STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

Study name:	A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis Protocol Number: 1820201
Statistical Analysis Plan (SAP) Version being approved:	RVC-1820201_SAP_v1.0_04SEP2020
Tables, Figures and Listings (TFL) Shell version being approved:	RVC-1820201_Table Shells_v1.0_04SEP2020 RVC-1820201_Listing Shells_v1.0_04SEP2020 RVC-1820201_Figure_Shells_v1.0_04SEP2020

The above SAP / TFL Shell has been reviewed and approved by Worldwide:

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

The above SAP / TFL Shell has been reviewed and approved by the Sponsor:

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN - TABLES, FIGURES AND LISTINGS SHELL APPROVAL

Statistical Analysis Plan

Title: A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis

Protocol Number: 1820201

Version 1.0

Issue Date: 04-SEP-2020

Author: [redacted]

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Revance Therapeutics, Inc. protocol "1820201" study titled "A Phase II, Prospective, Randomized, Double-Blind, Multi-center, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis".

The proposed analyses are based on the contents of the protocol amendment version 4.0 (dated 15-JUL-2019).

This is a Phase 2, randomized, double-blind placebo-controlled, multicenter study of 2 doses of DaxibotulinumtoxinA (DAXI) for injection in adult subjects with unilateral plantar fasciitis (PF).

Subjects recruited from approximately 20 investigator sites in the United States (US) will be randomized [redacted]

At Week 8, in cases of no improvement, either based on the Numeric Pain Rating Scale (NPRS) score (i.e. no change or worsening of the NPRS score from baseline) or on the investigator's clinical judgment of no clinical improvement following treatment, regardless of whether the subject showed a treatment benefit based on the NPRS score evaluation, a subject will be considered an "early study completer" and will exit the study. Week 8 will serve as the early completion visit for the subject. Subjects who experience any treatment benefit at Week 8, defined as any decrease in NPRS score from baseline, will continue to be observed up until Week 24.

2 STUDY OBJECTIVES

The objective of this study is to compare the efficacy and safety of 2 doses of DAXI for injection versus placebo for managing plantar fasciitis.

3 ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint is:

- Change from baseline in NPRS score, which is recorded within 15 minutes after stepping out of bed in the morning (average over 5 days, defined as 4 days prior to study visit and on the study visit day) at Week 8.

[redacted]

3.4 Safety Endpoints

- Frequency, severity and relationship to study drug of treatment-emergent adverse events during the first 8 weeks post treatment and the overall study duration
- Frequency, severity and relationship to study drug of treatment-emergent serious adverse events during the first 8 weeks post treatment and the overall study duration

4 SAMPLE SIZE

The sample size calculations are based on the minimal clinically important difference of 2 points for NPRS (Farrar, 2001; Michener, 2011). [redacted]

5 RANDOMIZATION

Subjects that complete the screening and run-in periods and have met all inclusion and none of the exclusion criteria will be randomized [redacted]

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

Subjects excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population includes all subjects randomized who received study treatment, with treatment arms classified based on randomization assignment, regardless of the actual treatment received. Efficacy analysis will be performed using the ITT population.

6.1.2 Per Protocol (PP) Population

The Per Protocol (PP) population is defined as a subset of the ITT population that excludes subjects with the major protocol violations/deviations that affect safety and/or efficacy identified during the deviation review meetings [redacted]

6.1.3 Safety Population

The Safety Population includes all randomized subjects who received study treatment, with treatment arms classified based on the treatment each subject actually received, regardless of randomization assignment.

6.1.4 Non-COVID-19 Impacted Population

The Non-COVID-19 Impacted Population is defined as a subset of the ITT population that excludes subjects with any COVID-19-related protocol deviations.

6.1.5 Completed Subject

Study completion may occur at Week 8 or at Week 24. Thus, there will be two types of completers in the study, and they are as follows:

- Week 8 Early Study Completers: subjects who do not demonstrate improvement at Week 8, either based on the NPRS score (i.e. no change or worsening of the NPRS score from baseline) or on the investigator's clinical judgment of no clinical improvement following treatment, regardless of whether the subject showed a treatment benefit based on the NPRS score evaluation. These subjects complete the study at Week 8. Assessments for Week 8 visit are recorded under the Week 24/ET visit for these subjects. However, for the analysis, this will be remapped back to Week 8 visit.
- Week 24 Study Completers: subjects who demonstrate improvement at Week 8, defined as any decrease from baseline on NPRS score, and continued in the study for follow-up until conclusion of Week 24 visit.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the dose of study drug at Day 1. For re-screened subjects, if assessment was not done on the second screening, the initial screening result will be considered.

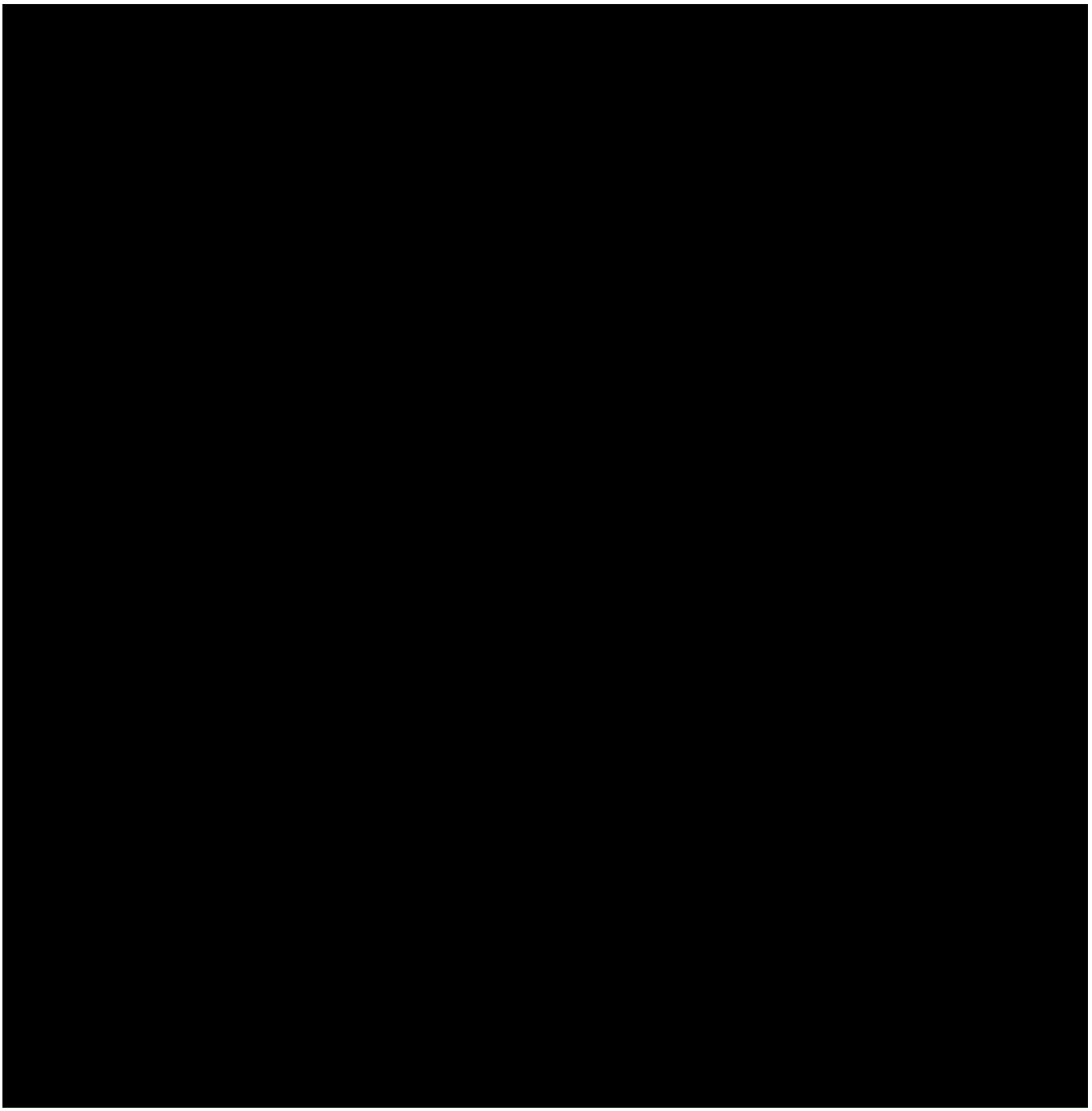
6.2.3 Duration/Study Day/Time

Study day will be calculated as the number of days from the date of dosing of study drug.

- date of event – date of dosing of study drug + 1, for events on or after dosing of study drug
- date of event – date of dosing of study drug, for events before dosing of study drug.

For all time to event analyses, subjects not reporting the specified endpoint will be censored at the time that the subjects were last known not to have experienced the endpoint. In complex

cases where the censoring time of the subject is uncertain, the case will be reviewed by the Worldwide Statistician and a censoring time will be assigned before database lock.



6.2.7 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.8 Columbia-Suicide Severity Rating Scale

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Suicidal Behavior (Baseline/Screening version) / Suicide (Since Last Visit version)

Suicidal Ideation at baseline – A "yes" answer at baseline (Screening visit) to any one of the 5 suicidal ideation questions (categories 1-5) for Lifetime or Past 6 Months on the C-SSRS Baseline/Screening version

Suicidal Behavior at baseline – A "yes" answer at baseline (Screening visit) to any one of the 5 suicidal behavior questions (categories 6-10) for Lifetime or Past 6 Months on the C-SSRS Baseline/Screening version

Suicidal Ideation since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS Since Last Visit version

Suicidal Behavior since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS Since Last Visit version

There will be no imputation of missing data for C-SSRS.

6.2.9 Early Withdrawal Assessments

For the analysis, assessments performed at early withdrawal visits for the subjects who discontinued will be assigned to the next scheduled visit the assessment was scheduled to be assessed. For early study completers, the assessments for Week 24/ET visit will be remapped back to Week 8.

6.2.10 Unscheduled Visits

Only scheduled post-baseline vital signs, ECG values, and foot and ankle examination will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR. For laboratory assessments, if a repeat assessment is available, this will be tabulated instead of the scheduled assessment. Post-baseline unscheduled assessments that were not a repeat for a scheduled assessment will be disregarded but will be listed in the relevant appendices to the CSR.

6.2.12 Change from Baseline

Change from baseline in absolute terms is defined as the baseline value subtracted from the post-baseline value. This calculation method will be used as part of the calculation for percentage change from baseline calculations.

6.2.13 Percent Change from Baseline

Percent change from baseline will be calculated as change from baseline multiplied by 100 then divided by the baseline value.

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[1].

6.3.1 Decimal Places

Decimal places for derived data described in section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer, for example number of days or total score, will be presented with zero decimal places.

Means, medians and quartiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P-values will be quoted to 4 decimal places. P-values < 0.0001 will be presented as p<0.0001.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects randomized, and number of subjects in each analysis population (Safety, ITT, and PP) will be summarized by treatment group and overall based on all randomized subjects.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment group and overall for the Safety Population.
- The number of subjects who are Week 8 Early Study Completers and Week 24 Study Completers will be summarized by treatment group and overall for the Safety Population.

6.5 Protocol Deviations

Protocol deviations will be classified as Major, Minor and by Criticality. Additionally, any COVID-19-related protocol deviations will be identified. Protocol deviation categories will be

tabulated by treatment group and classification for the Safety Population. The number of subjects impacted by COVID-19, that is, with any COVID-19-related protocol deviation, number of subjects with missed visits, delayed visits, with visits performed remotely, and with missed assessments will be summarized by treatment group for the Safety Population. A listing of critical and major protocol deviations, as well as COVID-19 related protocol deviations will be provided within Appendix 16.2 of the CSR.

6.6 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by treatment group and overall, and by treatment group within each investigator site for age (years), gender, fertility status (for female subjects), ethnicity, race, screening height, weight, and BMI based on the Safety Population.

6.7 Medical History

Separate tabulations of previous and ongoing conditions at screening will be presented by treatment group and overall for the Safety Population. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) v.22.0 primary system organ class and preferred term.

6.8 Prior and Concomitant Medications, and Therapies and Relevant Surgical Procedures

Separate tabulations will be produced for prior and concomitant medications presented by treatment group and overall for the Safety Population. Prior medications are defined as all medications starting before the date of dosing of study drug. Concomitant medications are defined as medications taken on or after the date of dosing of study drug. A medication that started before the date of dosing of study drug but ongoing during the study will be classified as both prior and concomitant. Prior and concomitant medications will be coded using WHO Drug Dictionary (Mar 2019) and will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2.

Any type of rescue medication is not permitted in the study prior to Week 8. However, at Week 8, if the subject has less than 20% reduction from baseline in the NPRS score, a physician-

prescribed physical therapy will be permitted upon subject's request. Prior therapies are defined as all therapies starting before the date of dosing of study drug. Concomitant therapies are defined as therapies that started on or after the date of dosing of study drug. A therapy that started before the date of dosing of study drug but ongoing during the study will be classified as both prior and concomitant. Physician-prescribed therapies will also be classified as concomitant. Number of subjects with prior, concomitant, and physician-prescribed therapies, and with relevant surgical procedures will be presented by treatment group and overall for the Safety Population.

6.9 Exposure to Study Drug

The number of randomized subjects that received injection, foot injected (left or right), and whether or not injection was guided with ultrasound will be summarized by treatment group and overall.

6.10 Treatment Compliance

Study subjects will receive a one-time single treatment, [redacted] Thus, treatment compliance will not be calculated. However, listing of study drug administration will be provided.

6.11 Efficacy Analyses

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated.

For the analysis of NPRS-related endpoints, unless otherwise stated, the following will apply. Baseline NPRS score will be the average over 5 days, that is, 4 days prior to Day 1 visit and on Day 1 visit. A minimum of 3 non-missing NPRS scores out of the 5 days is required for the subject's baseline NPRS score. Post-baseline NPRS scores are to be calculated as the average over 5 days, that is, 4 days prior to study visit and on study visit day. A minimum of 3 non-missing NPRS scores out of the 5 days is required for the subject's post-baseline NPRS score. If there are more than 2 days of missing NPRS scores, the NPRS score for the particular post-baseline visit will be set to missing. Non-missing out-of-window NPRS score, that is, time of assessment is more than 15 minutes after first step out of bed in the morning, within the 5 days will be flagged for sensitivity analysis but will still be considered in the calculation of NPRS scores. If a subject missed/skipped a clinic visit, the post-baseline NPRS score for that particular visit will be calculated as the average over 5 days, that is, 4 days prior to expected visit date and

on the expected visit date. The expected visit date is determined relative to the day of dosing (Day 1). For example, if the missed/skipped visit is Week 4, the expected visit date will be Day 1 visit date + 28 days. In the event that the 4 days leading to the expected visit date overlaps with the previous visit's date, only the NPRS scores on the day after the previous visit's date up to the expected visit date will be used to obtain the post-baseline NPRS score for that particular visit given that there is a minimum of 3 days' worth of NPRS scores. Otherwise, the post-baseline NPRS score for that particular visit will be set to missing. If a subject has more than one valid NPRS score at a given timepoint, the NPRS score corresponding to the assessment that has non-missing response on the question "What time did you get out of bed" will be used. However, if all the assessments at a given timepoint have response on the question "What time did you get out of bed", the NPRS score corresponding to the closest assessment to the target visit date will be used. If the assessments are equidistant from the target visit date, the NPRS score at a later assessment will be used.

