NCT02959983

Study ID: CMO-US-GI-0429

Title: A Phase 4 Multicenter, Multinational, Prospective, Randomized, Placebo-Controlled, Double-Blinded Parallel Group Study to Assess Efficacy of Eluxadoline in the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D) in Patients Who Report Inadequate Control of IBS-D Symptoms with Prior Loperamide Use (RELIEF)

Statistical Analysis Plan Date: 18-Oct-2017

Allergan

Biostatistics

Analysis Plan – Clinical Study Report

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Study Phase:	IV
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Version:	1.0
Issue Date:	October 18, 2017

List of Abbreviations

Abbreviation	Definition
AE	adverse event
BID	twice daily
BSS	Bristol Stool Scale
CDS-HRQOL-4	Healthy Days Core Module
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
EQ-5D	EuroQoL-5 Dimension
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HEOR	health economics and outcomes research
IBS	irritable bowel syndrome
IBS-AR	irritable bowel syndrome adequate relief
IBS-D	irritable bowel syndrome with diarrhea
ICF	informed consent form
ITT	intent-to-treat
IxRS	interactive response system
MedDRA	Medical Dictionary for Regulatory Activities
SAE	serious adverse event

US	United States
WAP	worst abdominal pain
WPAI: IBS-D	Work Productivity and Activity Impairment questionnaire: Irritable Bowel Syndrome with Diarrhea

Table of Contents

1. Introduction

The analyses described in the SAP are based upon the final protocol dated 12 August 2016. Where differences exist between analyses specified in the protocol and this SAP, the SAP will be followed.

This is a Phase 4, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of eluxadoline 100 mg BID in patients with IBS-D who report that use of loperamide to treat their IBS-D symptoms in the prior 12 months failed to adequately control their symptoms of IBS-D. (RELIEF)

Approximately 340 patients will be randomly assigned (in a 1:1 ratio) to 1 of 2 treatment groups below:

• Group 1: eluxadoline 100 mg oral tablets BID with food

• Group 2: matching placebo oral tablets BID with food

During the screening period (up to 1 week), screening procedures, including Prior Symptoms Management Questionnaire (refer to Appendix 10.7), will be performed. After that, eligible patients will enter a pretreatment period (up to 3 weeks). At the beginning of the pretreatment period, patients will receive instructions for completing an electronic patient-reported outcome (ePRO) diary to collect daily information related to their IBS-D symptoms and use of loperamide rescue medication. At the end of the pretreatment period, patients who meet the study inclusion criteria related to ePRO diary compliance, stool consistency (Bristol Stool Scale [BSS]) , average worst abdominal pain (WAP) score , and use of loperamide rescue medication will be randomized into a 12-week double-blind treatment period via central randomization.

Patients randomized into the study will return to the clinic for study visits at week 4, week 8, week 12 (end-of-treatment study visit), and for a post-treatment follow-up visit at week 14. A complete schedule of events is provided in Appendix 10.1, Table 10–1 and Table 10–2. Patients who discontinue from the study before the week 12 visit should return to the study site to complete the early withdrawal assessments as soon as possible after stopping the study drug.

During the double-blind Treatment period, patients will record via the ePRO diary their daily IBS-D symptoms including BSS, WAP, abdominal discomfort, abdominal bloating, bowel movement frequency, number of episodes of urgency in a day, if any, number of episodes of fecal incontinence, and use of loperamide rescue medication.

The actual ePRO data entered by the patients will not be provided to the investigative site staff at the time of randomization or during the study to prevent any potential bias in subsequent patient entries. However, periodic notifications will be generated to inform the investigator of patients' ongoing compliance with ePRO diary entries and to alert investigators if patients have experienced episodes of constipation or have required excessive loperamide rescue medication for acute treatment of uncontrolled diarrhea.

1.1 Primary Study Objective

The primary objective of this study is to evaluate the efficacy of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.

1.2 Secondary Objectives

The secondary objectives are to evaluate the safety and tolerability of eluxadoline 100 mg BID versus placebo BID over 12 weeks of treatment in patients with IBS-D who report that use of loperamide in the prior 12 months failed to provide adequate control of their IBS-D symptoms.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat Population (ITT): The ITT population will include all randomized patients. Patient disposition, demographics, baseline characteristics, efficacy, and HEOR data will be analyzed using the ITT population. Patients will be analyzed according to their randomization assignment, regardless of the actual treatment received. In this study, only randomized patients are considered as enrolled.

Safety Population: The Safety Population will include all patients enrolled who received at least 1 dose of study drug. Safety data will be analyzed using the safety population. Patients will be grouped and analyzed according to the treatment they actually received.

2.2 Baseline Definition and Visit Window for Analysis

For the score of BSS, WAP, abdominal discomfort, and abdominal bloating, the baseline value is defined as the weekly average in the week prior to randomization.

For bowel movement, urgency episodes, and episodes of fecal incontinence, the baseline value is defined as the average number per day in the week prior to randomization.

[redacted]

For all other variables, the baseline value is the last observation prior to receiving the first dose of study medication as usual.

For weekly assessment such as treatment satisfaction and degree of relief of IBS symptoms, the visit window is defined as target day ± 3 days. For example, the treatment satisfaction assessment is collected weekly, starting from end of Week 1, the visit window will be day 4 (- 3 days) -- day 7 (target day) -- day 10 (+ 3 days).

2.3 Data Conventions

Based upon interactive voice response compliance data from the completed Phase 3 trials in patients with IBS-D, we are anticipating 15% to 20% missed ePRO diary entry days for those patients who were not discontinued. For this study, missed daily ePRO diary entries will not be considered as protocol violations. The minimum of the non-missing diary entries for each study endpoint will be specified in corresponding sections and the method of handling missing data for each endpoint is described in corresponding sections. Only observed data (i.e., no imputation) will be used for analyses except for the second definition of weekly composite responder (details are described in Section 6.5.1 14)).

If there is more than one visit within a visit window (e.g., unscheduled visits), the visit closest to the target date of the visit will be used for analyses. If two visits are equidistant from the target date, then the data from the later visit will be used for analyses.
If the date of a visit is out of the visit window, the data will only be displayed in listings.
All data collected will be displayed in listings.

3. Disposition and Exit Status

3.1 Screening Log Data

A summary table will be provided for the number of screen failures for study enrollment and the break-down of screen failures by failure reasons.

3.2 Disposition and Exit Status

The number of patients in ITT population and Safety population in each treatment group will be summarized for overall and by site. Another table will summarize the number of completers and non-completers with sub-categorization of reason for discontinuation and p-value for comparison between treatment groups.
A listing for patients who prematurely discontinued during double-blind treatment period will be provided.

4. Demographics and Other Baseline Characteristics

4.1 Demographics and Baseline Characteristics

A demographic and baseline disease characteristic table will be provided with p-values for testing differences between treatment groups.

4.2 Medical History

Medical history will be coded by MedDRA 20.0. The medical history data will be summarized by SOC and preferred term in MedDRA and by treatment groups.

4.3 Prior Medications

Prior medications are defined as any medication taken between Day -14 to Day -1.
Medications are to be coded by WHO DDE B2. The prior medication records will be summarized by preferred drug name under ATC level 2 classification and by treatment groups.

4.4 Concomitant Medications

Concomitant medications are defined as any medication that are ongoing or start after the first dose of study drug has been administrated and through the early termination or follow-up visit.
Medications are to be coded by WHO DDE B2. The concomitant medication records will be summarized by preferred drug name under ATC level 2 classification and by treatment groups.

4.5 Prior IBS-D Symptom Management Questionnaire

The number and percentage of patient's taking each category of medication (Loperamide, Antidiarrheals (other than loperamide), Antidepressants, Anticholinergics/Antispasmodics) will be summarized with p-values for testing differences between treatment groups. Furthermore, the responses to follow-up questions will be summarized by each category of medication and by questions.

Further text answers will be provided in a listing.

5. Duration to Study Treatment(s) and Compliance of Treatment

Duration of treatment is defined as: [(last dose date - first dose date) + 1].

The duration of treatment will be summarized by descriptive statistics. A listing will present the first dose date and the last dose date, the dates and days of interruption, and the overall days of exposure.

The total dose for a patient is defined as the sum of the patient reported dose on each day with dosing information (i.e., without any imputation) during 12-week treatment period. The total dose will be summarized by descriptive statistics.

Study drug compliance will be calculated as the number of tablets taken divided by the target number of tablets to be taken during 12-week treatment period.

$$\text{Overall Compliance (\%)} = \frac{\text{(Number of tablets taken)} \times 100\ \%}{\text{Target number of tablets to be taken}}$$

The target number of tablets to be taken is calculated as: (last dose date – first dose date + 1) x 2, since the dose is 1 tablet BID. The number of tablets taken is obtained by: (no. dispensed – no. returned).
If the drug is not returned at one visit for a patient, the compliance for the patient will be set to missing and the patient will be excluded from the analysis.

Treatment compliance will be summarized by descriptive statistics and also as frequency counts and percentages for the following categories (<80 % vs ≥80%).

The diary entry compliance will be summarized by compliance days categories (< 60 days vs > = 60 days) during the 12-week treatment period (84 days). For partial diary entry, the diary entry compliance is defined as if a patient's diary entry has EITHER WAP score and BSS score OR WAP score and bowel movement frequency data for a day, this patient will be considered as diary entry compliance for the day.

A listing will be provided for drug administration data, including number of tablets dispensed, returned, and the number not returned also not taken, etc.

6. Efficacy Analyses

[redacted]

6.3 Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of primary composite responders determined over the 12-week double-blind treatment period. A primary composite responder is defined as a patient who meets the daily composite response criteria for at least 50% of days with diary entry during the interval of week 1-12.

A patient must meet BOTH of the following criteria on a given day to be a daily composite responder:

- Daily pain response: WAP score in the past 24 hours improved by ≥40% compared to baseline pain (average of daily WAP in the week prior to randomization).

- Daily stool consistency response: BSS score <5 (i.e., score of 1, 2, 3, or 4); or the absence of a bowel movement if accompanied by ≥40% improvement in WAP compared to baseline pain.

To be eligible to be a primary composite responder, a patient must have a minimum of 60 days of diary entries, including partial entries, over the interval of week 1-12. A partial diary entry should consist of EITHER WAP score and BSS score OR WAP score and bowel movement frequency equals 0 to determine whether a patient is a daily responder. Any patient with fewer than 60 days of diary entry will be considered as a non-responder.

6.3.1 Primary Analyses for Primary Efficacy Endpoint

The primary analysis is to evaluate the proportions of primary composite responders between the eluxadoline and placebo groups. These 2 proportions are represented as $\pi_{\text{Eluxadoline}}$ and π_{Placebo}. The primary hypotheses for this study are described below:

H_0: $\pi_{\text{Eluxadoline}} - \pi_{\text{Placebo}} = 0$
vs
H_A: $\pi_{\text{Eluxadoline}} - \pi_{\text{Placebo}} \neq 0$

The number and the percentage of responders and non-responders will be summarized in a table with p-value from chi-square test to test the different response rates between treatment groups.

6.3.2 Other Analysis for Primary Efficacy Endpoint

As a supportive analysis, the primary endpoint will also be analyzed using logistic regression model with treatment group, the baseline pain score, and the baseline stool consistency score as exploratory variables.

