Pivotal Trial of WaveLight® EX500 Excimer Laser System for the Correction of Myopia with and without Astigmatism Using InnovEyes™ in Conjunction with InnovEyes™ sightmap

STUDY ID

RFP911-C001

STATISTICAL ANALYSIS PLAN

NCT04219891

Short Title:

Statistical Analysis Plan
RFP911-C001

Full Title:

Statistical Analysis Plan
RFP911-C001

Protocol Title: Pivotal Trial of WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes™ in conjunction with InnovEyes™ sightmap

This is Version 8.0 of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 6.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective of the study is to evaluate the effectiveness and safety of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.

Decision Criteria for Study Success:

The effectiveness criteria will be considered to have been met if the percentage meets or exceeds the target rate at the time of refractive stability for all primary effectiveness endpoints.

The safety criteria will be considered to have been met if the percentage is less than the target rate at the time of refractive stability for all of the primary safety endpoints.

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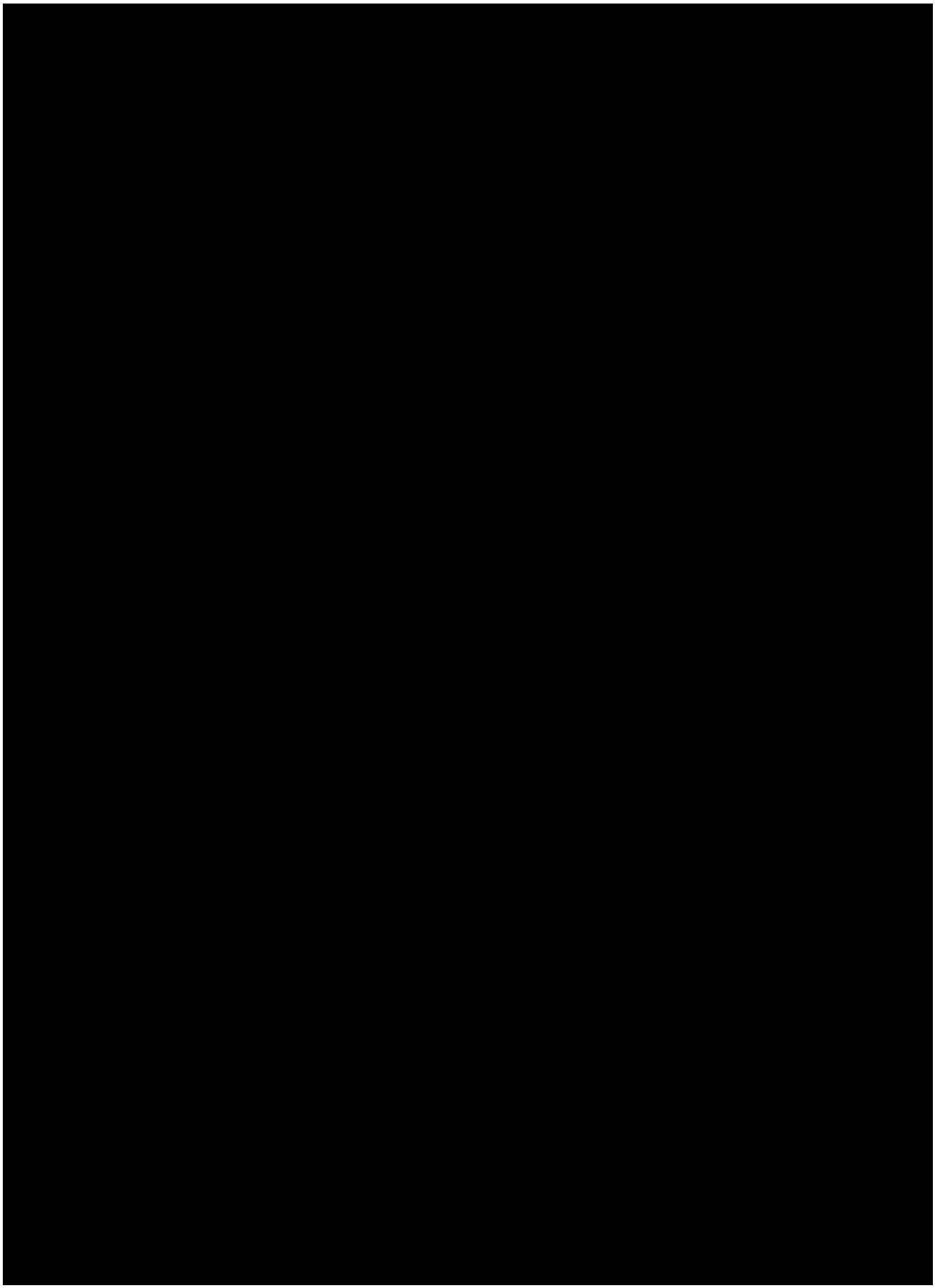

