpoint did not meet clinical endpoint criteria adjudicated by the CEC. At the time that a clinical endpoint is reported, information will also be collected that would be required if, in the future, it is determined to be an SAE. This information will include AE term, severity, action taken with IMP, relatedness, etc.

Any clinical endpoint occurring after the 30-day follow-up period that the investigator becomes aware of and considers related to IMP must be reported to the Sponsor as an SAE.

Please contact your monitor regarding any questions about the reporting of clinical endpoints and whether these clinical endpoints should be reported as AEs and/or SAEs.

11.2. Major Adverse Cardiovascular Events

The following MACE are included in the primary efficacy endpoint:

- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization

Also additional clinical endpoints include:

- Non-CV death (assessed as a secondary efficacy endpoint)
- Hospitalization for unstable angina (assessed as a secondary efficacy endpoint)

The CEC will adjudicate all reported MACE and additional clinical endpoints to determine which events meet the criteria detailed in the CEC Charter.

11.3. Assessment of Diabetes

The DC will review and utilize data that is recorded in the eCRF and is available in the clinical laboratory database to verify potential events of new-onset diabetes. The verification will occur beginning from the point where the patient signs the informed consent through 30 days after the patient's last study visit. Verification will be completed according to the guidelines detailed in the DC charter. Sites will continue to follow study procedures for recording diabetes and diabetes-related diagnoses as medical history, AEs, or SAEs.

Criteria for a diagnosis of diabetes for inclusion in the diabetes efficacy and safety populations are described in Section 15.4.

11.4. Assessments of Lipids and hs-CRP

Central clinical laboratory samples will be collected and analyzed for the parameters detailed in Table 3. Calculated LDL-C (or measured directly if TGs are >400 mg/dL or LDL-C is <50 mg/dL), non-HDL-C, TC, HDL-C, and TG at Week -5 and Week -4, and at Months 0, 3, 6, 12, 18, 24, and every 6 months until end of study.

Central clinical laboratory samples will be collected and analyzed for hs-CRP at Months 0, 6, 12, and end-of-study.

Blood draws for lipids (not safety) must meet the criteria below. If these criteria have not been met, these blood samples will NOT be collected. **If these criteria can be met by rescheduling a clinic visit to occur within 3 days, these blood samples will be collected at the rescheduled clinic visit only.**

- Blood samples will be drawn after a minimum 10-hour fast (water and concomitant medications is allowed). If the patient has fasted but IMP was taken the morning of a clinic visit, blood samples may be drawn, and the clinic visit does not need to be rescheduled.

Patients are to be in a seated position during the blood collection. Collection schedule and instructions are provided in the Central Clinical Laboratory Manual. A description of the sample collection, storage, and shipping, as well as monitoring and management of abnormal laboratories, are described in Section 12.1.6.

When vital signs and laboratory samples are to be collected at the same time point, vital signs measurements will precede laboratory sample collection.

Table 3: Central Clinical Laboratory Parameters (Lipids and hs-CRP)

Clinical Laboratory Test	**Clinical Laboratory Test**
Basic Lipid Parameters	Other Parameters
• Total cholesterol (TC) • Calculated low-density lipoprotein cholesterol (LDL-C) and non-HDL-C • High-density lipoprotein cholesterol (HDL-C) • Triglycerides (TG)	• High-sensitivity C-reactive protein (hs-CRP)

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

At all clinic visits, investigators will review all safety information including vital signs, AEs, SAEs, potential endpoints, concomitant medications, and ECG reports and will ensure that the collected data are recorded into the appropriate eCRF. Additionally, central clinical laboratory samples will be collected and sent for analysis and the investigator will review the results to ensure continued patient safety while participating in the study.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor or its designee if appropriate.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator is responsible for following AEs that are serious or that caused the patient to discontinue before completing the study until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

12.1.1. Demographic/Medical History

Demographic data and a complete medical history will be obtained from the patient. For medical history, conditions and surgeries that are relevant and/or clinically significant should be captured with at least a start date (month and year) and whether the condition is ongoing or resolved. In particular, a careful medical history for diabetes, neurocognitive conditions, statin-associated muscle effects, and other statin-associated adverse effects should be collected.

12.1.2. Vital Signs

Vital signs will include DBP and SBP as well as heart rate.

Vitals will be collected prior to blood collection. Blood pressure and heart rate will be measured using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, BP may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The patient should be in a seated position with feet touching the floor. Patients should be seated quietly for several minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level. At each clinic visit, 2 BP measurements will be collected. Each BP measure must be recorded within ±2 mmHg.

12.1.3. Weight and Height

Body weight will be measured on a calibrated scale in the morning while fasted and after voiding.

Height will be measured using standard clinic procedures.

Body mass index (BMI) will be calculated systematically using the formula:

$$\text{BMI } (kg/m^2) = \text{weight in kg}/(\text{height in meters})^2$$

12.1.4. Physical Examination

Physical examinations will include an assessment of the following:

- General appearance
- Skin
- Eyes, ears, nose, and throat
- Head and neck
- Extremities
- Musculoskeletal examination
- Respiratory examination
- Cardiovascular assessment, including rhythm and presence of cardiac abnormalities
- Abdominal examination
- Neurologic examination including documentation of the presence of abnormalities in mental status and motor and sensory function
- Any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings prior to the start of IMP will be recorded on the Medical History/Current Medical Conditions page of the eCRF. Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

Note: Additional information will be collected regarding muscle-related AEs. See Section 13.1.3.

12.1.5. Electrocardiogram

ECG collection will be collected in the supine position. ECGs will be assessed using machine readings and physician review.

Unscheduled ECG assessments will be completed at the discretion of the investigator.

12.1.6. Central Clinical Laboratory Tests

12.1.6.1. Central Clinical Laboratory Parameters (Safety)

Patients will be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 4. Collection schedule, schedule of laboratory parameters by visit, and instructions are in the Clinical Laboratory Manual provided by Central Laboratory.

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential (absolute values only)	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (Alk-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
Urinalysis (Microscopic) – only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cells (RBC) • White blood cells (WBC)	Coagulation – only in patients receiving anti-coagulant therapy that in the investigator's judgement require monitoring at Visit T1 and 3 to 5 days post Visit T1 using local or central lab • Prothrombin time (PT) • International normalized ratio (INR)

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), optional reflexive Hepatitis C RNA only if HCV is positive • Serum or urine pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; only for postmenopausal females <55 years old) • Thyroid-stimulating hormone (TSH)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • hs-CRP

12.1.6.2. Sample Collection, Storage, and Shipping

Central clinical laboratory samples will be collected by appropriate clinical site personnel and then shipped according to a separate Laboratory Manual provided by the Central Laboratory. Samples will be processed by the Central Laboratory.

12.1.6.3. General Monitoring and Management of Abnormal Clinical Labs

It is the investigator's responsibility to review the results of all laboratory tests as they become available and to sign and date the review. For each laboratory test outside of the laboratory normal range, the investigator needs to ascertain if this is a clinically significant change from baseline for the individual patient, with baseline defined as the last value or observation before the first dose of double-blind IMP. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

If a laboratory value is determined to be an abnormal and a clinically significant change from baseline for the patient, the investigator should determine if it qualifies as an AE (please see Section 13.2.3), and if yes, an appropriate eCRF will be completed. All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

12.1.6.3.1. Monitoring and Management of Elevated Liver Function Tests

If at any time after randomization a patient experiences a new ALT and/or AST >3 × ULN, the patient will undergo repeat confirmatory liver function test (LFT) assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat LFT assessment will include: 1) measurement of ALT, AST, alkaline phosphatase, total and direct bilirubin, prothrombin time (PT)/international normalized ratio (INR), eosinophil count, CK; 2) history of concomitant medication use; 3) history of exposure to environmental chemical agents, including ethanol; and 4) query for related symptoms. Additionally, further

testing such as antihepatitis A virus (total), HBsAg (confirmation of screening measurement), HCV (confirmation of screening measurement), and anti-cytomegalovirus/immunoglobulin M, Epstein-Barr, liver ultrasound or magnetic resonance imaging (MRI) scanning may be warranted to rule out additional pathology depending on clinical presentation and should be discussed with the Sponsor personnel or the authorized Medical Monitor. Although samples will be collected, some repeat LFT parameters may not be measured until elevation is confirmed.

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN but ≤5 × ULN, consideration should be given to administering no further doses of IMP. At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN and no alternative reason for elevation is identified, patient should be discontinued IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1). At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following and no alternative reason for elevation is identified, patient should be discontinued IMP treatment, the patient should be given no further IMP treatment, but should continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1):
  - TB >2 × ULN
  - INR >1.5 × ULN (unless the patient is on stable dose of anticoagulation medication)
  - Appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia

12.1.6.3.2. Monitoring and Management of Elevated Creatine Kinase

If at any time after randomization a patient experiences a marked CK elevation >5 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available. If initial CK elevation is >10 × ULN, patients will be instructed to discontinue IMP immediately (instead of continuing IMP until repeat lab value is assessed). It is very important that repeat confirmatory assessment occur as soon as possible (within a day of stopping IMP).

Repeat CK assessment will include query for the nature, duration and intensity of any muscle symptoms; review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology), concomitant medications, and consider diagnosis of other conditions which can cause myopathy; physical examination for muscle tenderness, weakness, and rash; measure serum creatinine, dipstick urinalysis ± microscopy if indicated; and basic metabolic panel.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic

the investigator with input from the Sponsor may consider continuing IMP with continued CK assessments every 1-2 weeks.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality as listed below, the patient should be discontinued from IMP treatment:
  - >5 × ULN that is associated with symptoms of muscle pain, muscle weakness, or dark urine; or
  - >10 × ULN, even in the absence of symptoms.
- If the patient is discontinued from IMP treatment, the patient should continue being followed for safety using the protocol-specified visit schedule (see Appendix 1). At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after creatine phosphokinase (CPK) has returned to the baseline level.

12.1.6.3.3. Monitoring and Management of Elevated LDL-C

Postrandomization, LDL-C results will be masked to investigators in order to maintain the blind. Beginning at Month 6 and for the remaining duration of the study, the central laboratory will notify the investigator if the patient's LDL-C level is ≥25% higher than baseline (mean of values at S2 and T1). The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria. The patient will be counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. If confirmed, the patient's LDL-C-lowering treatment regimen may be adjusted, if possible, per standard of care and local practice. Any initiation and/or dose change of LDL-C-lowering medications will be documented on the eCRF. Additional LDL-C-lowering medications initiated will not be provided by the Sponsor.

Investigators will not measure LDL-C at a local lab during the study.

12.1.6.3.4. Monitoring and Management of Elevated TG

Post-randomization, TG results will be masked to investigators in order to maintain the blind. Beginning at Month 3 (Visit T3) and for the remaining duration of the study, the central laboratory will notify the investigator if patient's TG level is >1000 mg/dL (11.3 mmol/L). The patient will be counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the TG value meets the threshold criteria. If confirmed, the patient's TG- lowering treatment regimen may be adjusted, if possible, per standard of care and local practice. Any initiation and/or dose change of TG medications will be documented on the eCRF. Additional TG-lowering medications initiated will not be provided by the Sponsor. If, despite adjustment of TG-lowering therapies, the TG level remains >1000 mg/dL, the patient will discontinue study medication but will remain in the study.

12.1.6.3.5. Monitoring and Management of Potential Hypoglycemia with Associated Metabolic Acidosis

Patients will be educated on the signs and symptoms of hypoglycemia. If such signs and symptoms are experienced, patients will be advised to report them to the study site (see Section 13.3 for additional details).

Clinical laboratories (bicarbonate levels) will be assessed to determine the possible occurrence of metabolic acidosis. If the laboratories are consistent with metabolic acidosis, immediate follow up with the patient for further medical evaluation will occur (see Section 13.3 for additional details). This event should be captured as an AE.

12.1.6.4. Total Blood Volume of Central Clinical Laboratory Samples

The total number of venipunctures and total volume of whole blood collected during the study will be limited to that needed for safety, efficacy, and biomarker assessment. Total whole blood volume collected over the study duration is not to exceed approximately 200 mL for each patient.

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1. Adverse Events

13.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the patient are recorded in the patient's medical record.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from IMP
- Treatment-emergent AEs (TEAEs) are defined as AEs that begin or worsen after randomization and the first dose of double-blind IMP
- Adverse Drug Reaction (see Section 13.1.2)

13.1.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction (ADR). "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

13.1.3. Reporting for Adverse Events

All AEs occurring during the course of the study (starting from signing informed consent to the end of study) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the investigator. Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally,

the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at screening or baseline should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. For each AE, the following information will be recorded:

- Description of the event (eg, headache)
- Date of onset
- Date of resolution (or that the event is continuing)
- Action taken as a result of the event
- Seriousness of the event
- Severity of the event
- Outcome of the event
- Investigator's assessment of relationship to IMP.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated white blood cells [WBC], cough, abnormal chest x-ray, etc, can all be reported as "pneumonia").

The investigator will carefully evaluate the comments of the patient and the response to treatment in order that he/she may judge the true nature and severity of the AE. The question of the relationship of AEs to IMP administration should be determined by the investigator or study physician after thorough consideration of all facts that are available.

Additional information may be collected regarding muscle-related AEs including type of muscle-related symptoms, location of the muscle-related AE, and potential cause of the muscle-related AE.

Additional information may be collected regarding malignancy AEs including patient risk factors, diagnostic details, organ and tissue type, staging, test results, and treatment approach.

13.1.4. Severity

It is the investigator's responsibility to assess the intensity (severity) of an AE.

The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild: Events are usually transient and do not interfere with the patient's daily activities
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe: Events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

Note: A severe AE need not be serious and an SAE need not, by definition, be severe.

13.1.5. Relationship

It is the investigator's responsibility to assess the relationship between the IMP and the AE. The degree of "relatedness" of the AE to the IMP may be described using the following scale:

- Not Related: No temporal association and other etiologies are likely the cause
- Unlikely: While cannot be definitively ruled as not related to IMP, a causal association is remote, and other etiologies are more likely to be the cause. For reporting and summarization, events assessed as Unlikely to be related to IMP will be considered as Not Related to IMP.
- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the IMP cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the IMP is discontinued.
- Definite: Established temporal association with administration of the IMP with no other more probable cause. Typically, the event should resolve when the IMP is discontinued and recur on re-challenge.

13.1.6. Monitoring and Follow-up of Adverse Events

Patients having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. All follow-up results are to be reported to the Sponsor personnel or the authorized Medical Monitor. Any actions taken and follow-up results must be recorded either on the appropriate page of the eCRF or in appropriate follow-up written correspondence, as well as in the patient's source documentation. Follow-up laboratory results should be filed with the patient's source documentation.

For all AEs that require the patient to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution or stabilization of the event(s).

Patients with AEs related to IMP that are ongoing at study discontinuation or completion must be followed until resolution or for 30 days after study completion, whichever comes first, with the exception of patients reporting SAEs (see Section 13.2.4).

13.1.7. Treatment-Emergent Adverse Events

TEAE are defined as AEs that begin or worsen after randomization and the first dose of double-blind IMP.

13.2. Serious Adverse Events

13.2.1. Definition of Serious Adverse Event

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- An important medical event

NOTE: An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2.2. Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Preplanned or elective hospitalization including social and/or convenience situations (eg, due to inclement weather)
- Overdose of either Esperion study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page.

13.2.3. Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the corresponding laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

13.2.4. Reporting Serious Adverse Events

All SAEs occurring from the time of informed consent until 30 days following completion or discontinuation of study must be reported by the Principal Investigator or designee to the designated Safety contact within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. All SAEs that the investigator considers related to IMP that occur after the 30-day follow-up period of the study period must be reported to the Sponsor. As a reminder, adjudicated clinical endpoints will NOT be reported as SAEs in the eCRF and will NOT be reported in an expedited manner as an SAE since these events are known to occur in this patient population.

To report the SAE, the SAE information should be entered into the EDC RAVE database within 24 hours of becoming aware of the occurrence. Additional documentation, such as laboratory or diagnostic test results or discharge summaries may be sent separately via email [redacted] If you have questions, please call the designated Safety contact for assistance. All contact information is provided on the SAE report form for this study.

Detailed instructions and contact information for the Global and Regional Safety and Medical Monitor(s) will be provided in the SAE Completion Guidelines.

The investigator is required to submit SAE reports to the IRB/IEC in accordance with local requirements. All investigators involved in studies using the same investigational product will receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

All SAEs should be recorded on the eCRF and source documents. Criteria for documenting the relationship to IMP and severity will be the same as those previously described.

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the designated Safety contact.

The Sponsor (and/or legally transferred designee) will report SAEs and suspected and unexpected serious adverse reactions (SUSARs) as required by global regulatory authorities, IECs/IRBs, investigators/institutions in compliance with all reporting requirements according to local regulations, laws, and GCPs. The investigator should notify the appropriate IEC/IRB of SAEs occurring at the site and other AE reports received from the Sponsor, in accordance with local procedures and statutes.

13.2.5. Events Exempt from (Serious) Adverse Event Reporting

Adjudicated clinical endpoints will NOT be reported as AEs or SAEs and will NOT be reported in an expedited manner as an SAE to the designated Safety contact since these events are known to occur in this patient population.

All SAEs that occur during the course of the study, whether or not causally related to the IMP, must be reported immediately (within 24 hours of the investigator becoming aware of the event), except for clinical endpoints defined as the following:

- CV Death
- Non-CV Death
- Nonfatal MI
- Nonfatal stroke
- Hospitalization for unstable angina
- Coronary revascularization

A clinical endpoint that is reported by the site but, upon subsequent review by the CEC, is adjudicated to NOT meet all of the clinical endpoint criteria as defined by the CEC Charter will be reclassified as an AE, SAE, or procedure as appropriate. If that reclassified event meets one or more of the seriousness criteria for AEs, the event must be reported in an expedited manner (within 24 hours of notification of investigator) as an SAE to the designated Safety contact in the same manner as other SAEs. In this instance, the date of awareness of the event for SAE reporting purposes will be the day that the investigator is informed that the reported clinical endpoint did not meet clinical endpoint criteria adjudicated by the CEC. At the time that a clinical endpoint is reported, information will also be collected that would be required if, in the future, it is determined to be an SAE. This information will include AE term, severity, action taken with IMP, relatedness, etc.

13.2.6. Reporting of Patient Death

The death of any patient during the study or within 30 days after study discontinuation or completion must be treated as a clinical endpoint for adjudication. This event will not be reported as an SAE.

13.2.7. Reports of Pregnancy and Lactation

Although not considered an SAE (unless an event occurs with a serious outcome), pregnancy and lactation information on female patients will be collected by the designated Safety contact. If a female patient should become pregnant during the course of the study, the Principal Investigator or designee must contact the designated Safety contact within 24 hours of the Principal Investigator or designee first becoming aware of the pregnancy.

To report a pregnancy, the pregnancy information should be recorded on the Clinical Pregnancy Report Form and sent to the Safety contact within 24 hours of becoming aware of the pregnancy via email [redacted] Additionally, the patient's pregnancy should be followed through to its conclusion with the final outcome recorded on the Pregnancy Outcome Form and sent to the safety contact using either the email or fax noted previously. If you have questions, please call the designated Safety contact for assistance.

Patients who become pregnant will discontinue study medication immediately and will continue to be followed until the pregnancy is completed. Patients who lactate during the study may be required to discontinue study medication.

13.3. Adverse Events of Special Interest

[redacted]

Hepatic Safety: [redacted]

Musculoskeletal Safety: [redacted]

Diabetes and Glycemia: [redacted]

Hypoglycemia Associated with Metabolic Acidosis: [redacted]

[redacted]

Renal Impairment: [redacted]

Neurocognitive Events: [redacted]

Atrial Fibrillation: [redacted]

Tendon Rupture/Tendinopathy: [redacted]

Malignancy: [redacted]

14. STUDY COMMITTEES

14.1. Executive Committee (EC)

The EC will oversee the design and conduct of the study and the interpretation of study results. It is responsible for reviewing, at regular intervals, the progress of the study. The EC will comprise designated representatives from Cleveland Clinic Coordinating Center for Clinical Research (C5Research), other institutions, and the Sponsor.

14.2. Data Monitoring Committee (DMC)

An independent DMC will review accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid in regularly scheduled intervals approximately 4 times per year to ensure there is no avoidable increased risk of harm to patients. Safety data reviewed by the DMC will include AEs, including AESI, clinical endpoints, and lipids. The DMC is responsible for making recommendations about alteration or early termination of the study based upon their review of the blinded and unblinded data. The DMC will be chaired by an external academic cardiologist who is an expert in this therapeutic area and who has no conflicts of interest. Analysis for the DMC will be provided by an independent Statistical Analysis Data Center, which is external to the Sponsor. Additional details will be provided in a DMC Charter.

14.3. Clinical Event Committee (CEC)

A blinded independent expert CEC will adjudicate designated clinical endpoints, including all MACE endpoints, as well as all non-CV deaths. Additional details regarding clinical endpoint definitions are included in the CEC charter. The charter will also outline the committee's composition, timelines, members' roles and responsibilities and the operational aspects. The CEC of C5Research will provide adjudication services.

14.4. Diabetes Committee (DC)

A blinded independent DC will verify diagnoses of new-onset diabetes. Additional details regarding clinical endpoint definitions are included in the DC charter. The charter will also outline the committee's composition, timelines, members' roles and responsibilities, and the operational aspects.

14.5. Tendon Rupture Adjudication Committee (TRAC)

A blinded independent expert TRAC will adjudicate events of tendon rupture. Additional details regarding event definitions are included in the TRIAC. The TRIAC will also outline the committee's composition, timelines, members' roles and responsibilities, and the operational aspects.

15. STATISTICS

15.1. General Considerations

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the first time that the DMC reviews data for this study. The SAP will supersede the protocol in the event of any differences between the 2 documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

15.2. Determination of Sample Size

This event-driven trial is designed to provide at least 90% power to detect an approximate 15% relative risk reduction in HR corresponding to the primary composite MACE endpoint (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) at an overall study significance level (alpha) of 0.05. There are no interim analyses.

A statistical relationship between on-treatment LDL-C differences between the bempedoic acid group and the placebo group and CV event risk reduction is used to derive the postulated treatment effect of 15% stated above. Assuming a 3.59% annual event rate in the placebo group, a minimum of 1620 primary composite MACE events are needed.

The average treatment duration for all patients is estimated to be approximately 42 months (3.5 years), with an enrollment phase of approximately 33 months, a minimum treatment duration to be approximately 36 months (~3 years) and a lost-to-follow-up (LTFU) rate of 1% per year. Based on these assumptions, approximately 14,000 patients (approximately 7000 in the bempedoic acid group and 7000 in the placebo group) will be randomized into the study to achieve the 1620 patients experiencing an adjudicated primary endpoint event.

It is expected that 50% of the 1620 patients experiencing an adjudicated primary 4-component MACE (810 patients) will experience an adjudicated 3-component MACE (CV death, nonfatal MI, or nonfatal stroke). Additionally, the median treatment duration for the sample size calculation was assumed to be 42 months (~3.5 years) when the annual placebo event rate was 3.59%. Therefore, the study will not stop until at least 1620 patients have experienced an adjudicated primary MACE endpoint, with 50% of the patients experiencing an adjudicated 3-component MACE, and a minimum of 24 months (2 years) have elapsed since the last patient was randomized.

Six key secondary efficacy endpoints are also of interest for statistical testing in this study. To preserve the study-wise (family-wise) Type 1 error at 5%, a gatekeeping or stepdown approach will be followed and is described in detail in Section 15.7.

15.3. Interim Analysis and Stopping Rules

There are no interim efficacy analyses during the study. The study may be altered or terminated based upon recommendations from the DMC as described in Section 14.2.

15.4. Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses and summaries, is defined as all randomized patients and is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of study medication (investigational product). Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

The Diabetes Efficacy Population, used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients in the FAS fulfilling one or more of the following criteria at baseline captured by information recorded as medical history, prior medication, and/or laboratory data:

- Medical history indicating type 2 diabetes
- Prior glucose-lowering medication with confirmation of diagnosis of diabetes by a DC (Section 14.4) if prior medication is the only criteria met for diagnosis of diabetes
- HbA_{1C} measurement ≥6.5%
- Two or more measurements of fasting glucose ≥126 mg/dL (7.0 mmol/L)

The Inadequately Controlled Diabetes Efficacy Population, is defined as the subset of patients in the Diabetes Efficacy Population with an HbA_{1C} of 7% or greater at baseline. This efficacy population will be used for the corresponding diabetes secondary and tertiary endpoints.

The Prediabetes Efficacy Population, used for efficacy analyses of time to new-onset diabetes and for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients in the FAS fulfilling all of the following criteria at baseline captured by information recorded as medical history, prior medication, and/or laboratory data:

- Having no medical history indicating type 2 diabetes
- Having no prior glucose-lowering medication unless verified by the DC that there is no diagnosis of diabetes (Section 14.4) if prior medication is the only criteria assessed for the diagnosis of diabetes
- HbA_{1C} measurement of 5.7% to 6.4% or 1 or more measurements of fasting glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), but not more than 1 value of fasting glucose ≥126 mg/dL (7.0 mmol/L).

The Normoglycemia Efficacy Population, used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients in the FAS not fulfilling the criteria at baseline for the Diabetes Efficacy Population or Prediabetes Efficacy Population.

The No Diabetes Efficacy Population used for efficacy analyses of HbA_{1C} and fasting glucose, is defined as the subset of patients not fulfilling the criteria at baseline for the Diabetes Efficacy Population.

The Diabetes, Prediabetes, Normoglycemia and the Inadequately Controlled Diabetes Safety Populations are used for safety analyses as needed, and defined similarly as Diabetes, Prediabetes, Normoglycemia, and the Inadequately Controlled Diabetes Efficacy Populations but using patients from Safety Population instead.

15.5. Disposition, Demographics, and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by treatment group. Demographic information and patient characteristics including, but not limited to, gender, race, age, and baseline vital signs will also be summarized by treatment group.

15.6. Primary Endpoint Analysis

The primary endpoint of this study is time to first occurrence of a confirmed (adjudicated) MACE, where MACE is defined as a composite primary efficacy endpoint that includes CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

The primary efficacy endpoint will be analyzed using Cox proportional hazards (PH) with treatment as a factor. The Cox PH will be performed using the FAS, with patients included in their randomized treatment group, regardless of the treatment they actually received. Note that the FAS includes patients who permanently discontinue treatment but remain in the study (patients are included regardless of their adherence to treatment). For this analysis, patients who are LTFU without experiencing a MACE will be censored at the time they are last known to be event-free. Patients who withdraw consent (withdraw from the study and refuse further contact) without experiencing a MACE will be censored at the time of consent withdrawal. Additionally, taking into account the period for CV event monitoring is every 3 months, when a patient who is LTFU or withdraws consent without experiencing a MACE is known to have later experienced a non-CV death, if the death was within 3 months of last contact, the patient will be censored at the time of death. If the death occurs more than 3 months after last contact, then the patient will be censored at the time of last contact. The hazards ratio (HR) and its 95% confidence interval (CI) and associated p-value will be provided.

In addition, Kaplan-Meier (K-M) curves will be provided, to provide a graphical description of the time to first occurrence of MACE.

Each individual component of the primary efficacy endpoint (CV death, nonfatal MI, nonfatal stroke, and coronary revascularization; each of the individual components are secondary time to event endpoints) will also be analyzed using Cox PH, to ensure consistency of the treatment effect across the components that comprise the composite endpoint. Each Cox PH will include treatment as a factor, and will be performed on the FAS with patients included in their randomized treatment group. The HR and its 95% CI will be provided for each individual component of the primary efficacy endpoint.

In addition, sensitivity analyses will be performed on the primary efficacy endpoint as needed. Additional details on the sensitivity analyses will be included in the SAP.

Finally, subgroup analyses will also be performed on the primary efficacy endpoint as needed. The primary efficacy analysis will be repeated within relevant subgroups including (but not

limited to) gender, age categories, and race. The HR and its 95% CI within each subgroup will be provided.

15.7. Secondary Efficacy Endpoint Analyses

Key secondary efficacy endpoints that are included in the statistical testing hierarchy will be analyzed as indicated in Section 15.7.1 and Section 15.7.2 below, and then tested in the hierarchy with the primary efficacy endpoint as follows:

1. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of MACE (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization; primary 4-component MACE)
2. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (3-component MACE)
3. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of fatal or nonfatal MI
4. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of coronary revascularization
5. Testing the hypothesis of no difference between bempedoic acid and placebo in time to first occurrence of fatal or nonfatal stroke
6. Testing the hypothesis of no difference between bempedoic acid and placebo in time to CV death
7. Testing the hypothesis of no difference between bempedoic acid and placebo in time to all-cause mortality

For the final analysis about the differences between bempedoic acid and placebo, each hypothesis in this hierarchical order will be tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. For other efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered nominal.

15.7.1. Secondary Efficacy Time-to-Event Endpoints

Secondary efficacy time-to-event MACE endpoints will each be analyzed in a manner analogous to that used for the primary efficacy analysis, using Cox PH model with similar censoring definitions and performed on the FAS. For each endpoint, the HR and its 95% CI and associated p-value will be provided. In addition, K-M curves will be provided for each of the secondary efficacy time-to-event endpoints. Note that for the analyses involving hemorrhagic and nonhemorrhagic stroke, any stroke for which the CEC is unable to determine the type will be included as an ischemic (nonhemorrhagic) stroke.

The time to first occurrence of new onset of diabetes during the treatment period will be analyzed by a Cox model in the prediabetes efficacy population. The date of new onset of diabetes will be the earliest date of the event observed during the treatment period. For this

analysis, patients who are LTFU discontinue the study drug early without experiencing a new onset of diabetes will be censored at 30 days after the last date of the treatment.

15.7.2. Secondary Efficacy Lipid and Other Biomarker Endpoints

Percent change from baseline to Month 6 in LDL-C and absolute change from baseline to Month 12 in HbA_{1C} will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and the relevant baseline as a covariate. The ANCOVA for LDL-C will be performed in the FAS. The ANCOVA for HbA_{1C} will be performed in the Inadequately Controlled Diabetes Efficacy Population. Two methods for data handling will be used: the first (primary) will involve specification of the missing data mechanism using a pattern mixture model (PMM), while the second (supportive) will be observed case data only. For each analysis, the least squares mean (LSM) and standard error (SE) will be provided for each treatment group, along with the placebo-corrected LSM, its 95% CI, and associated p-value. A nonparametric analysis based on Wilcoxon rank sum test and Hodges-Lehmann (H-L) estimate of location shift will be performed in FAS for percent change from baseline to Month 6 in hs-CRP. No imputation will be performed for the hs-CRP endpoint due to the extreme skewed distribution.

15.7.3. Tertiary Lipid and Biomarker Efficacy Endpoints

Tertiary lipid and HbA_{1C}-related endpoints will be summarized and analyzed as needed. For each parameter at each time point, the value of the parameter, change and the percent change from baseline will be summarized by treatment group. The Mixed Model Repeated Measure (MMRM) analysis including factors of treatment group, time point (as a categorical variable), baseline value, and treatment group-by-time point interaction will be performed in the observed FAS data. The LSM and SE will be provided for each treatment groups, along with the placebo-corrected LSM, its 95% CI, and associated p-value as needed. A nonparametric analysis based on Wilcoxon rank sum test and H-L estimate of location shift will be performed in observed FAS data for percent change from baseline to Month 12 and end-of study in hs-CRP. Changes in HbA_{1C} will be assessed in patients in the Normoglycemia Efficacy Population, Prediabetes Efficacy Population, No Diabetes Efficacy Population, Diabetes Efficacy Population, and Inadequately Controlled Diabetes Efficacy Population.

15.8. Safety Endpoints

General safety data in this study includes AEs, clinical safety laboratories, PEs, vital signs, and ECGs. The summarization of AEs will include only TEAEs, defined as AEs that begin or worsen after randomization and ingestion of the first dose of IMP. TEAEs and SAEs will be summarized by System Organ Class (SOC), severity, and relationship to IMP for each treatment group.

AE summaries will be provided overall and for subgroups such as gender and age. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, and urinalysis; PE findings; vital signs; ECG readings; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each postbaseline time point.

15.8.1. Adverse Events of Special Interest (AESI)

All AESI will be identified and evaluated by routine safety monitoring of AEs and laboratory values (where appropriate) and will be summarized by severity and relationship to IMP for each treatment group.

The following are considered AESI categories for this study:

- Hepatic Safety, including liver-associated enzymes, TB, and any Hy's law cases (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the setting of no known other cause)
- Musculoskeletal Safety, including CK
- Diabetes and Glycemia, including new onset of diabetes and worsening of diabetes
- Hypoglycemia Associated with Metabolic Acidosis
- Renal Impairment, including lab measures of renal function
- Neurocognitive Events
- Atrial Fibrillation
- Tendon Rupture/Tendinopathy. The TRAC will adjudicate events of tendon rupture per the TRIAC, and adjudicated events will be summarized.
- Malignancies

15.9. Additional Postrandomization Adjunctive Lipid-Modifying Therapy

The number and percent of patients in each treatment group requiring additional (postrandomization) adjunctive lipid-modifying therapy will be summarized by treatment group and by lipid-lowering therapy class. The reasons for their additional treatment (hyperlipidemia versus hypertriglyceridemia) will be summarized by treatment group and by lipid-lowering therapy class. Medications will be summarized by treatment group.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation (ICH) and GCP guidelines, national and international regulatory requirements, and the current Declaration of Helsinki throughout its duration by means of personal visits to the investigator's facilities and other communications.

These visits will be conducted to evaluate the progress of the study, verify the rights and well-being of the patients are protected, and verify the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of ICDs, results of tests performed as a requirement for participation in this study, and any other medical records (eg, laboratory reports, clinic notes, IMP dispensing log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, telephone logs, ECGs) required to confirm information contained in the eCRFs.

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA and European Medicines Agency (EMA) recommendations, and will be described in detail by the study-specific risk-based-monitoring plan.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, case report forms, medical records and source documents, drug disposition records, patient informed consent forms, etc.) as well as discussion on the conduct of the study with the investigator and staff. The CEC, DC, and TRAC will require that copies of relevant source documents be submitted for review by the committees for adjudication or verification as defined by their individual charters. These documents should be redacted by the site in accordance with local law.

The monitor should conduct these visits as frequently as appropriate for the clinical study. The investigator and staff should be available during these visits for discussion of the conduct of the study as well as to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

16.2. Audits and Inspections

Representatives of the Sponsor or its authorized clinical quality assurance group may visit a clinical site at any time during the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must be respected. The investigator and clinical site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its authorized representative.

The clinical study may also be inspected by the FDA or EMA (or other regulatory authority) to verify that the study was conducted in accordance with protocol requirements, as well as the applicable regulations and guidelines.

In the event the investigator is contacted by regulatory authorities who wish to conduct an inspection of the clinical site, the investigator will promptly notify the Sponsor of all such requests and will promptly forward a copy of all such inspection reports.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor (or designee) may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Institutional Review Board/Independent Ethics Committee Approval

Before initiation of the study, the investigator must obtain approval or favorable opinion of the research protocol, ICD, and any material related to patient recruitment from an IRB or IEC. For locations participating within the US, the IRB must comply with the provisions specified in 21 Code of Federal Regulations (CFR) Part 56, ICH and GCP guidelines, and applicable pertinent state and federal requirements. For locations participating outside of the US, the IRB or IEC must comply with the applicable requirements of each participating location, including ICH and GCP guidelines, except where a waiver is applicable.

IRBs and IECs must be constituted according to the applicable laws. It is the responsibility of each clinical site to submit the protocol, IB, patient informed consent, patient recruitment materials (if applicable), and other documentation as required by the IRB or IEC for review and approval. A copy of the written approval must be provided to the Sponsor.

The documentation should clearly mention the approval/favorable opinion of the protocol, the patient informed consent form, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs or IECs and provided to the Sponsor prior to the release of clinical study supplies to the clinical site and commencement of the study. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Clinical sites must adhere to all requirements stipulated by their respective IRB or IEC. This includes notification to the IRB or IEC regarding: protocol amendments, updates to the ICD, recruitment materials intended for viewing by patients, aggregate safety reports required by regulatory competent authorities, serious and unexpected AEs, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of final study reports and summaries to the IRB or IEC.

It is the responsibility of each clinical site to submit information to the appropriate IRB or EC for annual review and annual re-approval.

The investigator must promptly inform their IRB or IEC of all SAEs or other safety information reported from the patient or the Sponsor.

18.2. Ethical Conduct of the Study

The investigator agrees, when signing the protocol, to conduct the study in accordance with ethical principles that have their origin in the current revision of the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB or IEC review and ICDs.

The investigator agrees to allow monitoring and auditing of all essential clinical study documents by the Sponsor or its authorized representatives and inspection by the FDA, EMA, or other appropriate regulatory authorities. Monitoring and auditing visits by the Sponsor or authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The investigator will assure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperates with monitoring and audits, and will demonstrate due diligence in recruiting and screening study patients. The investigator must sign and return to the Sponsor the "Investigator's Signature" page (see Appendix 5) and provide a copy of current curriculum vitae. For this study and all studies conducted under an IND, the investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to the Sponsor (or designee). For EU investigators, equivalent information contained within the FDA 1572 form may be requested unless a waiver has been requested and received by the Sponsor from the FDA.

18.3. Written Informed Consent

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

The patient's signed and dated informed consent must be obtained before conducting any study procedures on the Sponsor-agreed ICD. Updates to the ICD during the conduct of the study will be communicated by written letter from the Sponsor to the investigator. The ICD should be provided in the appropriate language of the patient population.

The Principal Investigator(s) must maintain the original, signed ICD. A copy of the signed ICD must be given to the patient.

18.4. Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained.

The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor (or designee). If a patient's name appears on any document, it must be redacted and replaced with the patient identifier before a copy of the document is supplied to the Sponsor (or designee). The ICD must include appropriate statements explaining that patient data will be confidential and what actions will be taken to ensure patient confidentiality.

Any other confidentiality requirements specified by the site, IRB or IEC, or national or local regulations will be adhered to and detailed appropriately in the ICD.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

Applicable regulations require the Sponsor (or designee) to inspect all documents and records to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the patients in this study. These regulations also allow the Sponsor's records to be inspected by authorized representatives of the regulatory agencies. The investigator will permit study-related monitoring, audits, IRB or IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

19.2. Retention of Records

In compliance with the ICH/GCP guidelines, the investigator/Institution agrees to retain and maintain all study records that support the data collected from each patient, as well as all study documents as specified in ICH/GCP, Section 8 Essential Documents for the Conduct of a Clinical Trial. The investigator agrees to contact the Sponsor before destroying or relocating any study documentation and is expected to take measures to prevent accidental or premature destruction of these documents.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be contacted in writing regarding the name and address of the new person responsible as well as the disposition of document storage. Under no circumstances shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Essential records (including eCRFs, source documents, IMP disposition records, signed patient ICDs, AE reports, and other regulatory documents) as required by the applicable regulations, must be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the investigational product.

It is the responsibility of the Sponsor to inform the investigator/Institution as to when these documents no longer need to be retained.

19.3. Case Report Forms and Study Records

Access to eCRFs will be provided to the clinical site. As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (eg, IRB or IEC correspondence, clinical study materials and supplies shipment

manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any hand-written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (eg, laboratory reports, clinic notes, IMP disposition log, pharmacy records, patient sign-in sheets, telephone logs, X-rays, and ECGs). All draft, preliminary, and pre/final iterations of a final report are also considered to be source documents (eg, faxed and hard copy of laboratory reports, faxed and hard copy of initial results, and final report).

The investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor or its authorized representatives and inspection by the appropriate regulatory authorities.

Data reflecting the patient's participation with the IMP under investigation are to be reported to the Sponsor. The data are to be recorded on the eCRFs and/or other media provided or approved by the Sponsor.

A completed eCRF must be submitted for each patient who receives IMP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality. The eCRF should not be used as a source document unless otherwise specified by the Sponsor.

Neither the Sponsor nor a service provider contracted to analyze data and complete the study report is permitted to interpret a blank answer; therefore, all fields should be completed. All requested information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated as not available (N/A) or not done (N/D); do not leave a field blank.

Each set of completed eCRFs must be signed and dated by the investigator acknowledging review and that the data are accurate and complete. The completed database is to be returned to the Sponsor as soon as practical after completion by the mechanism prescribed for the protocol.

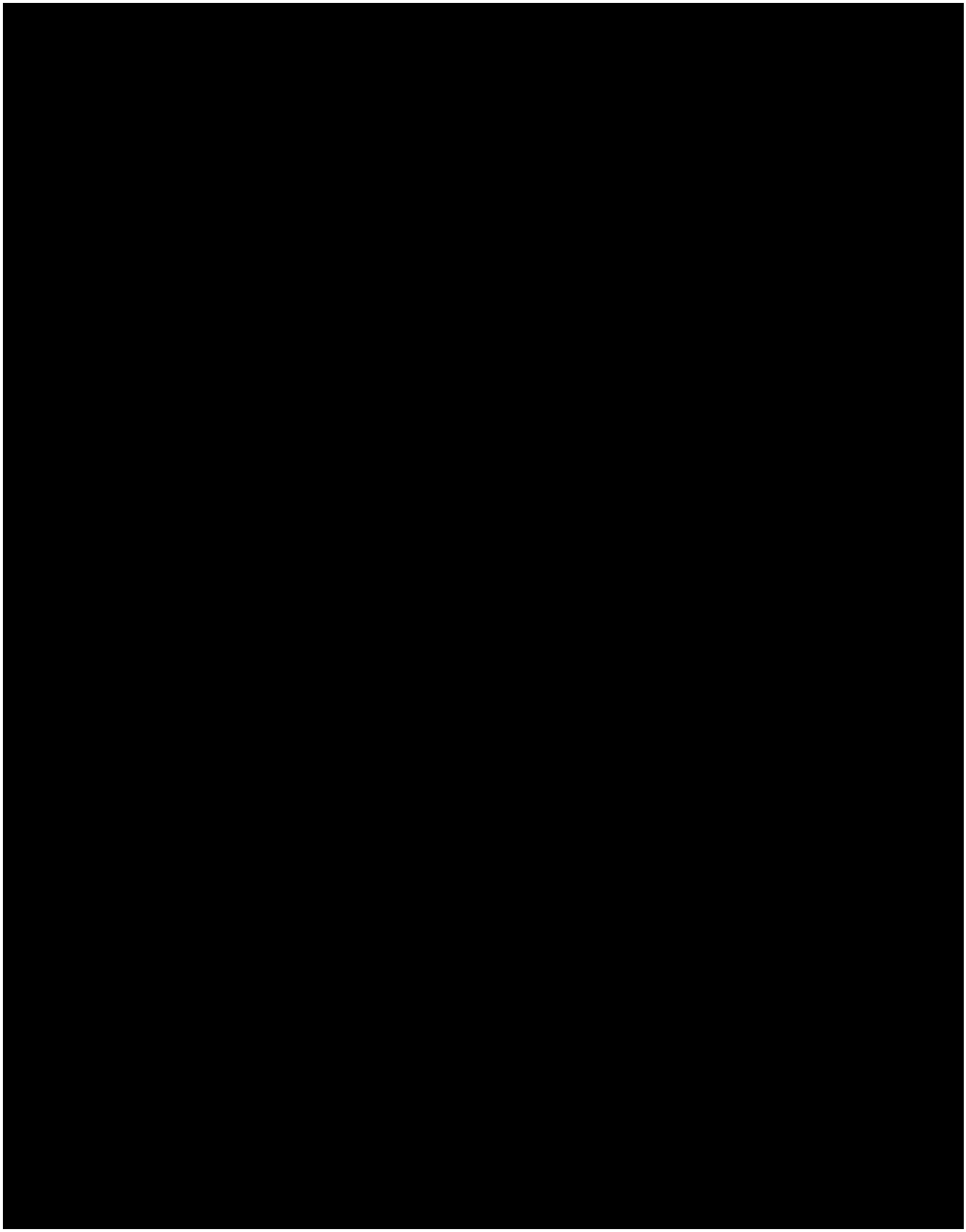
It is essential that all dates appearing on the Sponsor's patient data collection forms for laboratory tests, cultures, etc., be the dates on which the specimens were obtained or the procedures performed. The eCRFs will be electronically signed by the investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed in a timely manner as defined in the eCRF Completion Guidelines.

20. ADMINISTRATIVE CONSIDERATIONS

20.1. Investigators

The investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA/EMA regulatory requirements or ICH/GCP guidelines:

- Agree to conduct the study in accordance with the relevant current protocol
- Agree to personally conduct or supervise the described investigation(s)
- Agree to inform any patients, or persons used as controls, that the IMP are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met
- Agree to report adverse experiences that occur during the course of the investigation(s)
- Read and understand the information in the IB, including the potential risks and side effects of the IMP
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments
- Maintain adequate and accurate records and make those records available for inspection
- Ensure that an appropriate IRB/IEC will be responsible for the initial and continuing review and approval of the clinical investigation
- Agree to promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to patients or others
- Agree to not make changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to patients
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements.
- Refer also to:
  - FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
  - Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
  - Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
  - DIRECTIVE 2001/20/EC: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
  - Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf



20.3. Amendments and Study Termination

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IRB or IEC approval. Documentation of amendment approval by the investigator and IRB or IEC must be provided to the Sponsor or its authorized representative. When the change(s) involve only logistic or administrative aspects of the study, the IRB or IEC only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator will contact the Medical Monitor. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Medical Monitor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded on the eCRF and source documents will reflect any departure from the protocol and the source documents will describe the departure and the circumstances requiring it.

The Sponsor reserves the right to terminate this study at any time.

20.4. Financial Disclosure

Prior to the start of the study, investigators will release sufficient and accurate financial information that permits the Sponsor to demonstrate that an investigator and all study relevant assigned personnel have no personal or professional financial incentive regarding the future approval or disapproval of the IMP such that his or her research might be biased by such incentive.

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World Health Organization (WHO) Fact Sheet No 317 Updated January 2015.

23. APPENDICES

Appendix 1: Schedule of Assessments

Appendix 2: Sponsor's Signature

Appendix 3: Calculating Reynolds Risk Score

Appendix 4: Calculating SCORE Risk

Appendix 5: Investigator's Signature

Appendix 6: Summary of Changes in Amendment 1

Appendix 7: Summary of Changes in Amendment 2

Appendix 8: Summary of Changes in Amendment 3.1

Appendix 9: Summary of Changes in Amendment 4

Appendix 10: Summary of Changes in Amendment 5

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

	Screen and Run-In		Treatment														
							Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/Month	**Week -5**	**Week -4**	**Day 1/ Week 0**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		
Informed Consent	X																
Enrollment Criteria	X	X	X														
Demographics	X																
Medical History	X																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and Exercise Counselling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X														X	
Weight[2]	X		X	X	X	X		X		X		X		X		X	
Height	X																
12-Lead ECG		X														X	
Vital Signs[3]	X		X	X	X	X		X		X		X		X		X	
Serology[4]		X															
Serum or Urine Pregnancy/FSH[5]	X		X														
TSH	X																
Clinical Safety Labs[6]	X		X	X	X	X		X		X		X		X		X	

	Screen and Run-In		Treatment														
							Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/Month	**Week -5**	**Week -4**	**Day 1/ Week 0**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		
Basic Fasting Lipids[7]	X	X	X		X	X		X		X		X		X		X	
HbA_{1C}	X				X	X		X		X		X		X		X	
hs-CRP			X			X		X								X	
Randomization			X														
Single-Blind Drug Dispensing		X															
Single-Blind Drug Return			X														
Double-blind Drug Dispensing			X		X	X		X		X		X		X			
Double-Blind Drug Return					X	X		X		X		X		X		X	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = End of Study; FSH = follicle-stimulating hormone; HbA_{1C} = hemoglobin A_{1C}; HBsAg = hepatitis B surface antigen; HCV-Ab = hepatitis C antibody; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; hs-CRP = high-sensitivity C-reactive protein; Labs = laboratory tests; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; SBP = systolic blood pressure; TC = total cholesterol; TG(s) = triglyceride(s); TSH = thyroid-stimulating hormone.

[1] An additional visit approximately 1 week after Visit S1 and prior to Visit S2 MAY be completed if patient's LDL-C and/or TG level fail to meet entry criteria. Also, an additional visit and/or assessment between Visits S1 and T1 MAY be completed if the patient's DBP, SBP, TSH, eGFR, ALT, AST, and/or CK fail to meet entry criteria. If this optional visit/assessment is completed, the value from the repeat visit/assessment will be used to determine eligibility. Also, at Visit S1 an optional hs-CRP may be measured only if needed for Reynolds Risk Score and local hs-CRP value is not available. Finally, the number of days between Week -5 (Visit S1) and Week -4 (Visit S2) may be less than 7, and the number of days between Week -5 (Visit S1) and randomization may be less than 35 as long as eligibility can be determined.

[2] Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[3] Vital signs will include DBP, SBP, HR and will be collected prior to any blood sample collection. The patient will rest for several minutes prior to assessments.

[4] Serology for HBsAg and HCV-Ab.

	Screen and Run-In		Treatment														
							Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit		Phone Visit
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/Month	**Week -5**	**Week -4**	**Day 1/ Week 0**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**		**30 days ±10 after EOS**
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[5] Pregnancy test completed in premenopausal women only, serum test at Week -5 (Visit S1) and urine test at Day 1 (Visit T1); FSH competed on postmenopausal women <55 years of age.

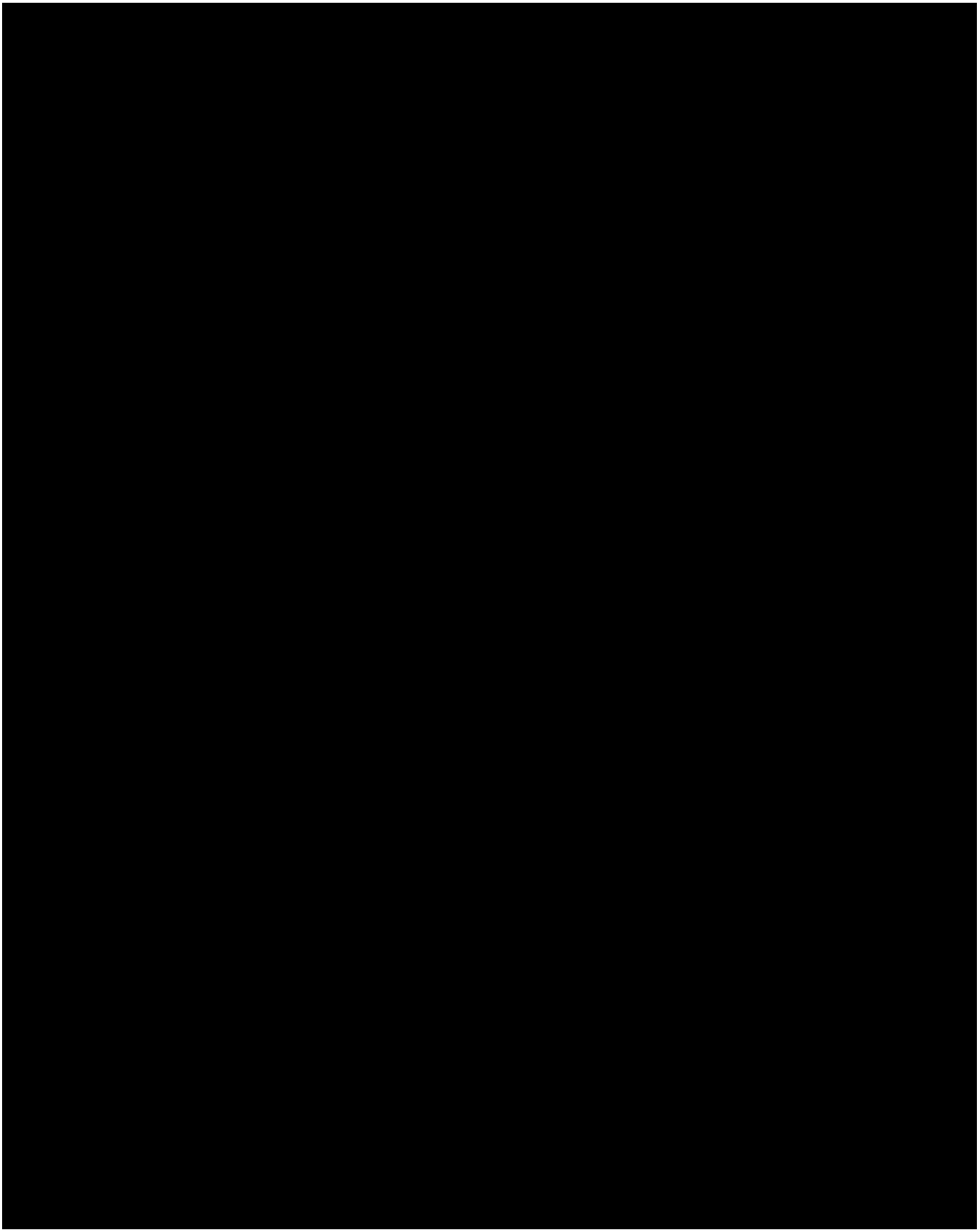
[6] Clinical safety laboratory tests include hematology, blood chemistry, and urinalysis. Urinalysis includes dipstick measured at the clinic and microscopic, if abnormal, completed by the central lab. A limited safety laboratory assessment (ALT, AST, TB, and CK) will completed at Visit T2 only. A coagulation panel will be completed only if needed for patients on anticoagulant therapy at Day 1 (Visit T1) and 3 to 5 days later.

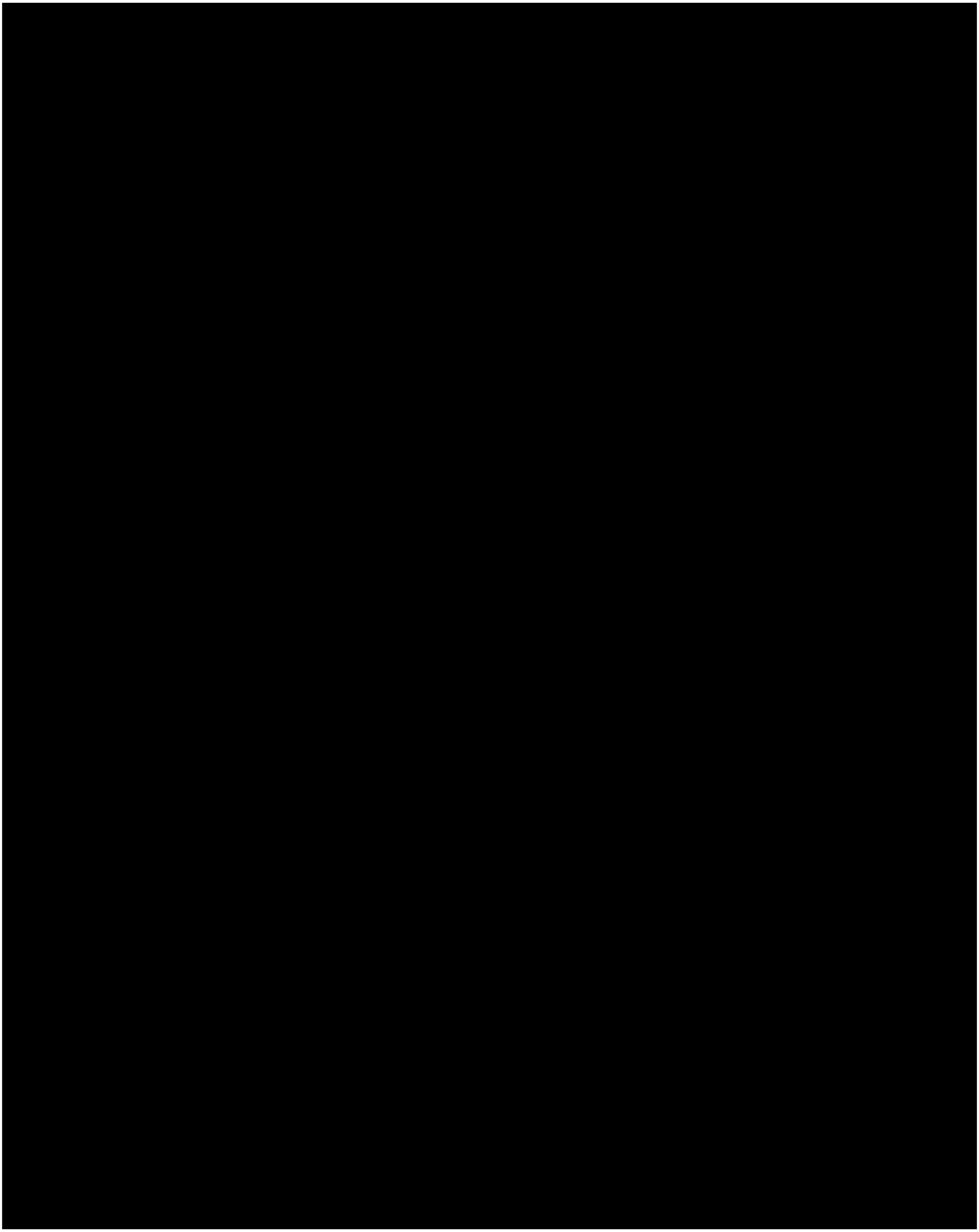
[7] Basic fasting lipids include TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs.

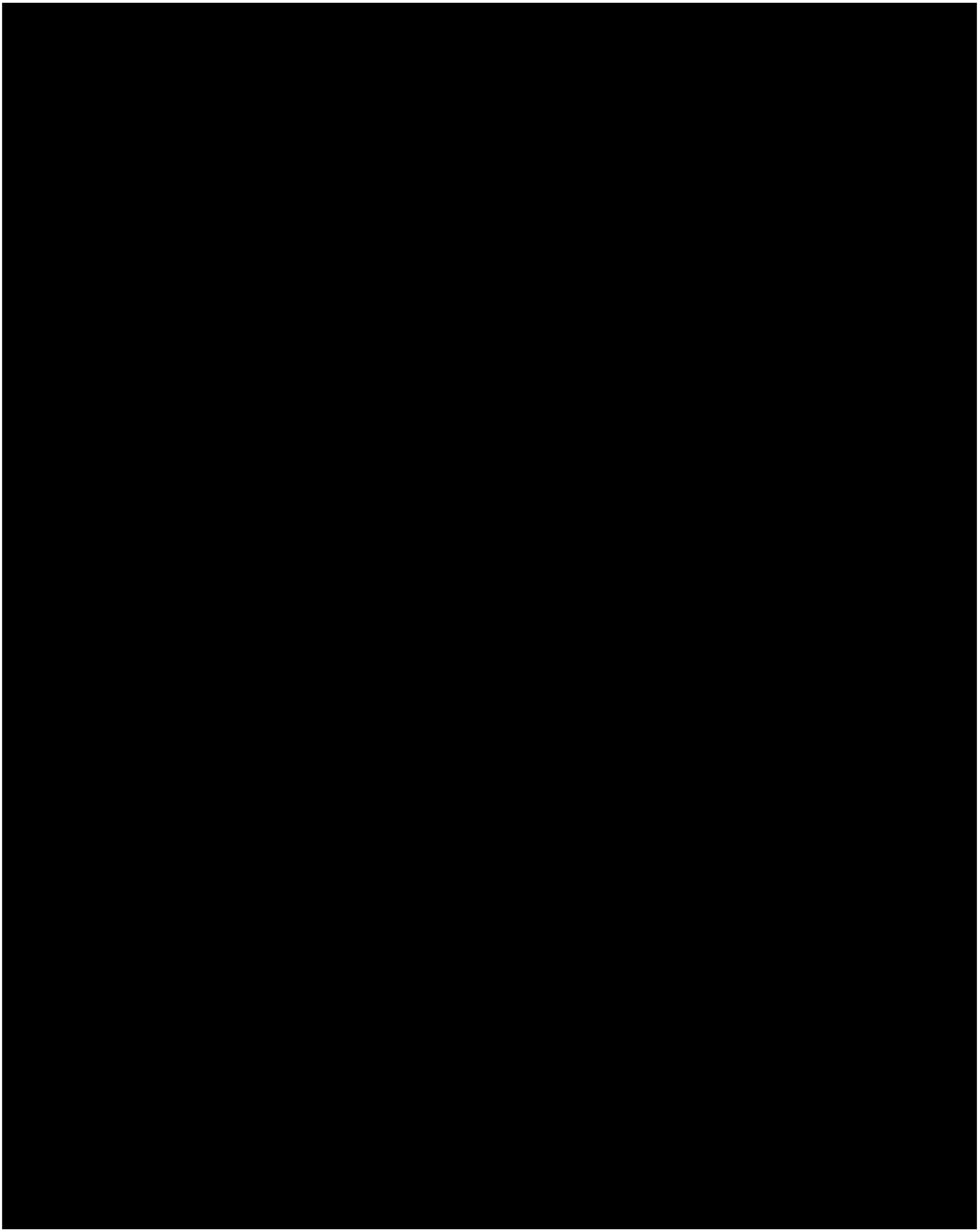
[8] After Visit T4 (Month 6), telephone and clinic visits (alternating every 3 months) will continue until the study is completed.

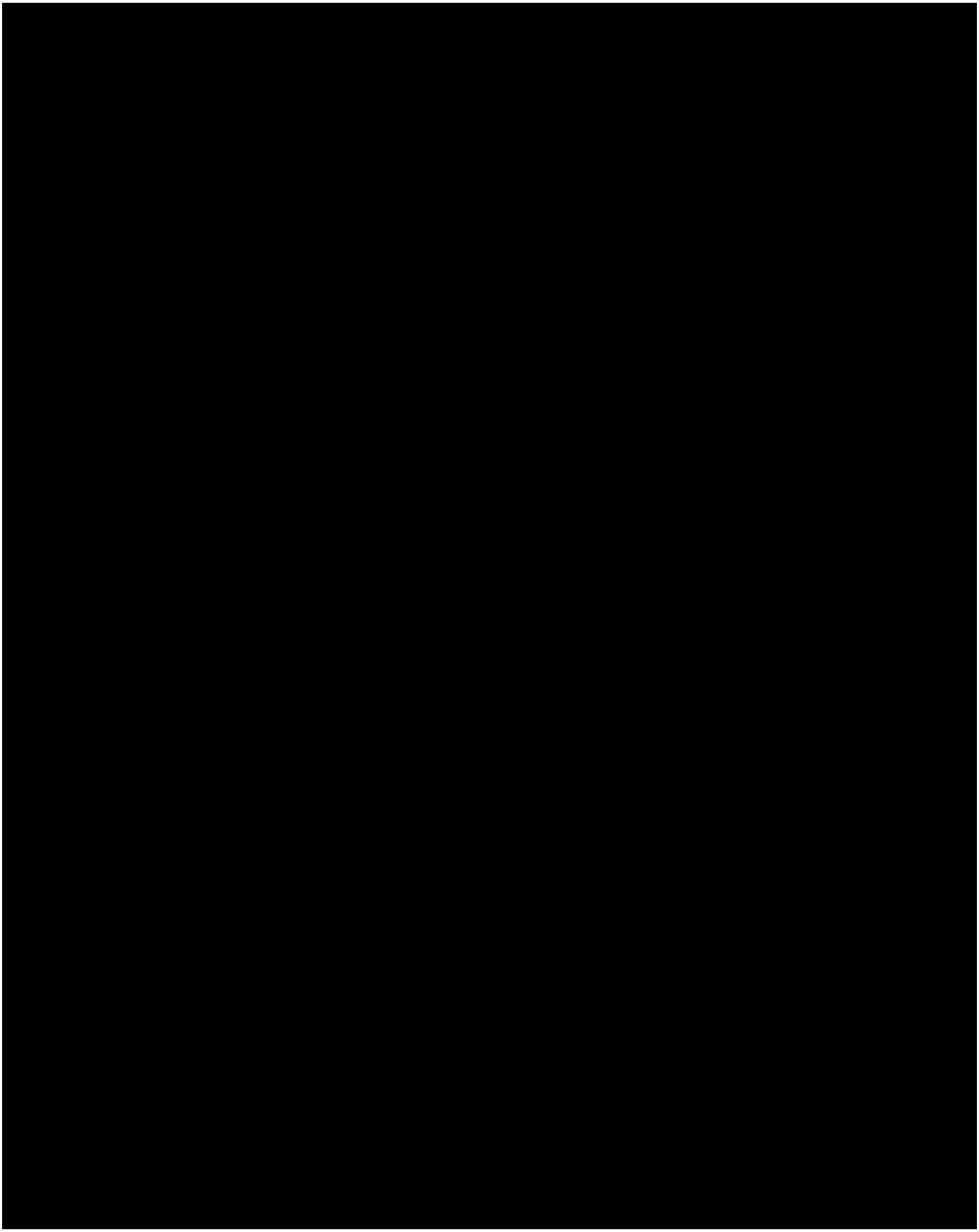
[9] All procedures will be completed at the End of Study or Early Termination Visit.

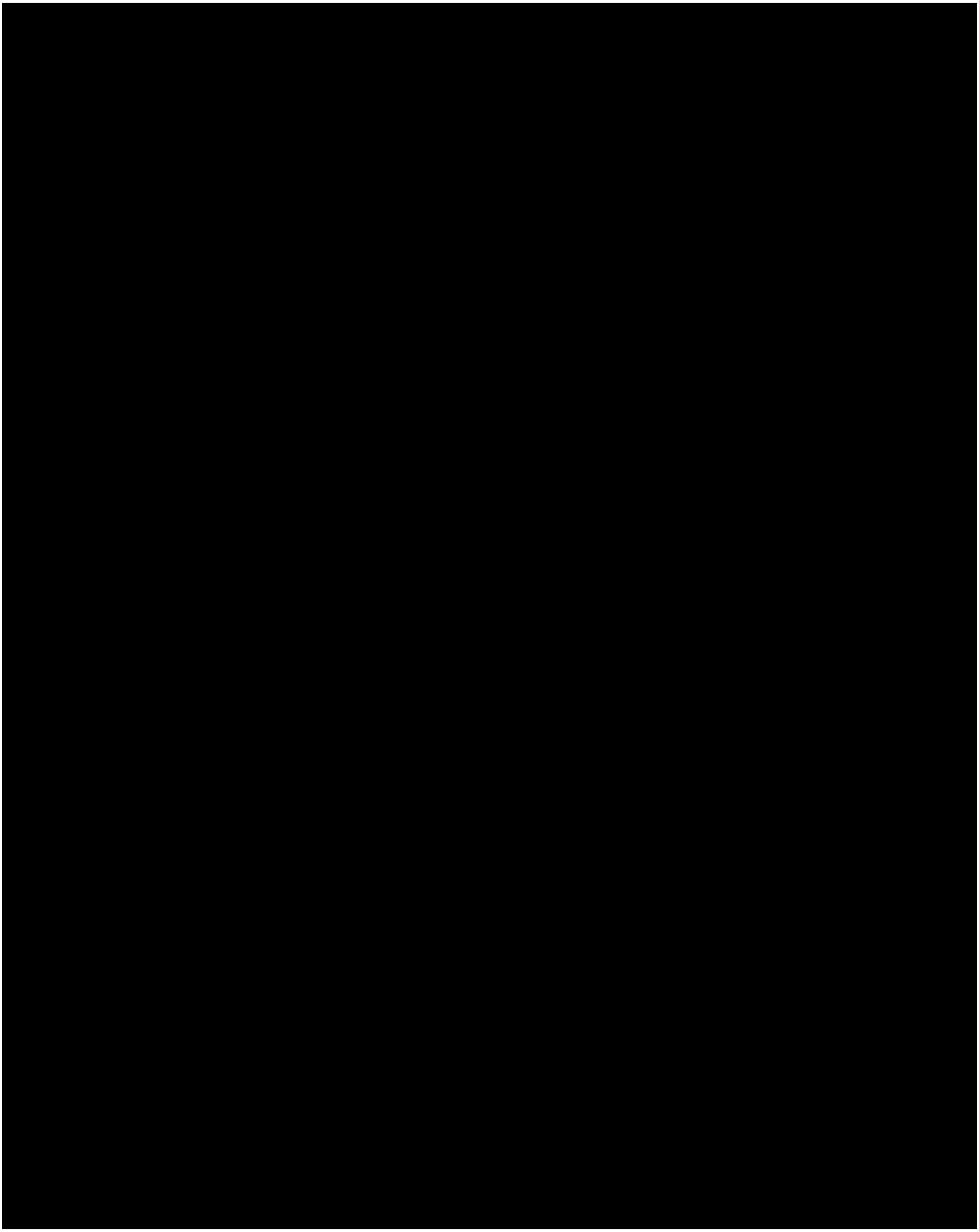
[10] Duration of treatment for each patient will vary and is dependent on accumulation of MACE in the entire study. For individual subjects, treatment duration will be a minimum of 24 months and may continue for up to approximately 57.5 months.