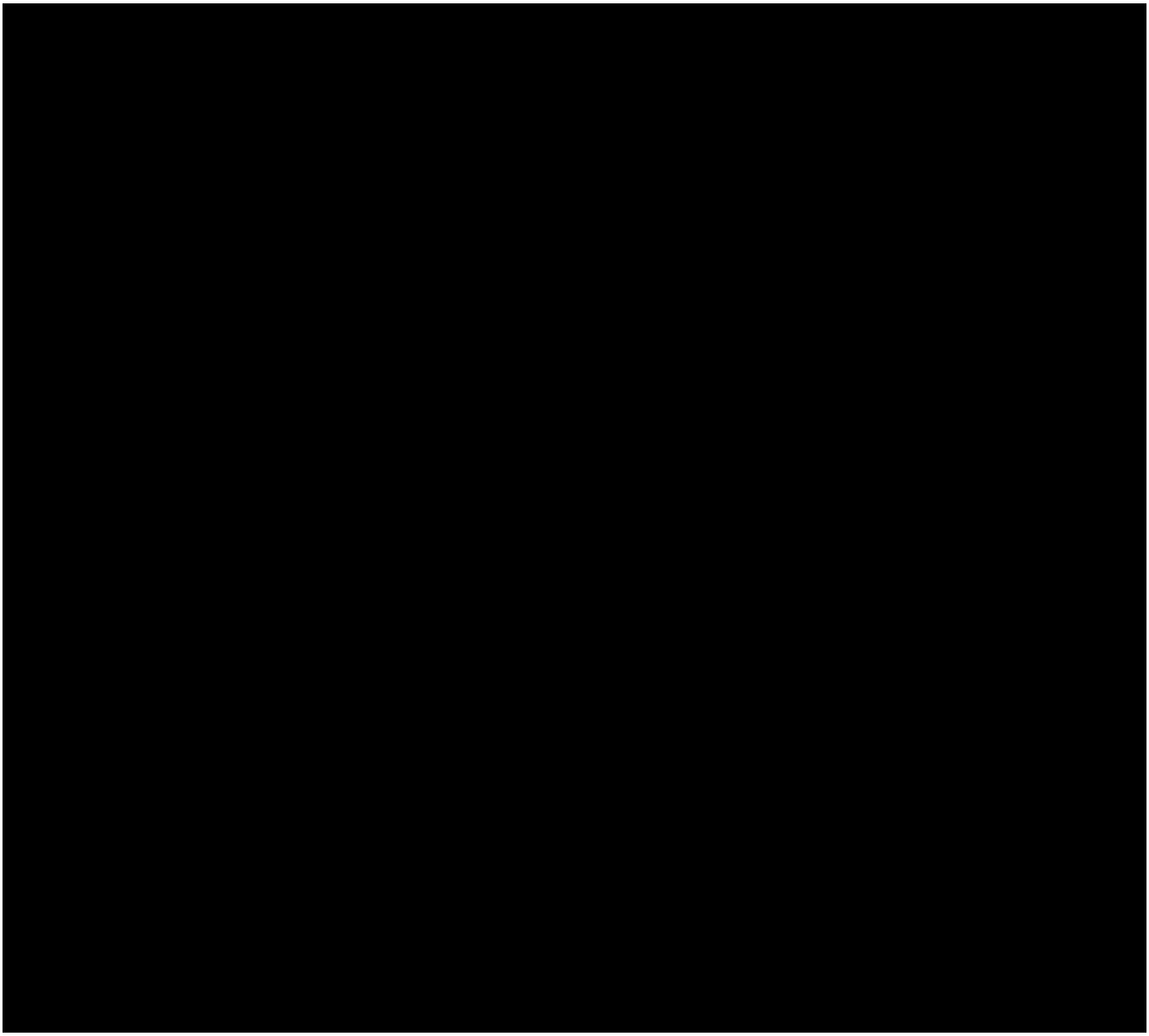
6.11.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline in the NPRS score, which is recorded within 15 minutes after stepping out of bed in the morning and averaged over 5 days (defined as 4 days prior to study visit and on study visit day) at Week 8.

The NPRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her pain. The common format is a horizontal bar or line. Similar to the VAS, the NPRS is anchored by terms describing pain severity extremes with a score of 0 representing "no pain" and a score of 10 representing "worst pain imaginable" or "pain as bad as you can imagine". [redacted]

6.11.2 Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed using the ITT population. [redacted]

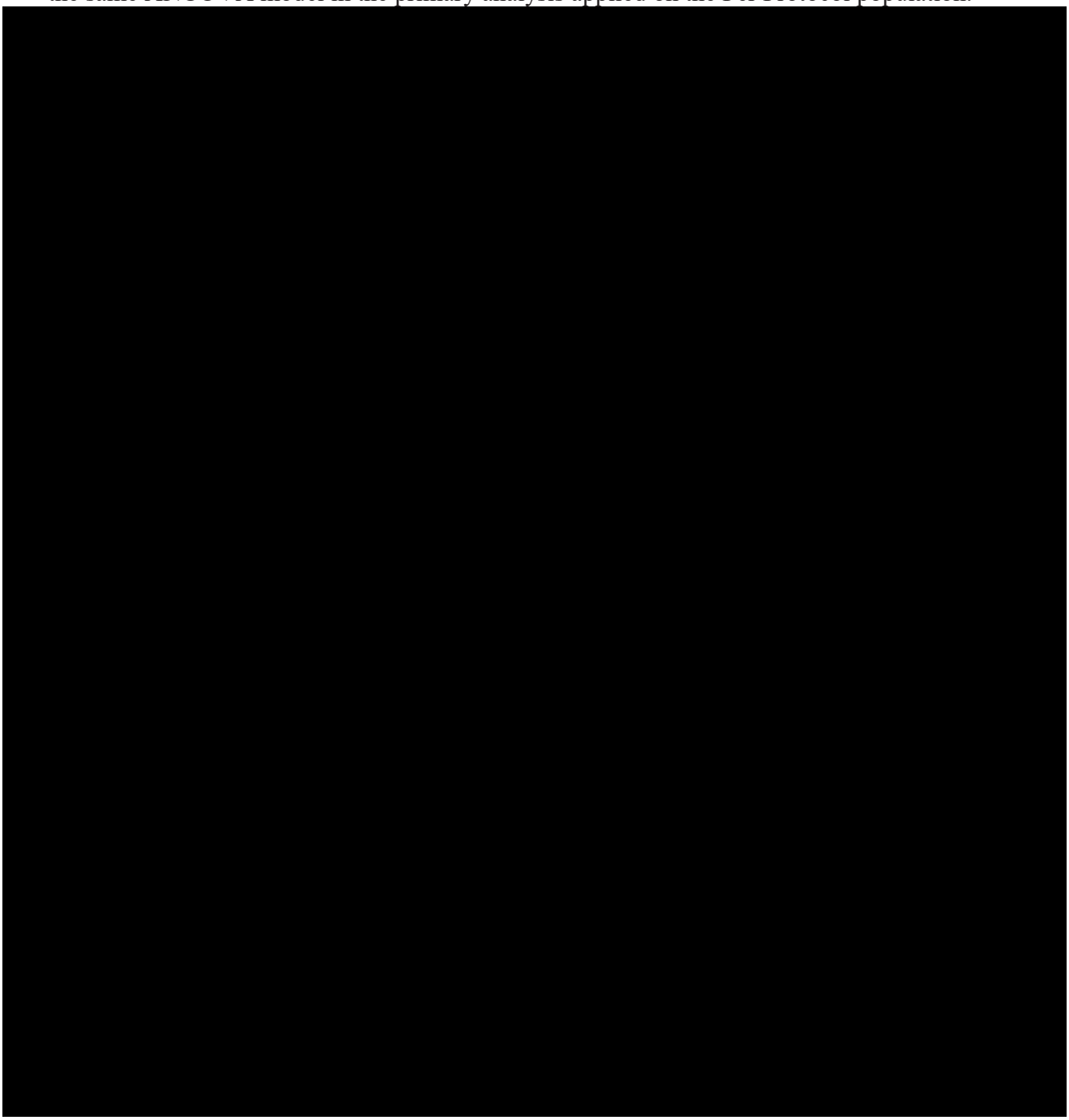


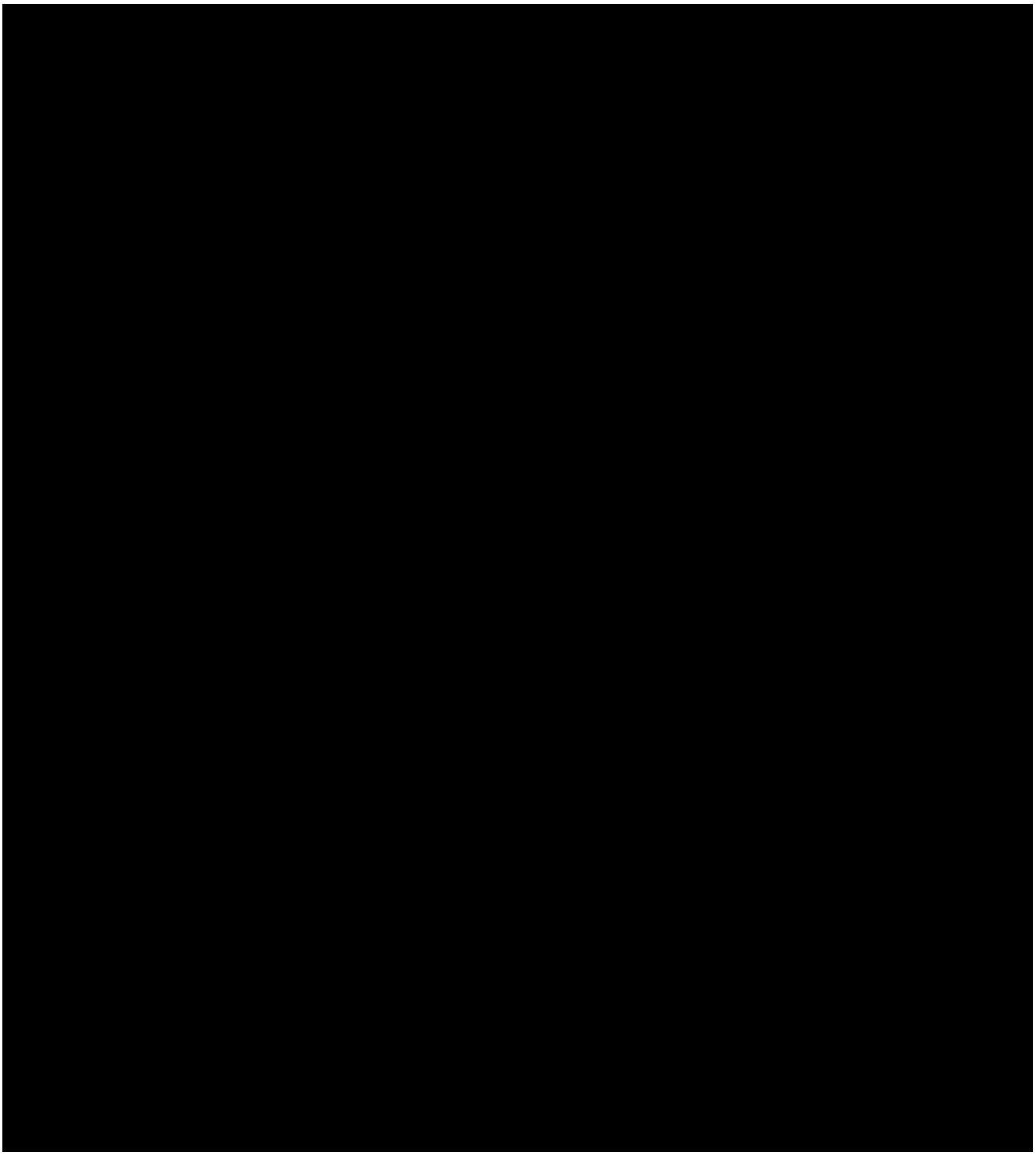
6.11.3 Sensitivity Analysis

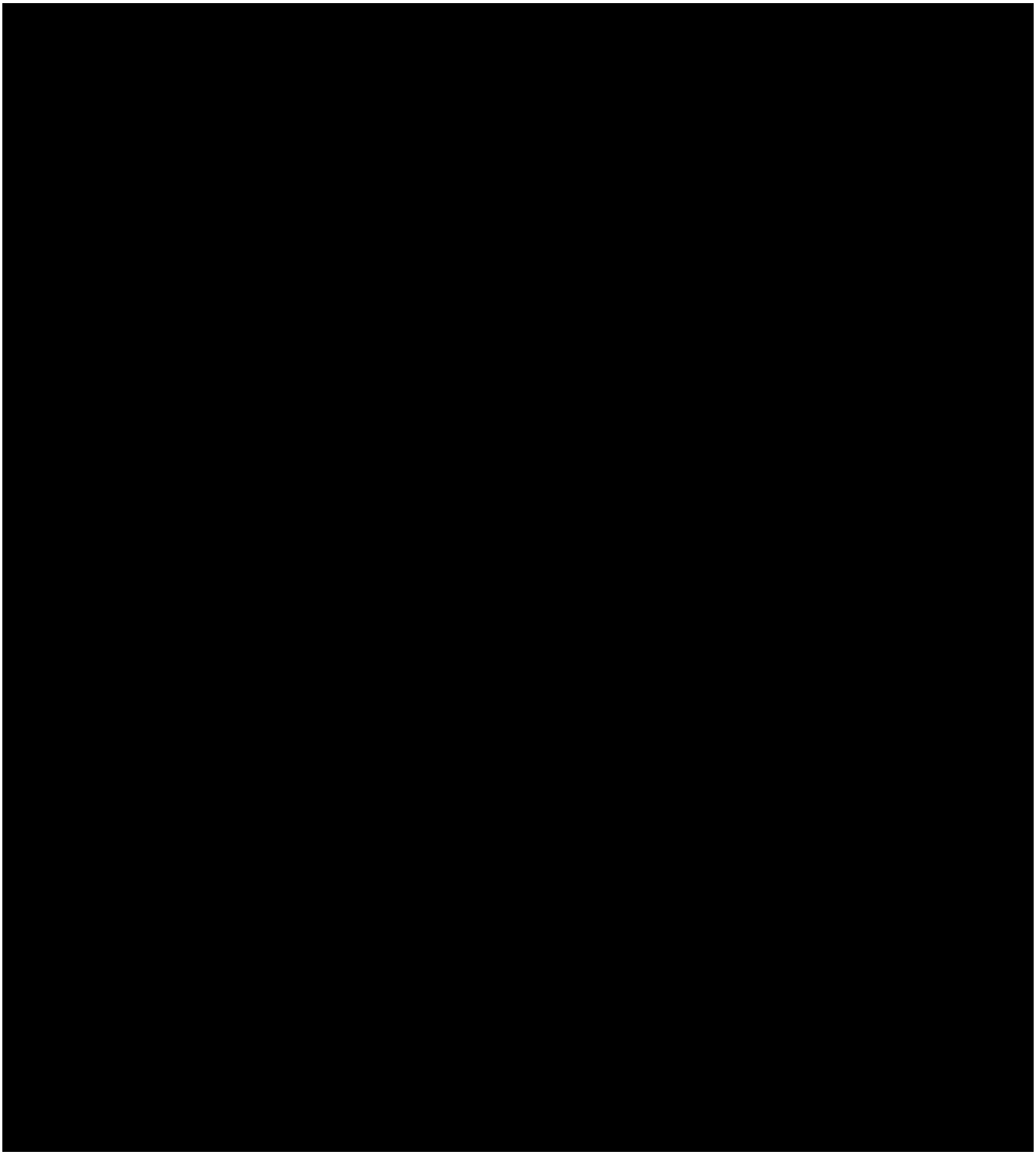
6.11.3.1 ANCOVA on change from baseline in NPRS score at week 8 – Per Protocol Population

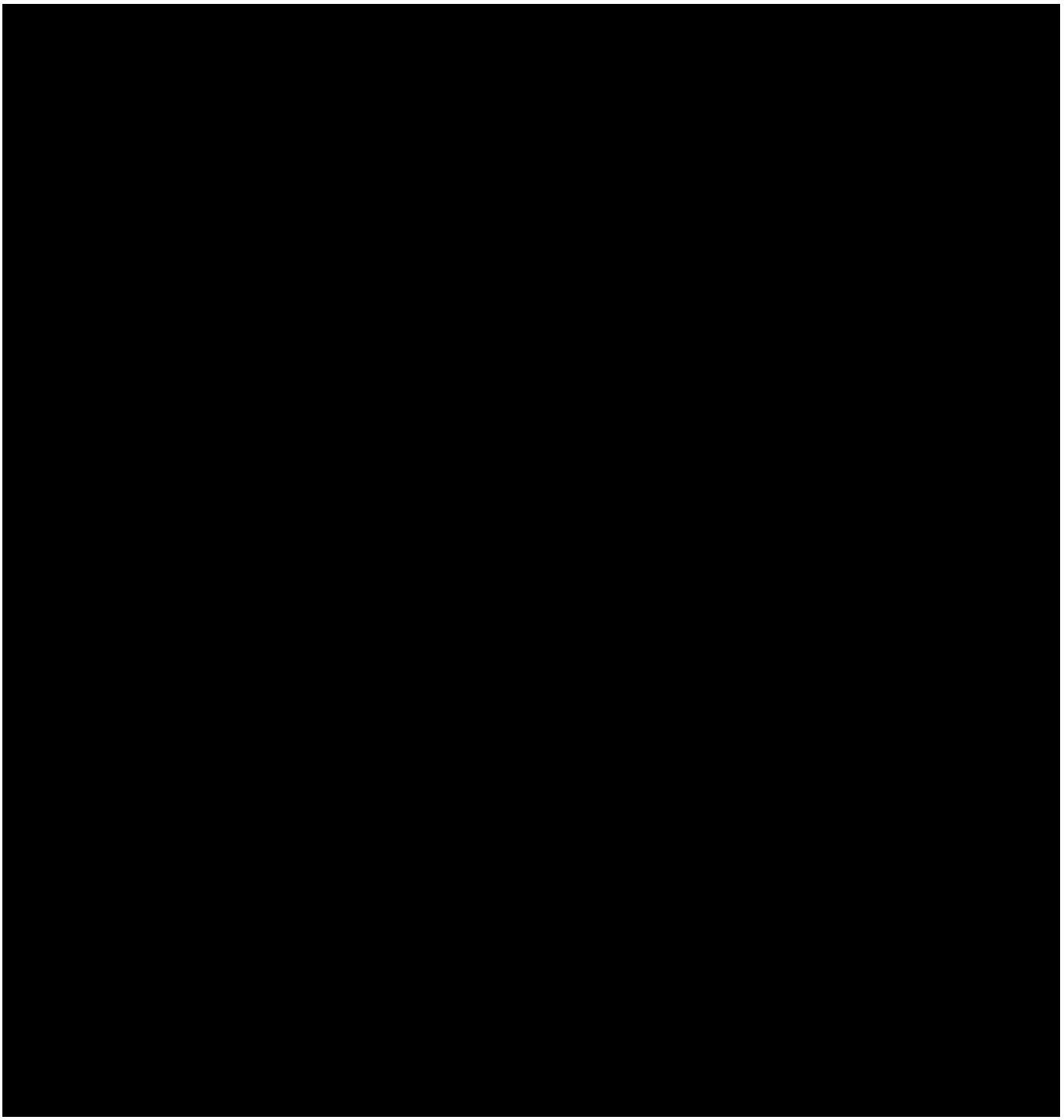
To assess the impact of major protocol violations to study results, the change from baseline in NPRS score at week 8, in which the Week 8 NPRS score is calculated as the average over 5