6.4 Secondary Efficacy Analyses

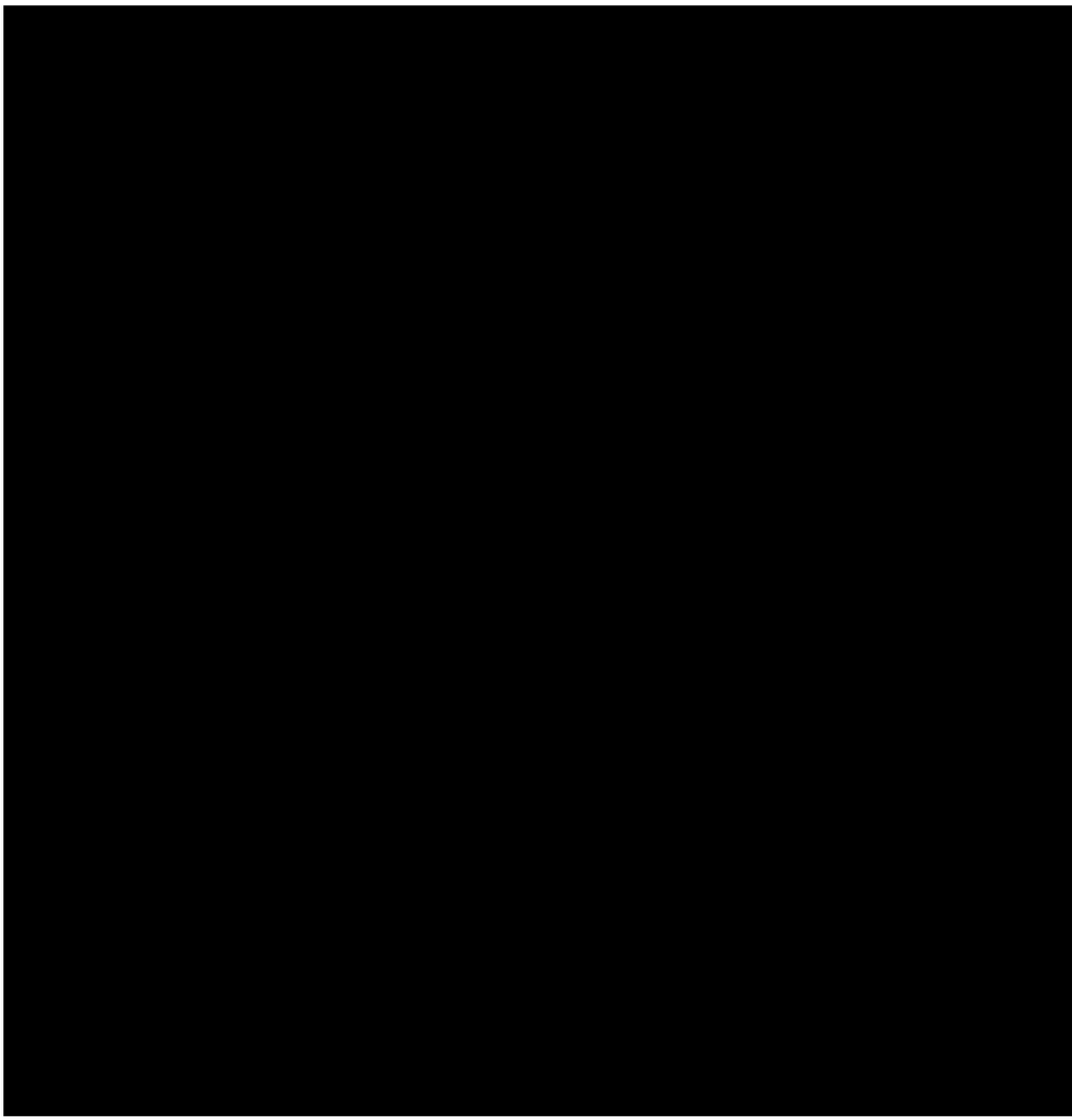
The following are the secondary efficacy endpoints:

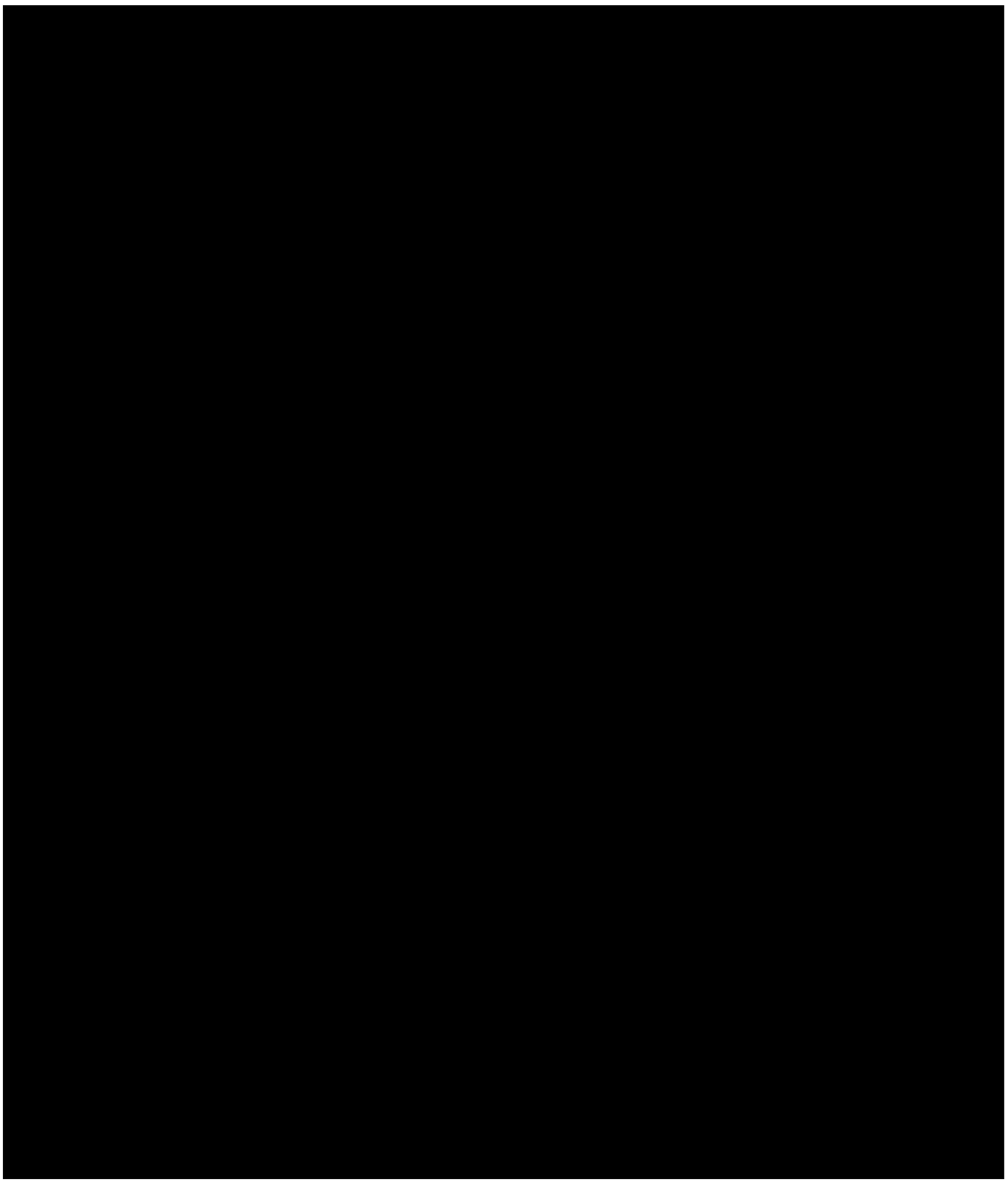
- Proportion of stool consistency responders: defined as patients who meet the daily stool consistency response criteria (BSS <5, or absence of a bowel movement) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For the 12-week treatment period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 6.3. For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 60 days (for 12-week period) or with fewer than 20 days (for 4-week interval) of diary entries will be considered as a non-responder.

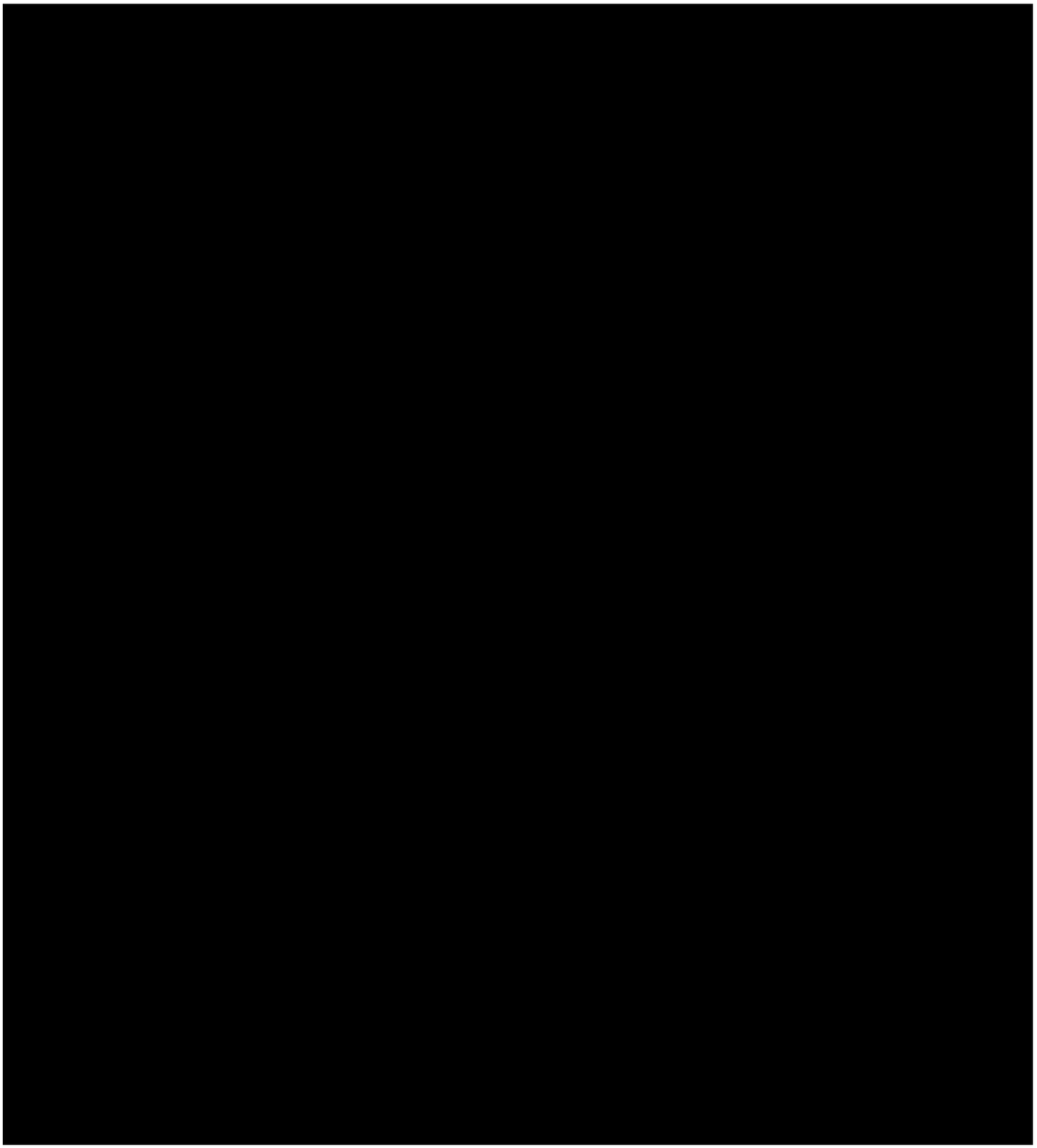
- Proportion of pain responders: defined as patients who meet the daily pain response criteria (as defined in Section 6.3) for ≥50% of days with diary entries over a certain time period. This endpoint is defined for the 12-week treatment period and for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For the 12-week treatment period, the ≥50% requirement is the same as specified for the primary efficacy endpoint in Section 6.3. For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 60 days (for 12-week period) or with fewer than 20 days (for 4-week interval) of diary entries will be considered as a non-responder.