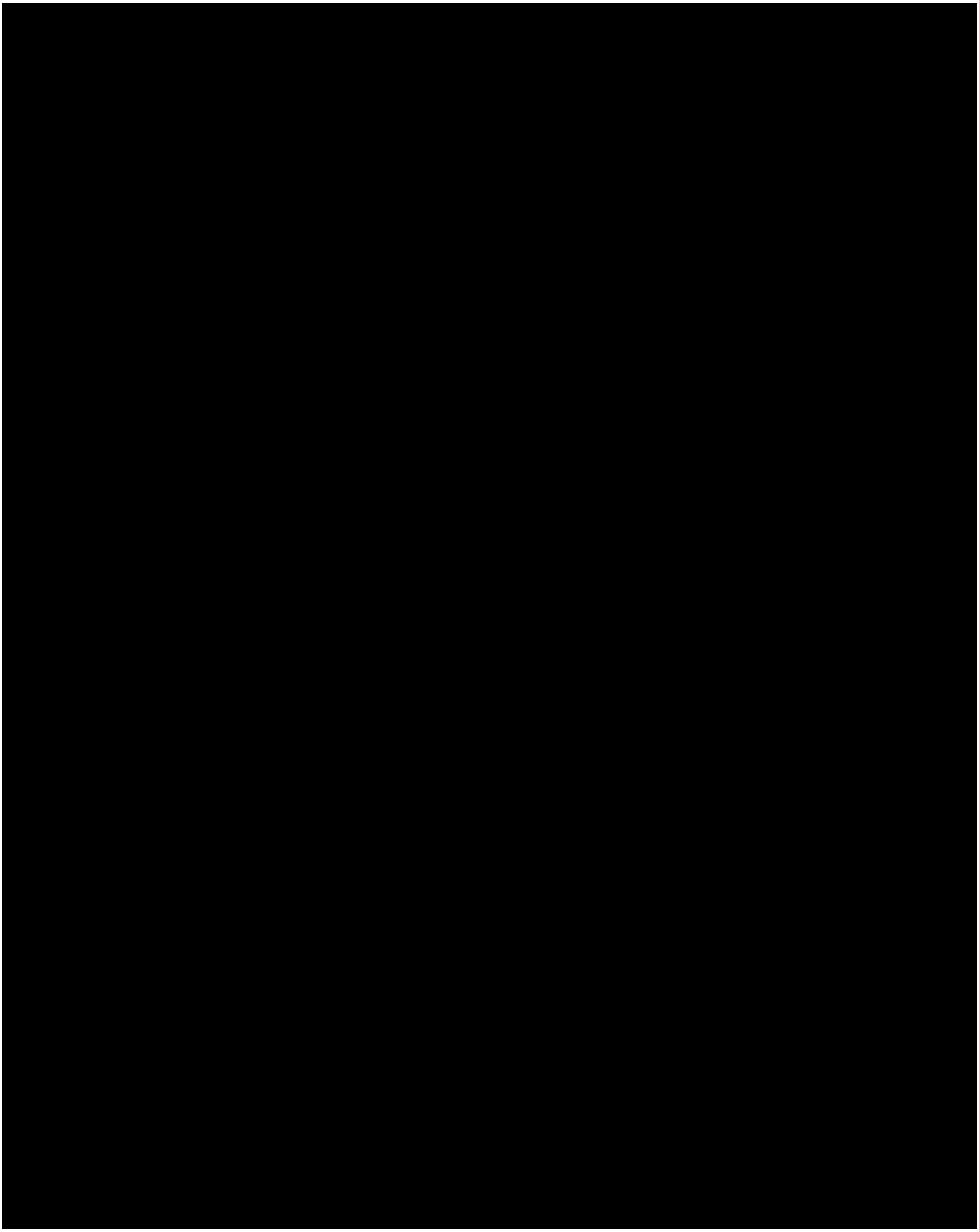


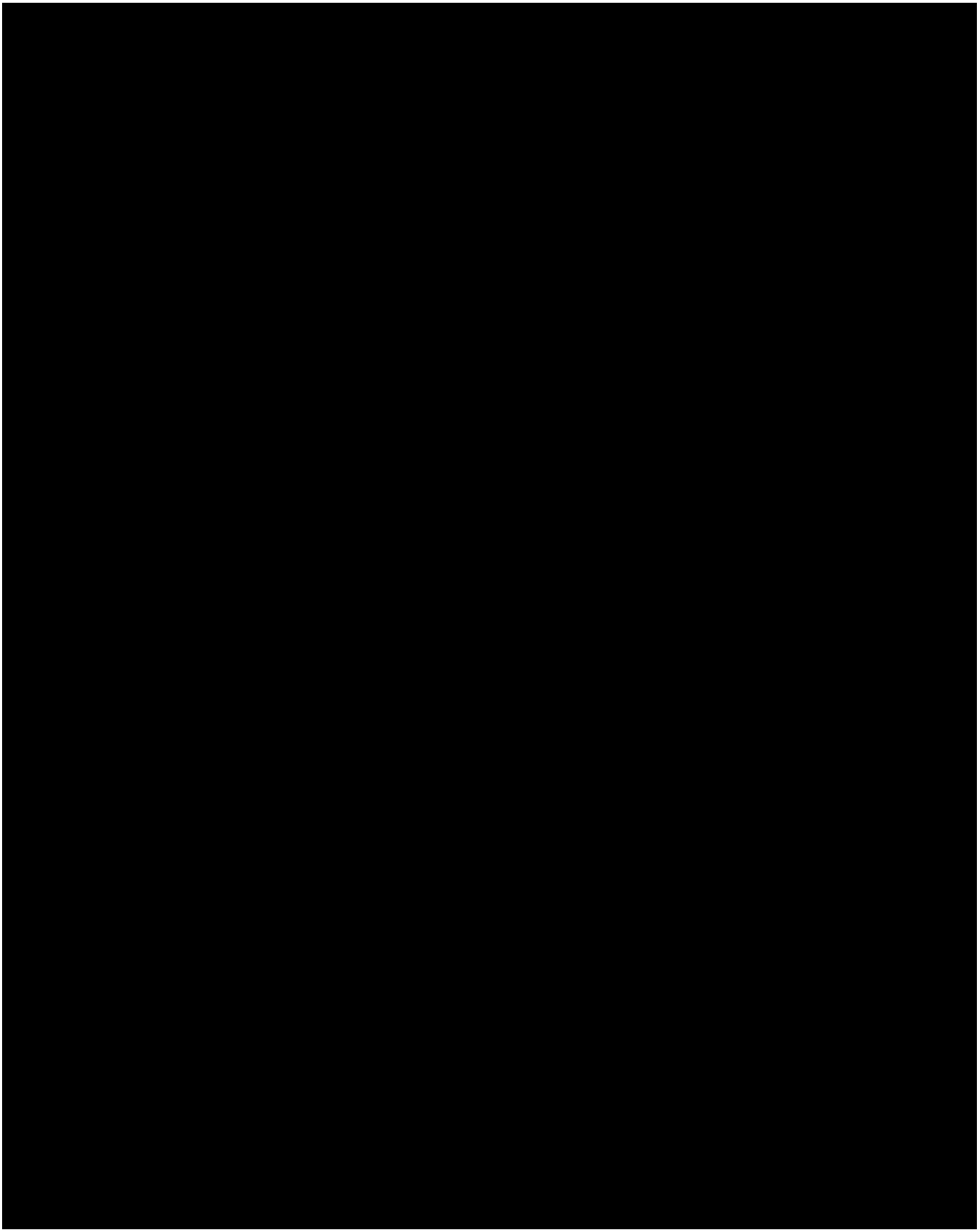


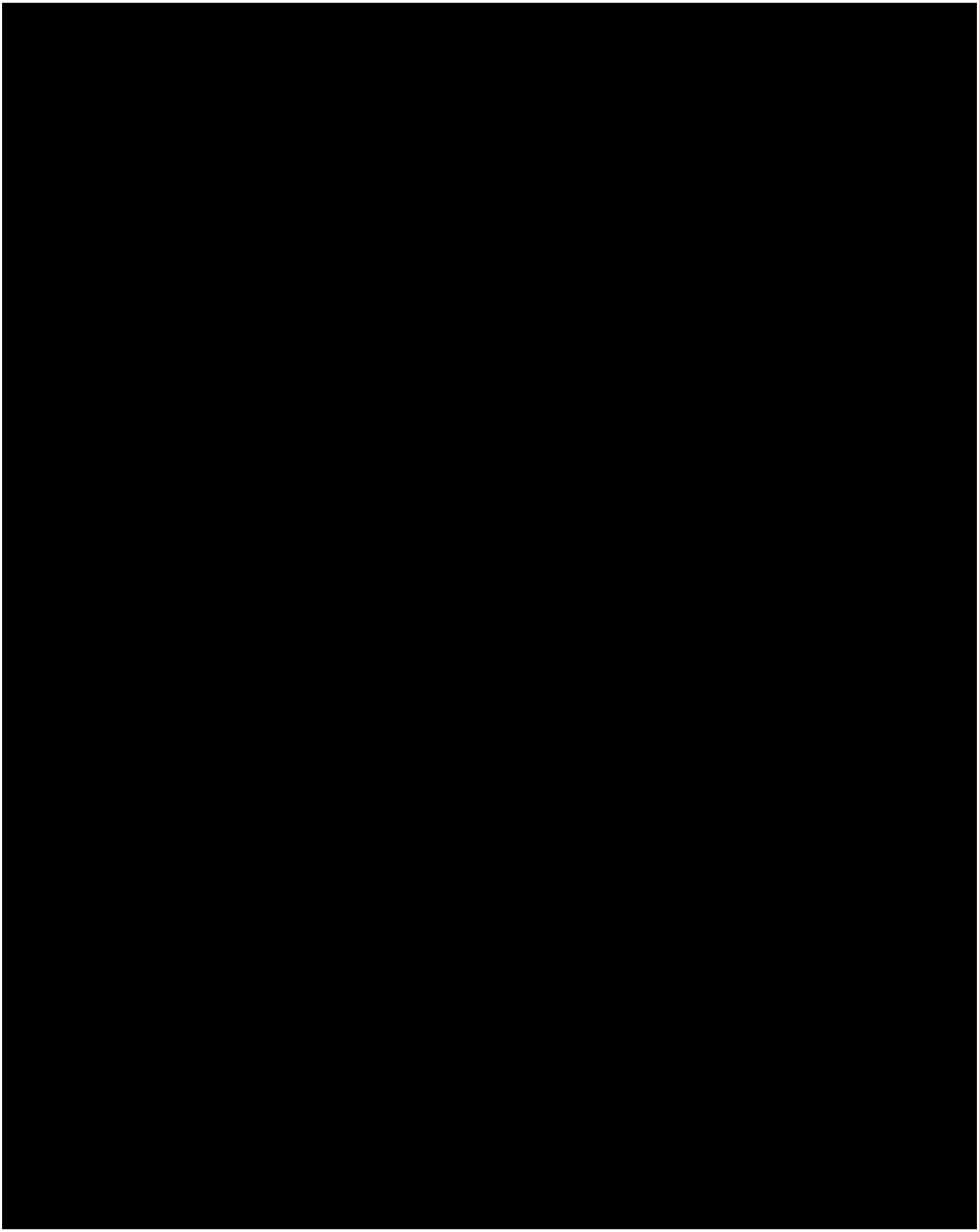


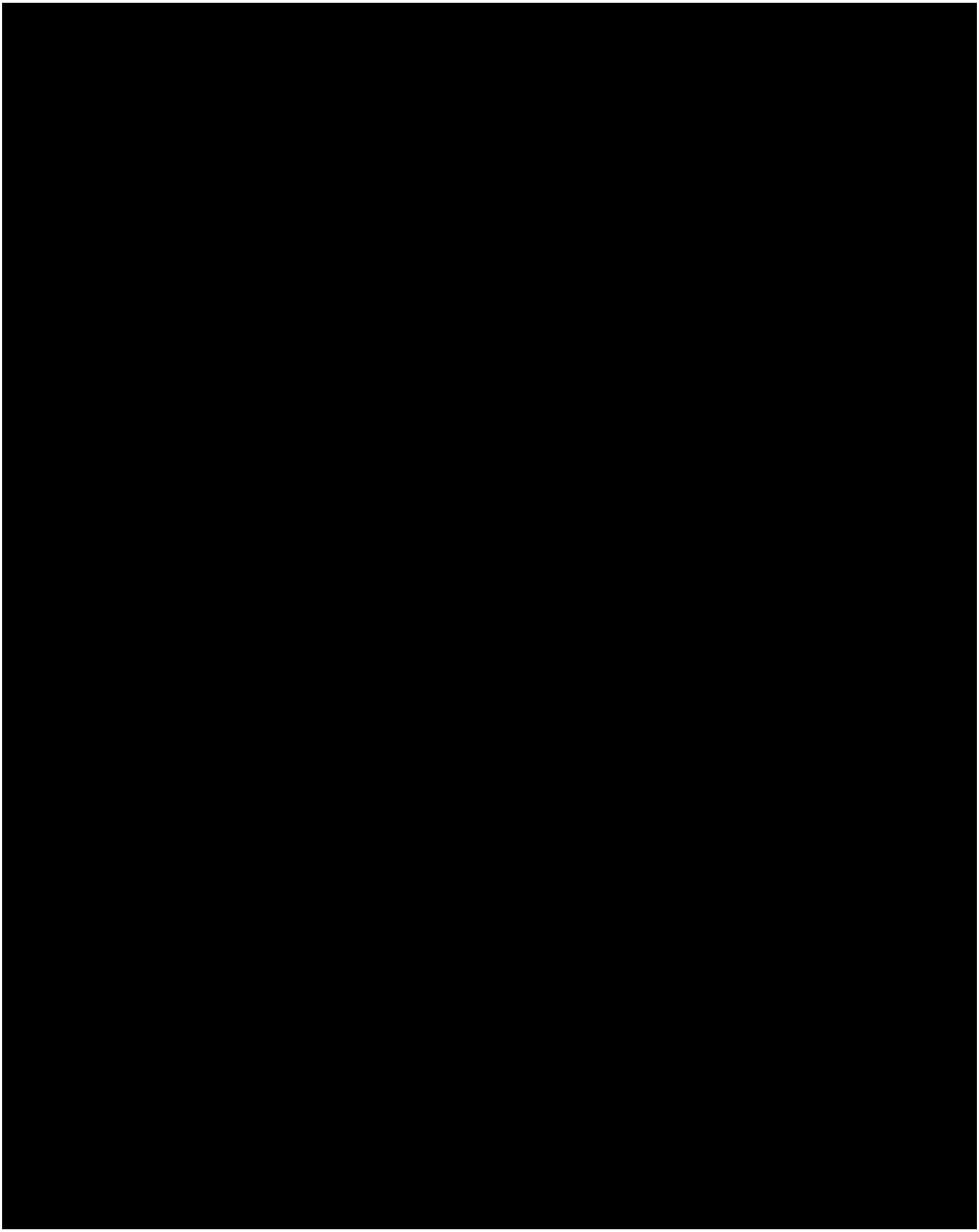


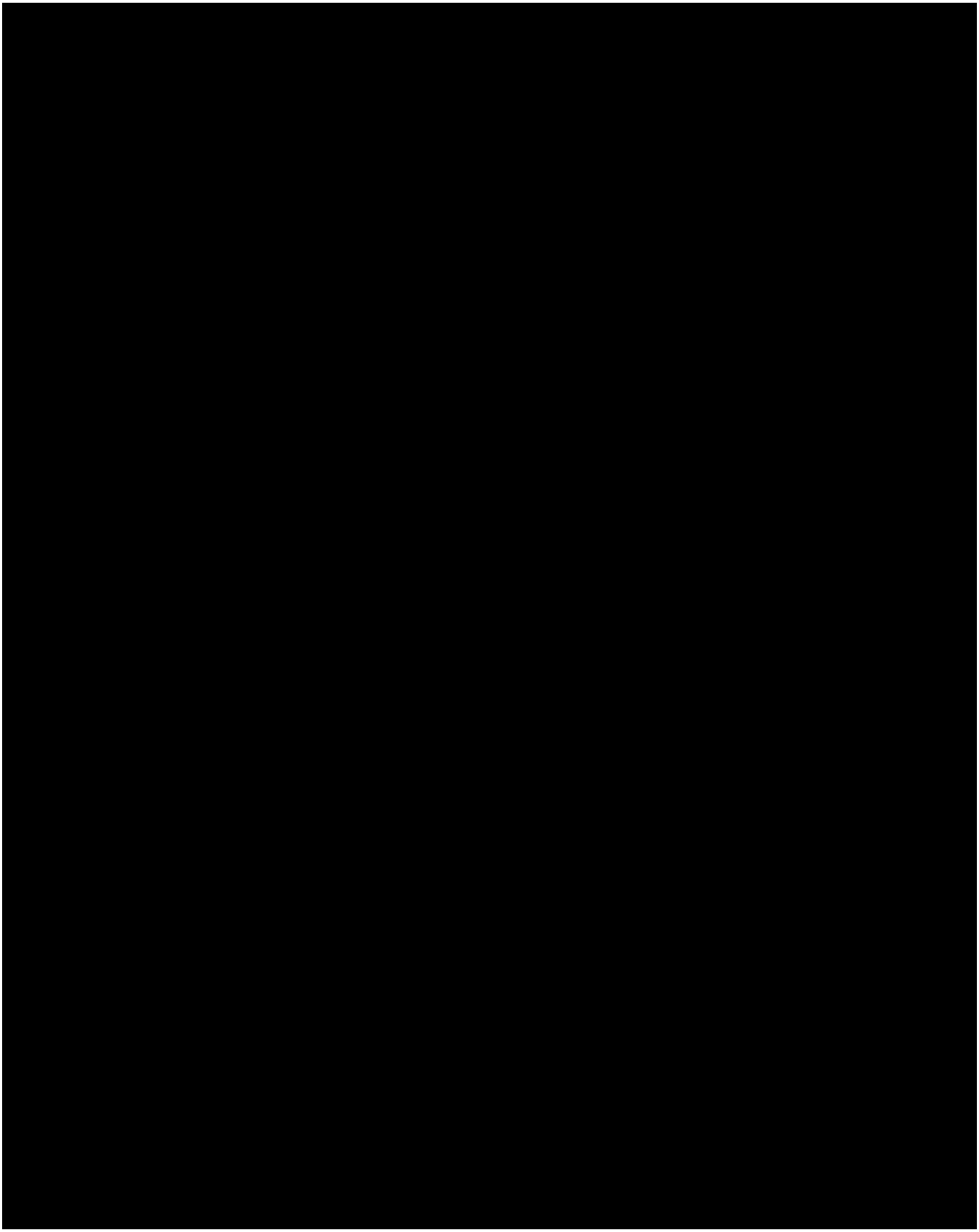


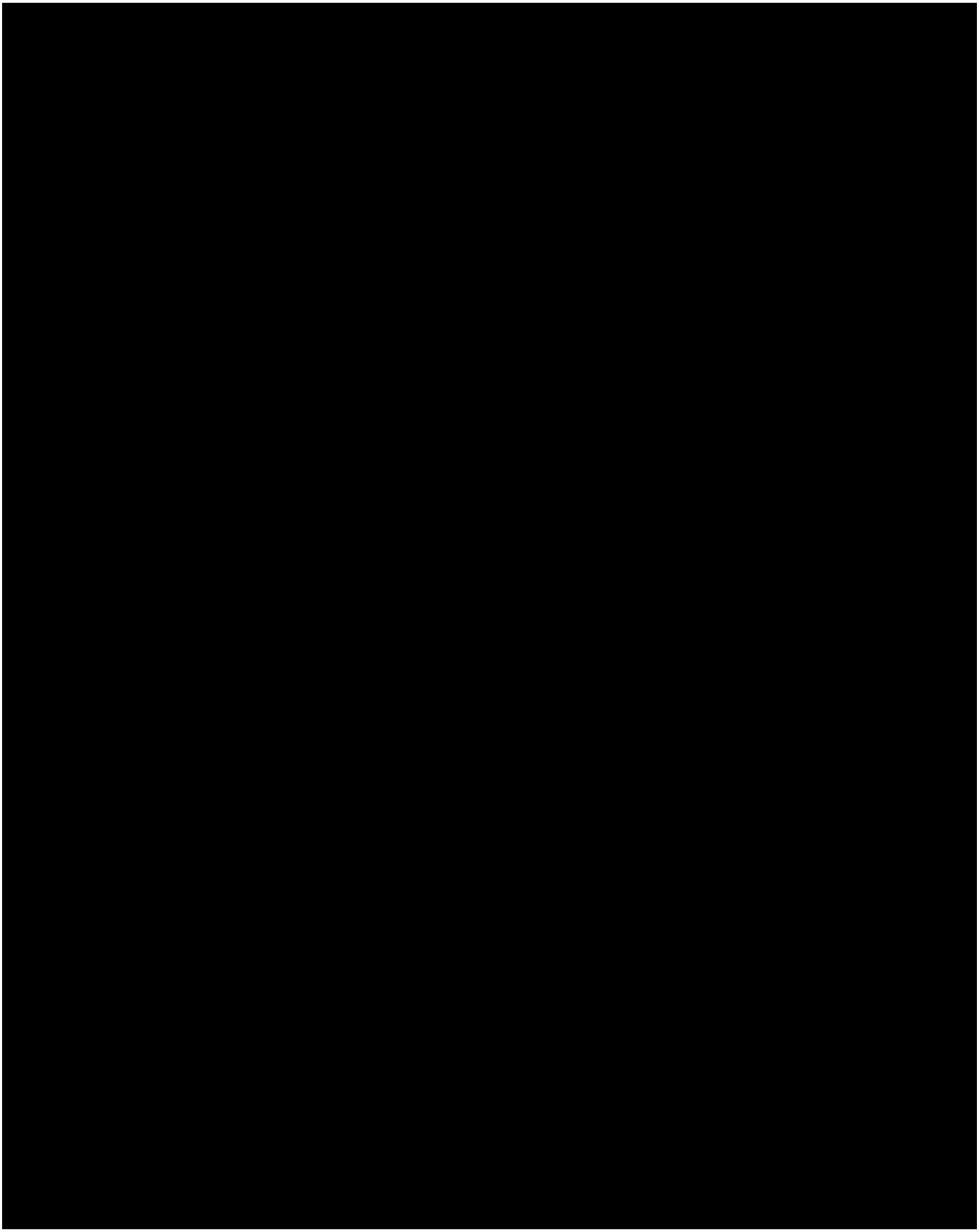


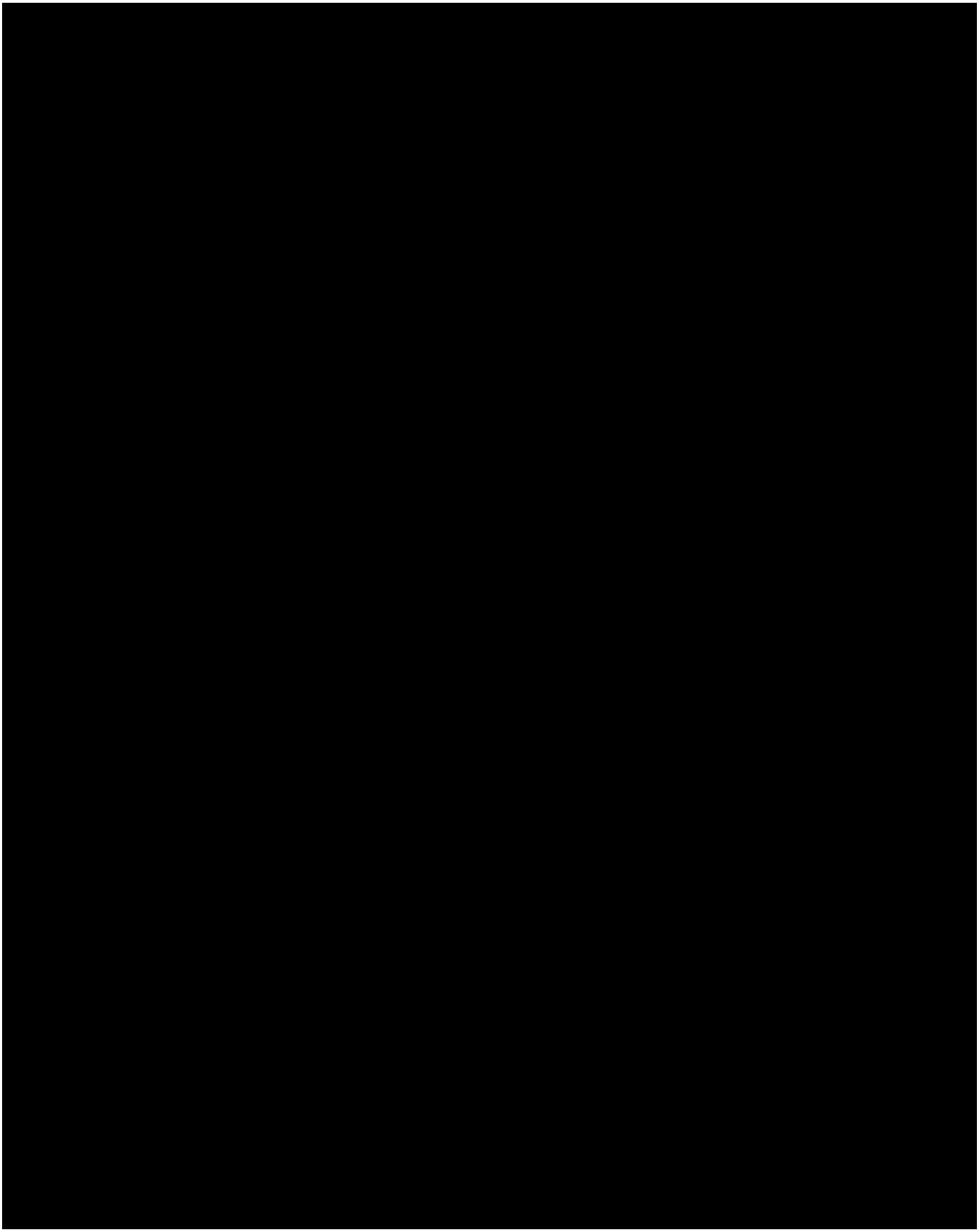


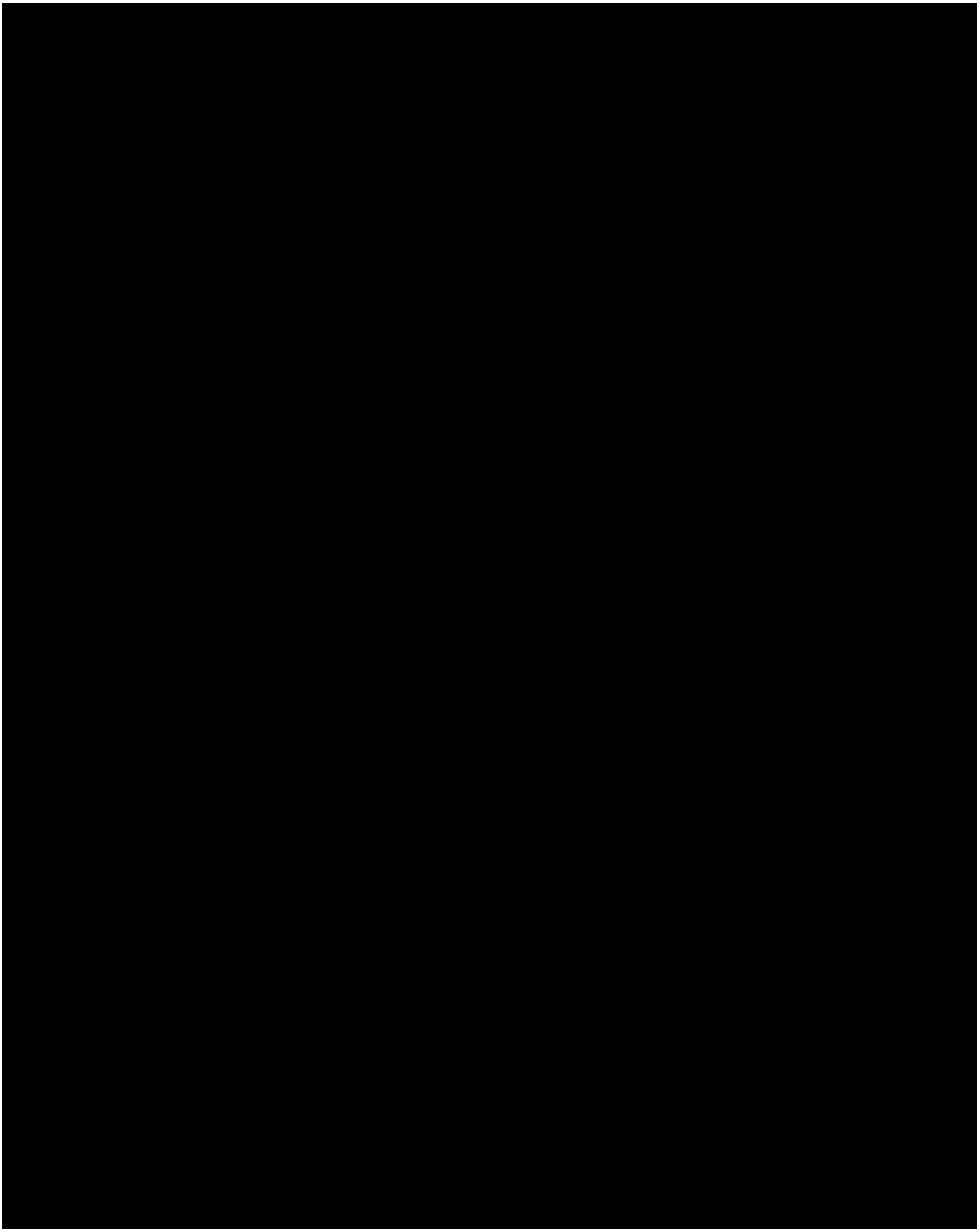


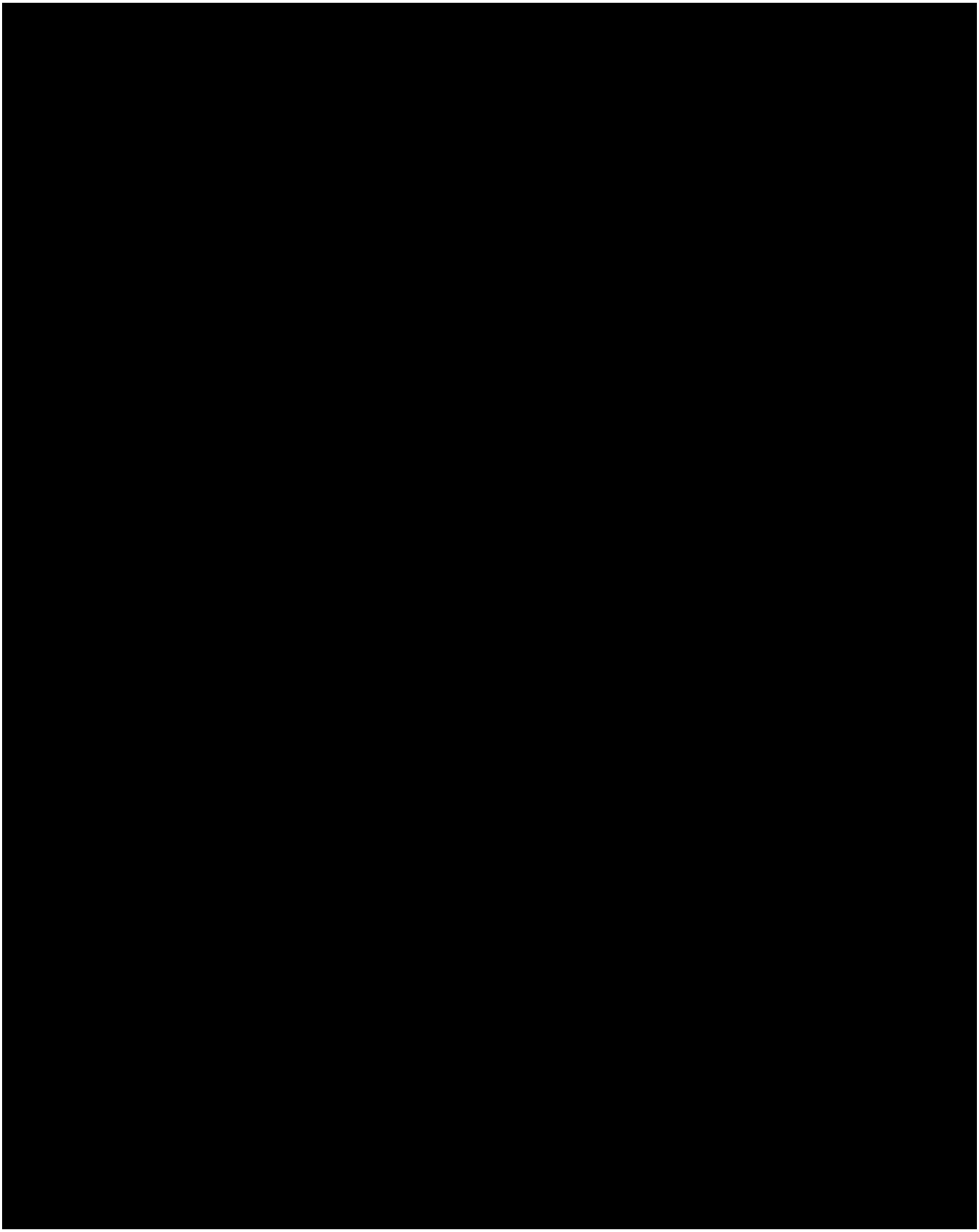


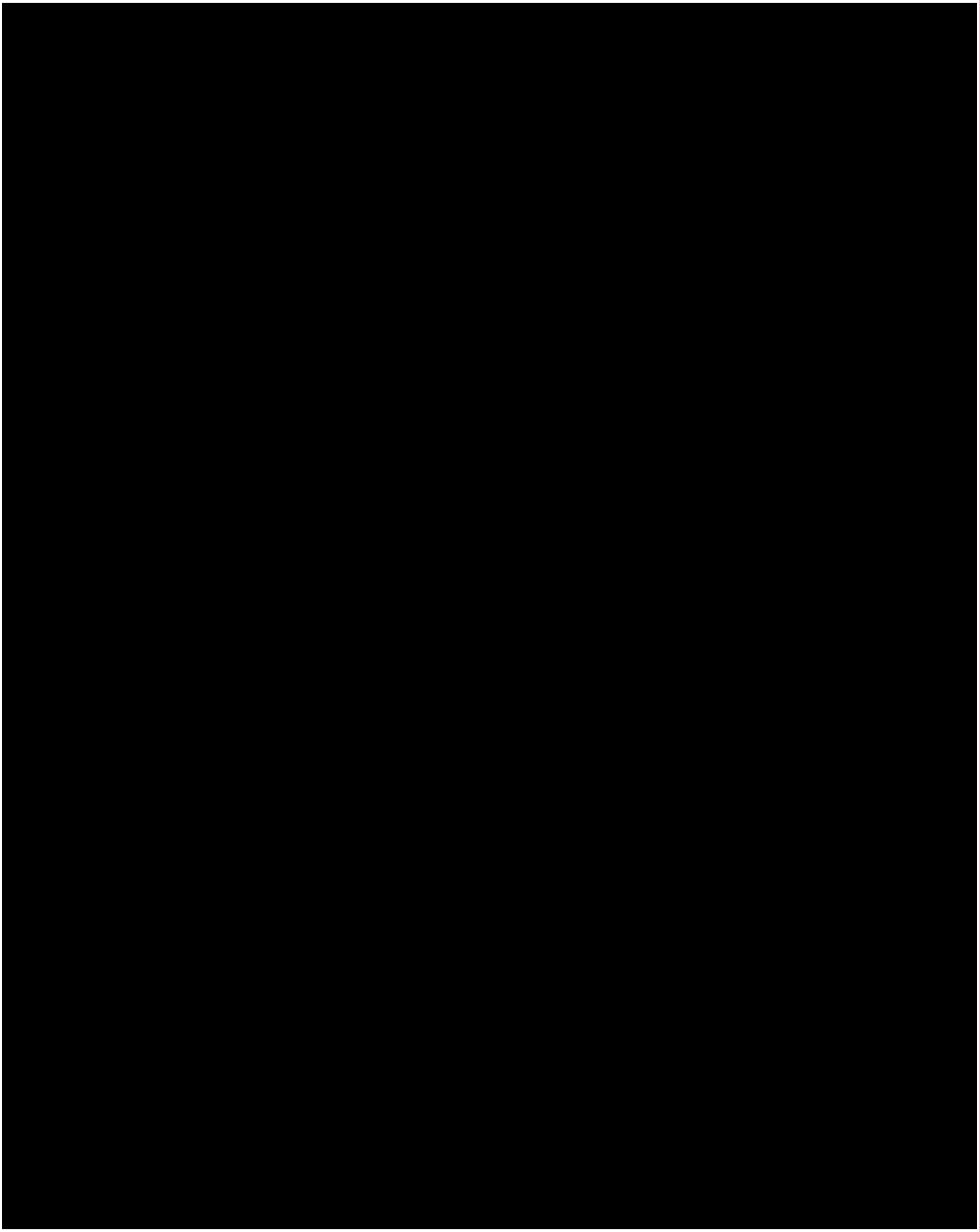


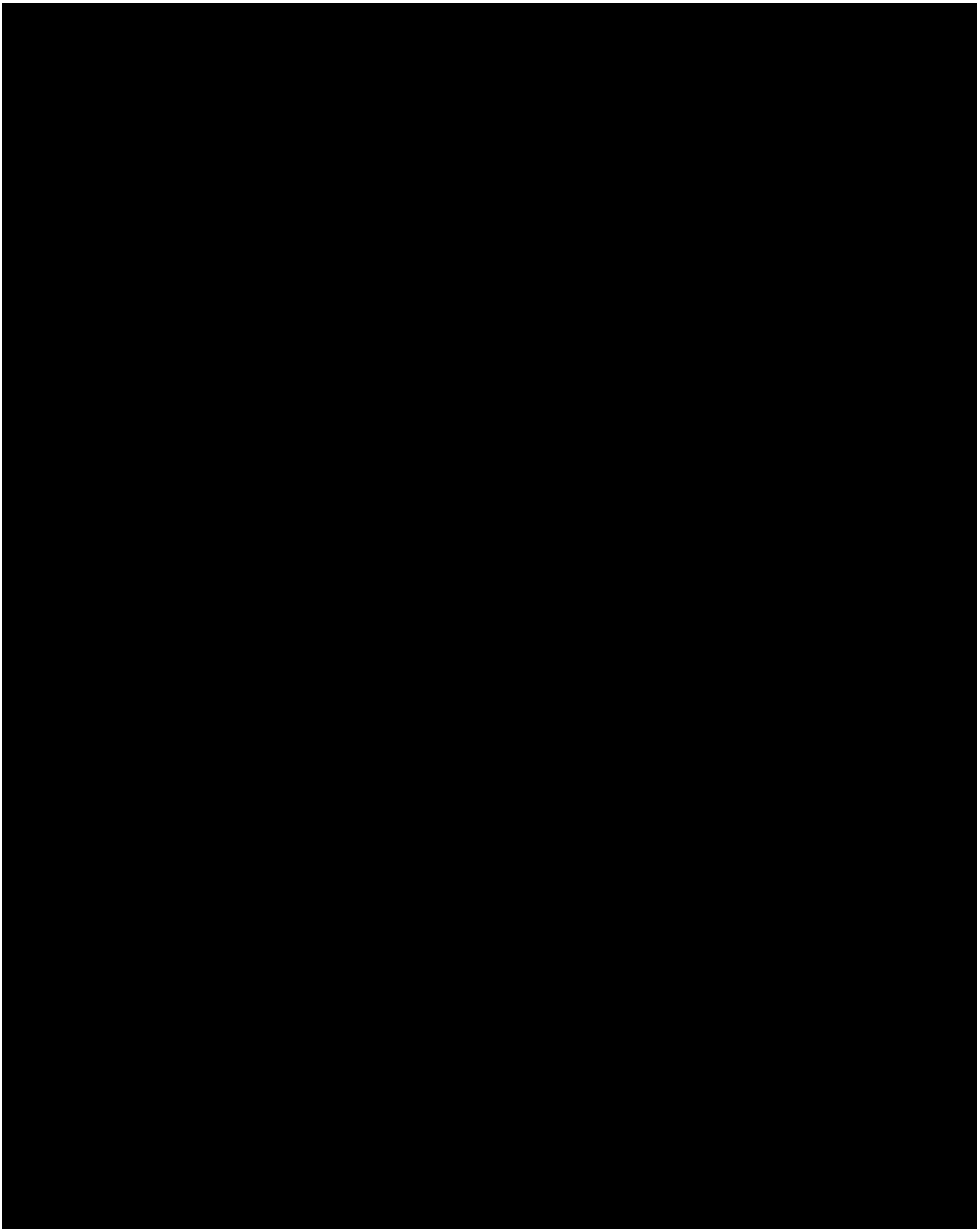


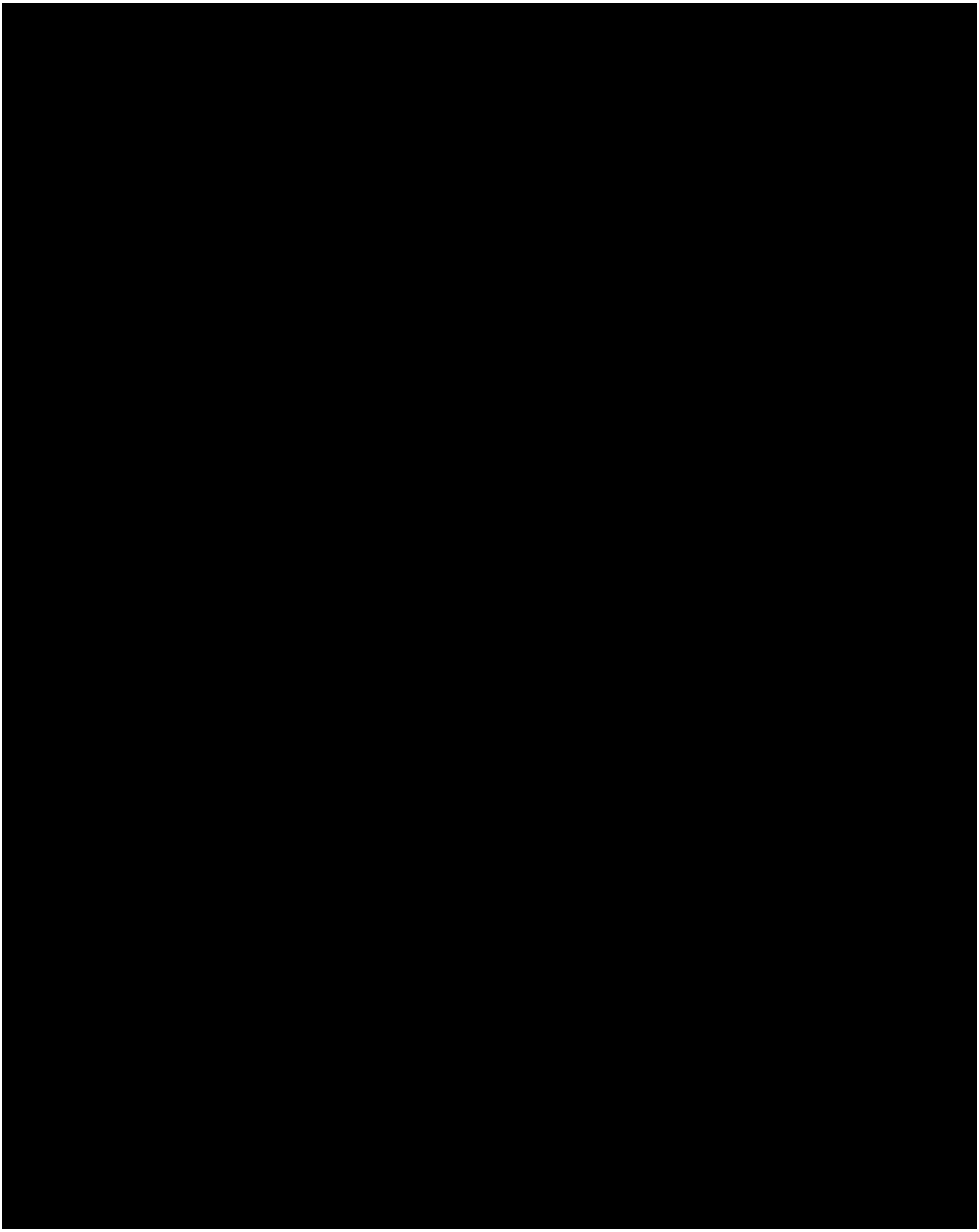


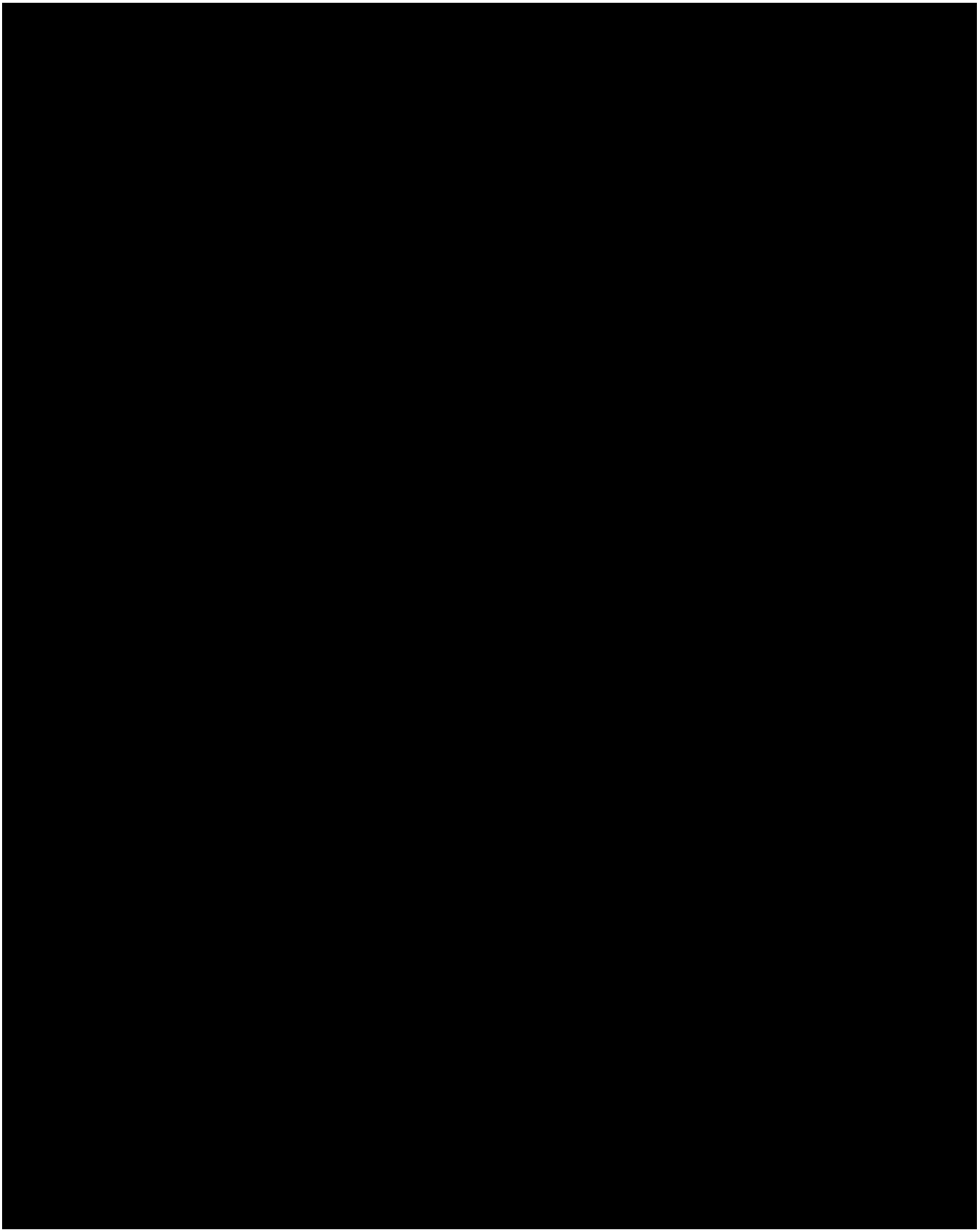


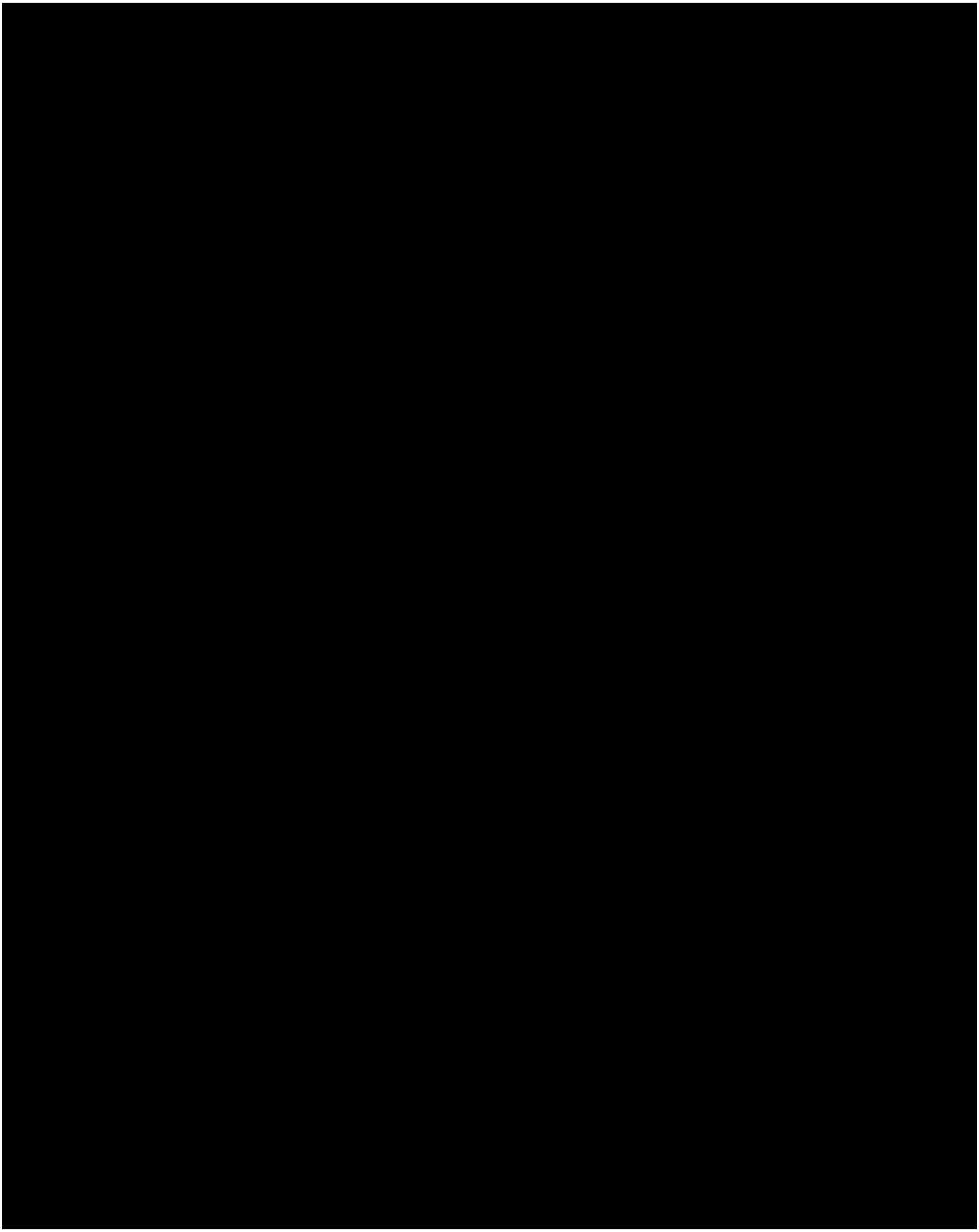


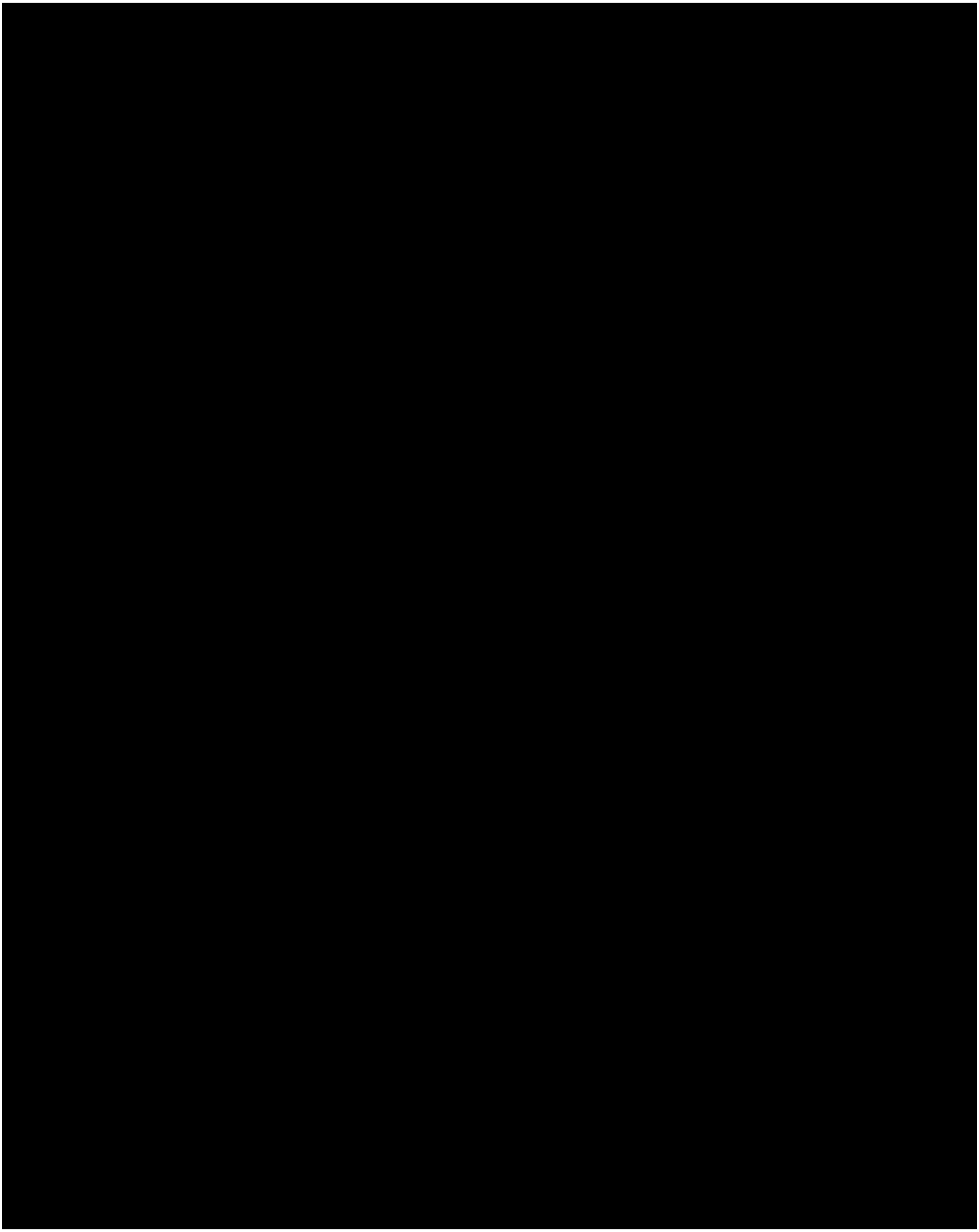


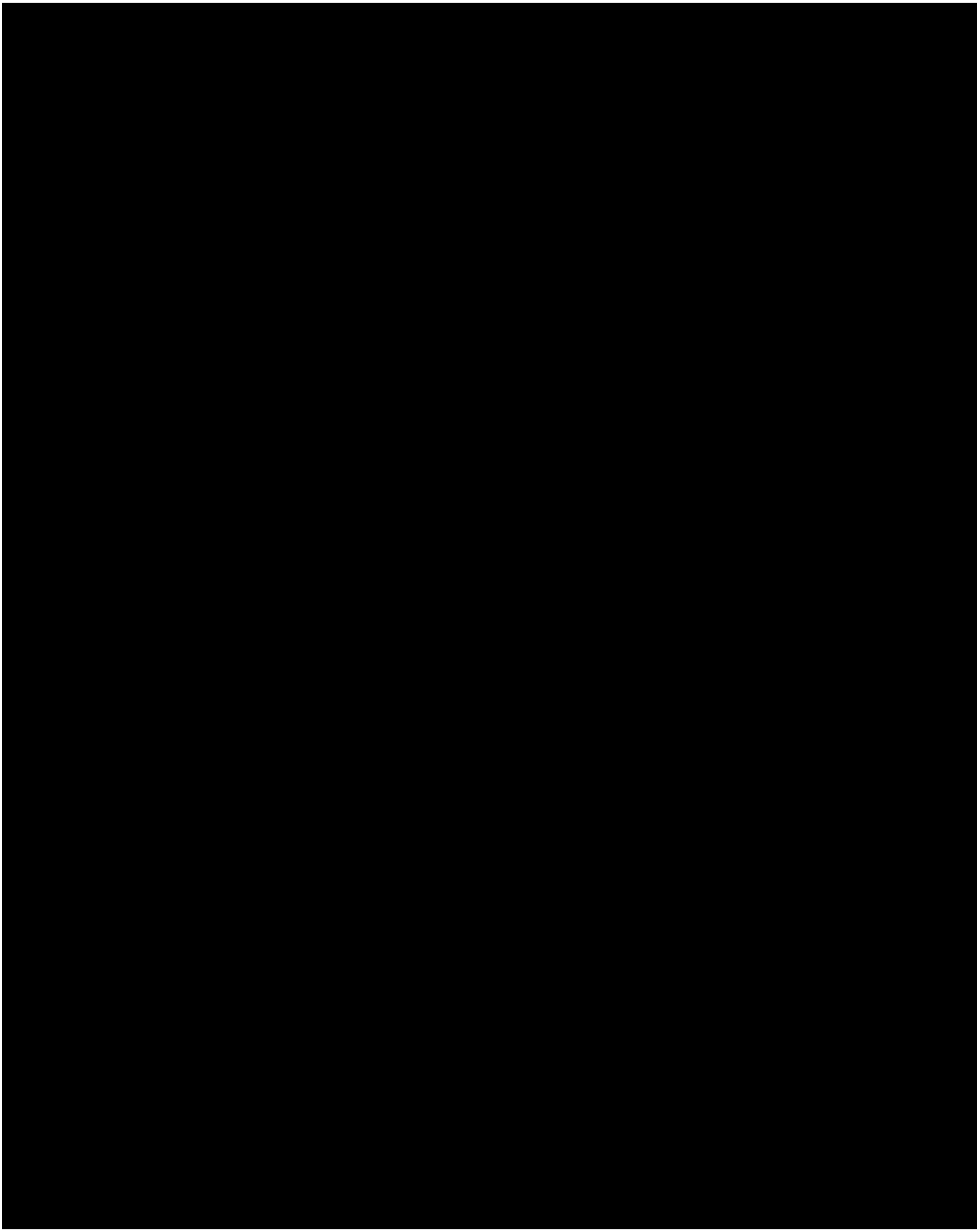


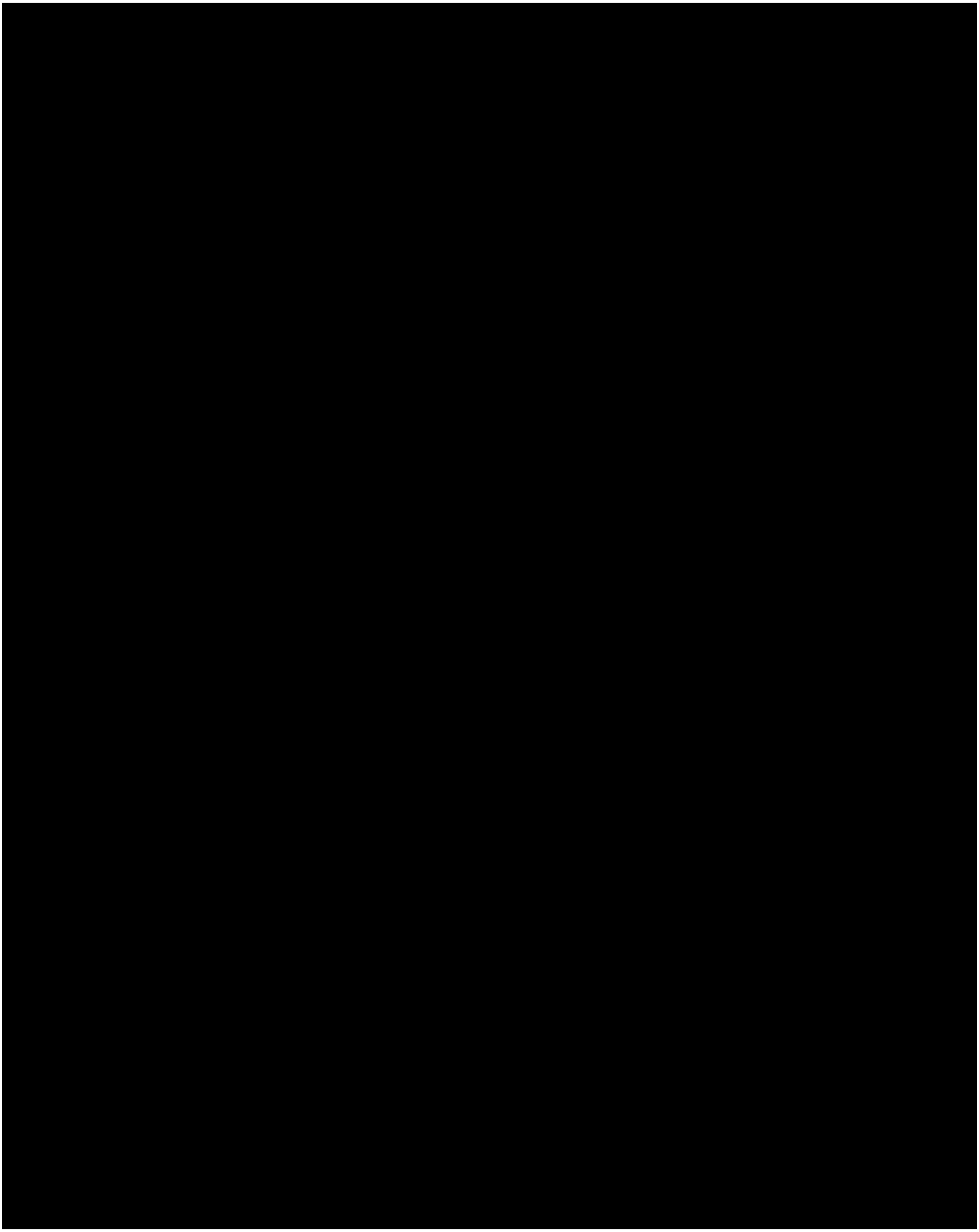


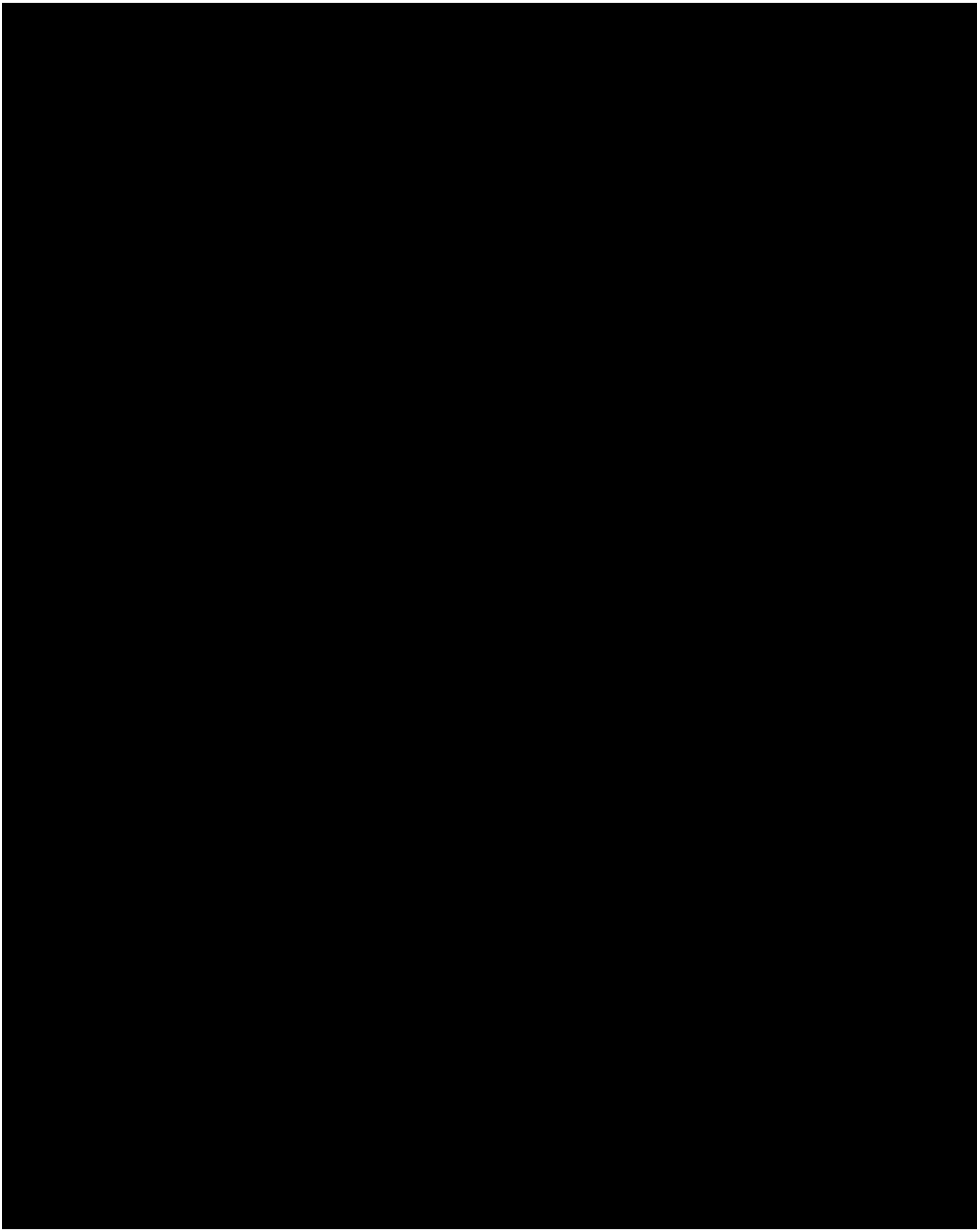


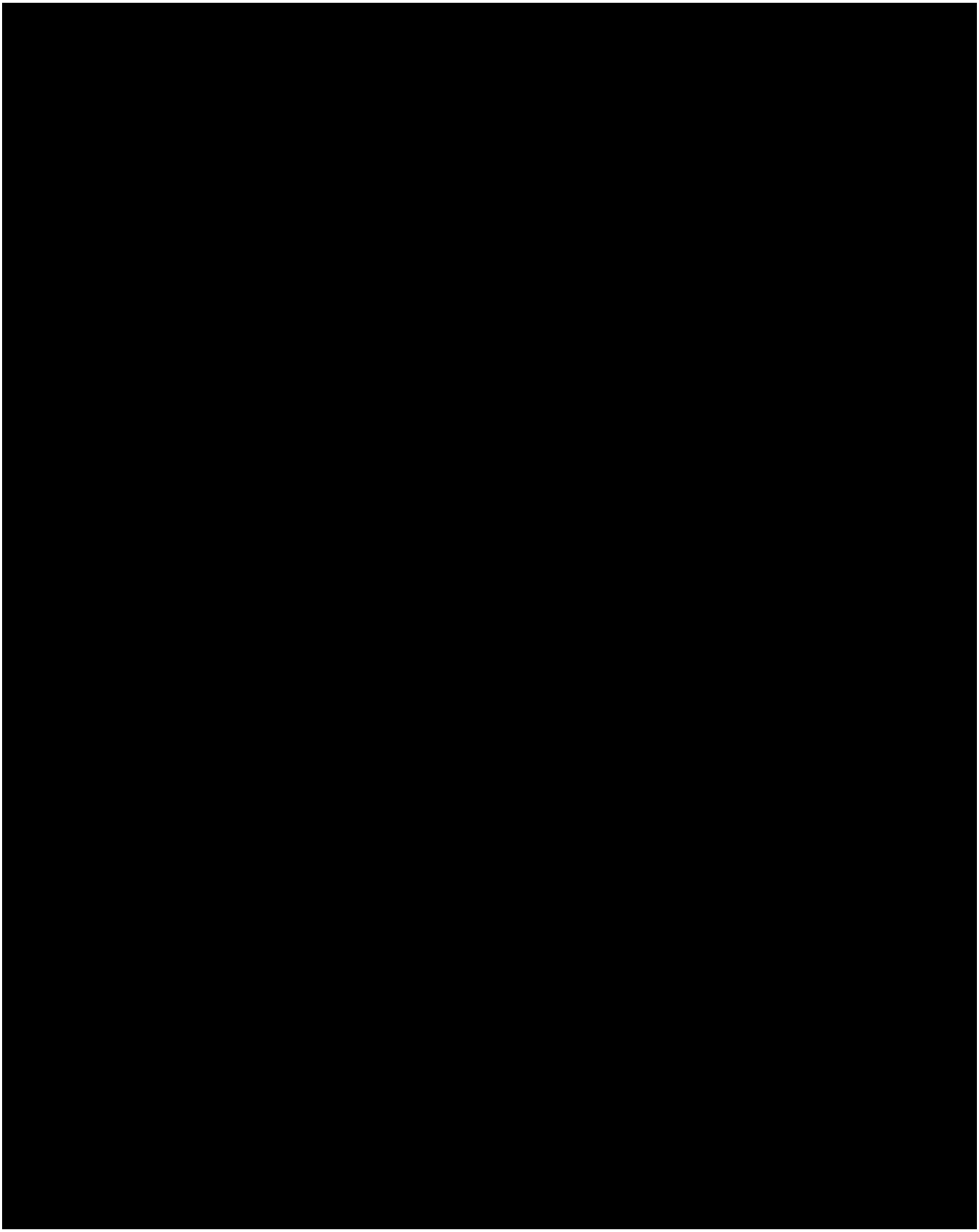


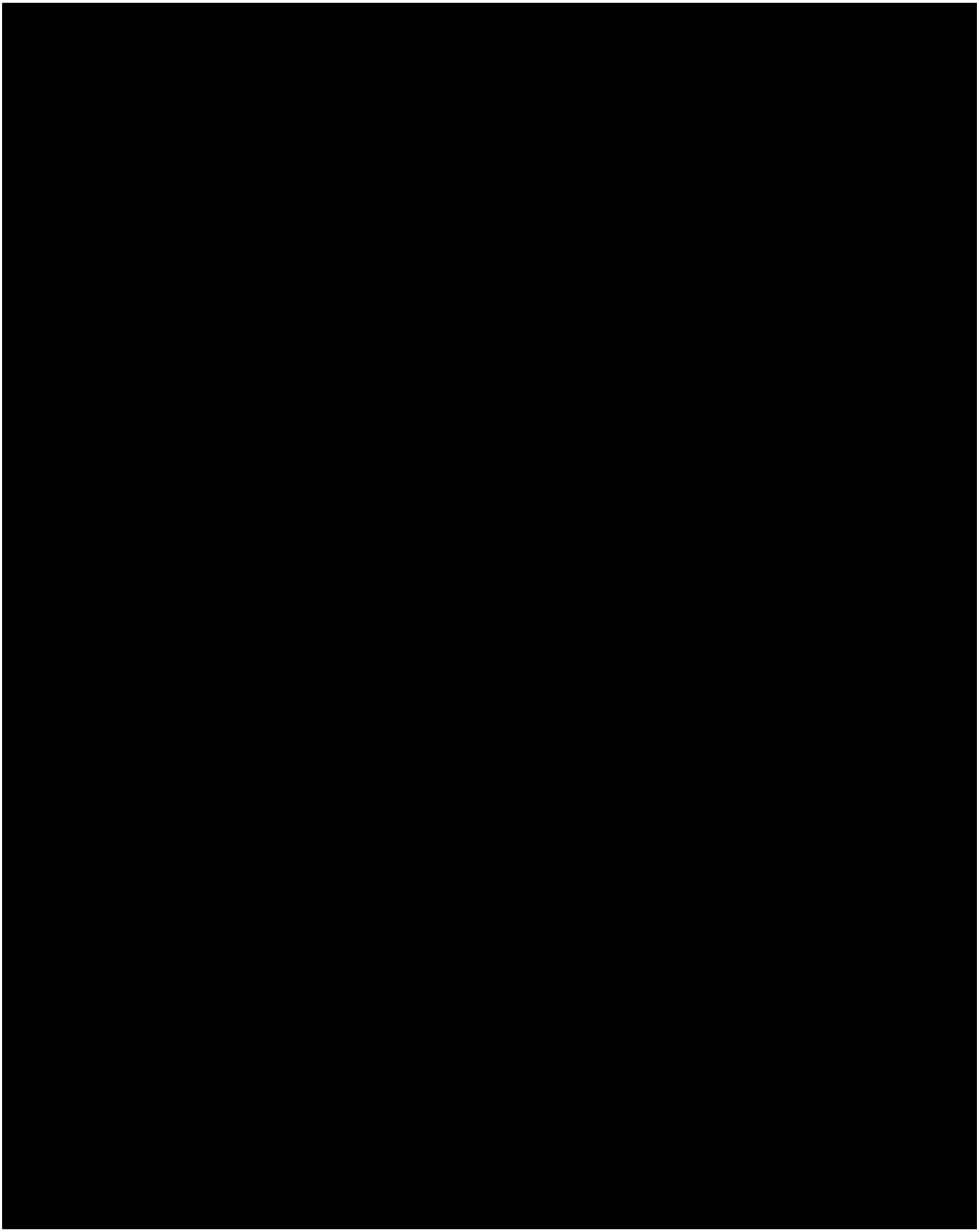


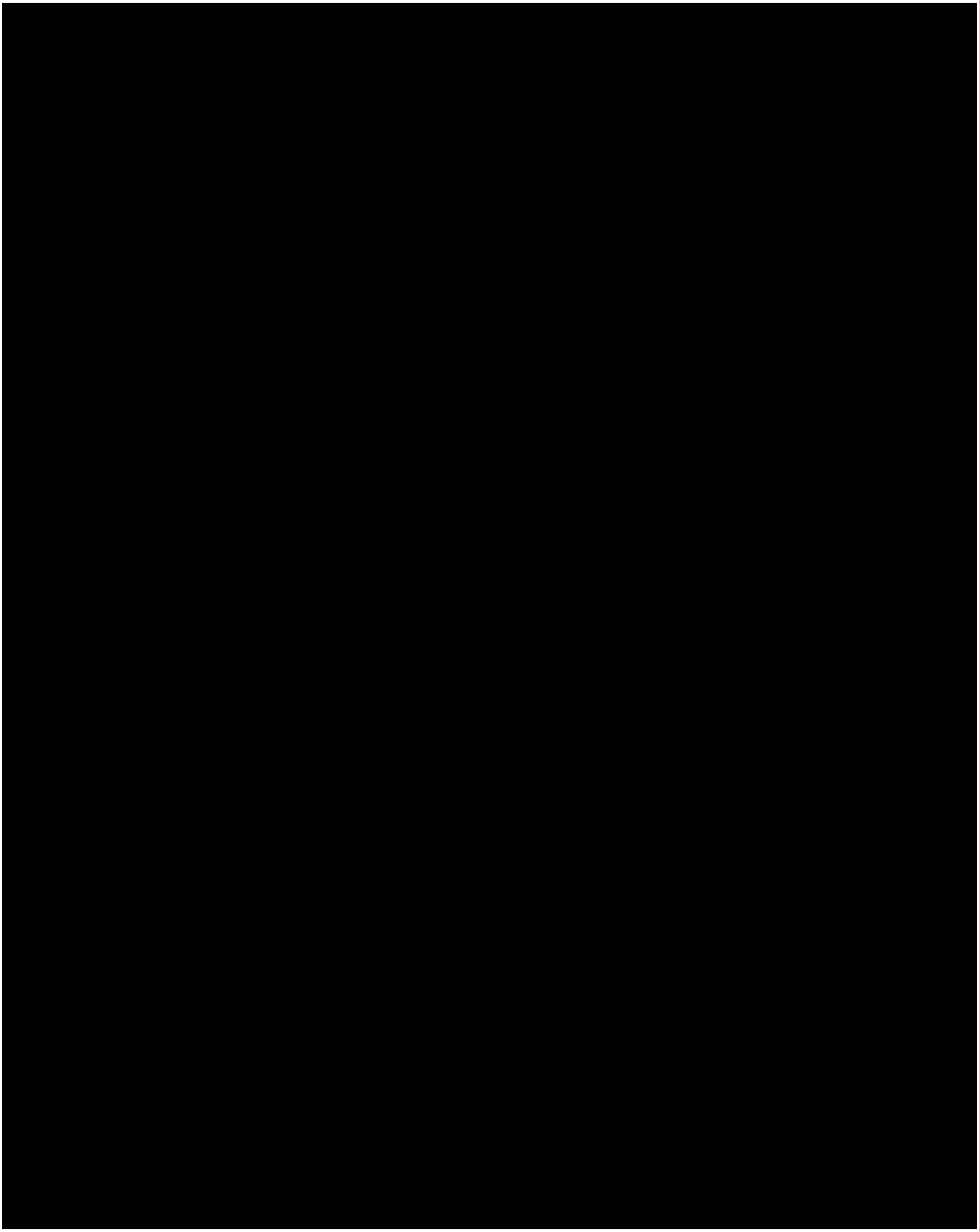