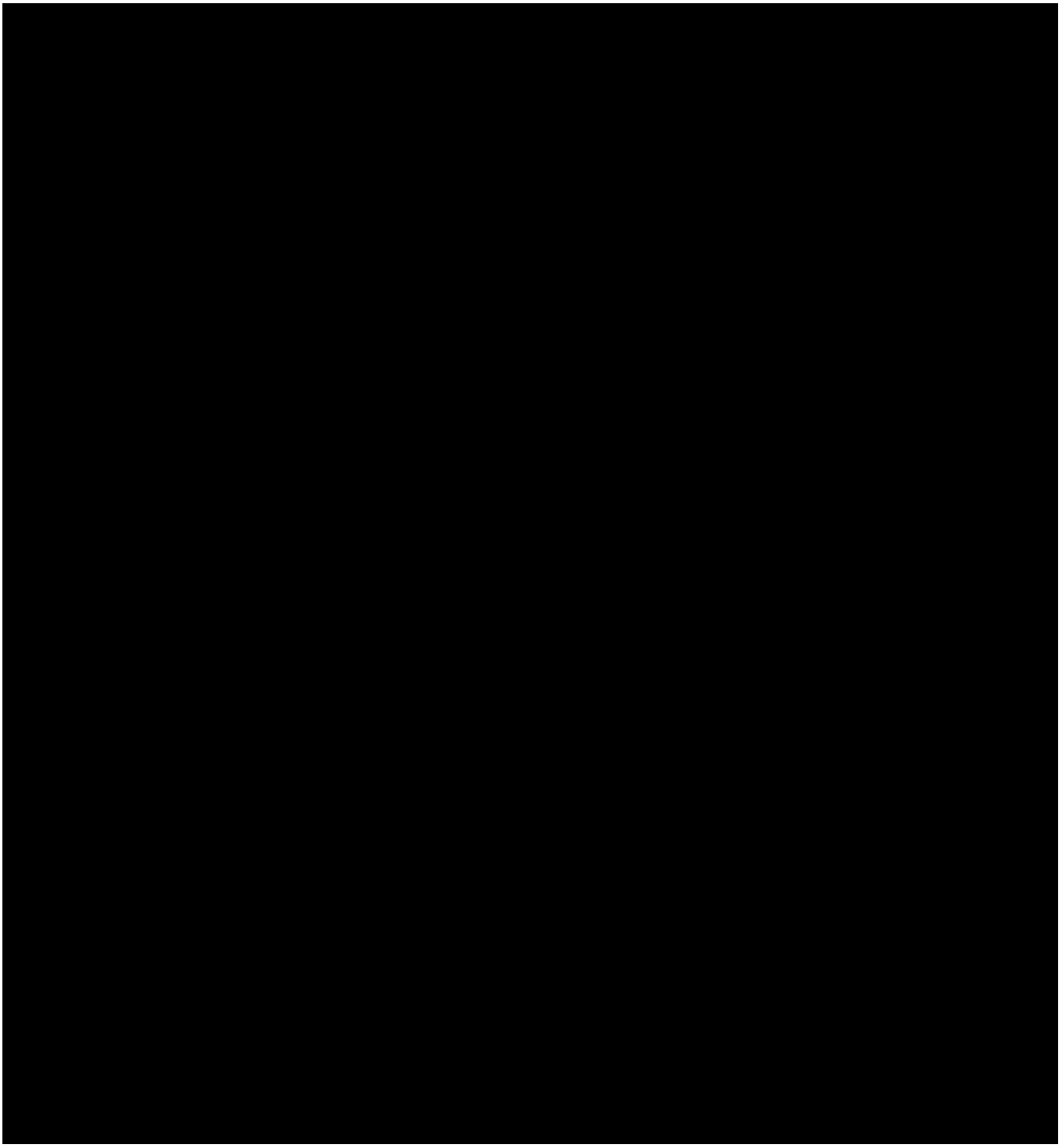
days, that is, 4 days prior to Week 8 visit date and on Week 8 visit date, will be analyzed using the same ANCOVA model in the primary analysis applied on the Per Protocol population.