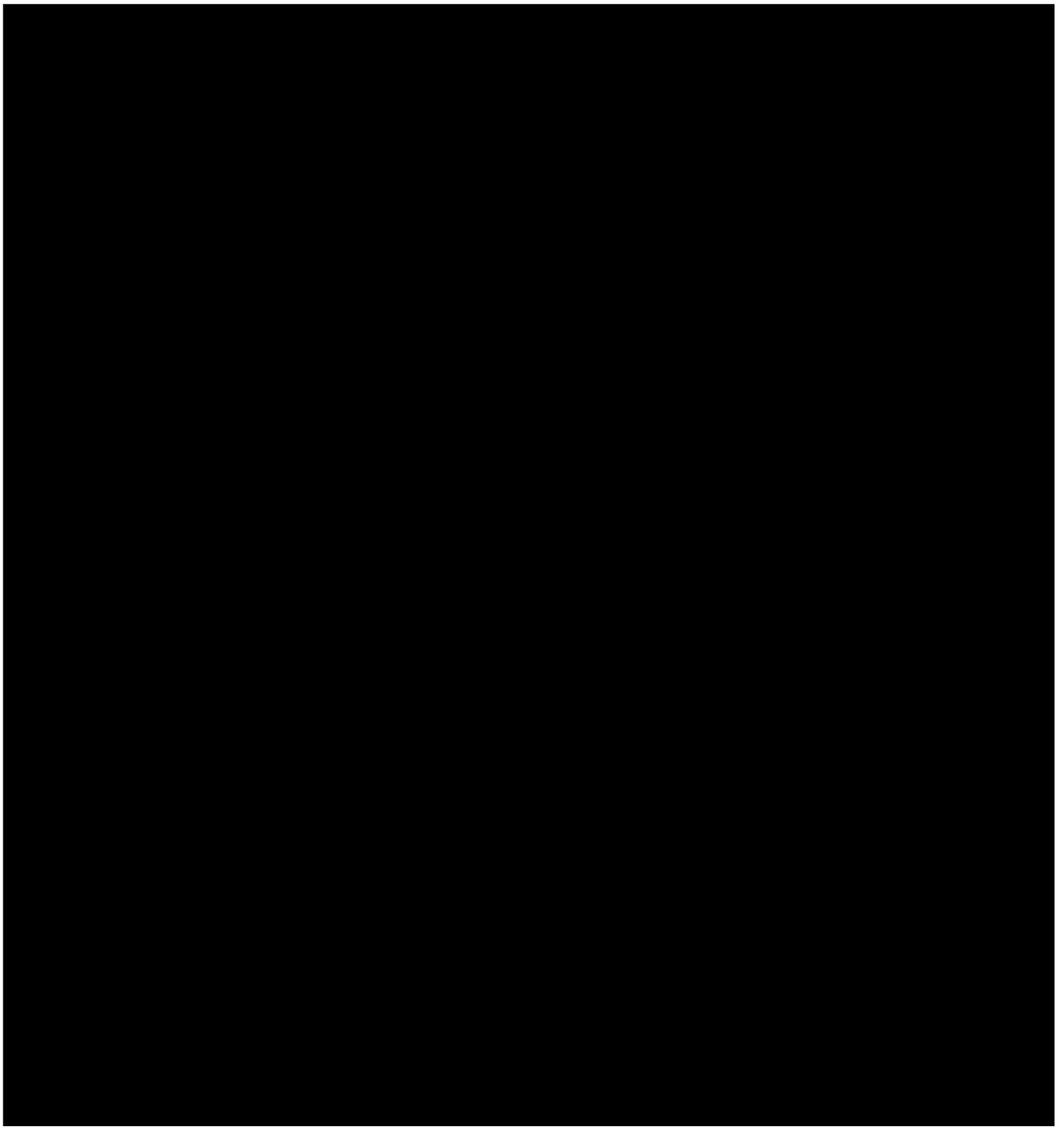
- Proportion of monthly composite responders: defined as patients who meet the daily composite response criteria (as defined in Section 6.3) for at least 50% of days with diary entry for each 4-week interval (week 1 to 4, 5 to 8, and 9 to 12). For each of the 4-week intervals, a responder must have a minimum of 20 days of diary entries over the 4 weeks. Any patient with fewer than 20 days of diary entries for the 4-week interval will be considered as a non-responder.

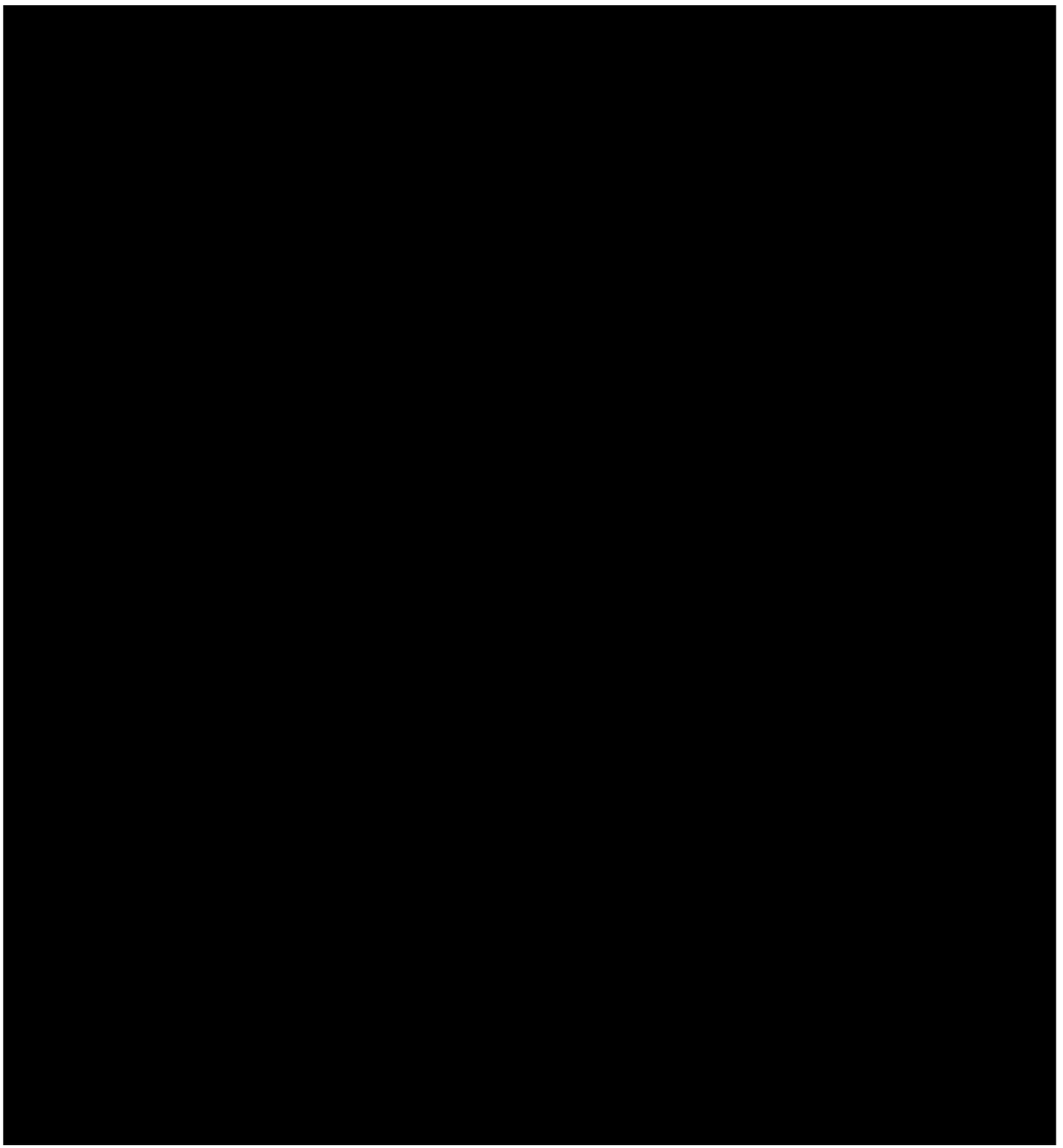
The secondary endpoints will be analyzed by the number and percentage of the corresponding responders with p-value from chi-square test to test the different response rates between treatment groups. No adjustment for the multiplicity of the endpoints will be performed.









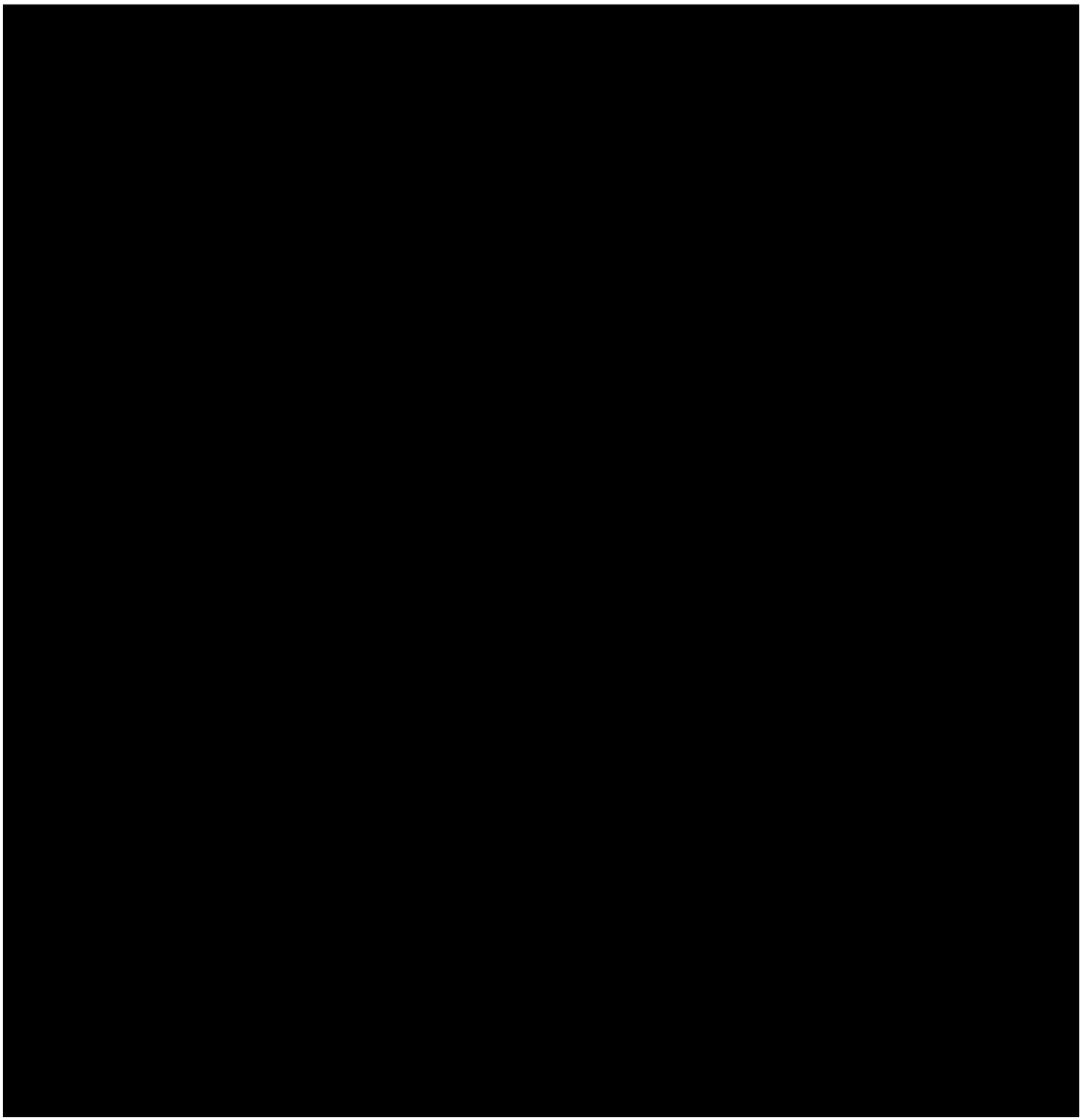


8. Interim Analyses

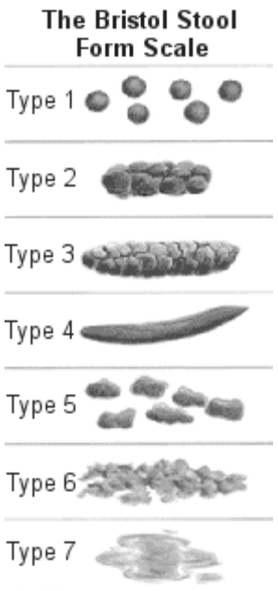
There will be no interim analysis for this study.

9. Deviations from Protocol

This analysis mentioned in protocol section 7.7.3, “The mixed-effect model for repeated measures method will be used to analyze these endpoints with treatment group as the factor and baseline endpoint values as covariate.” is not performed.