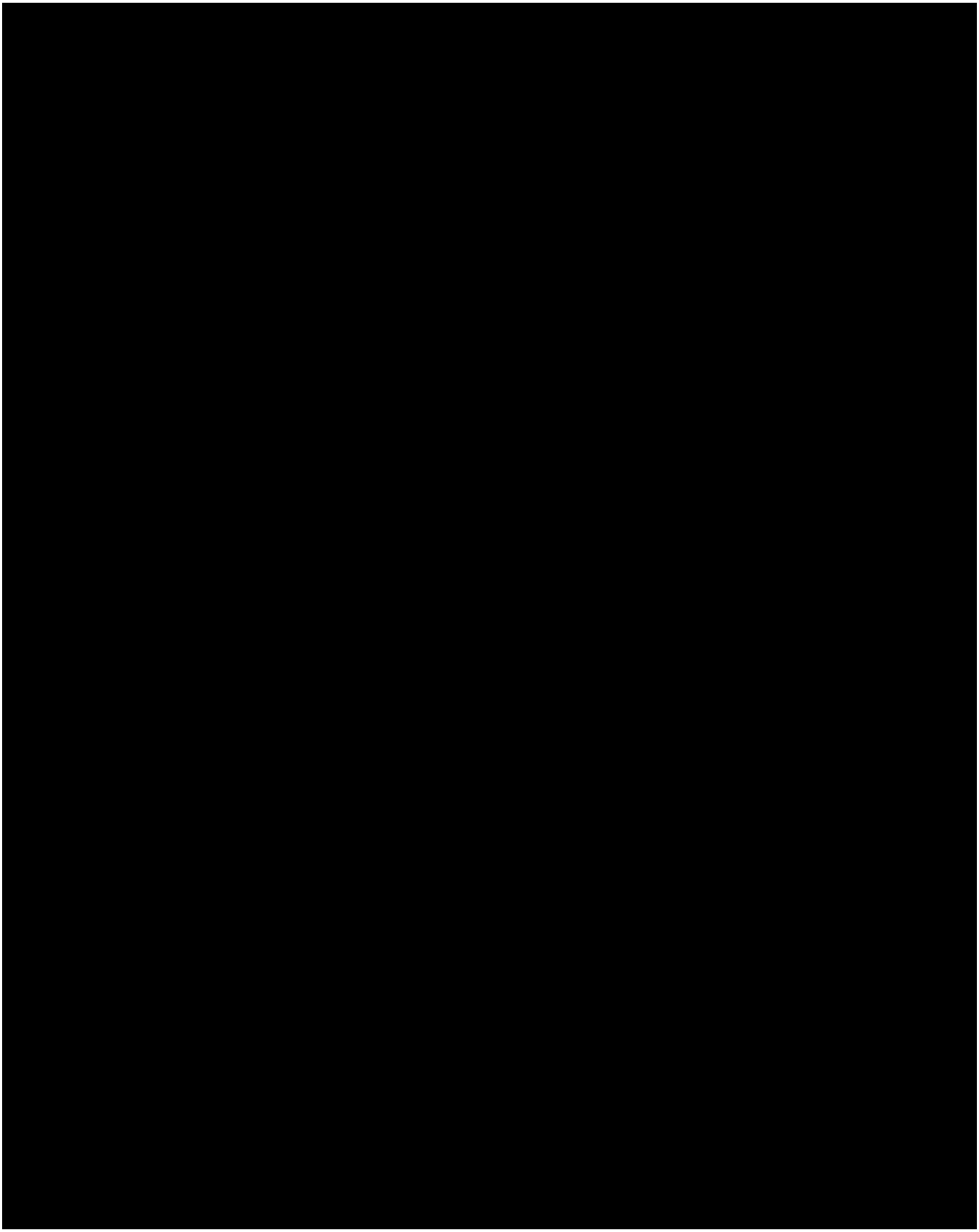


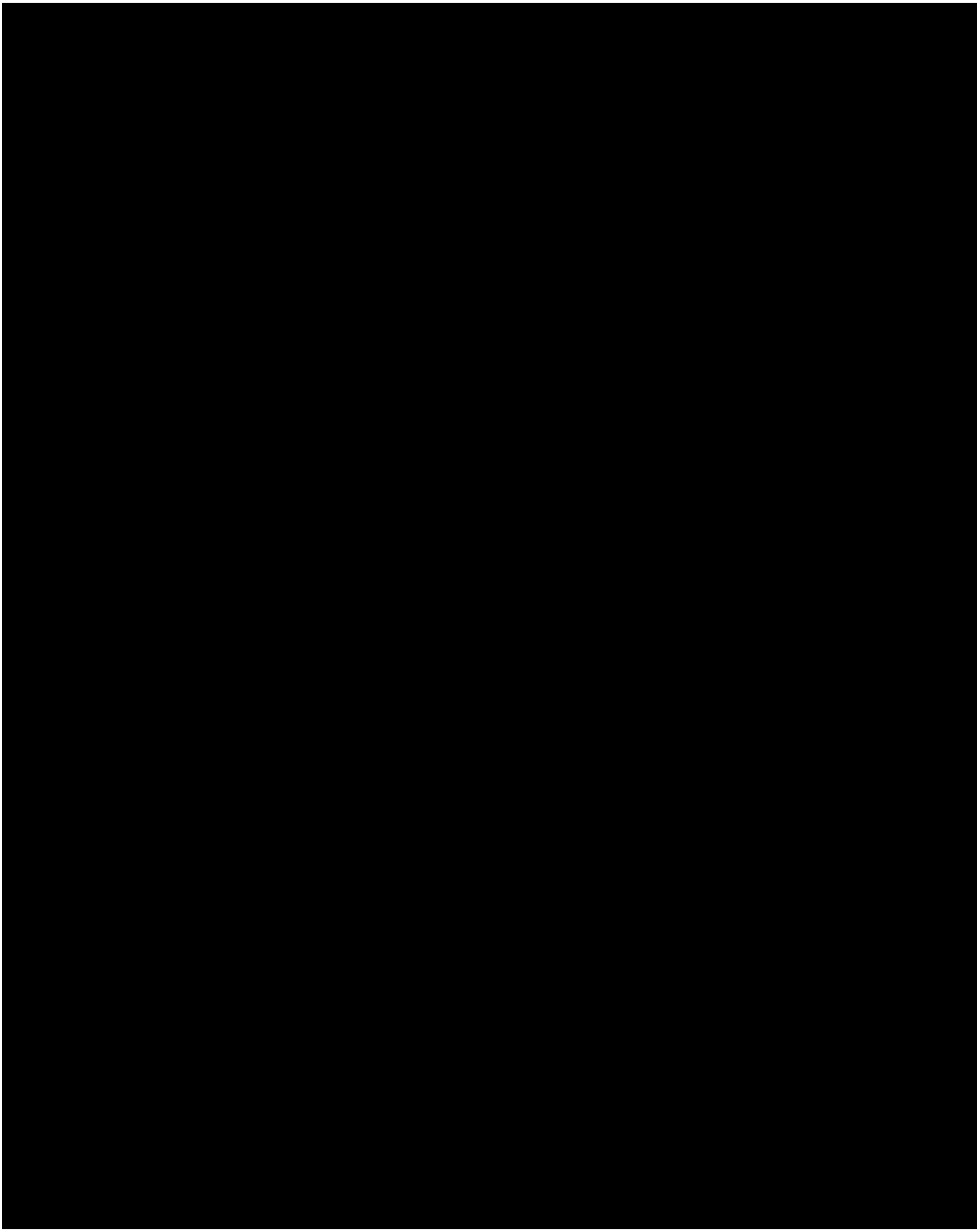


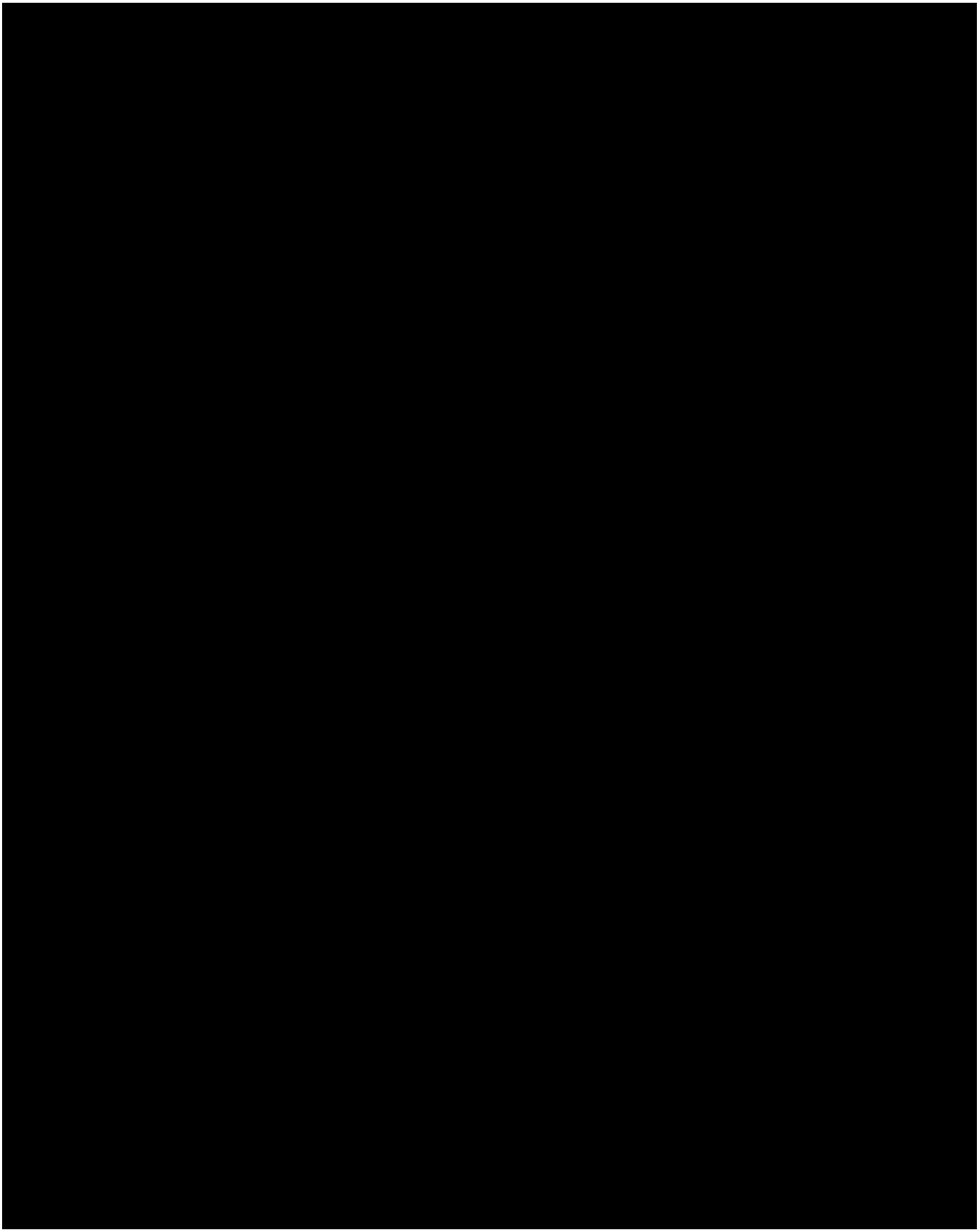


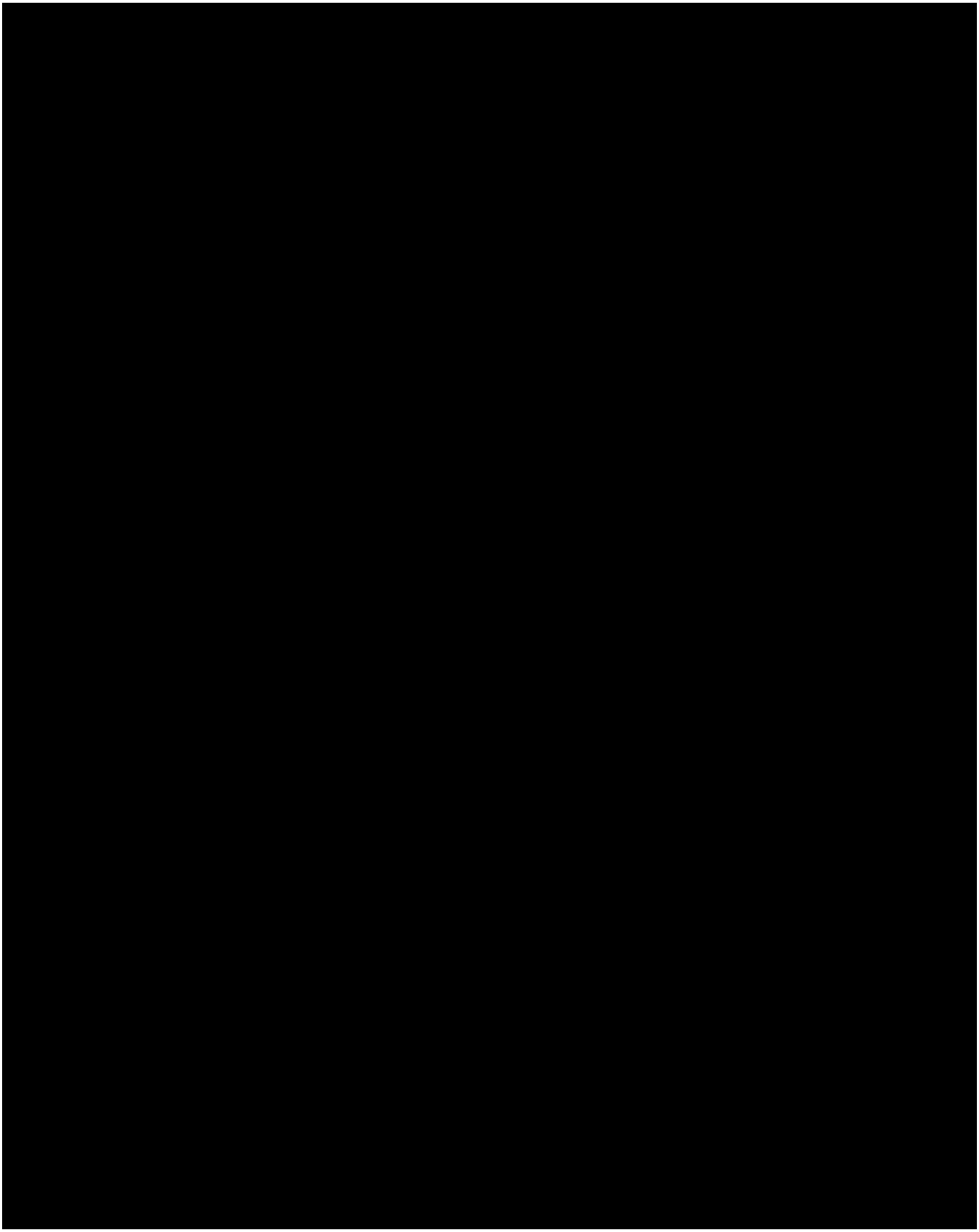


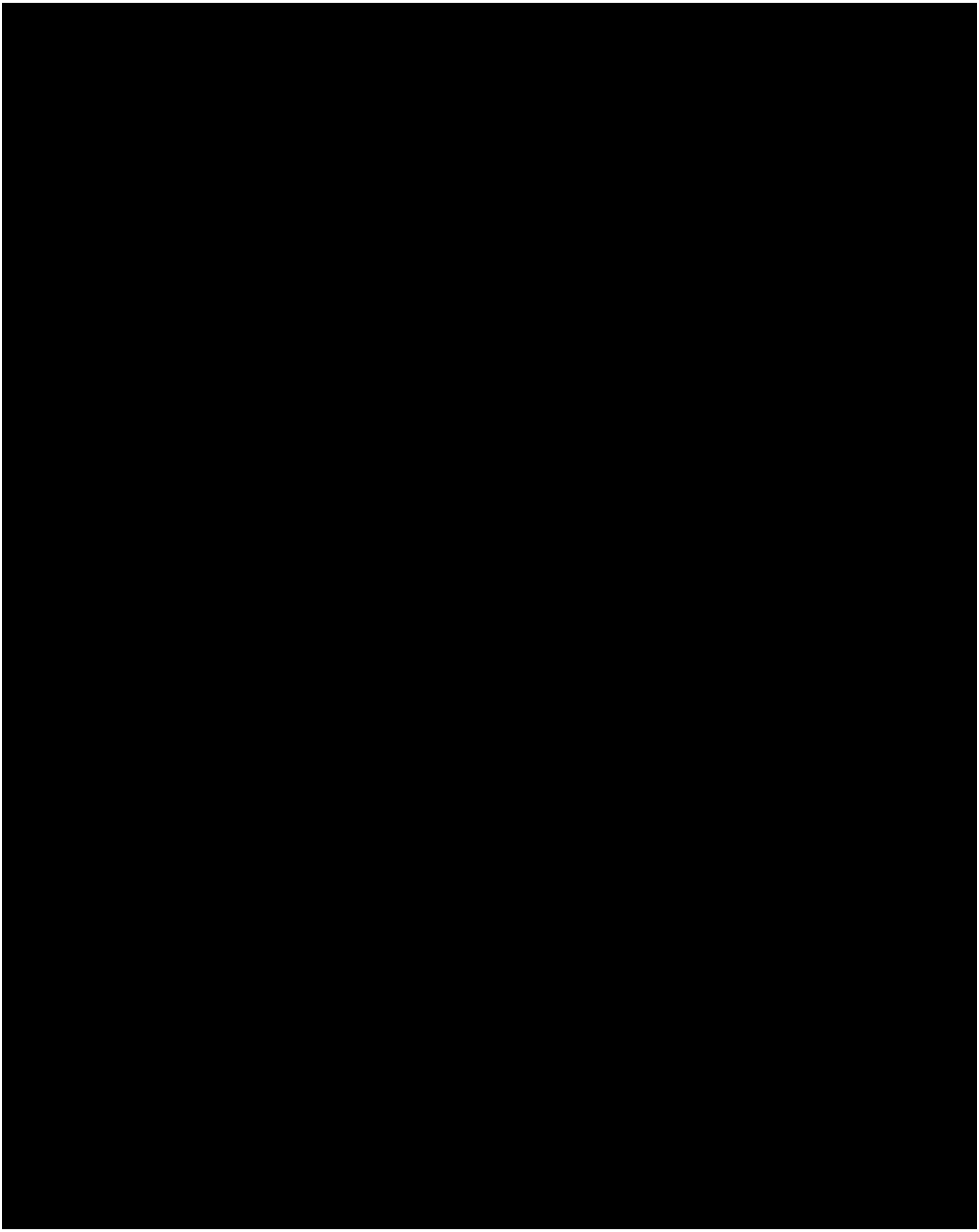


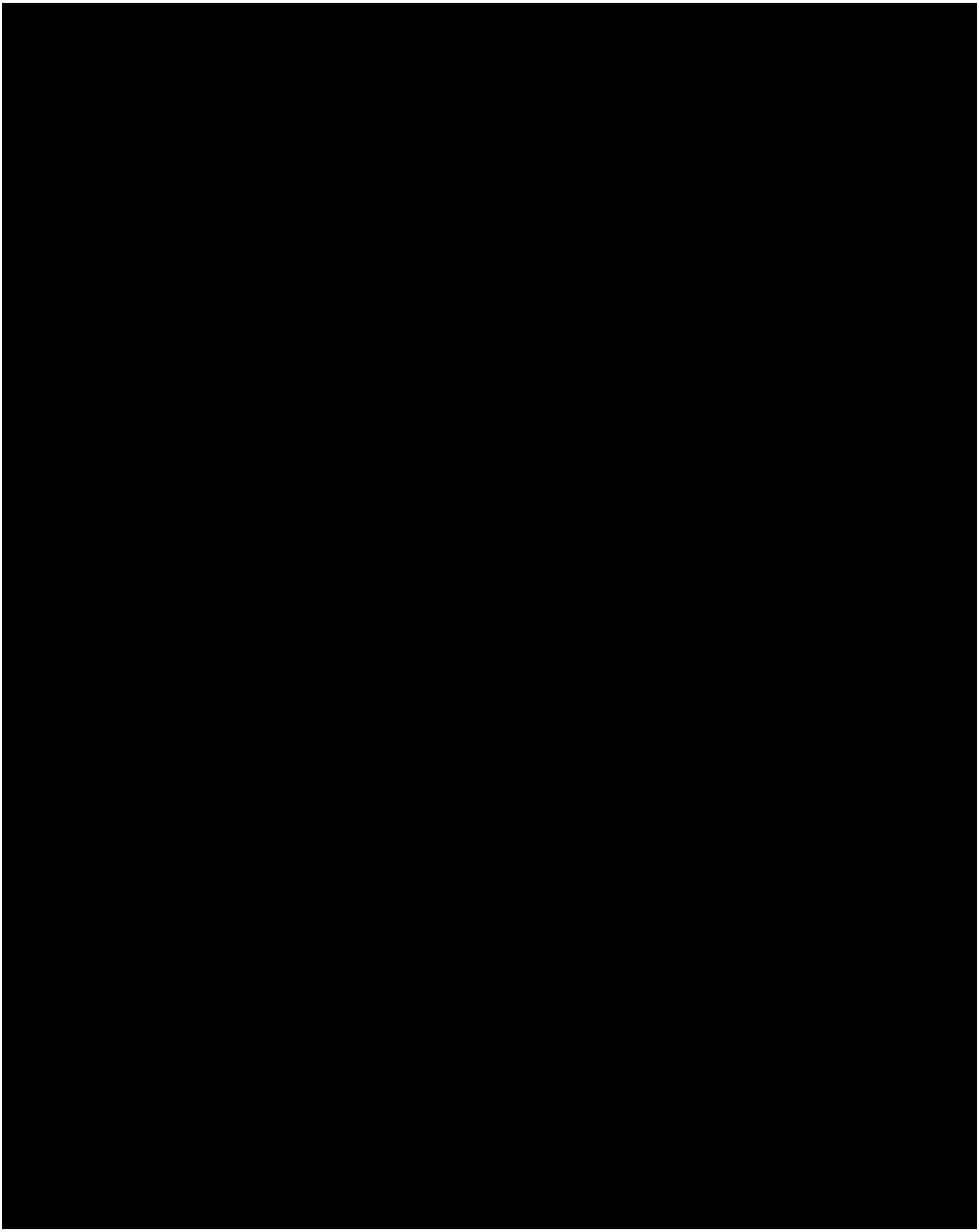


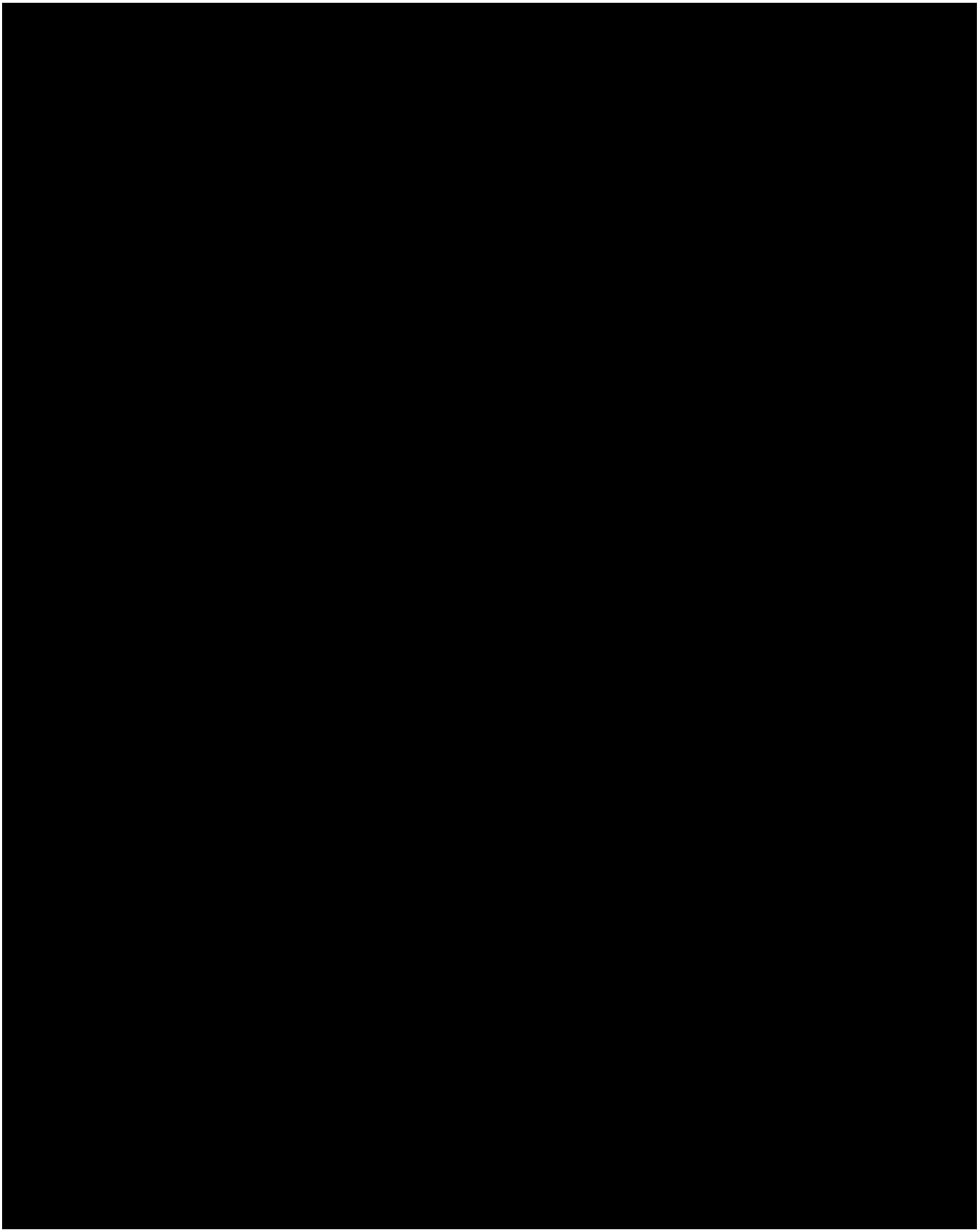


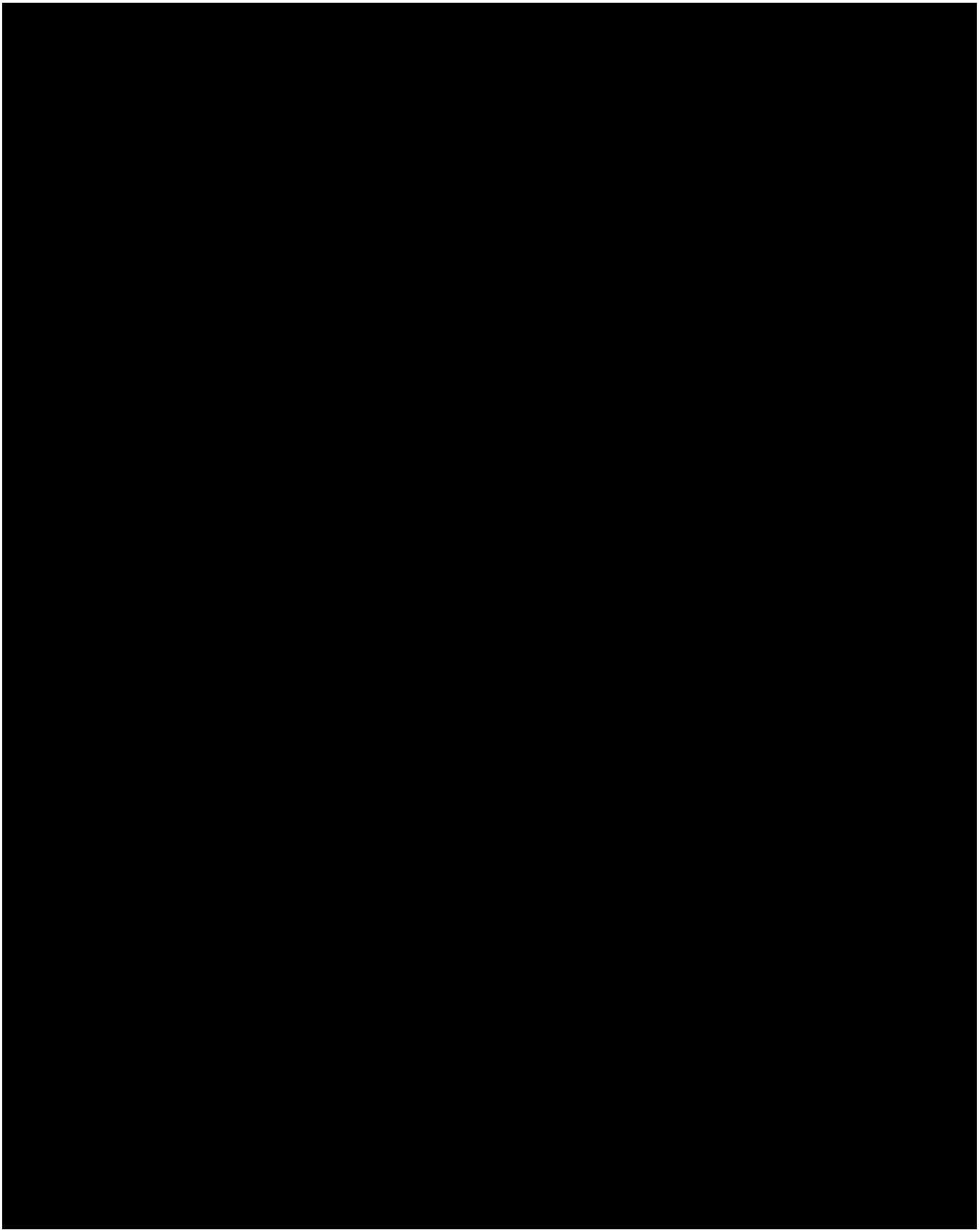


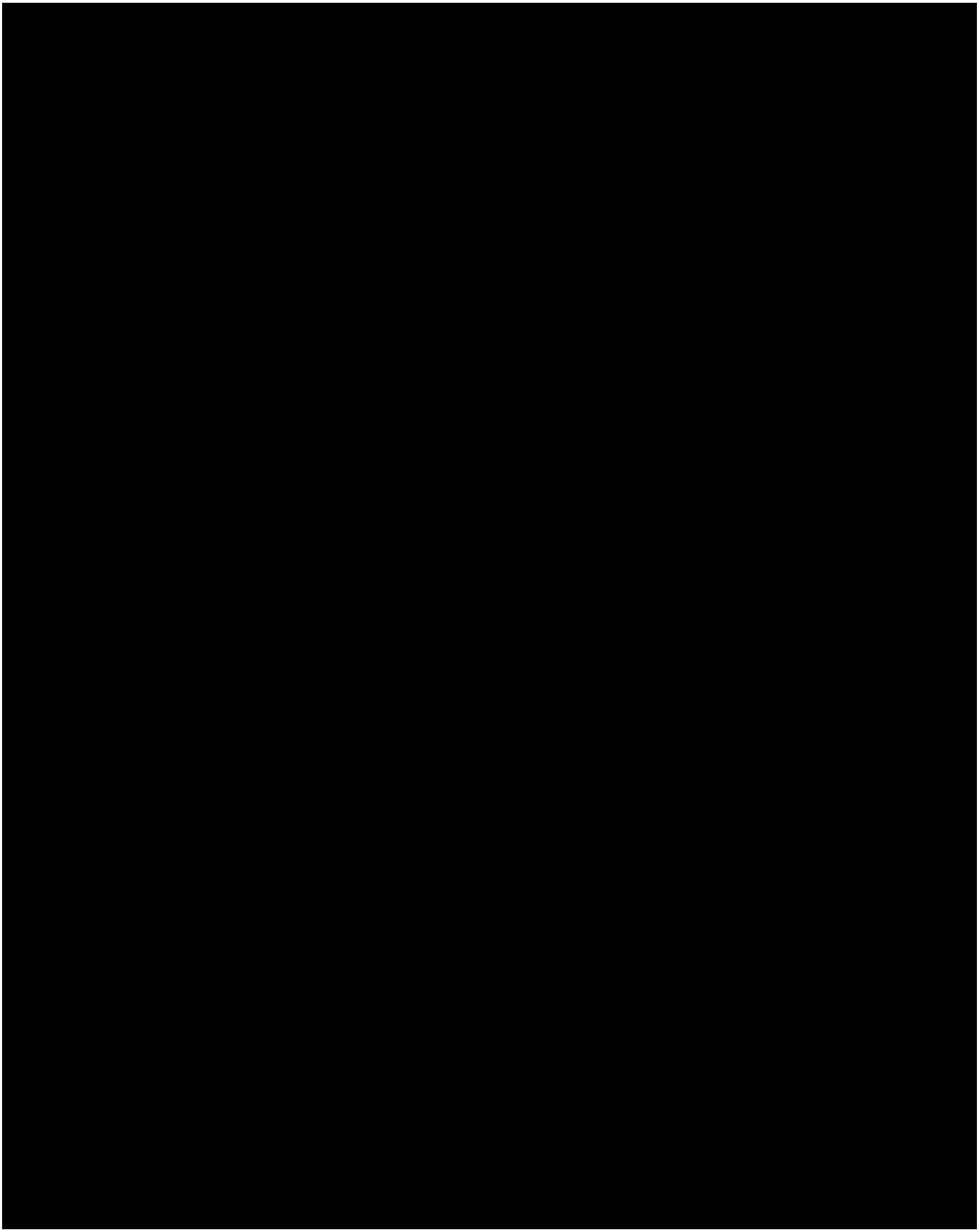


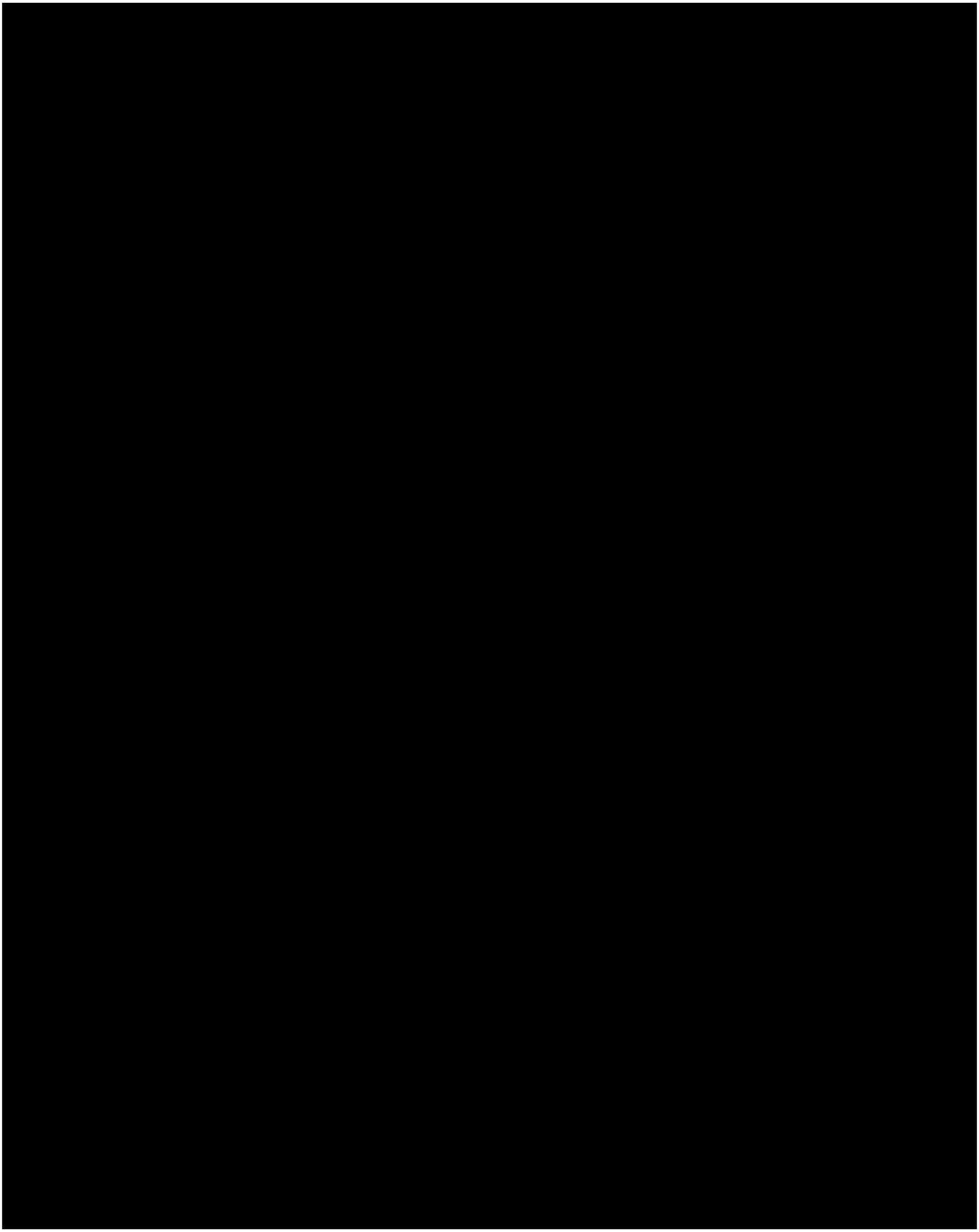


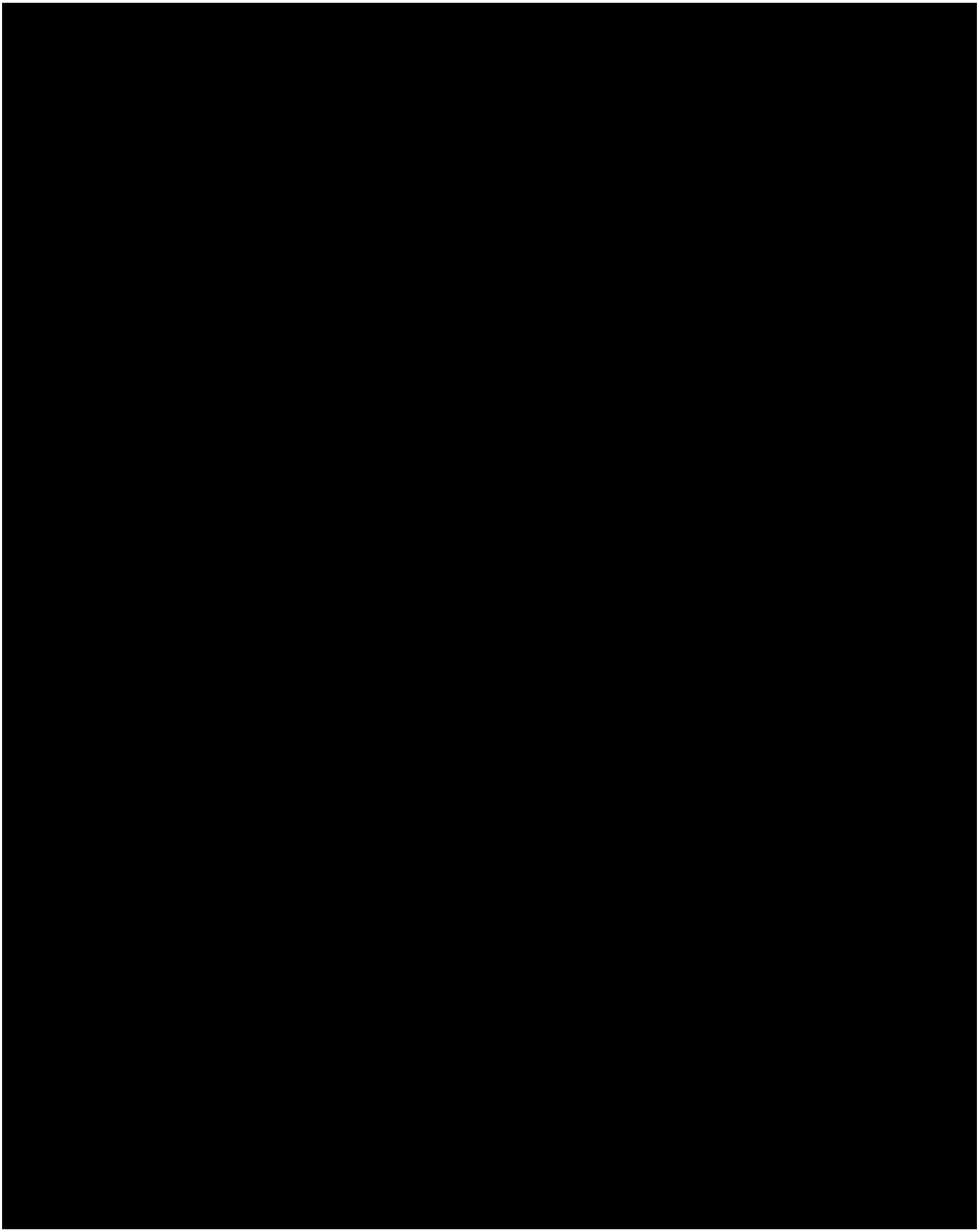


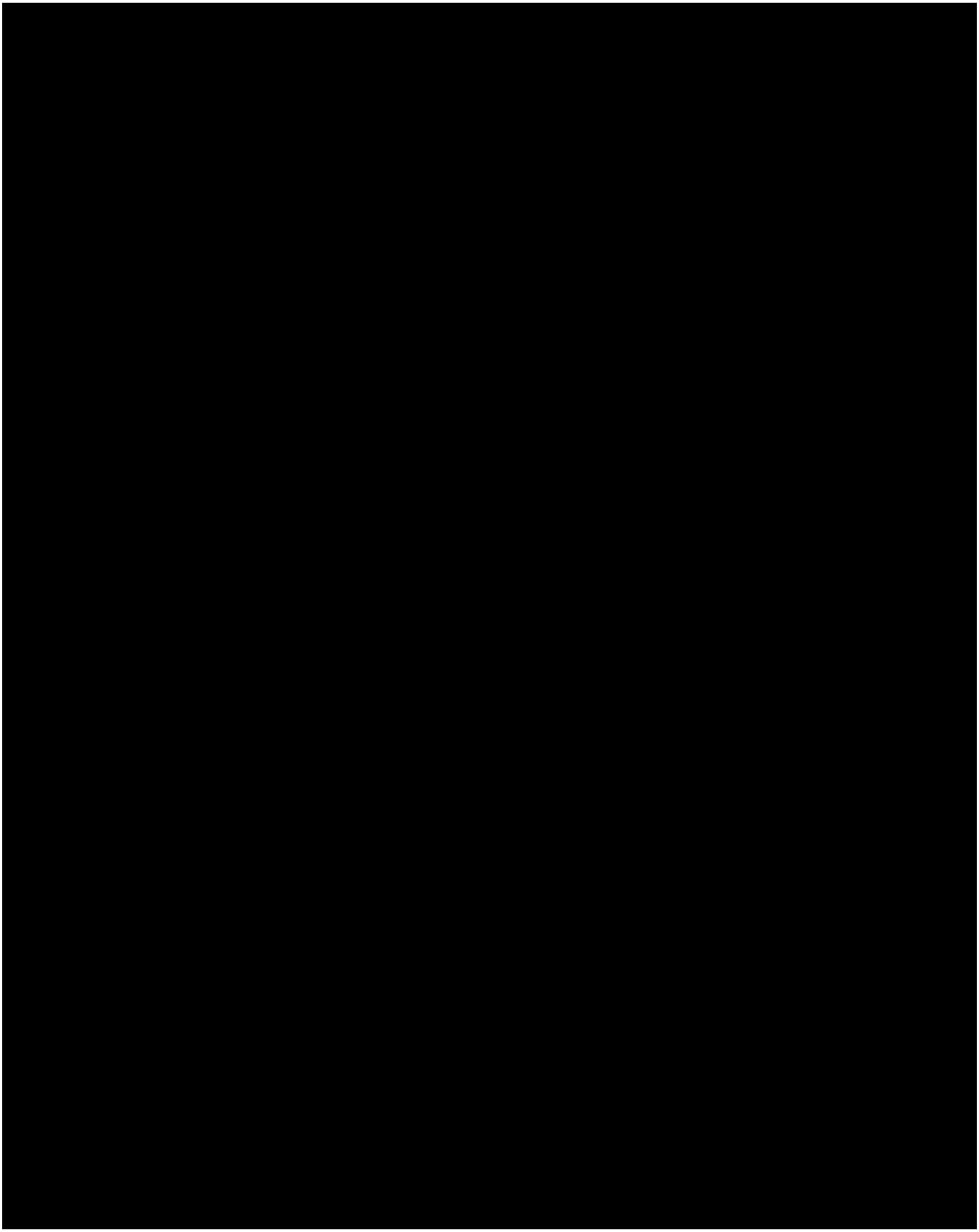


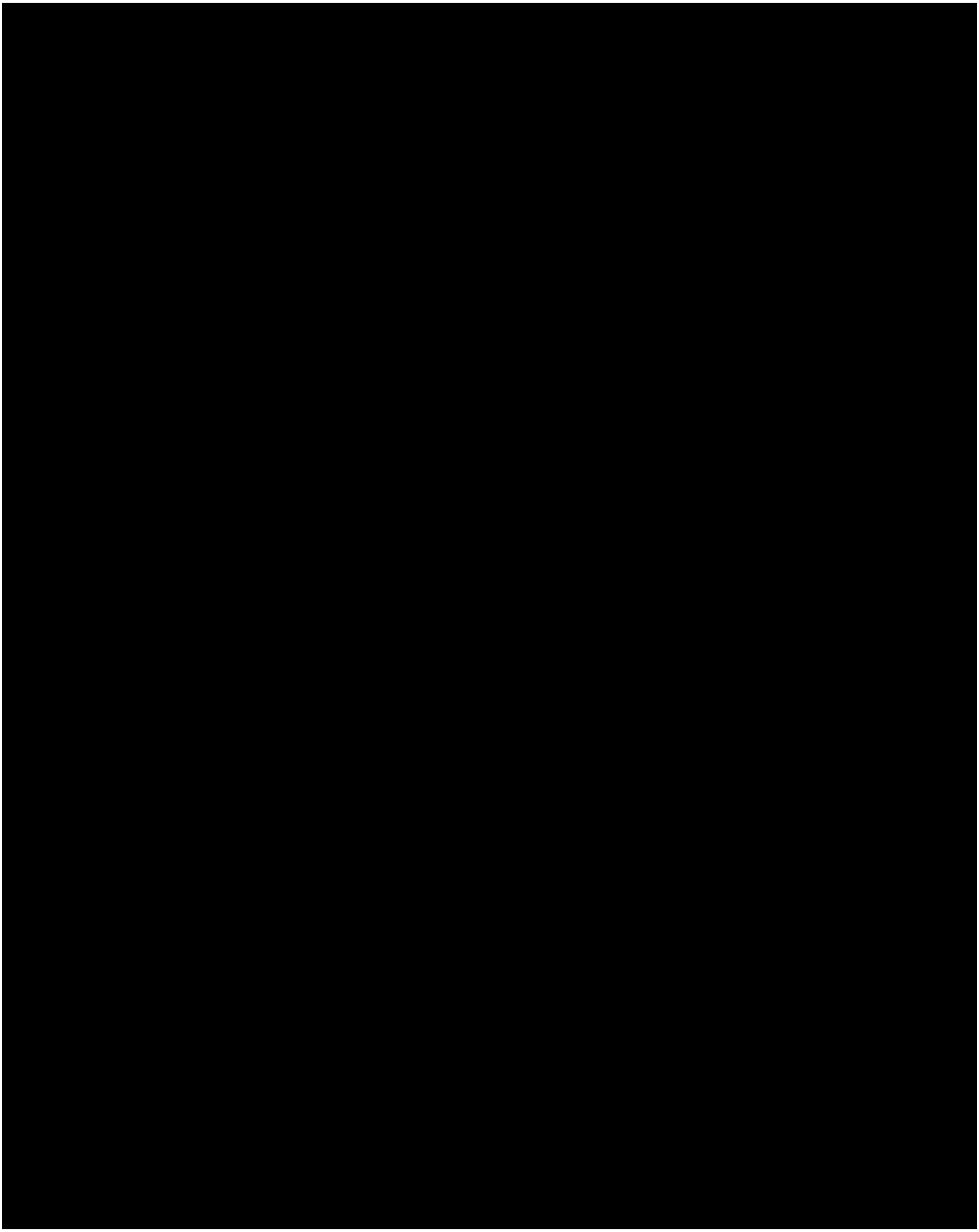


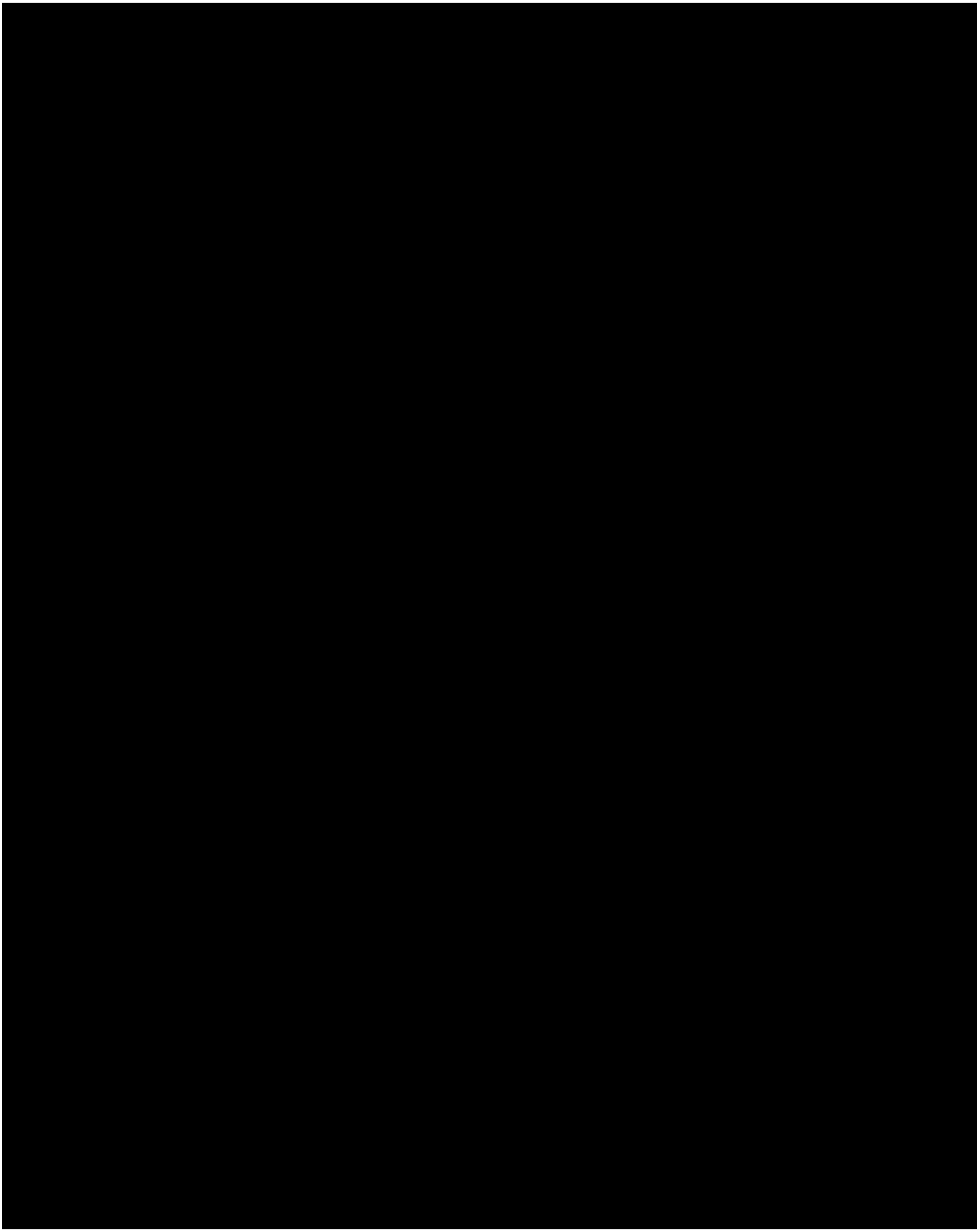


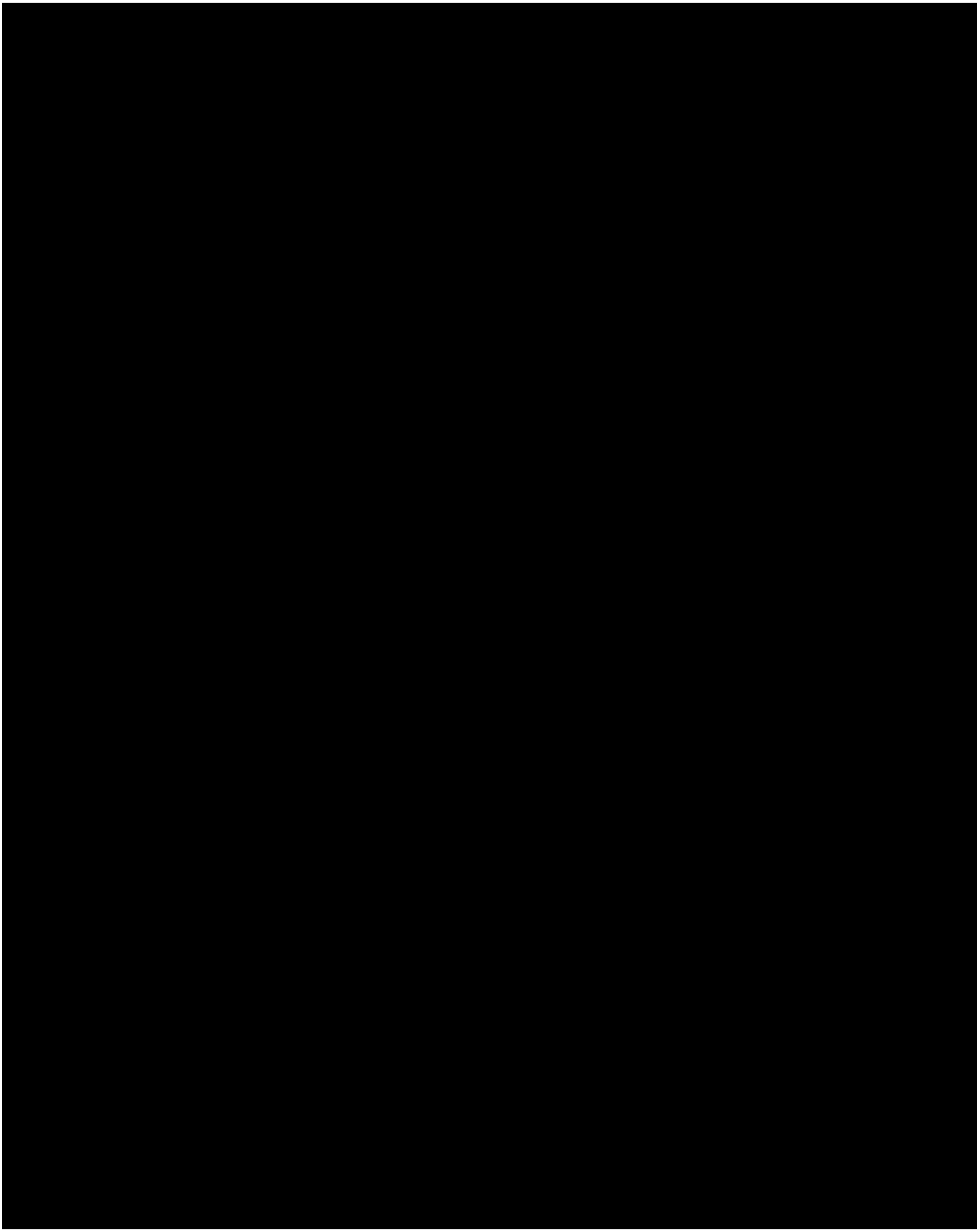


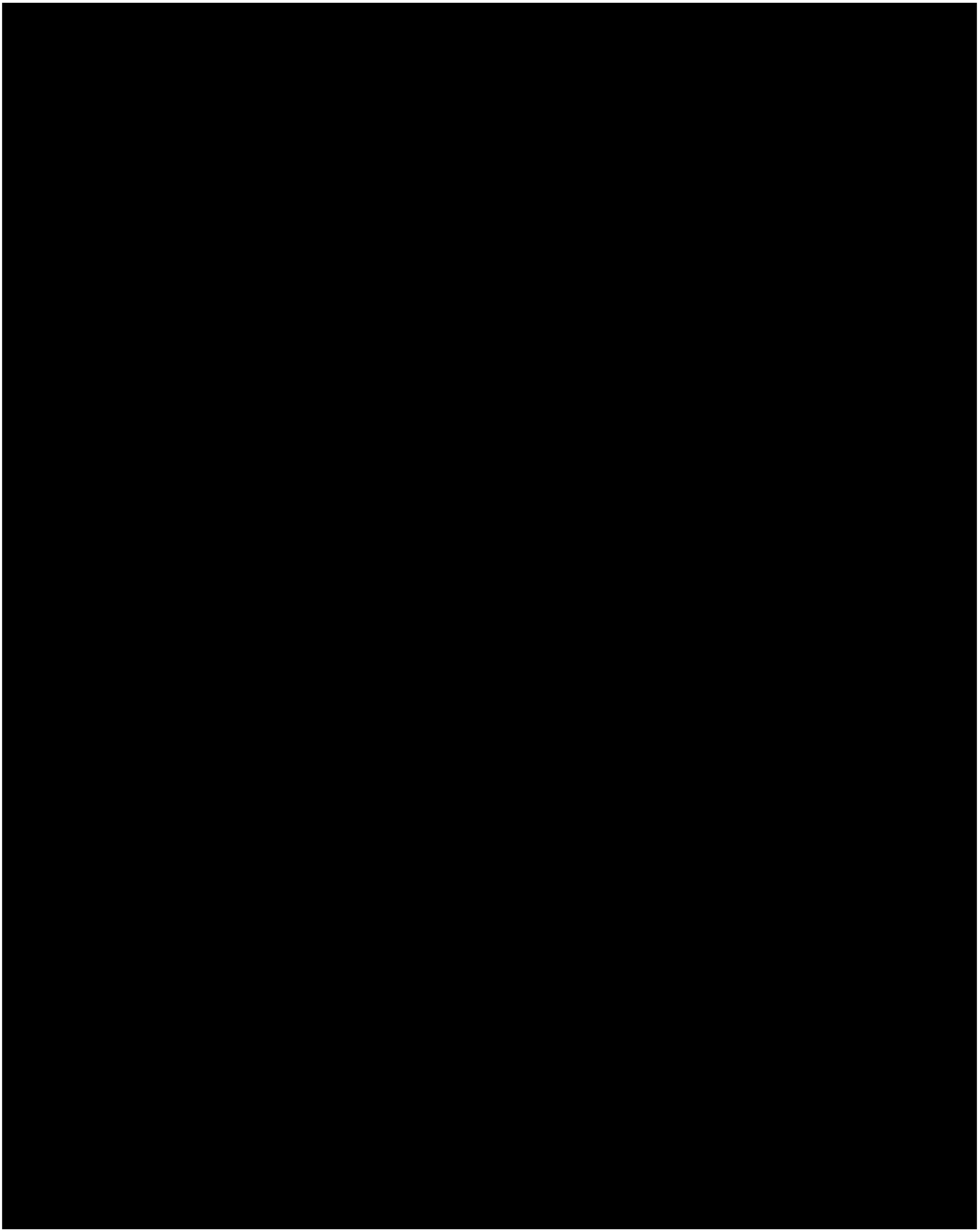


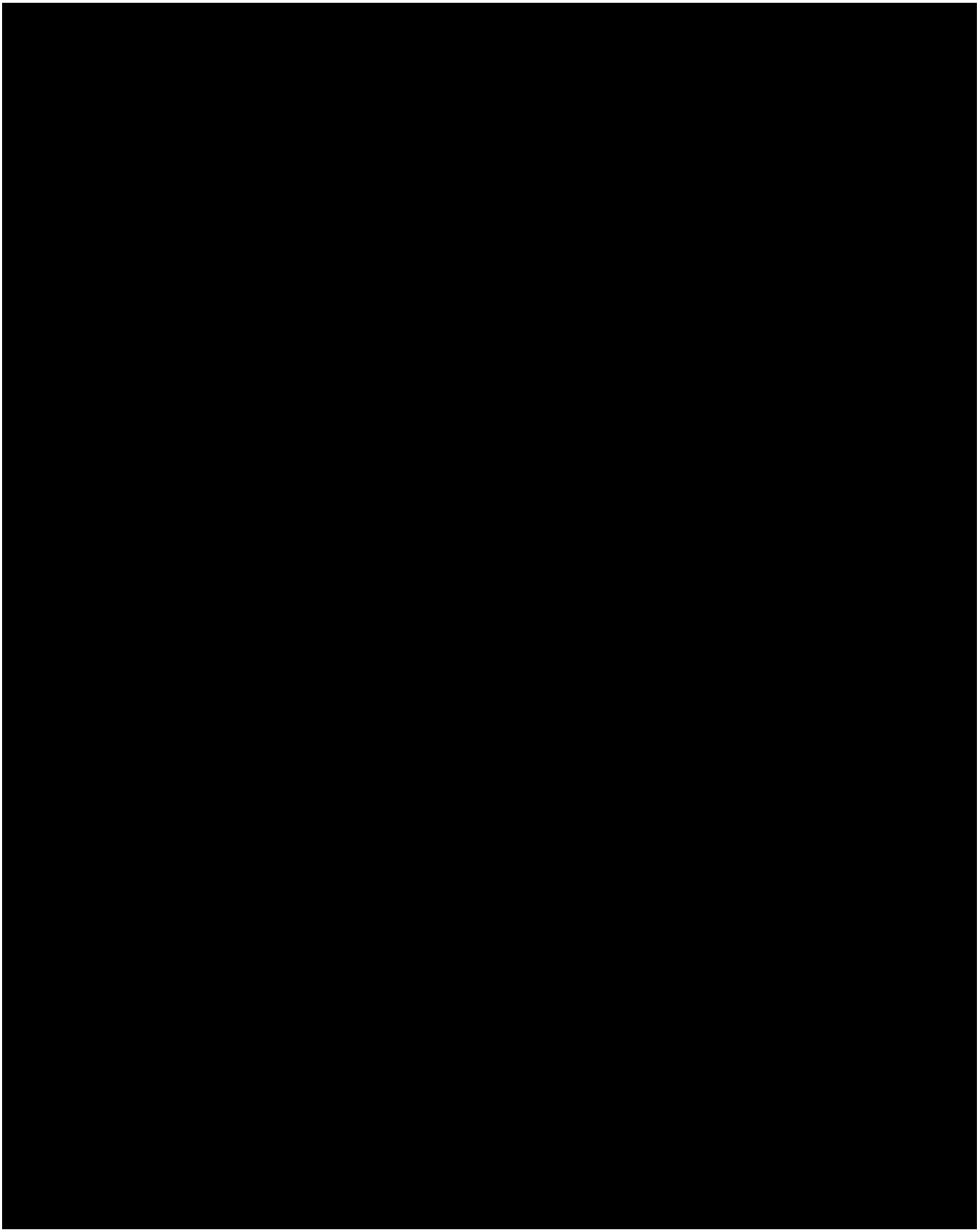


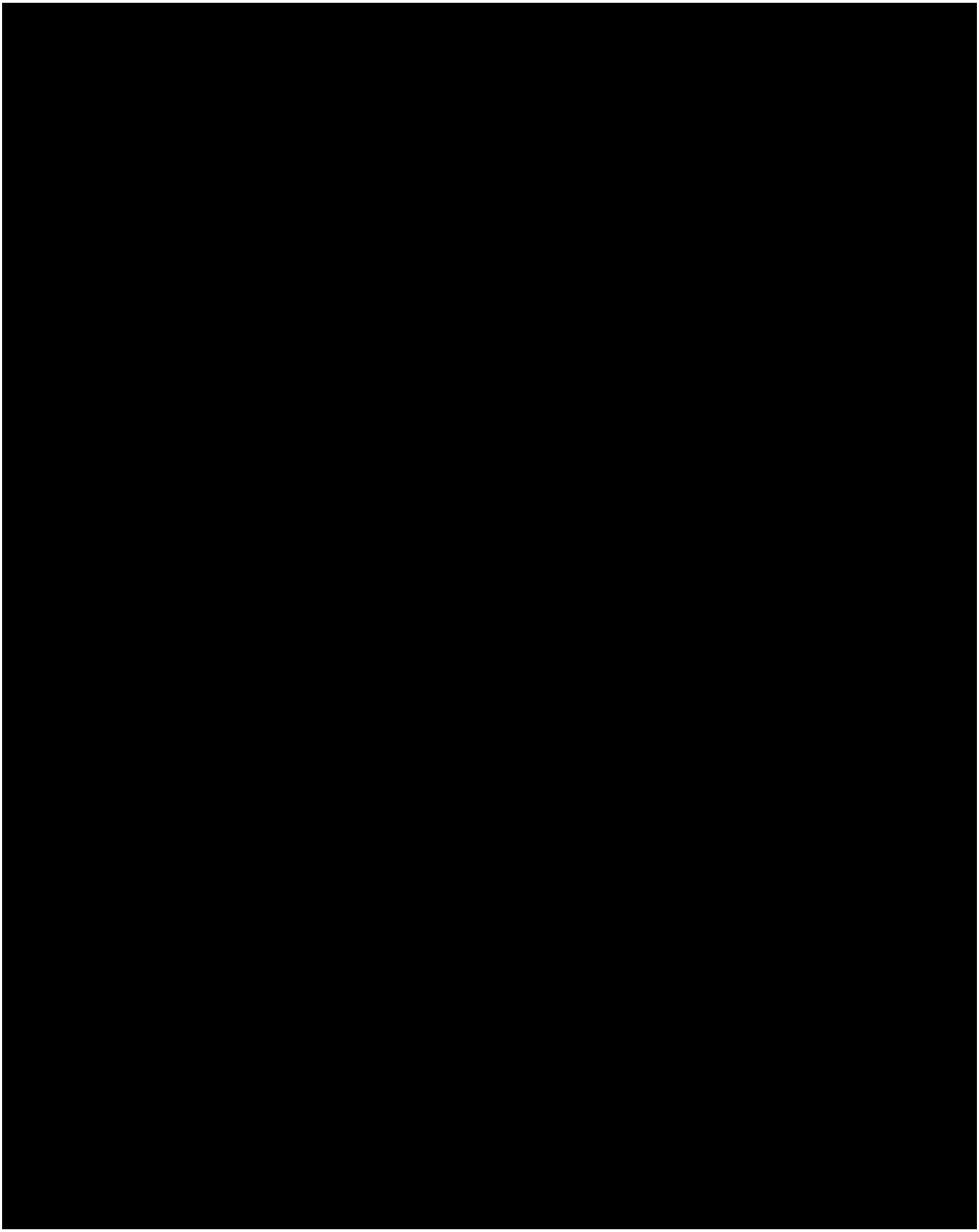


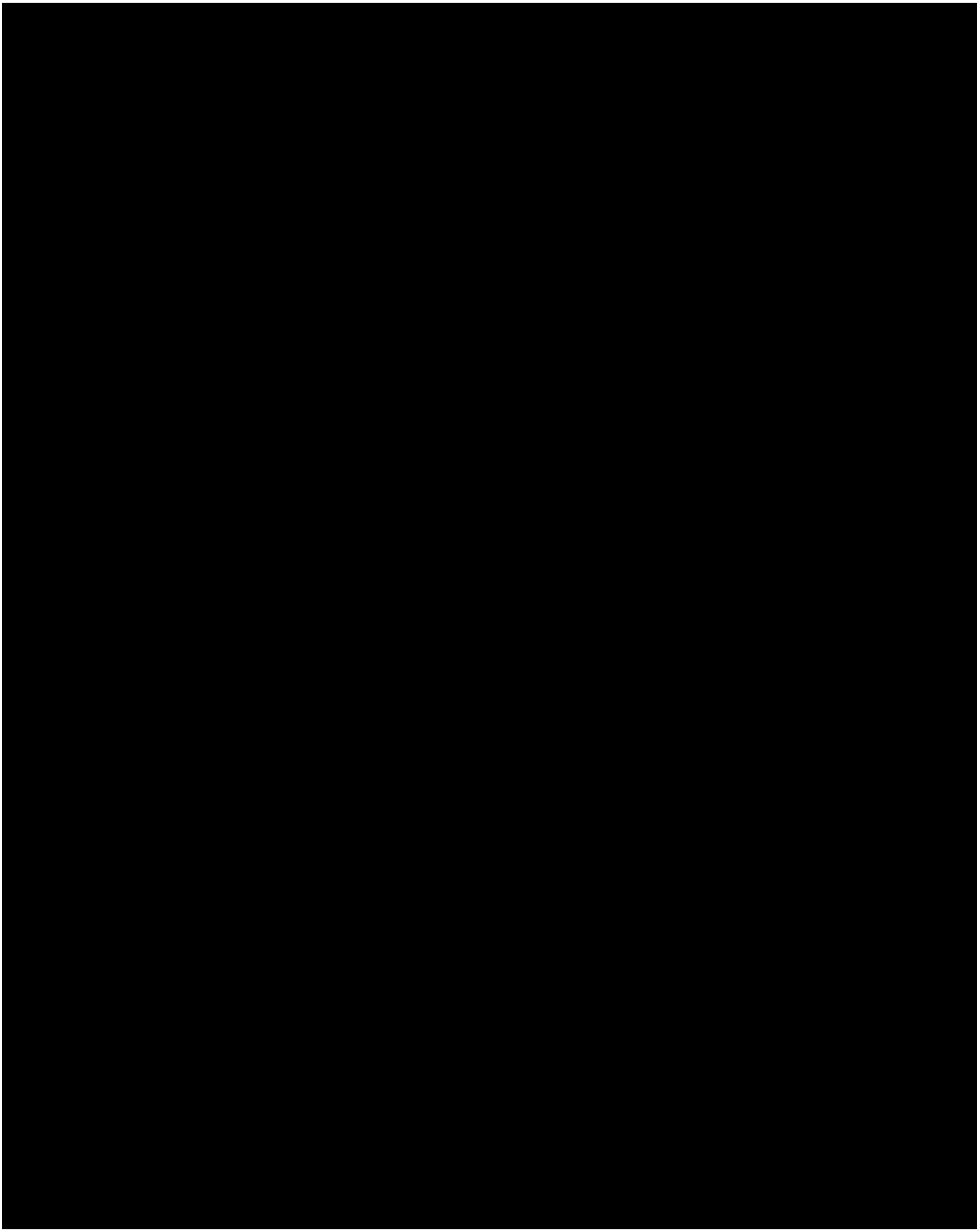


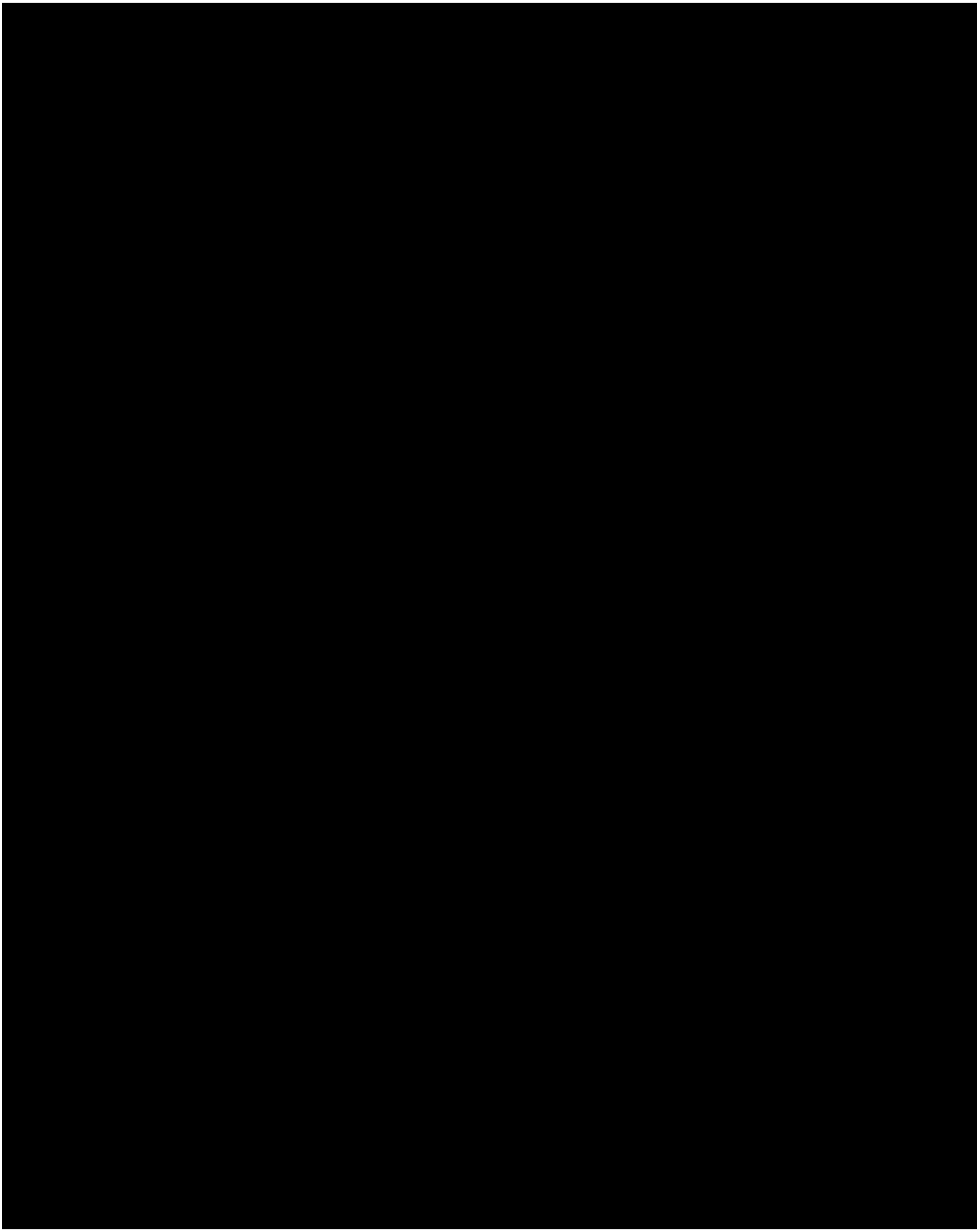


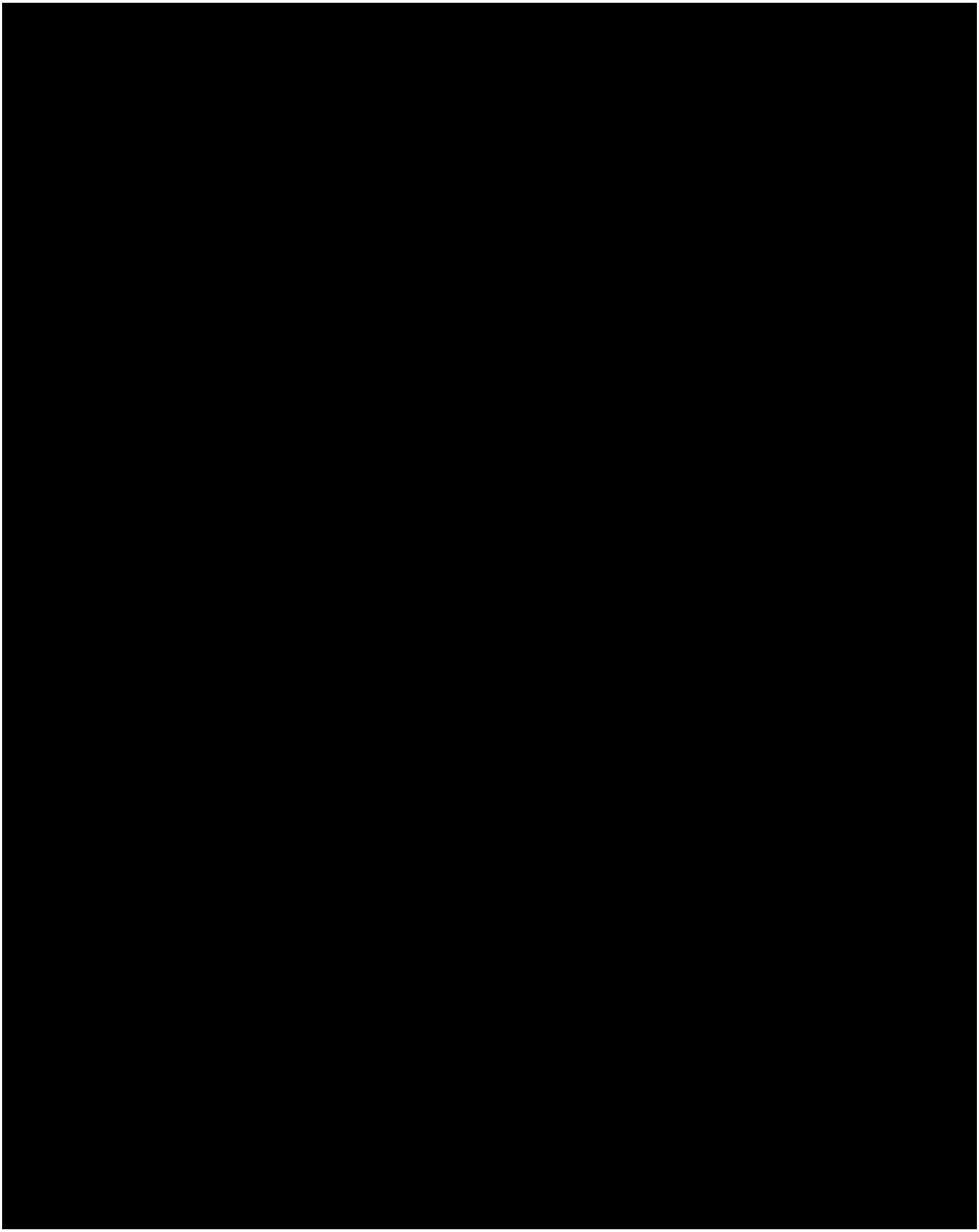