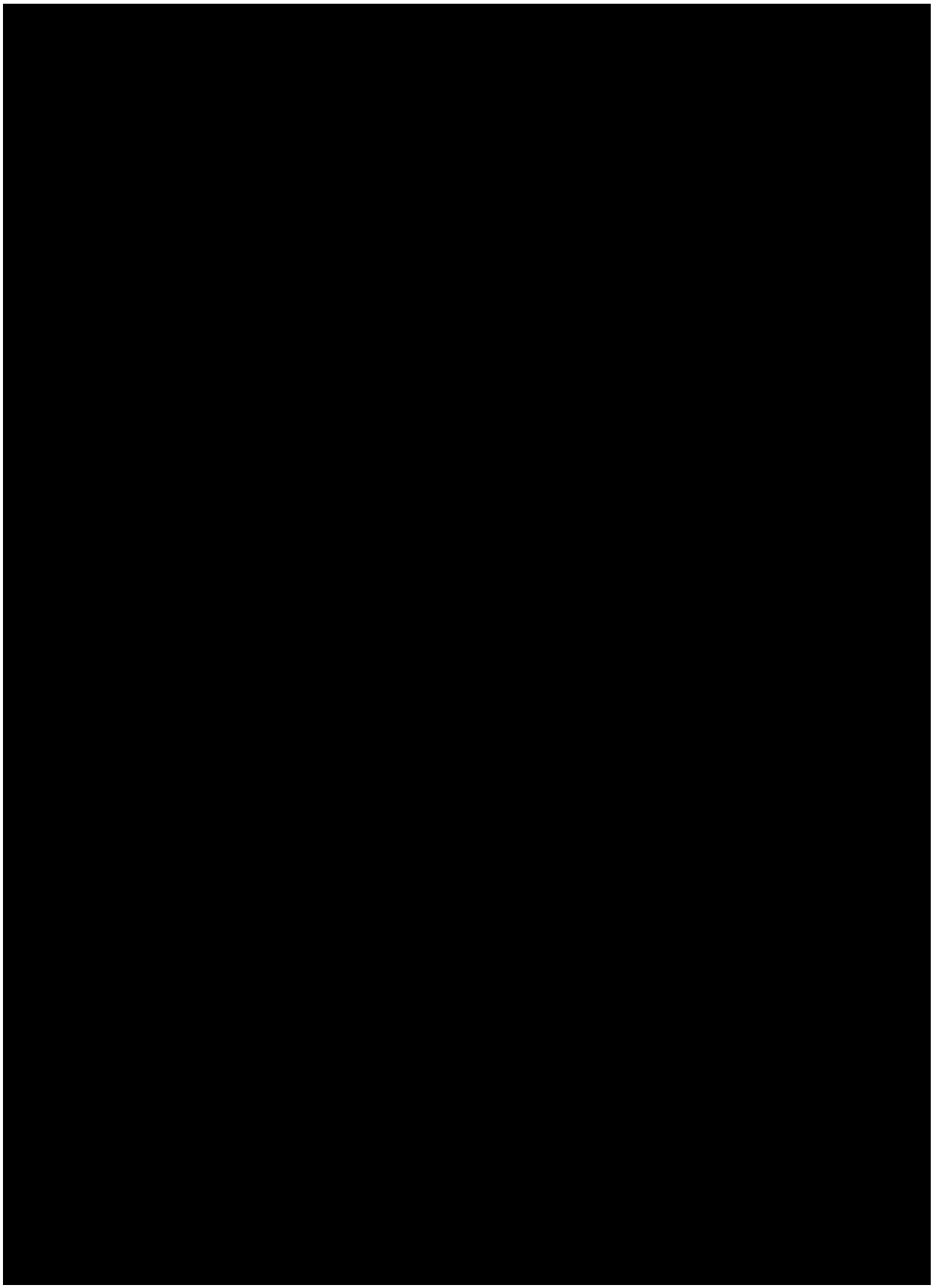

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

The primary objective of the study is to evaluate the effectiveness and safety of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.