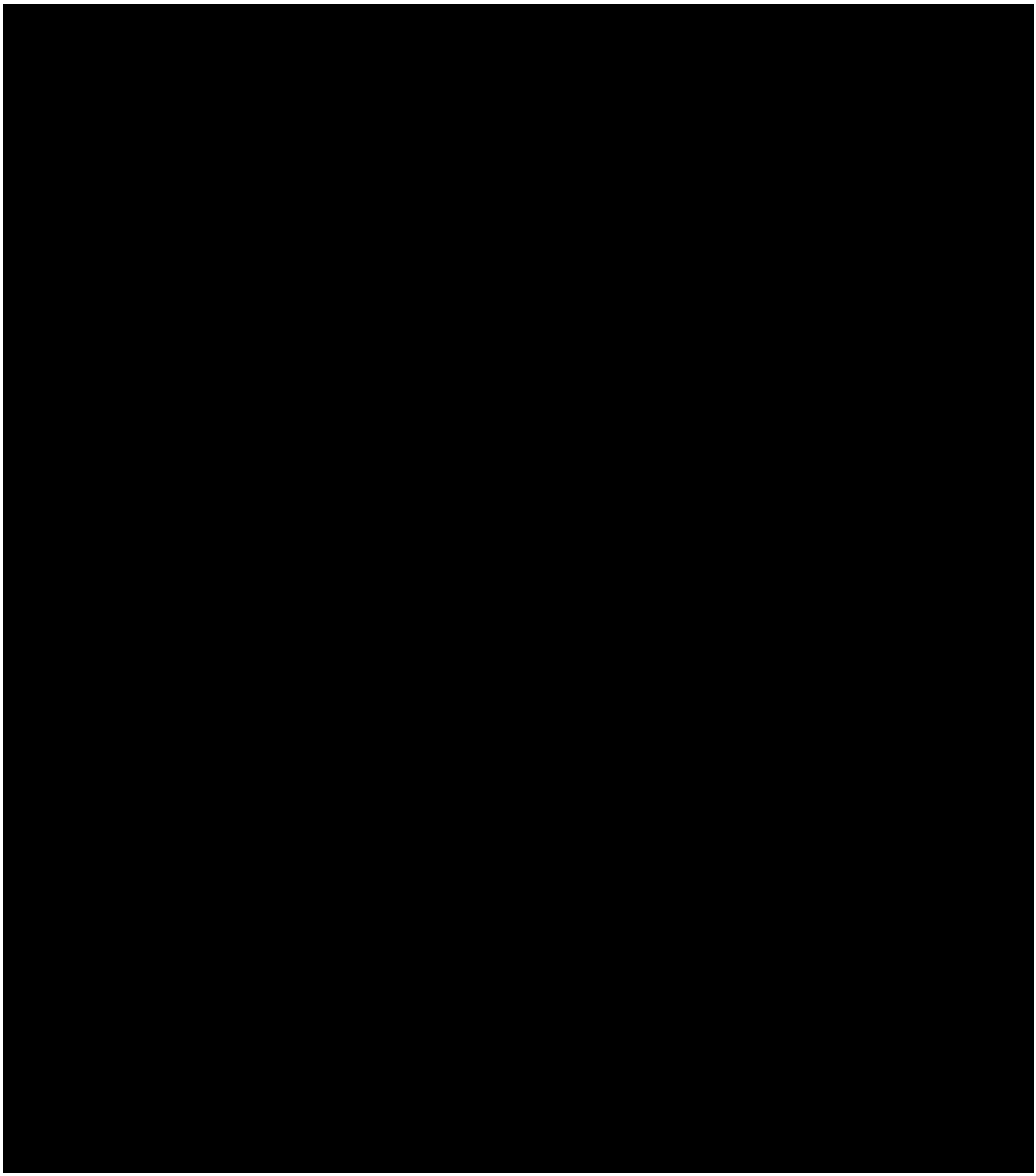


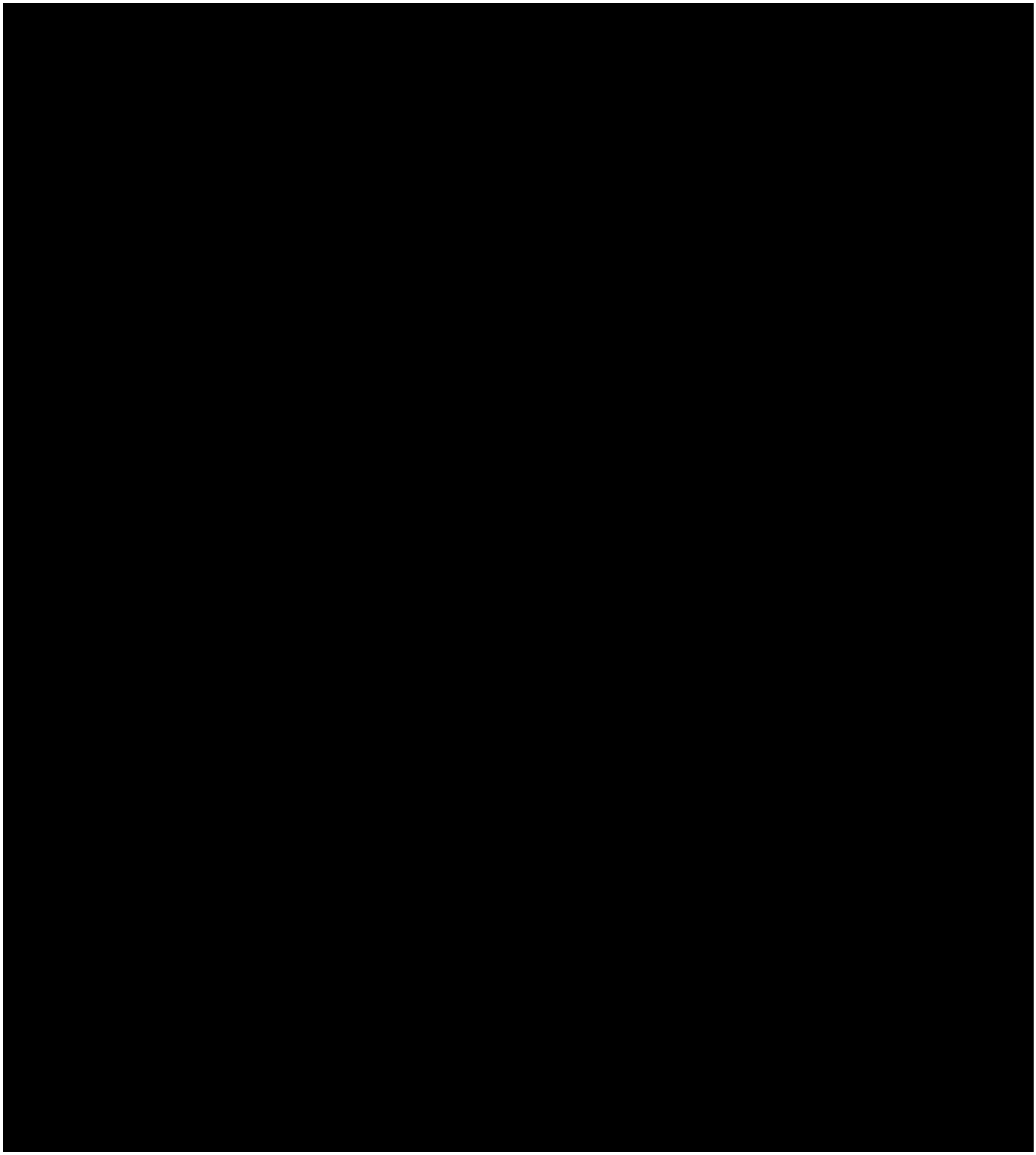


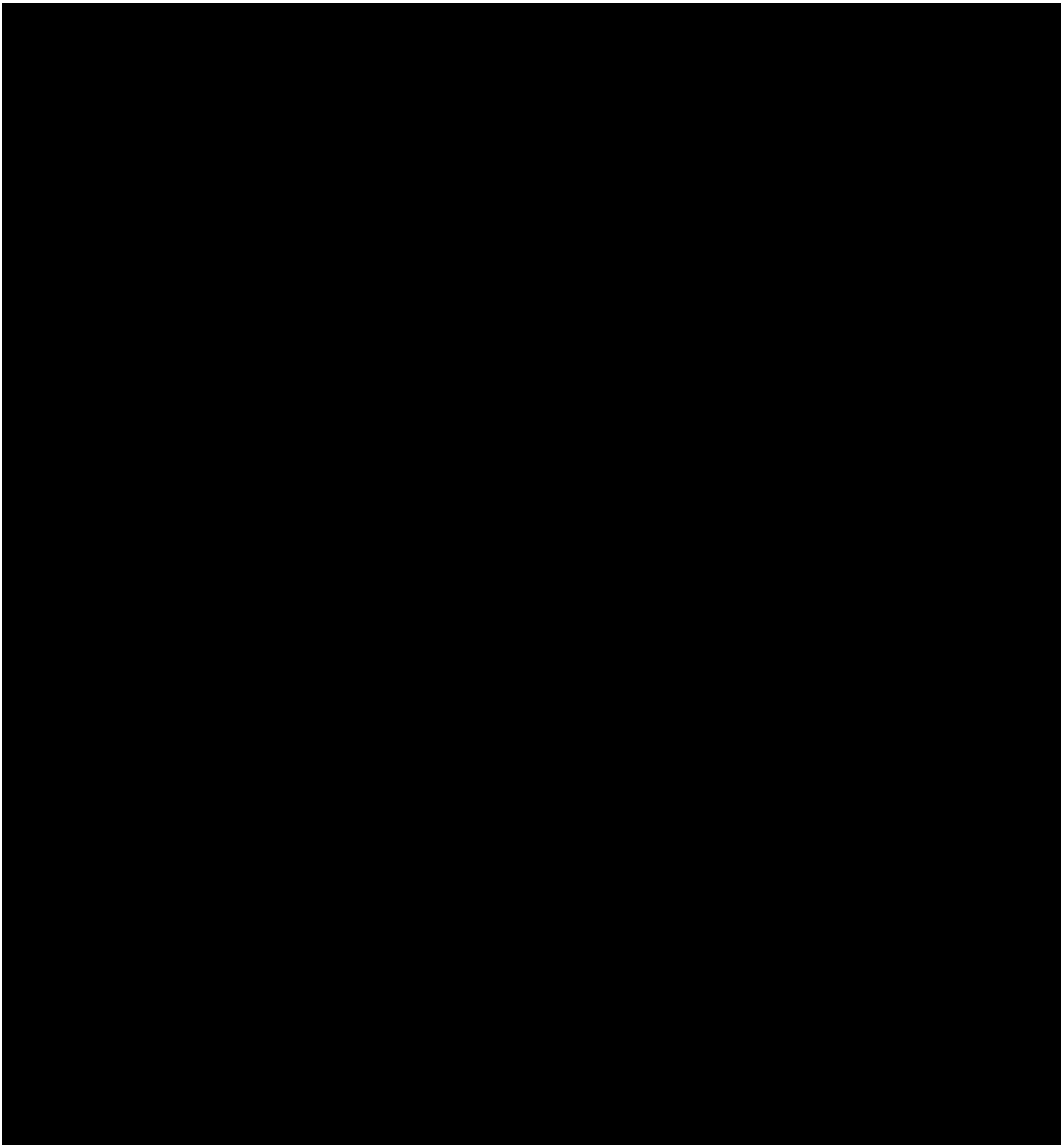


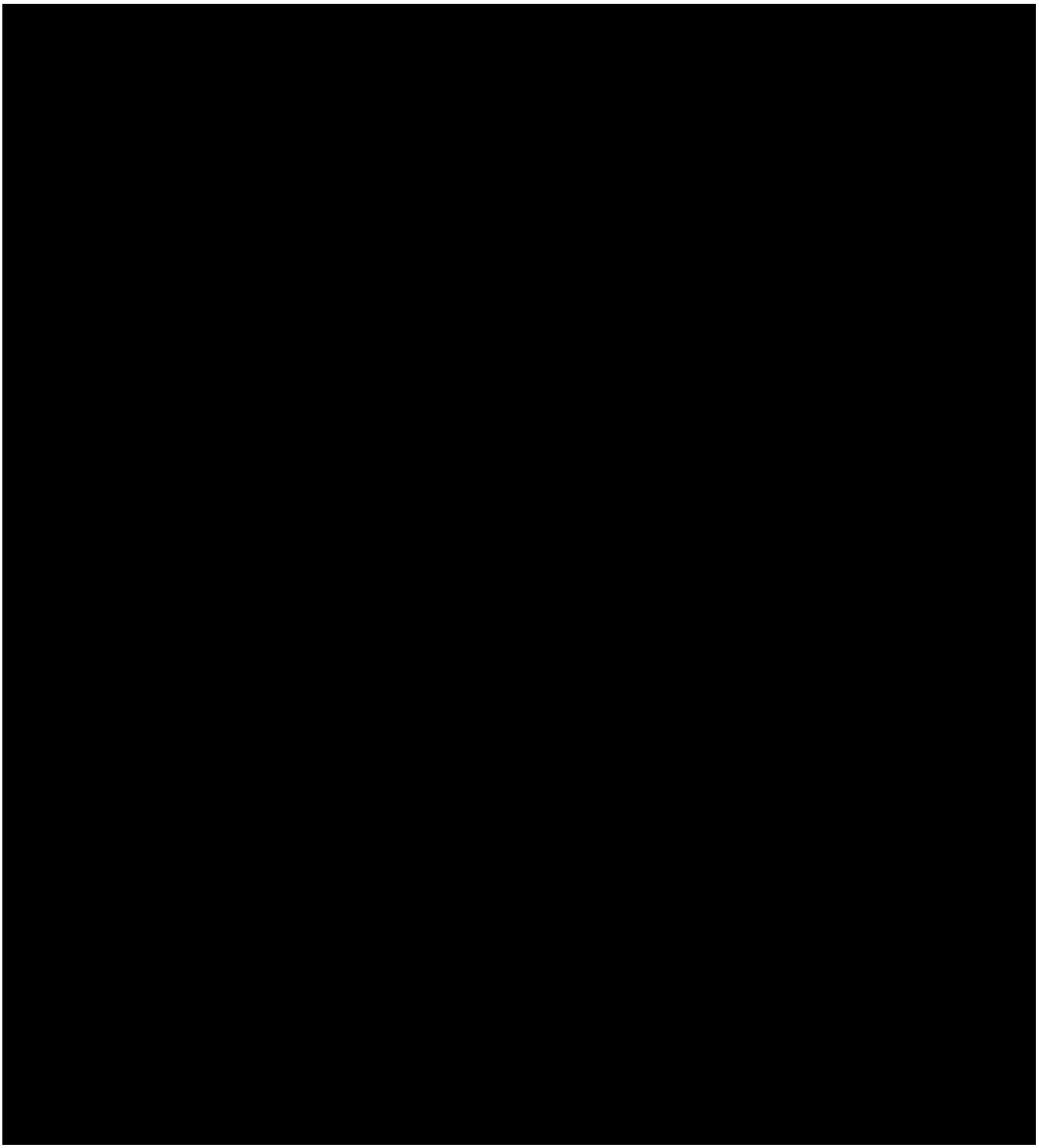


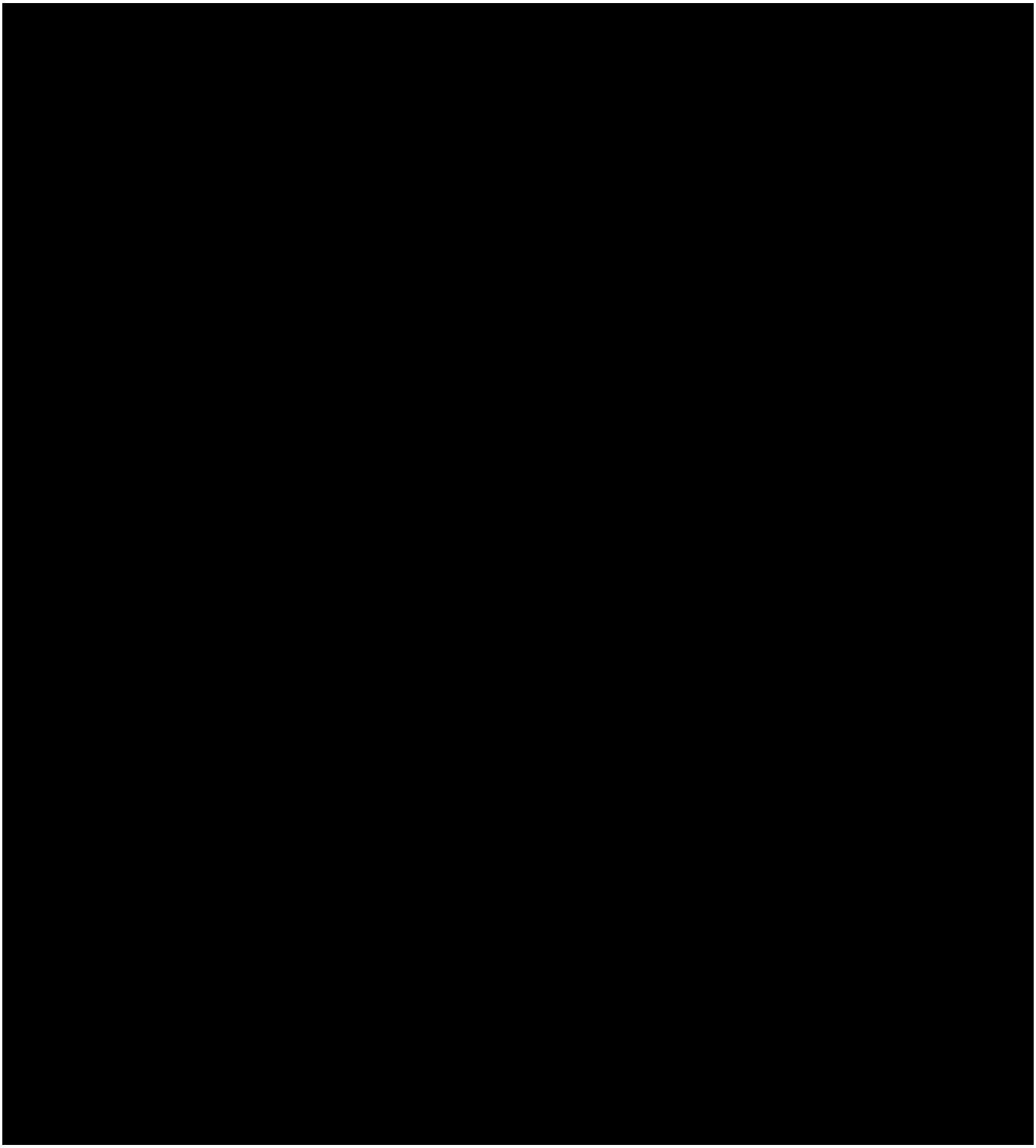


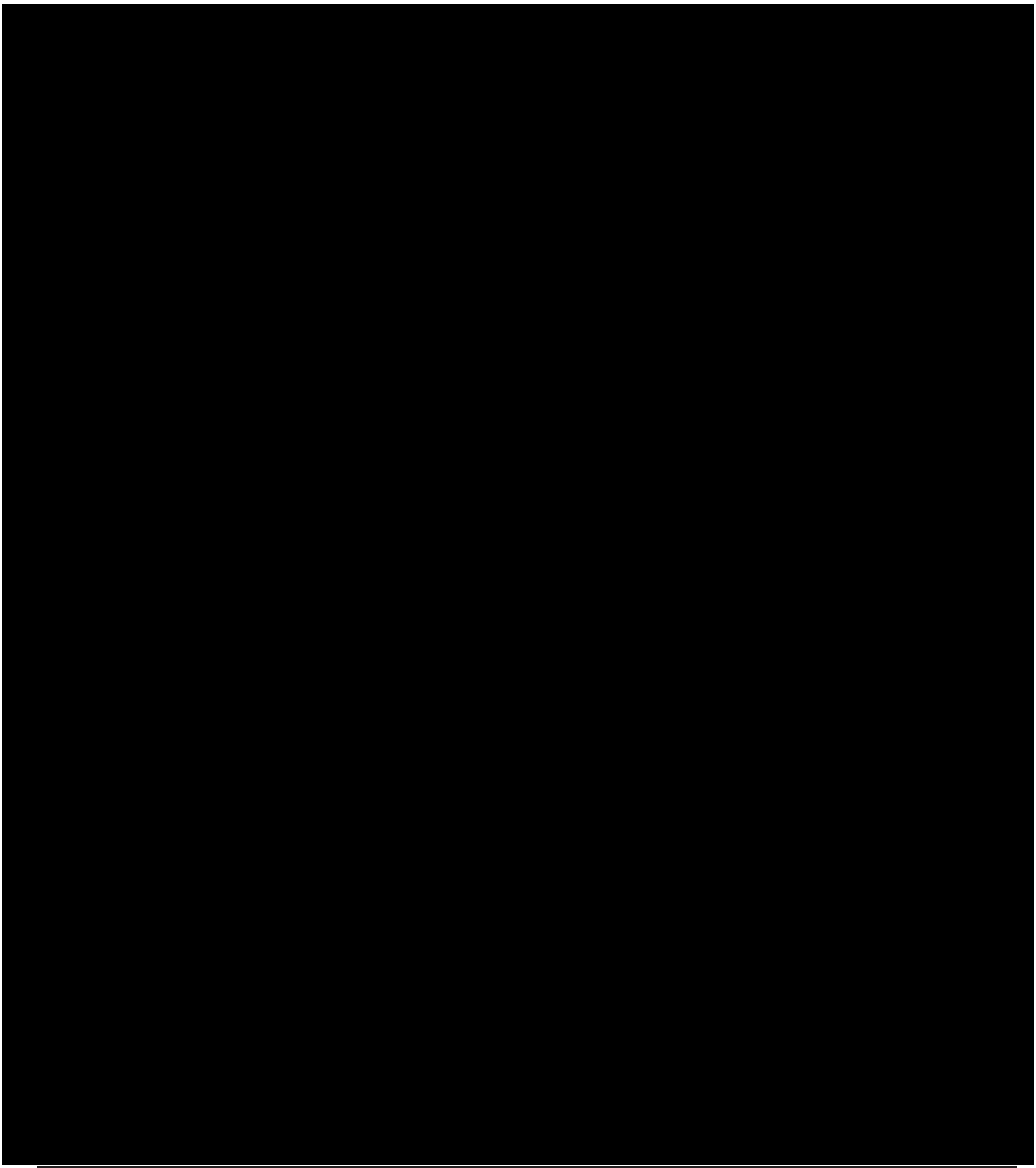


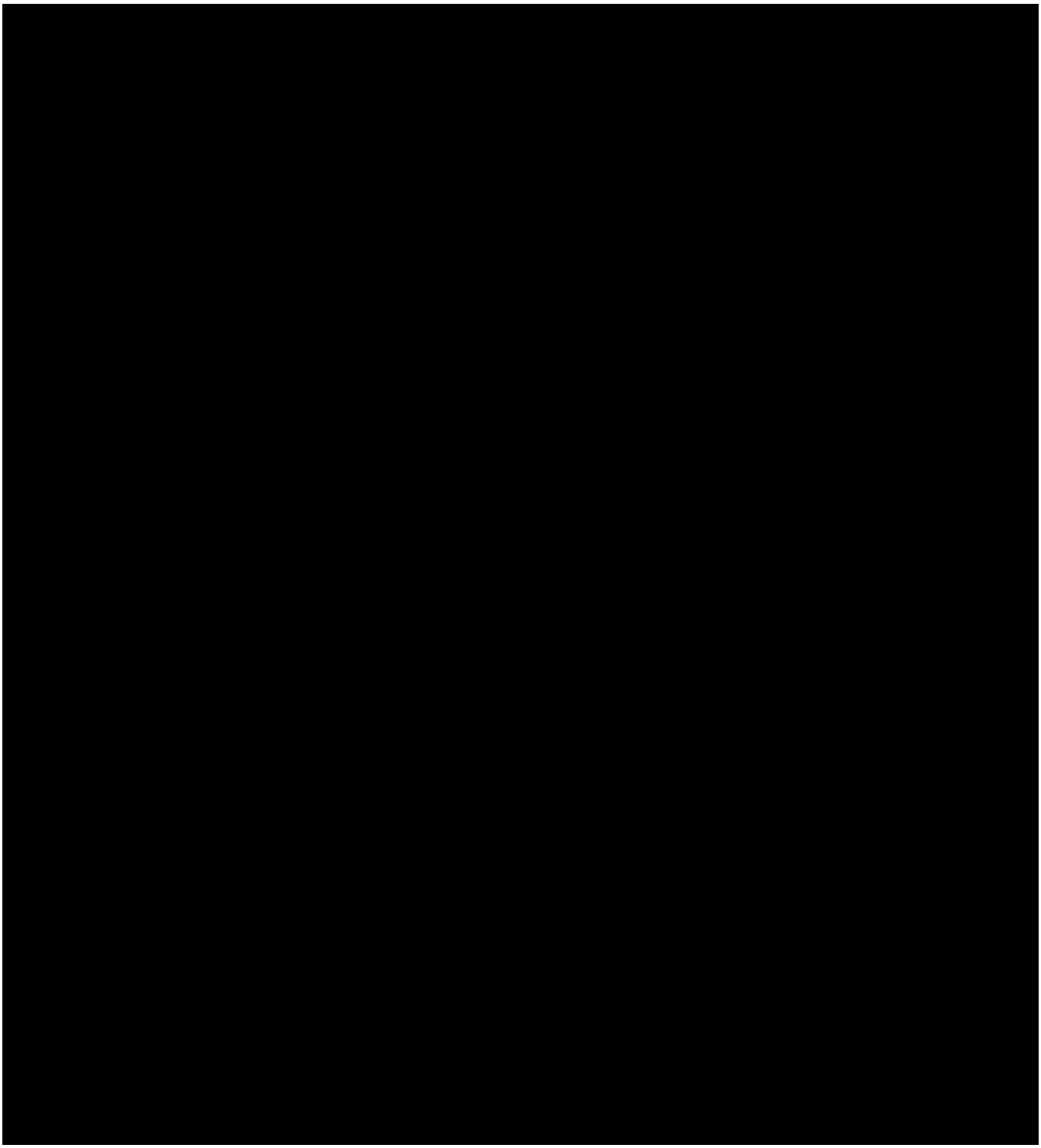


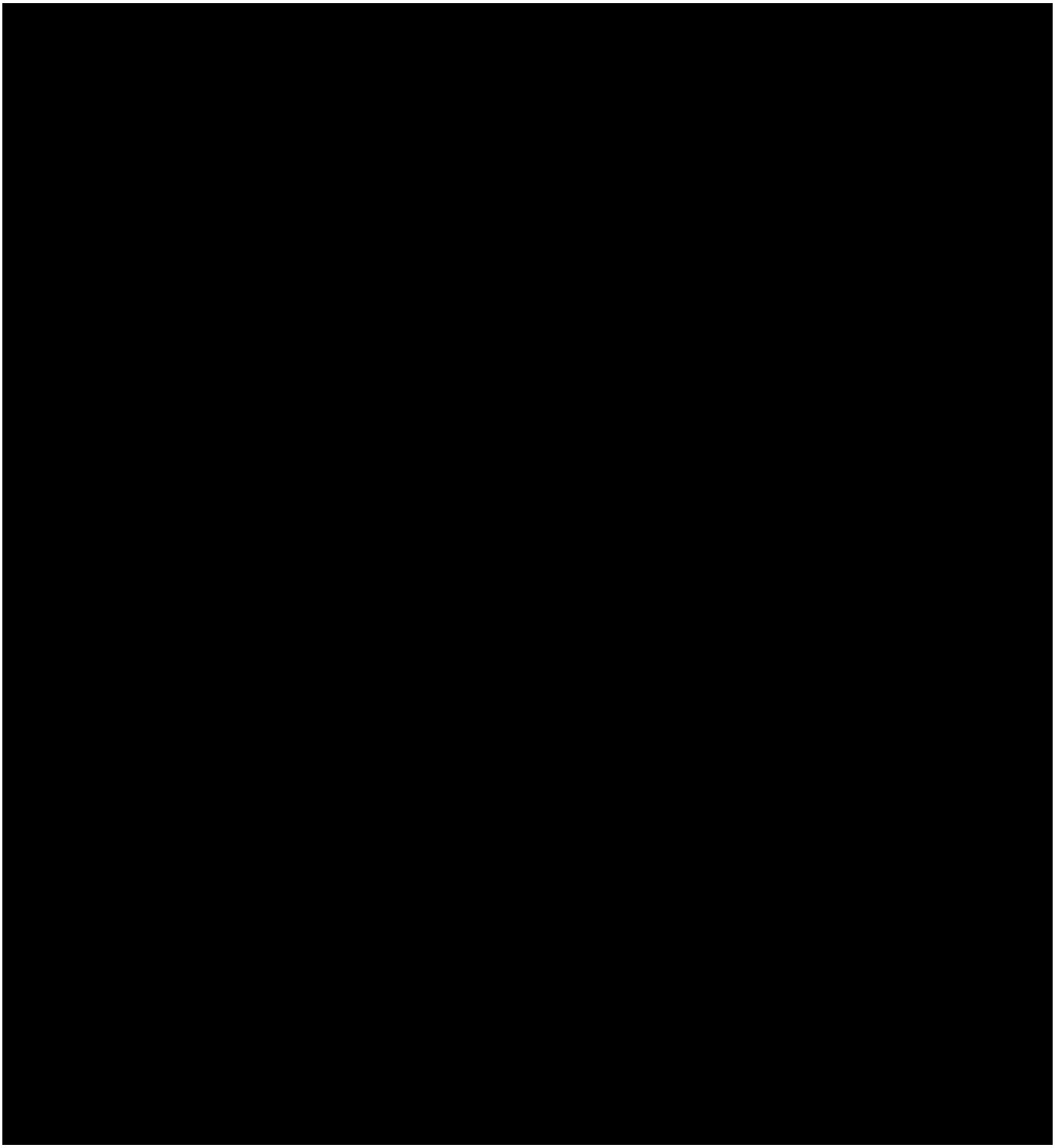


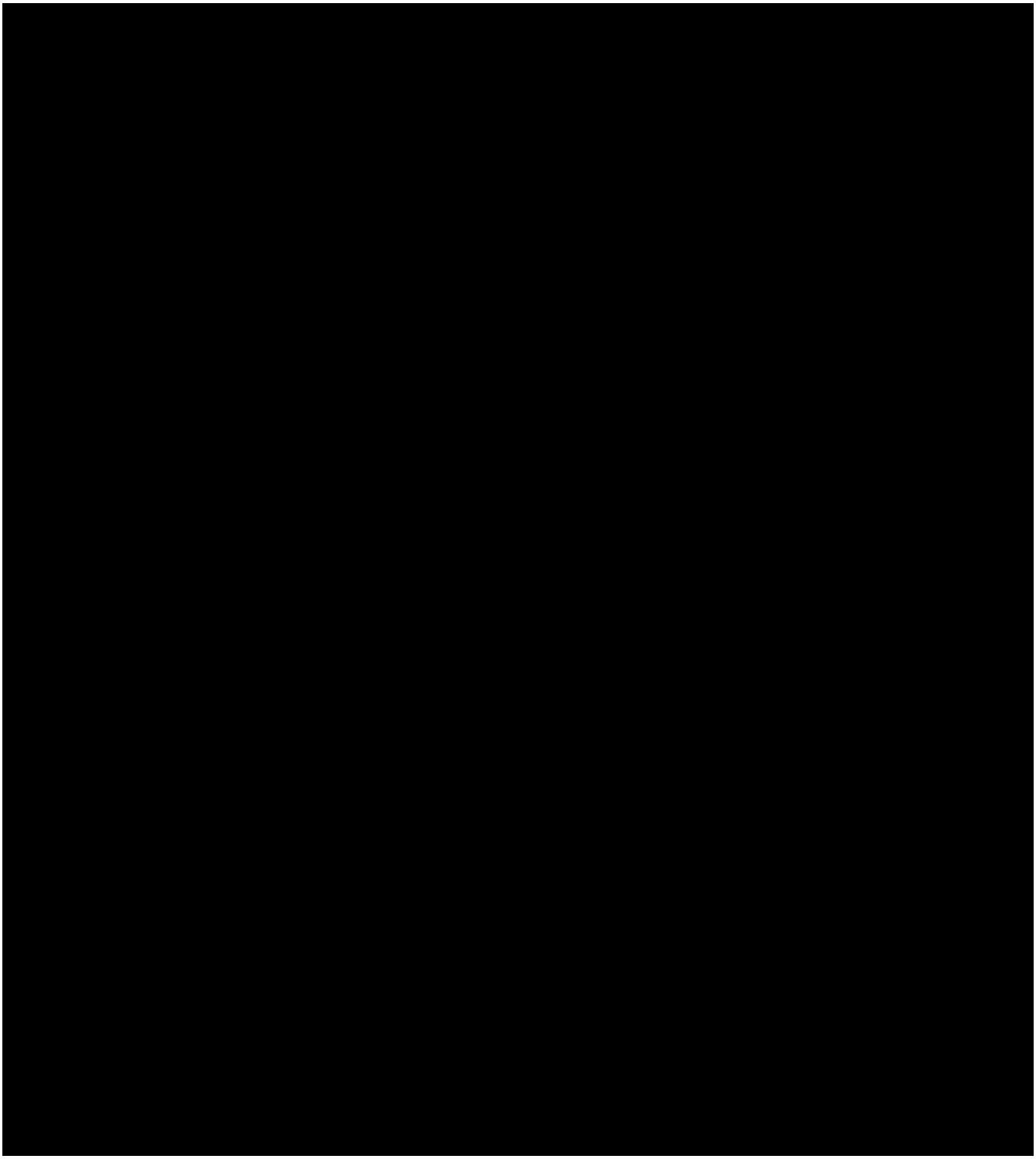


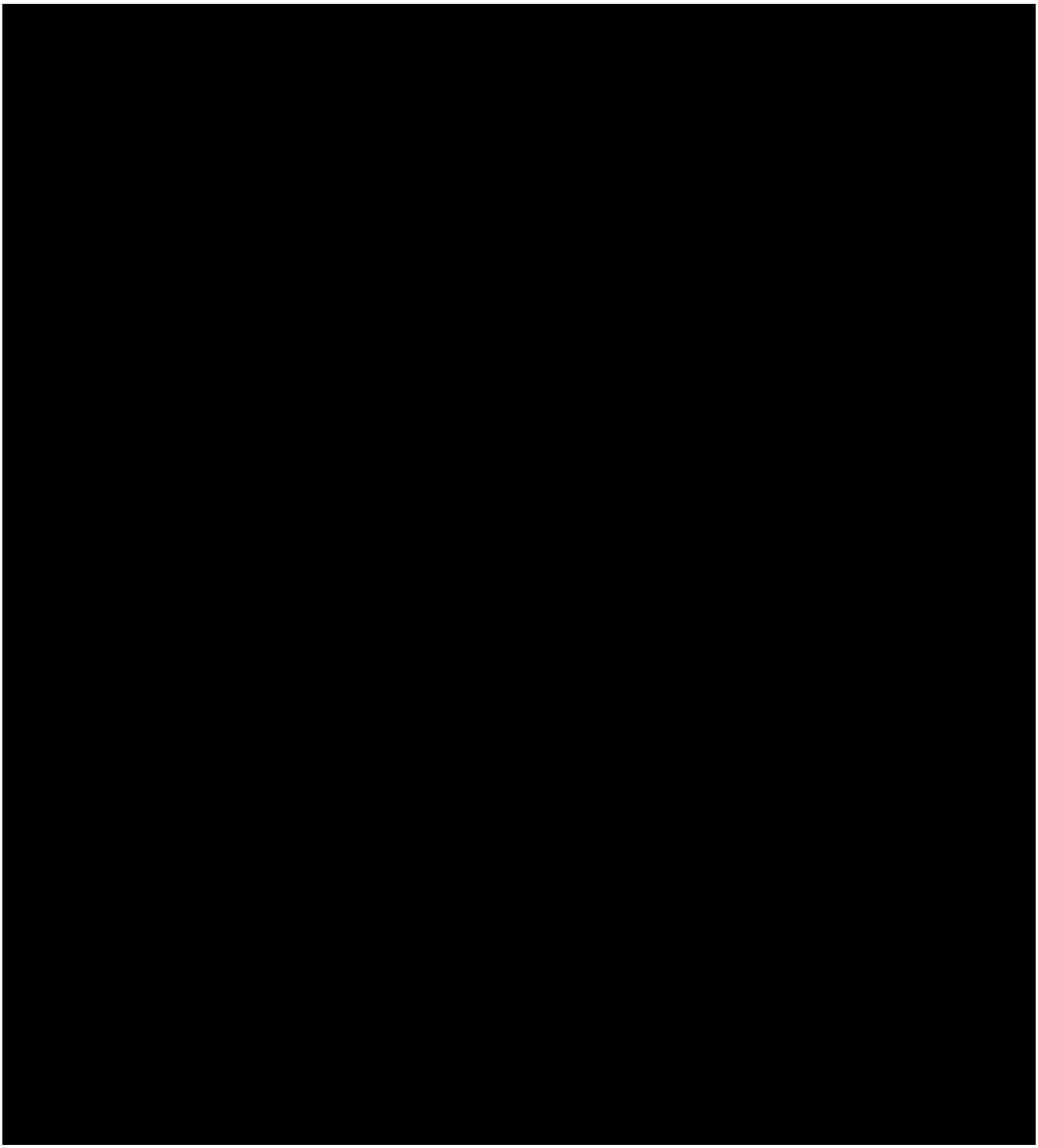


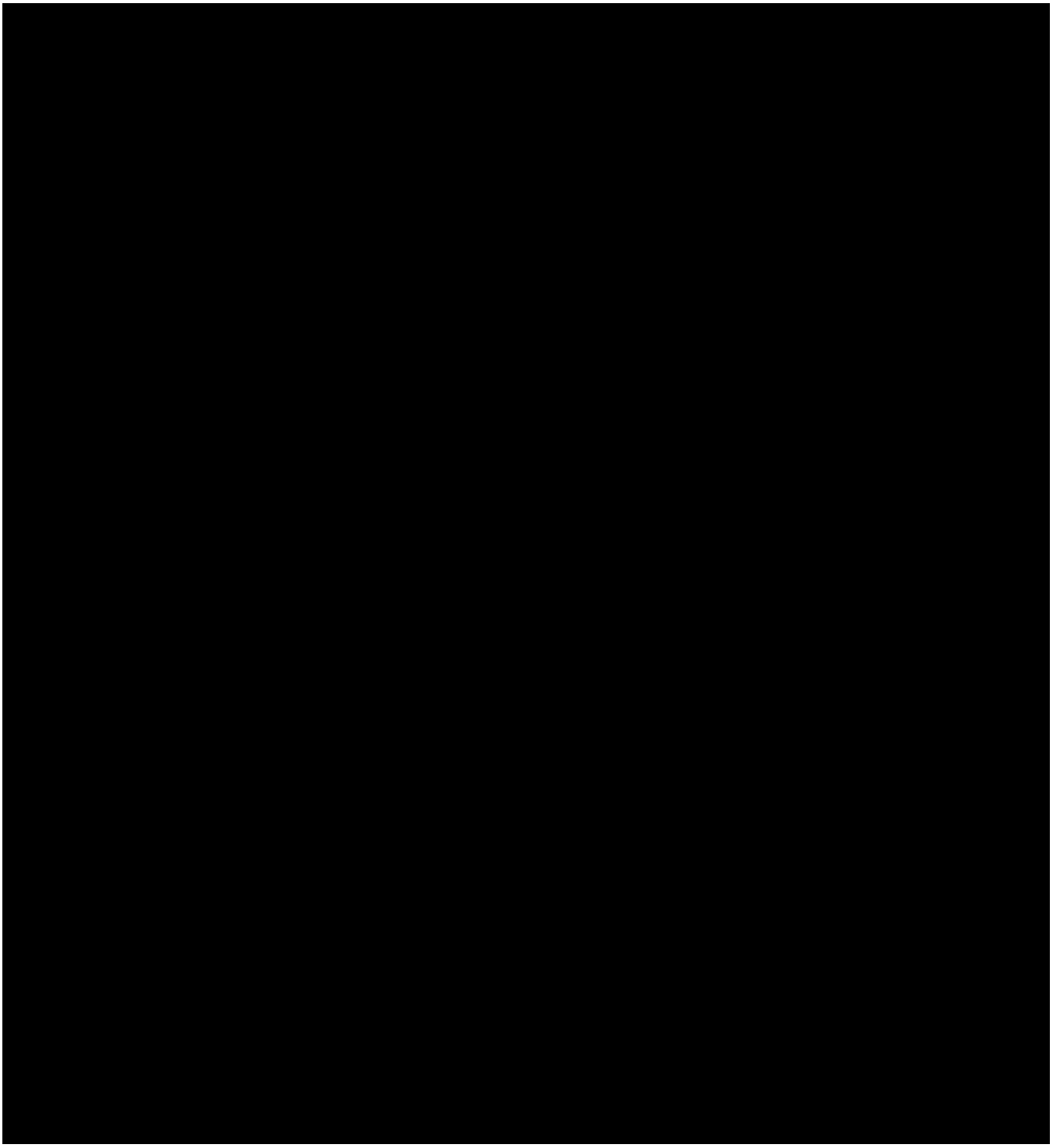












6.12 Safety Analyses

The safety analyses will be presented by the actual treatment received for the Safety Population.

6.12.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the dosing of study drug
- Any pre-existing AE that has worsened in severity on or after the dosing of study drug

A treatment-related AE is defined as an AE as being possibly related, probably related or related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

All AEs will be coded using Medical Dictionary of Regulated Activities (MedDRA) v22. Summaries over system organ class (SOC) and preferred term (PT) by treatment groups, and listings of all TEAEs, SAEs, AEs leading to death, and AEs leading to study discontinuation will be presented. The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs, treatment-related TEAEs, SAEs, Treatment-related SAEs, [redacted] TEAEs leading to study discontinuation, and TEAEs leading to death
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- Treatment-related Serious TEAE by system organ class and preferred term, incidence and

[redacted]

- Treatment-related TEAE by system organ class, preferred term and maximum severity,

[redacted]