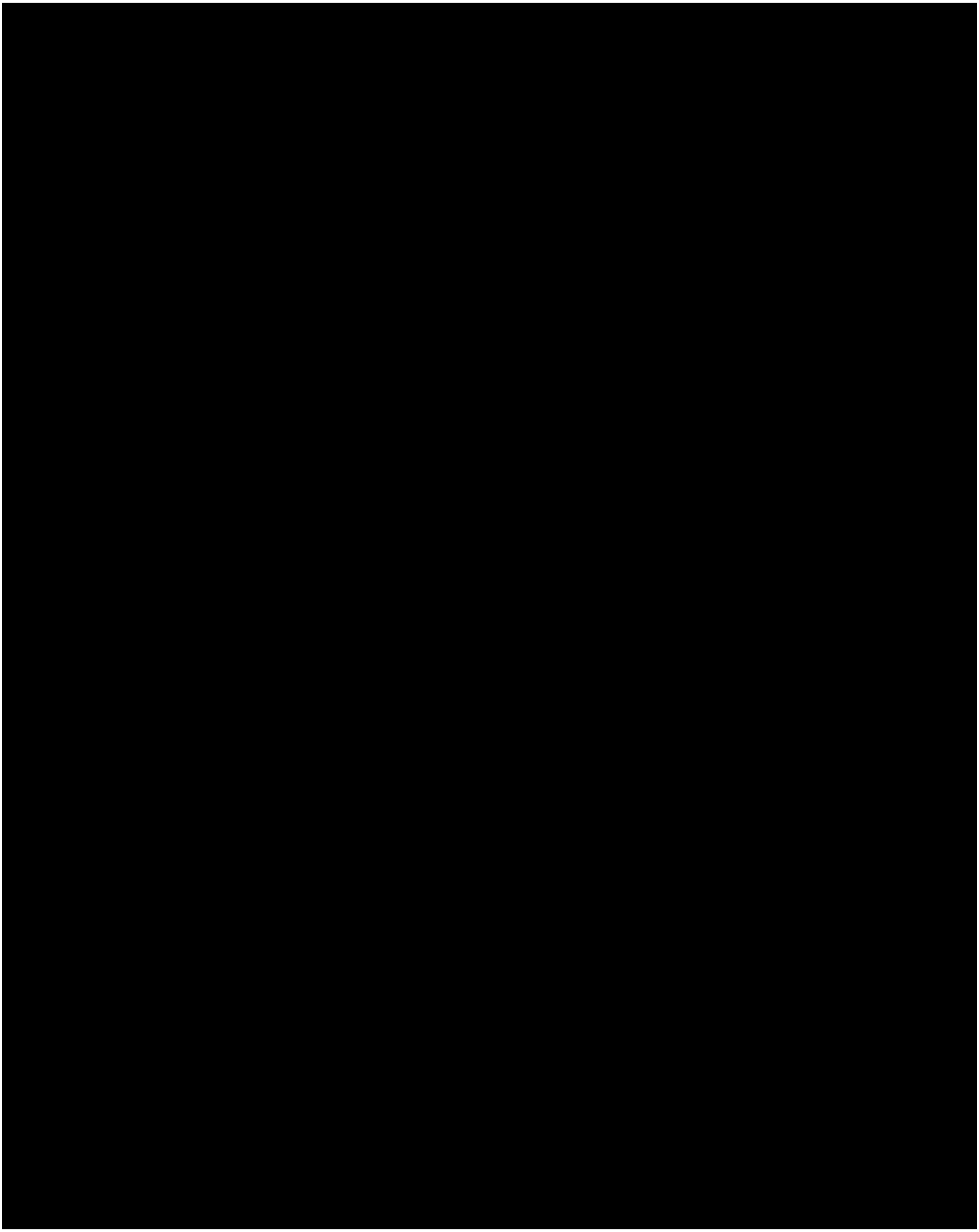


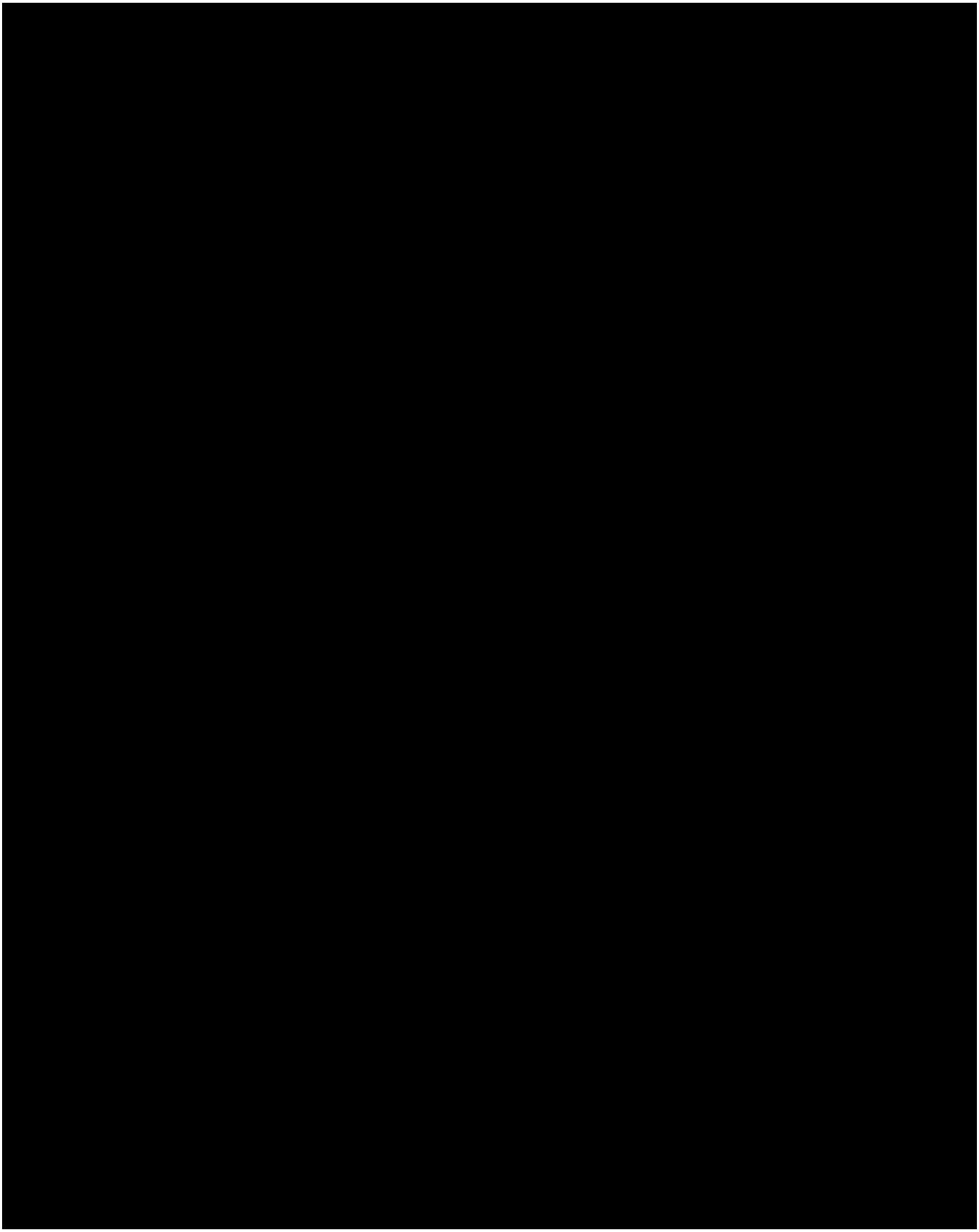


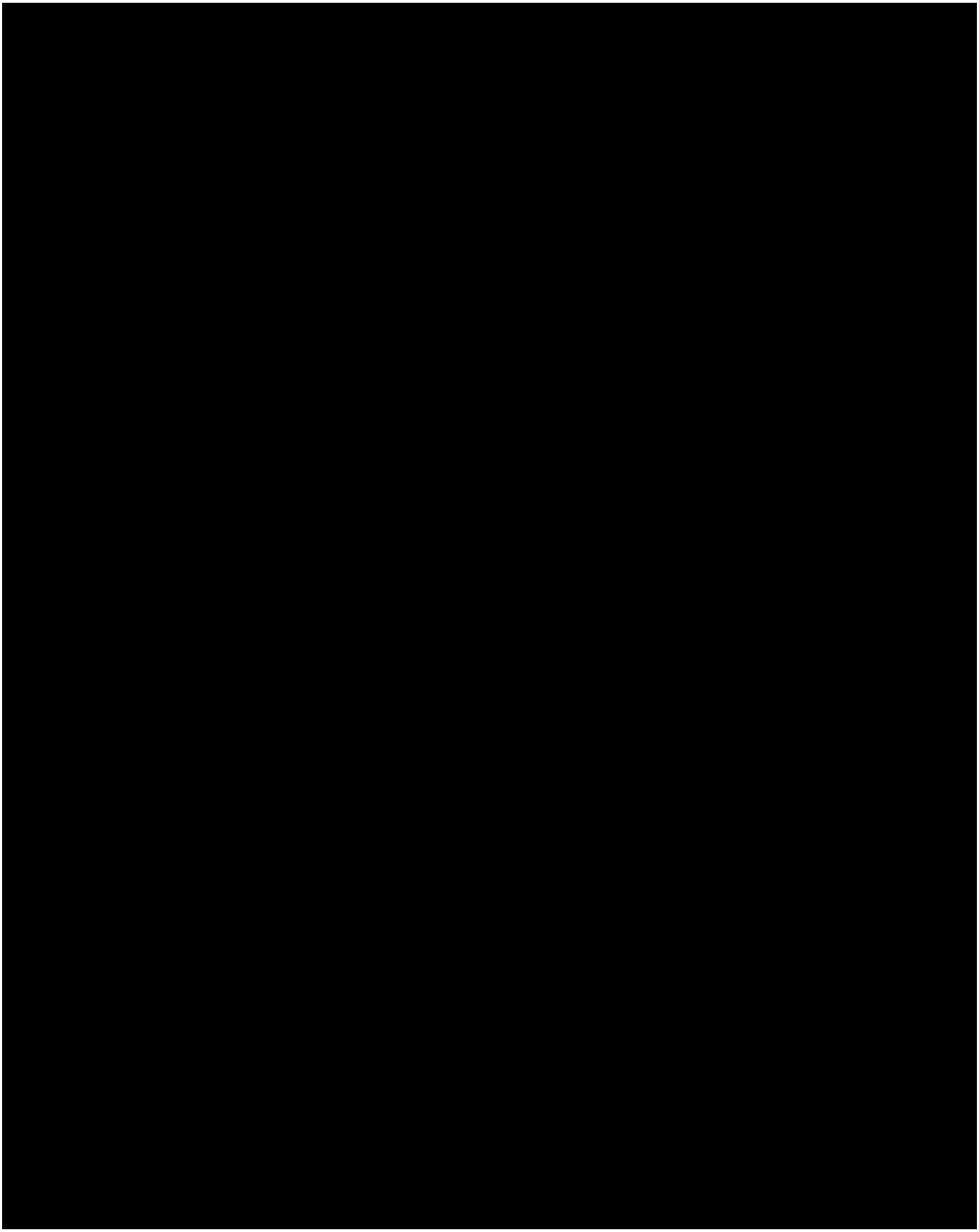


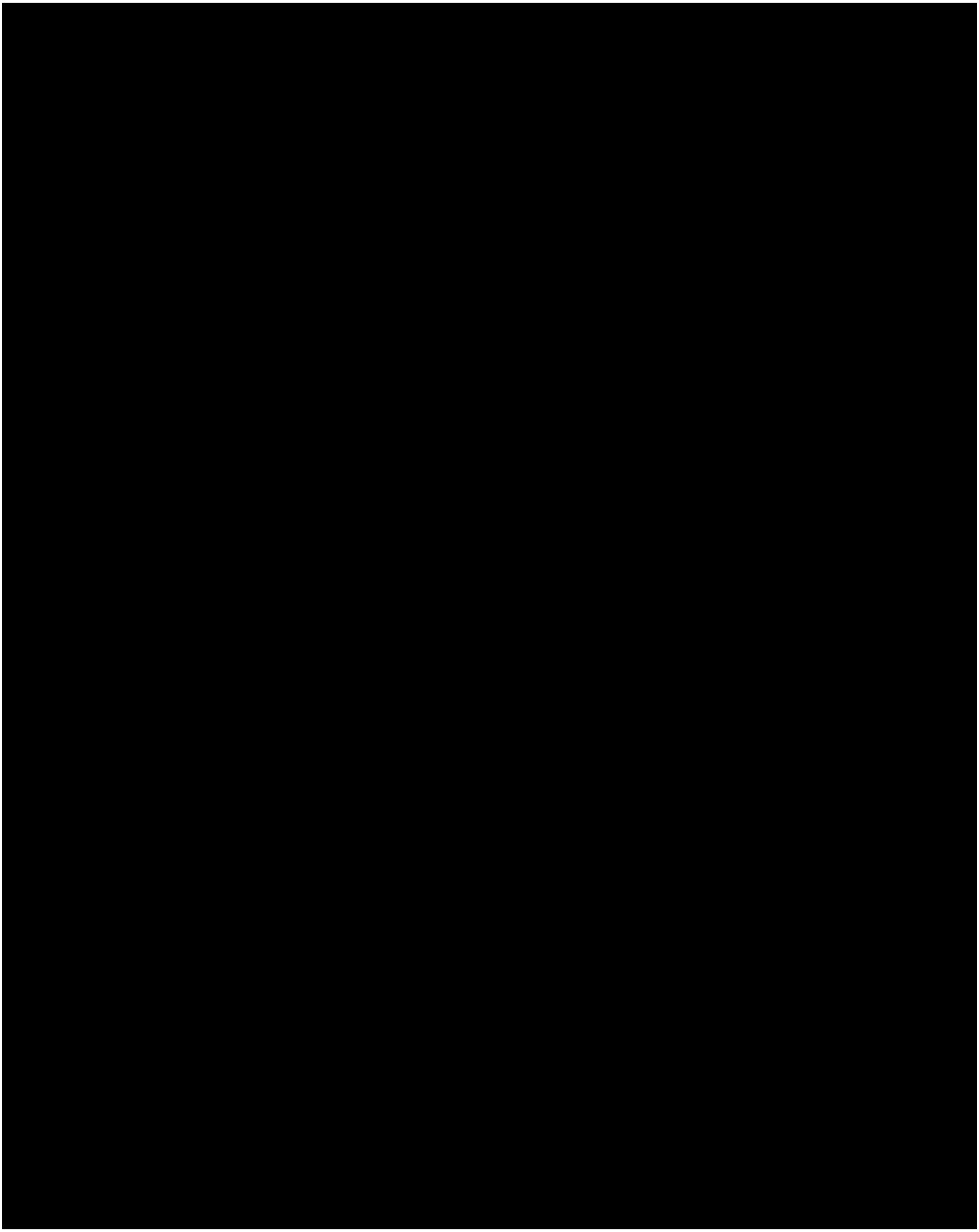


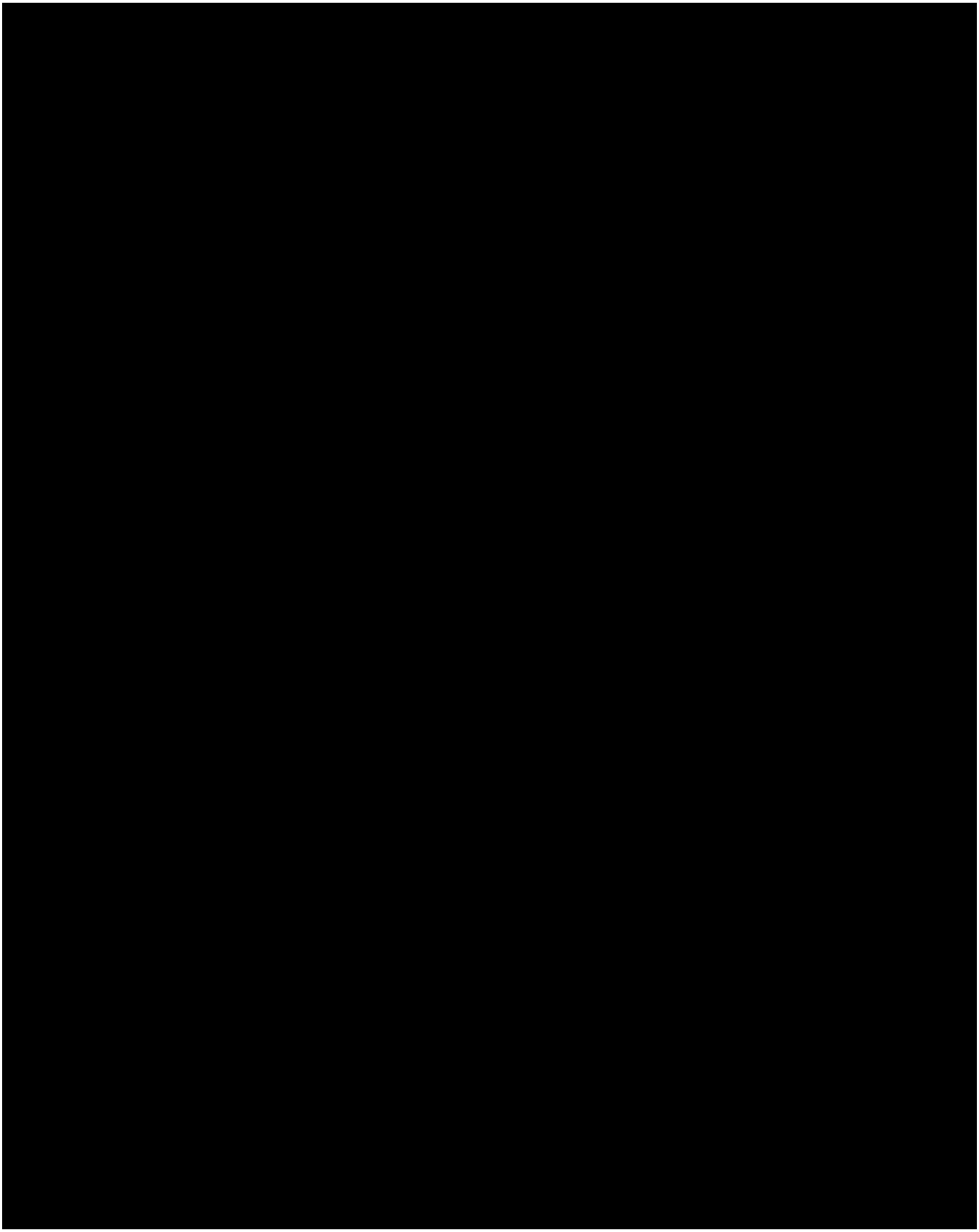


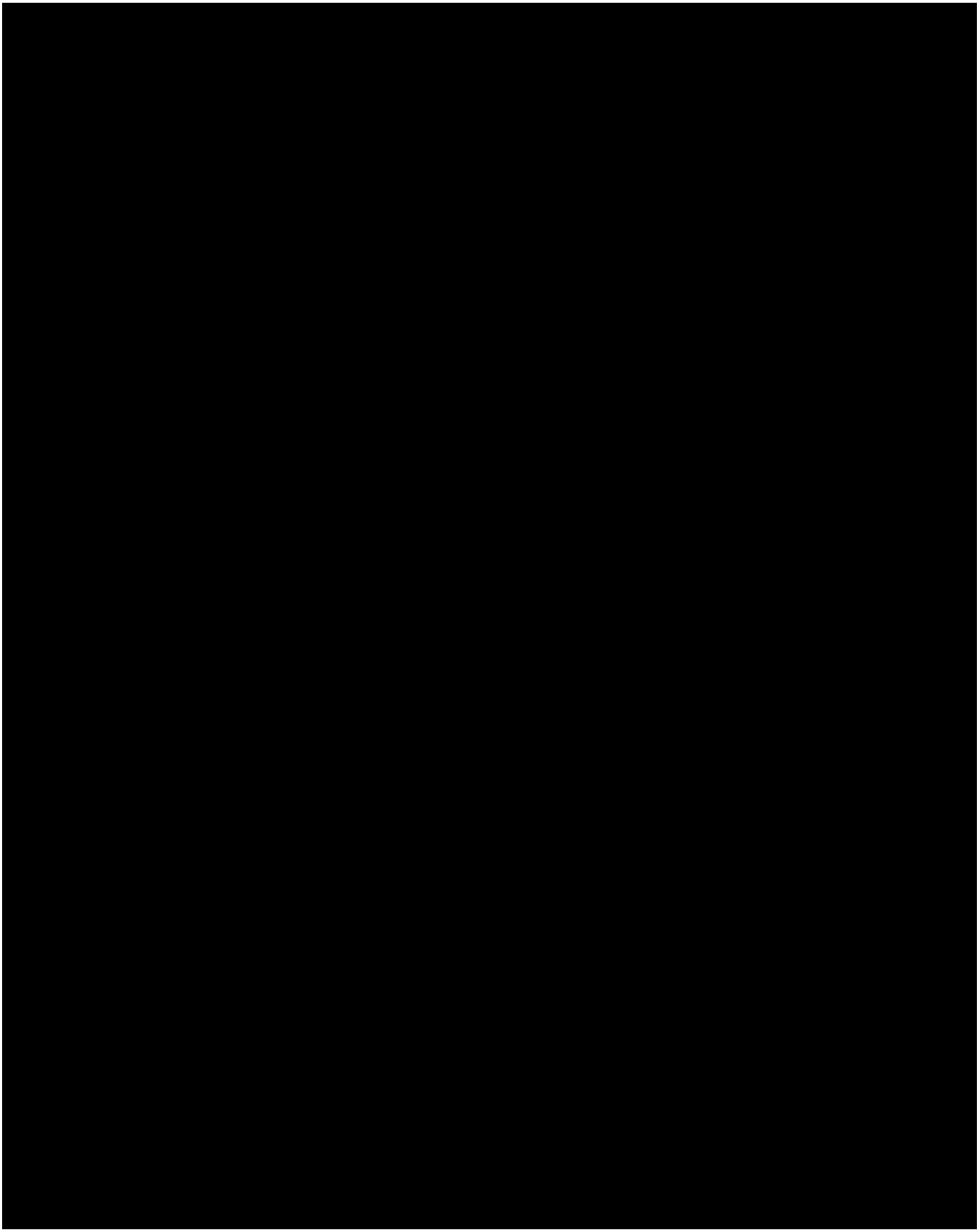


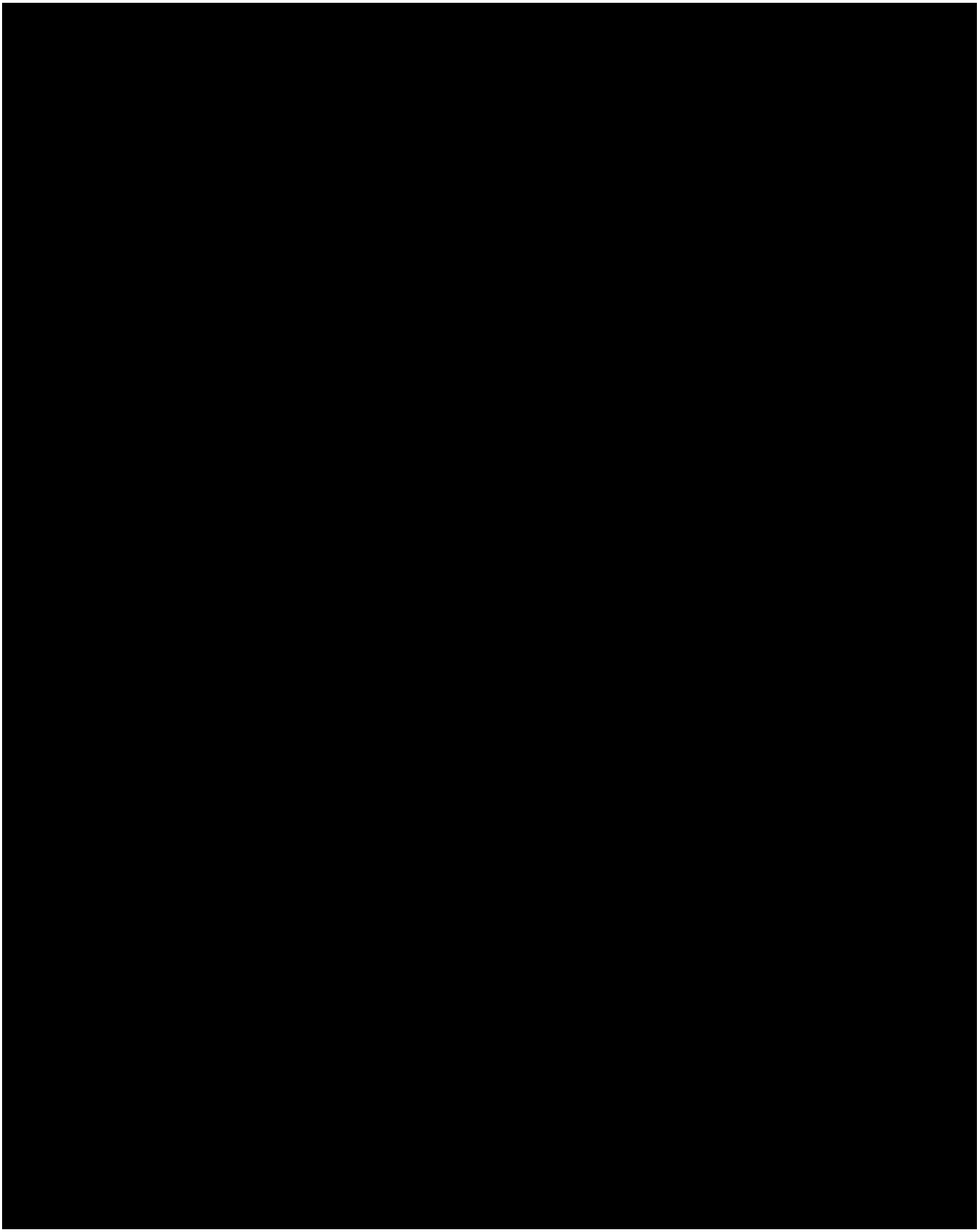


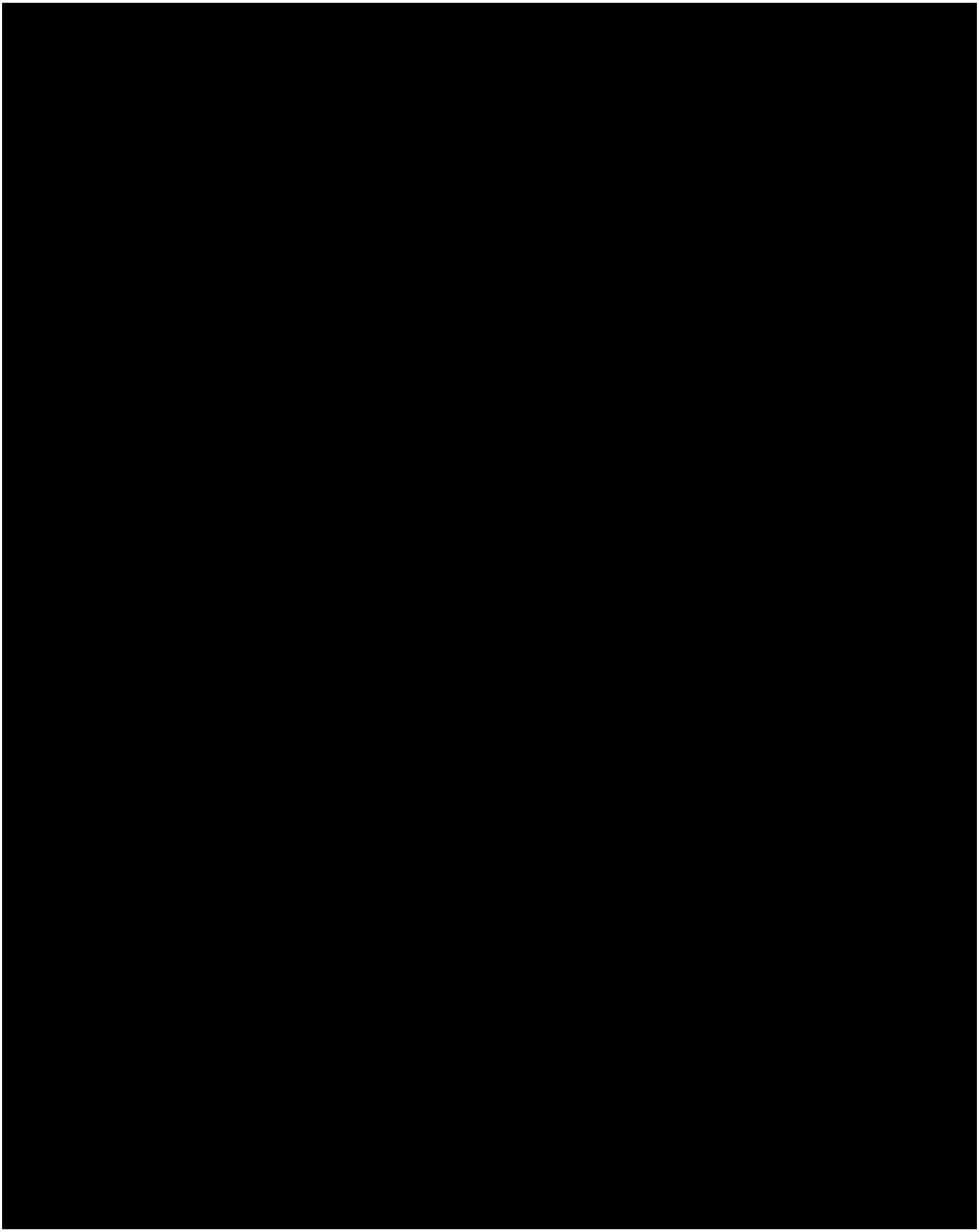


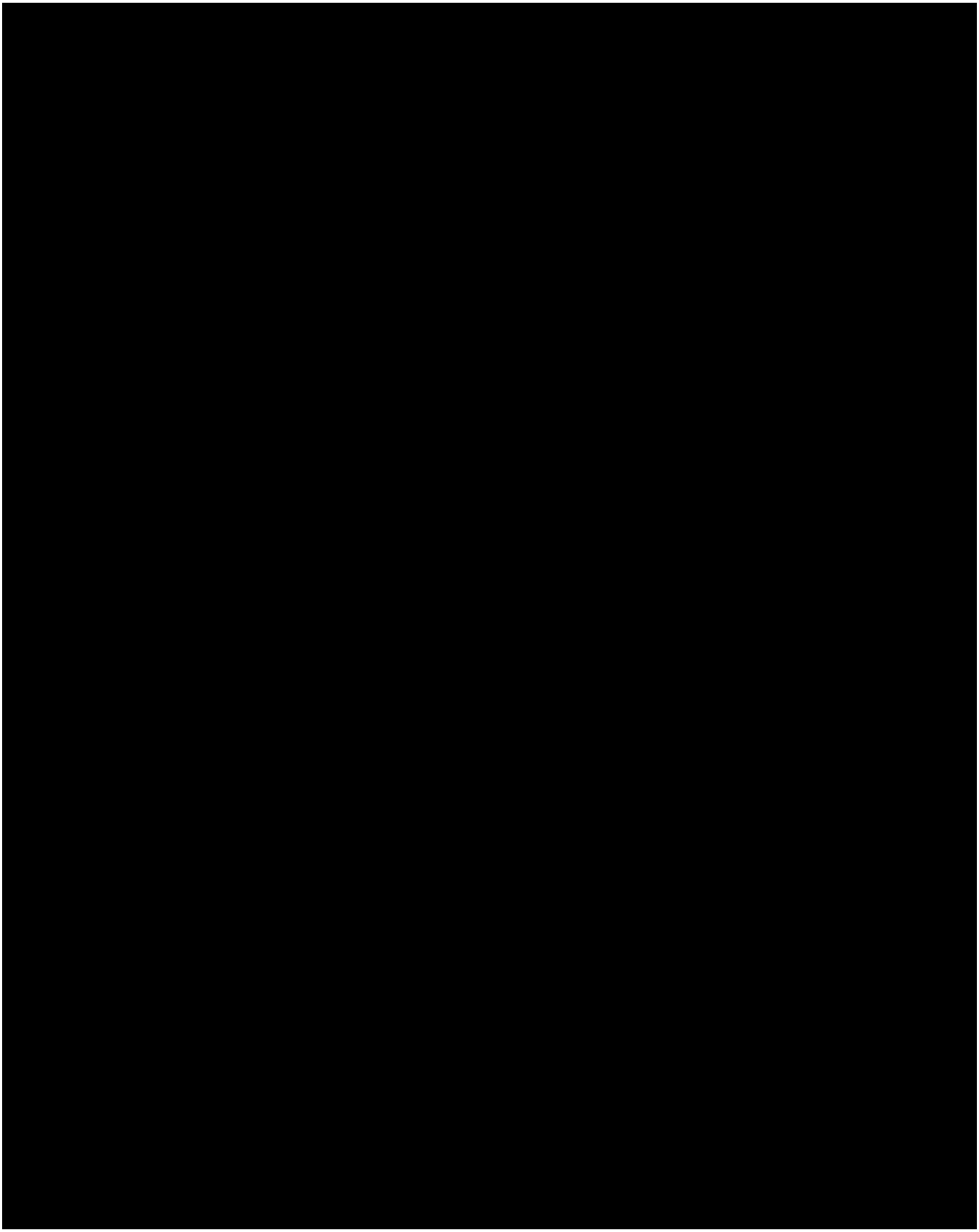


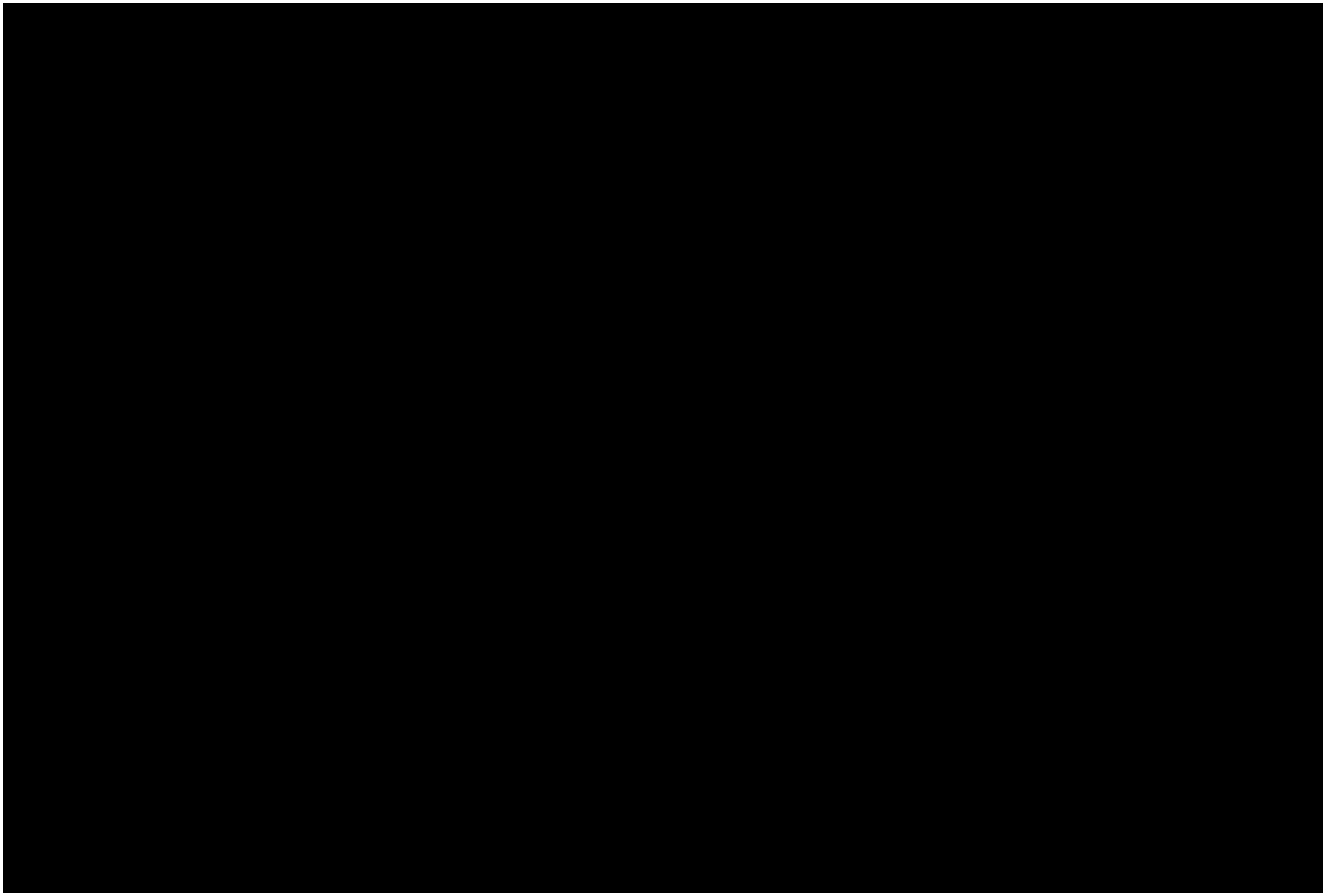


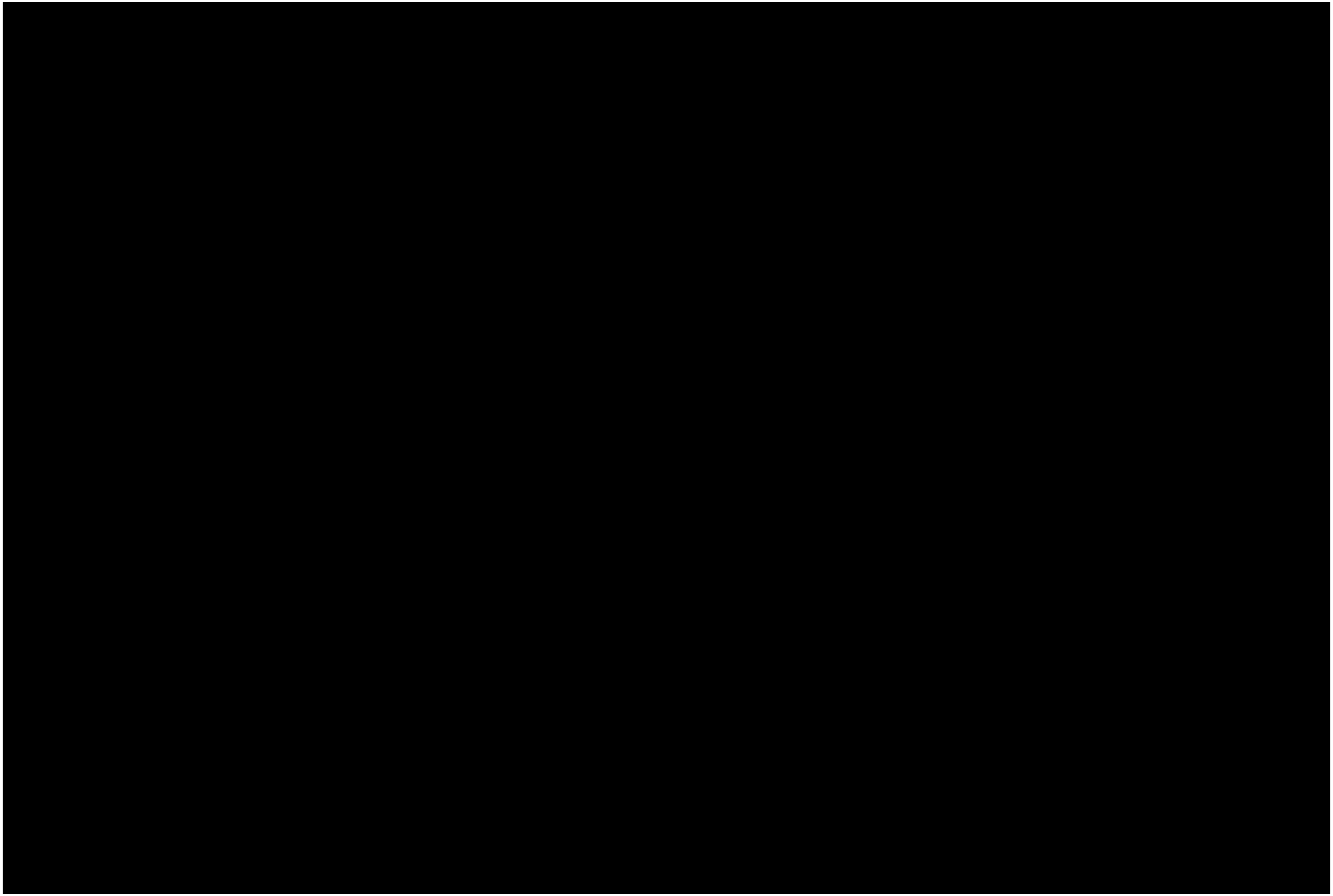


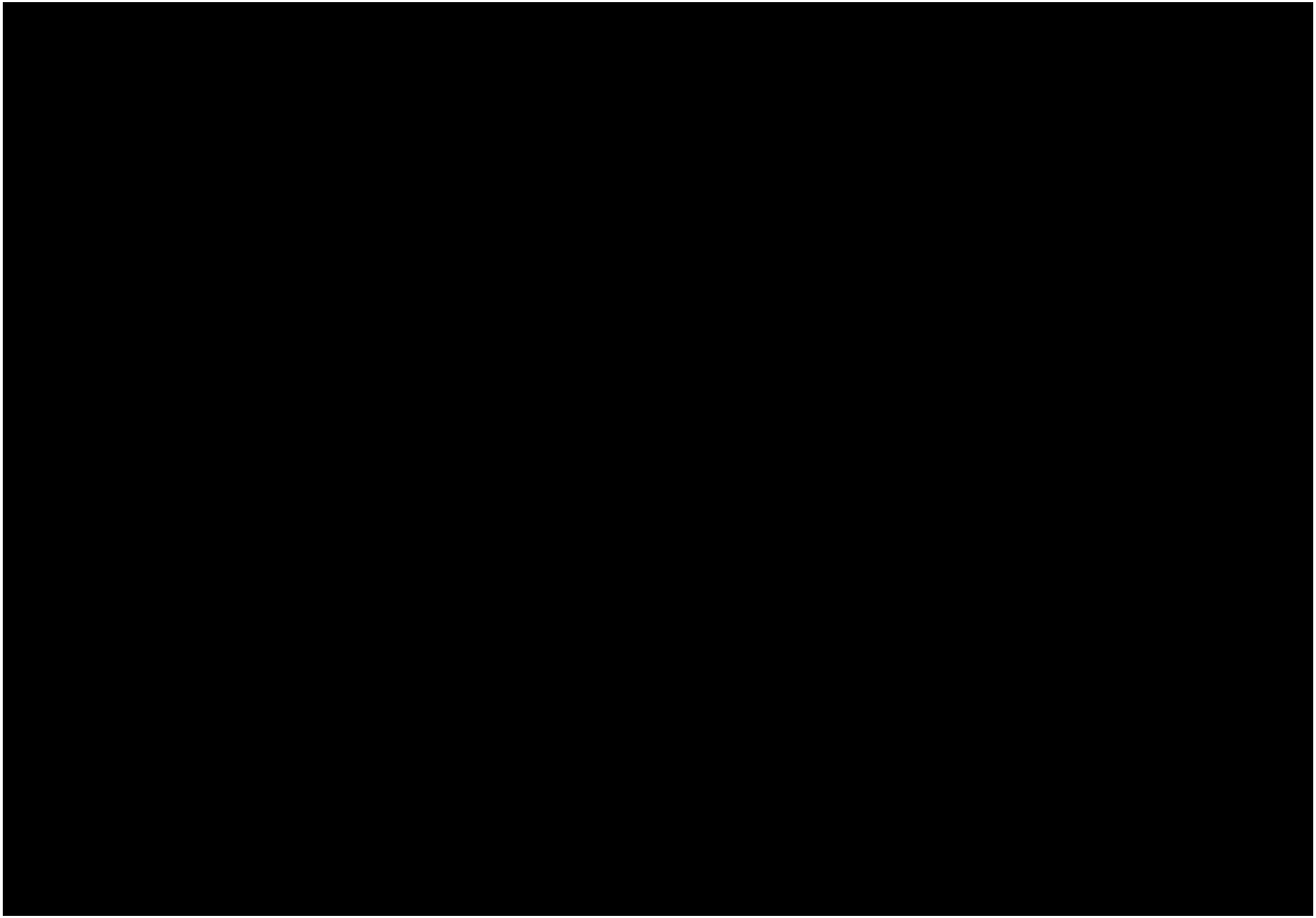


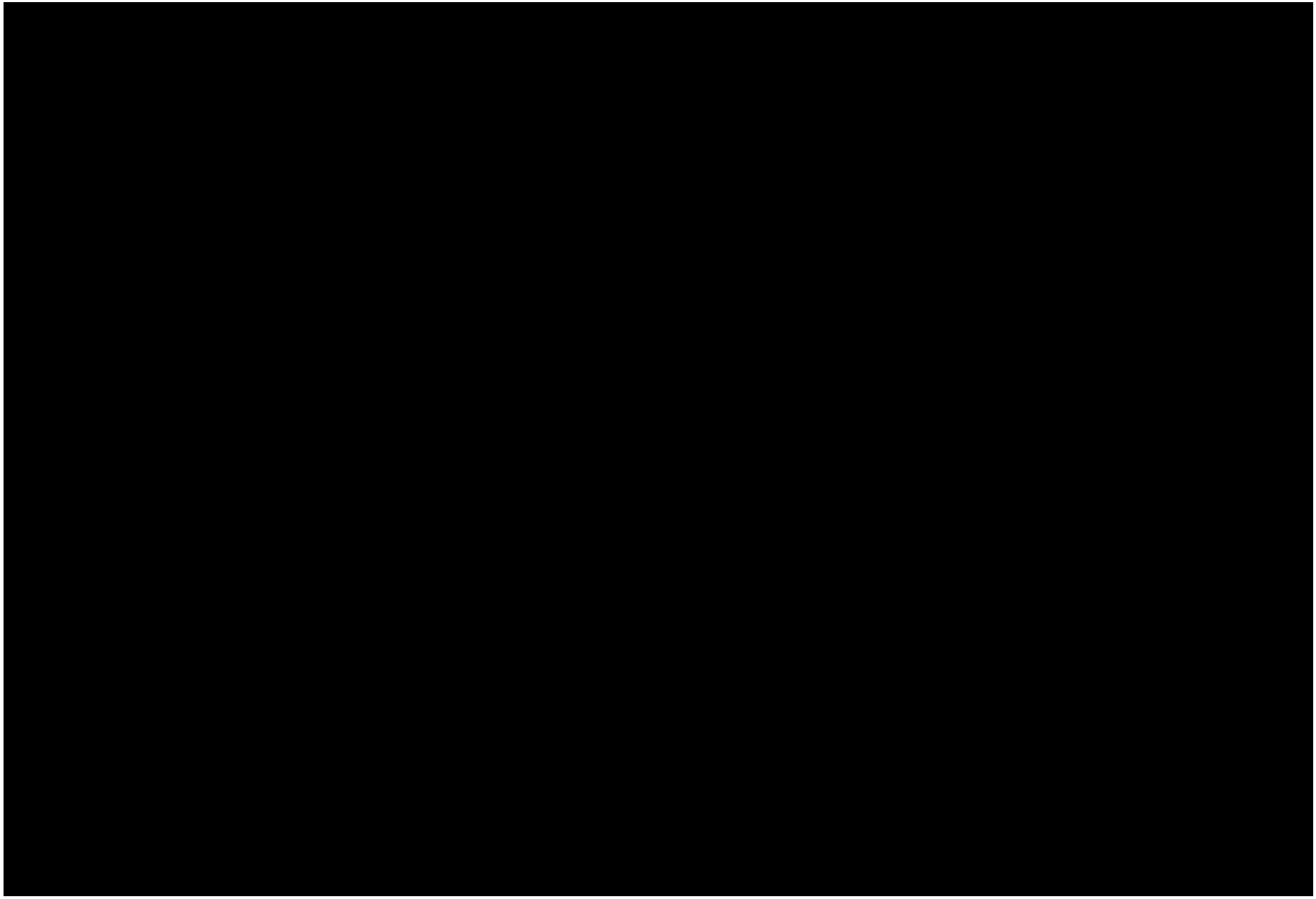


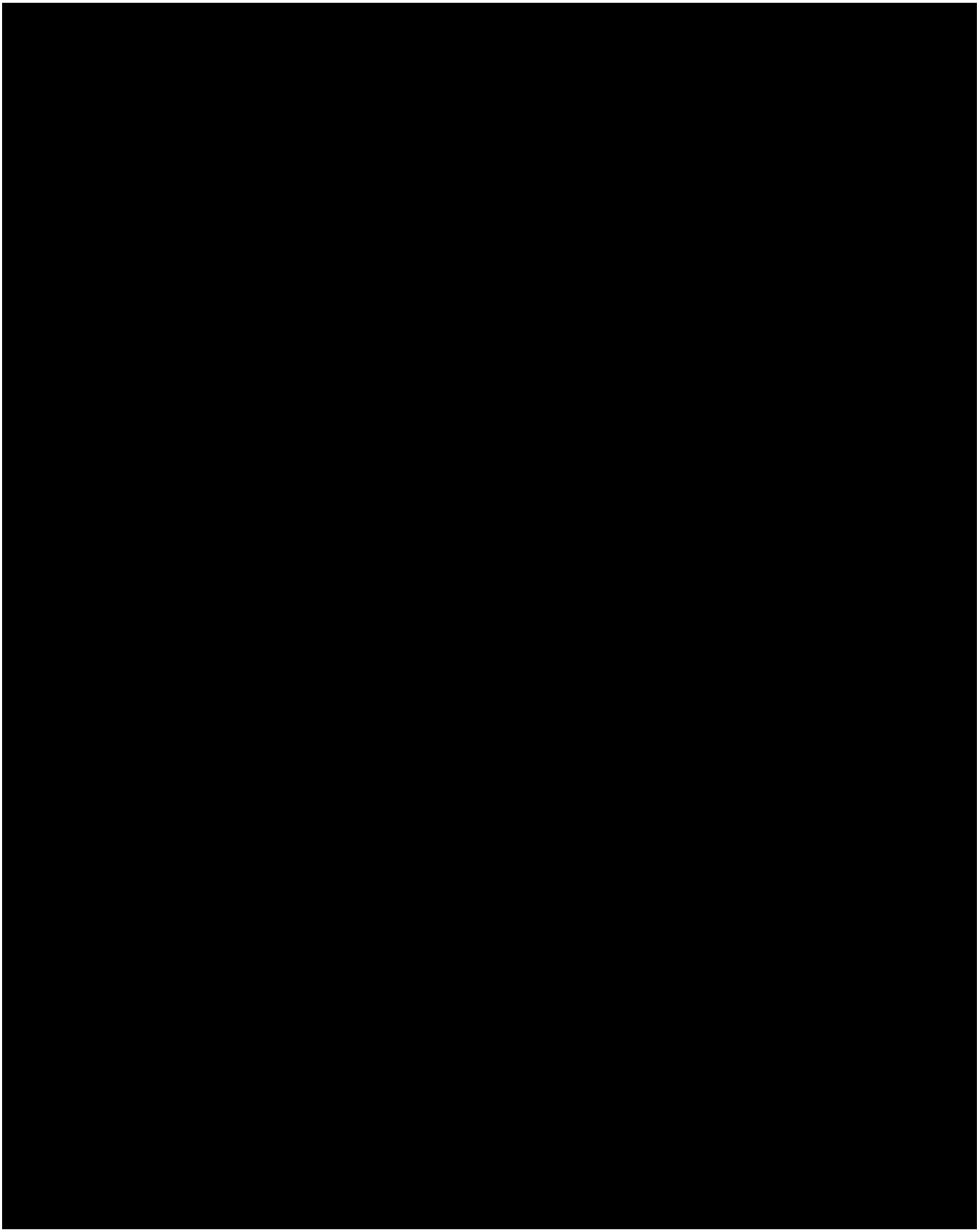


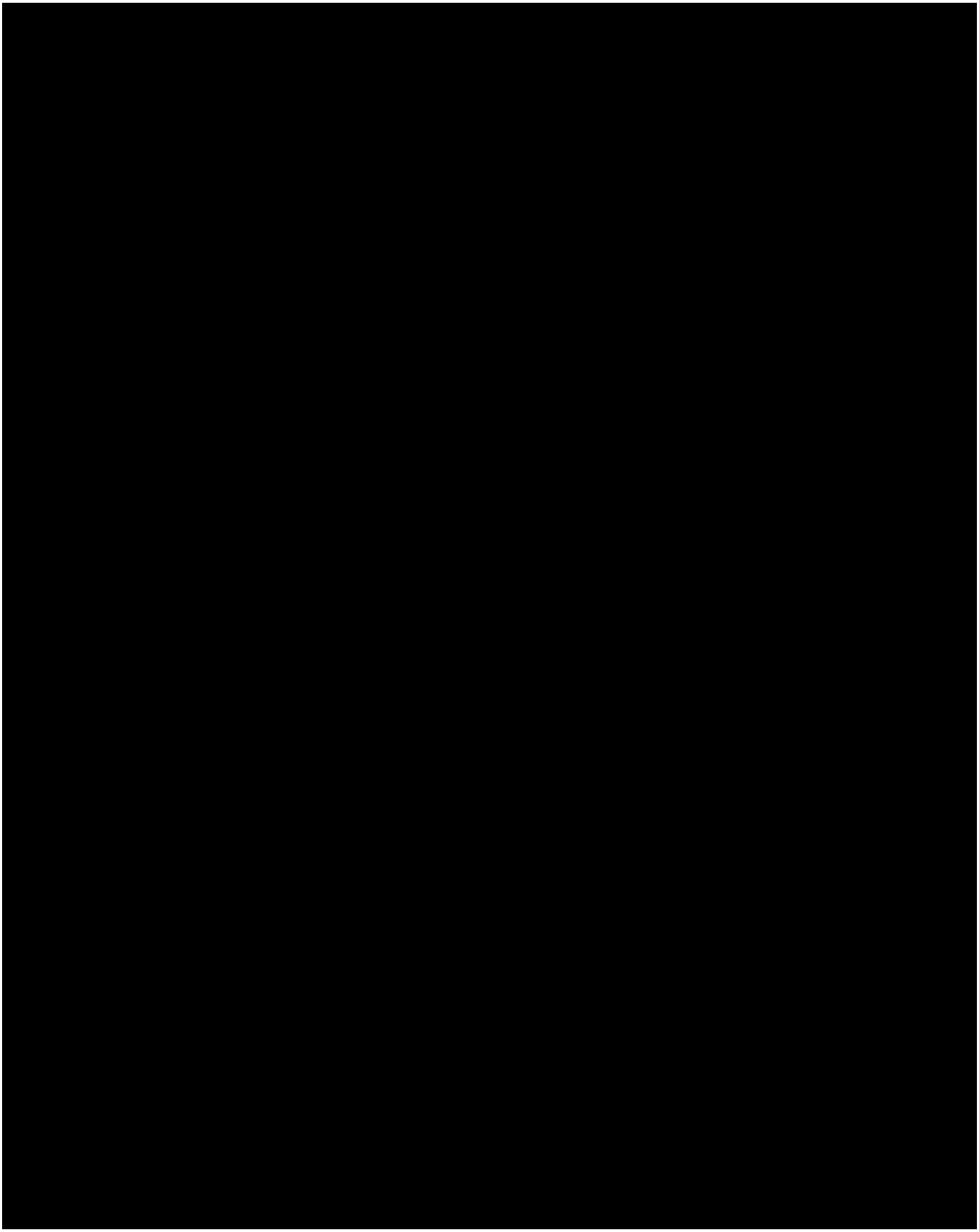


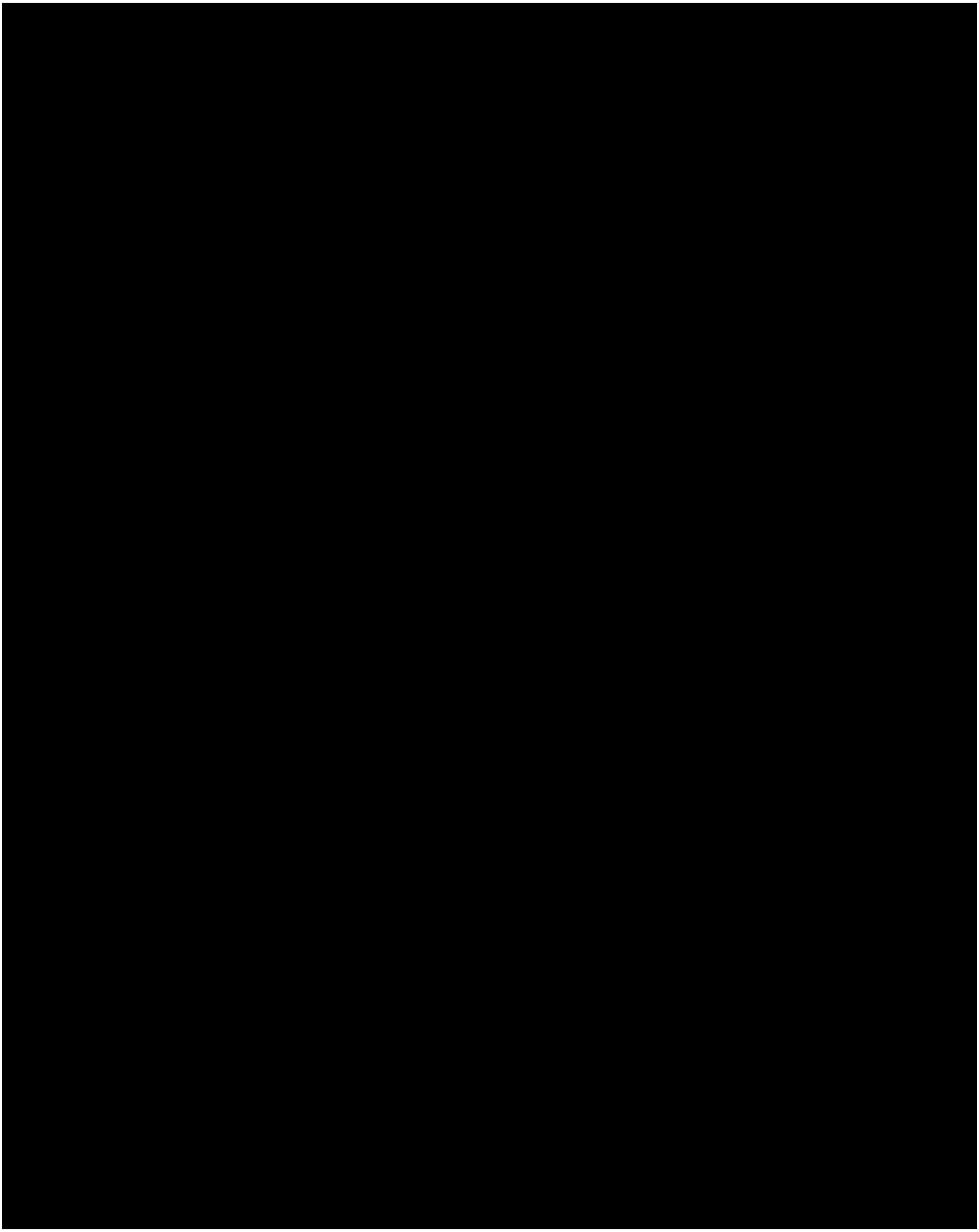


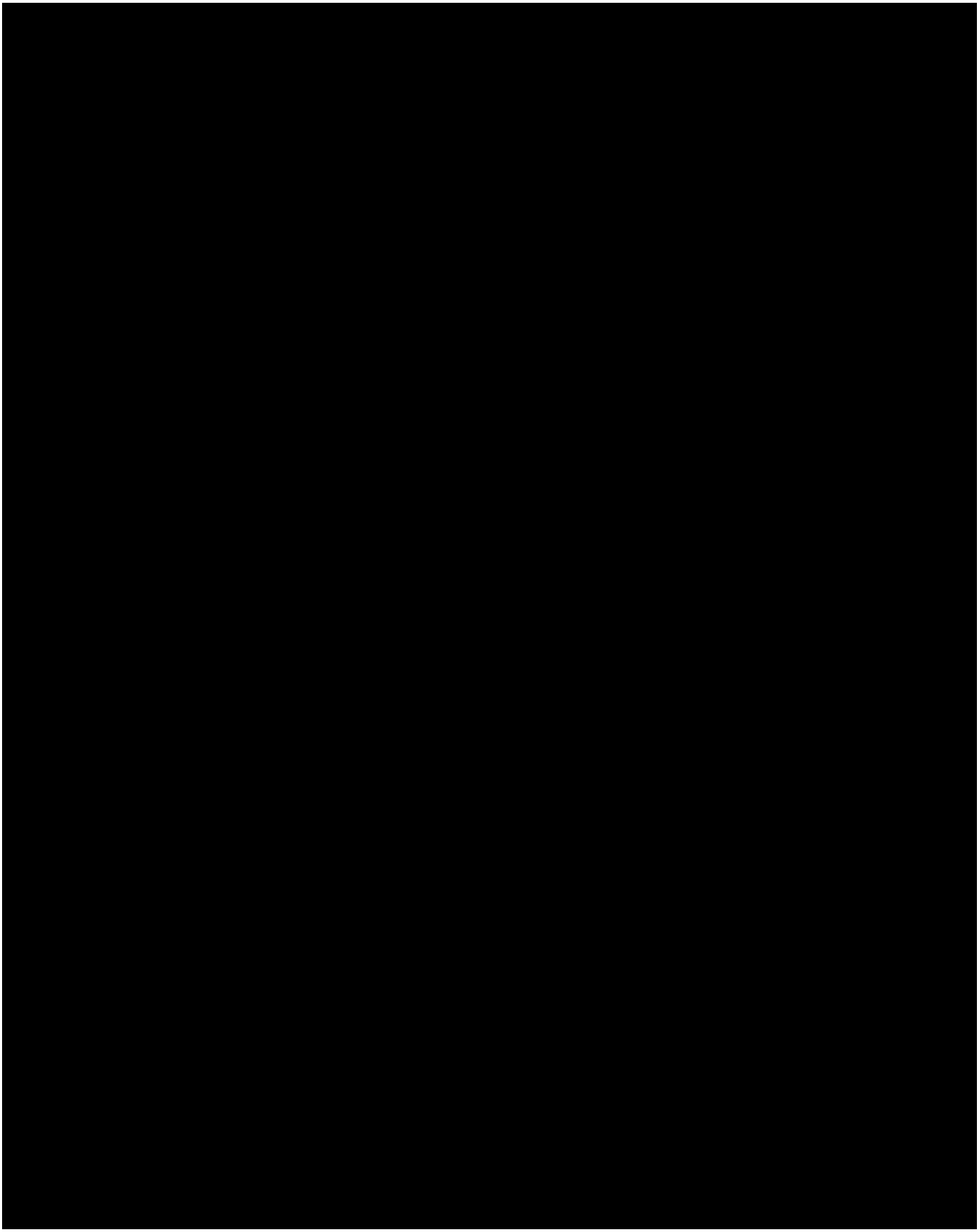


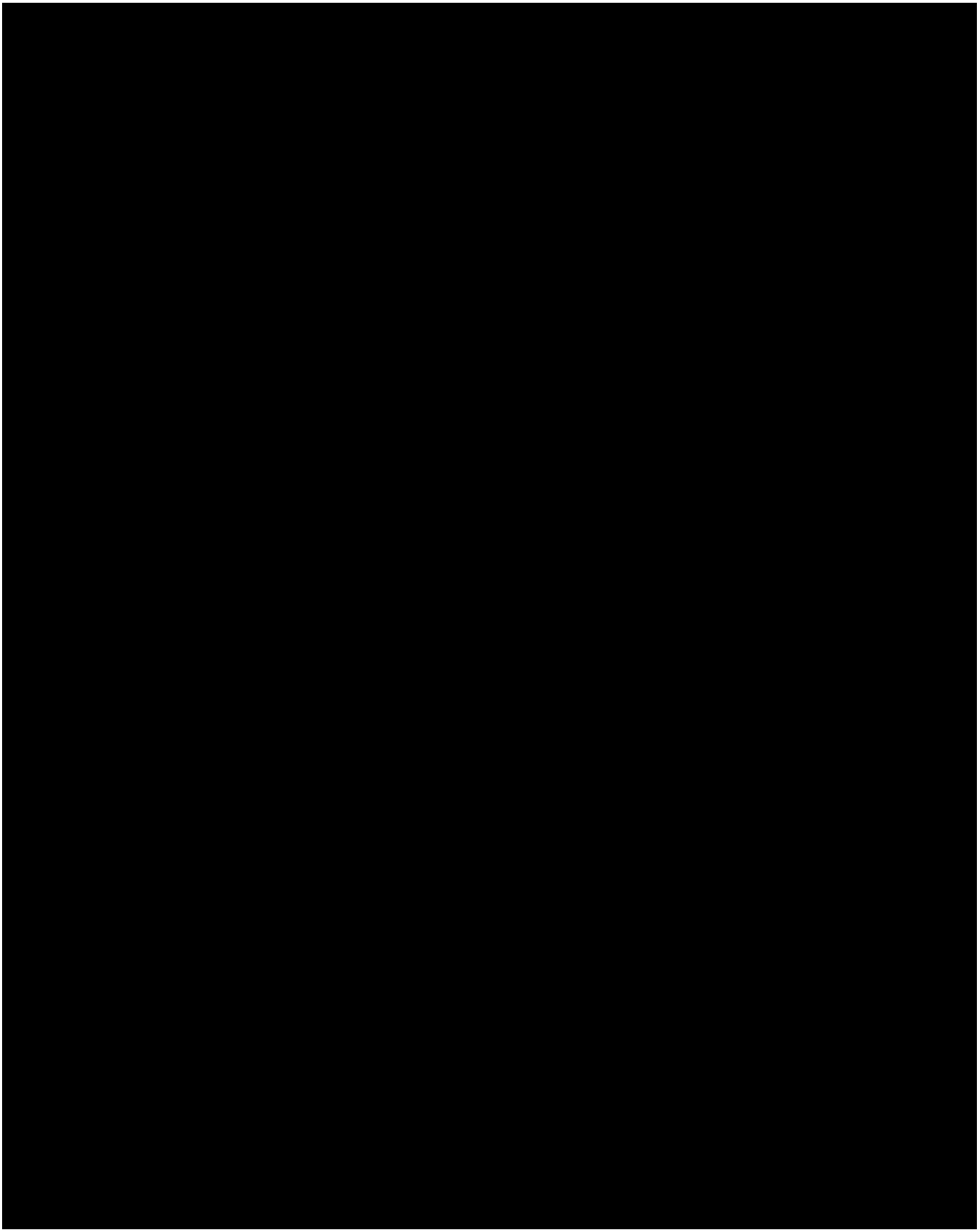


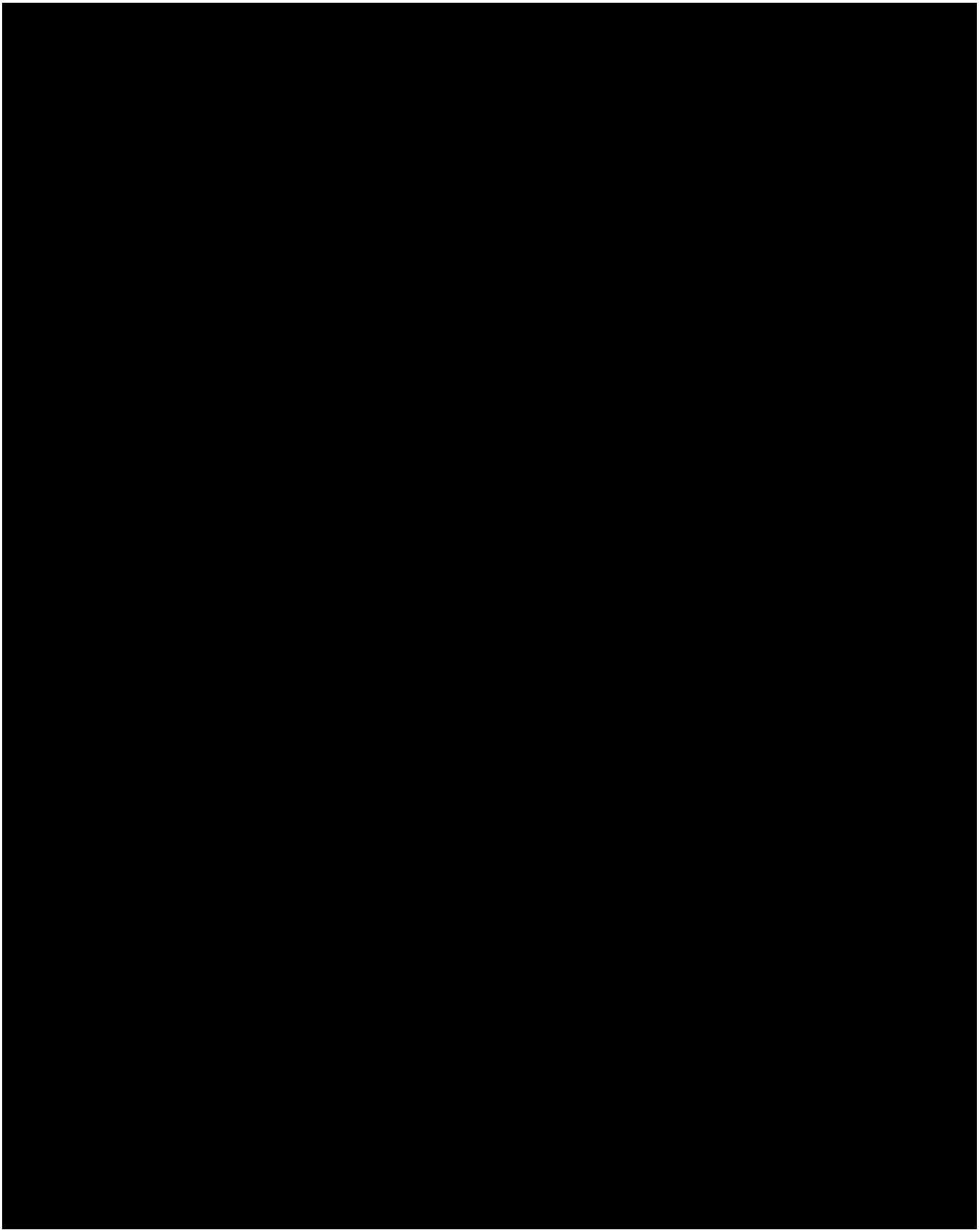


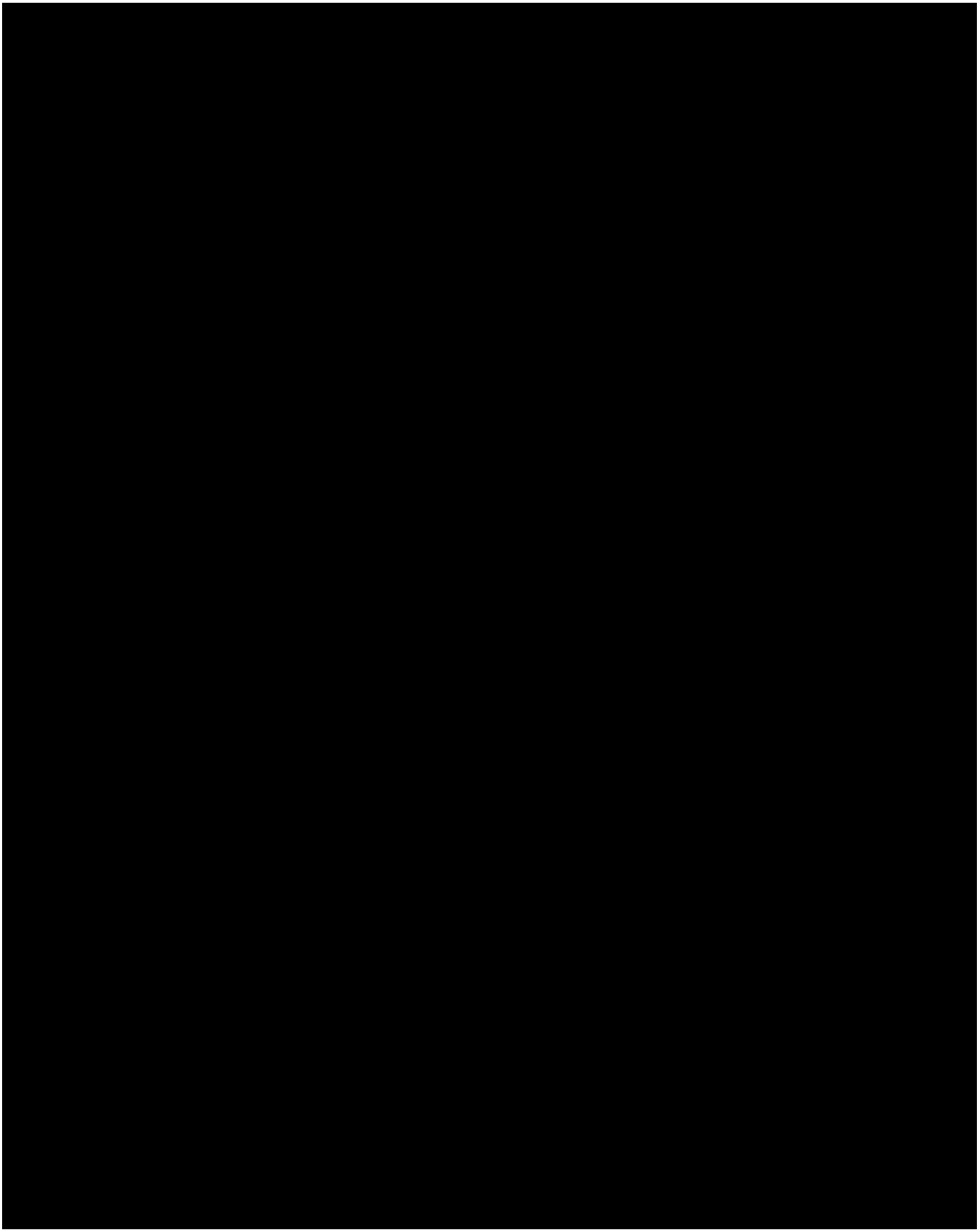