1.2 Study Description

This is a prospective, single-arm, multi-center, interventional study with planned bilateral InnovEyes LASIK treatment for subjects requiring refractive correction of myopia with or without astigmatism. All treated eyes will be targeted for emmetropia based upon the InnovEyes sightmap Measured Refraction. The postoperative state of each treated eye will be compared to the preoperative state of the same eye.

Subjects will be evaluated initially for suitability as candidates for bilateral LASIK. Potential subjects willing to participate will be consented and screened. Approximately 187 qualified subjects (up to 374 eyes) will receive bilateral InnovEyes LASIK and be followed for 1 year. Total duration of subject participation is approximately 1 year and includes 9 study visits consisting of Screening, Surgery, 1 day, 1 week, 1 month, 3 month, 6 months, 9 months, and 12 months. Subjects will be enrolled with intent to treat at least 20 eyes in each spherical diopter and each cylindrical diopter range (with only 10 eyes in the highest cylinder bin). Approximately 10 US study sites will participate in this clinical study. It is estimated that enrollment and follow-up of all subjects will take approximately 22 months.

The schedule of study procedures and assessments can be found in Section 10, Appendix – Schedule of Study Procedures and Assessments.

1.3 Randomization

This study is not randomized.

1.4 Masking

This is an open-label study with only WaveLight EX500 excimer laser system using InnovEyes in conjunction with InnovEyes sightmap.

1.5 Interim Analysis

An analysis will be performed once refractive stability is achieved; a final analysis will be performed once the one year follow up is complete.

2 ANALYSIS SETS

All eligible subjects will be screened to determine if they meet all inclusion and no exclusion criteria. Subjects who provide informed consent will be considered enrolled in the study. Evaluability of all subjects will be determined before database lock.

2.1 Safety Analysis Set

The safety analysis set (SAF) will contain all eyes that undergo surgery or attempted surgery (defined as eye drops given for flap treatment); the SAF will be the primary analysis set for the safety analysis.

2.2 Full Analysis Set

The full analysis set (FAS) will contain all eyes that successfully undergo surgery; the FAS will be the primary analysis set for the effectiveness analyses.

2.3 Consistent Cohort Analysis Set

The consistent cohort (CC) will contain all eyes in the FAS that have manifest refraction data at all post-operative visits from one month up to and including the visit where refractive stability is established. The CC will be the primary analysis set for the refractive stability analyses.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics, and baseline characteristics tables (including age, gender, race, and ethnicity; visual acuity, manifest refraction, InnovEyes sightmap measured refraction, and pupil size), listing of screen failures by reason, and listing of subjects excluded from key analysis sets. All descriptive summary statistics will be displayed with n and % for categorical data, and with mean, standard deviation, median, minimum, and maximum for continuous data. Demographic and baseline characteristics will be summarized for the FAS.

4 REFRACTIVE STABILITY

Stability analyses will be performed on eyes that have every follow-up exam from 1-month up to the stability time point (the CC), as well as on the eyes that have 2 consecutive exams, but not necessarily every follow-up exam. The following stability analyses will be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions:

- Percentage of eyes that achieve:
    - a change of less than or equal to 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
    - a change of less than or equal to 0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
- Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
- Mean ± SD MRSE for the preoperative and each postoperative visit;
- Assessment of cylinder stability for correction of spherocylindrical refractive errors;

Refractive stability is achieved at the latter of two postoperative manifest refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, when all of the following recommended criteria are met:

- At least 95% of the treated eyes have a change ≤ 1.00 D of MRSE between the 2 refractions;
- The mean rate of change in MRSE, as determined by a paired analysis, is ≤ 0.5 D per year (0.04 D/month) over the same time period;
- The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;
- The 95% confidence interval for the mean rate of change in MRSE includes zero or a rate of change attributable to normal aging; and
- Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup (at least 80% of the cohort).

The primary safety and effectiveness endpoints for the study can only be evaluated once refractive stability has been established within the CC, as well as on the eyes that had 2 consecutive exams, but not necessarily every follow-up exam.