- TEAEs leading to study discontinuation by system organ class and preferred term, incidence
- Listing of Serious AEs (presented in the Table section of the appendices)
- Listing of AEs leading to study discontinuation (presented in the Table section of the appendices)
- Listing of AEs leading to Deaths (presented in the Table section of the appendices)

[redacted]

[redacted]

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

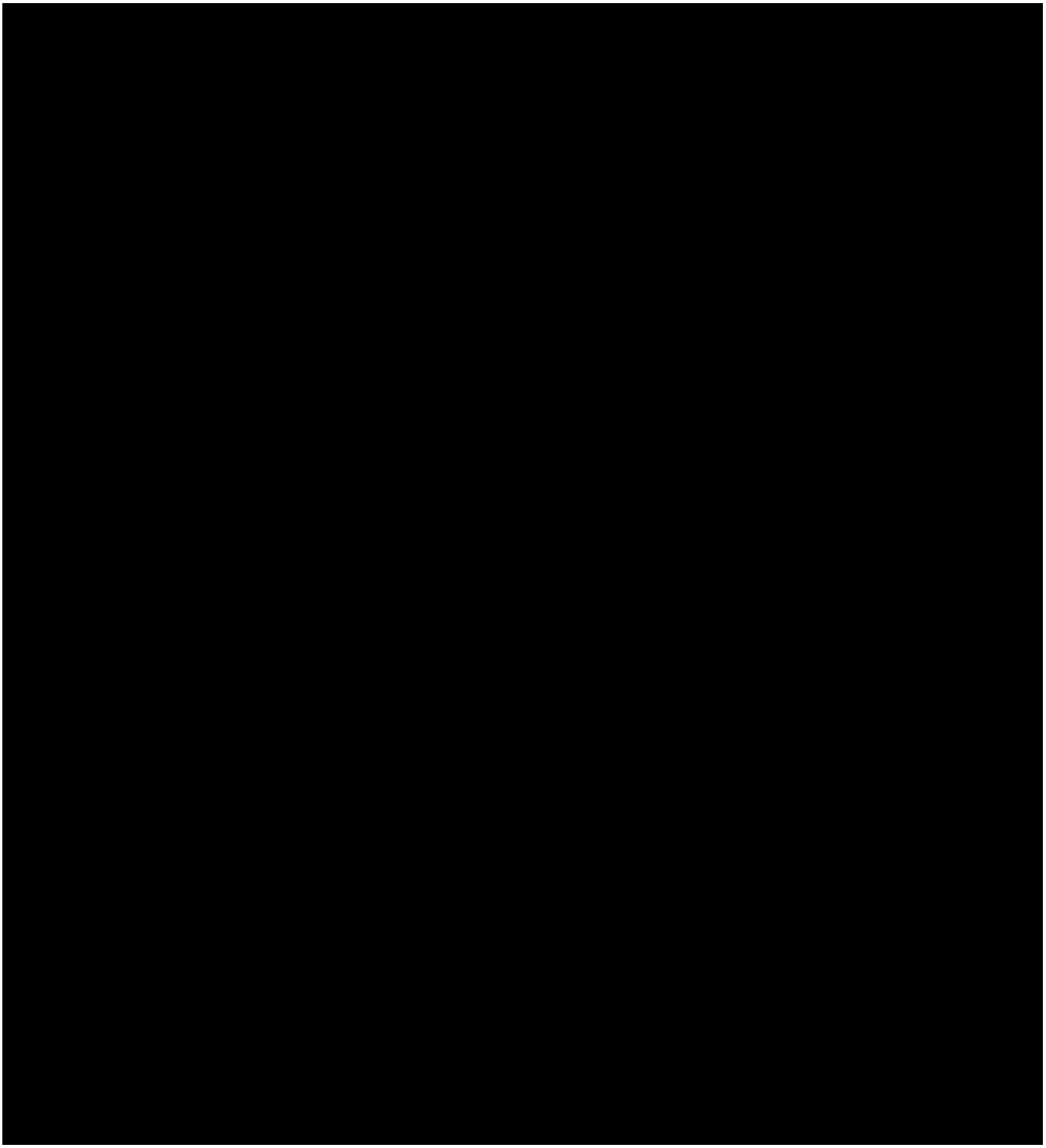
All AEs will be listed. [redacted]

6.12.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, urinalysis, and serum chemistry parameters. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each post-baseline visit will be presented. For categorical laboratory parameters, subject counts within each category will be summarized. Shift tables from baseline to each post-baseline visit will also be presented, as applicable.

A listing of out of normal range laboratory values that are marked by investigator as clinically significant throughout the study will be presented. All laboratory assessments, including urine and serum pregnancy tests, will also be listed.

[redacted]



6.12.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be tabulated at each post-baseline visits:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breaths/min)
- Body temperature (degrees Celsius or degrees Fahrenheit)
- Body weight (kg)

All vital signs measurements throughout the study will be listed.

6.12.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each post-baseline visits:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation (Normal, Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) from baseline to each post-baseline visit will be presented.