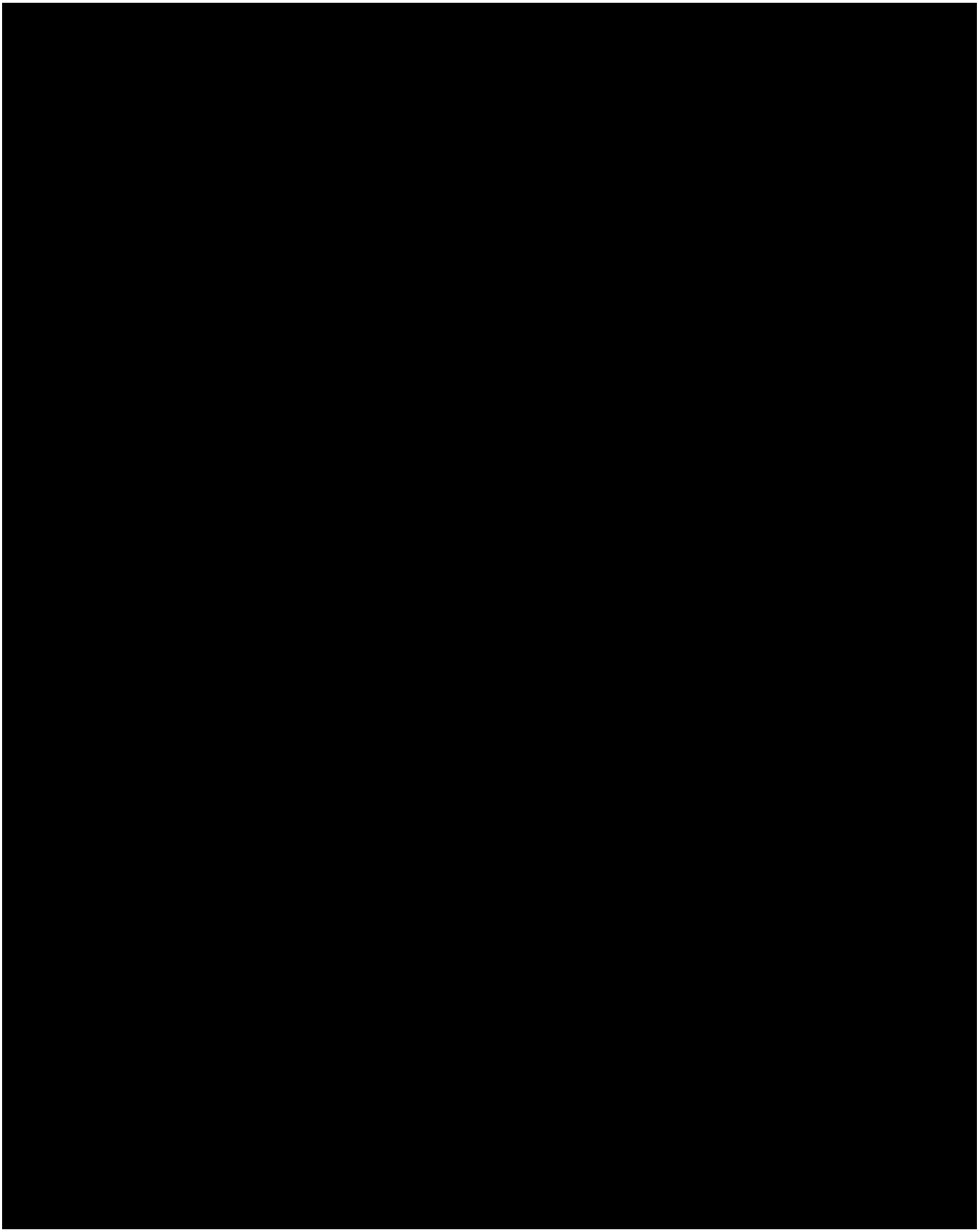


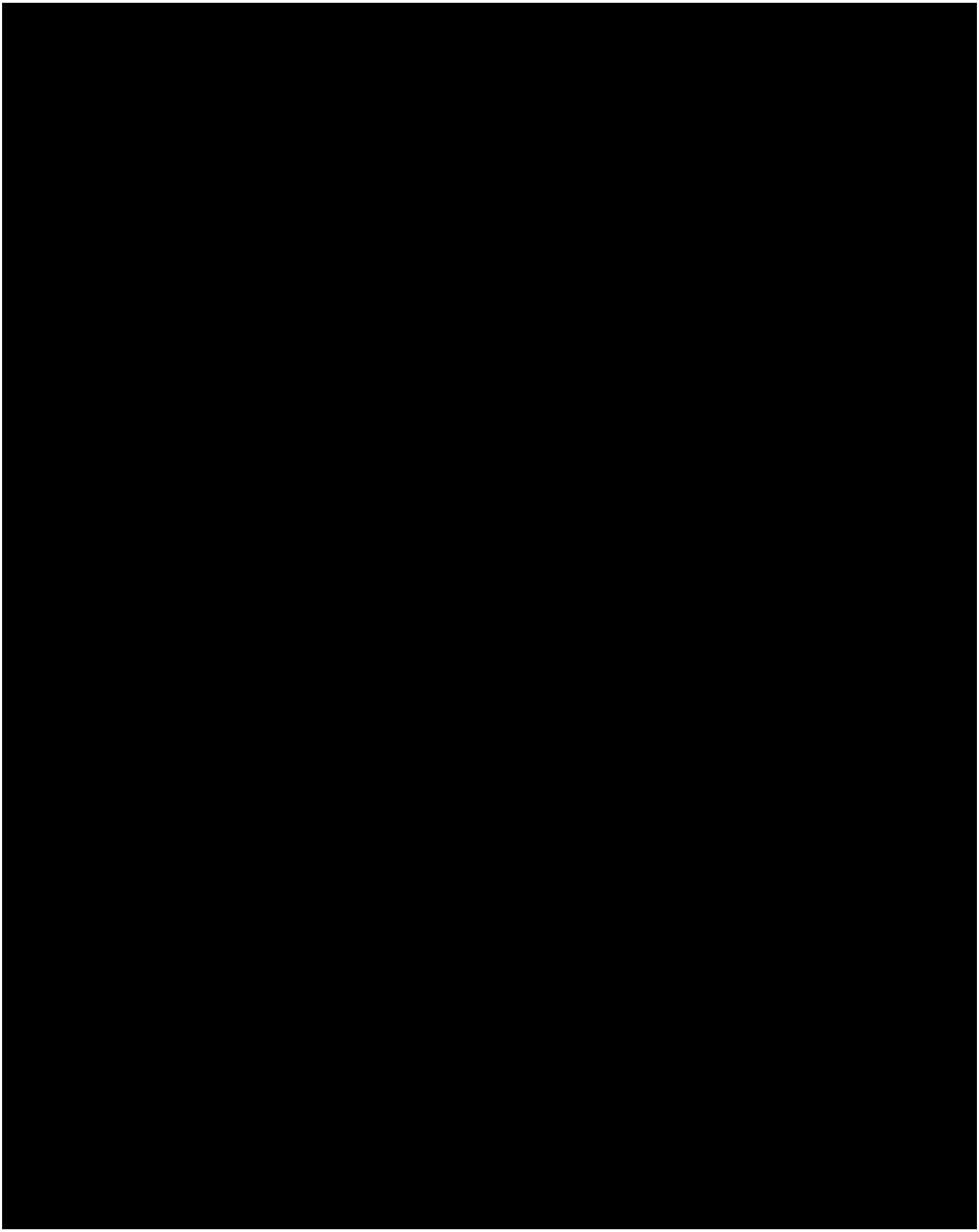


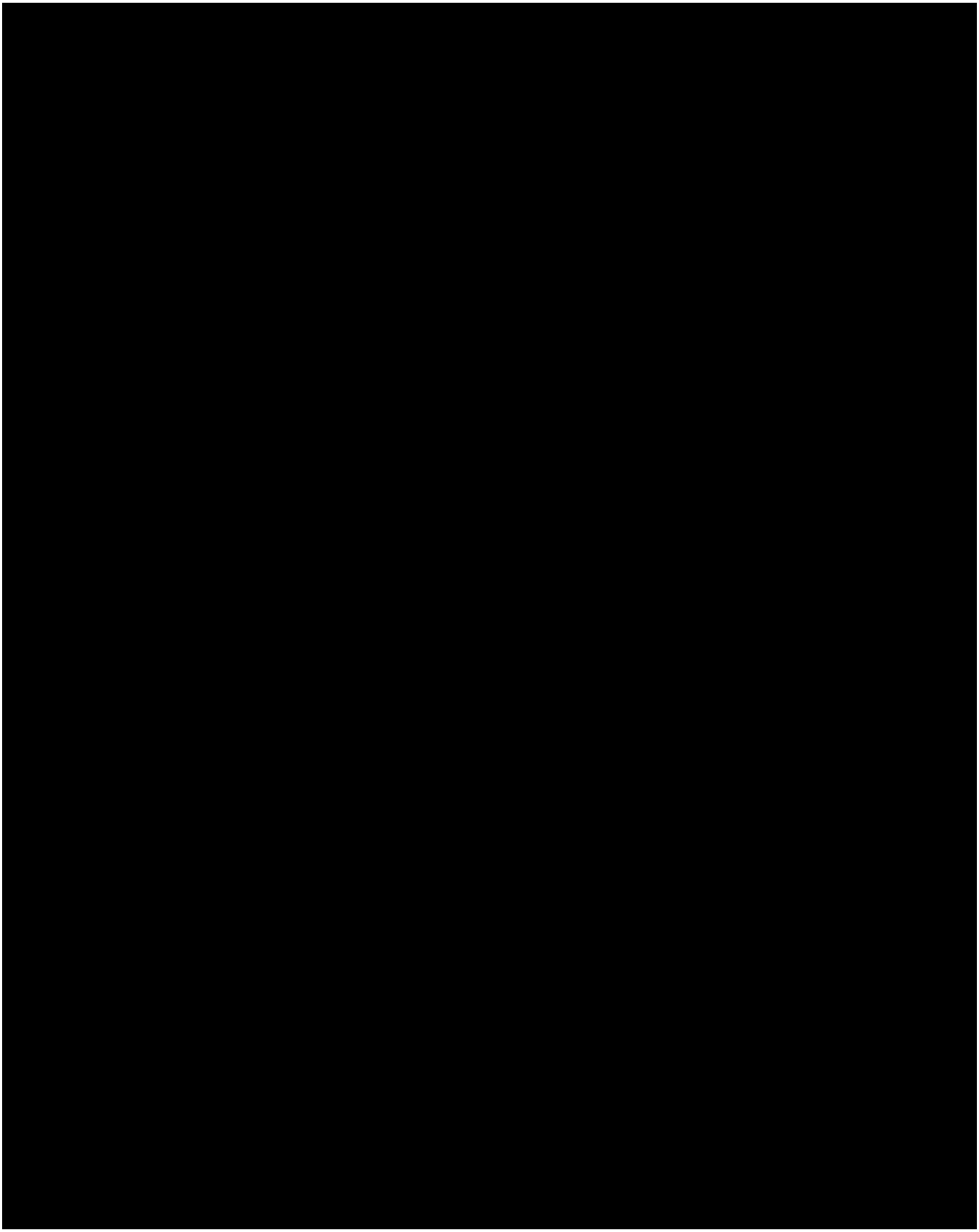


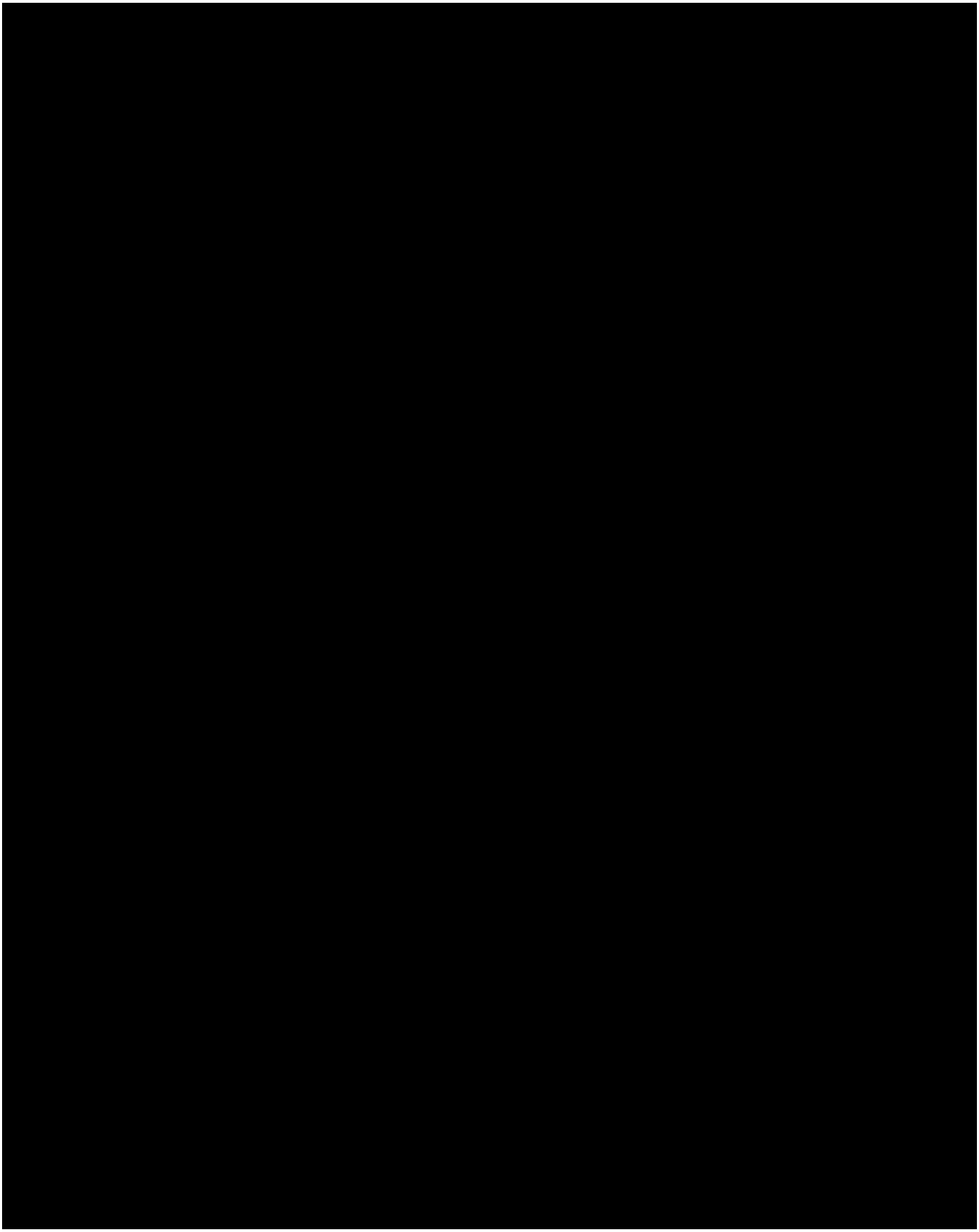


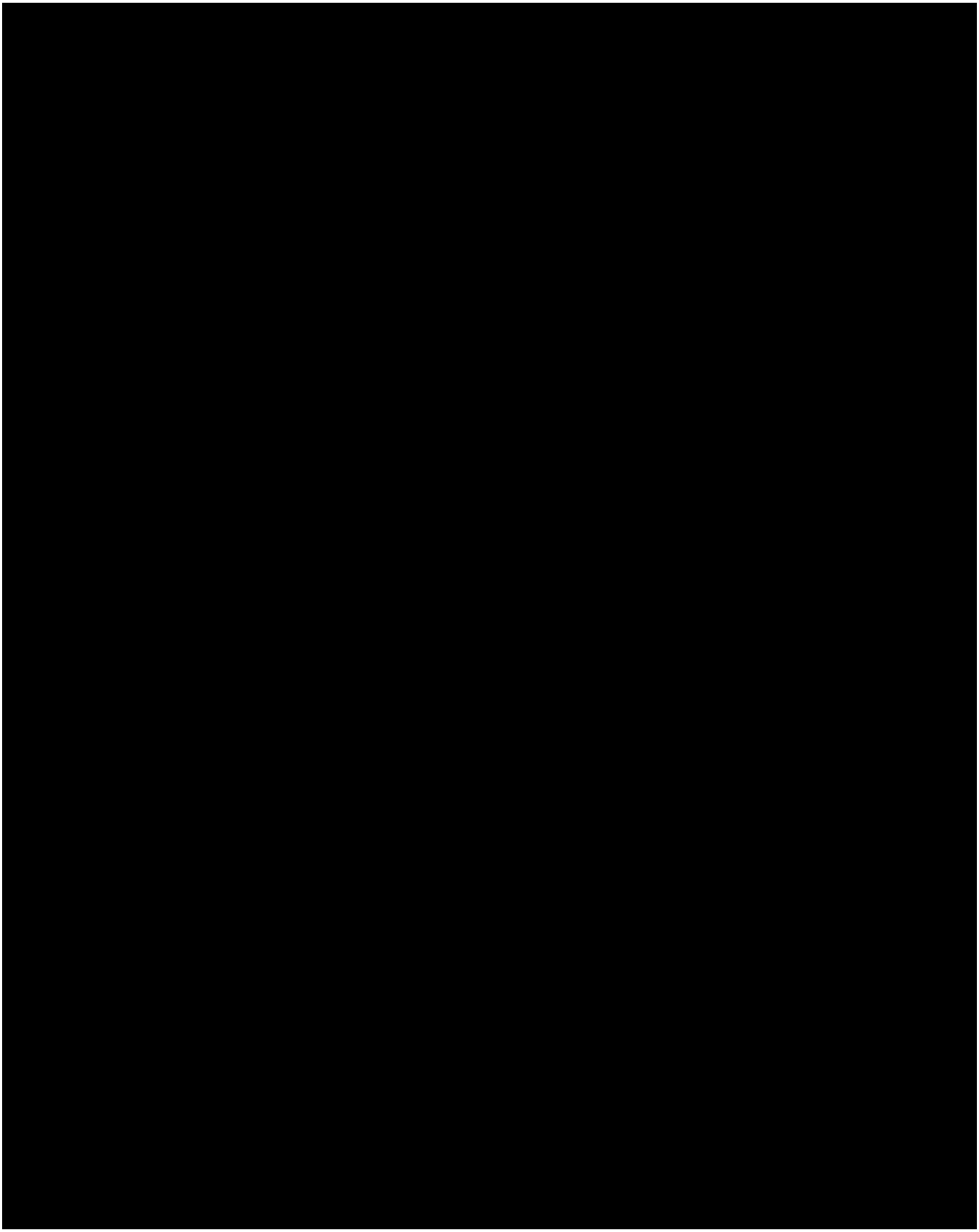


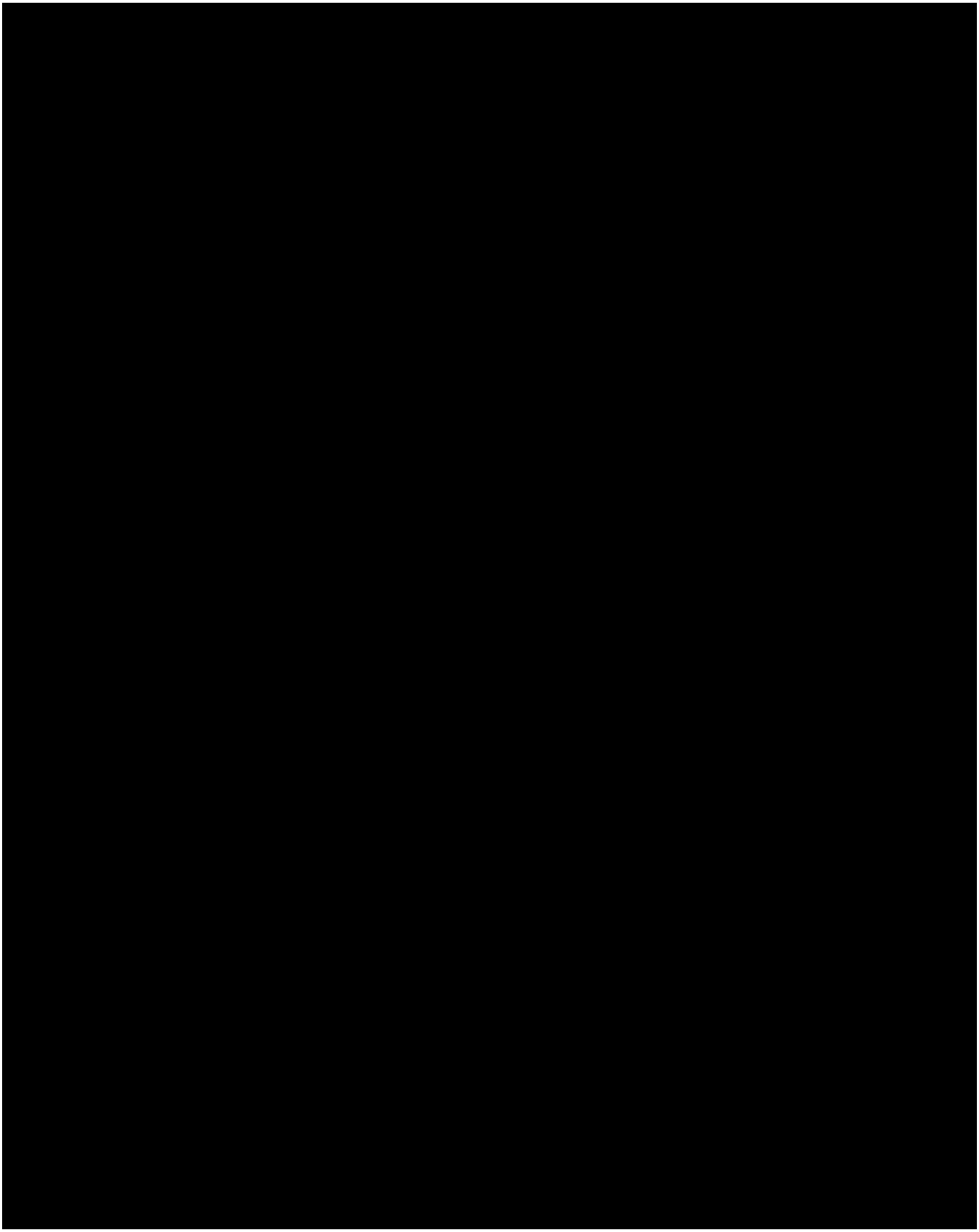


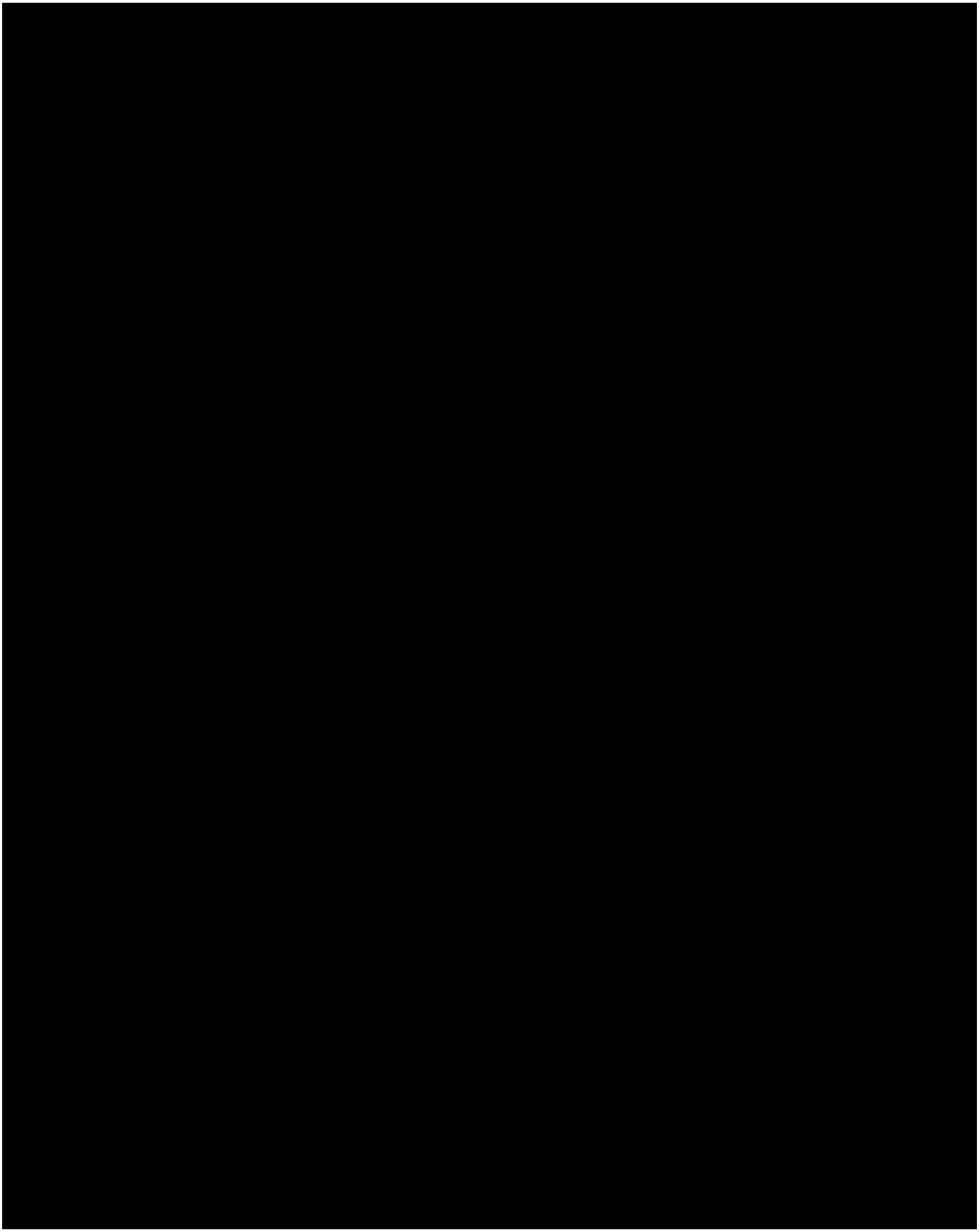


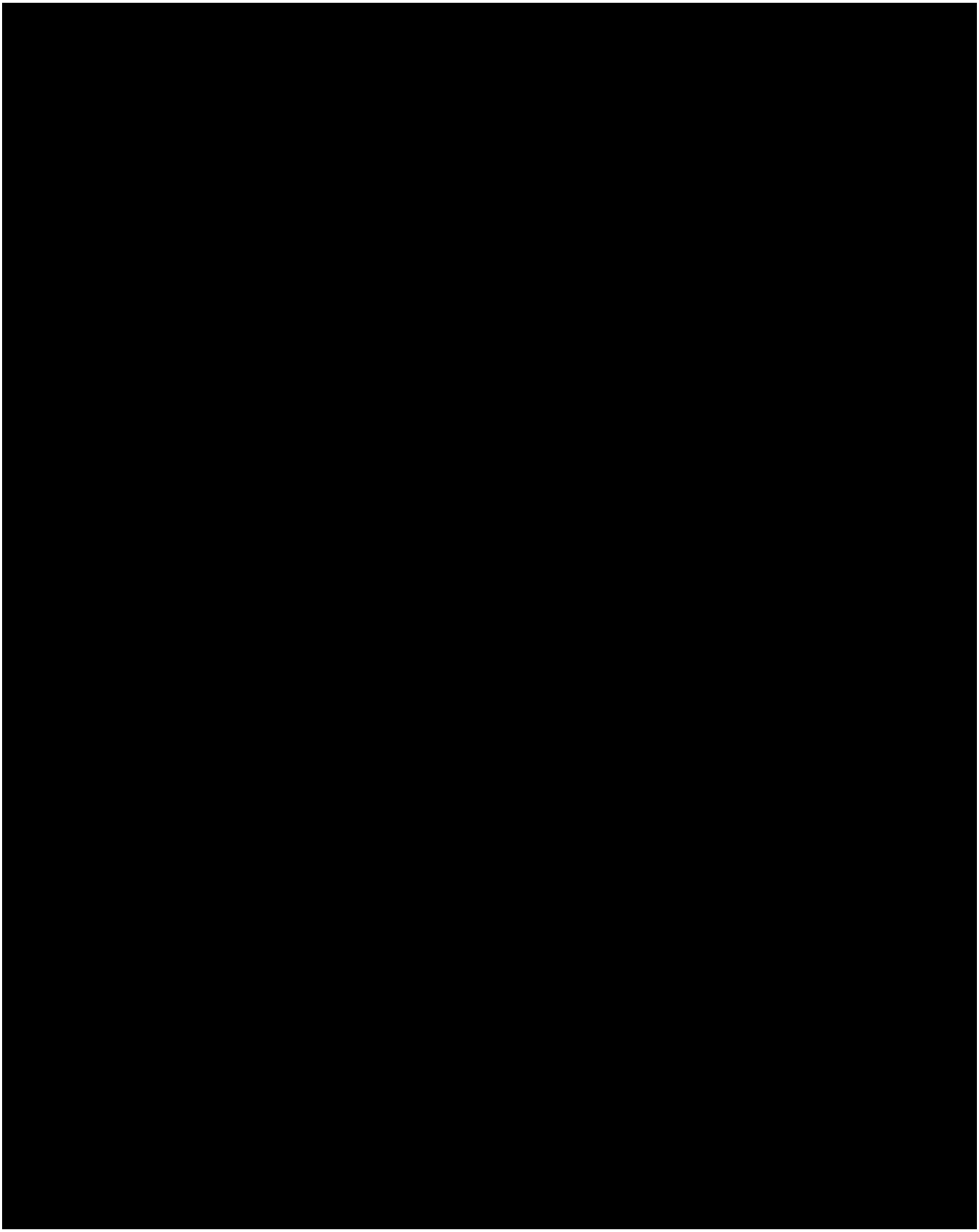


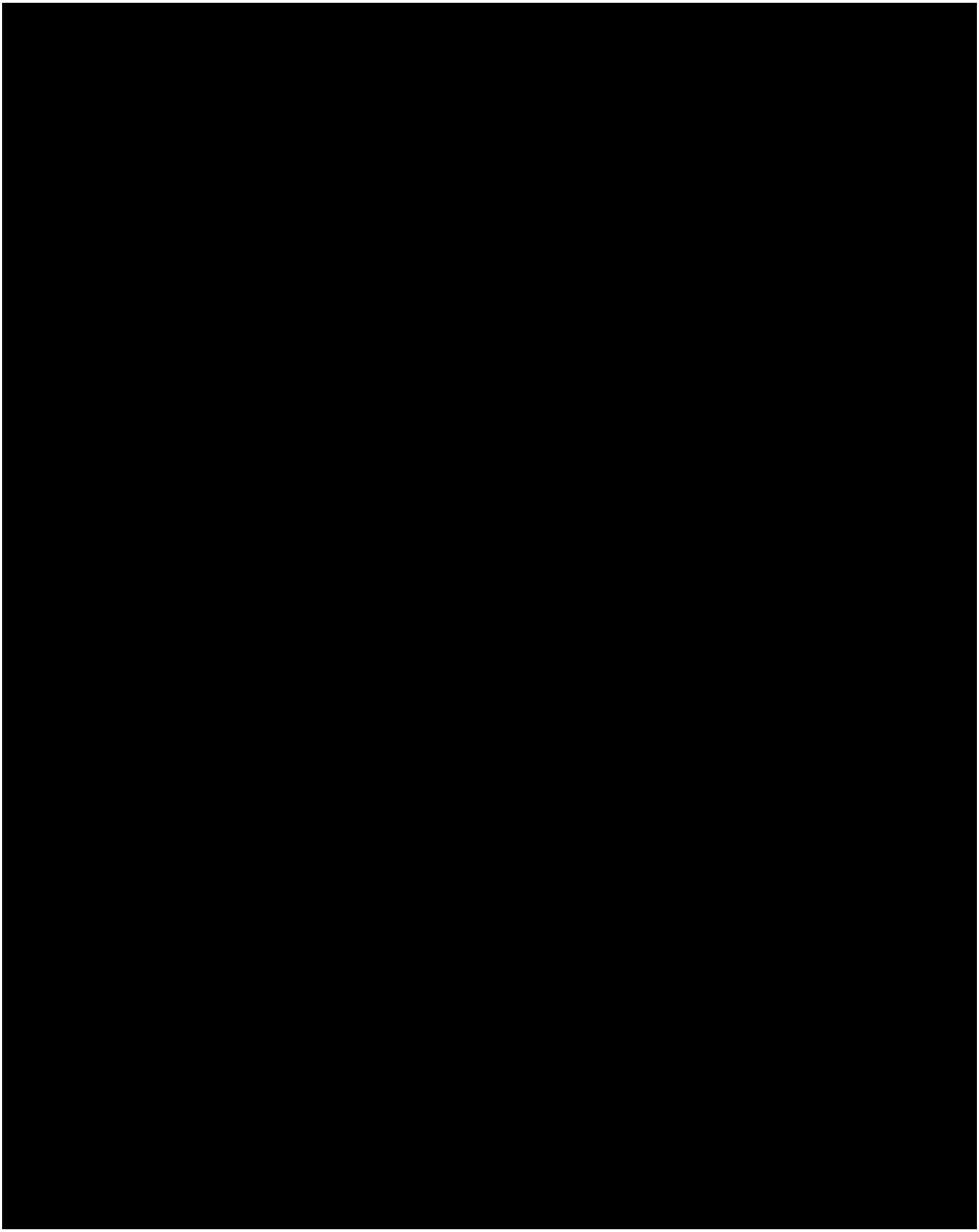


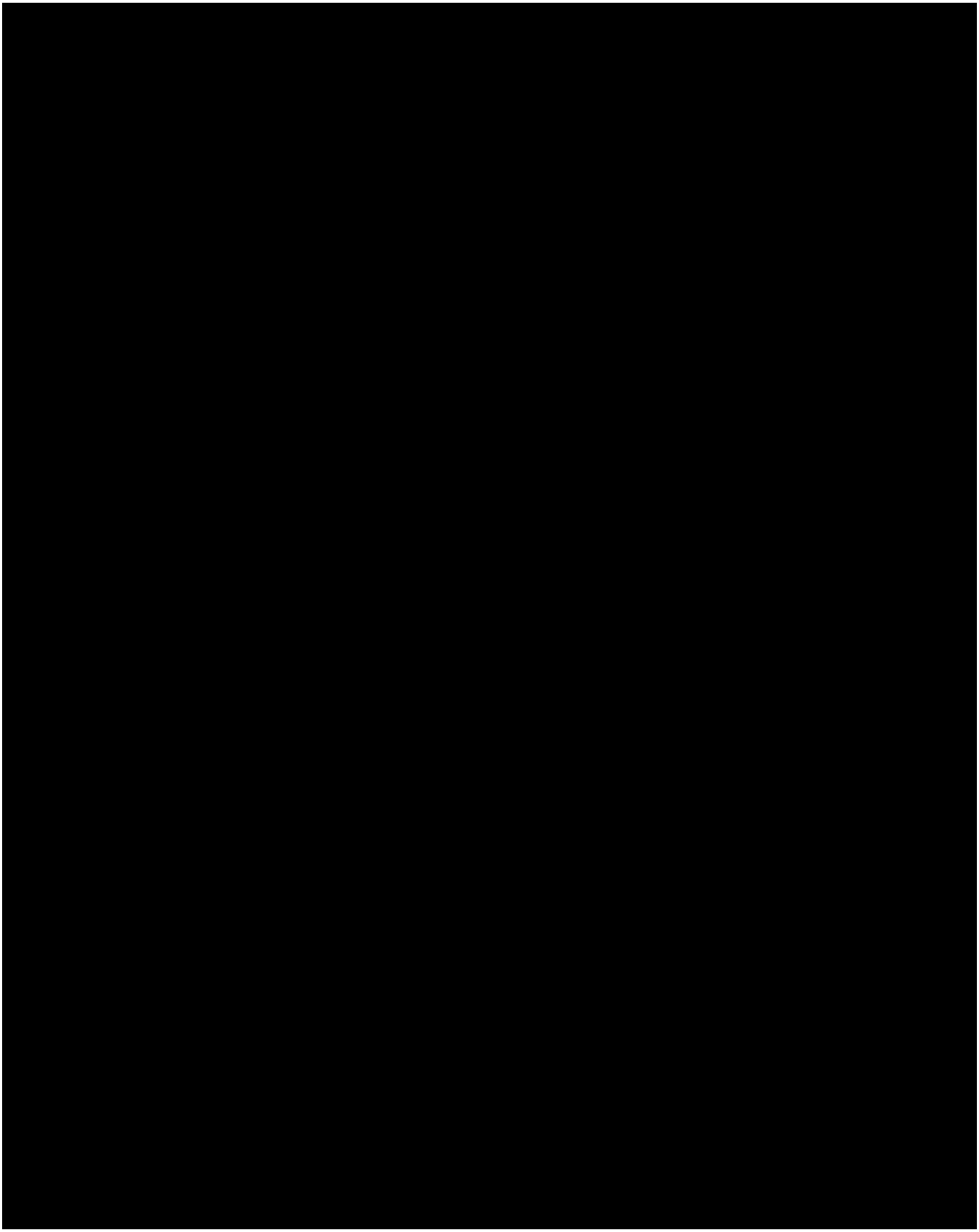


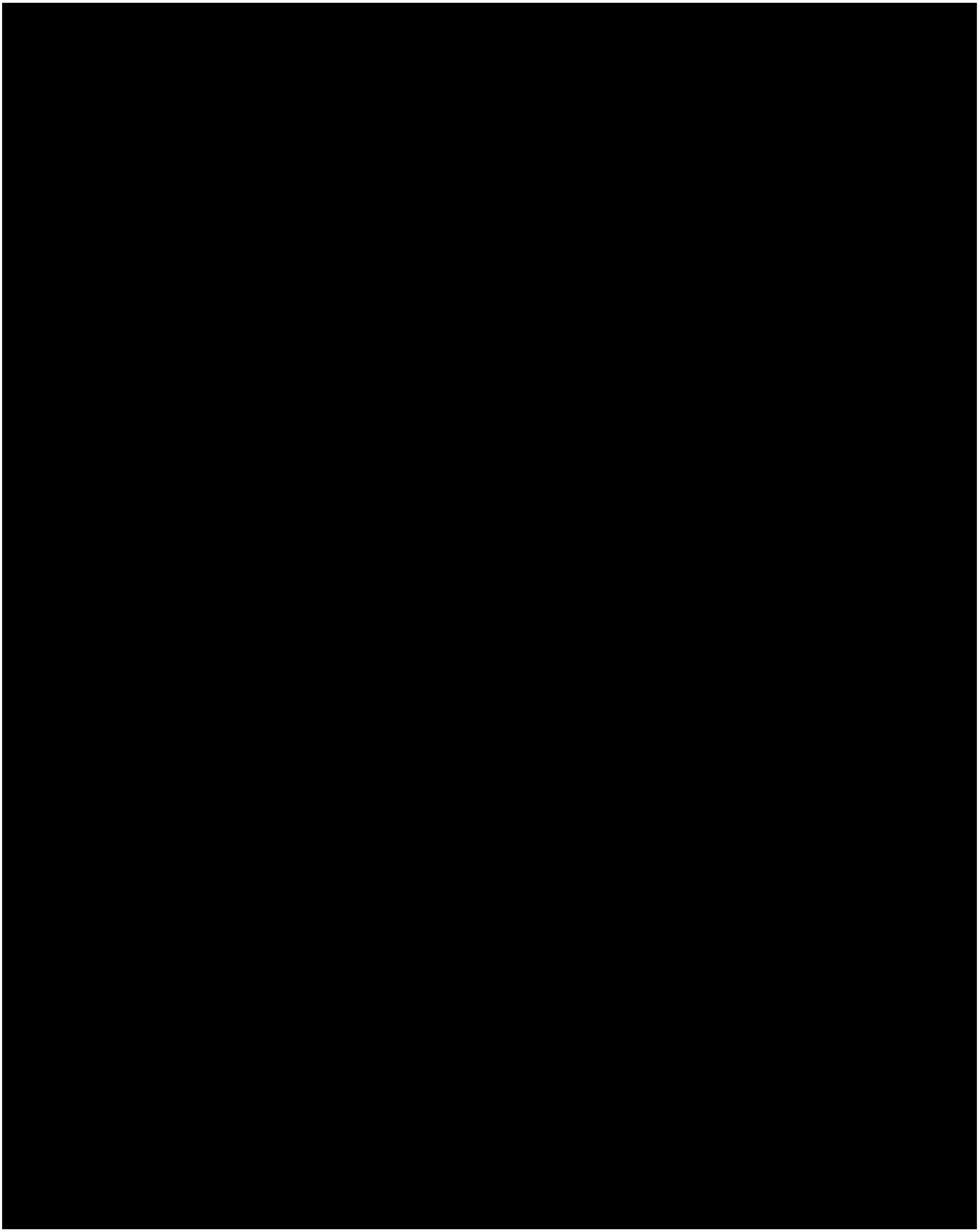


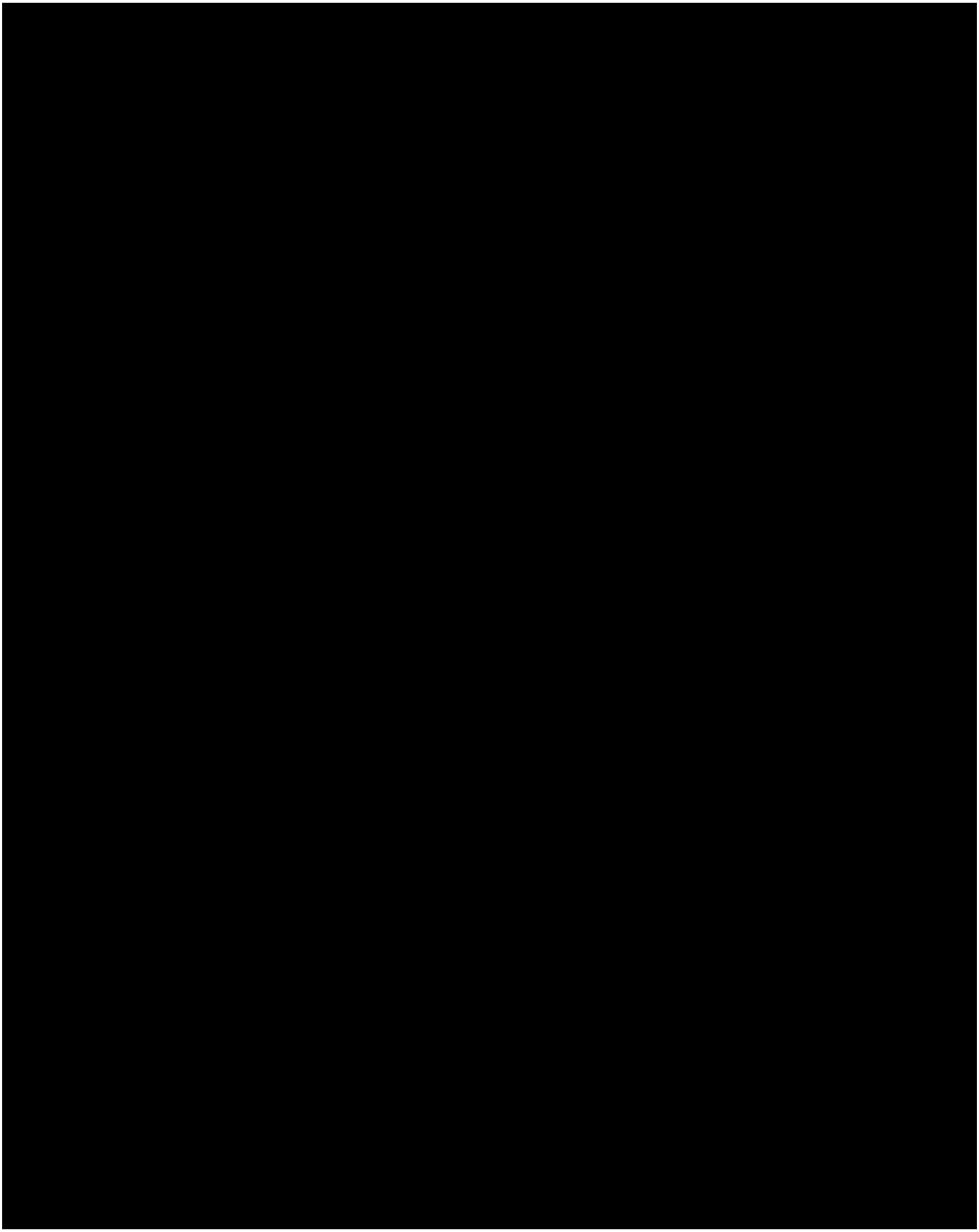


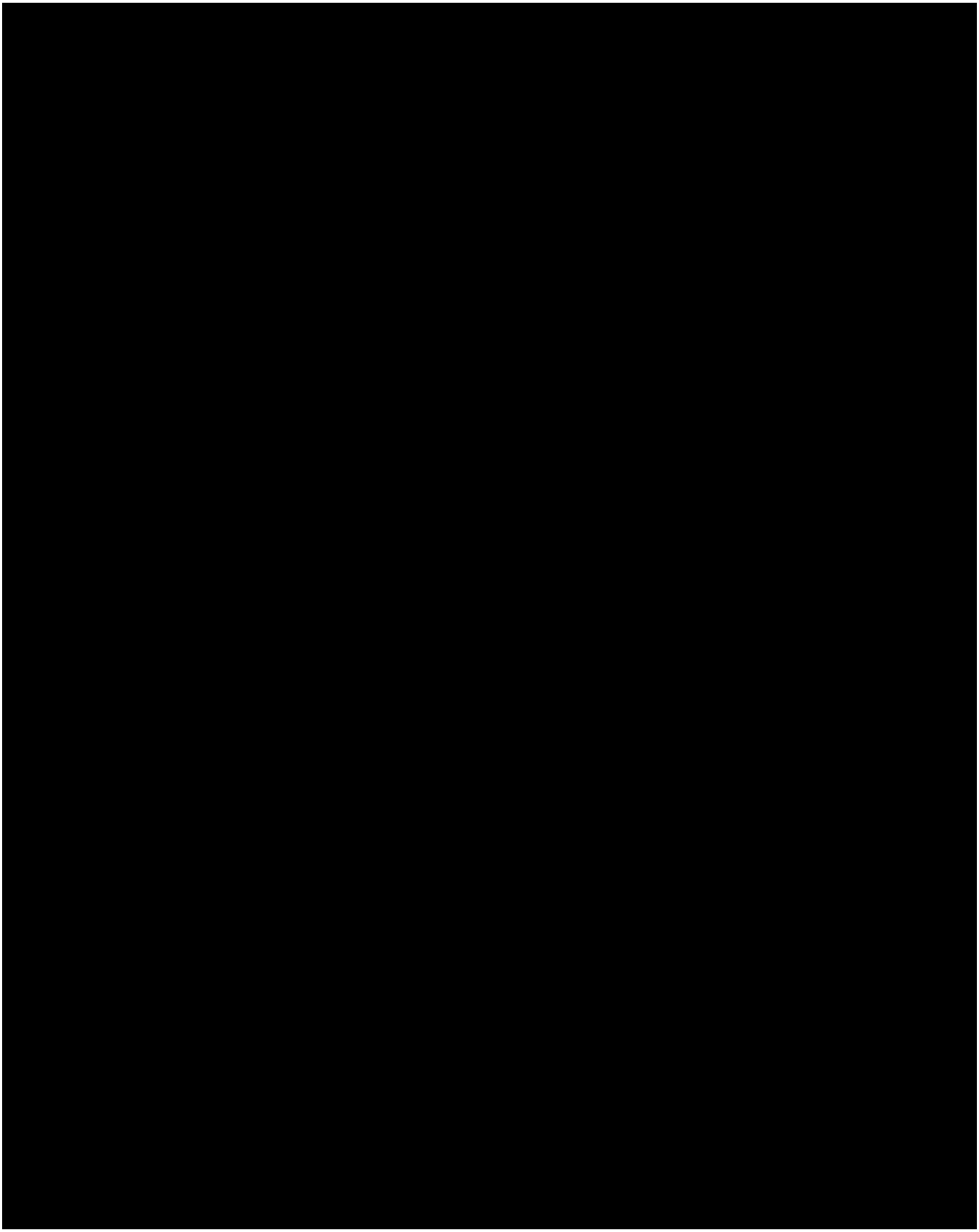


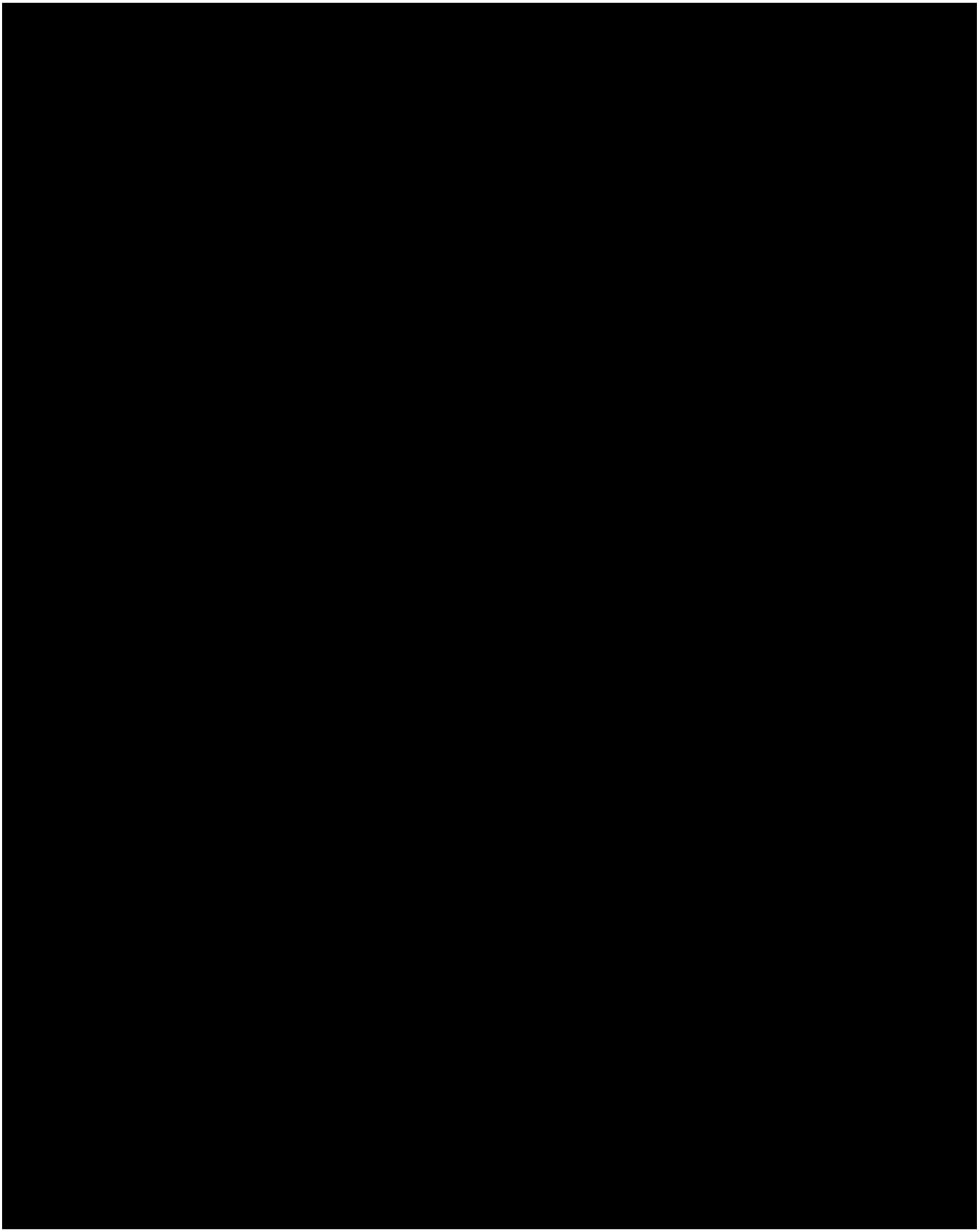


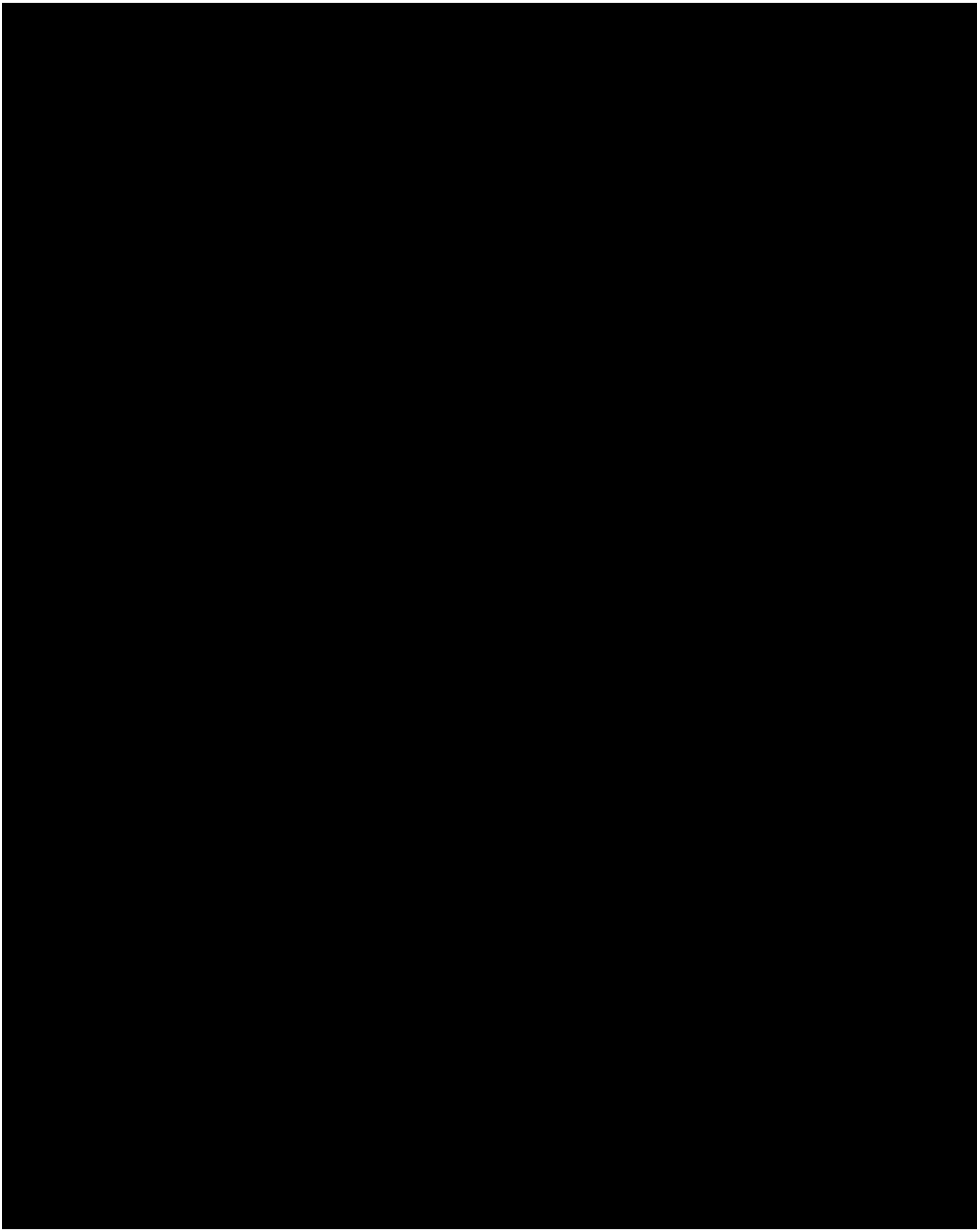


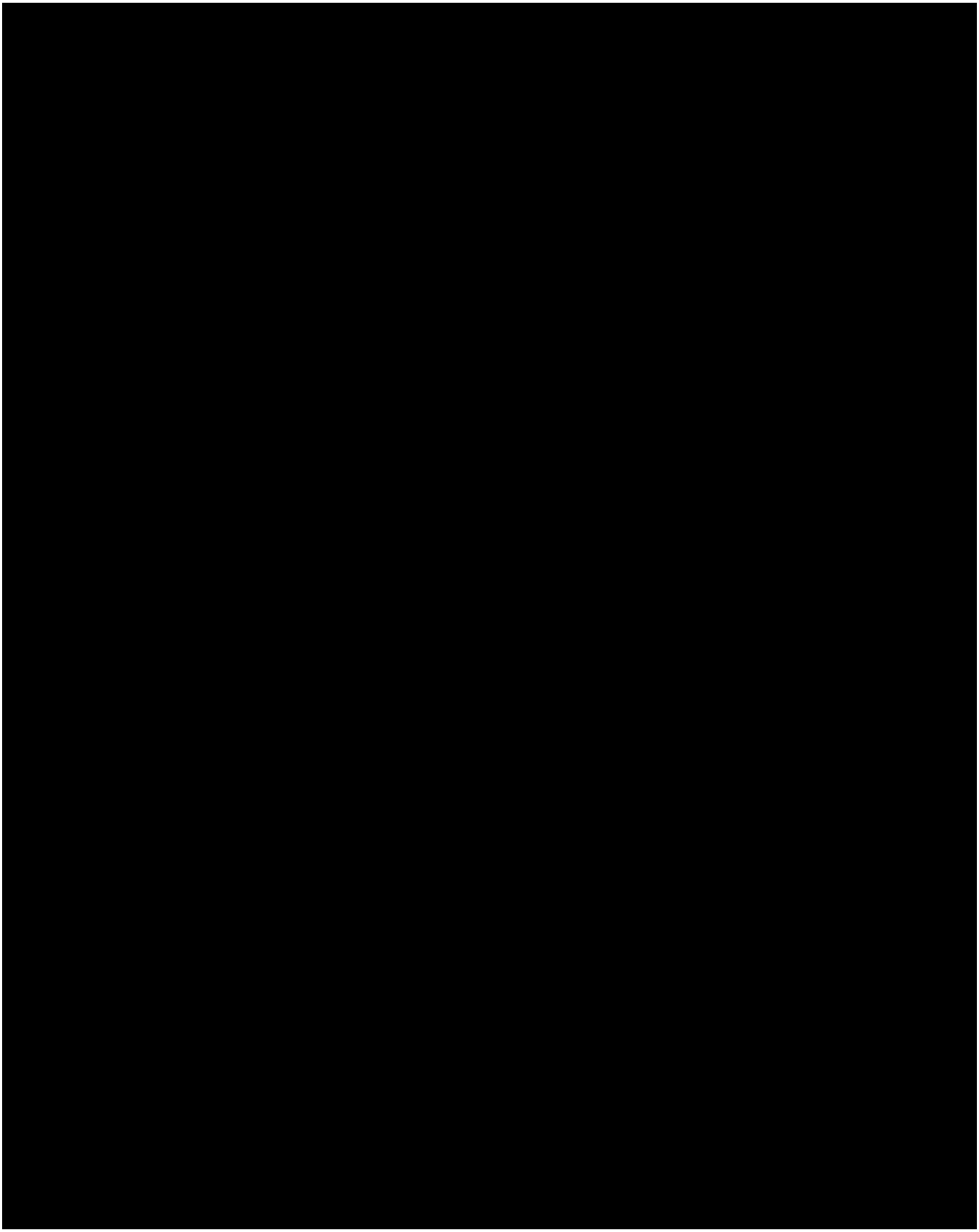


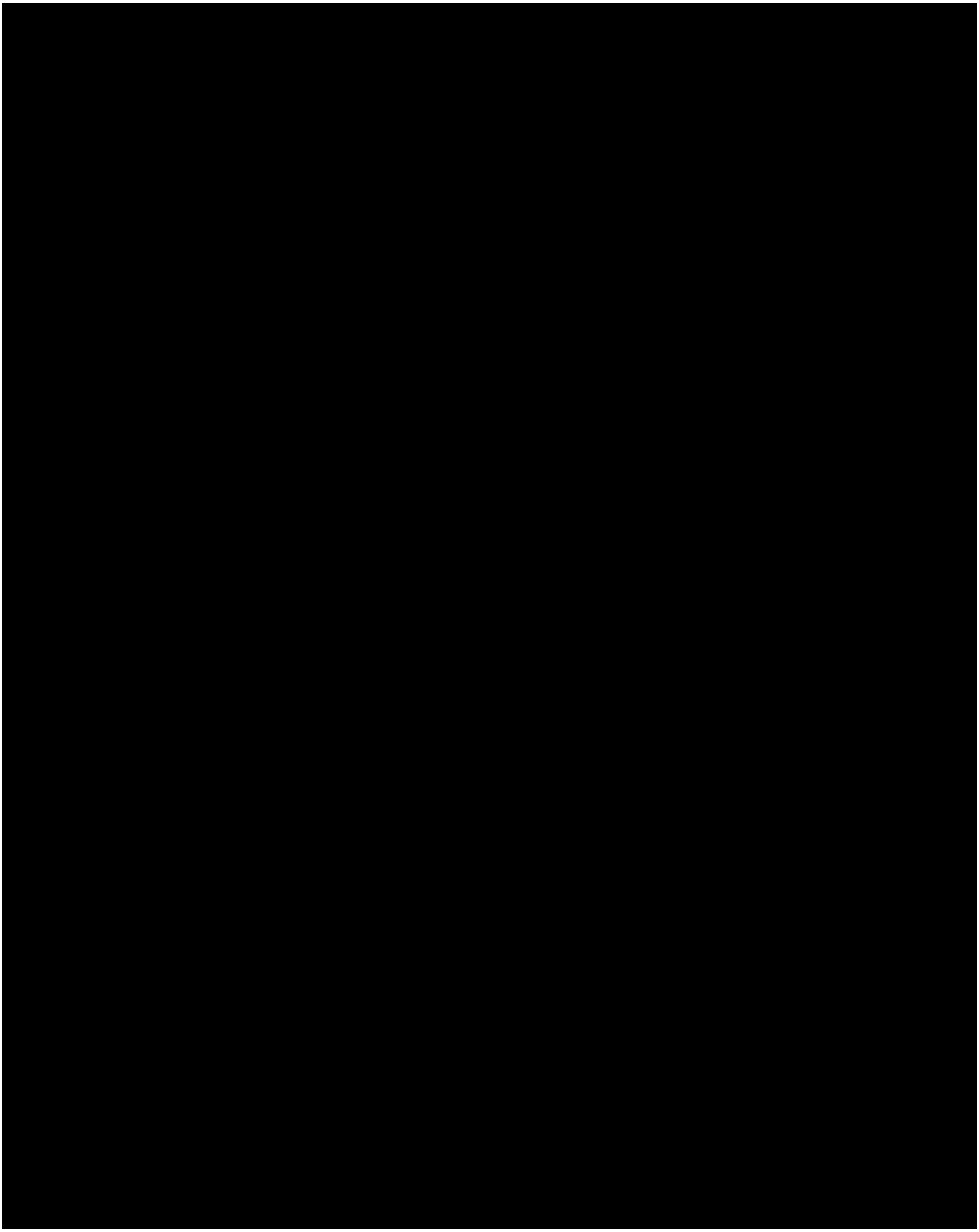


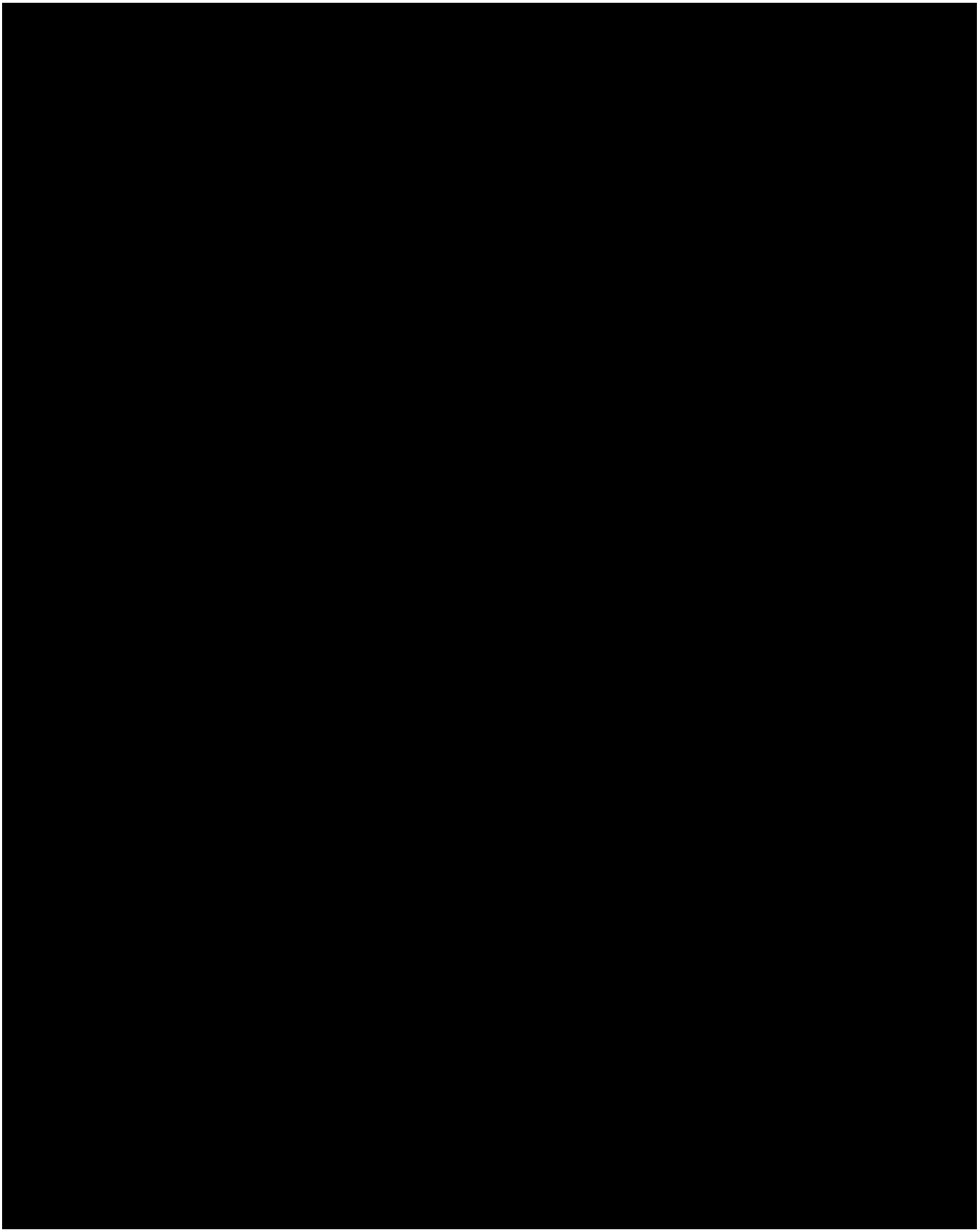


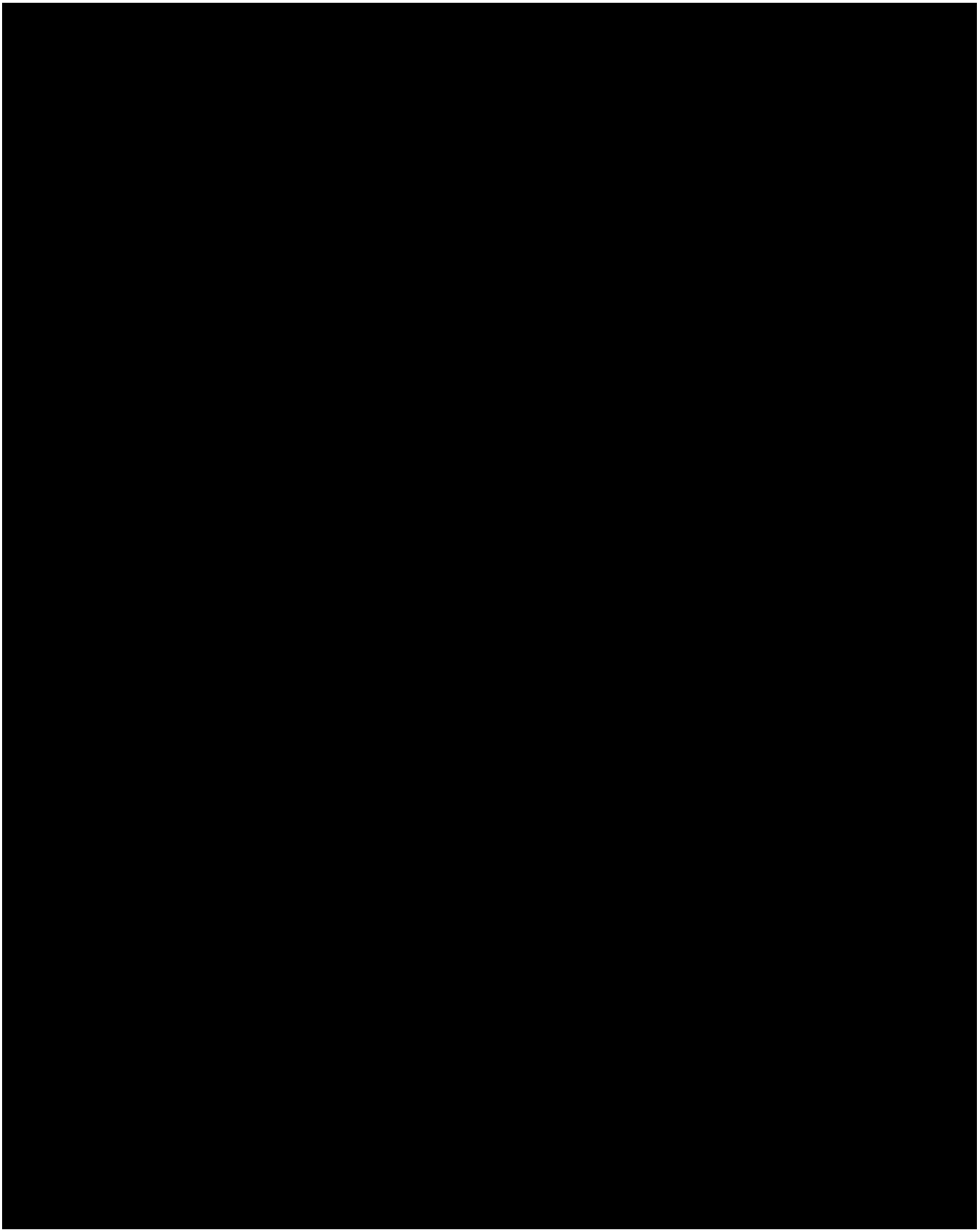


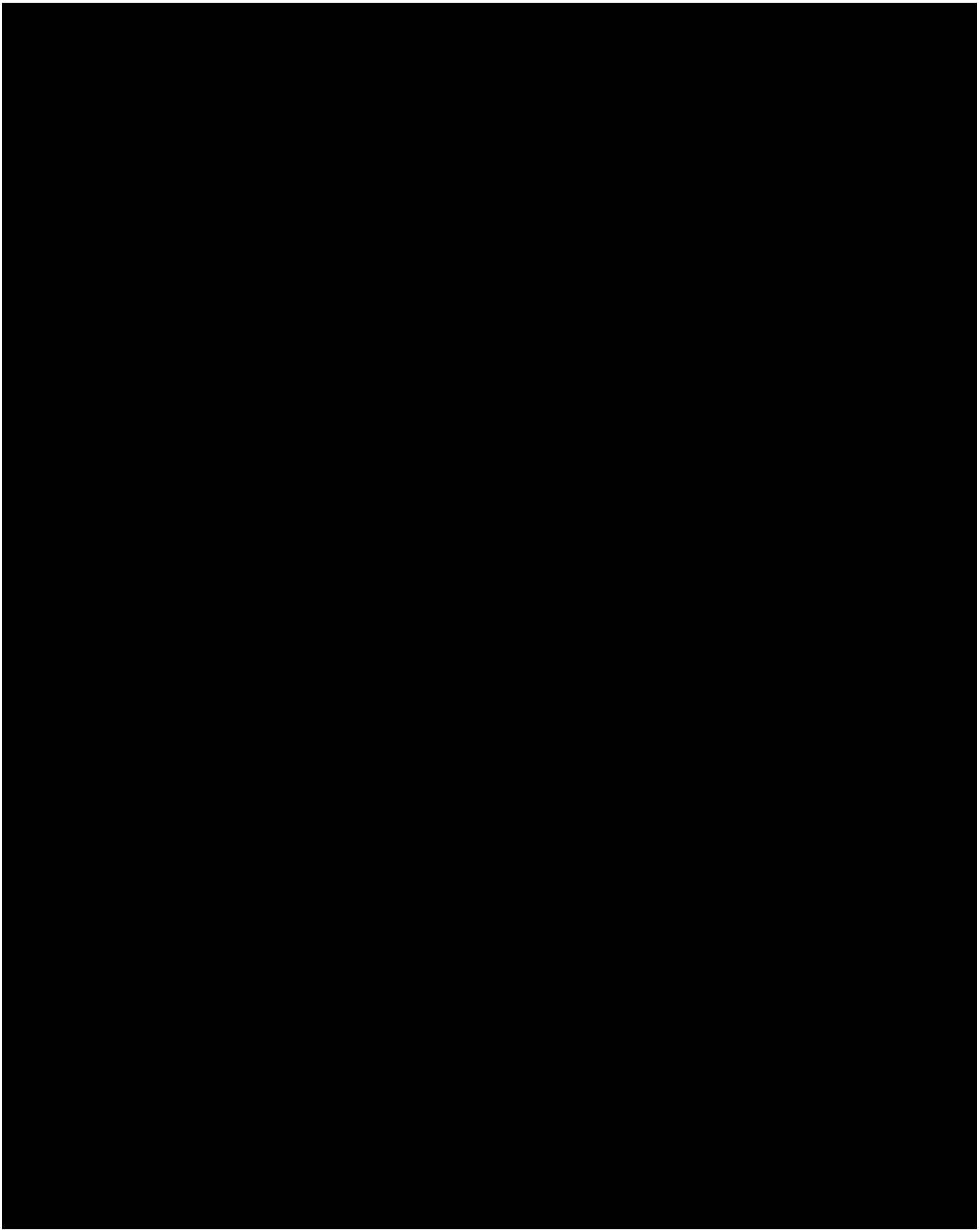


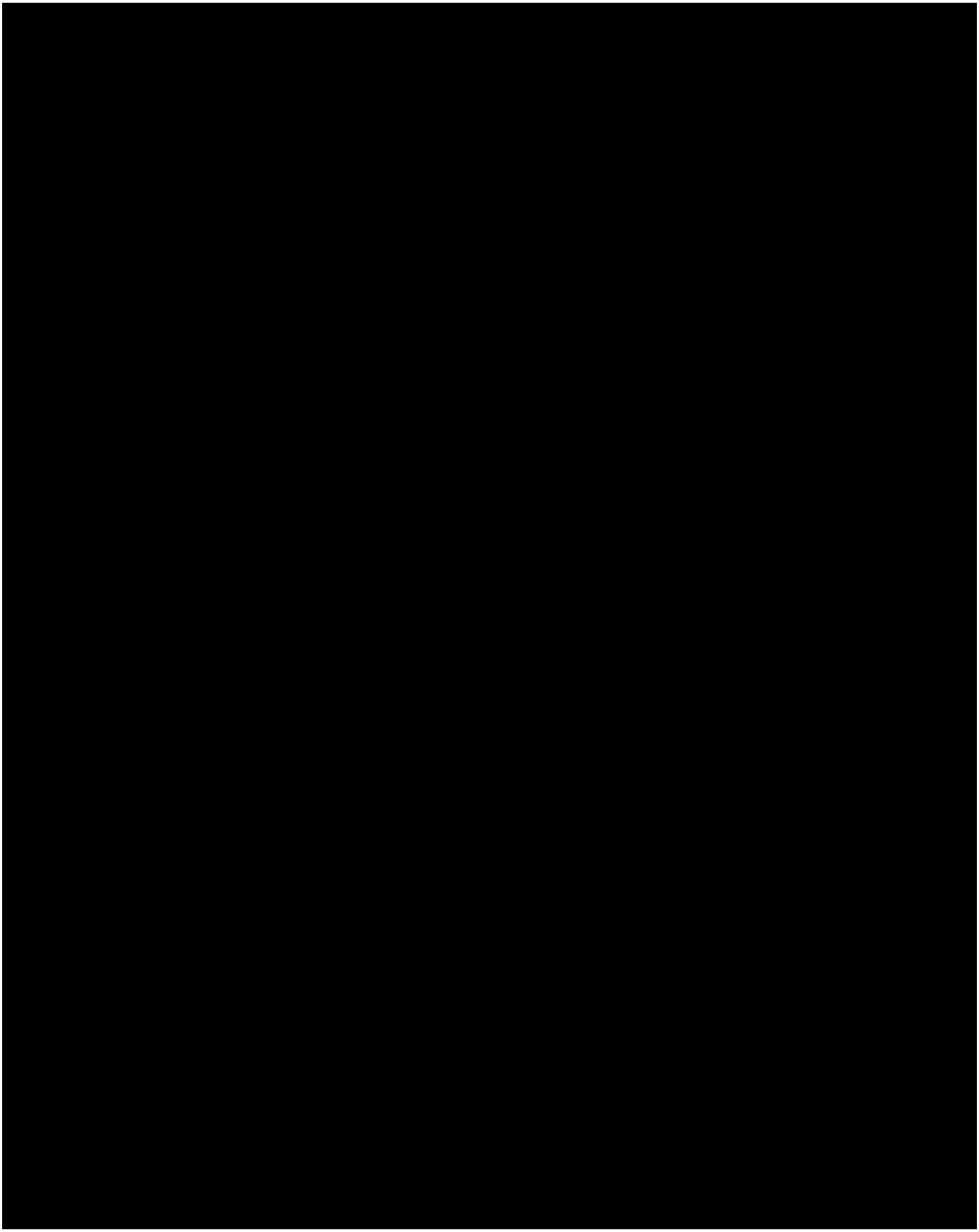