10.2 Bristol Stool Scale



Type 1 - Separate hard lumps like nuts (difficult to pass)

Type 2 - Sausage shaped but lumpy

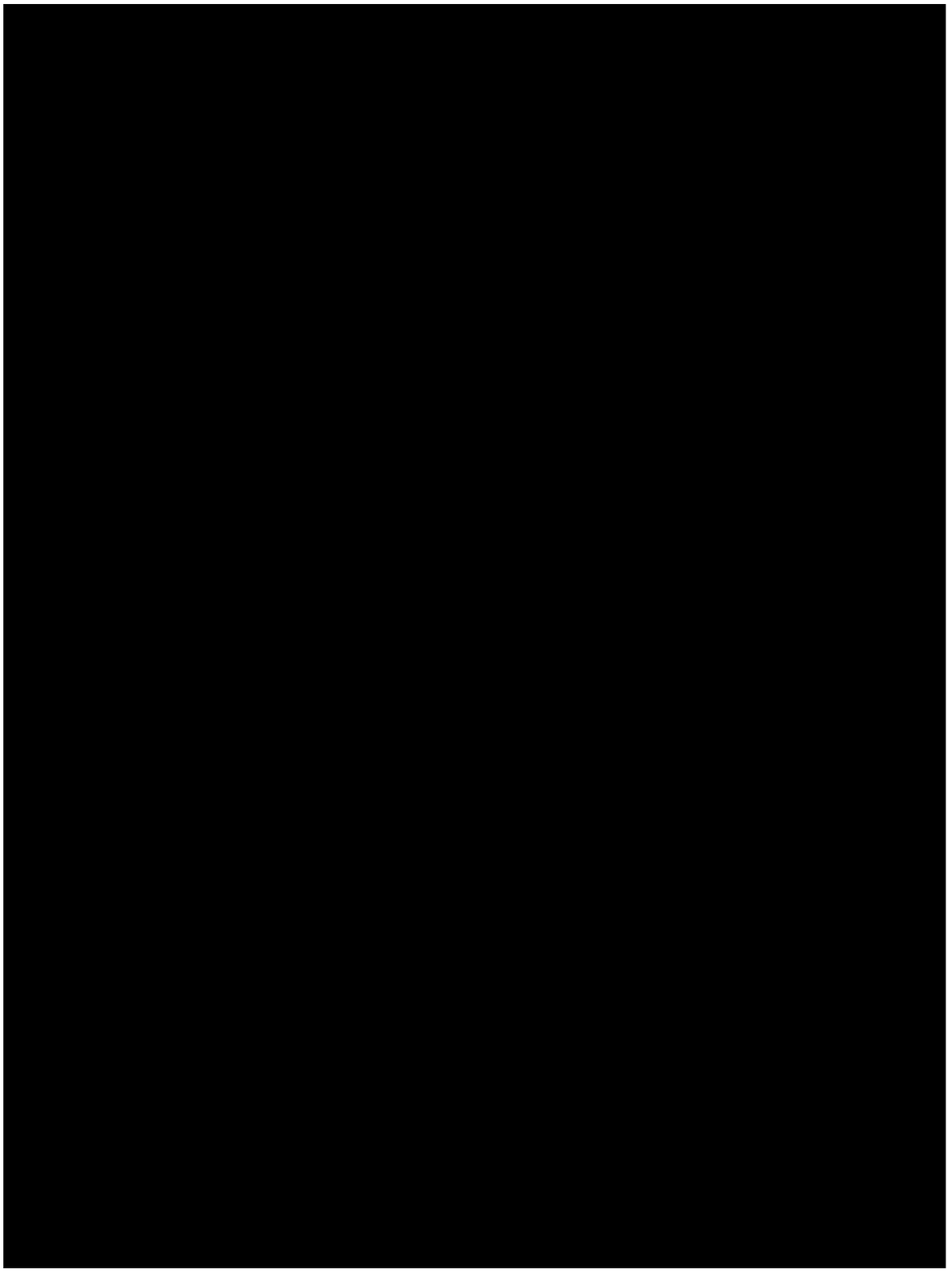
Type 3 - Like a sausage but with cracks on surface

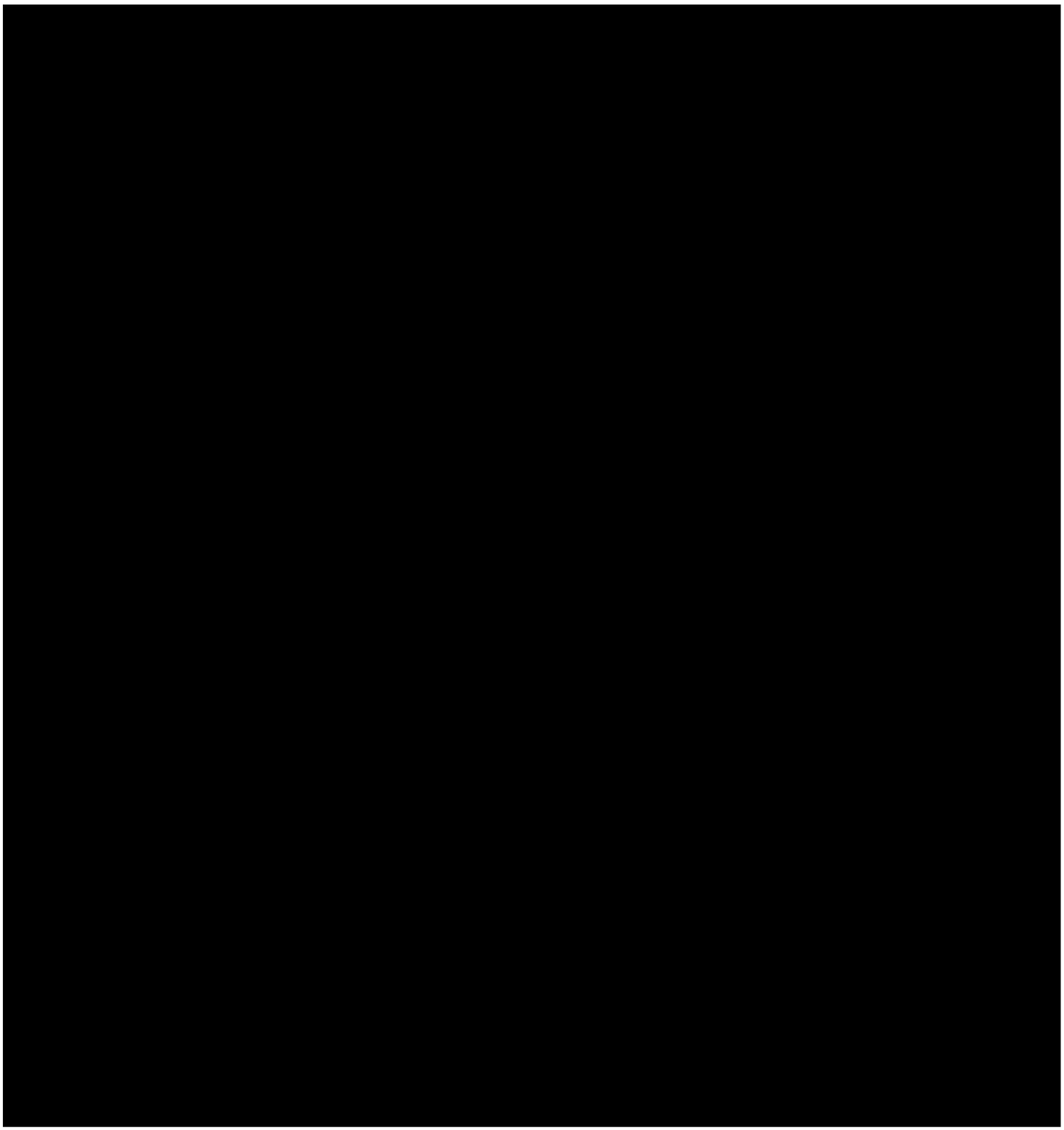
Type 4 - Like a sausage or snake, smooth and soft

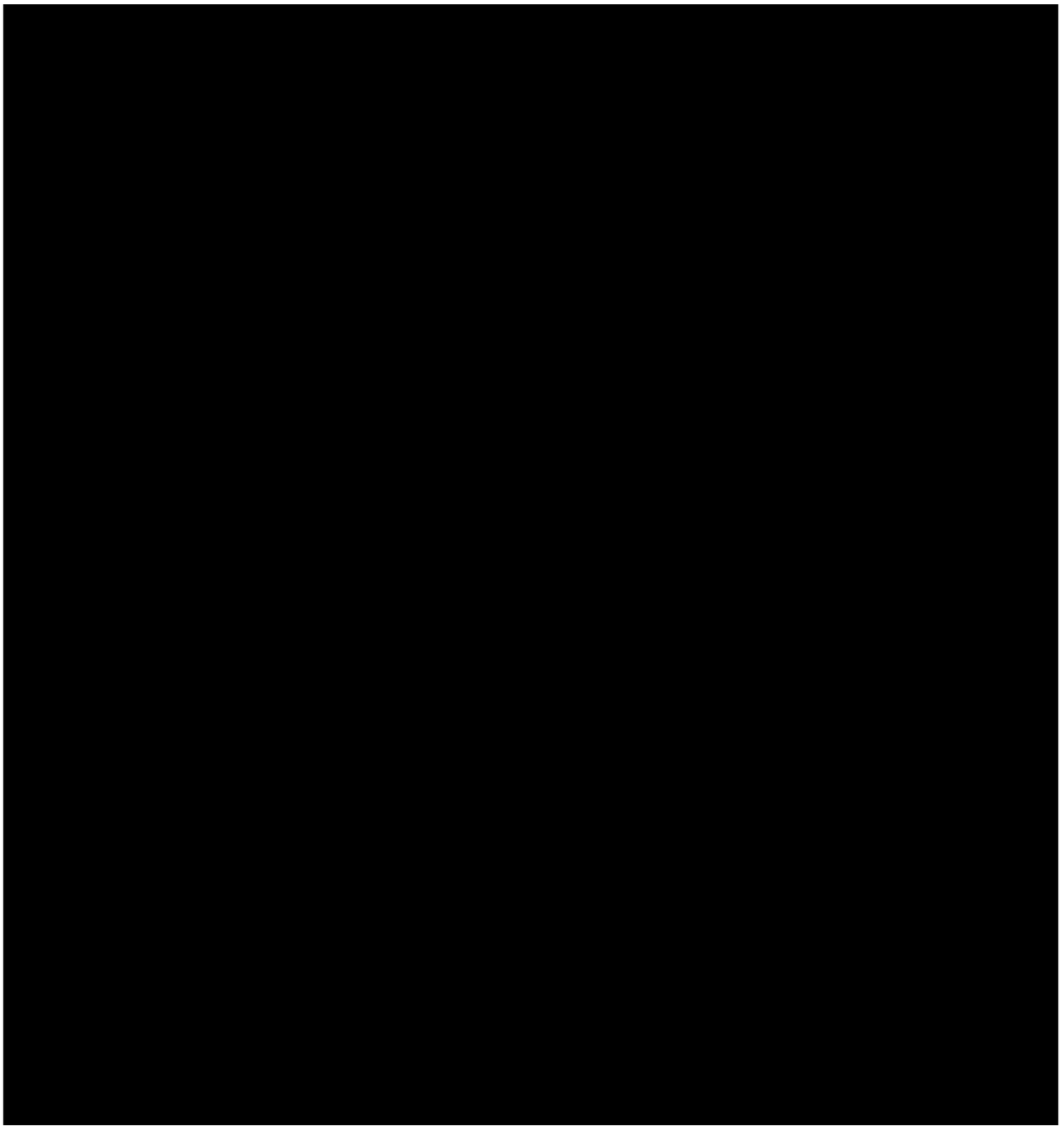
Type 5 - Soft blobs with clear-cut edges (passed easily)

Type 6 - Fluffy pieces with ragged edges, a mushy stool

Type 7 - Watery, no solid pieces (entirely liquid)