All ECG assessments throughout the study will be listed.

6.12.5 Foot and Ankle Examination

Examination for the foot will be conducted, including ankle, toe, and subtalar range of motion, foot motor strength, location of pain, and examination of the heel fat pad and Tinel's sign. The presence of toe deformities, bunions, ulcers, and/or sores will also be recorded. The feet will also be examined for signs of swelling, pitting edema, infection, or vascular abnormalities.

Descriptive statistics of the observed values will be presented for each quantitative parameter by treatment group and study visit. Subject counts within each category will be summarized by treatment group and study visit for the qualitative parameters.

All foot and ankle examination data throughout the study will be listed.

6.12.6 Physical Examination

The body systems within physical examination data at Screening will be summarized by treatment group and finding (Normal, Abnormal NCS, Abnormal CS).

All physical examination data throughout the study, including details of clinically significant findings for each body system, will be listed.

6.12.7 Injection Site Evaluation

The injection site evaluation is a global evaluation of the injection site which will be assed prior to dosing, after dosing, and on every follow up visit. Findings such as presence of erythema, edema, burning or stinging (sensation as described by the subject), itching (sensation as described by subject), bruising, and drainage will be recorded. Number of subjects that have findings related to injection site evaluation at each assessment visit will be tabulated by treatment group.

All injection site evaluation findings throughout the study will be listed.

6.12.8 C-SSRS

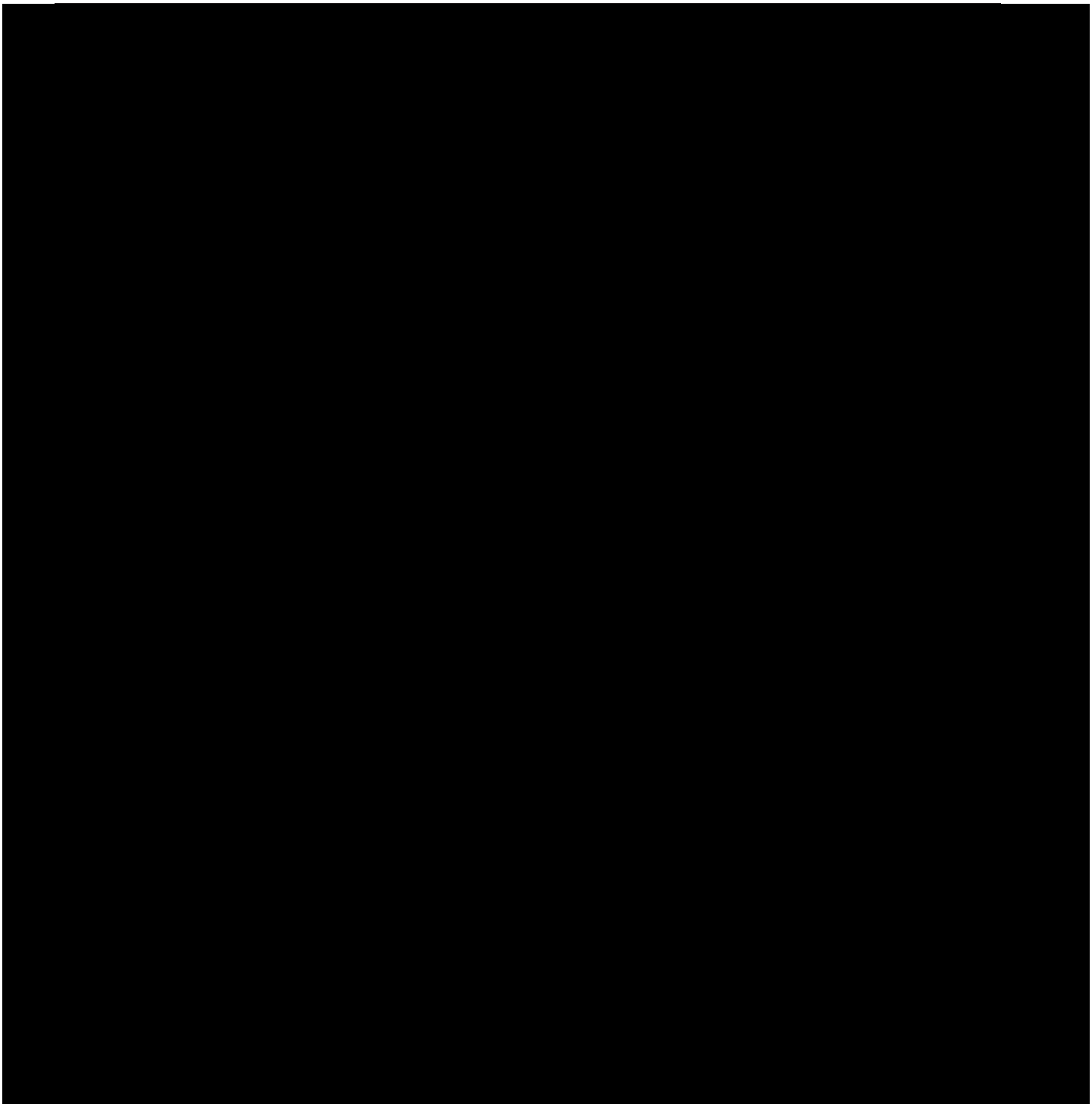
C-SSRS will be used to assess suicidal ideations and behaviors. Number of subjects that responded ‘yes’ to any of the C-SSRS Suicidal Ideation Items, as described in Section 6.2.8, will be presented by treatment group, and will be tabulated separately for screening and post-screening assessments. Similarly, number of subjects that responded ‘yes’ to any of the C-SSRS Suicidal Behavioral Items, as described in Section 6.2.8, will be presented by treatment group, and will be tabulated separately at screening and post-screening assessments. For subjects that were randomized under earlier versions of the protocol, that is, prior to addition of the C-SSRS on the study assessments, the screening version of the C-SSRS that were completed at the visit at which they are currently in when they signed the informed consent for the new version of the protocol (v4.0 dated 15-JUL-2019) will be not be tabulated but will be listed. Derived C-SSRS data as described in Section 6.2.8 will be listed for screening and post-screening assessments for all subjects.

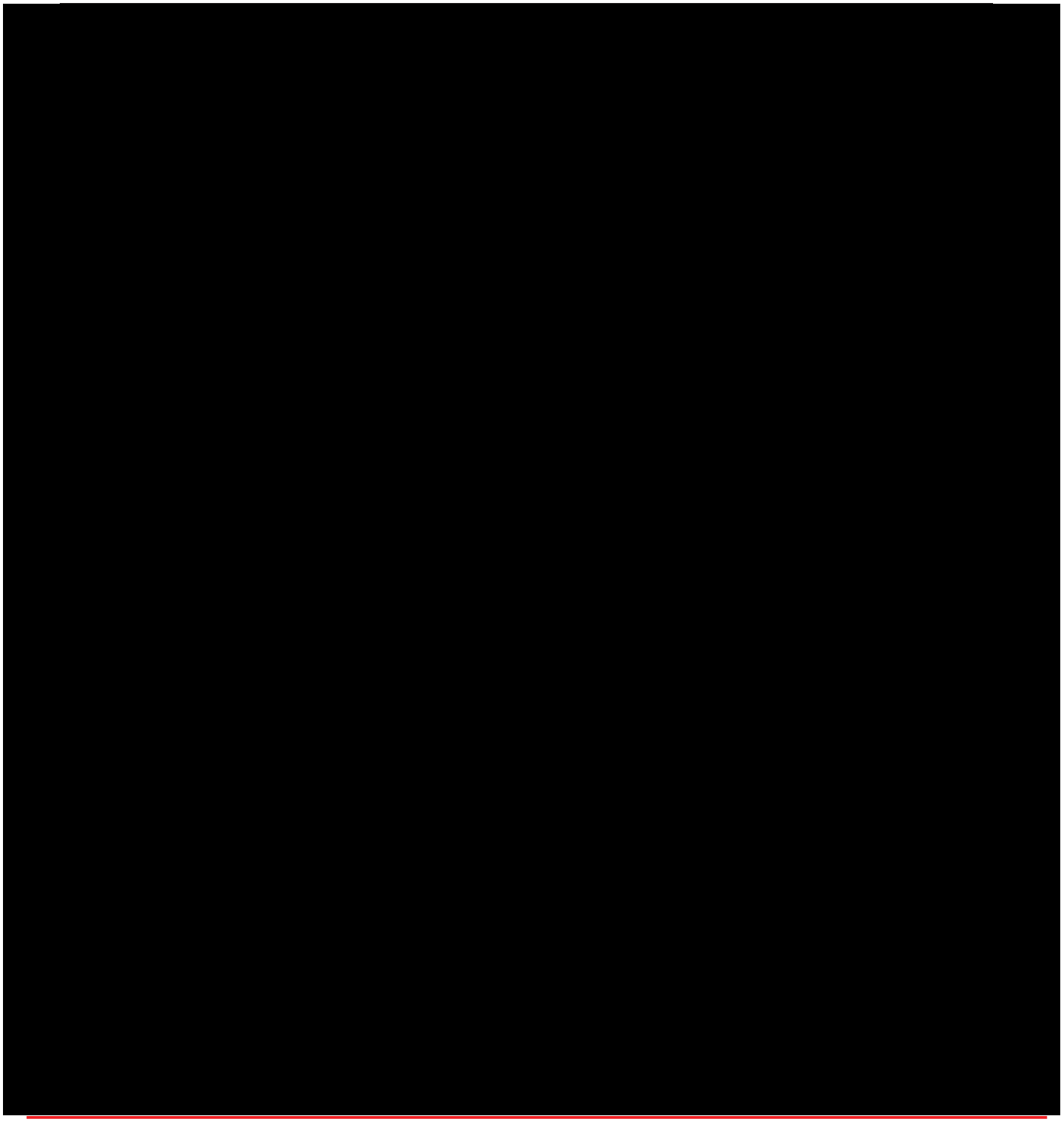
7 INTERIM ANALYSIS

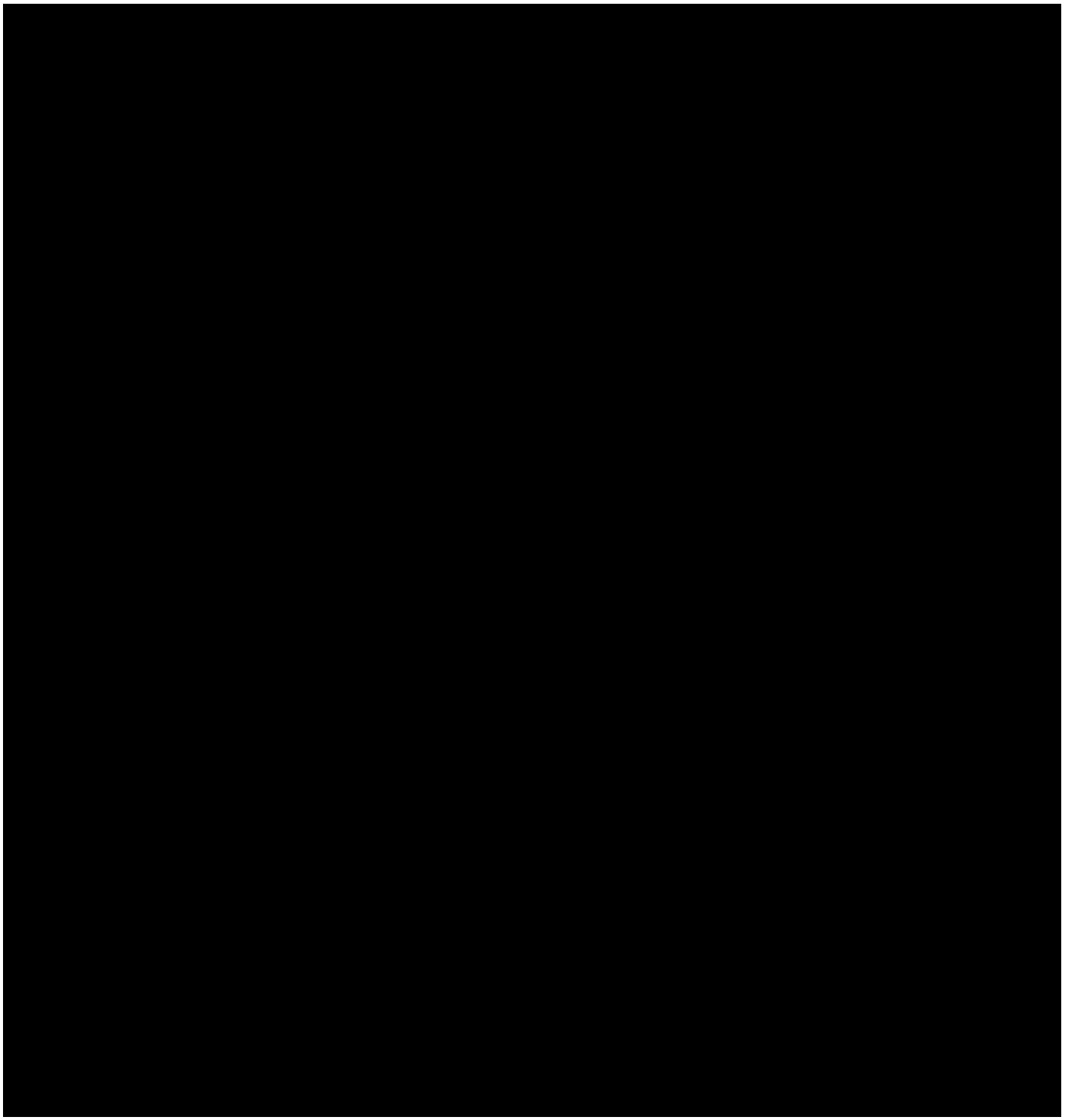
No interim analyses are planned.