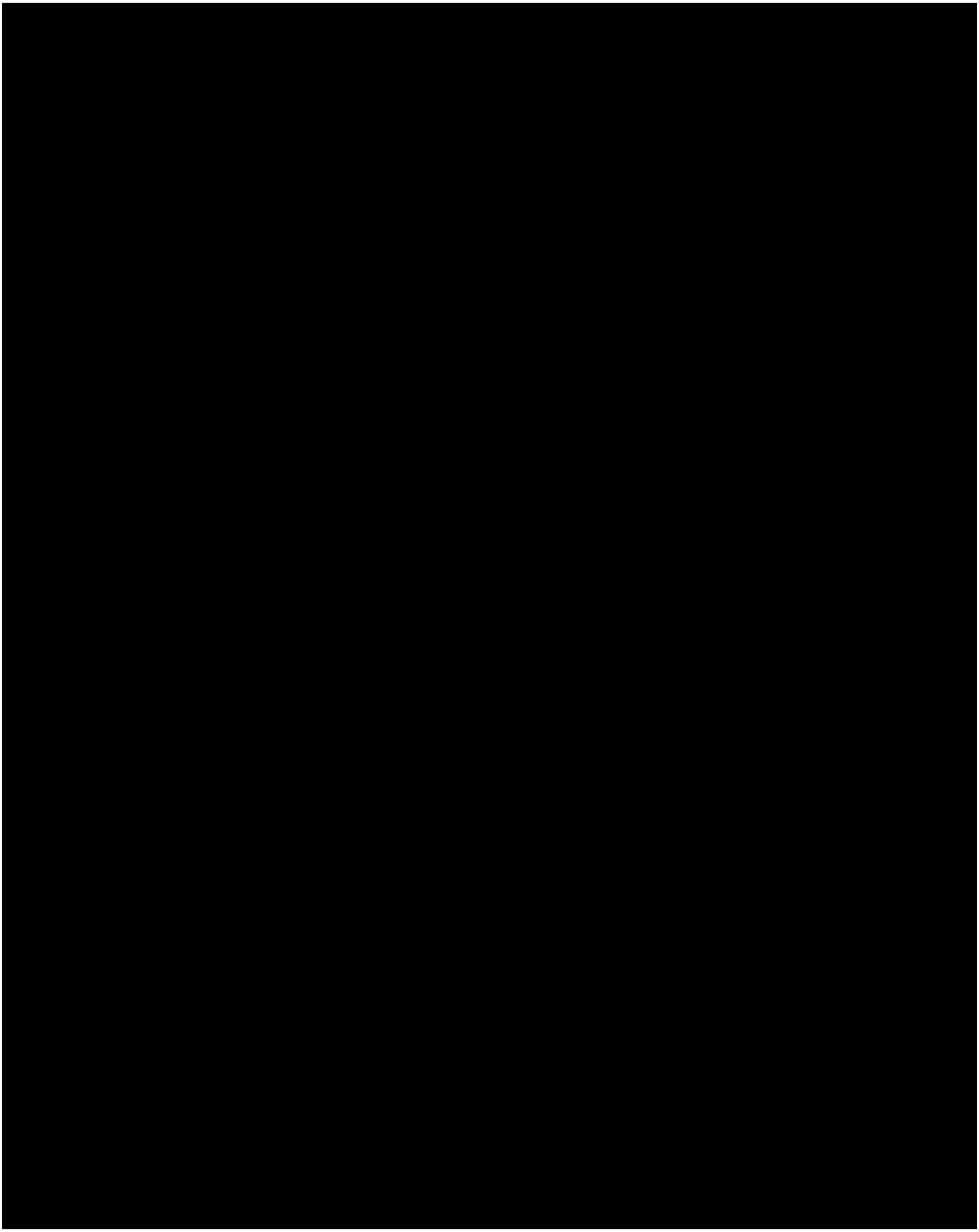


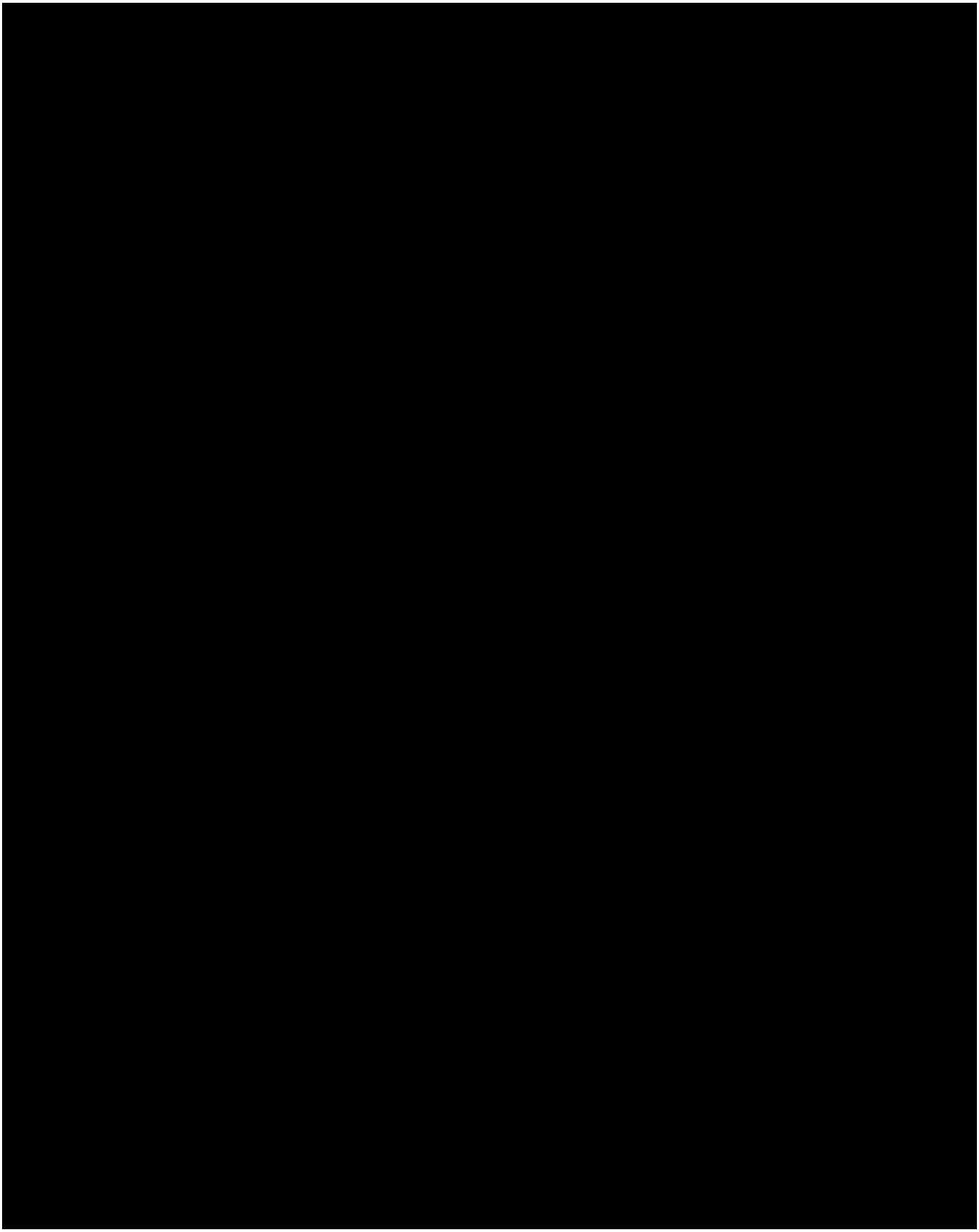


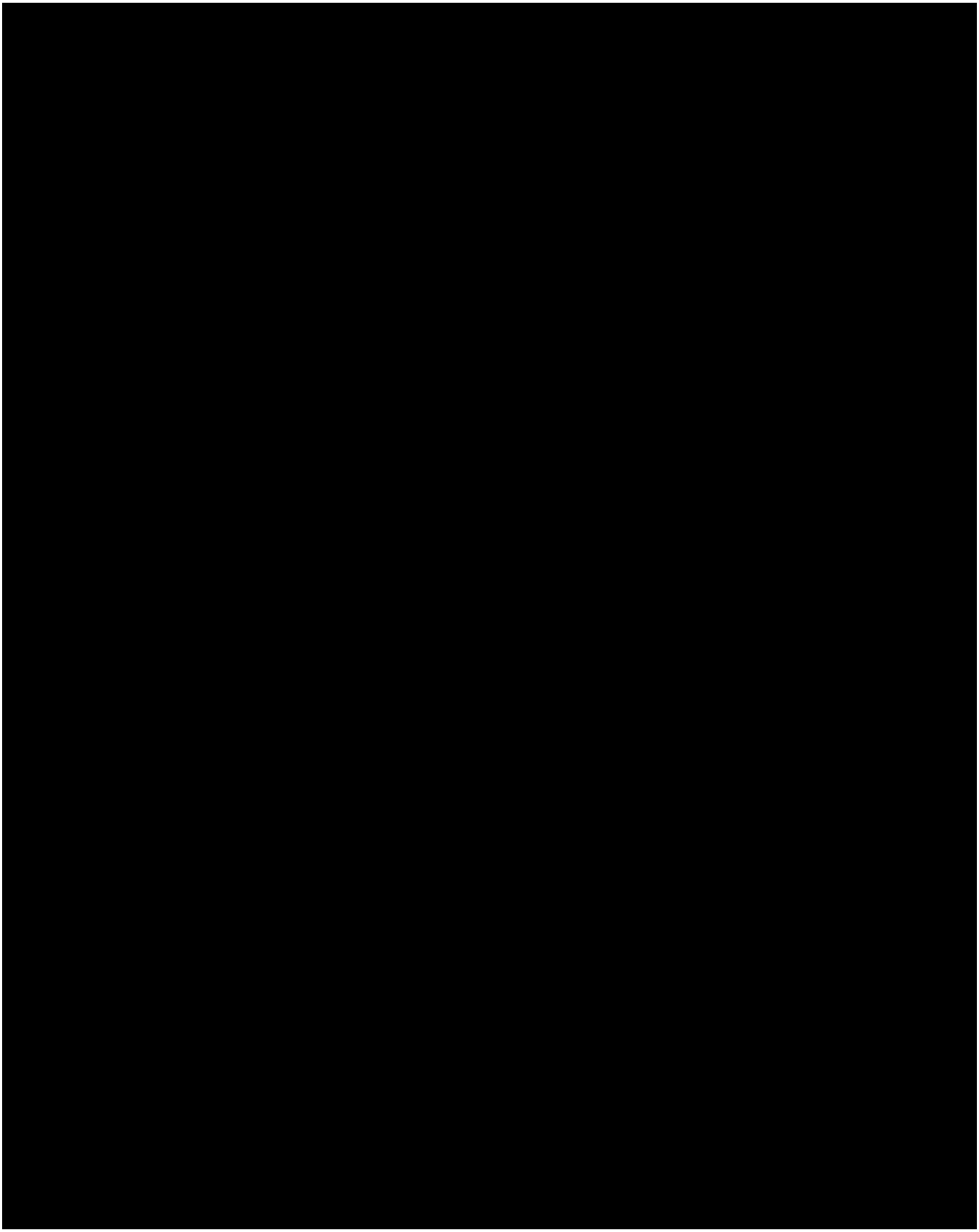


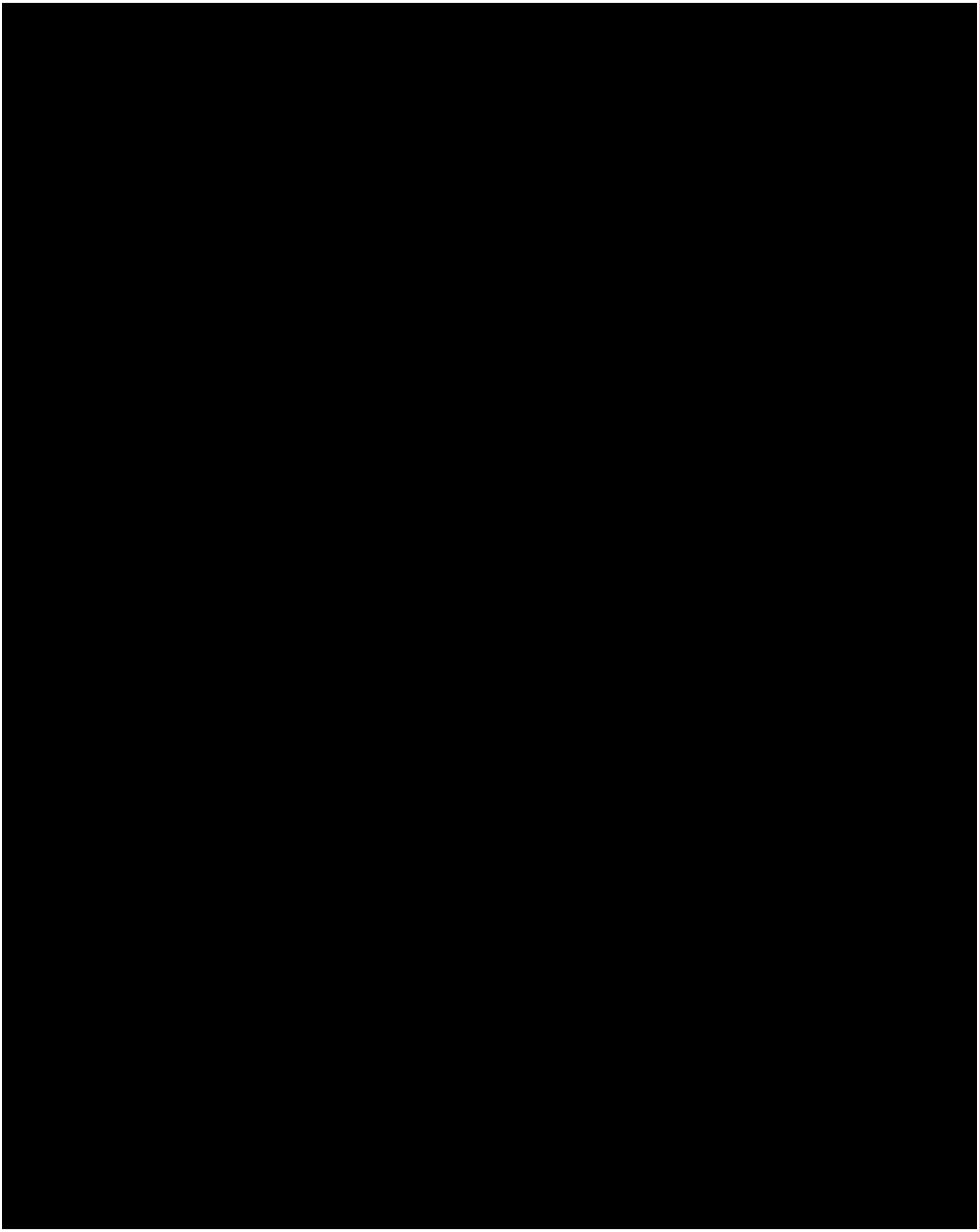


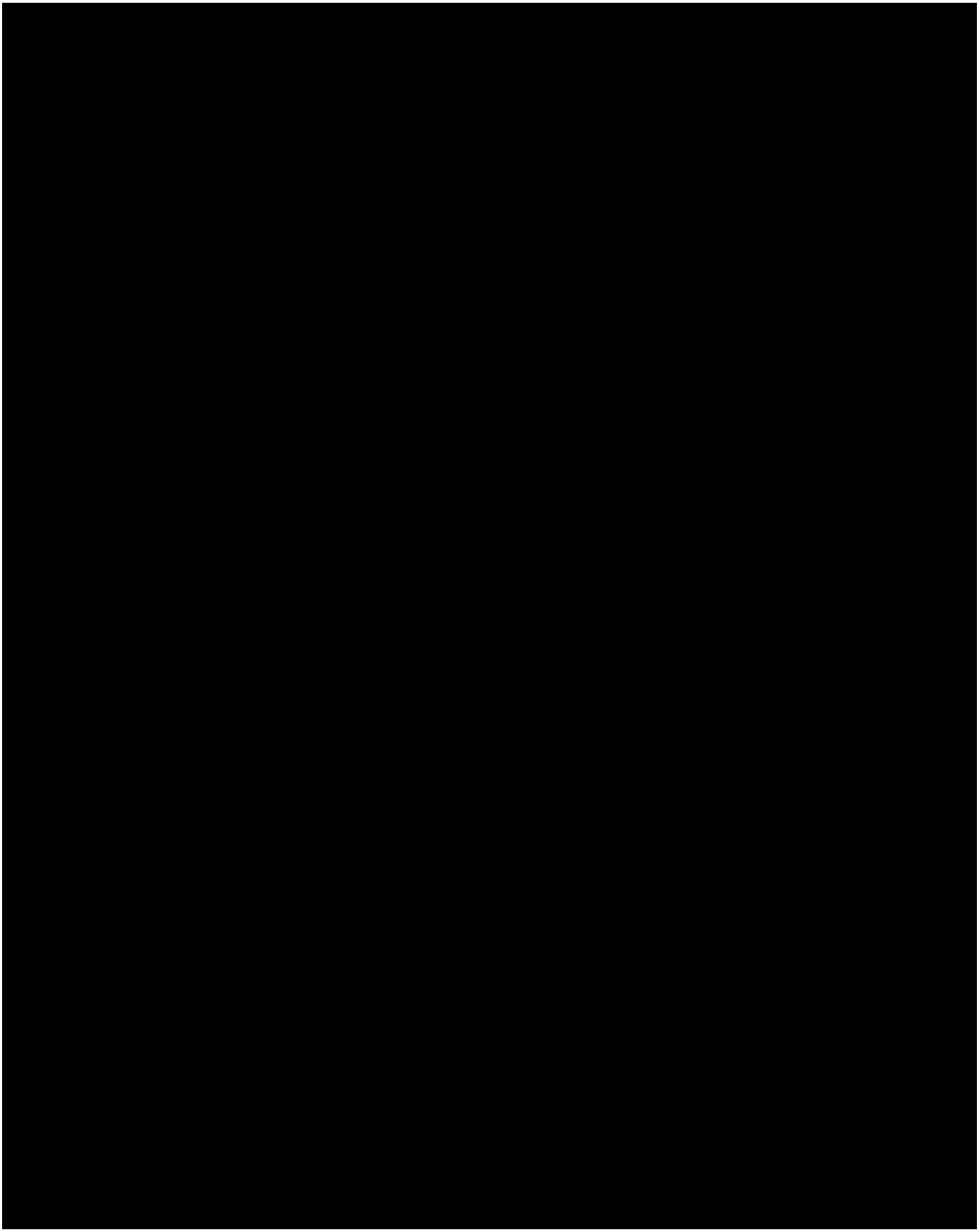


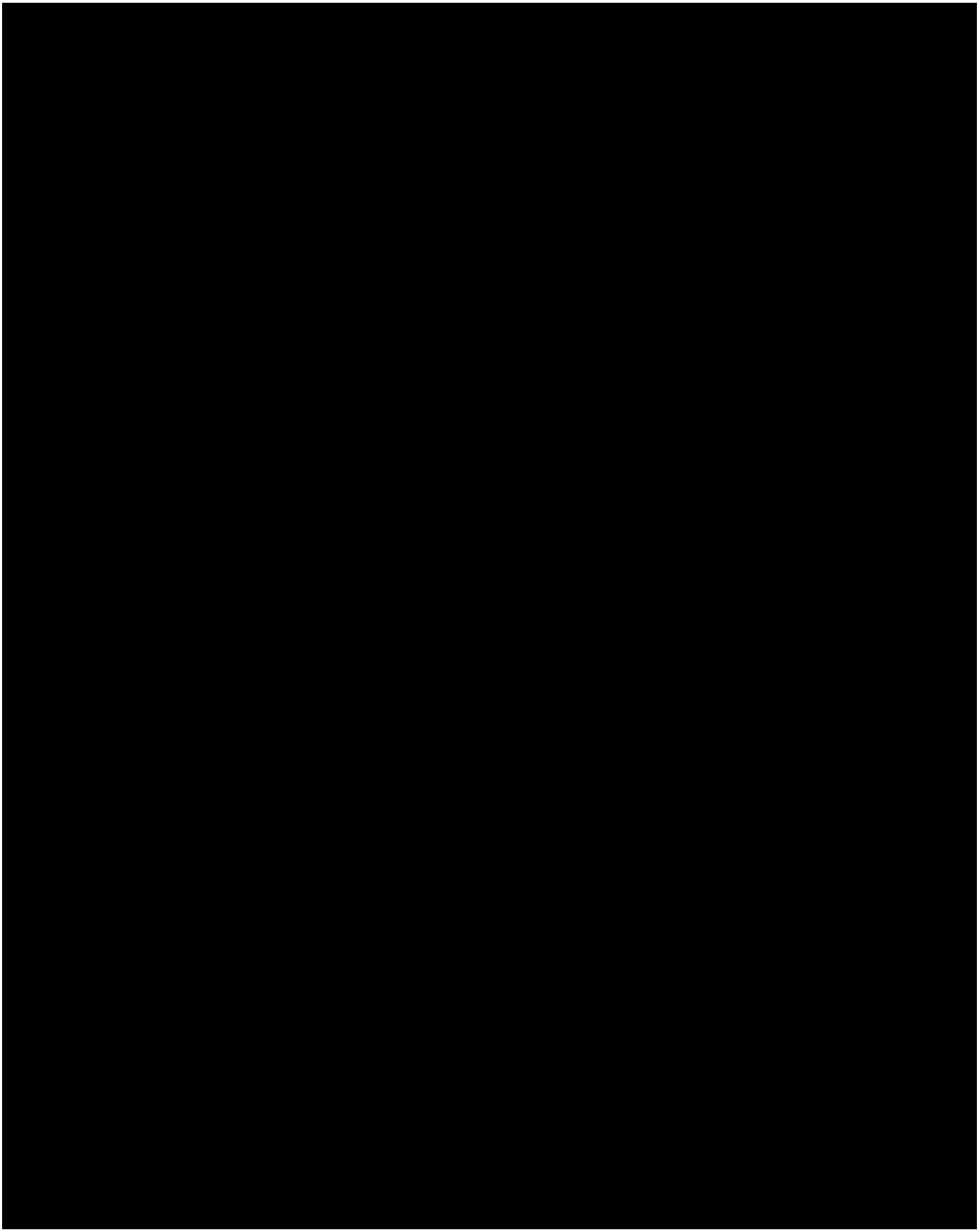


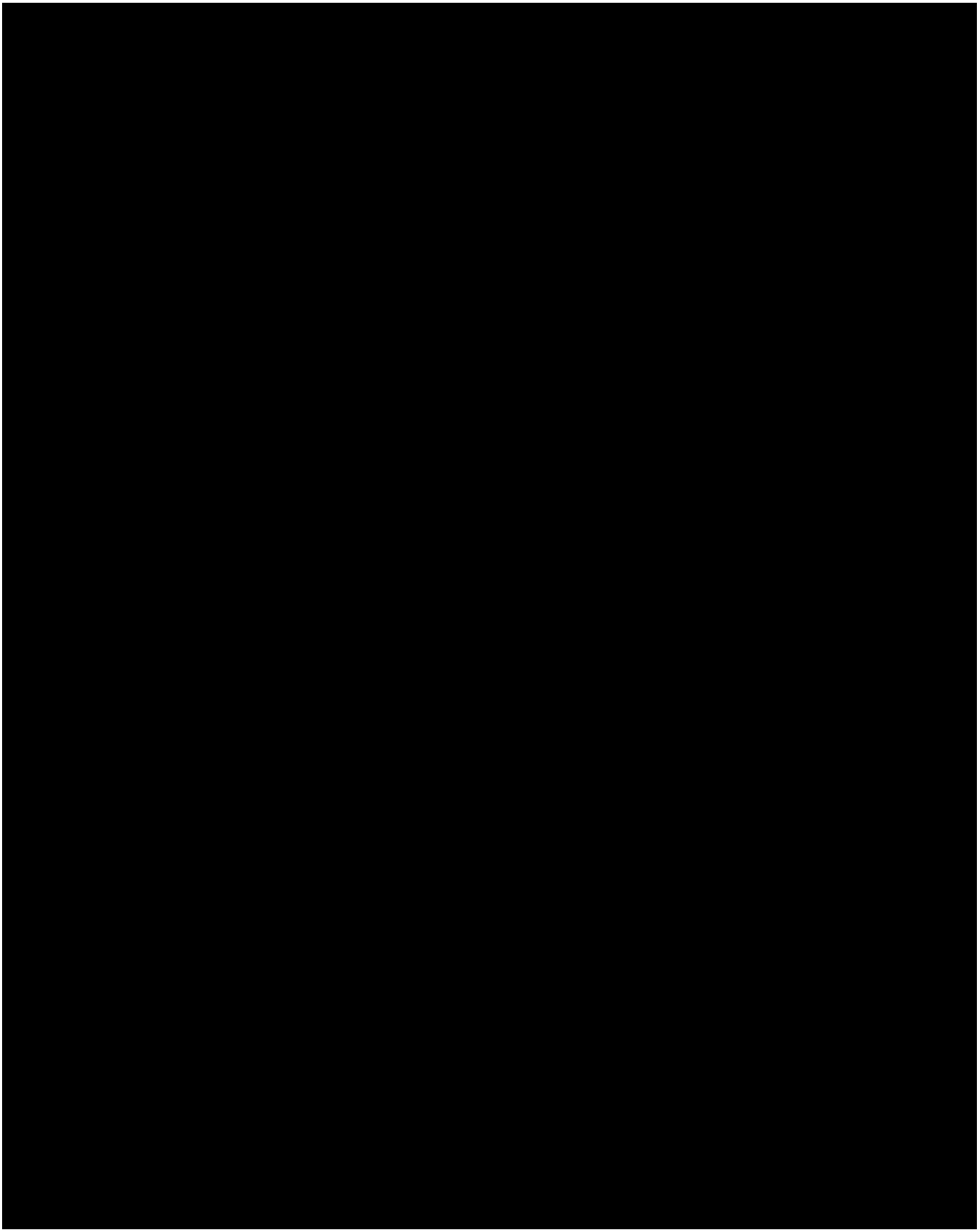


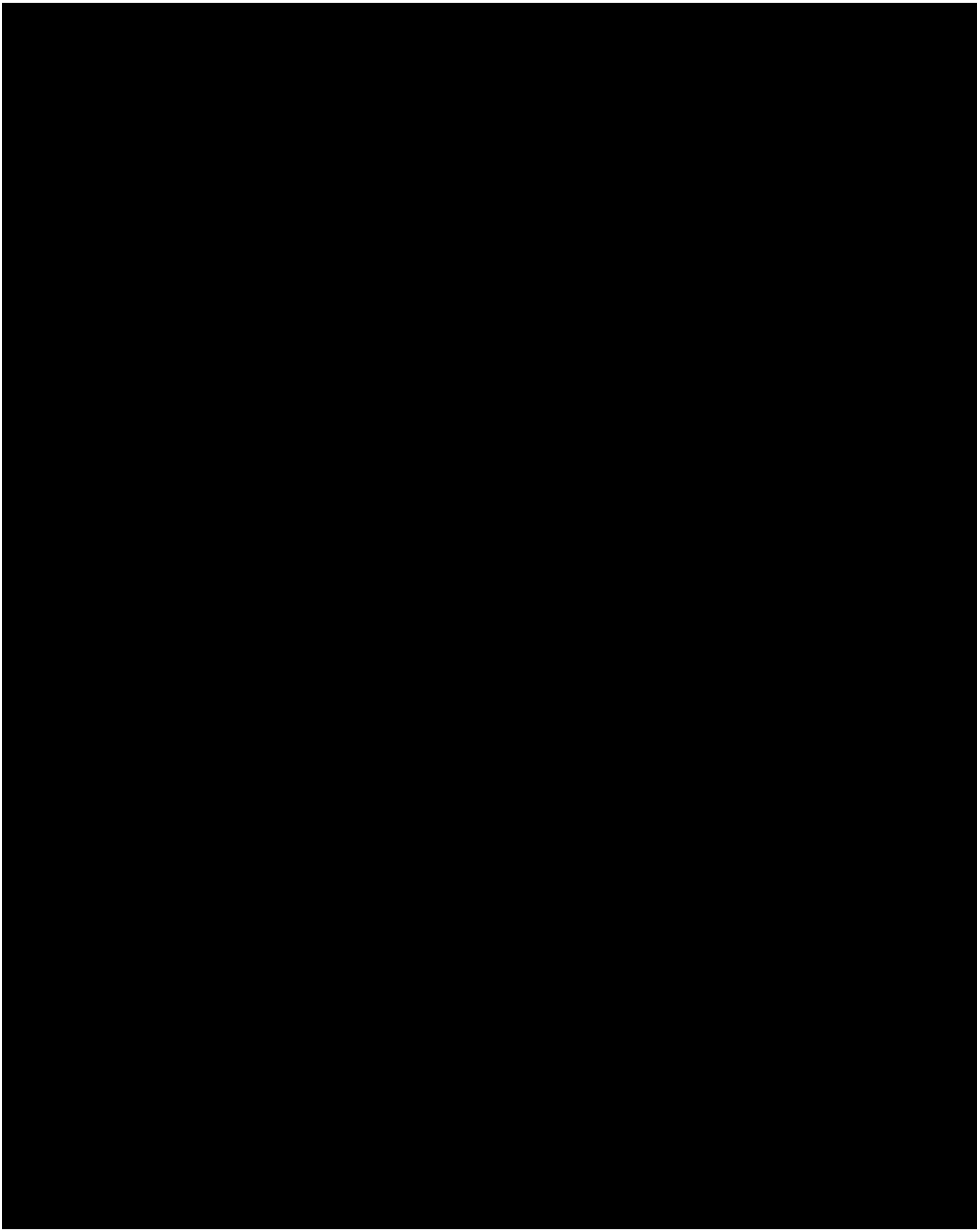


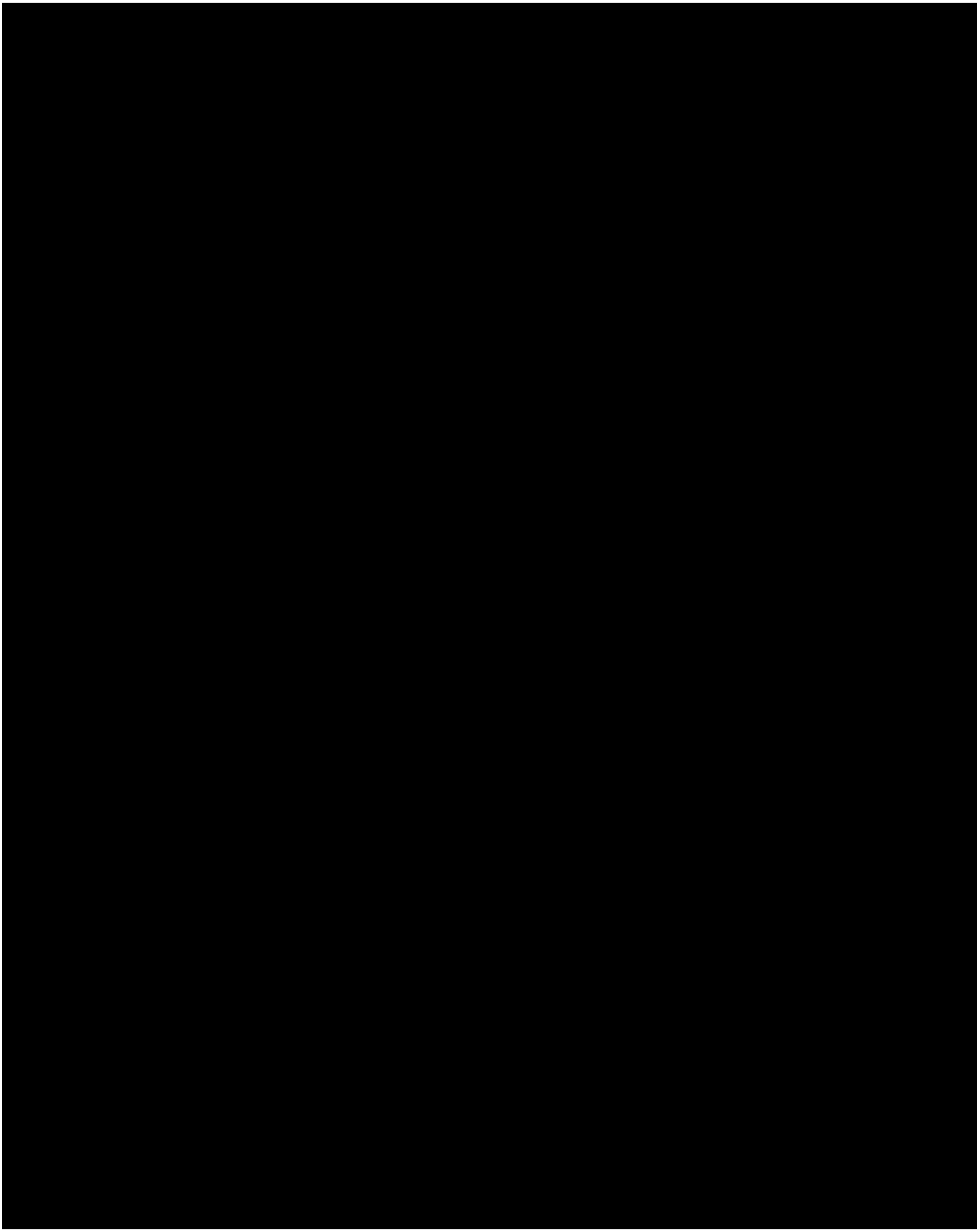


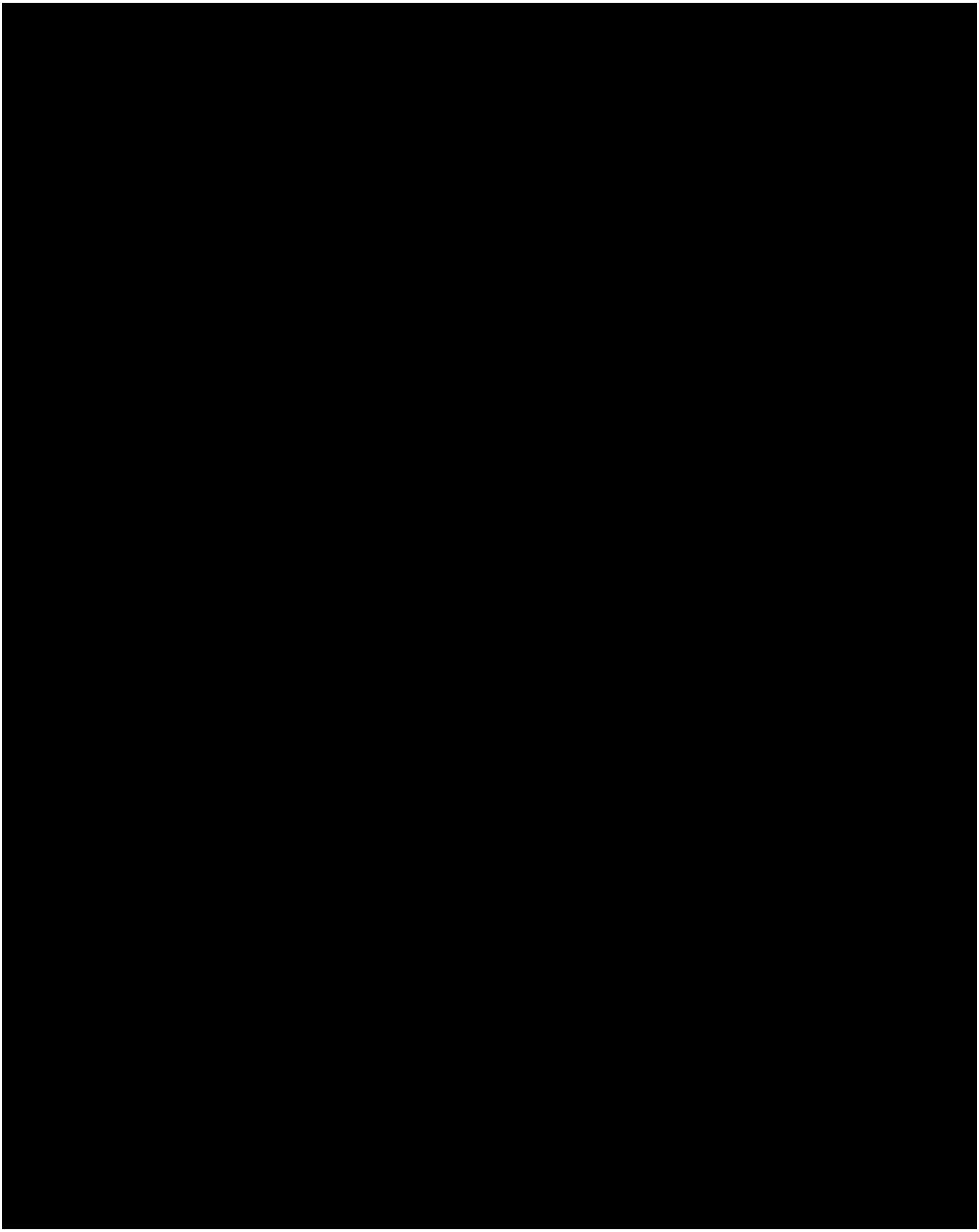


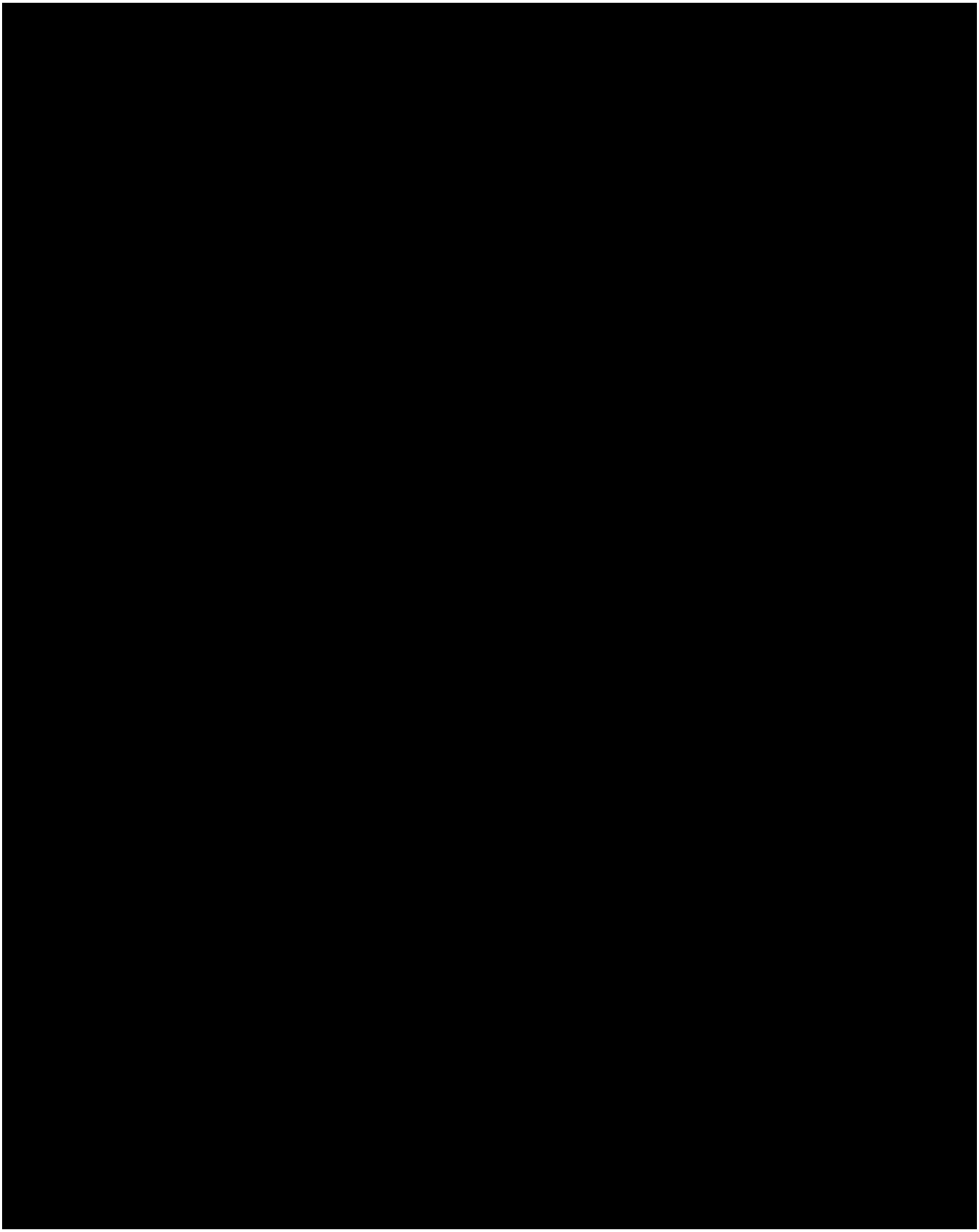


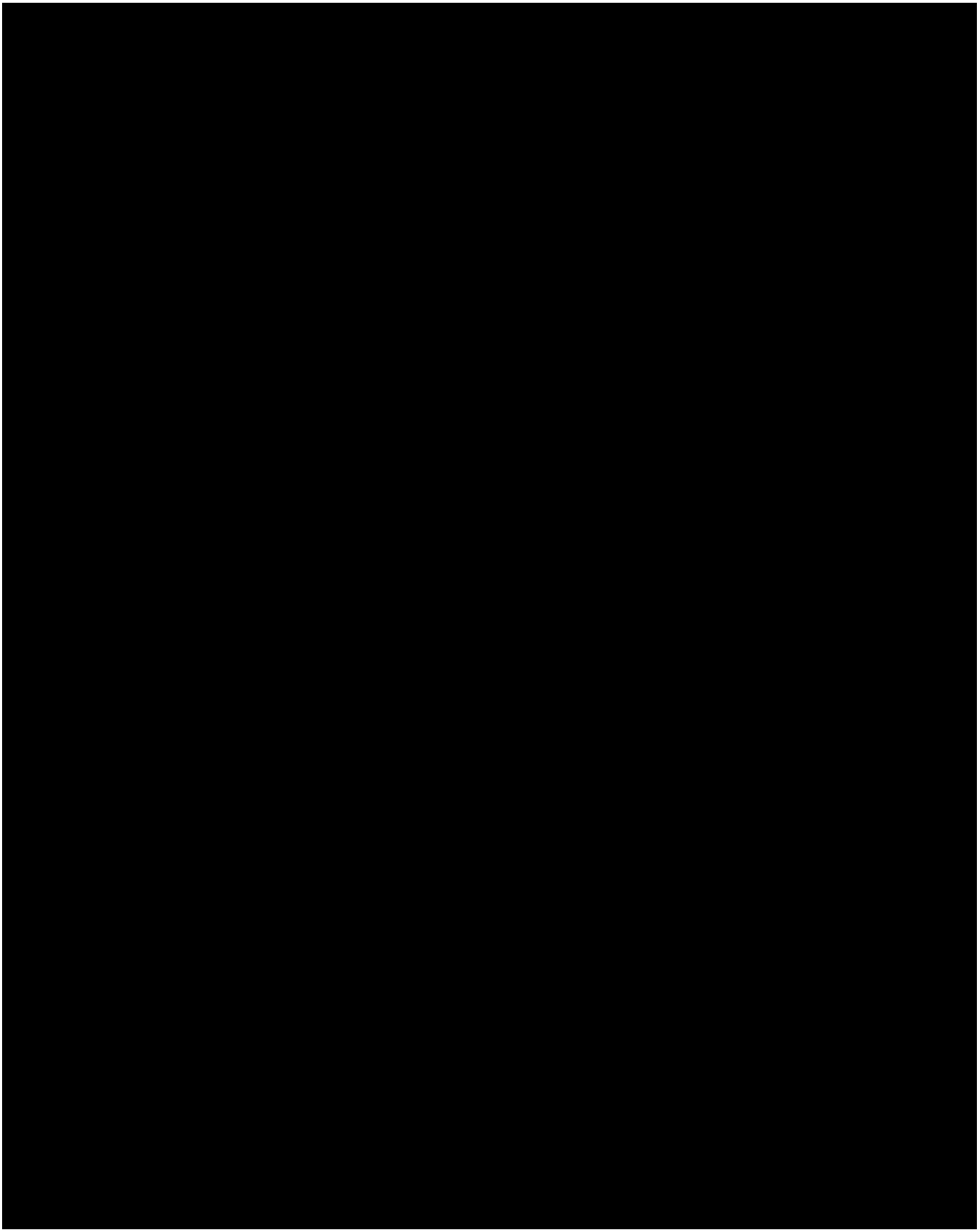


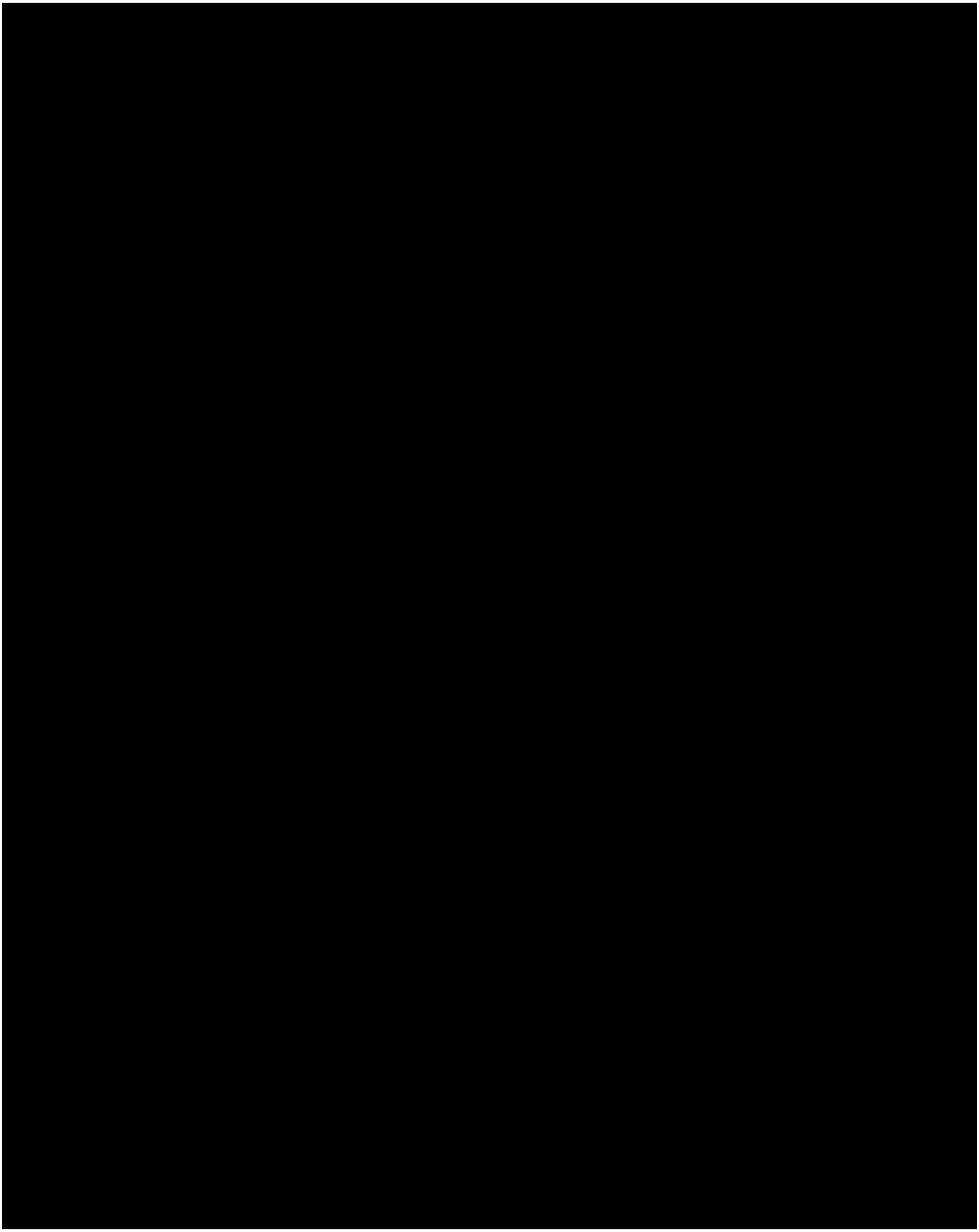


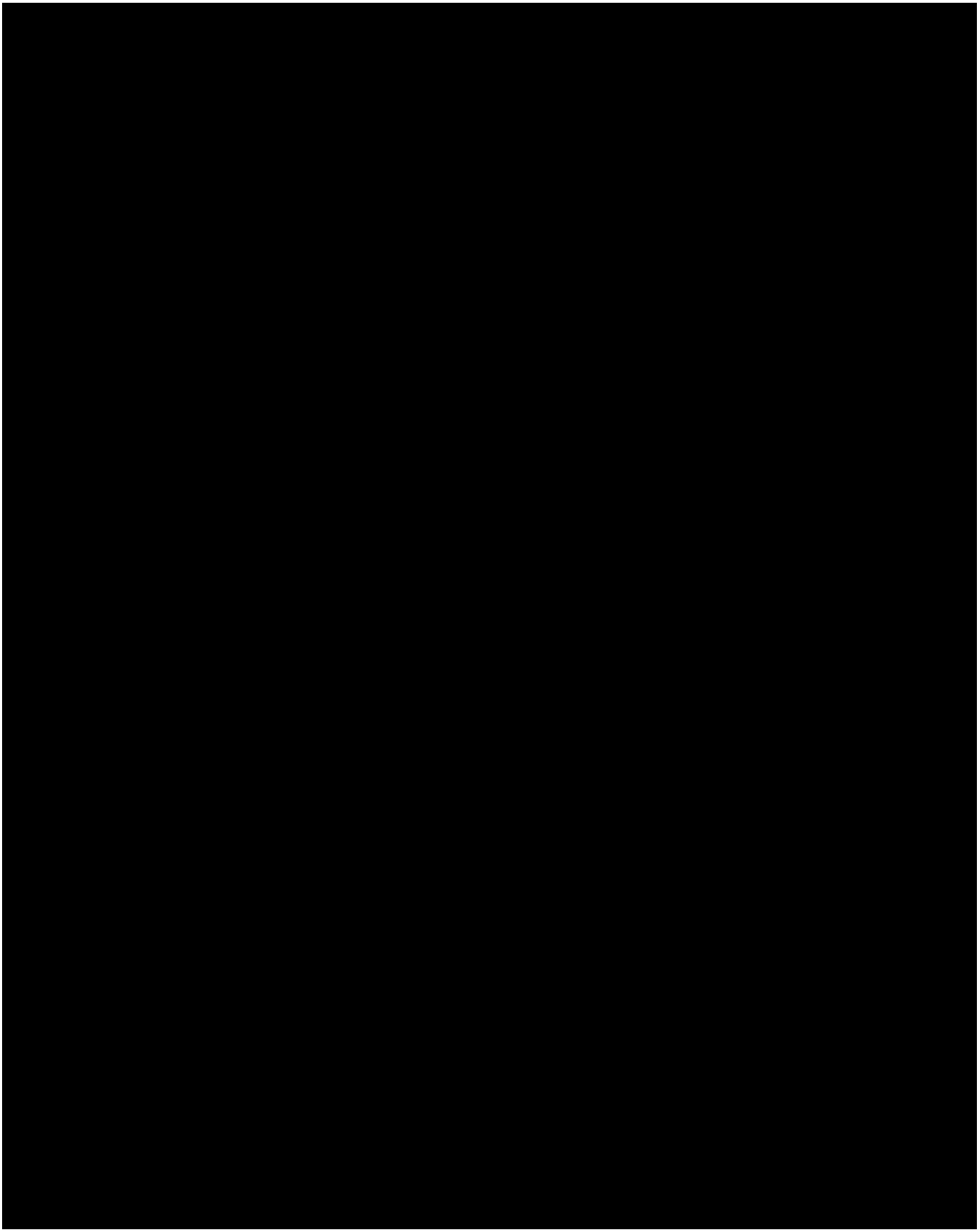


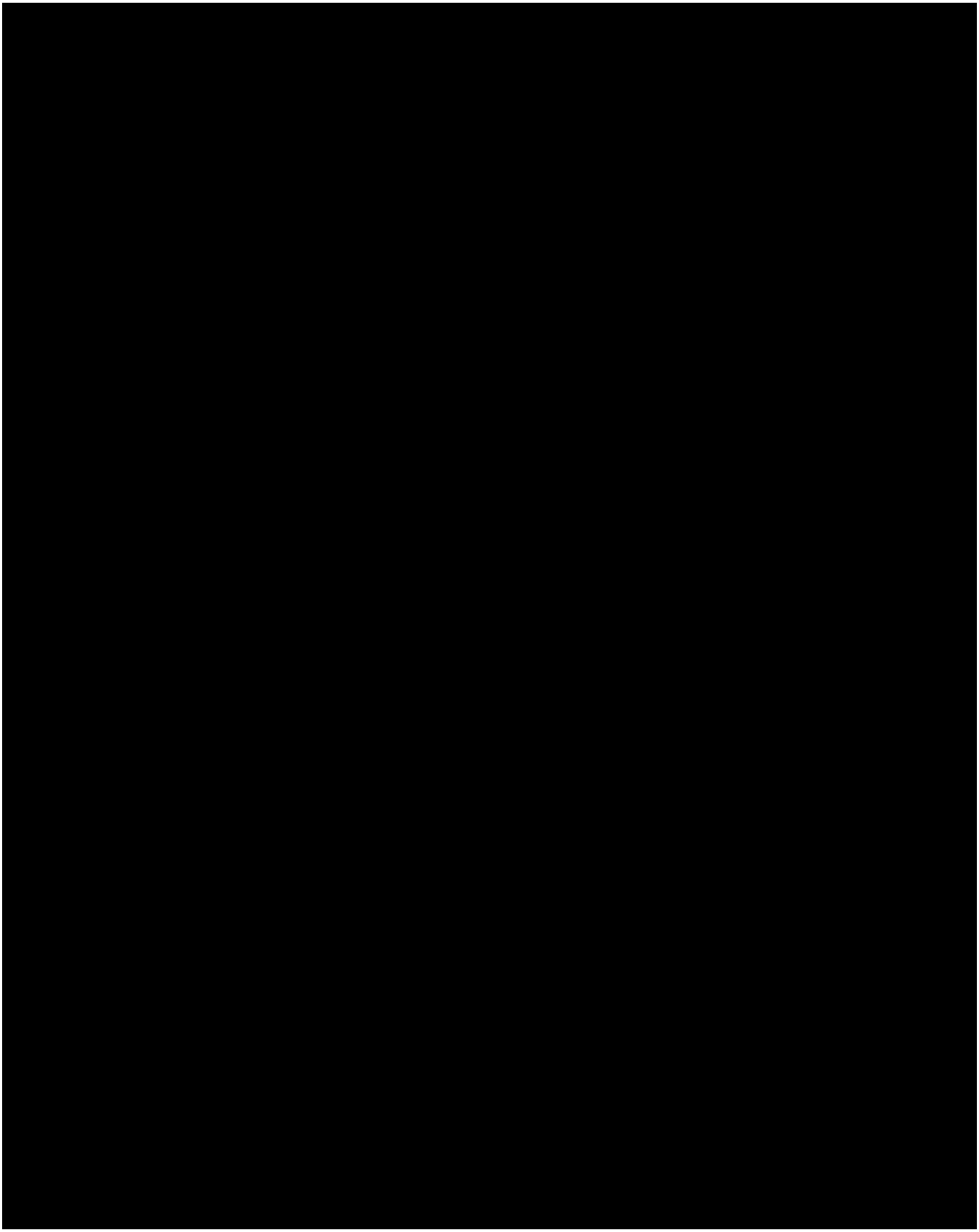


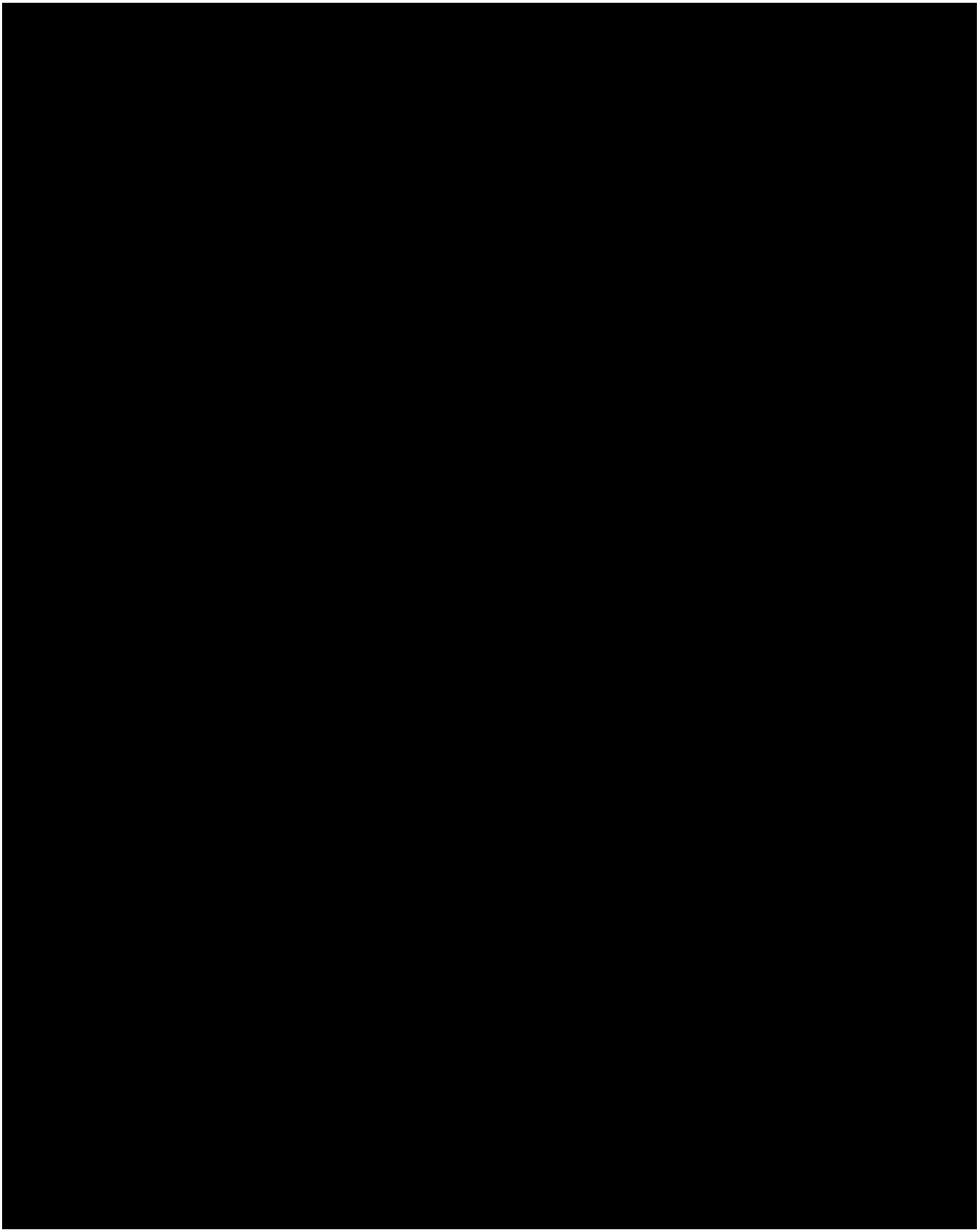


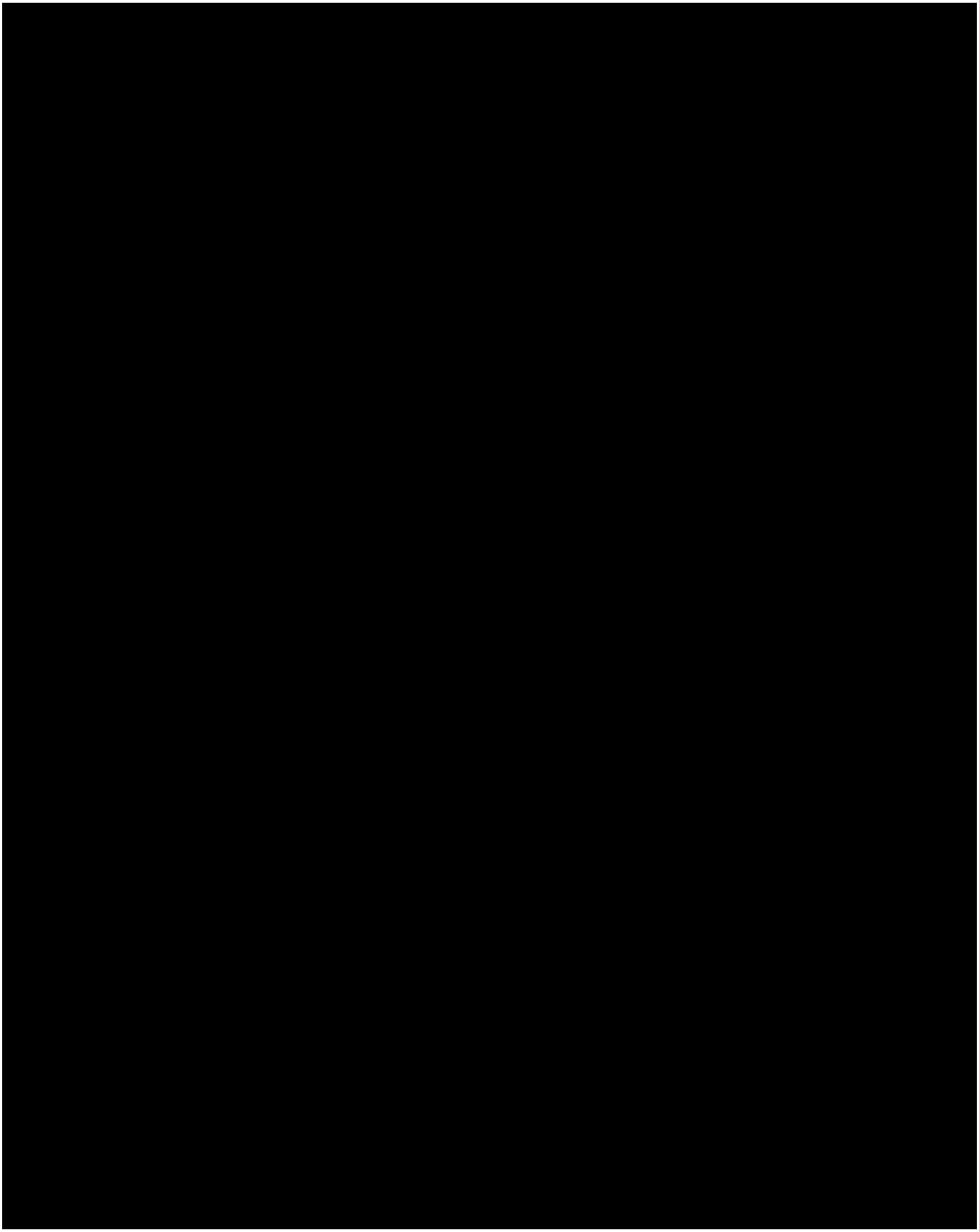


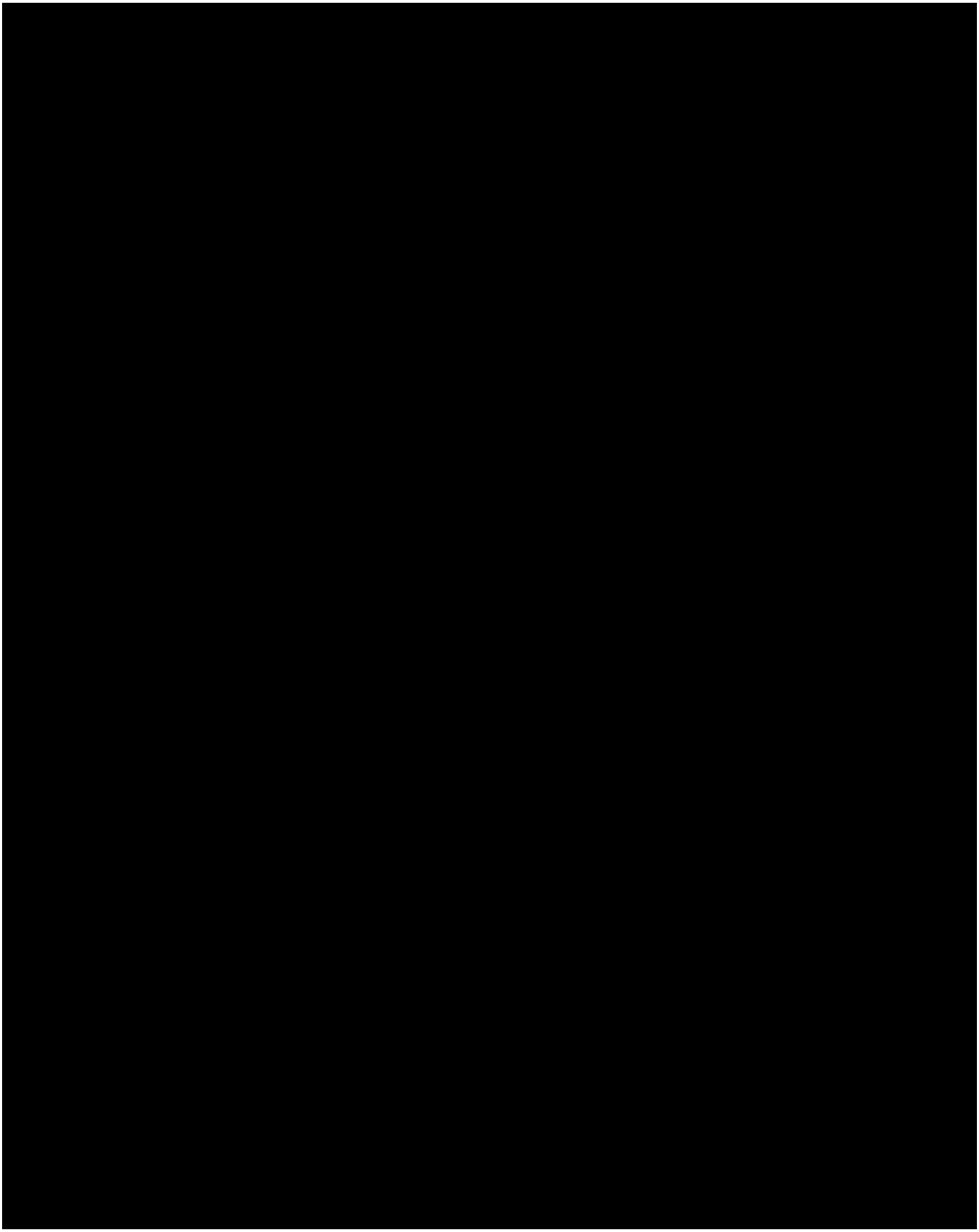


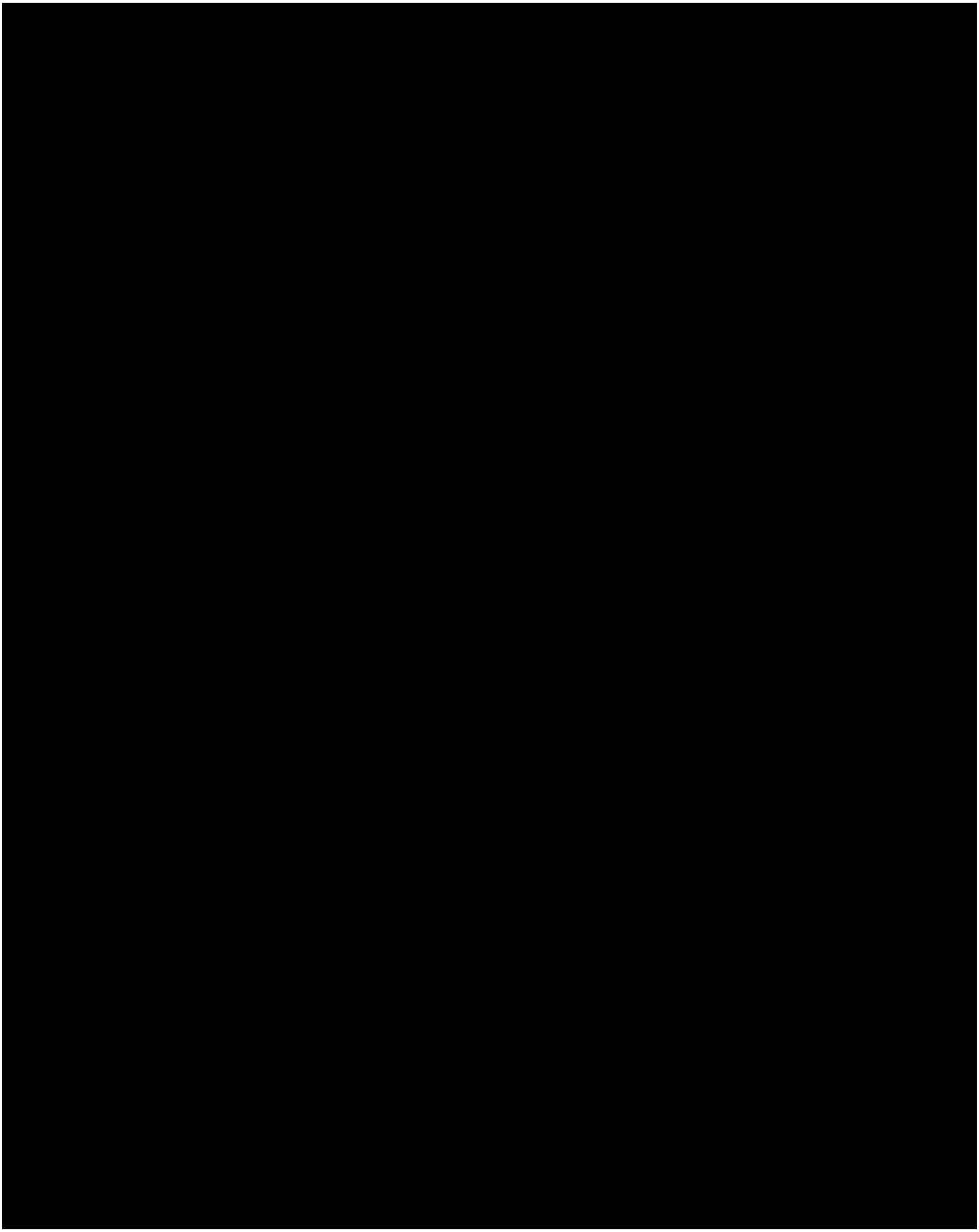


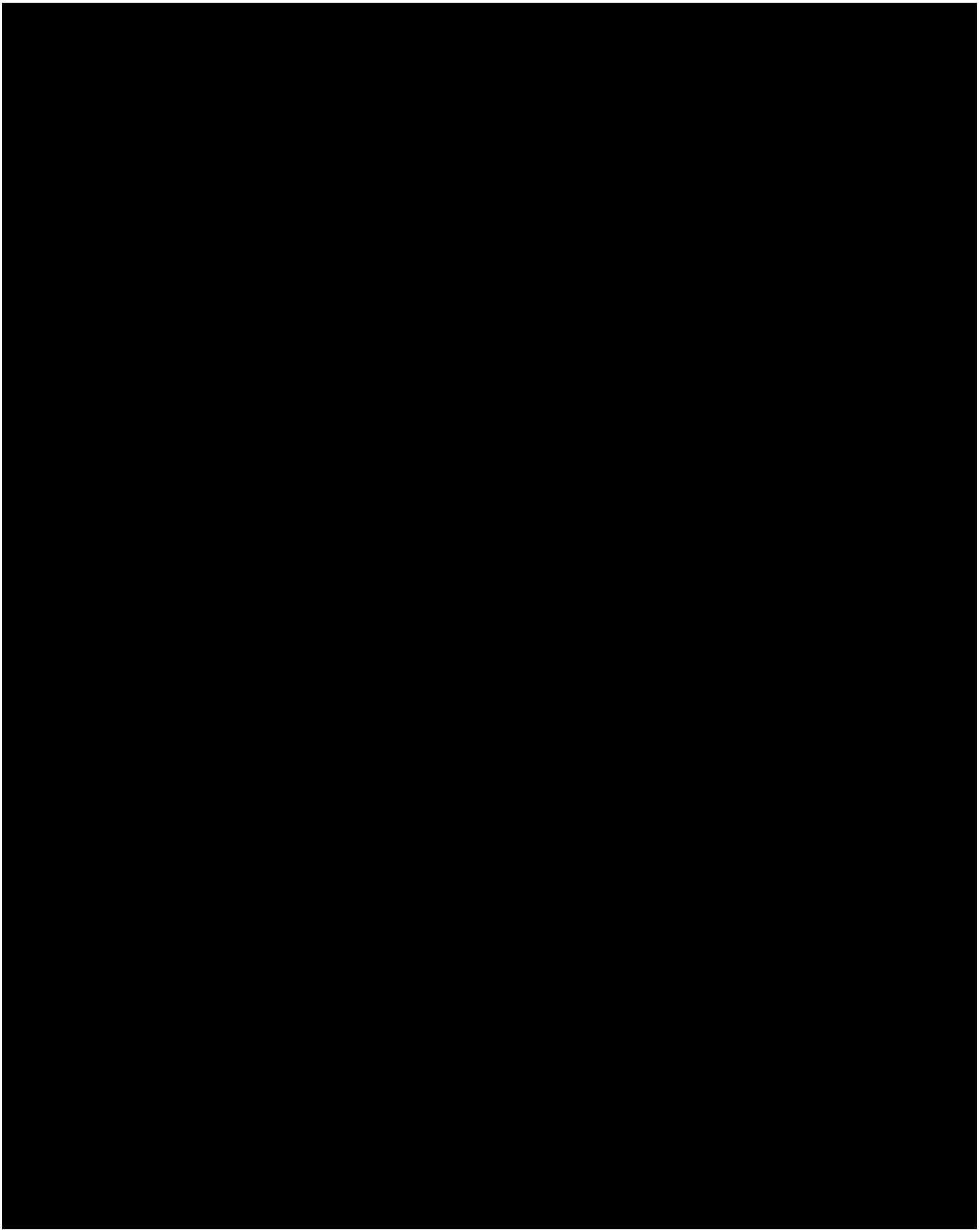


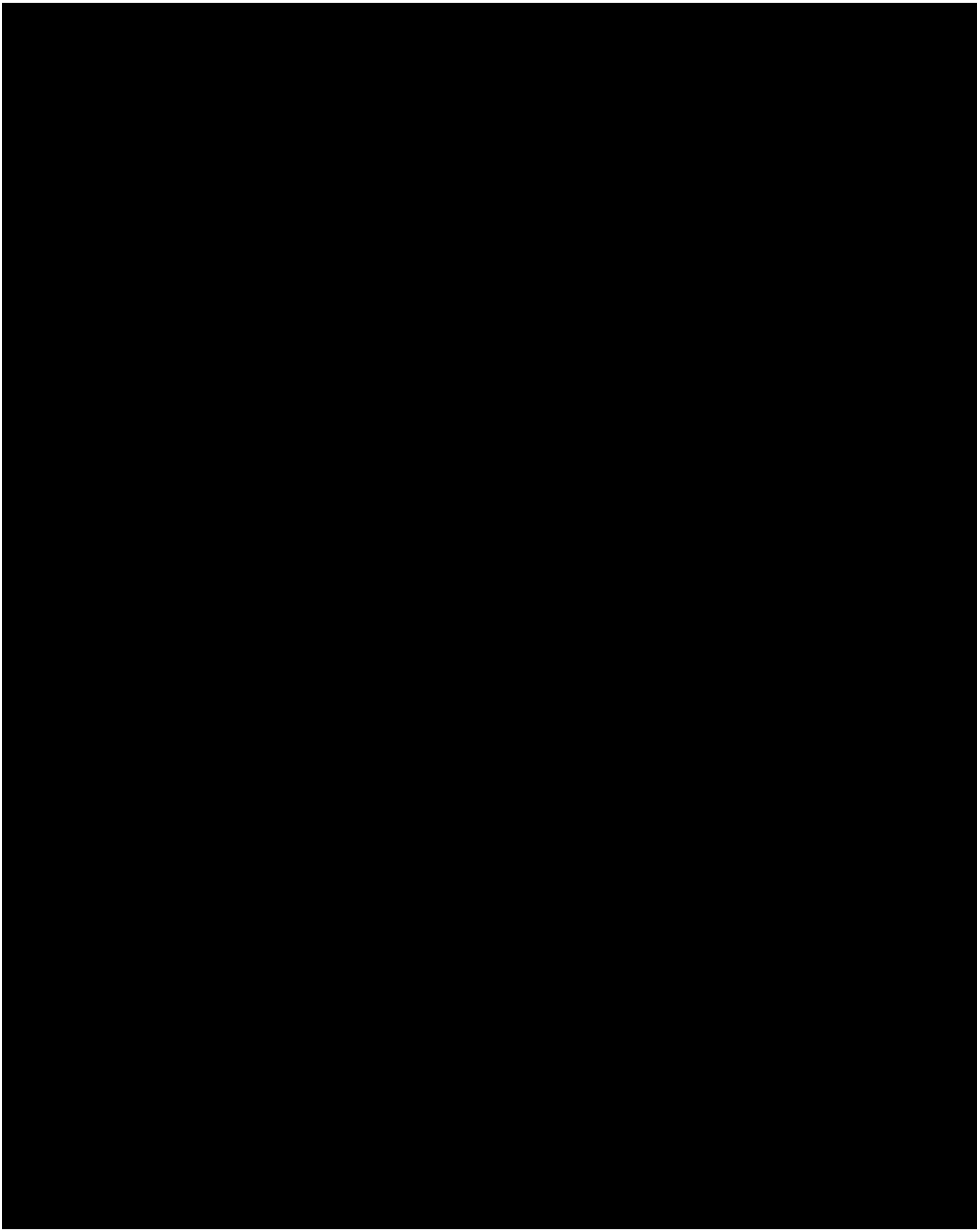