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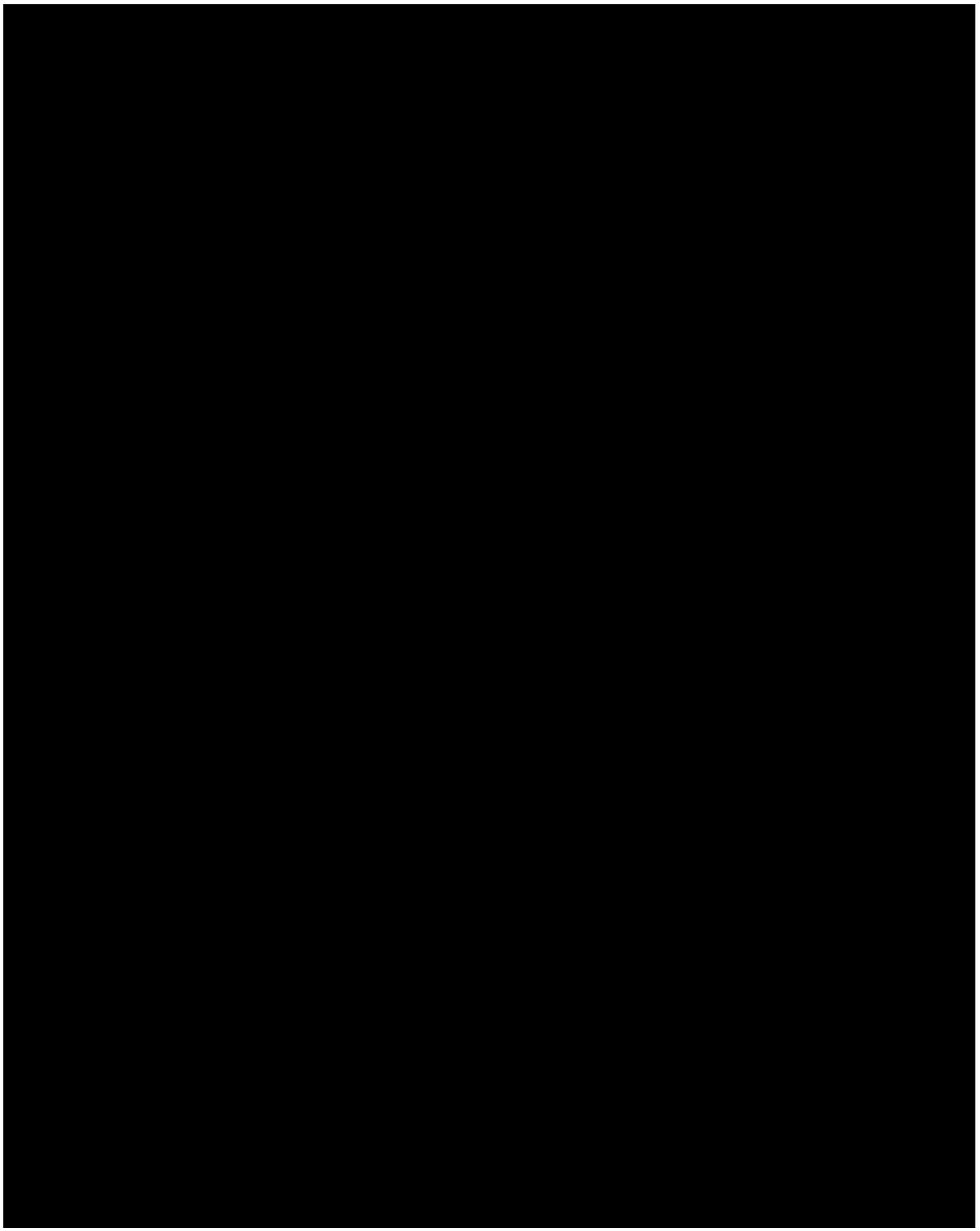
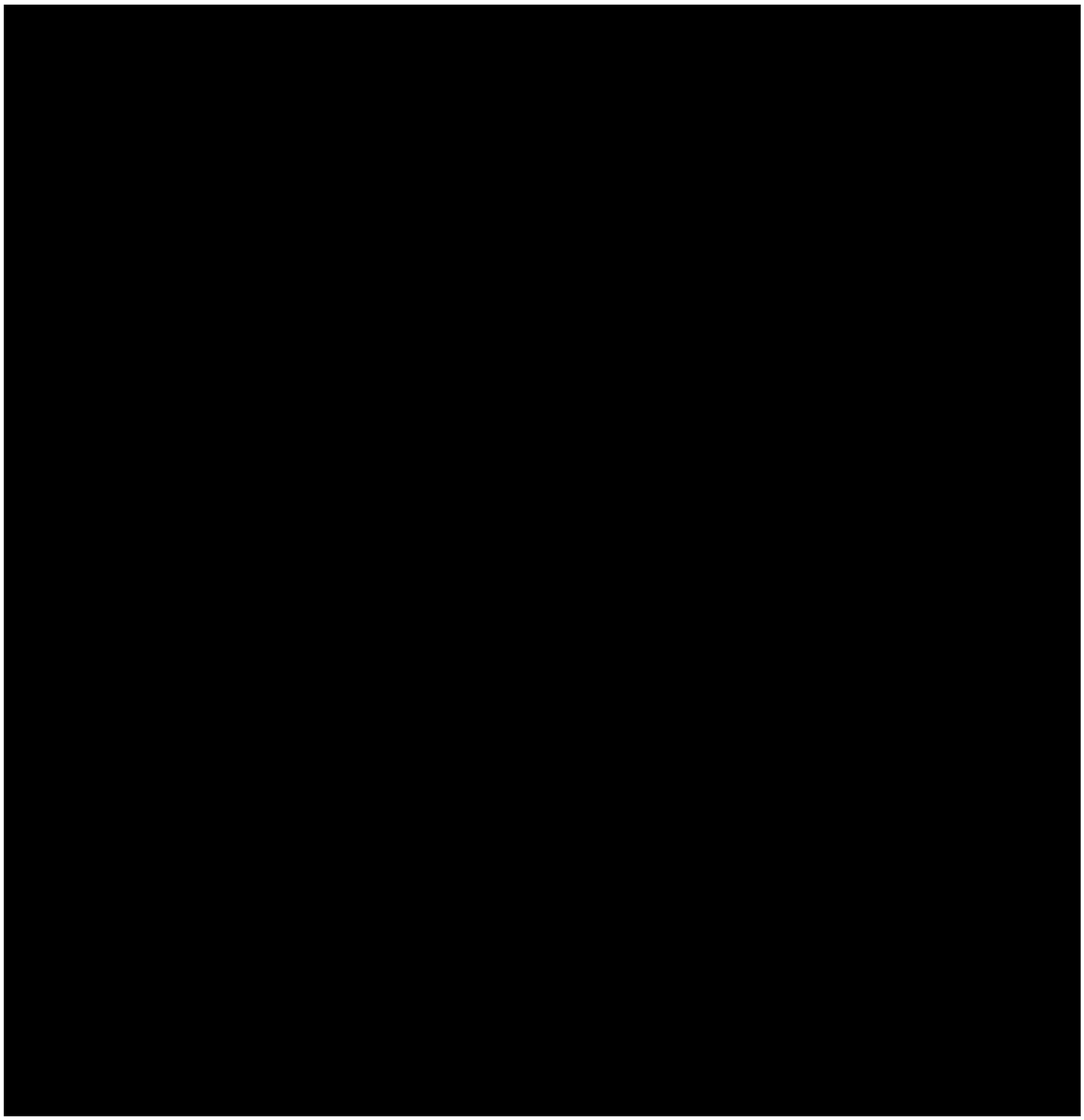