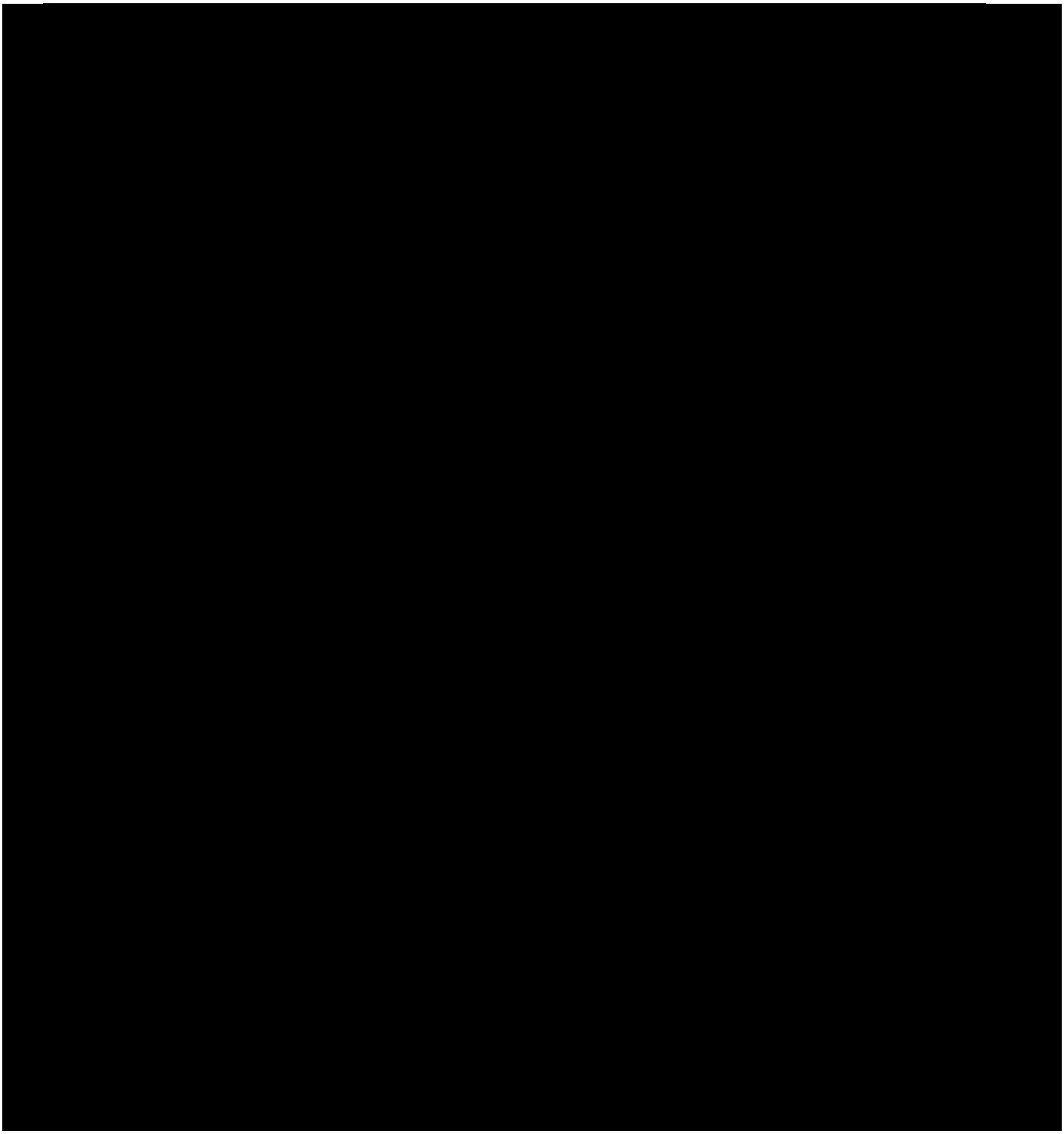
8 DATA SAFETY MONITORING BOARD ANALYSIS

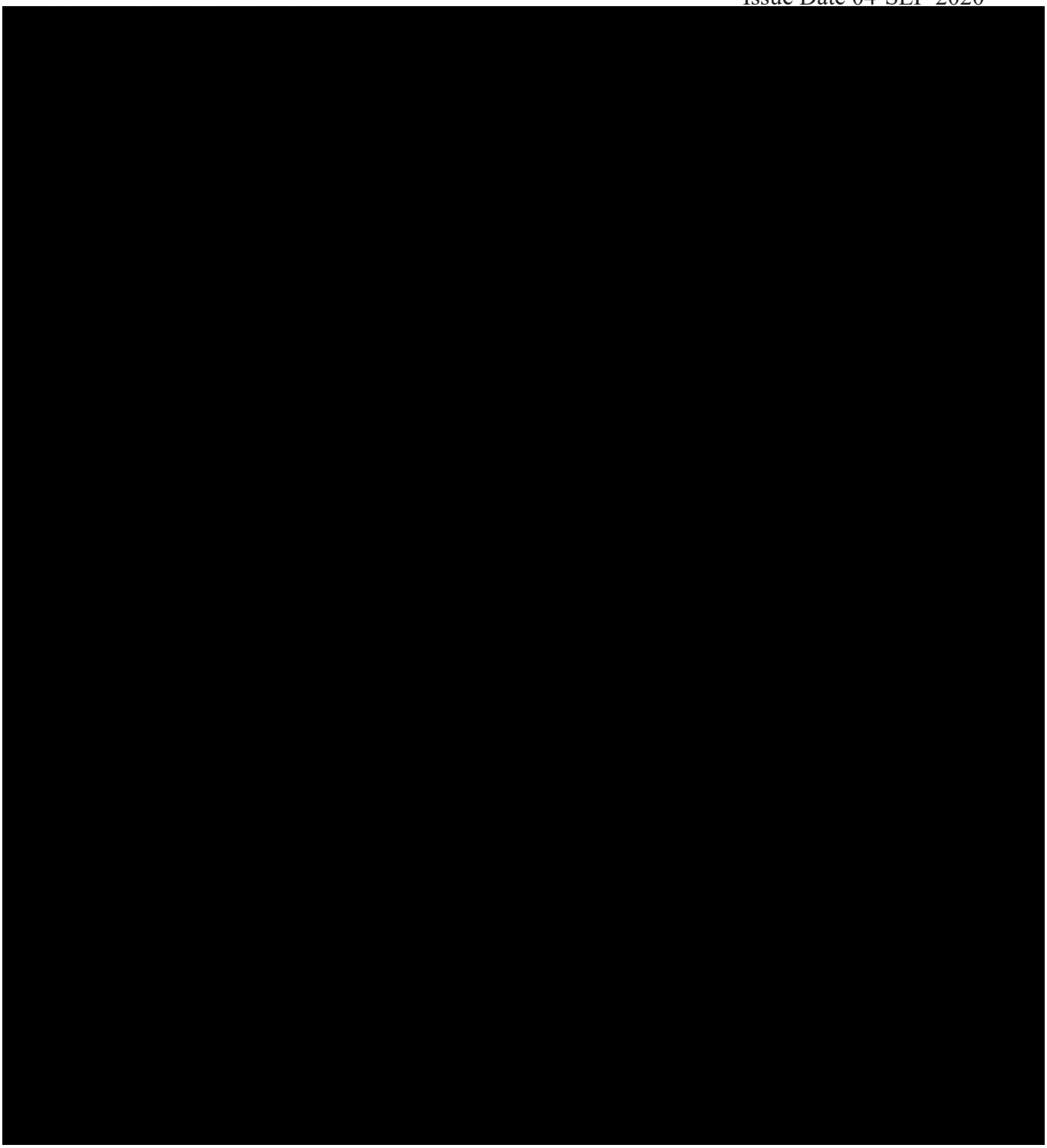
Data safety monitoring board (DSMB) analyses are described in DSMB analysis plan.