5 EFFECTIVENESS ANALYSIS STRATEGY

For analysis of refractive outcomes, the spherical component of the manifest and cycloplegic refractions (as tested at 4.0 m) will be adjusted for optical infinity by adding -0.25 D to the spherical magnitude for all post-operative assessments. Similarly, manifest refraction

spherical equivalent (MRSE) will be calculated using the respective adjusted manifest and cycloplegic sphere values.

Unless otherwise specified, MRSE will be based on the subject's manifest refraction, not on the value collected by the sightmap device (measured refraction). Additionally, all visual acuity categories will be determined using logMAR values.

For analyses involving visual acuity, Snellen lines will be based on the conversion from logMAR line ± 2 letters (e.g., 20/20 Snellen = -0.04 to 0.04 logMAR).

Note: Effectiveness analyses based on FAS or CC excludes all data/subjects that have met any of the Data Set Analysis Restrictions (DSARs) identified in the Deviation and Evaluability Plan (DEP).

5.1 Analysis of Primary Effectiveness Endpoints

In order to establish effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap, the following four co-primary endpoints are defined:

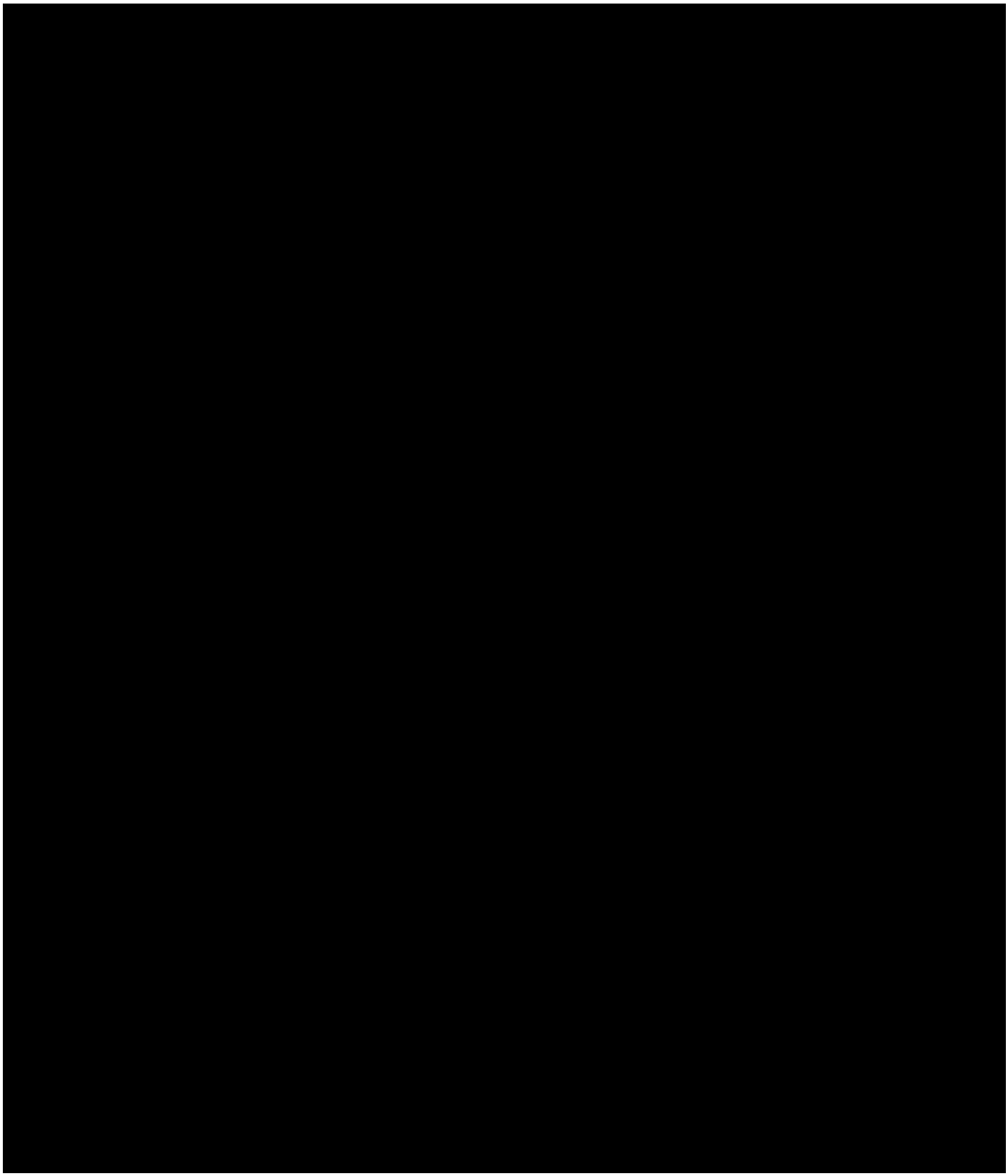
- Percentage of eyes with UCDVA of 20/40 or better (in eyes with preoperative BCDVA of 20/20 or better) at refractive stability (Target: ≥ 85%)
- Percentage of eyes with MRSE within 0.50 D at refractive stability (Target: ≥ 50%)
- Percentage of eyes with MRSE within 1.00 D at refractive stability (Target: ≥ 75%)
- Percentage of eyes that achieve refractive stability (Target: ≥ 95%)