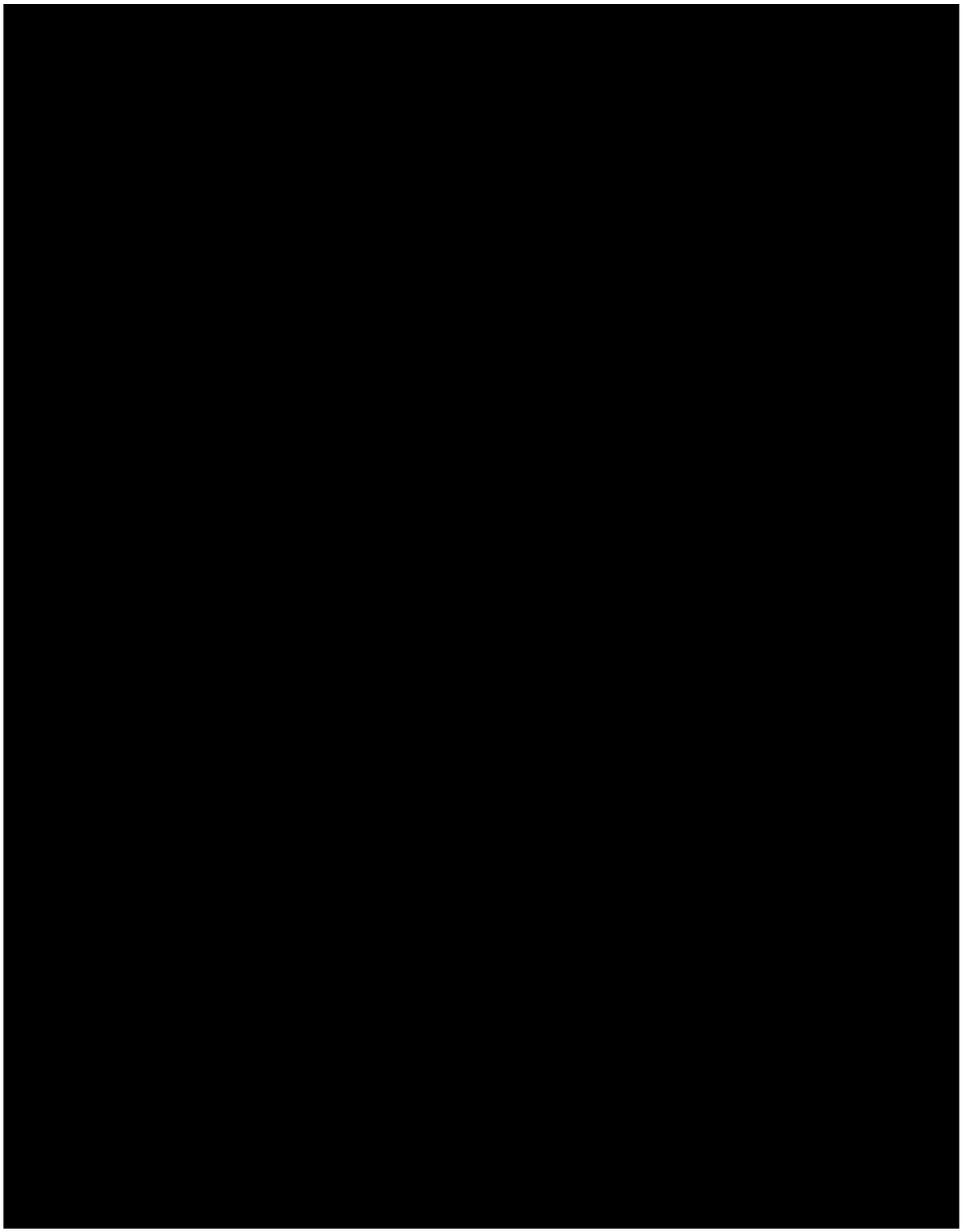
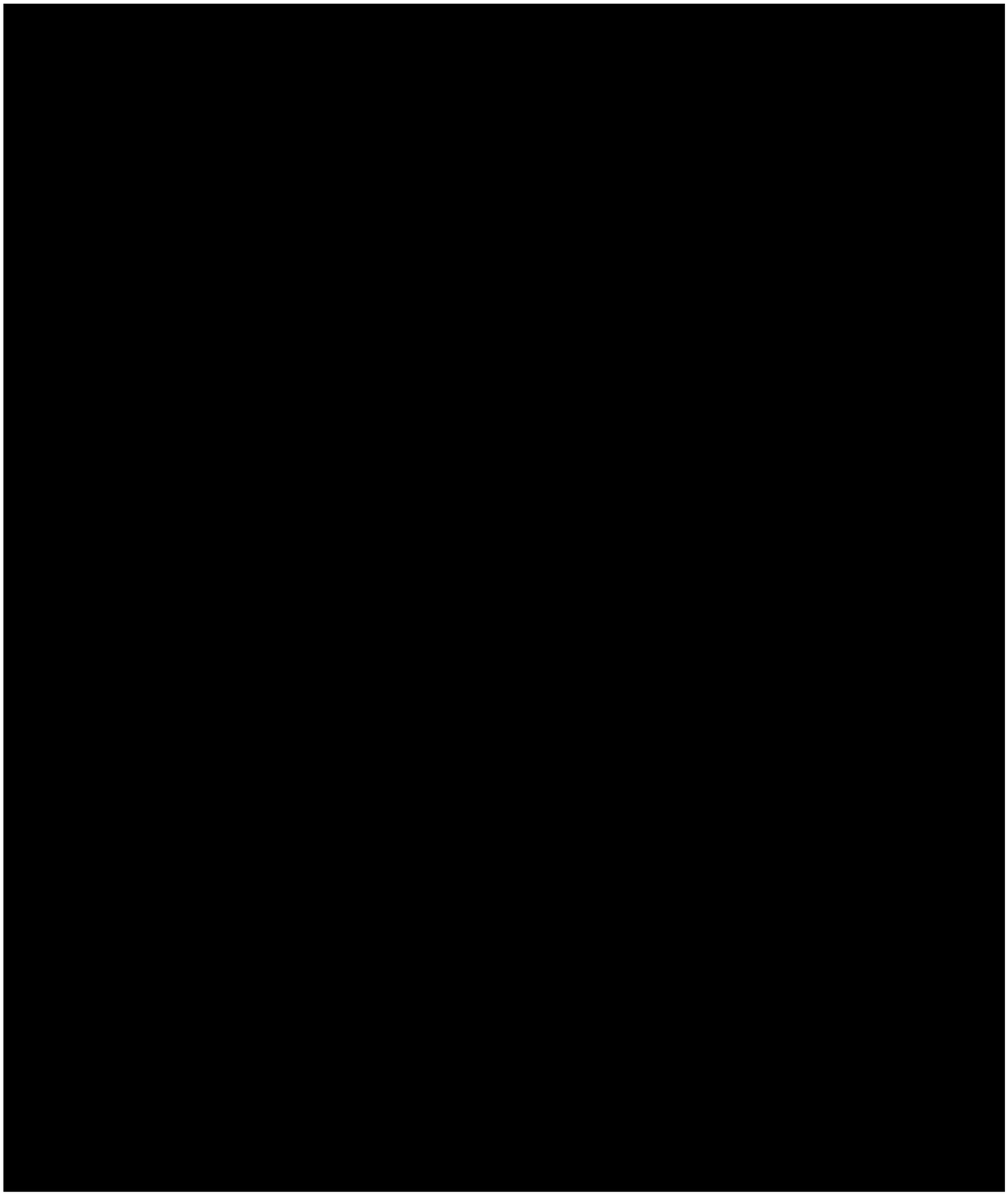
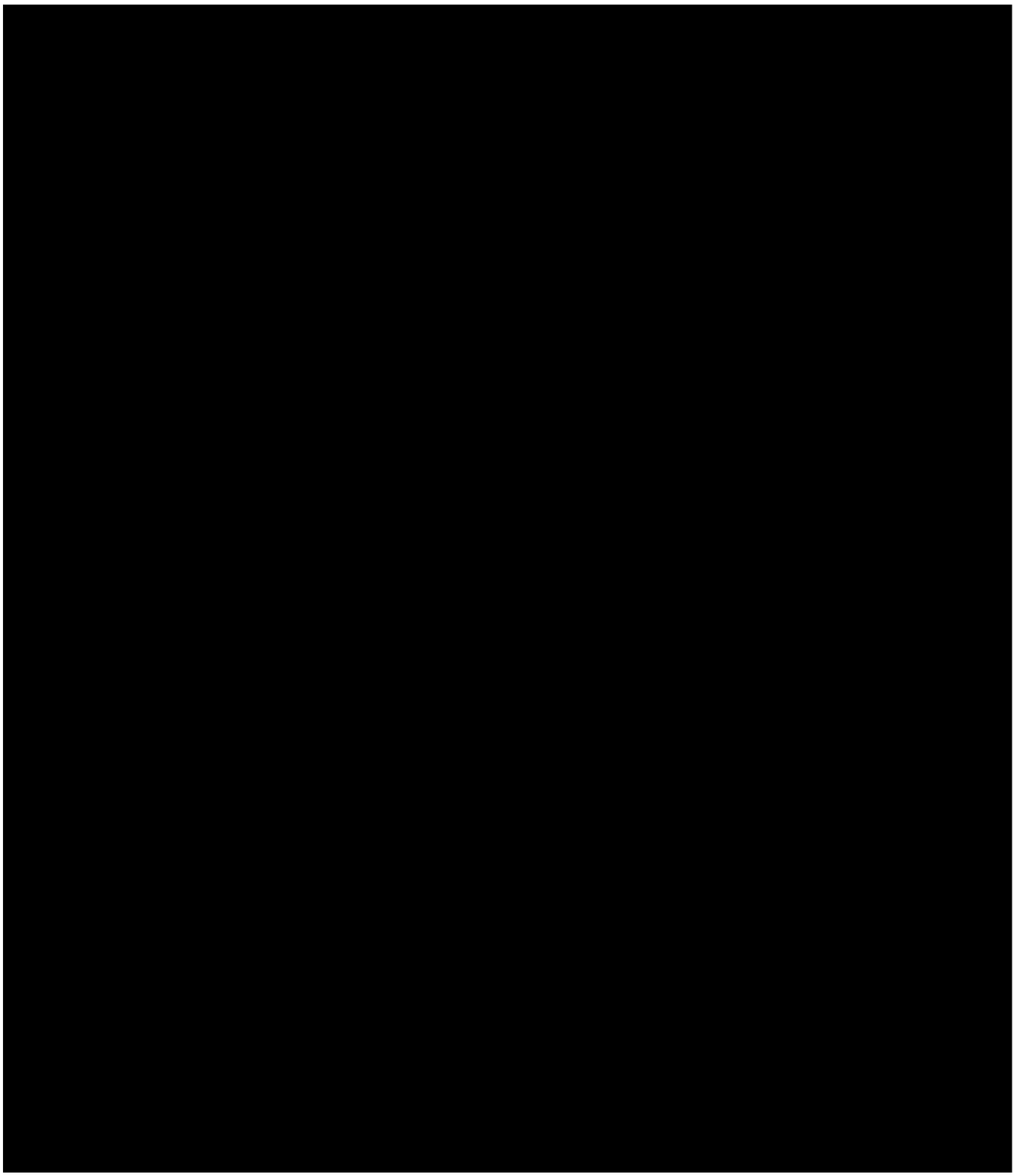
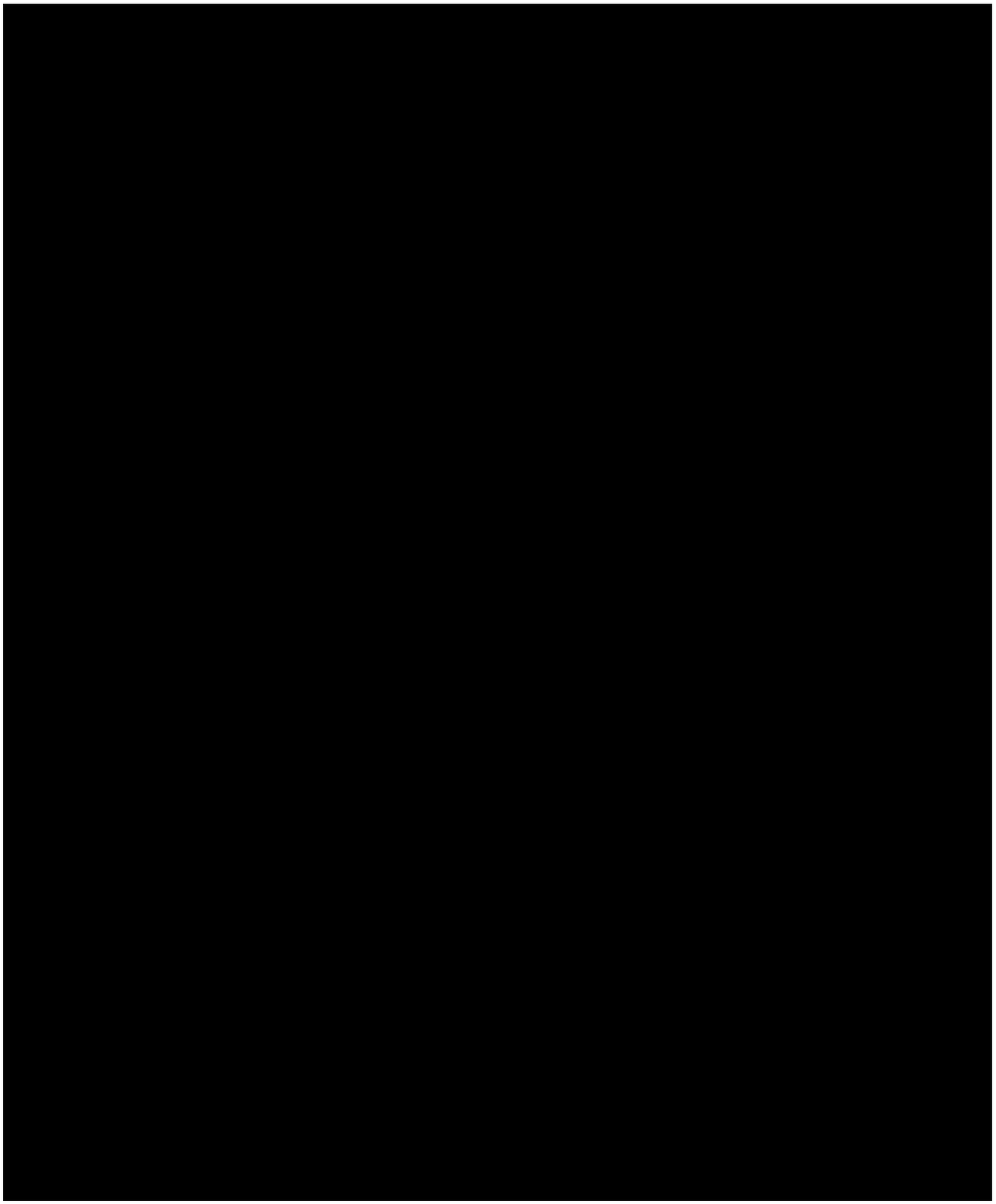