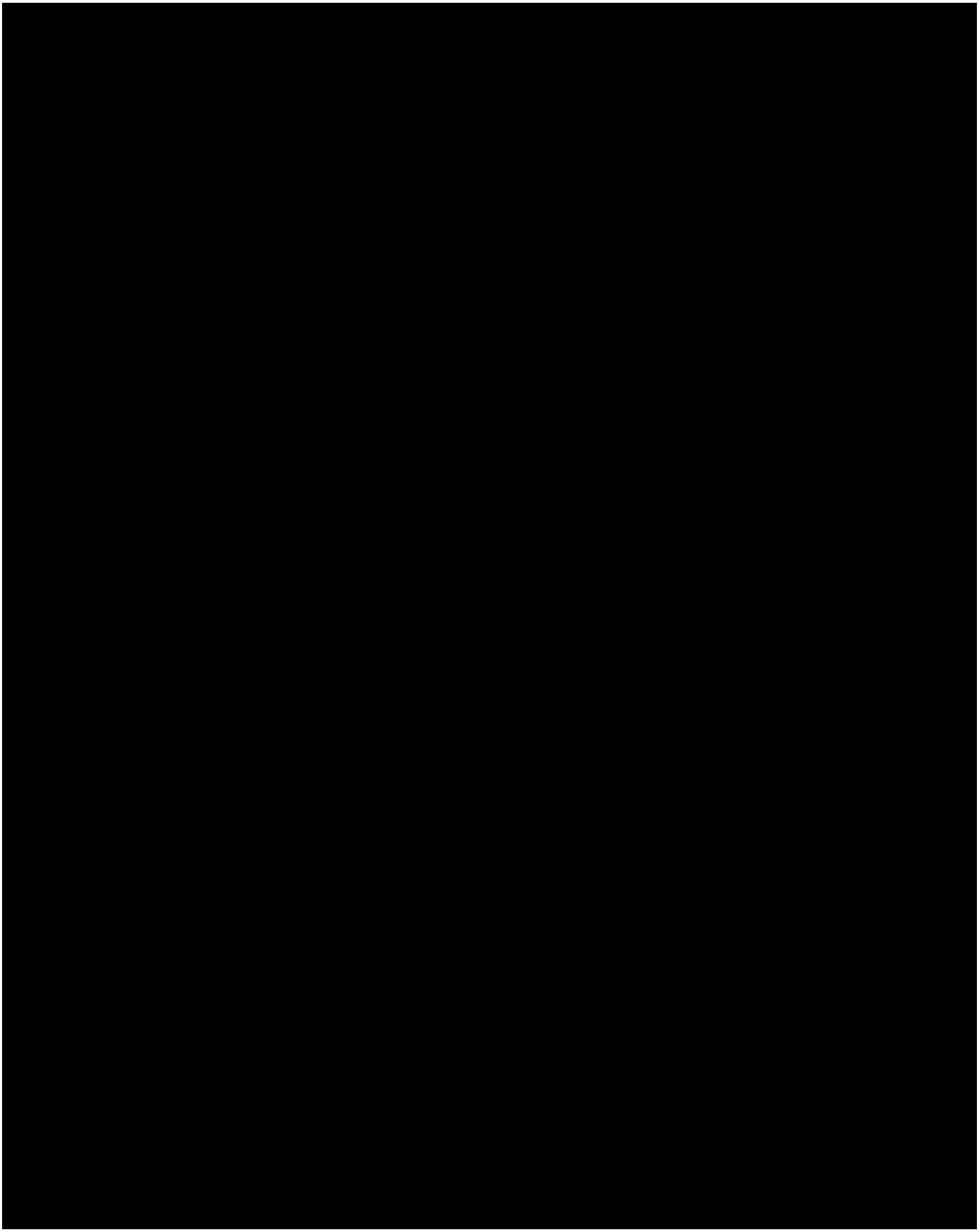


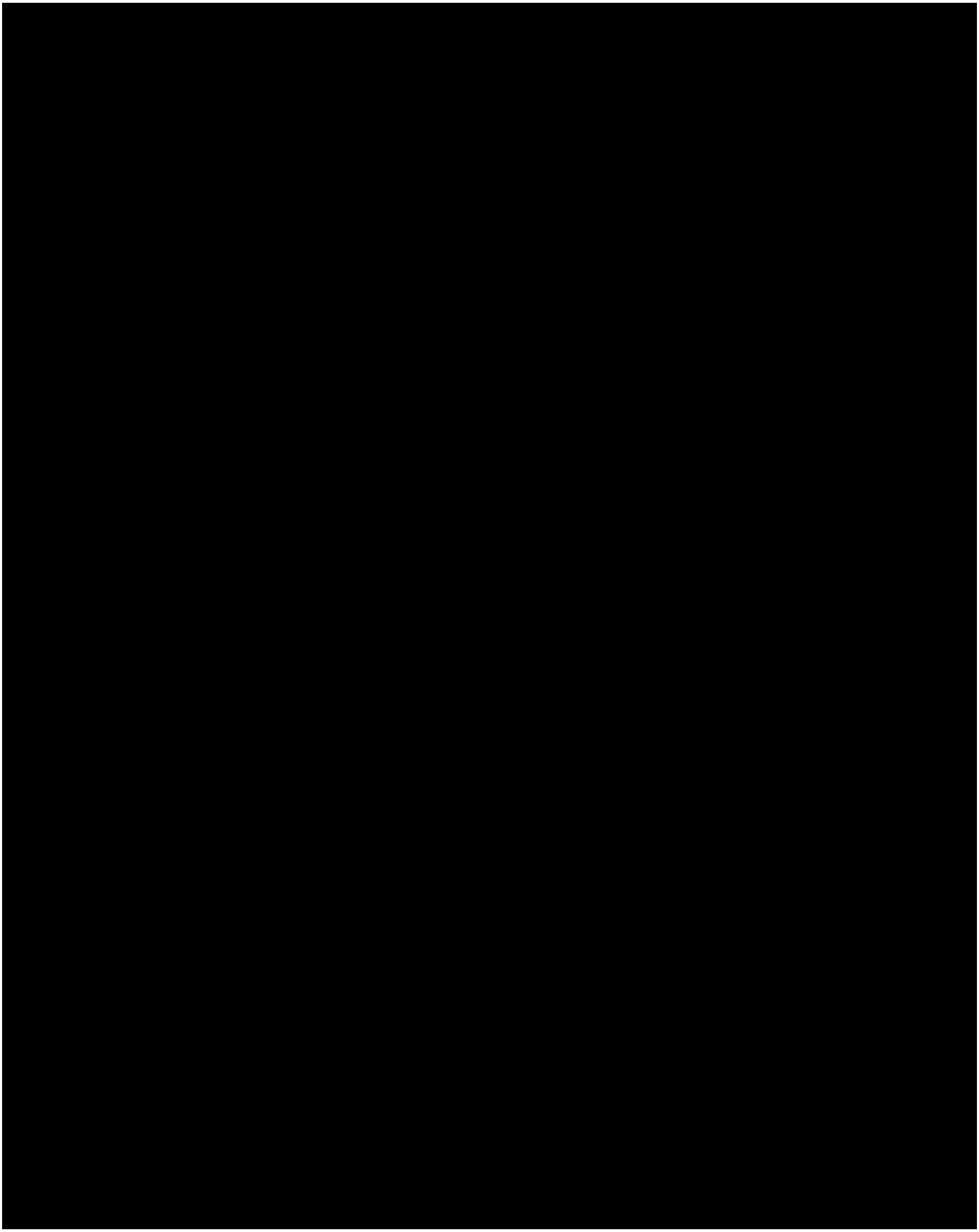


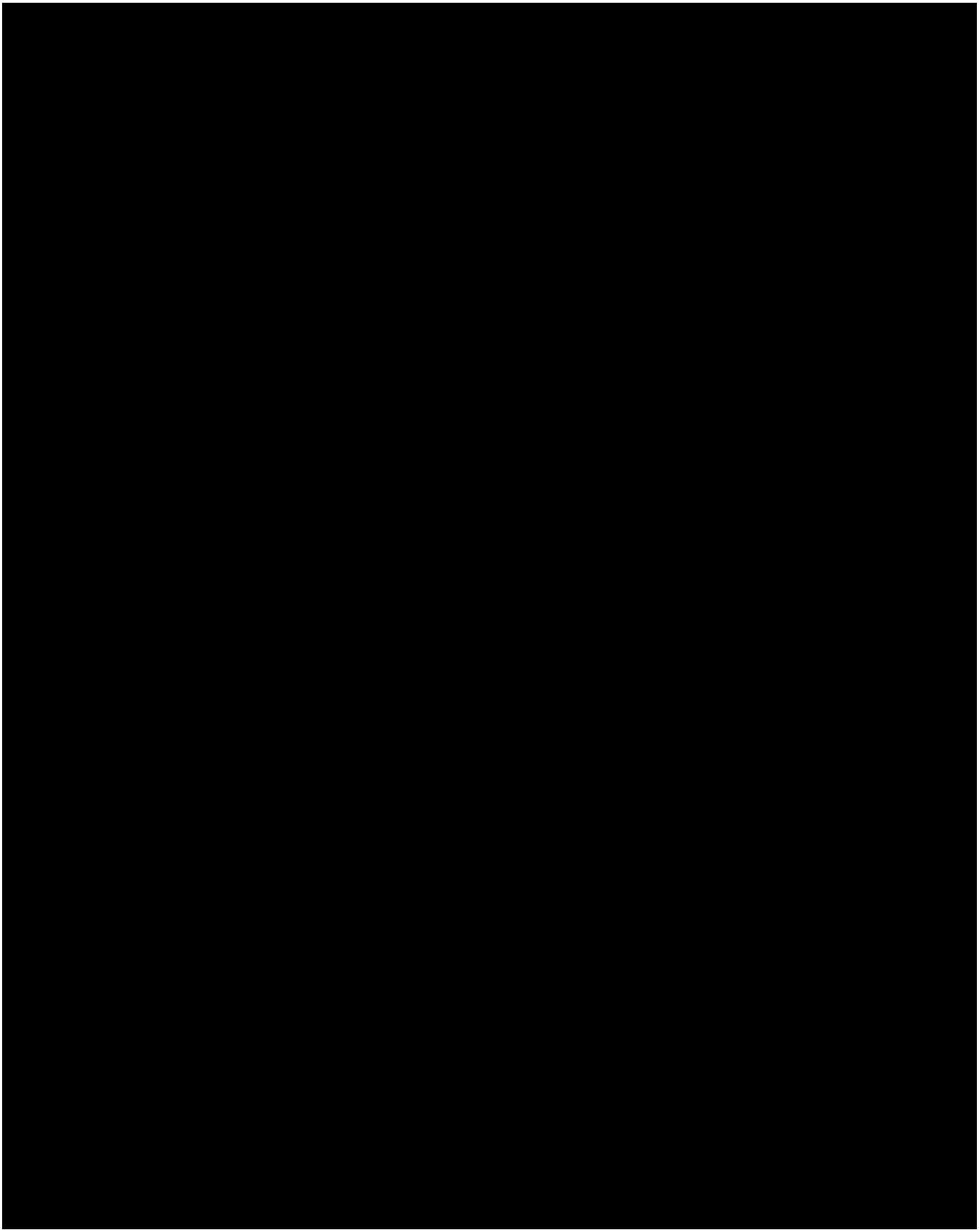


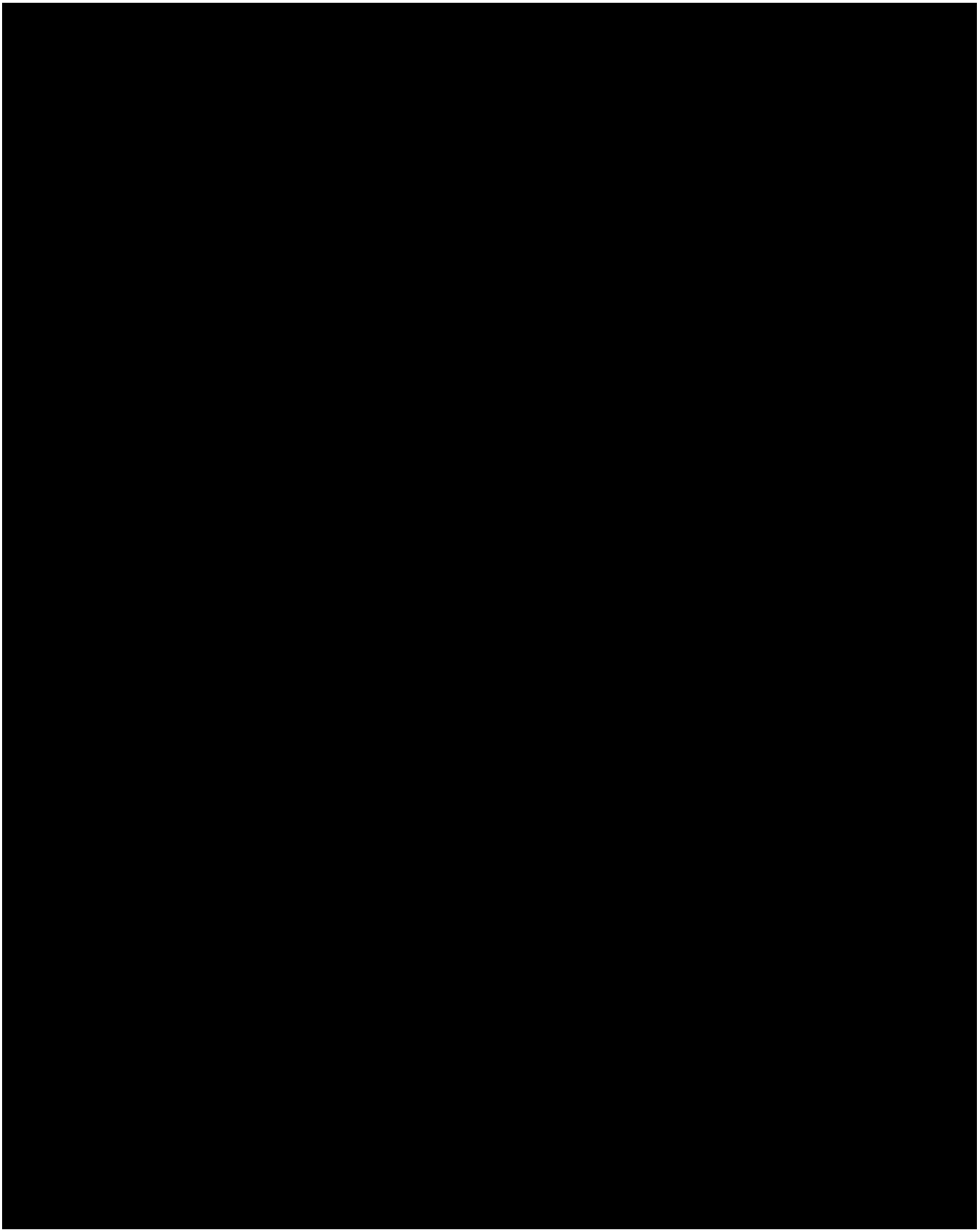


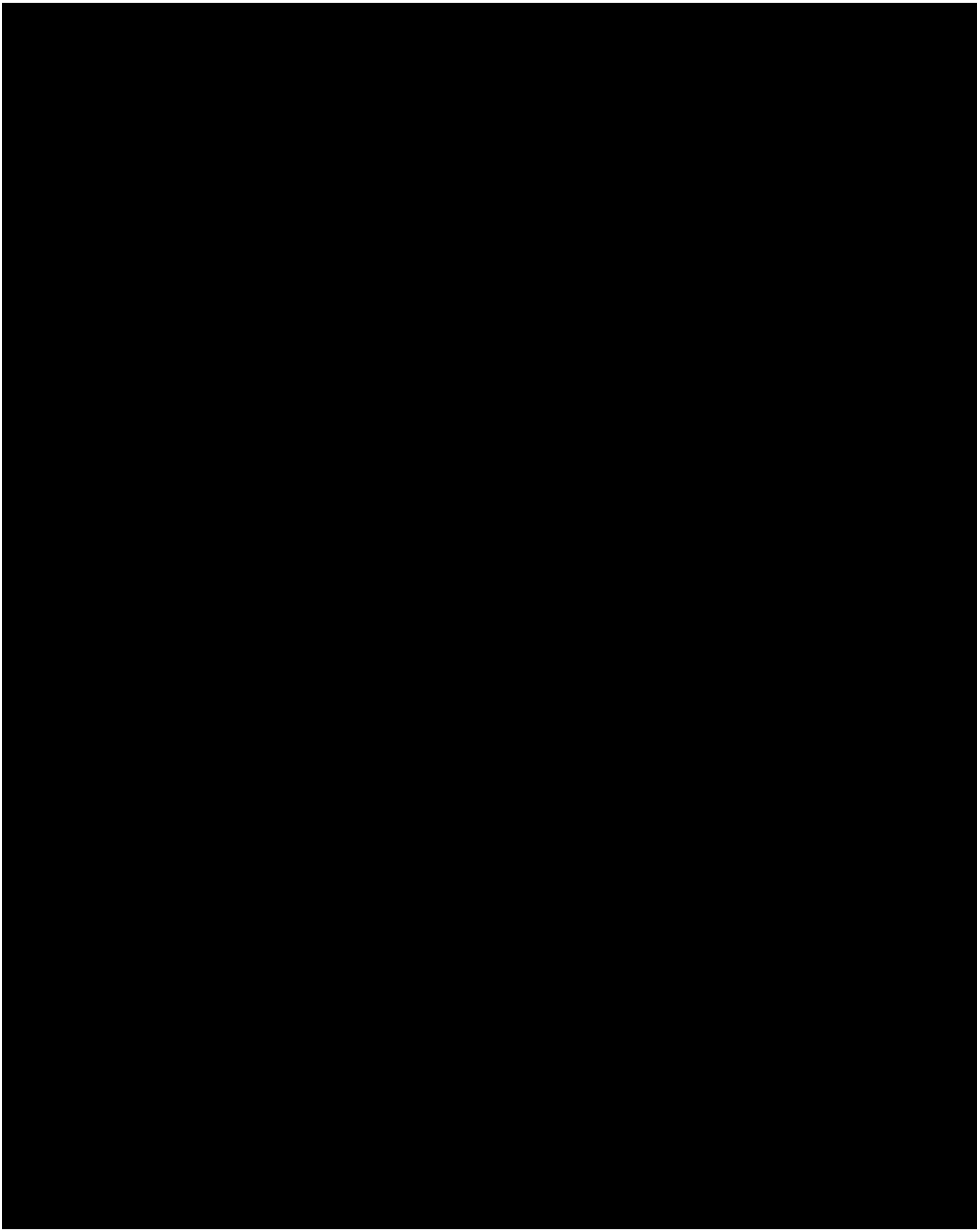


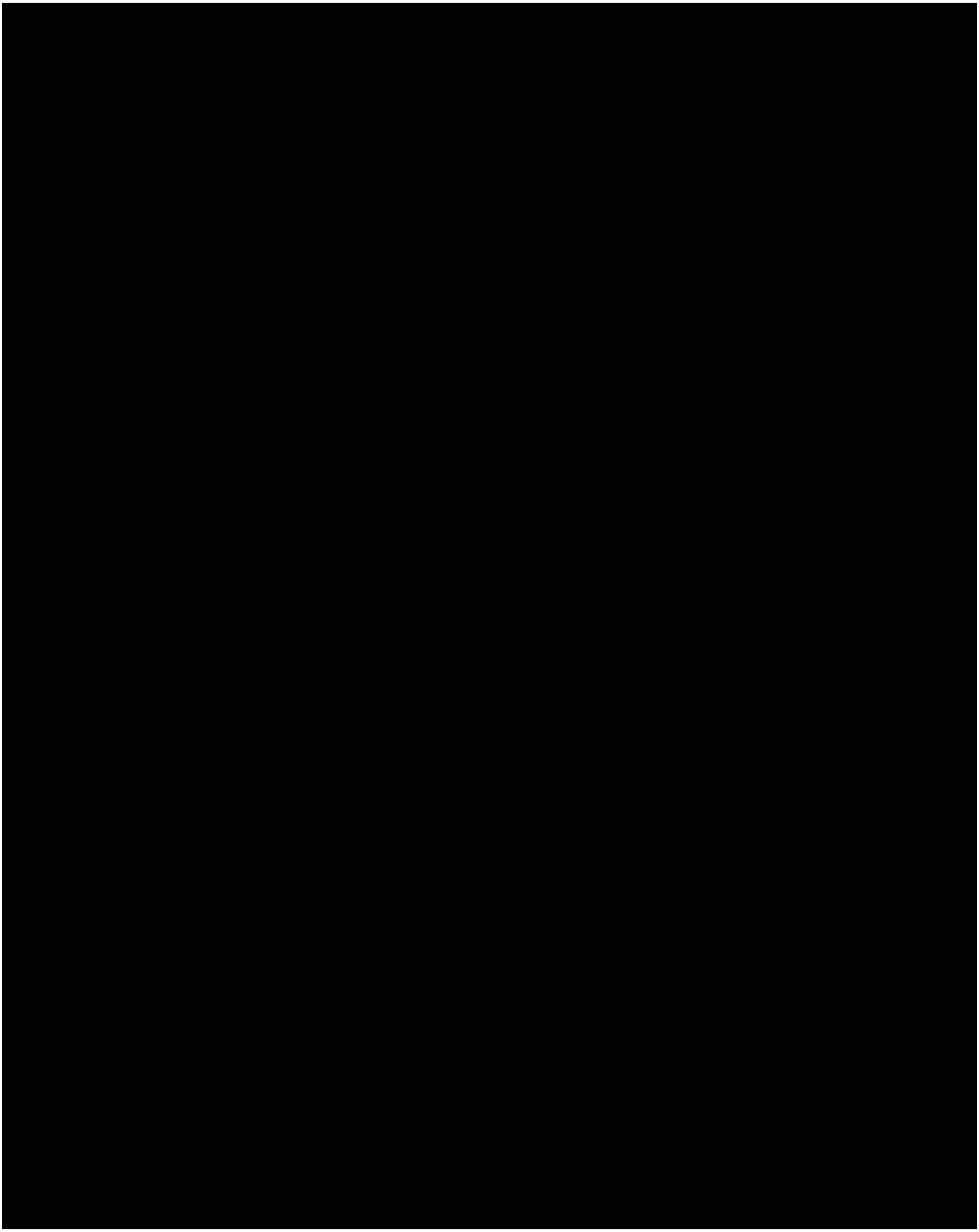


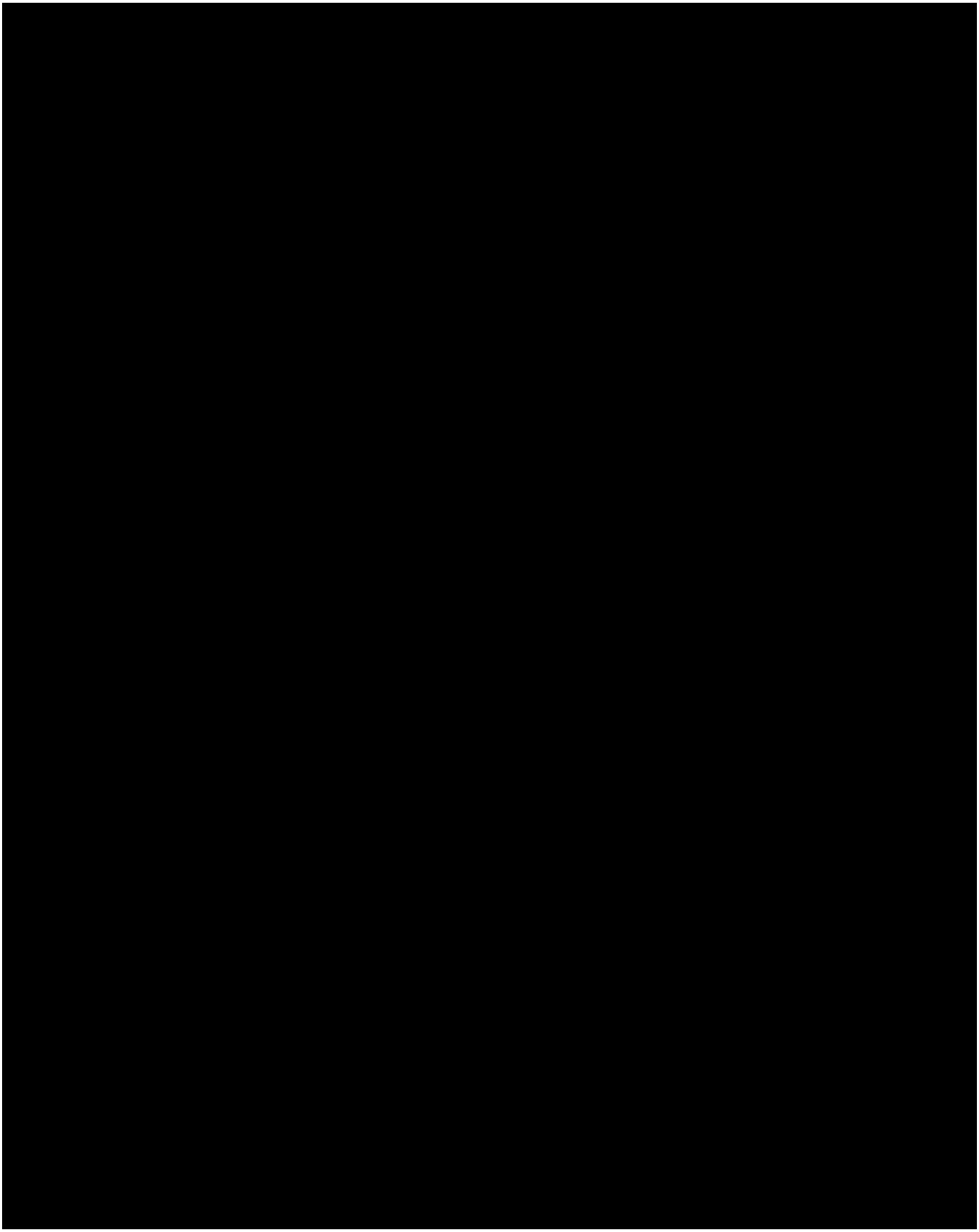


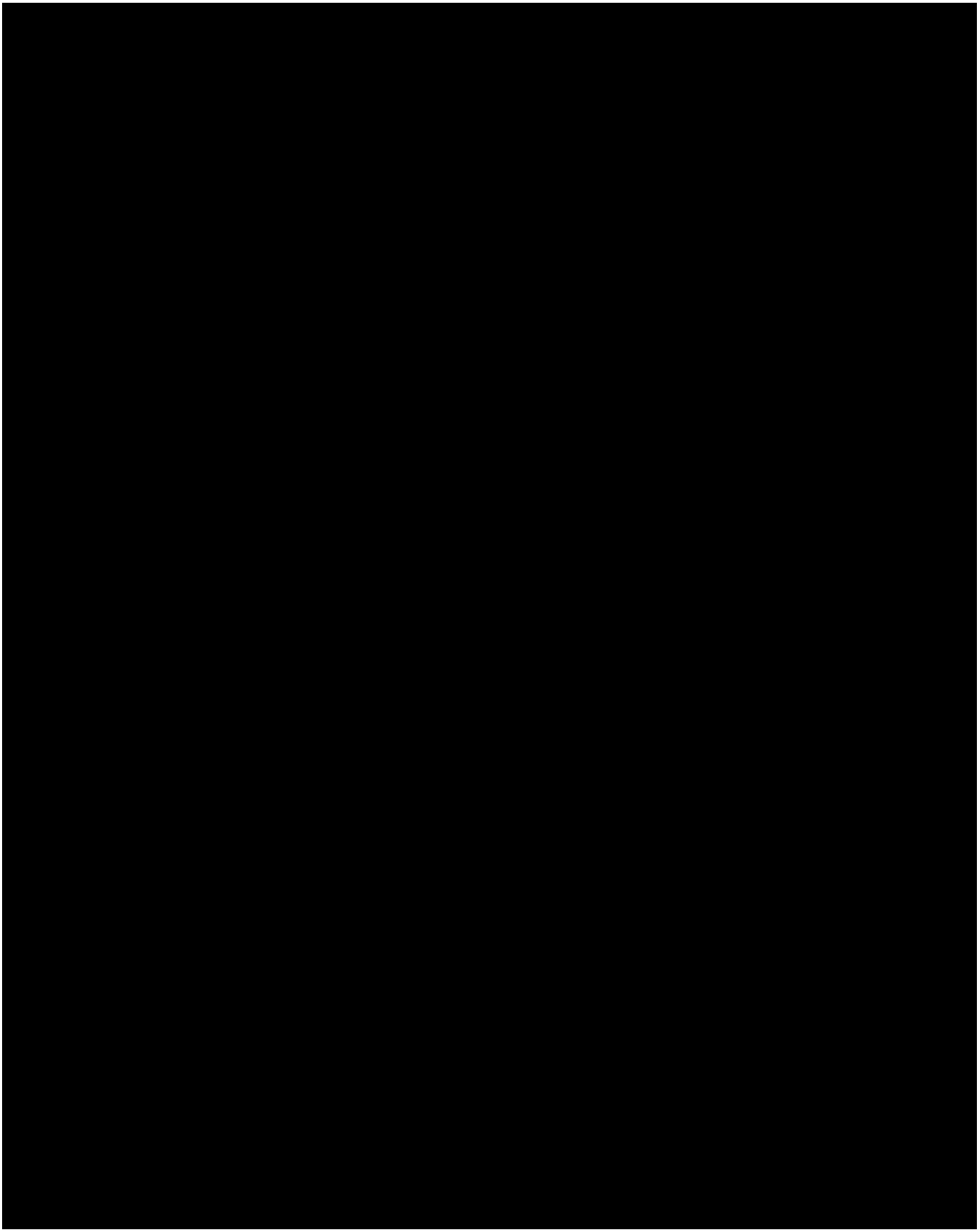


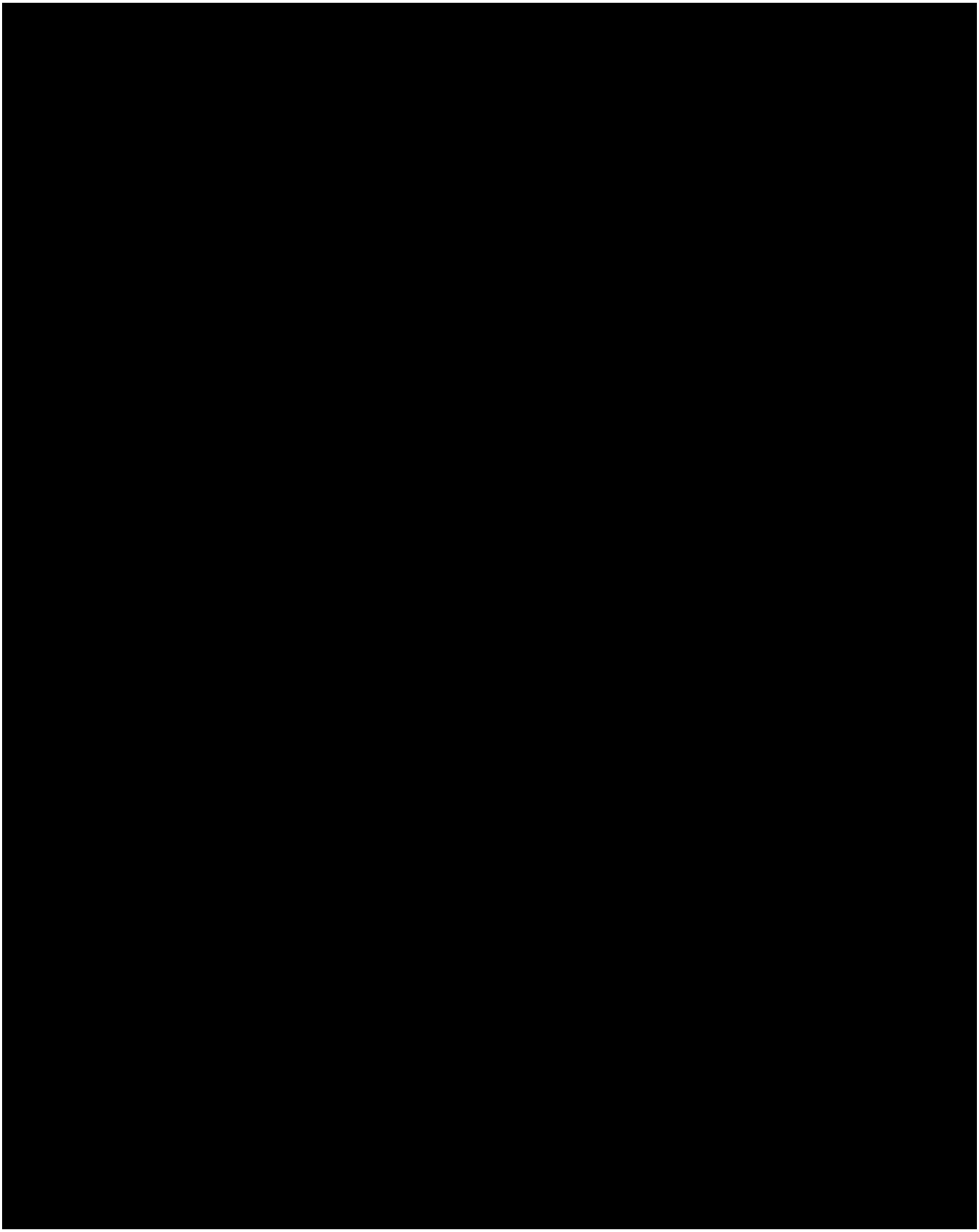


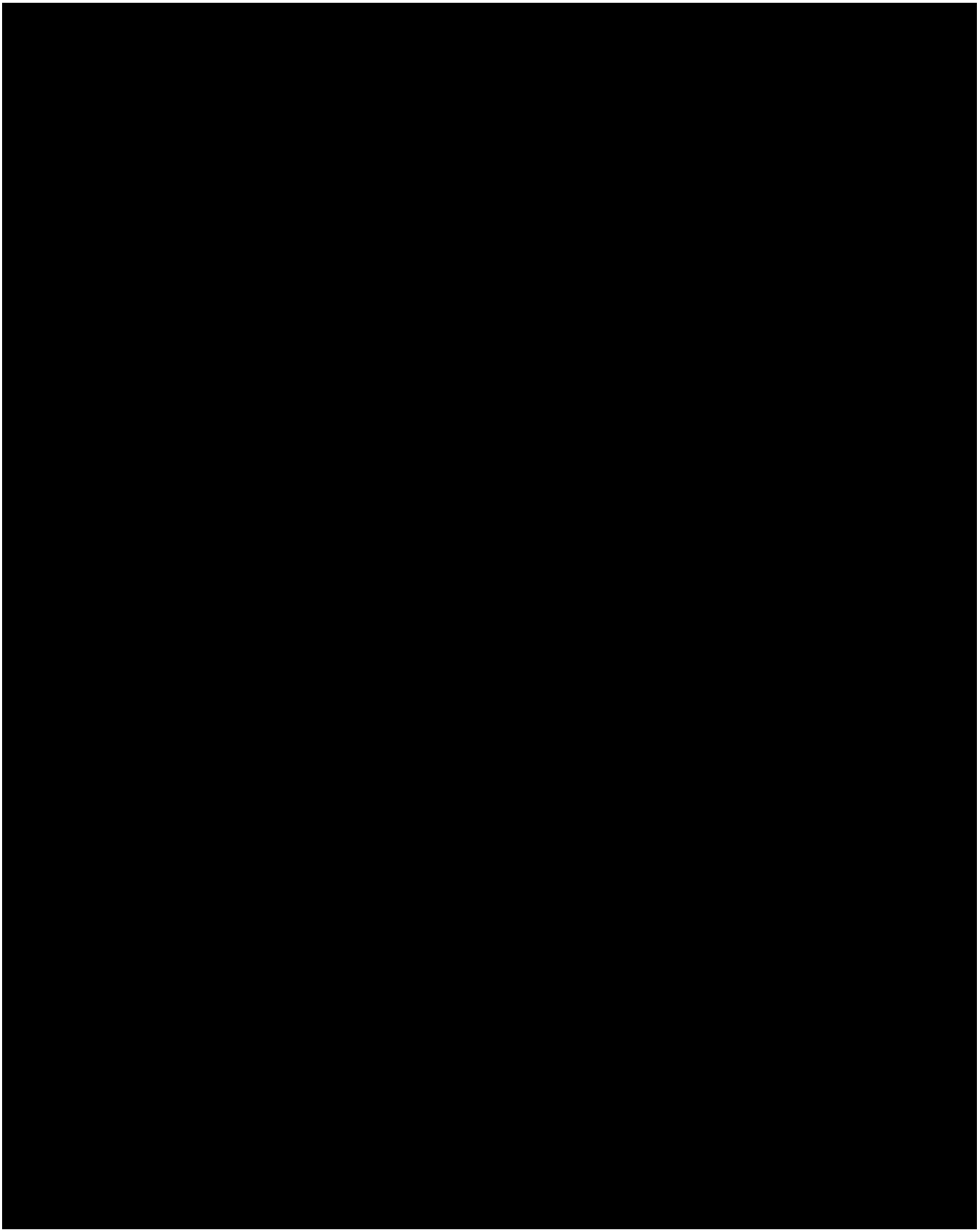


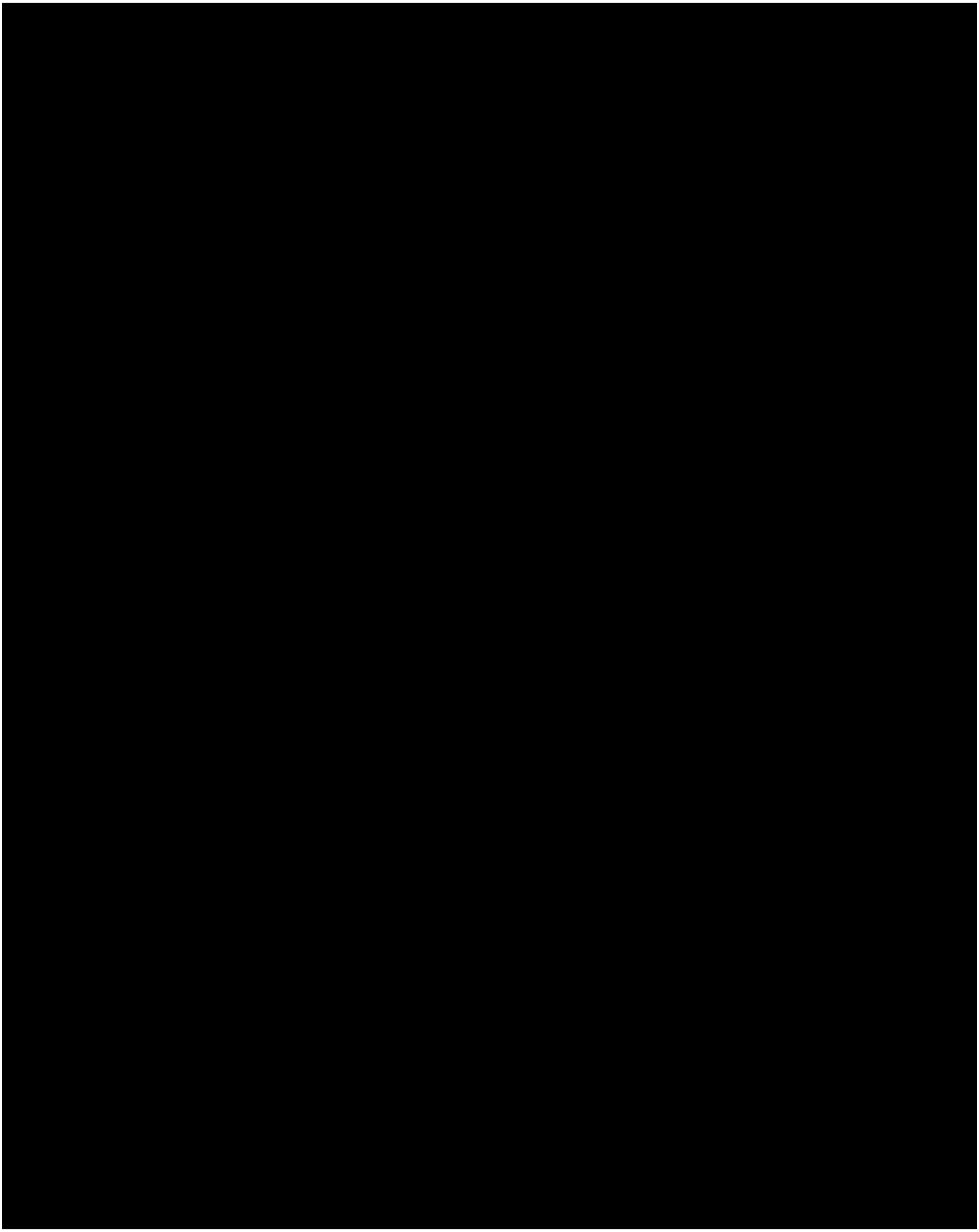


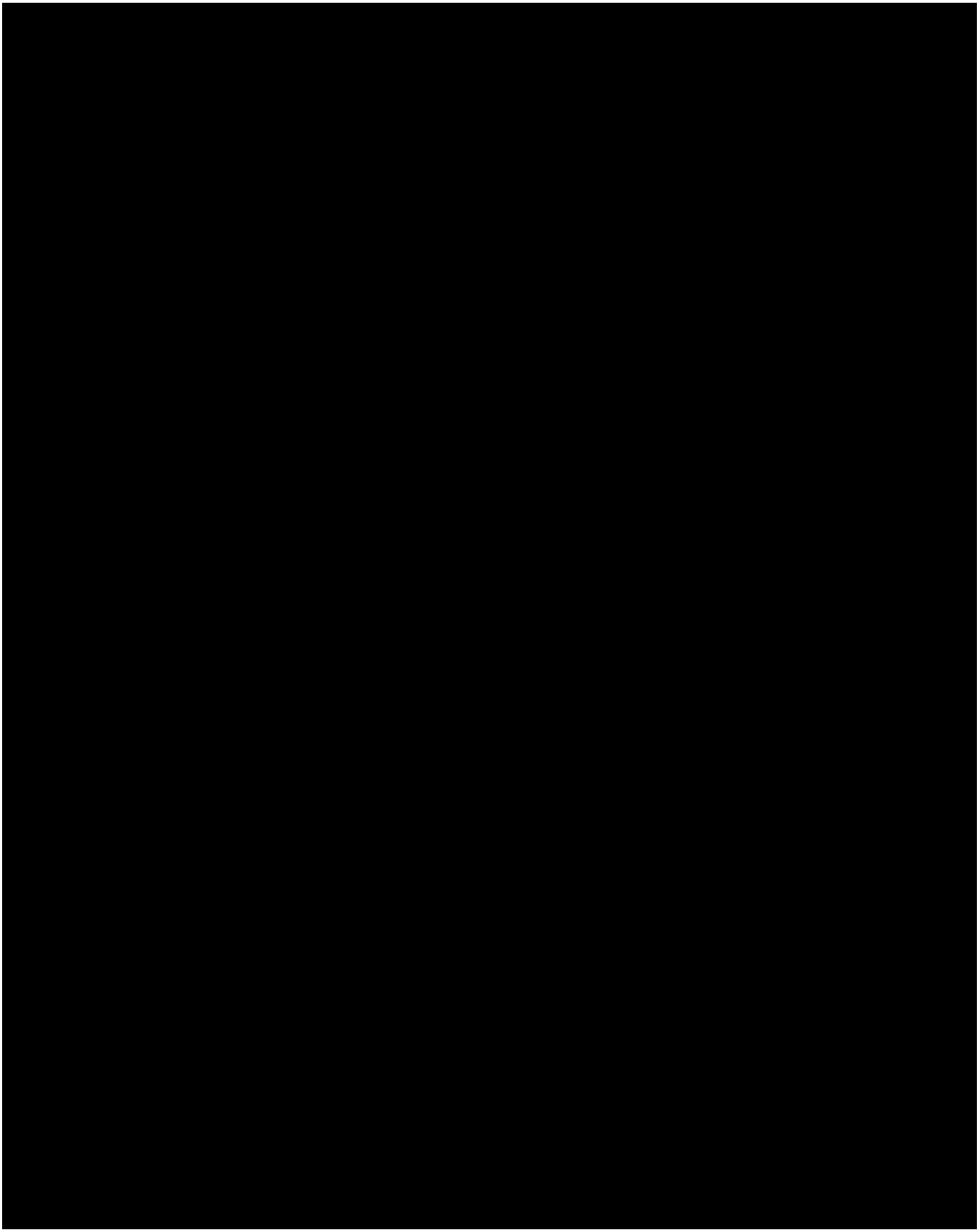


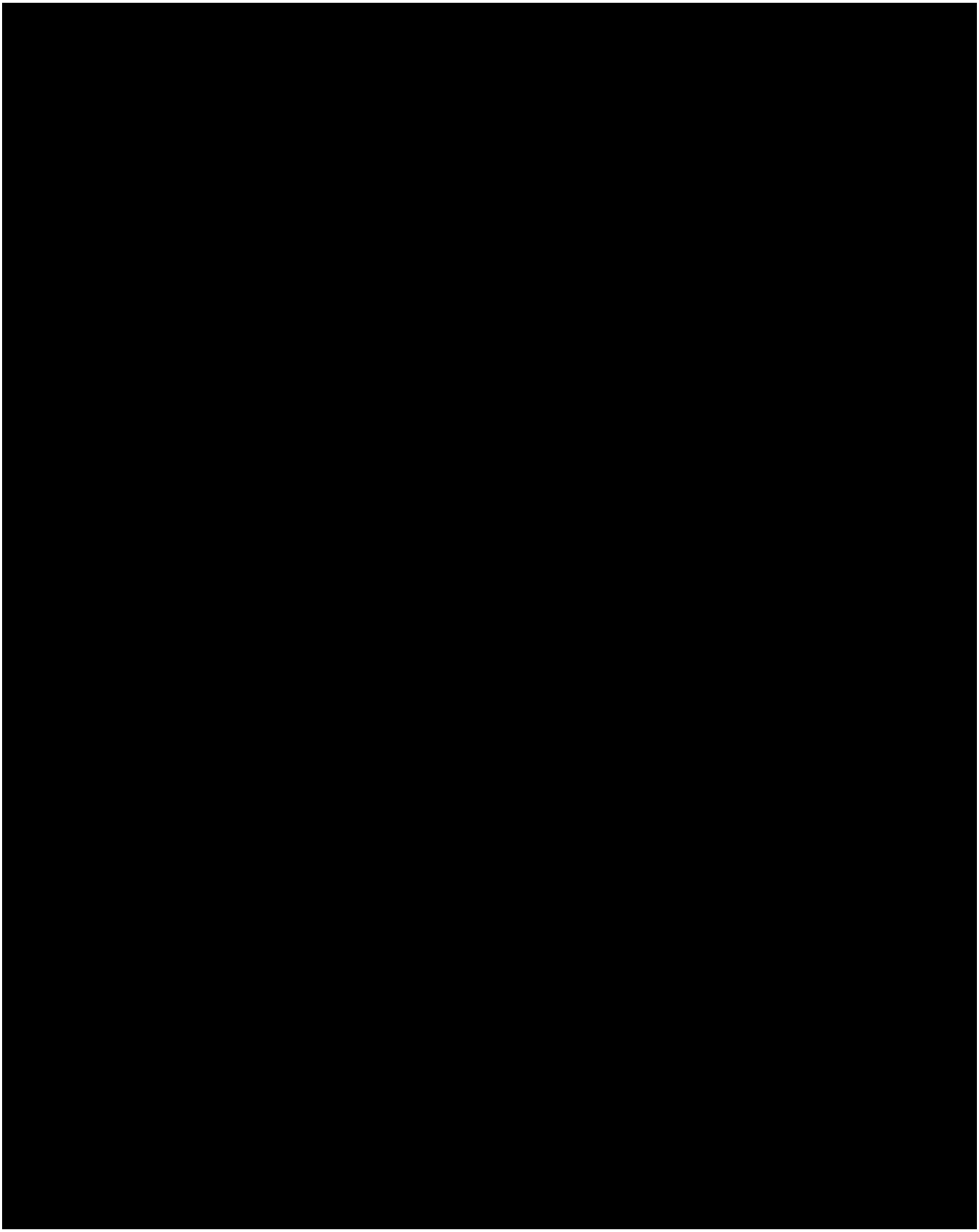


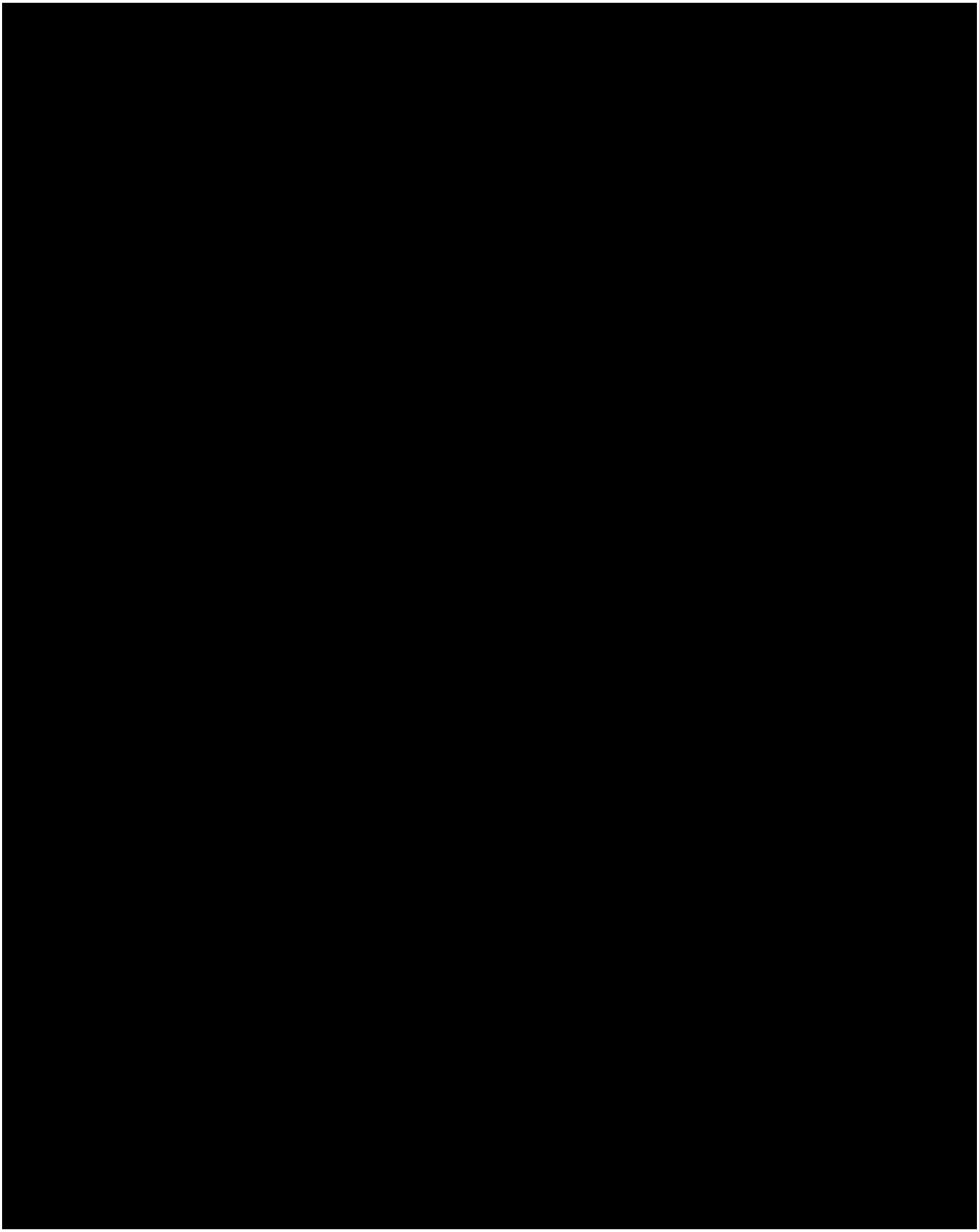


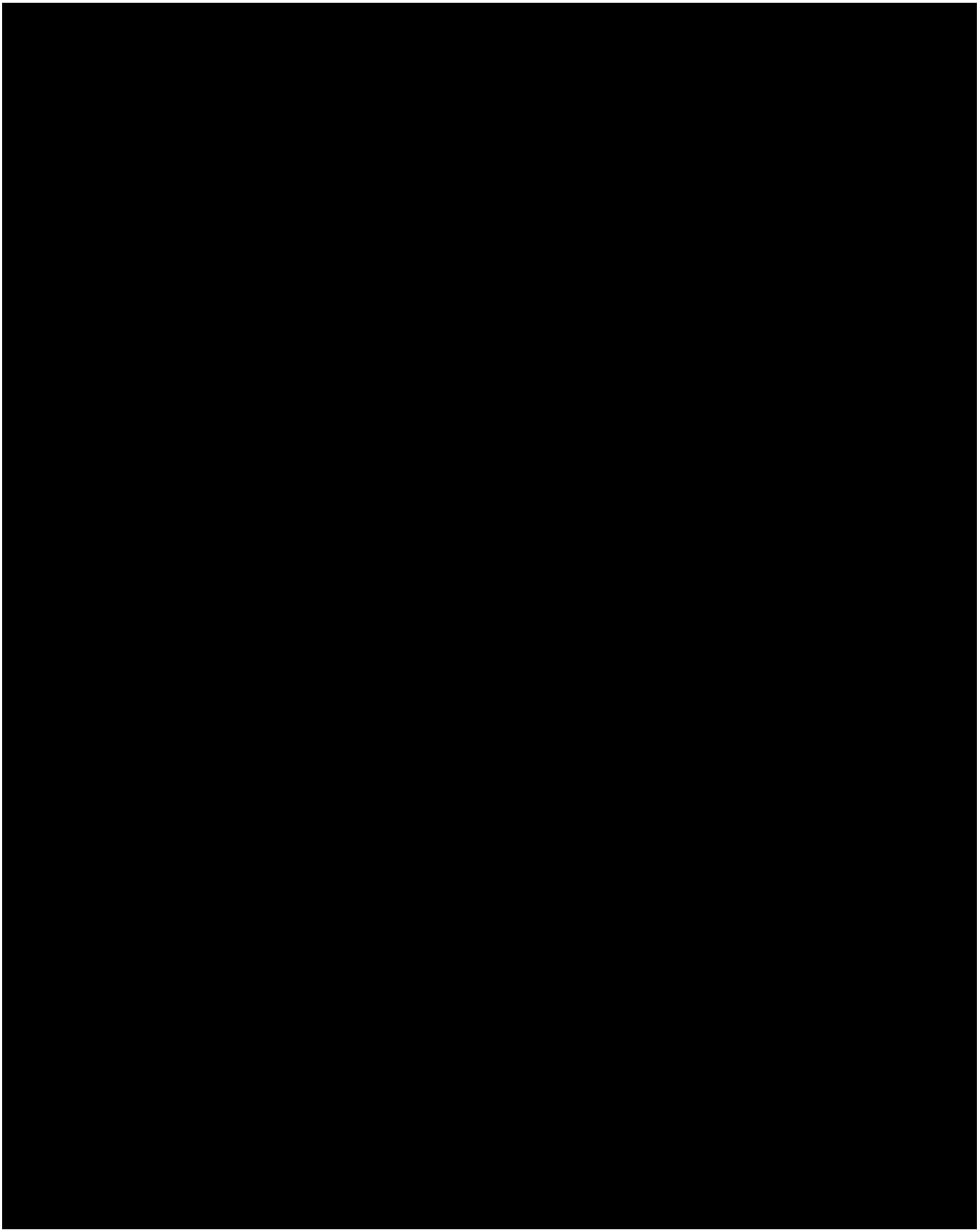


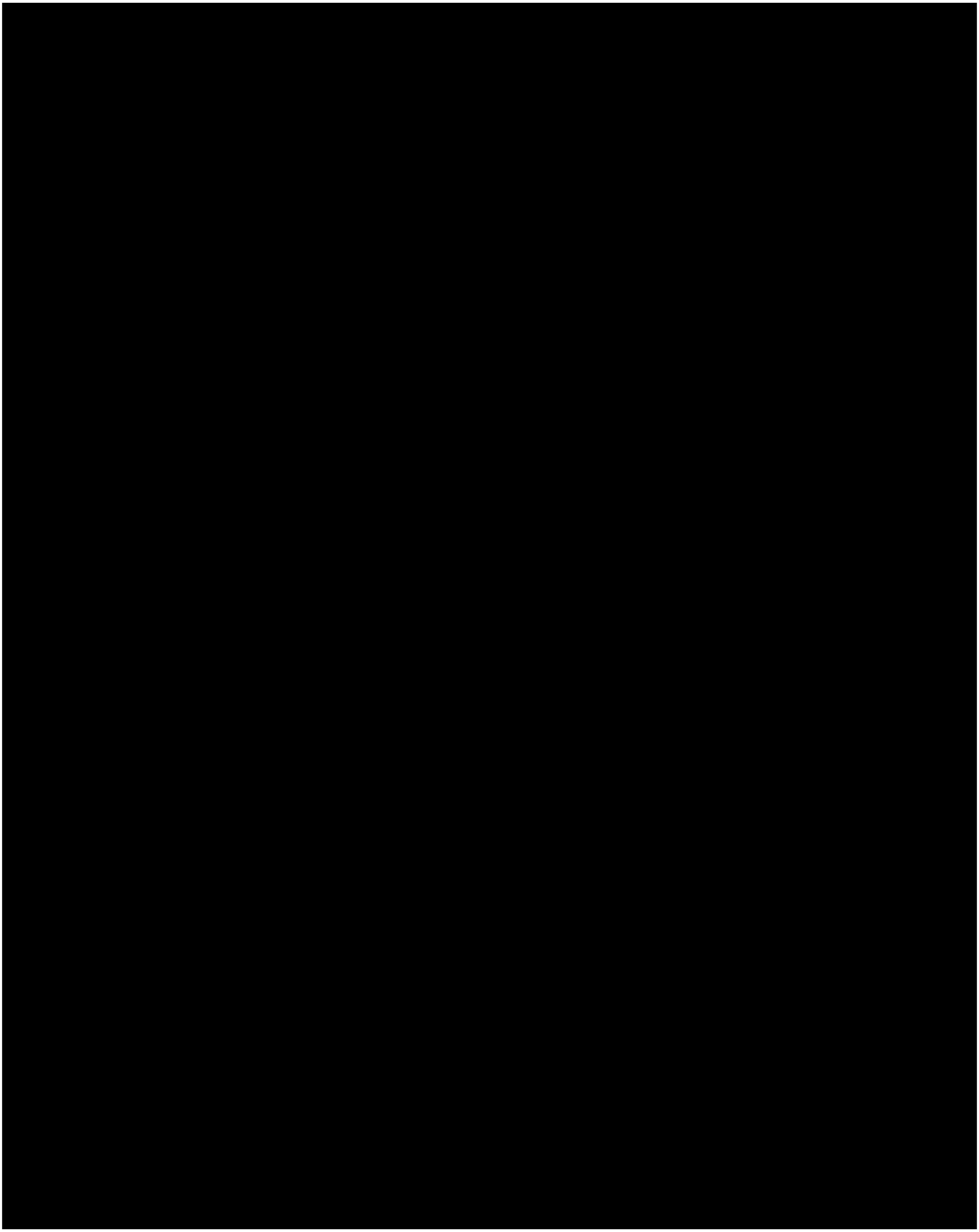


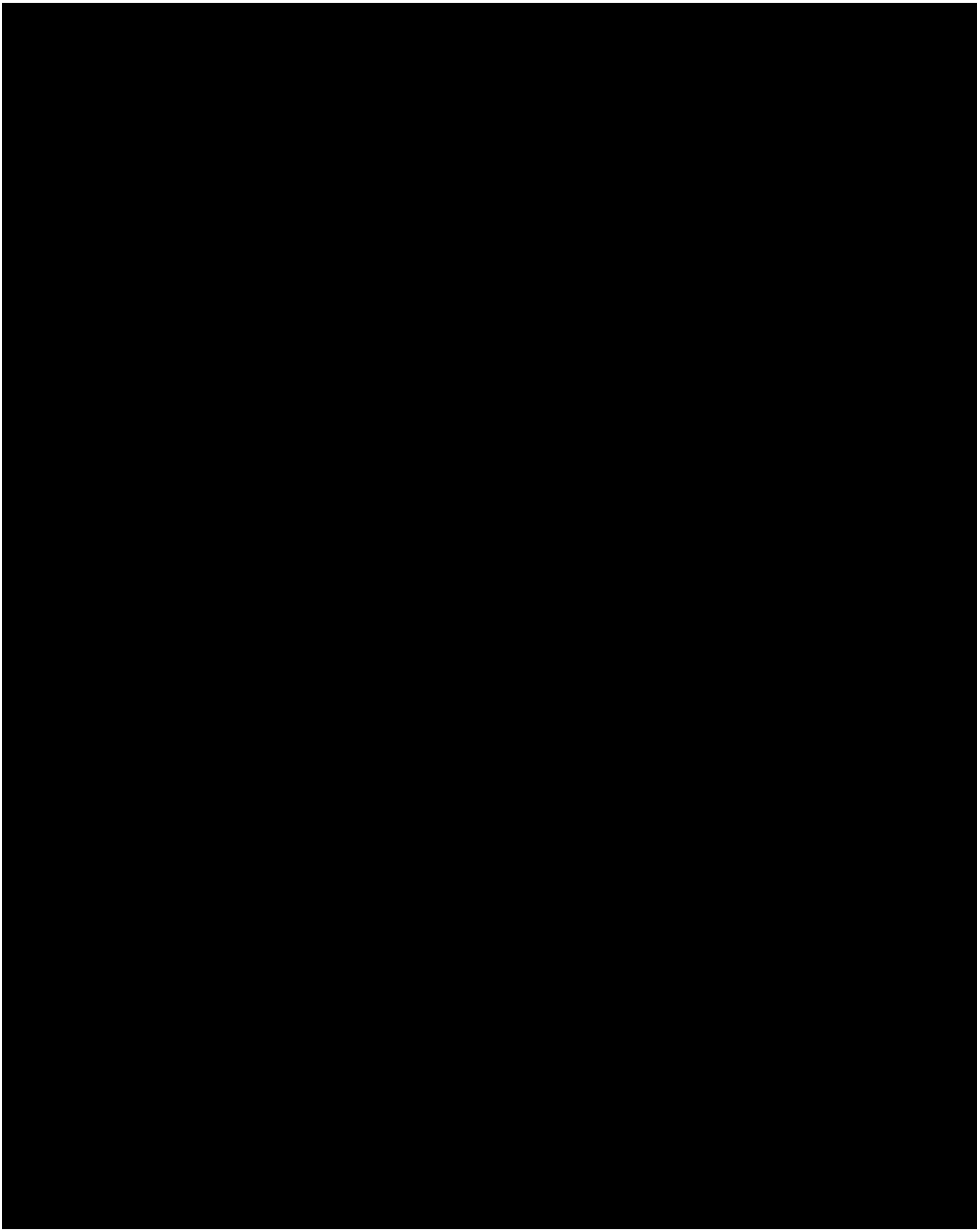


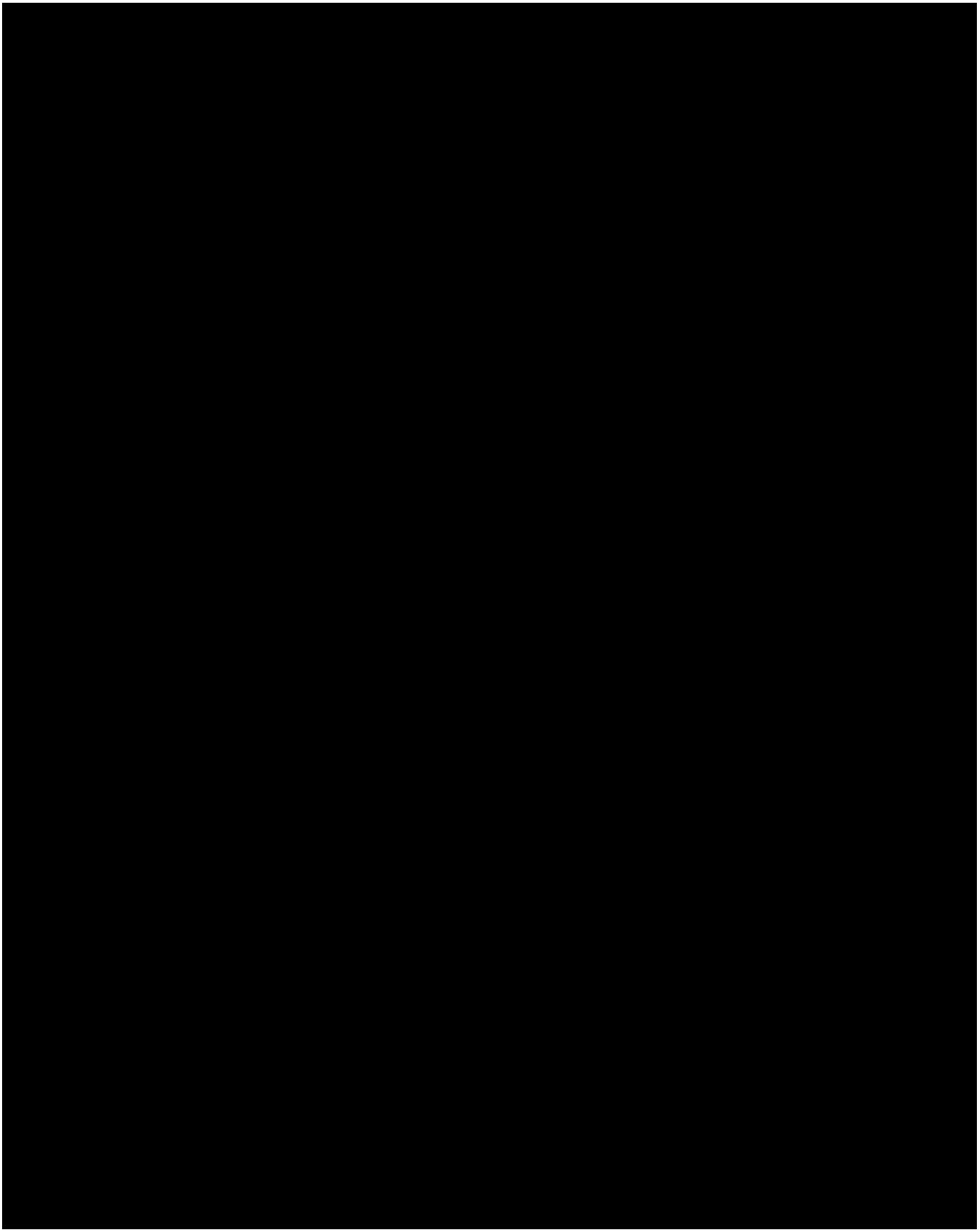


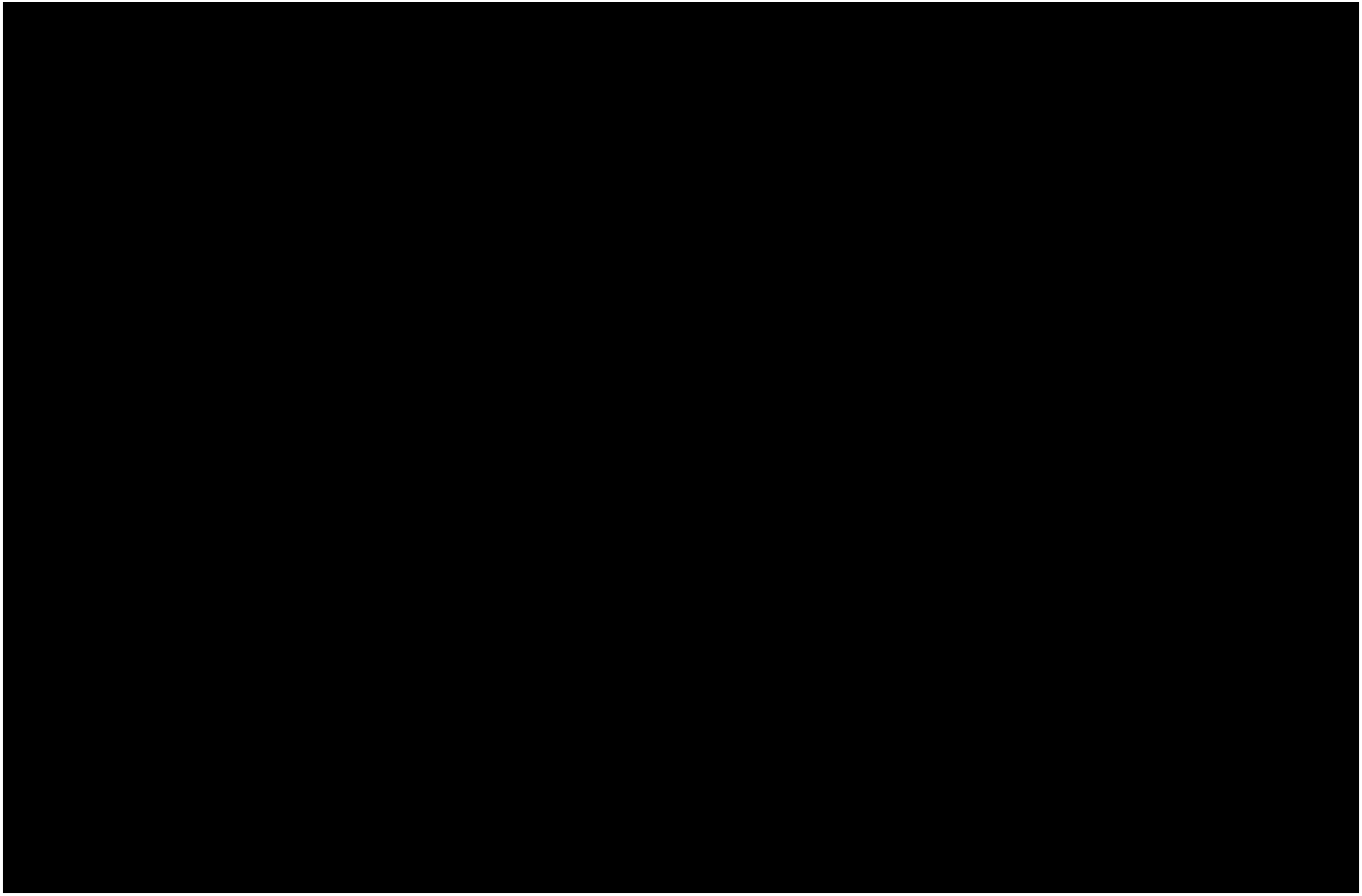


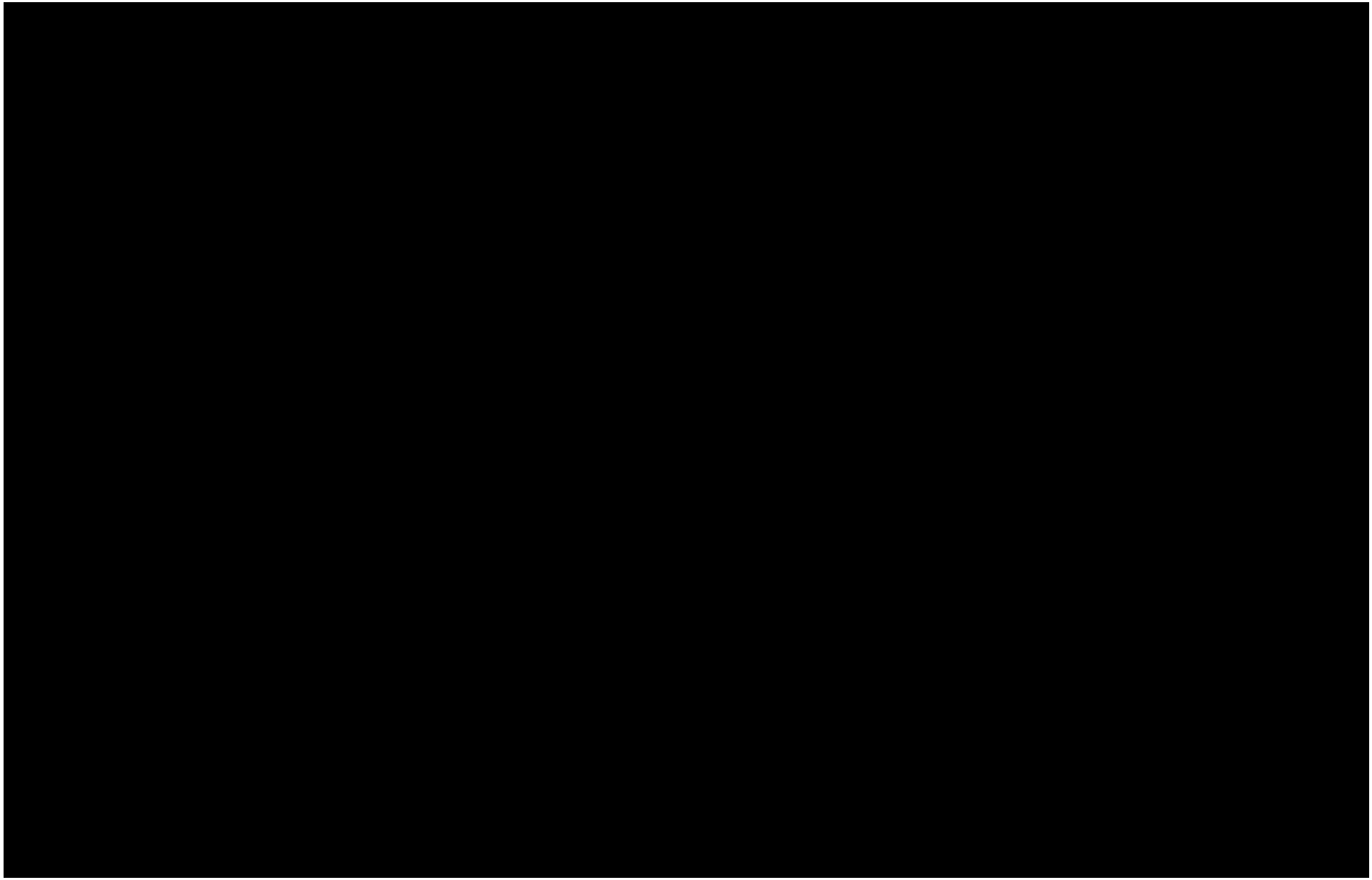


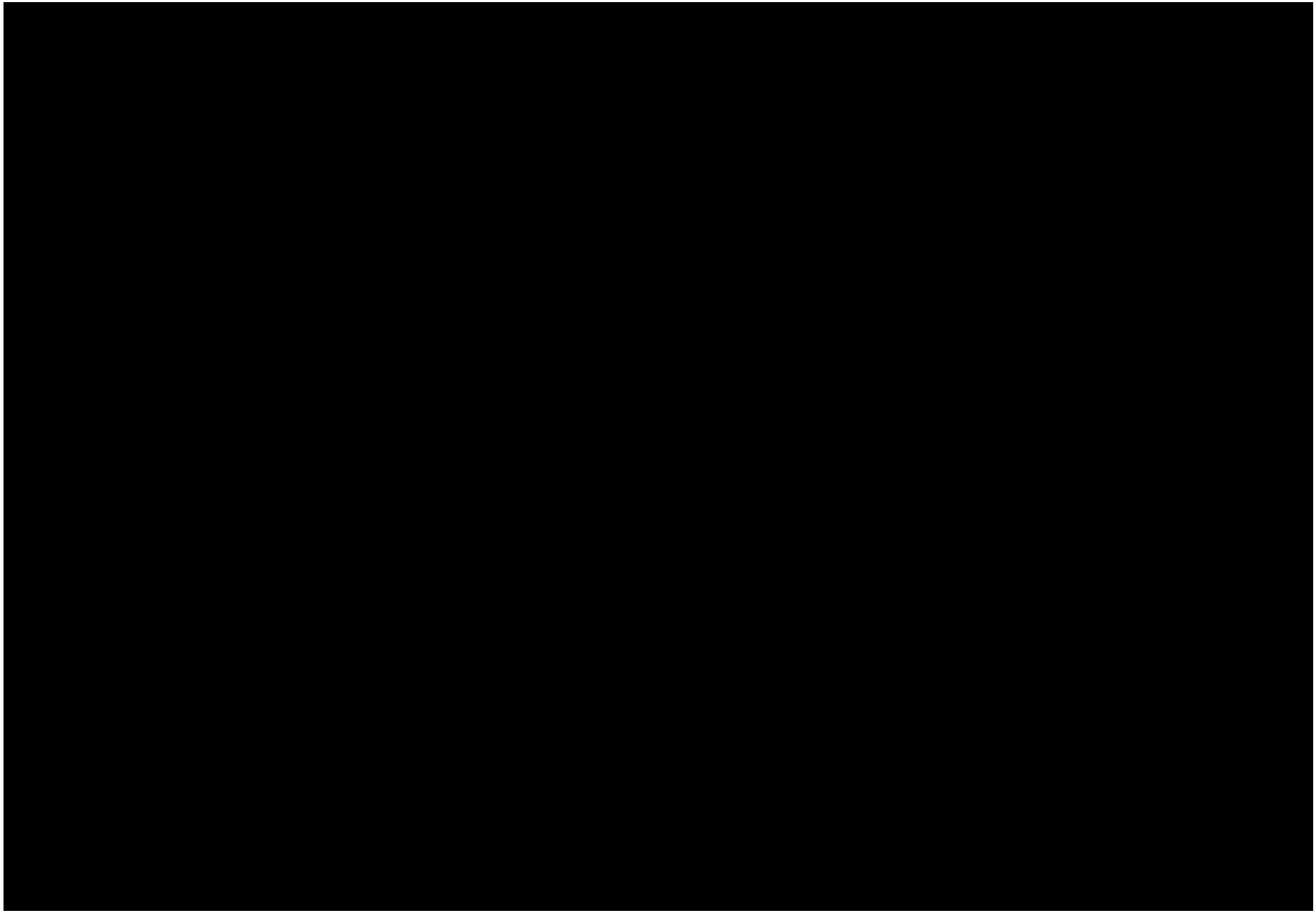