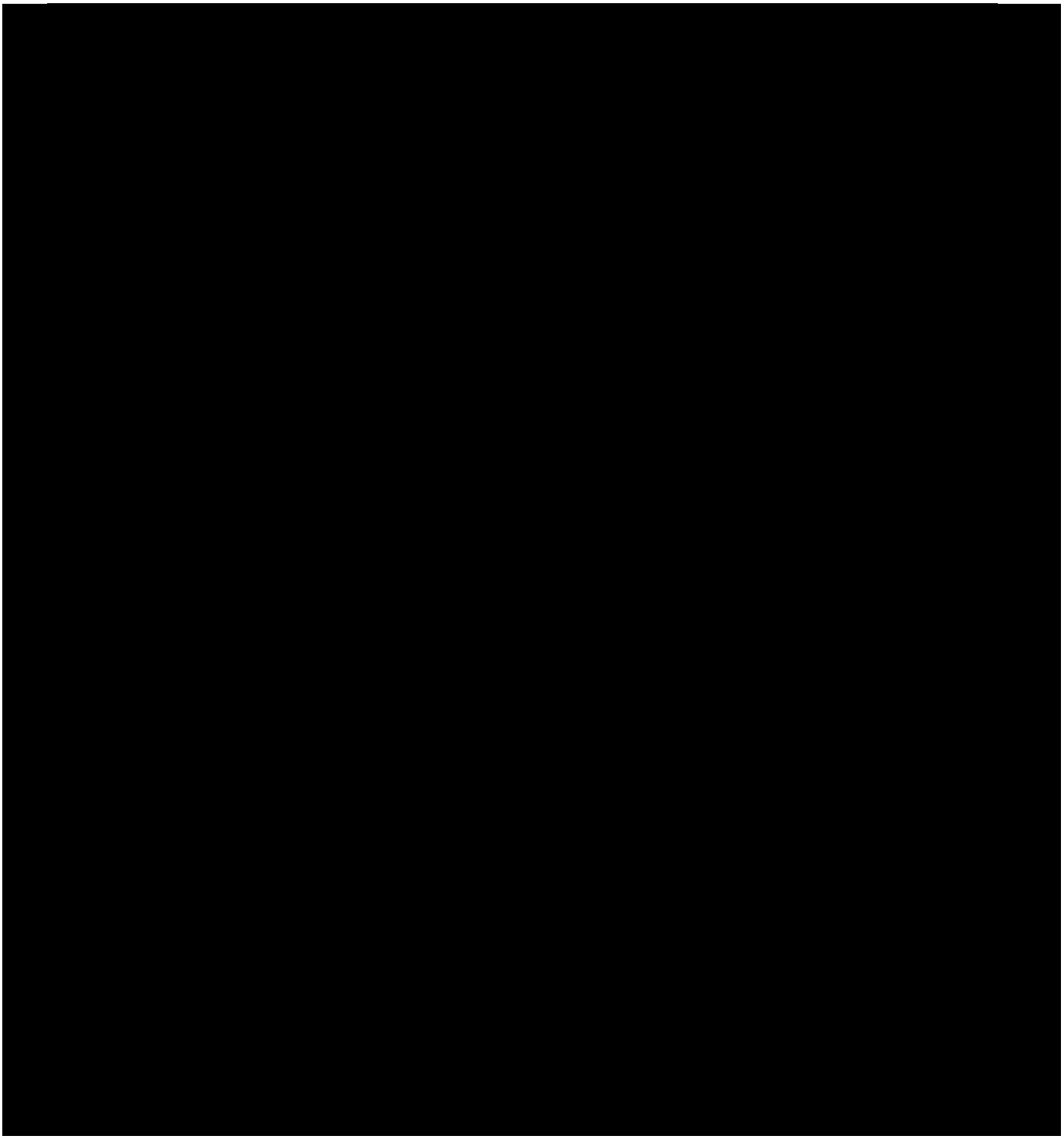


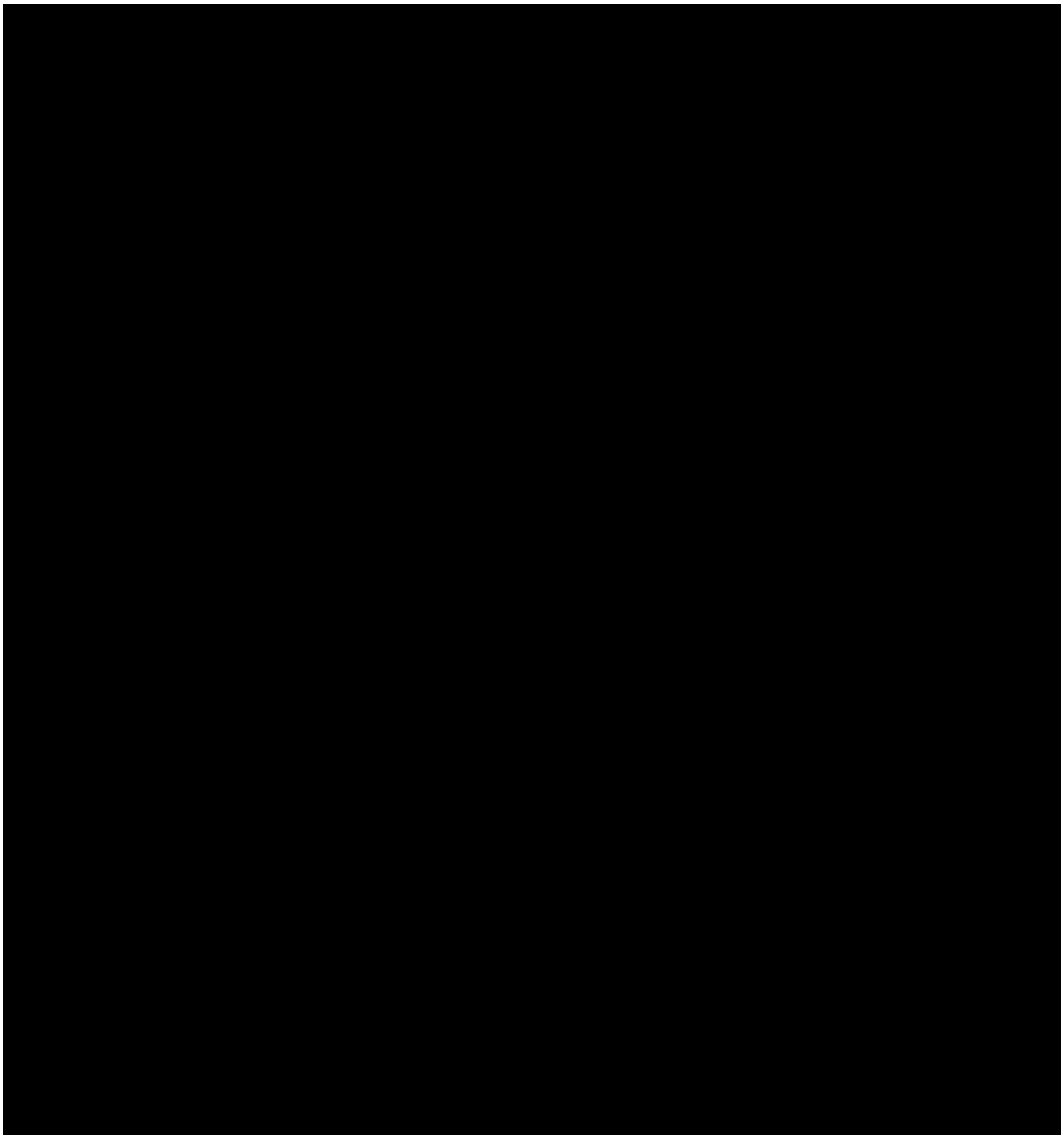


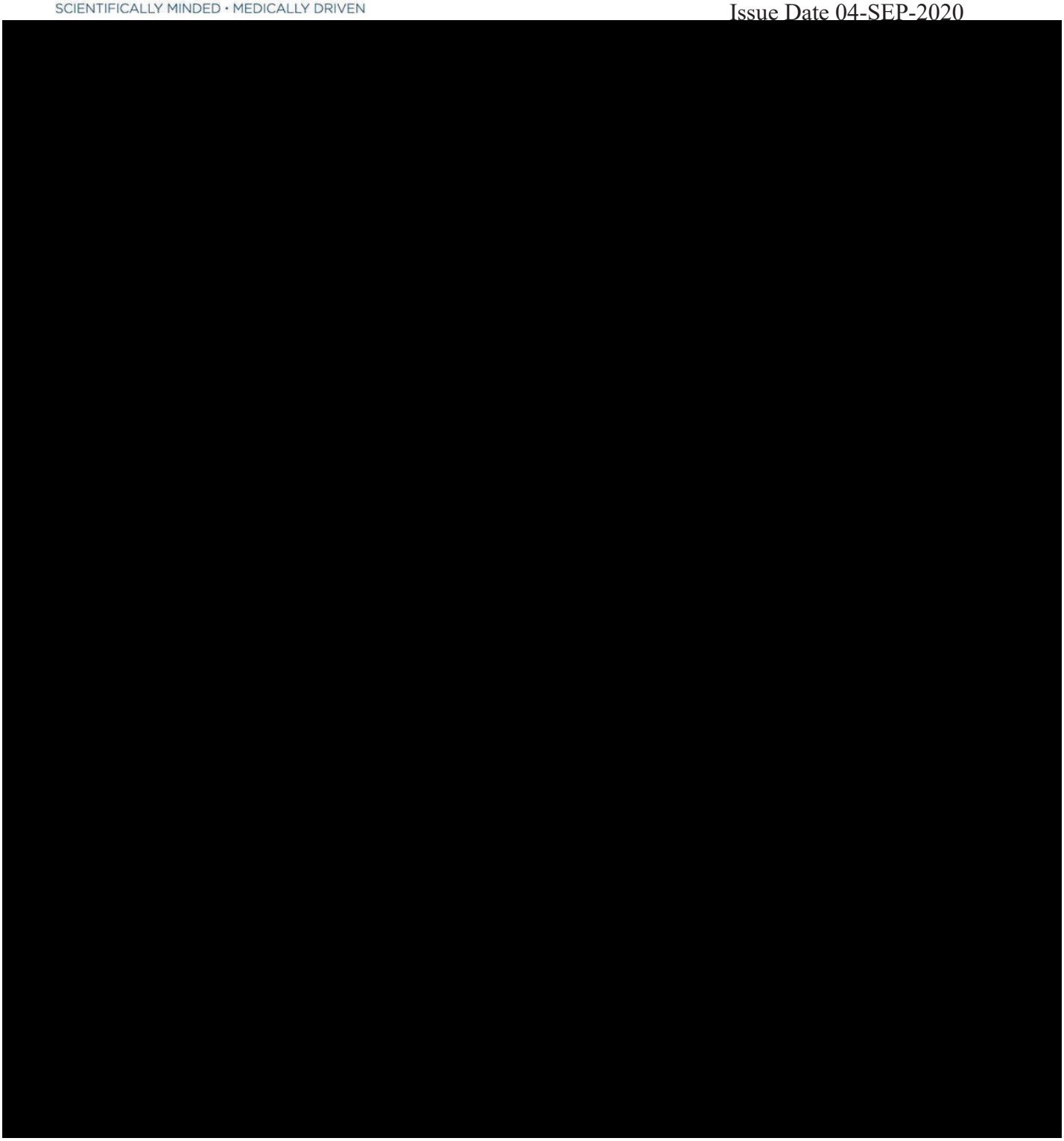


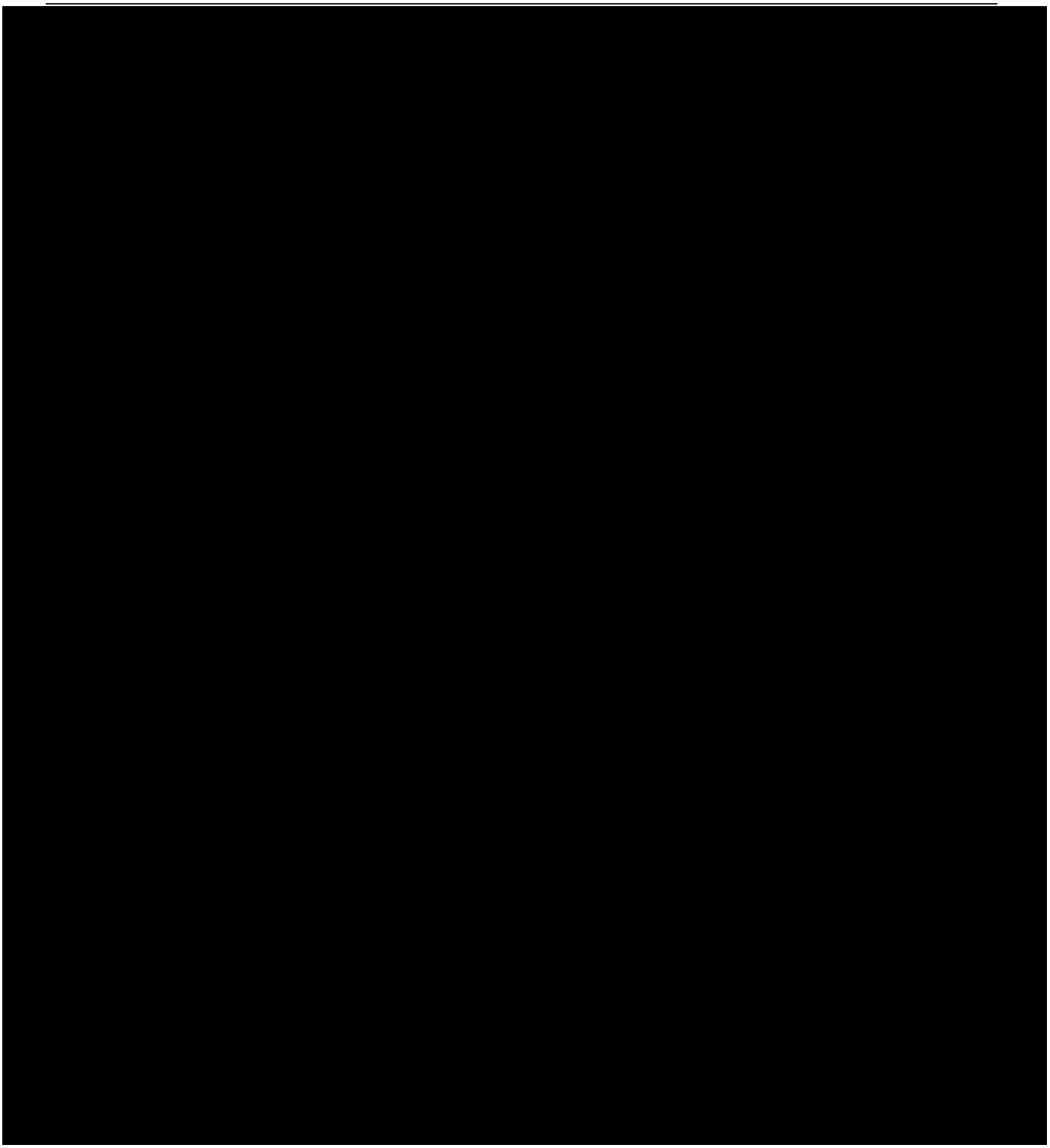


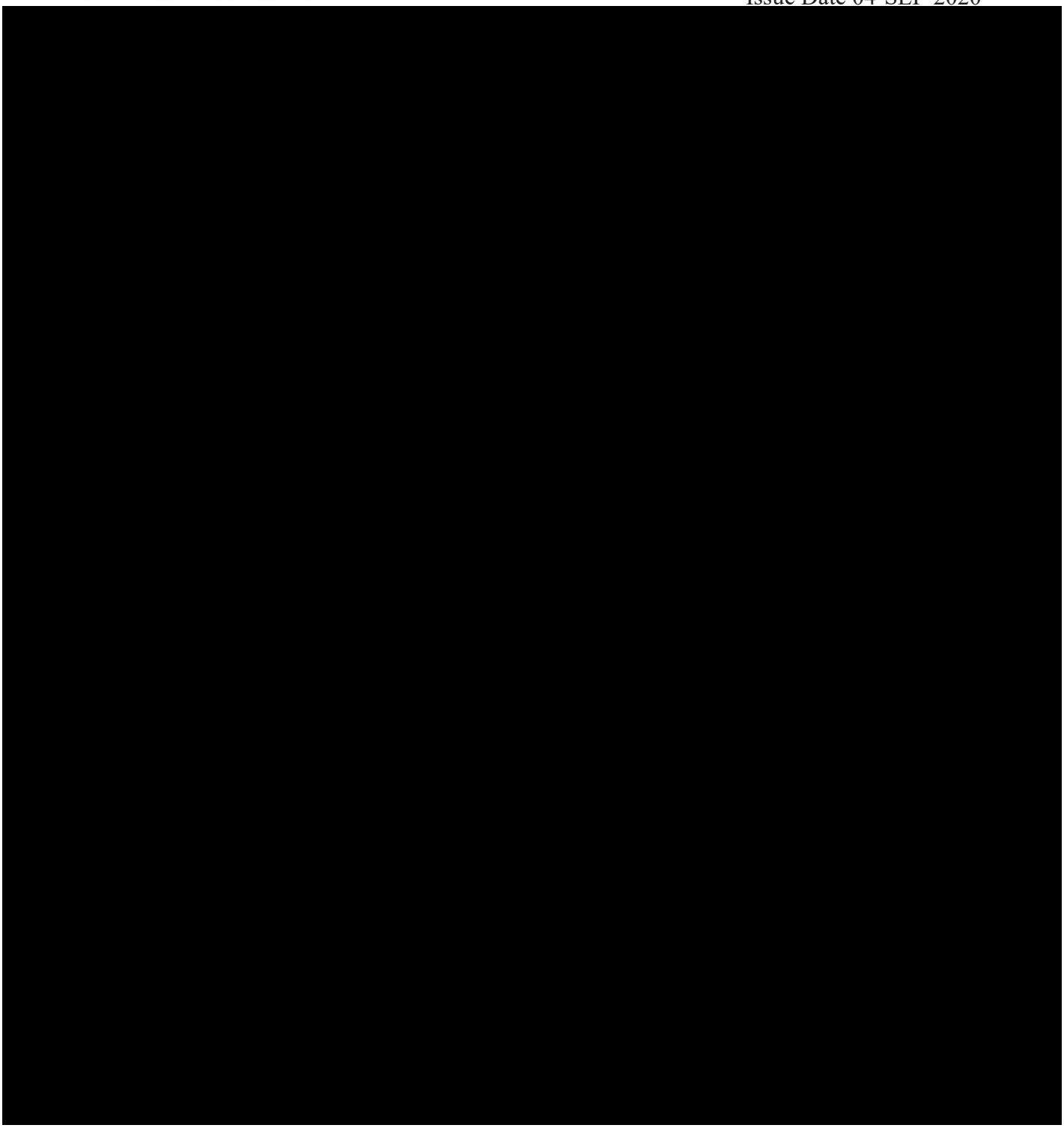


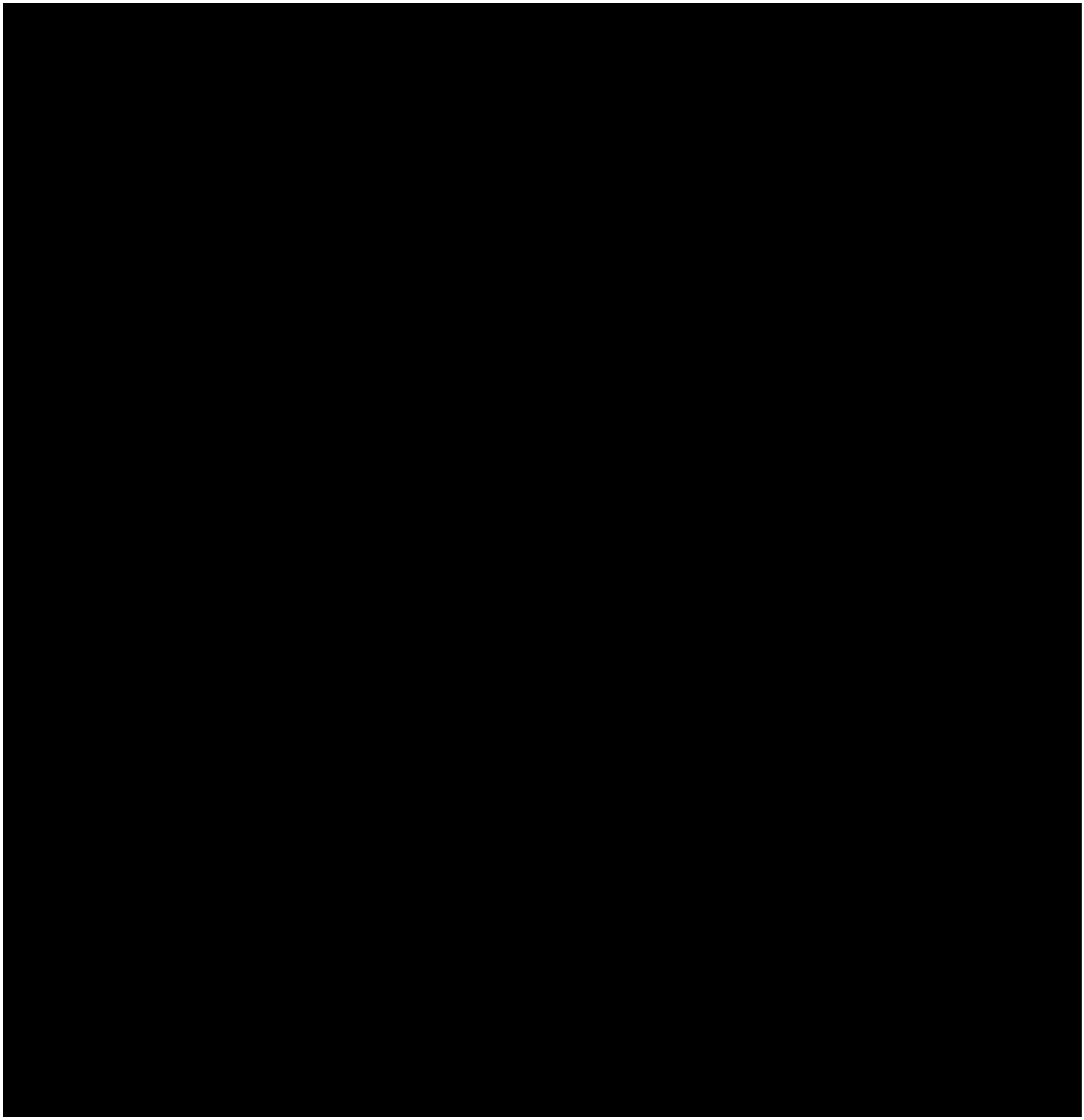


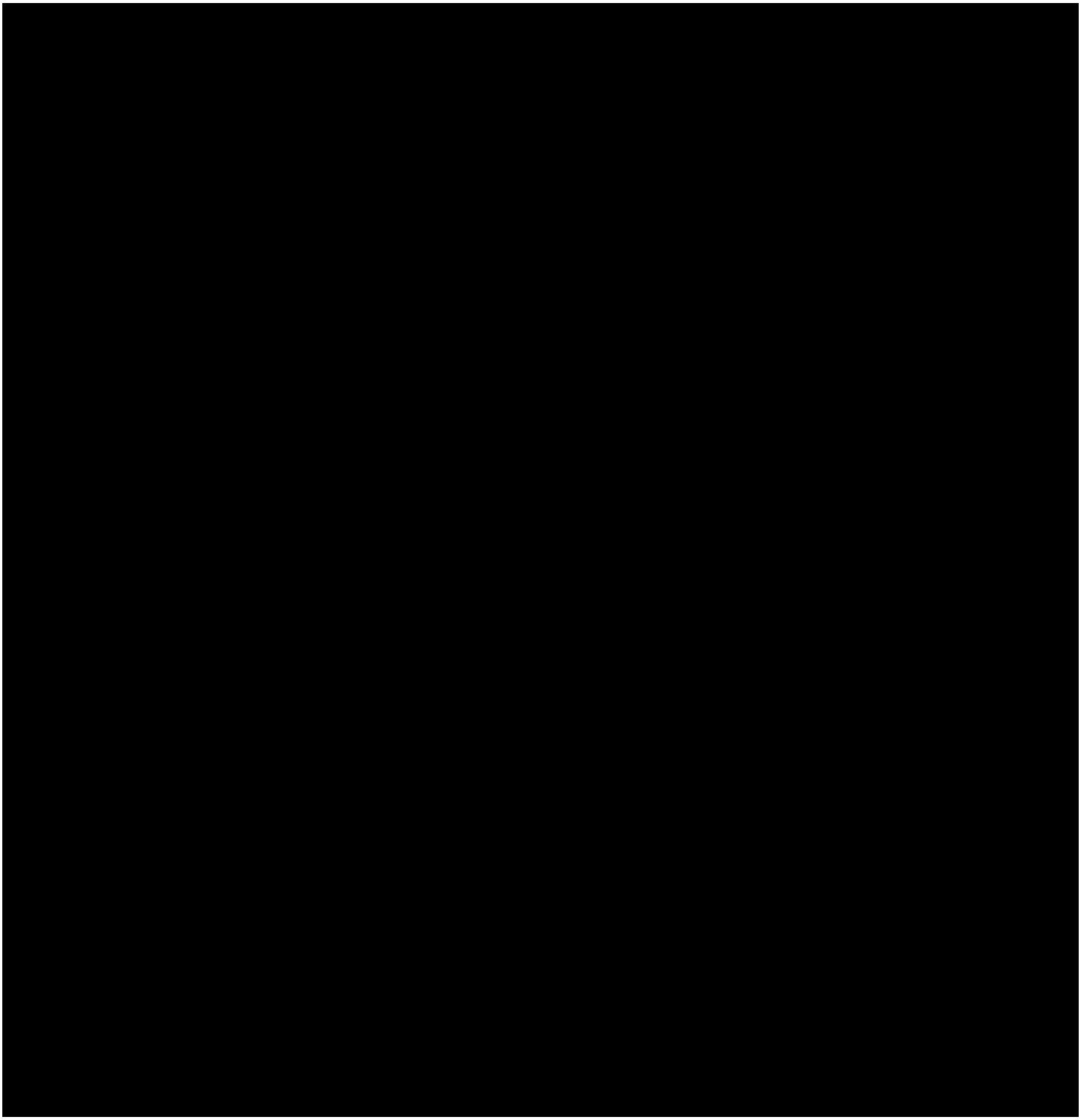


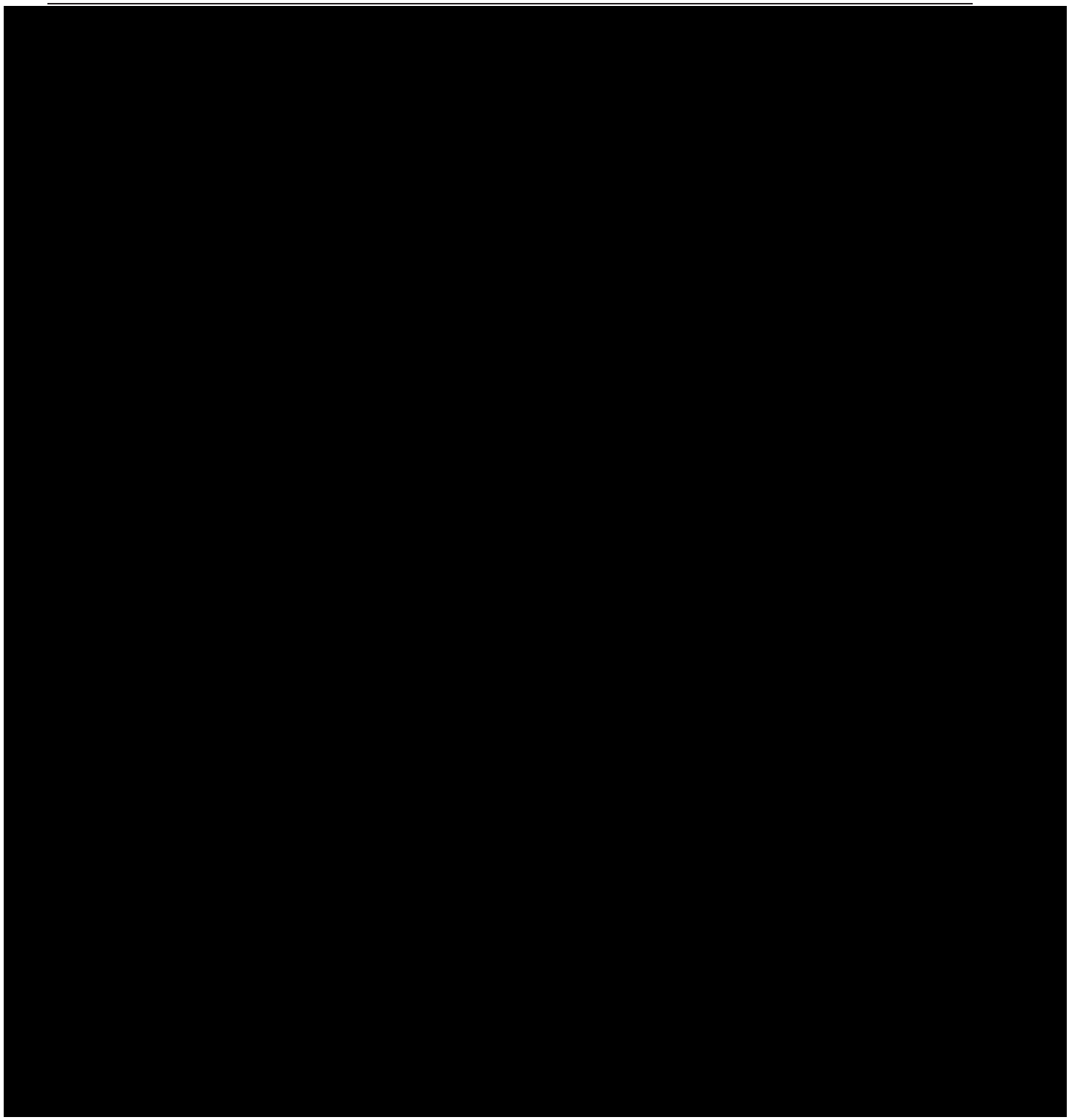












12 APPENDIX