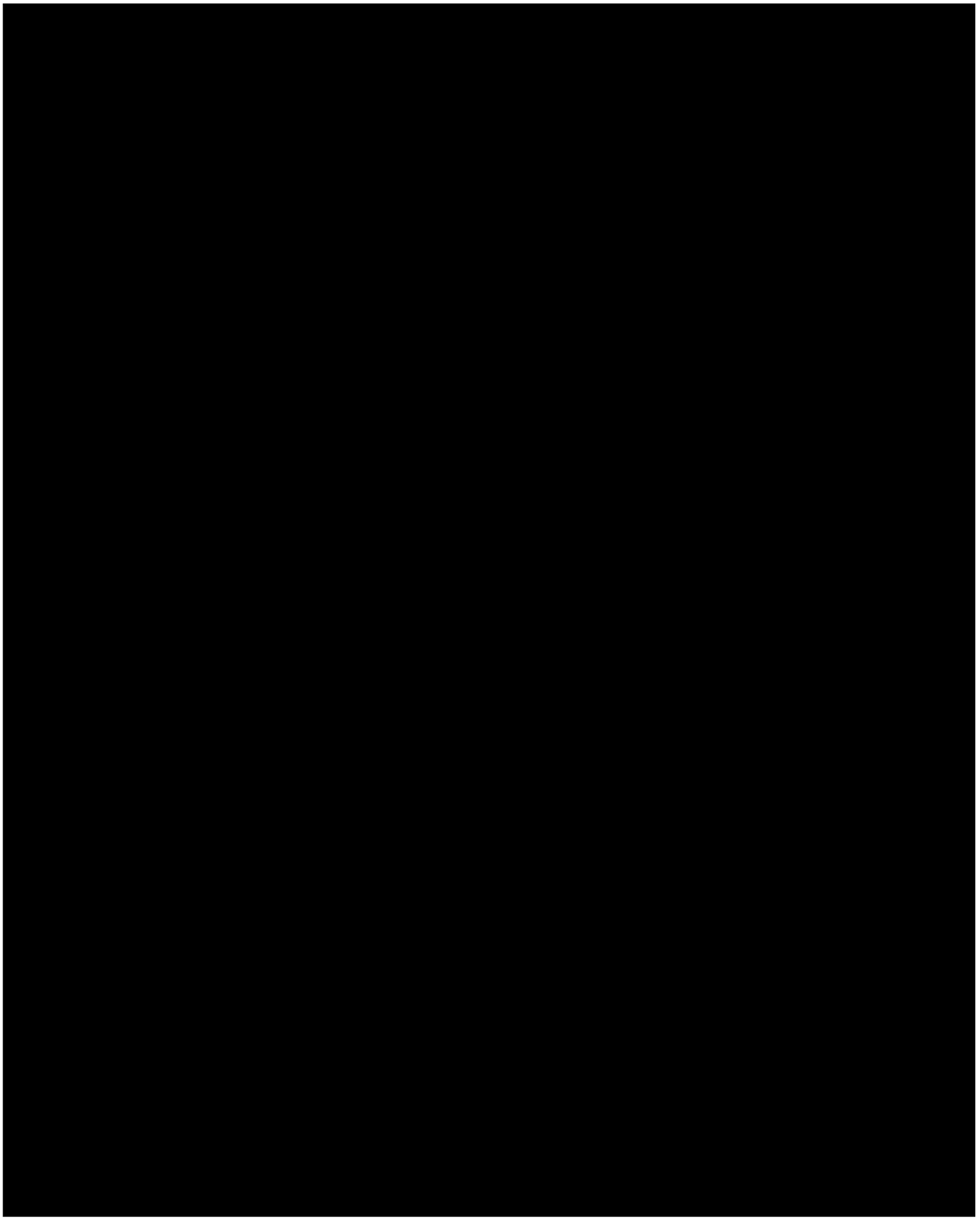




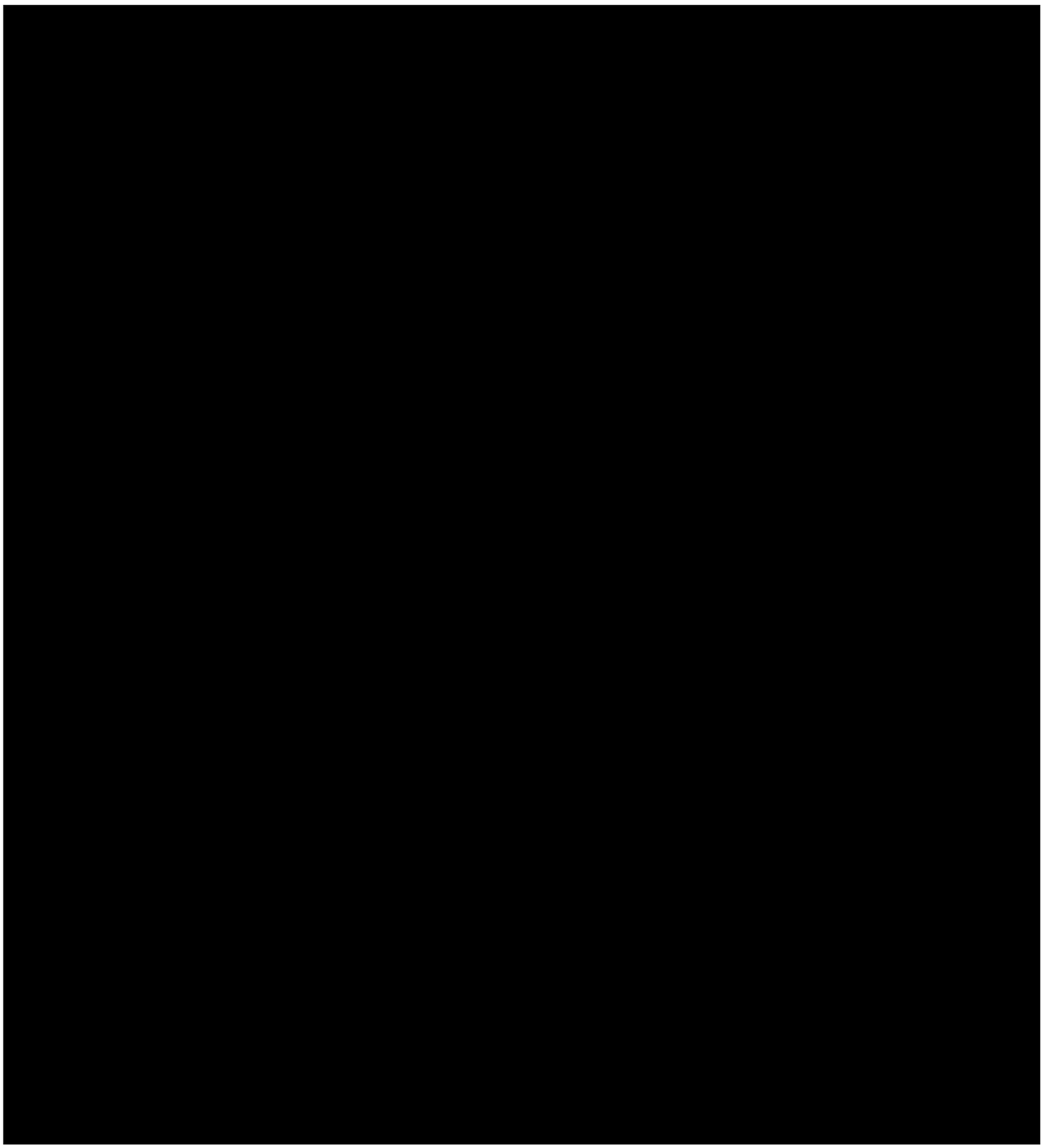


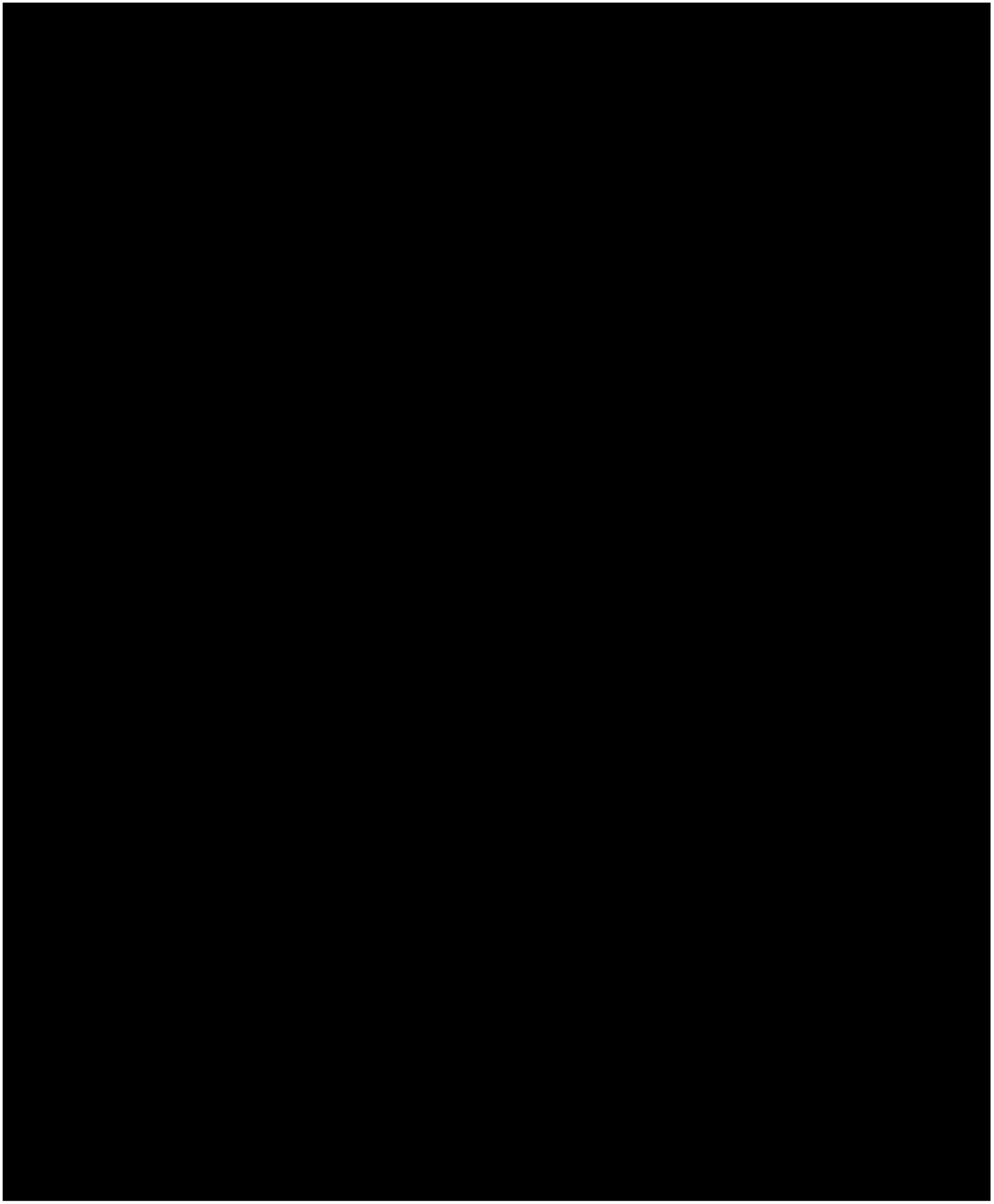


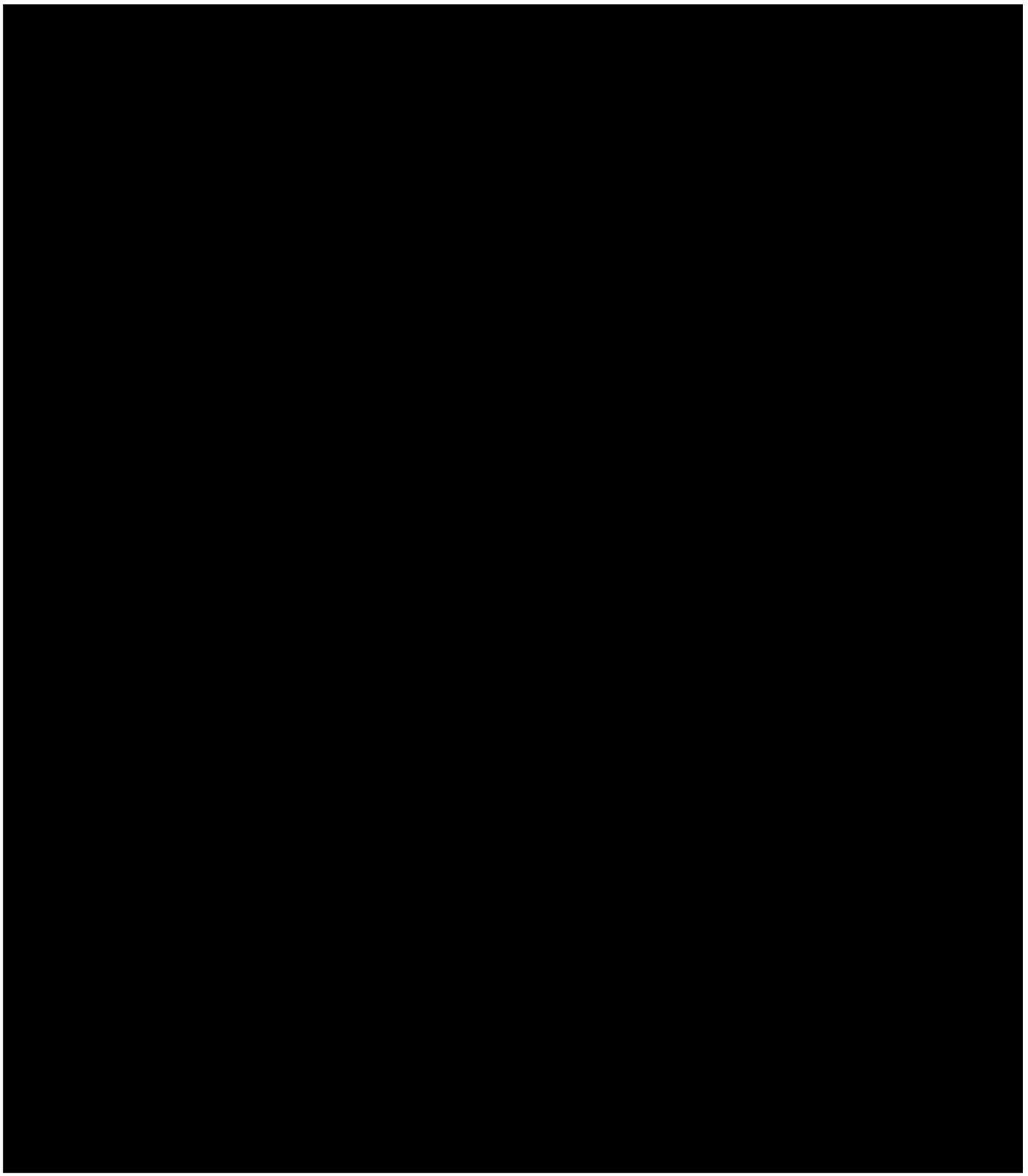


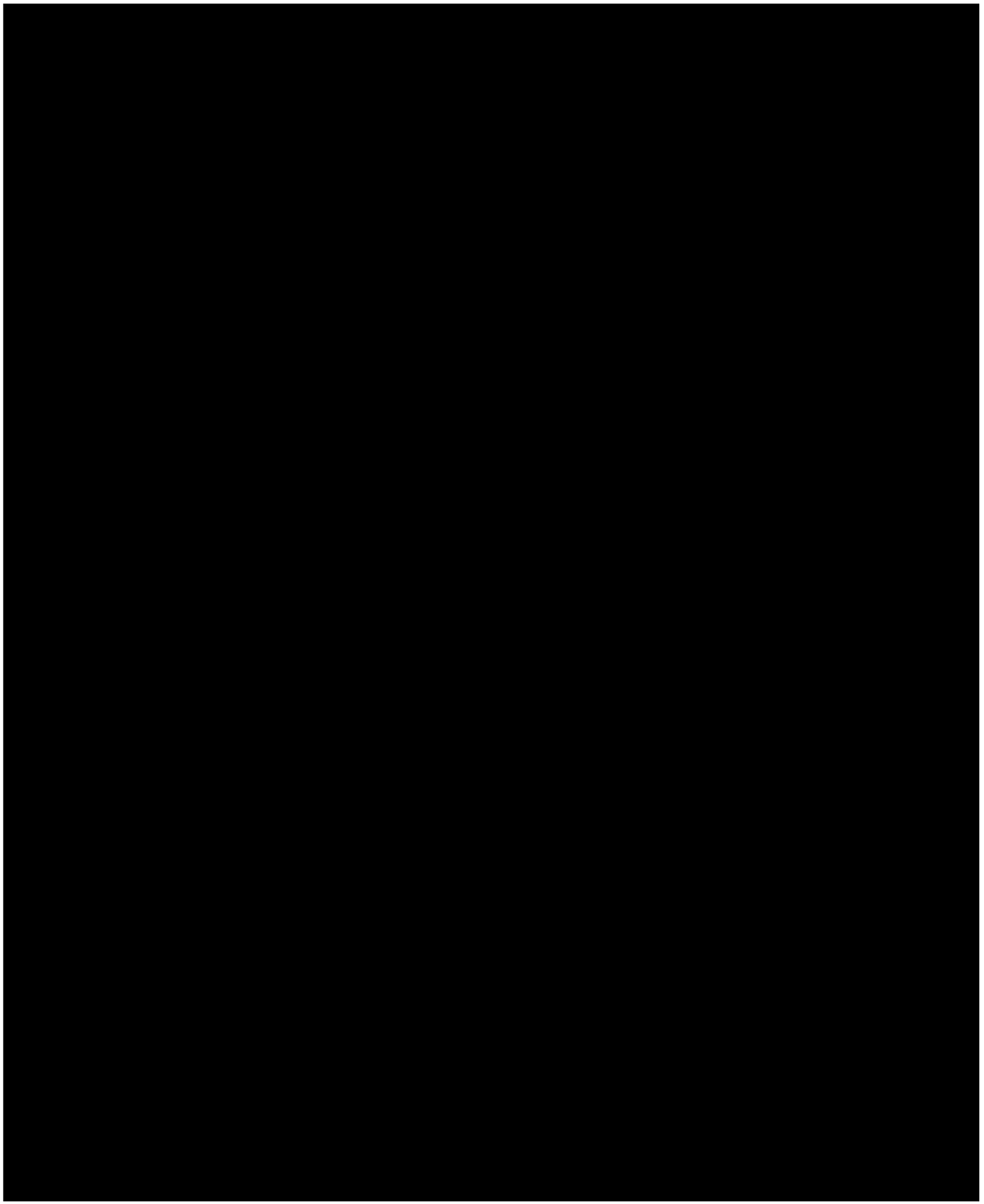


5 = It costs too much