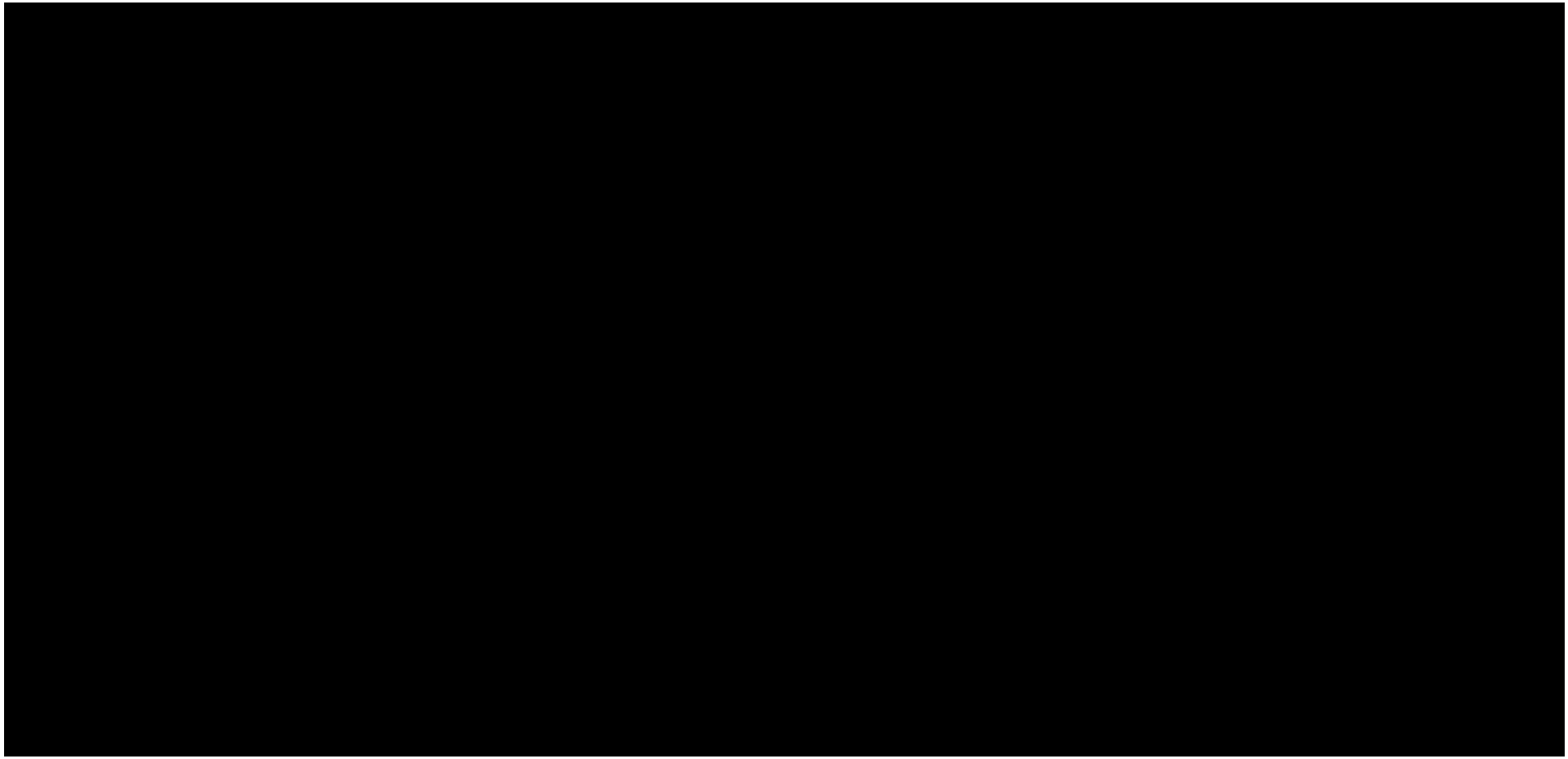


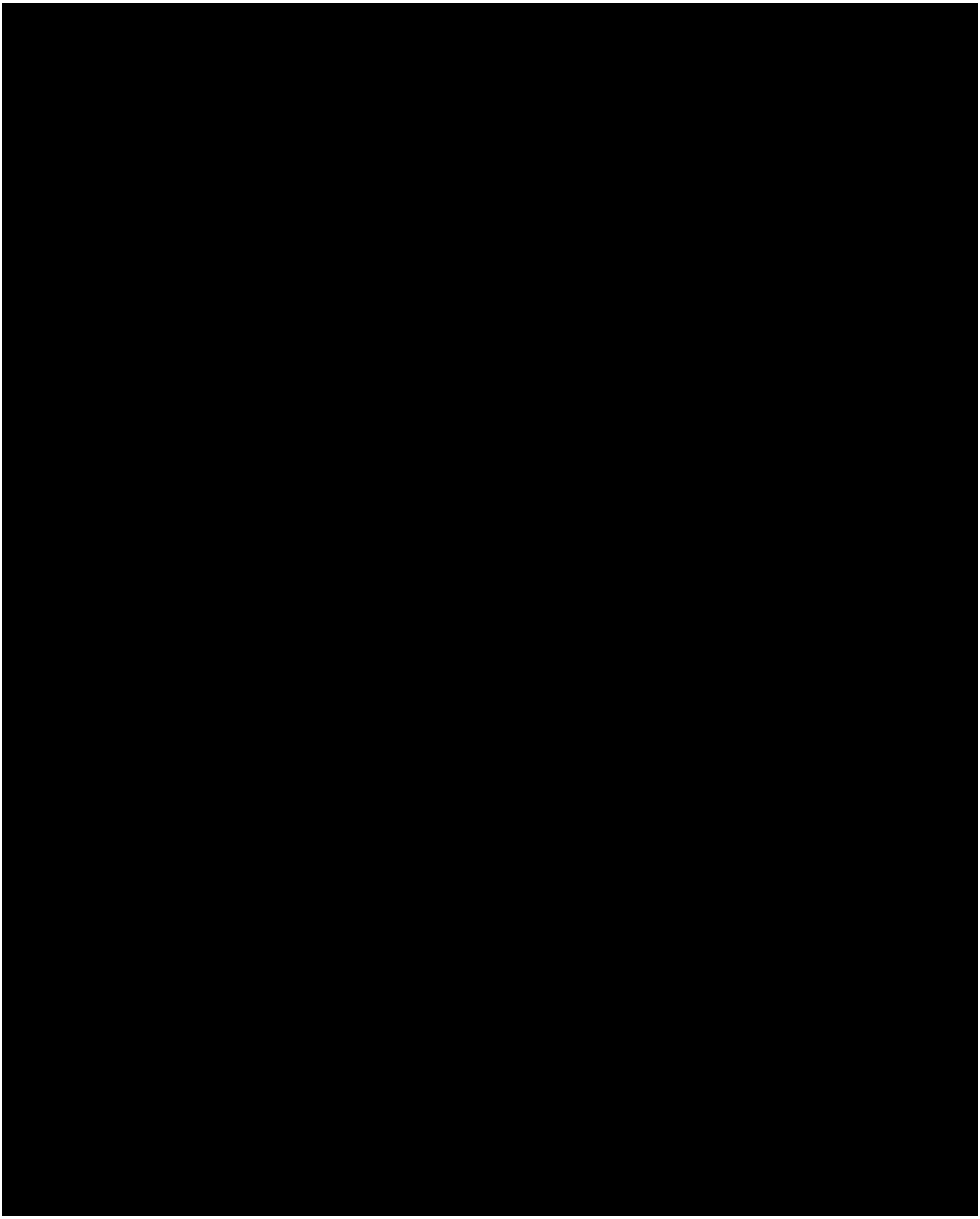


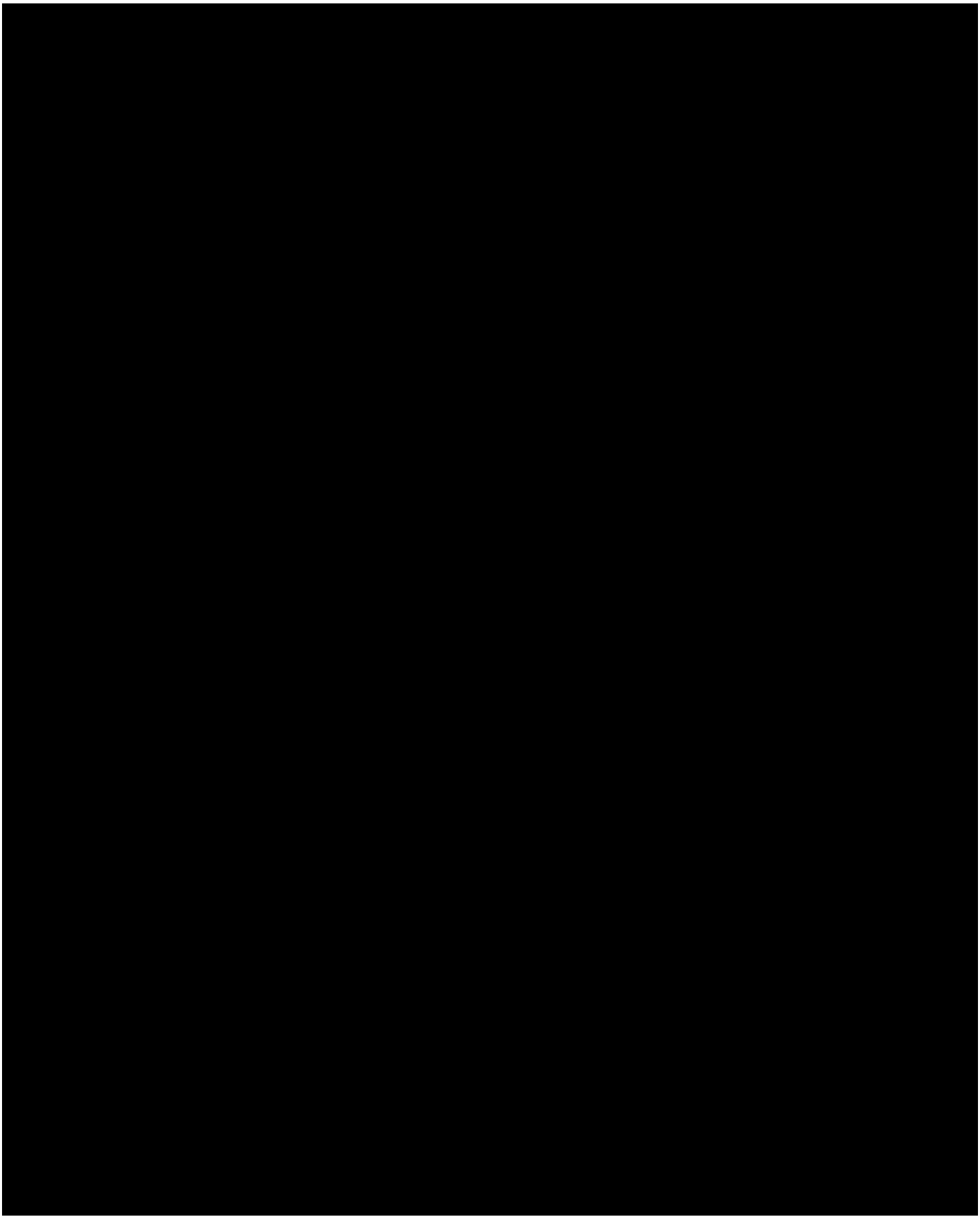


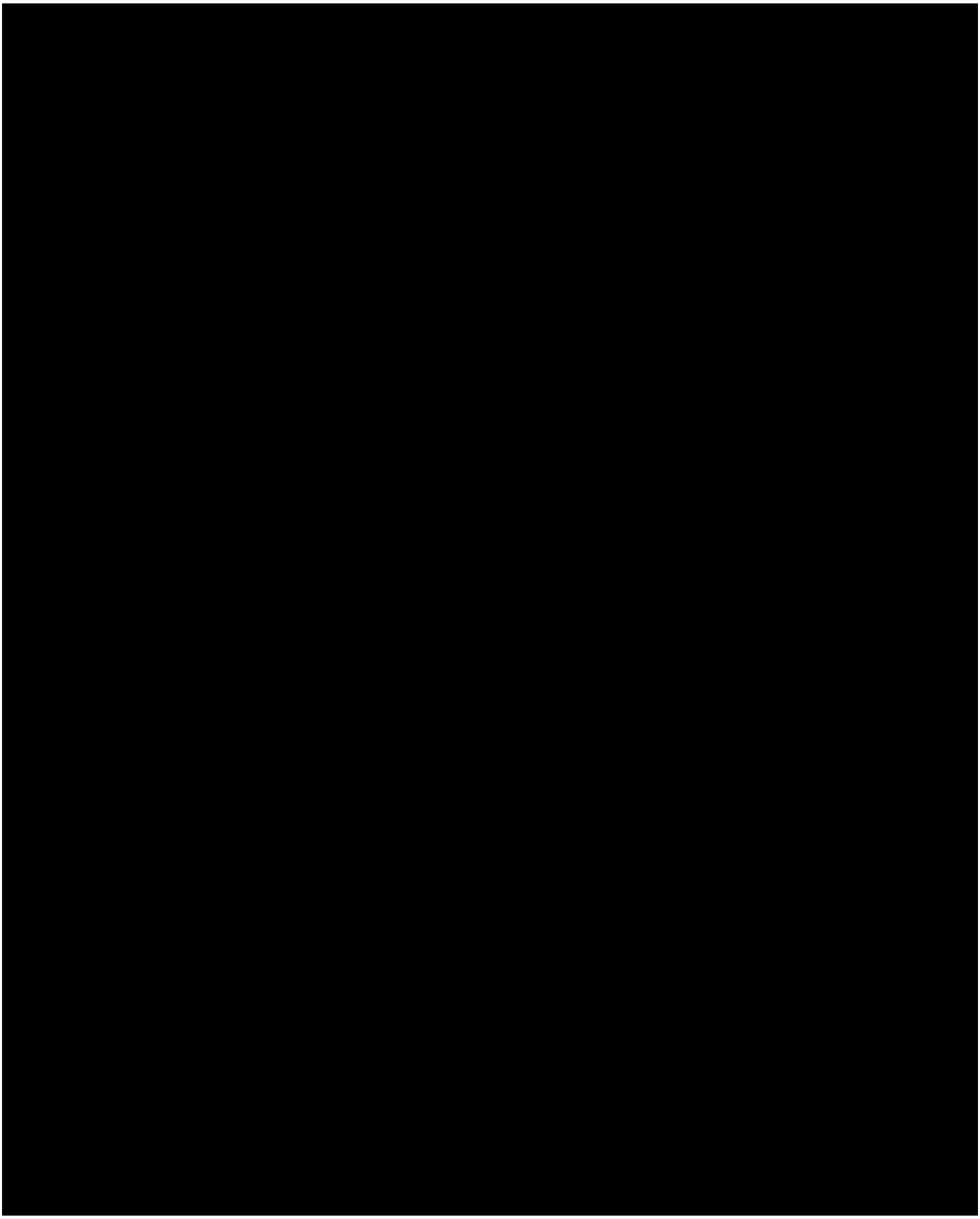


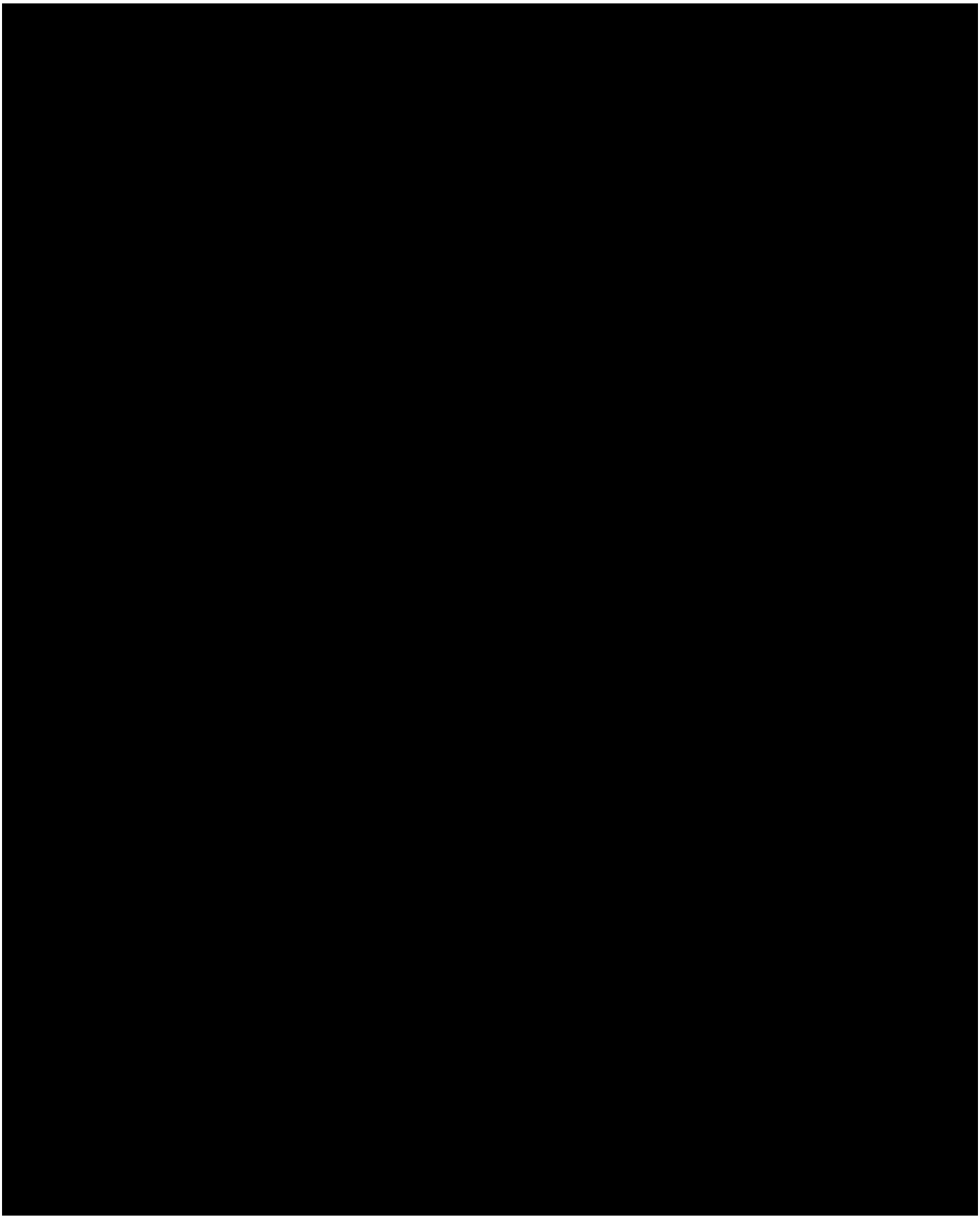


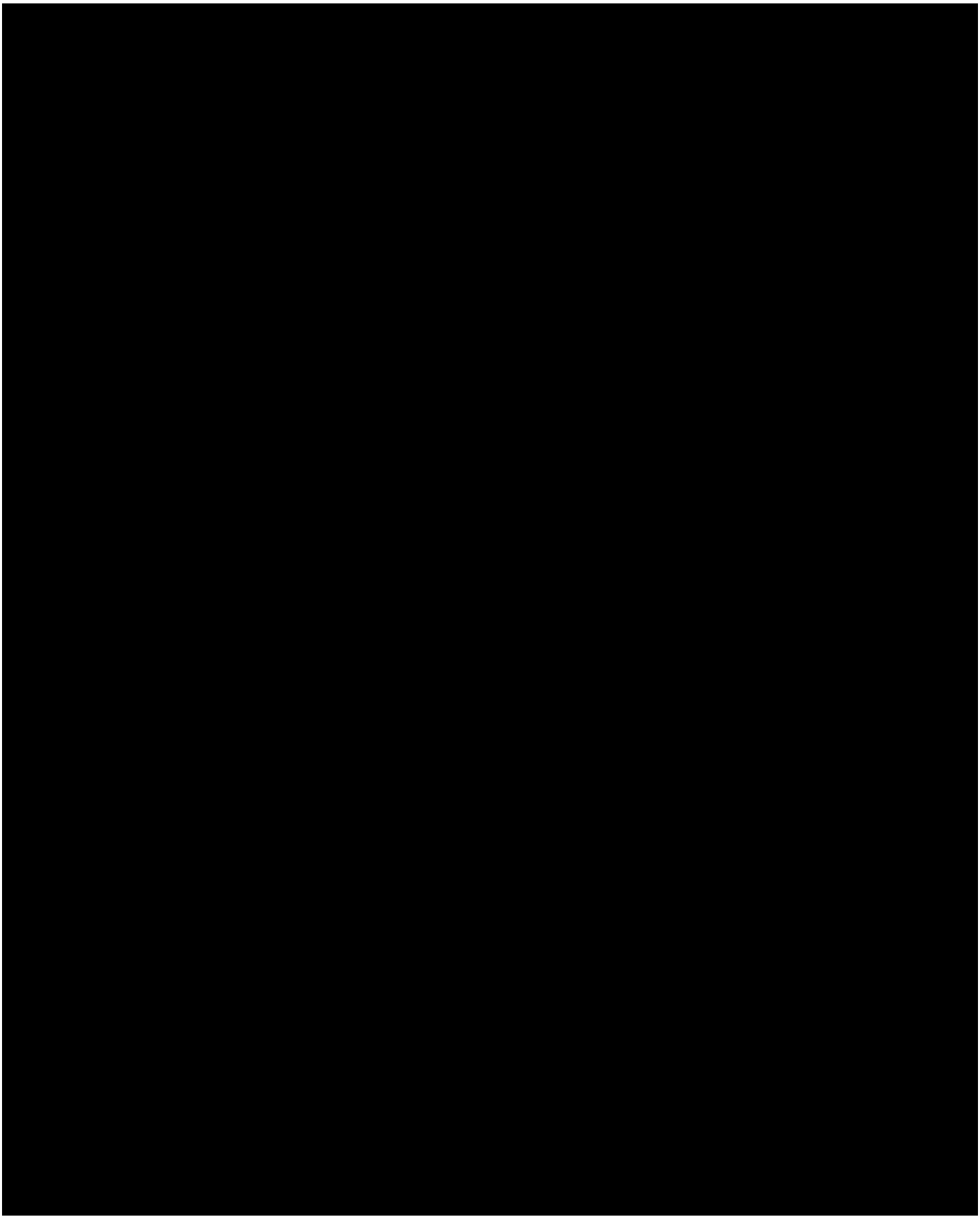


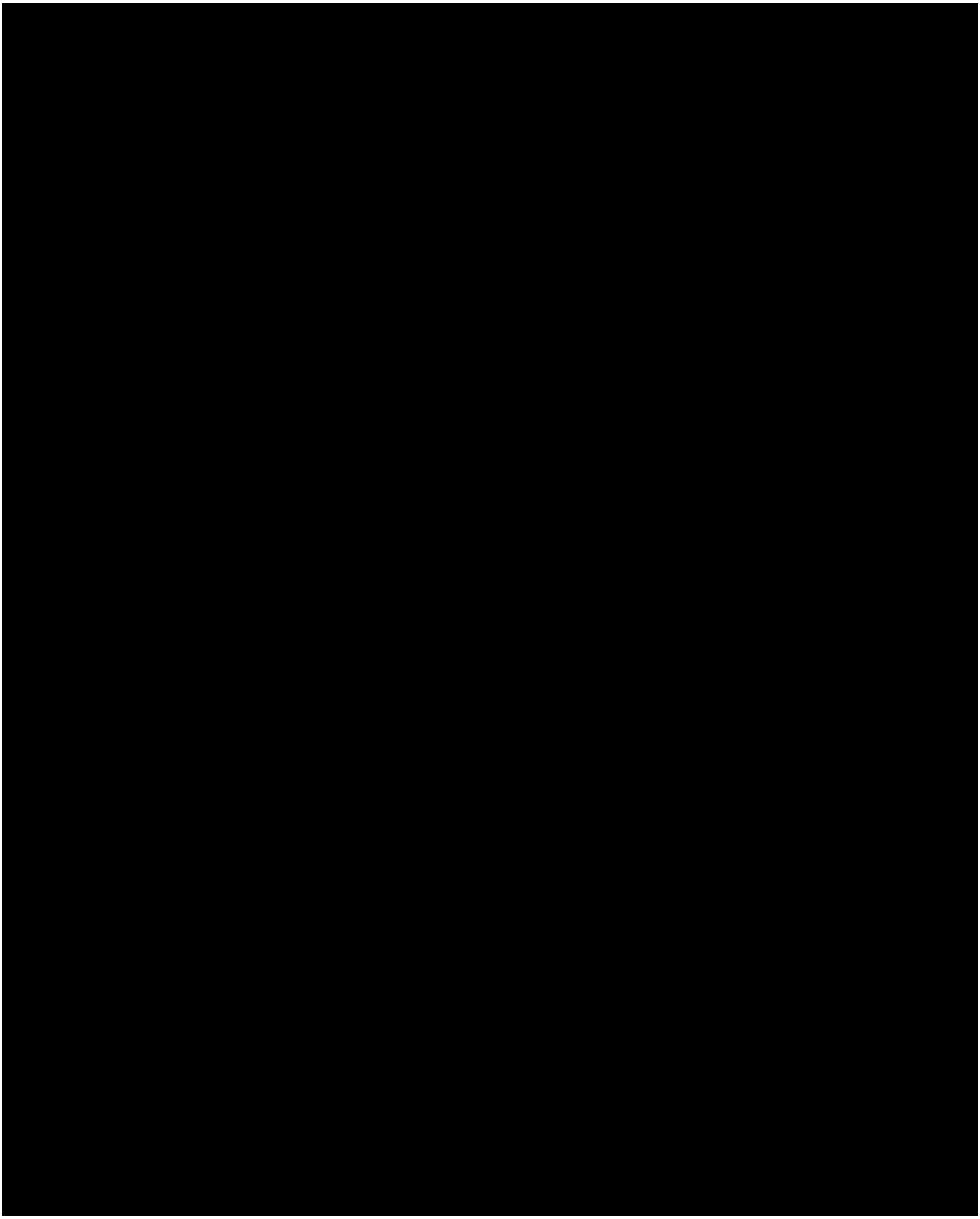


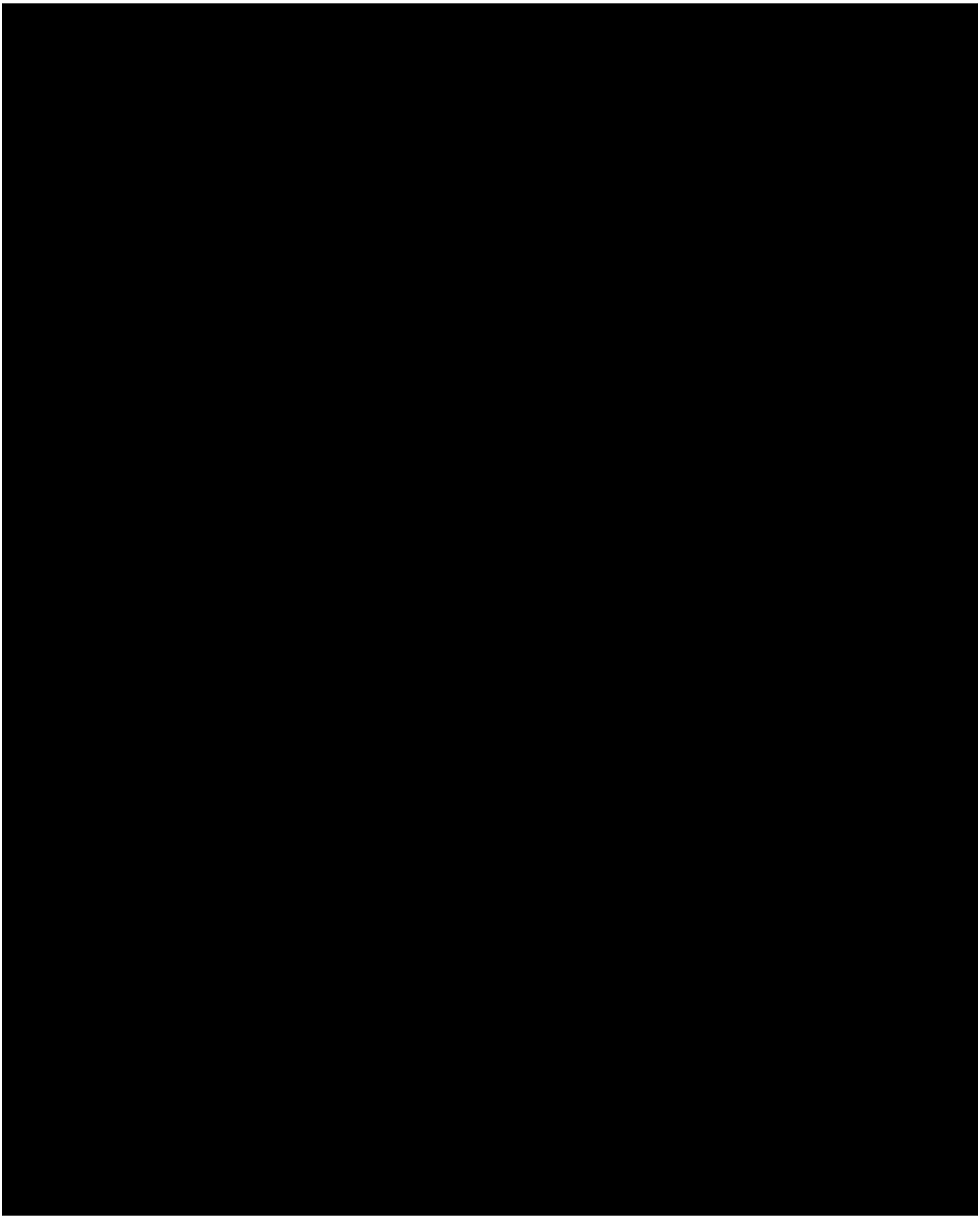


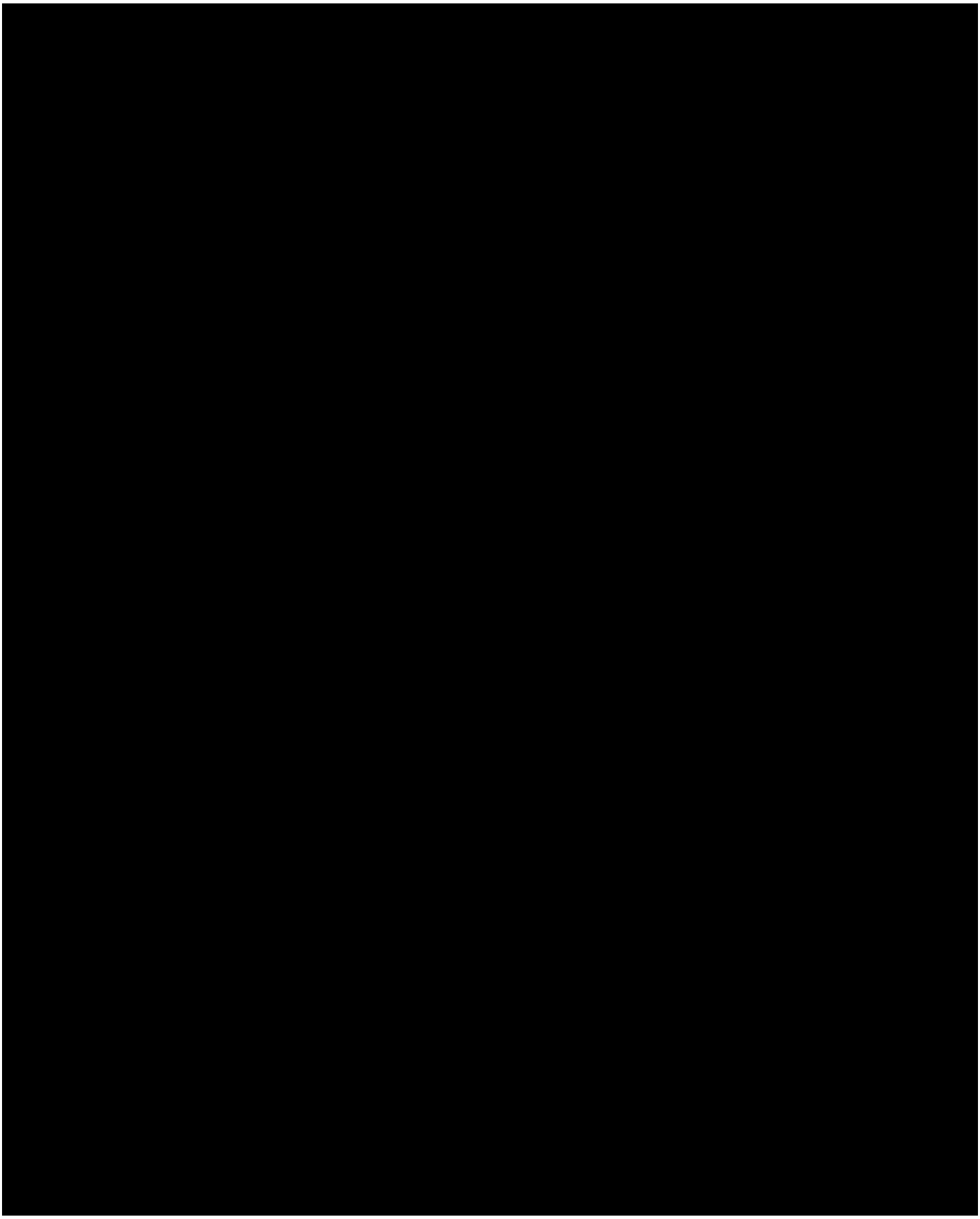


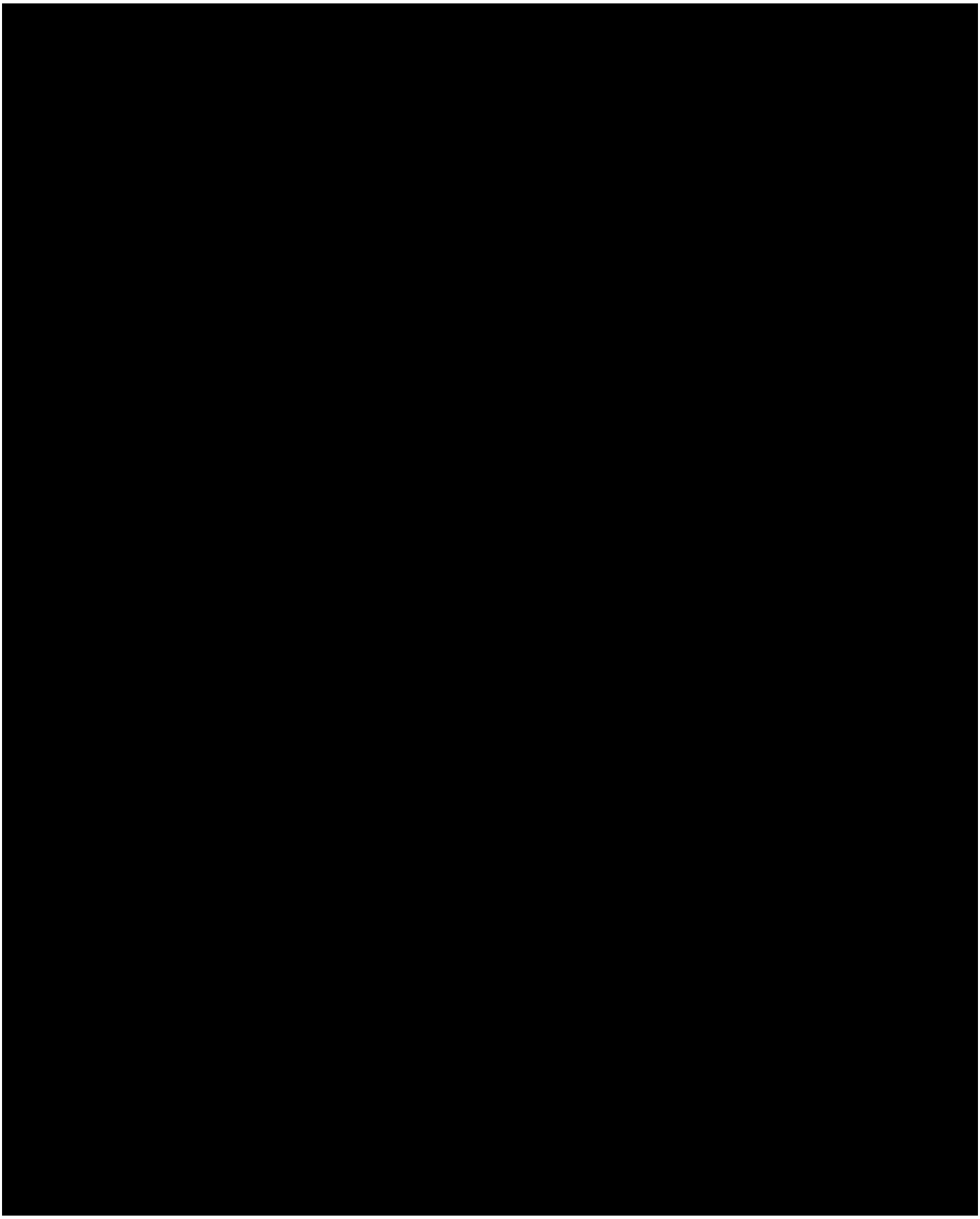


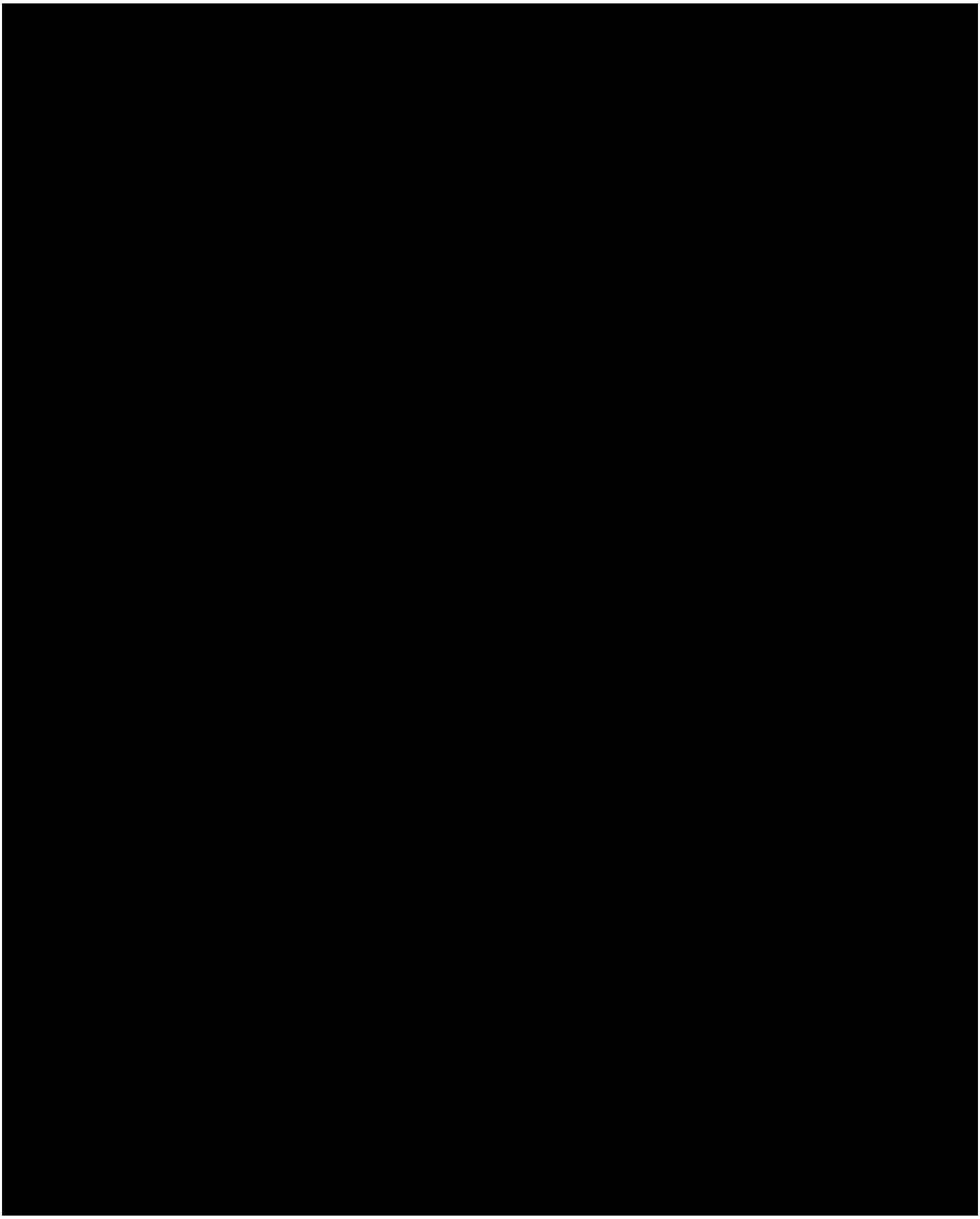


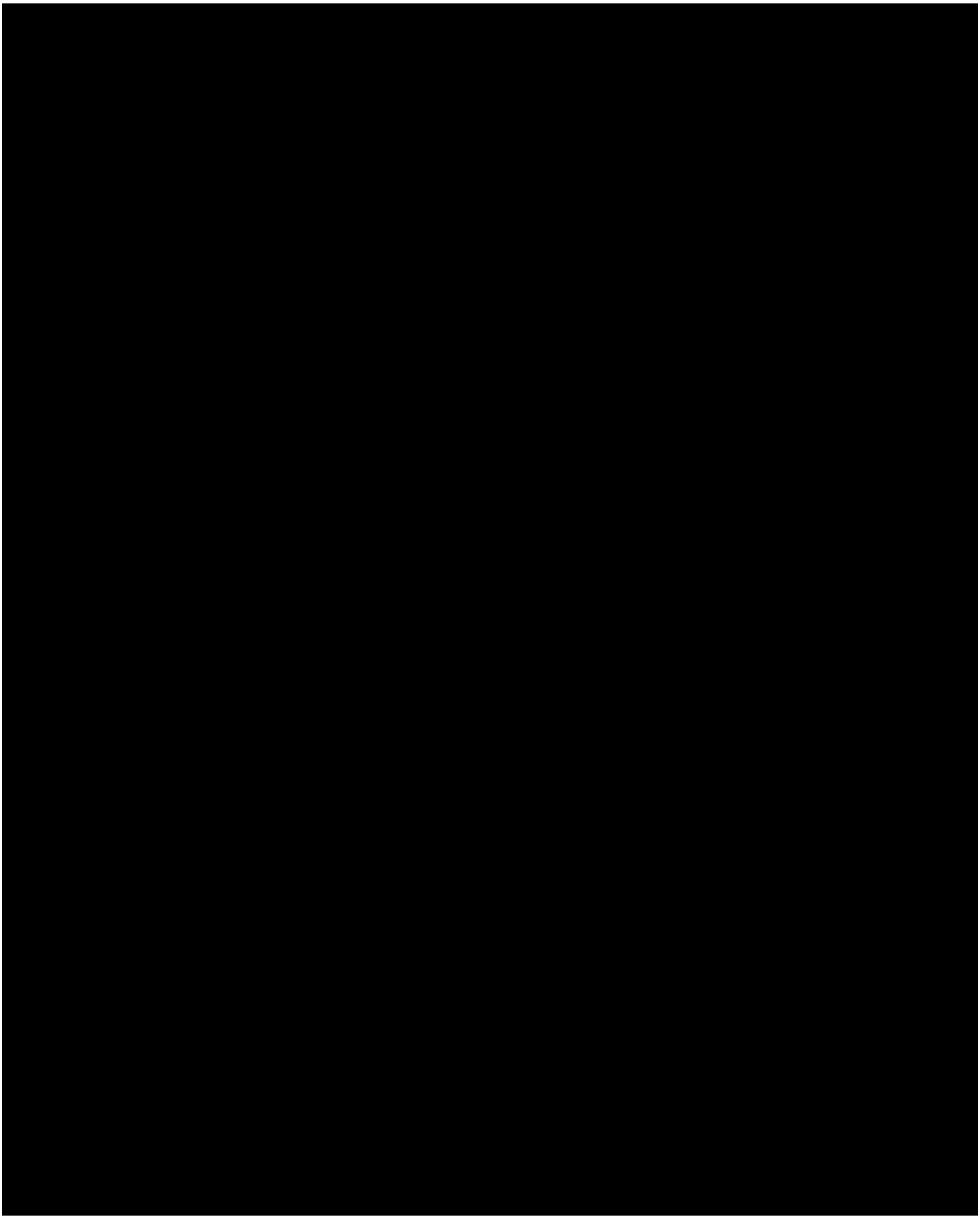


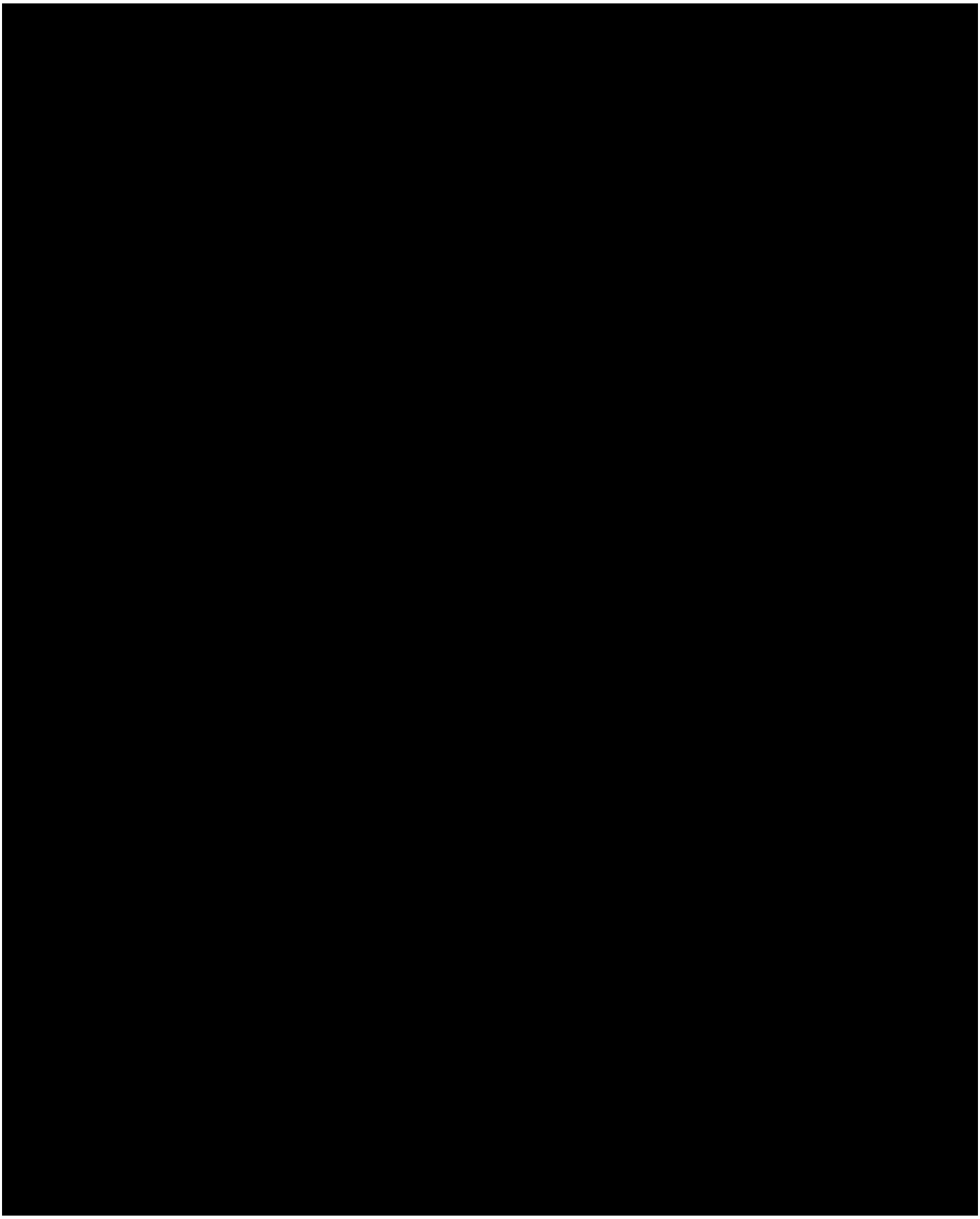


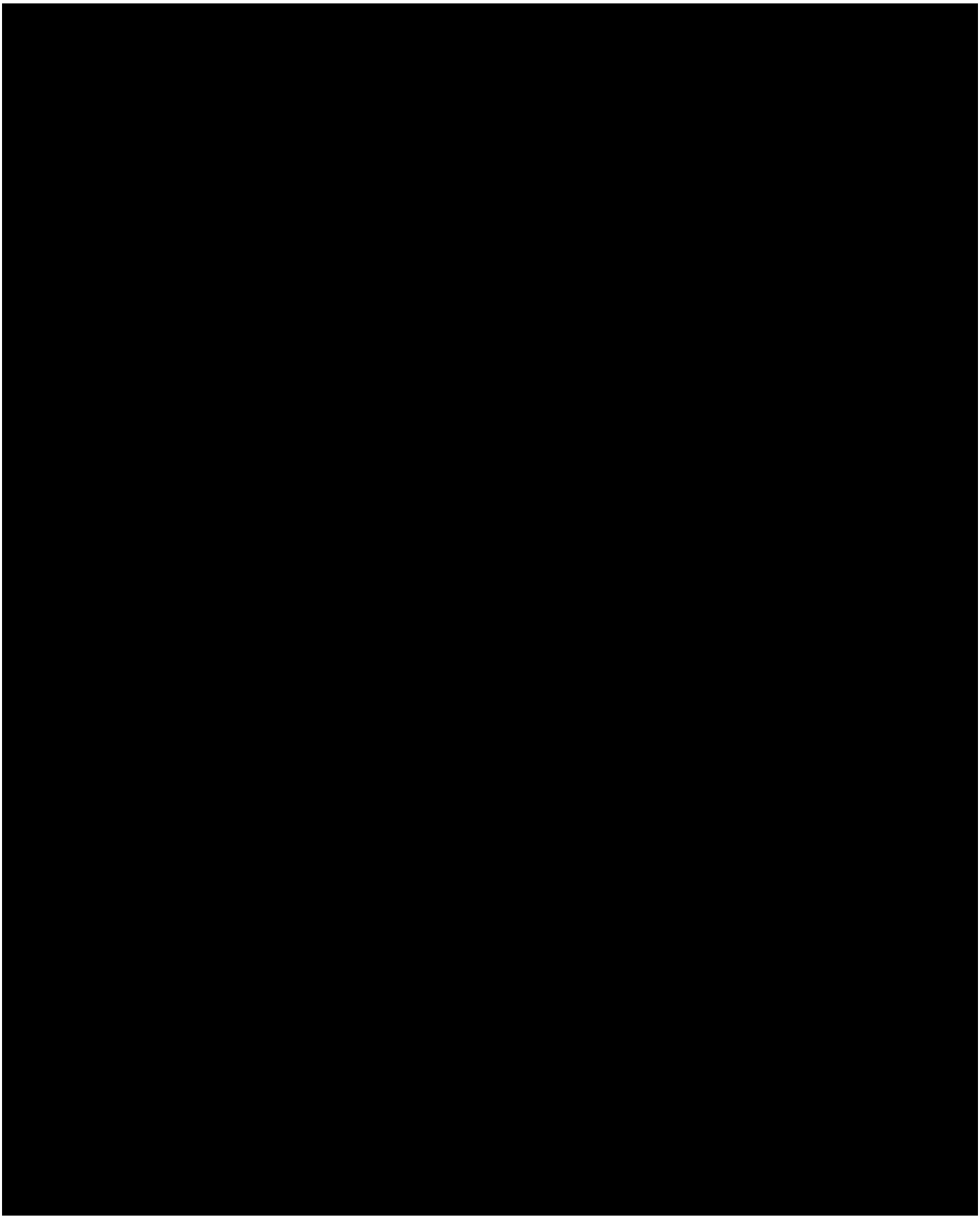


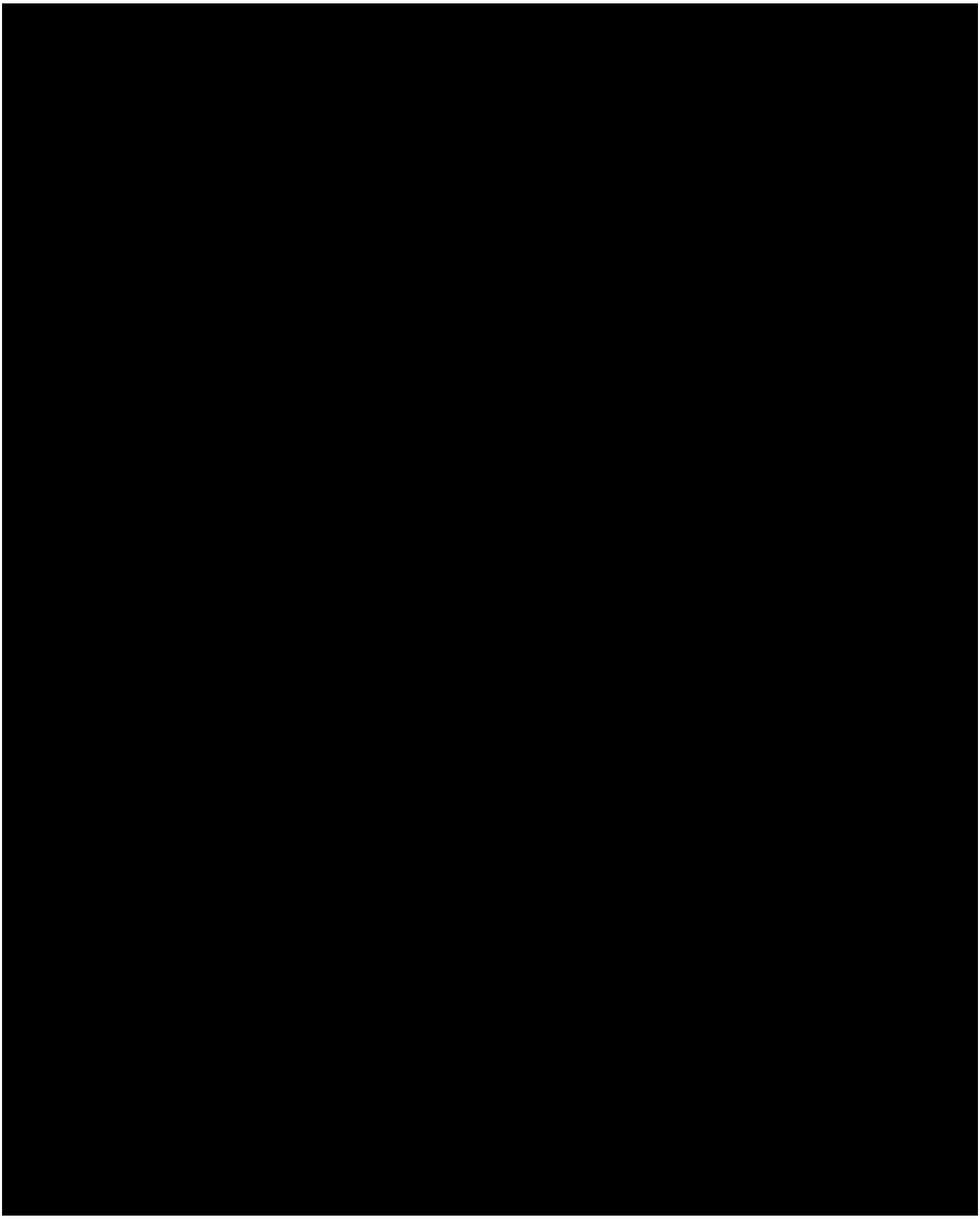


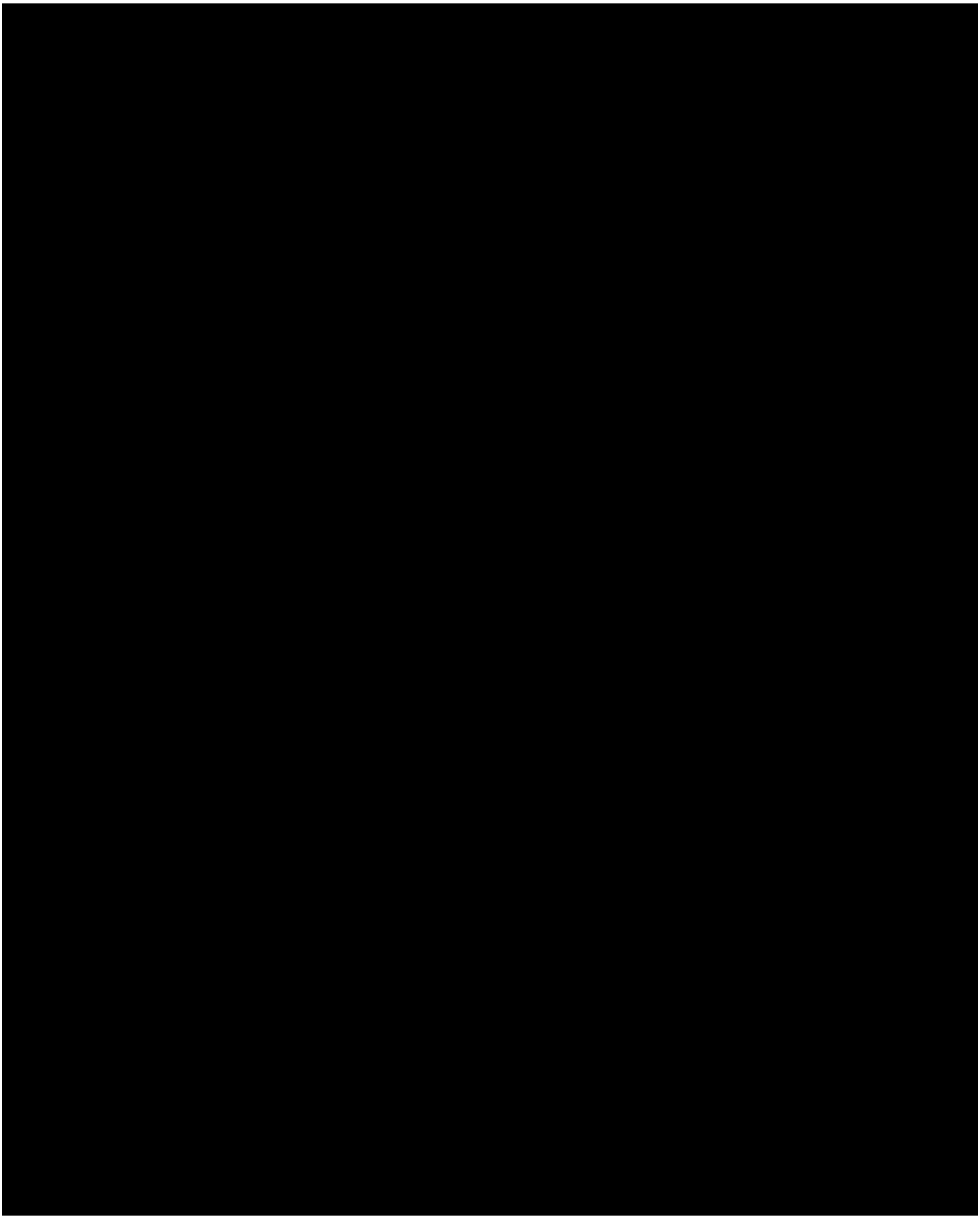


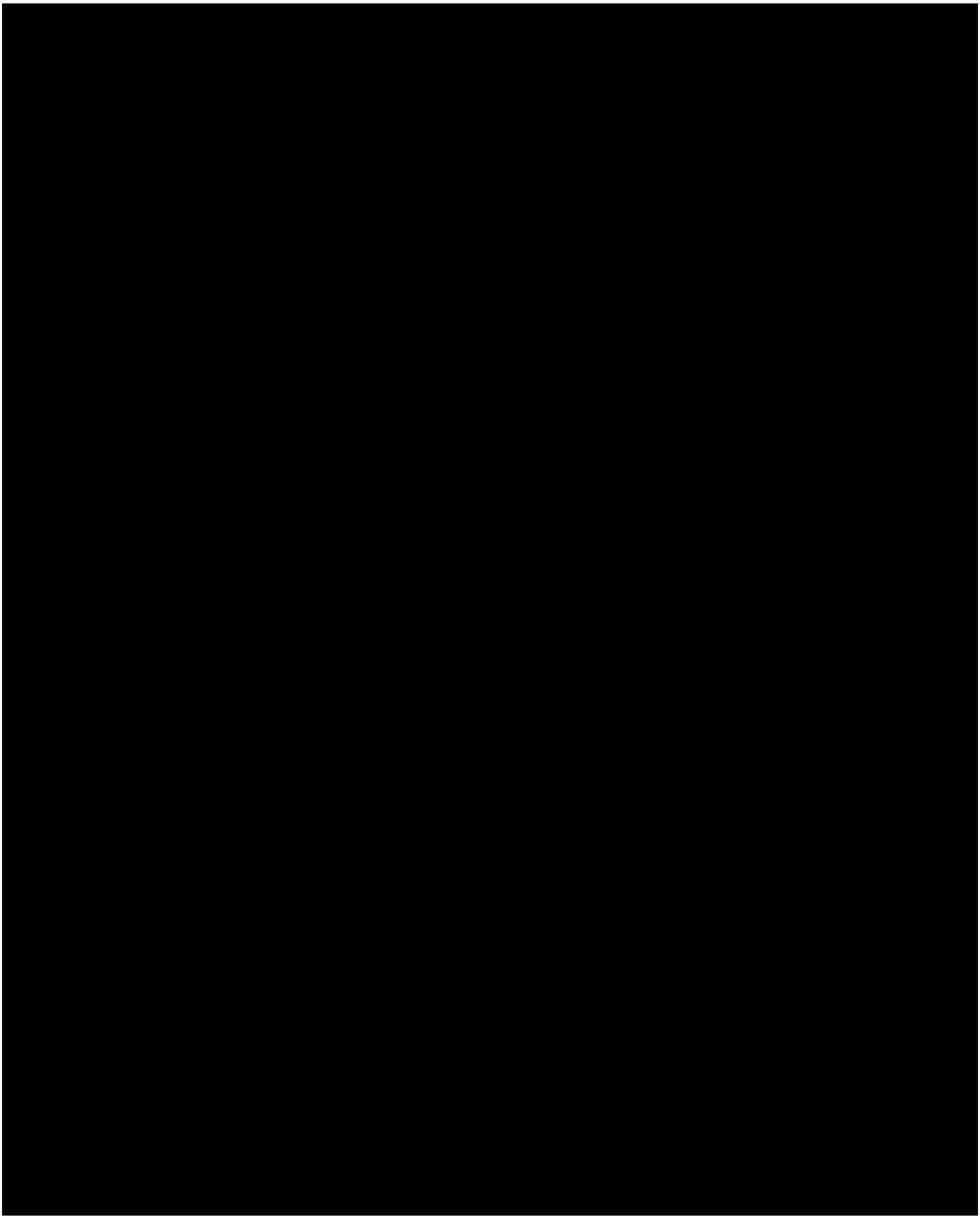


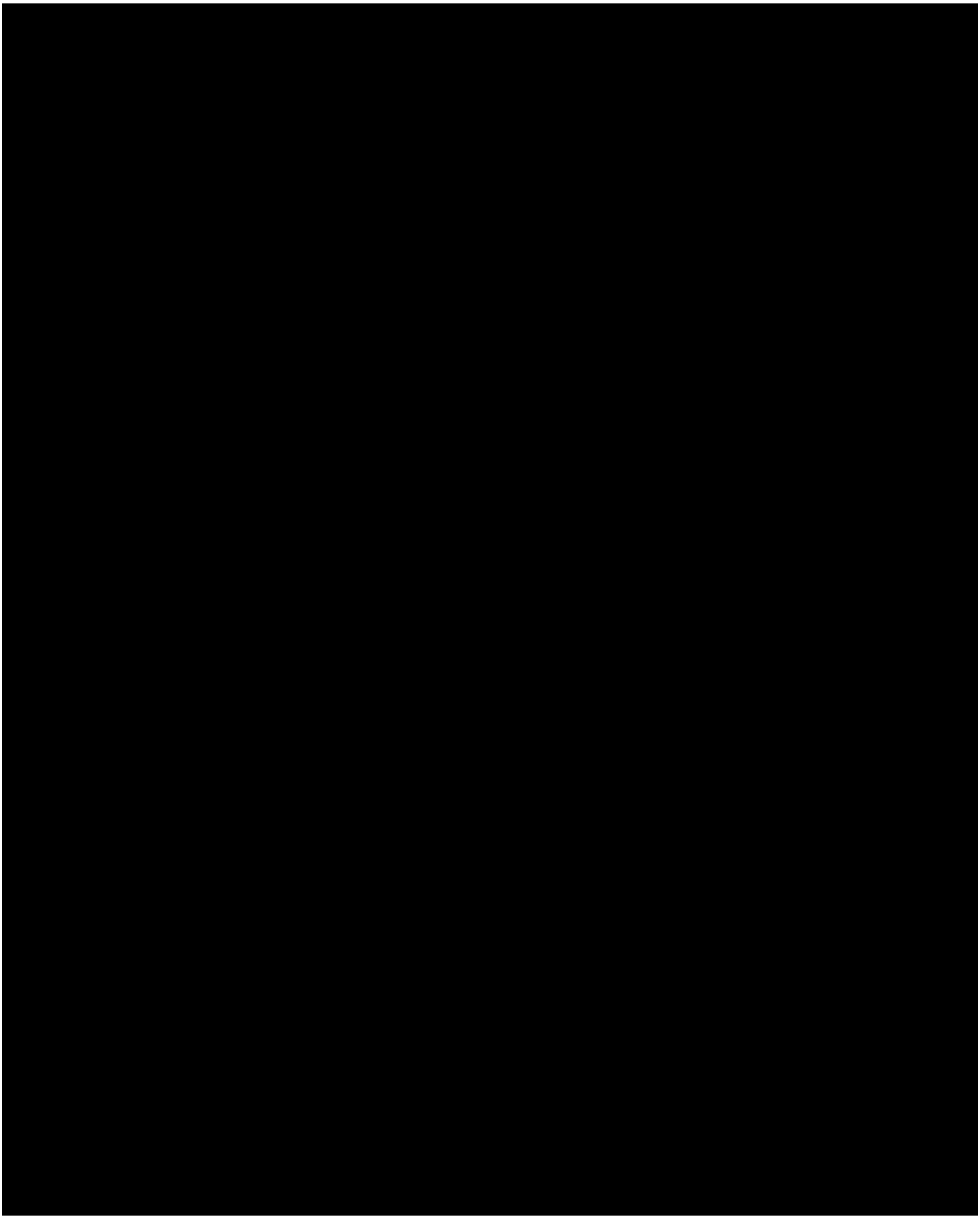


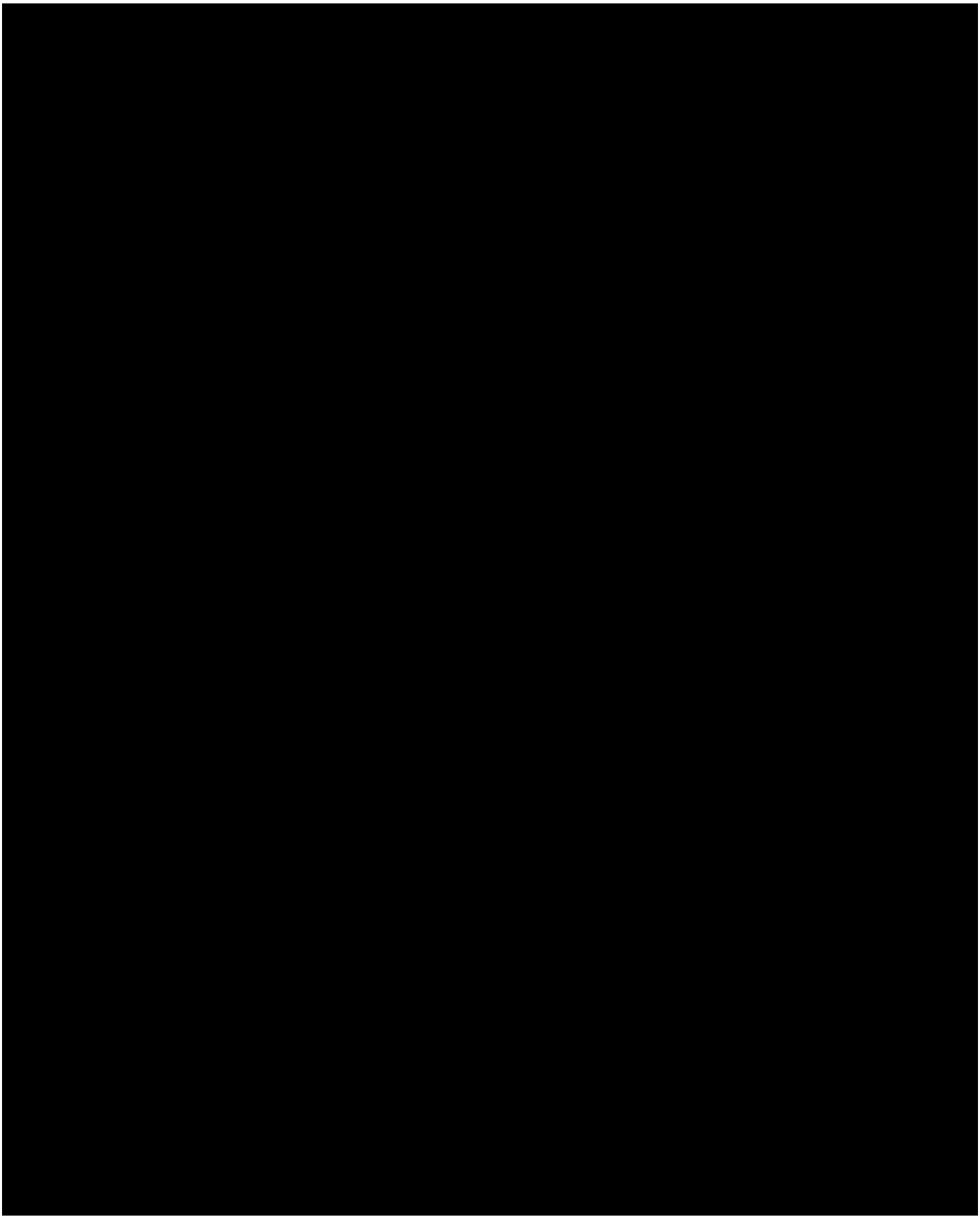












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