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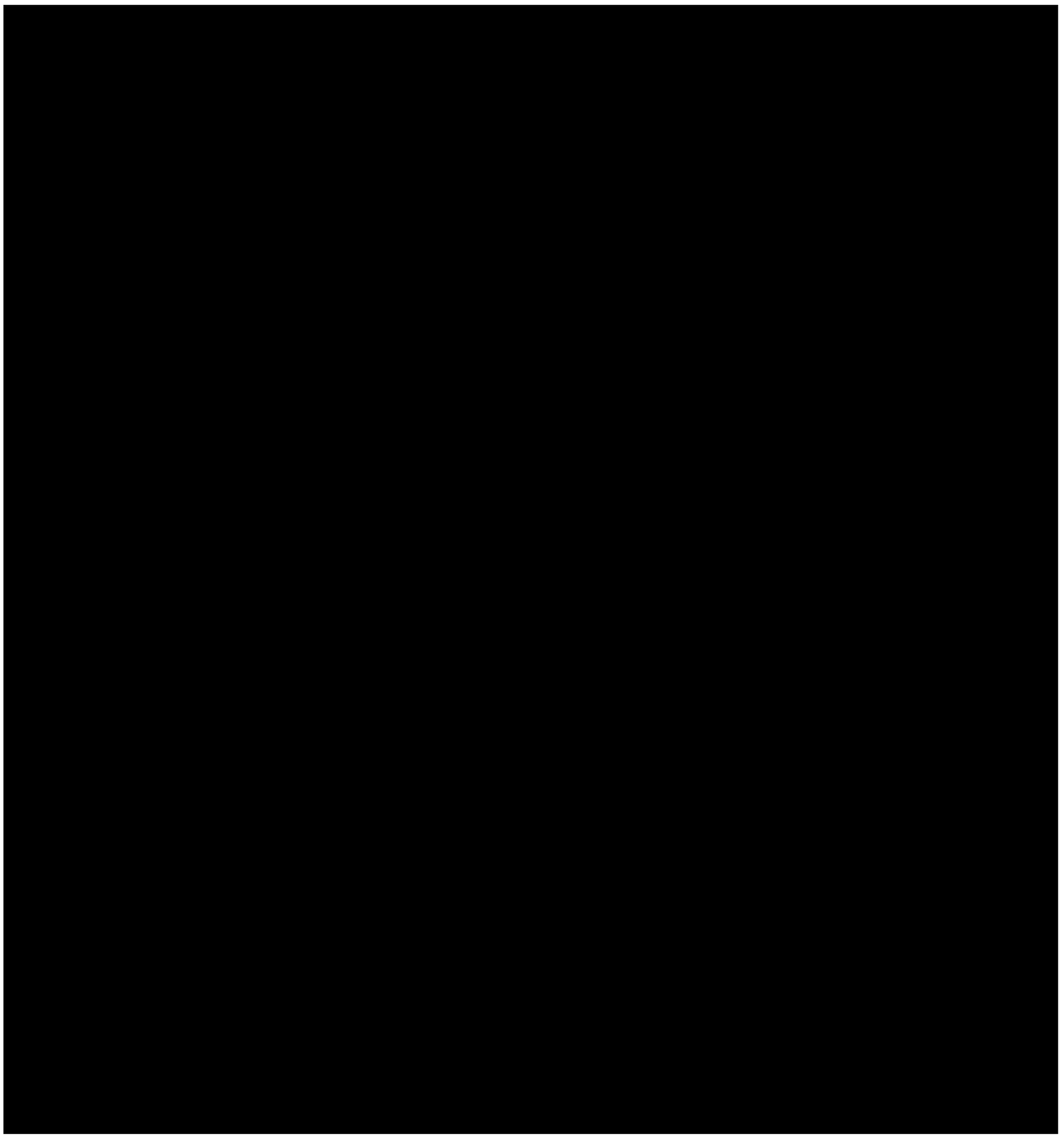

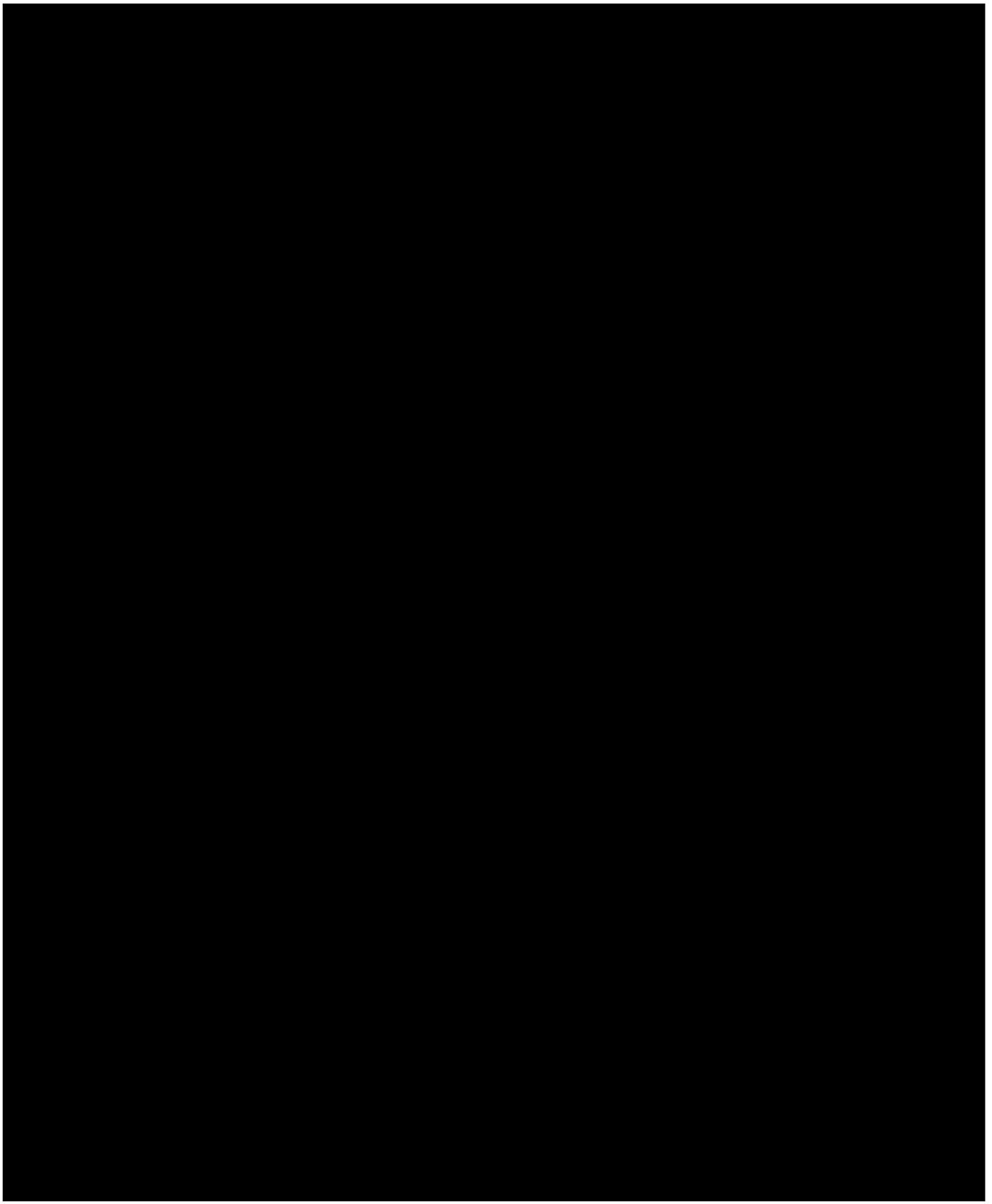

11. Signature Page

Study ID: CMO-US-GI-0429

Version: 1.0

Issue Date: October 18, 2017