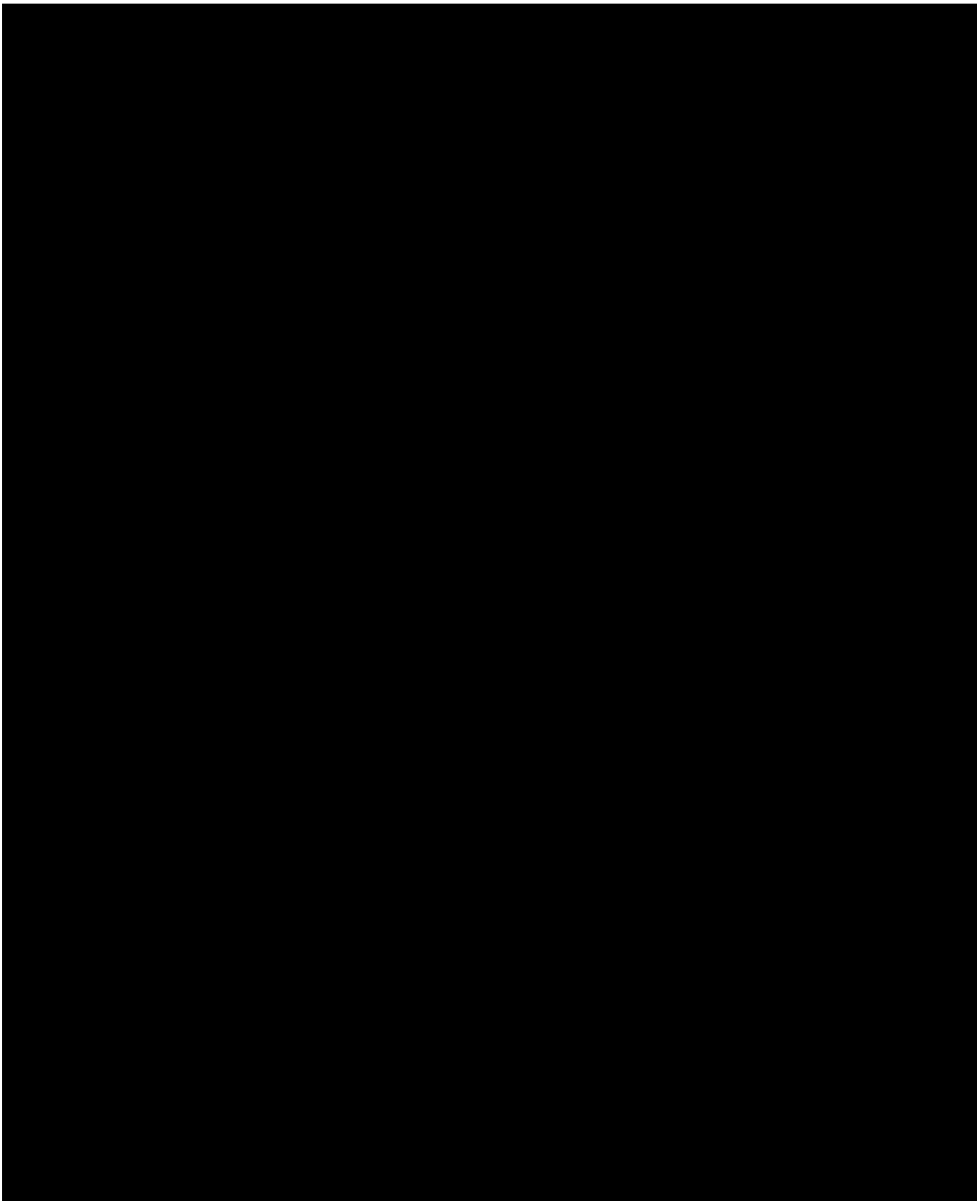
5.1.1 Statistical Hypotheses

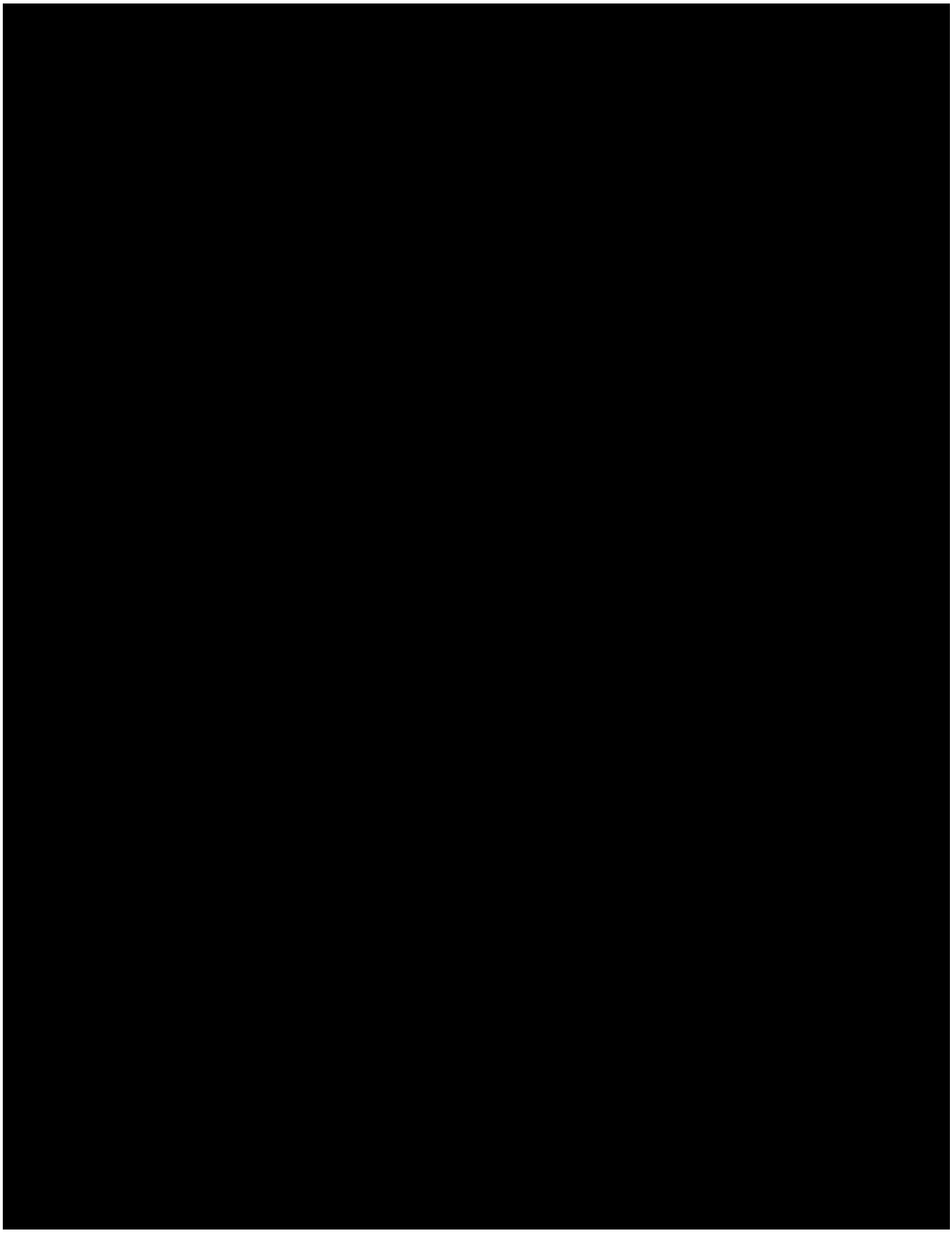
No hypothesis testing of the primary effectiveness endpoints is planned.

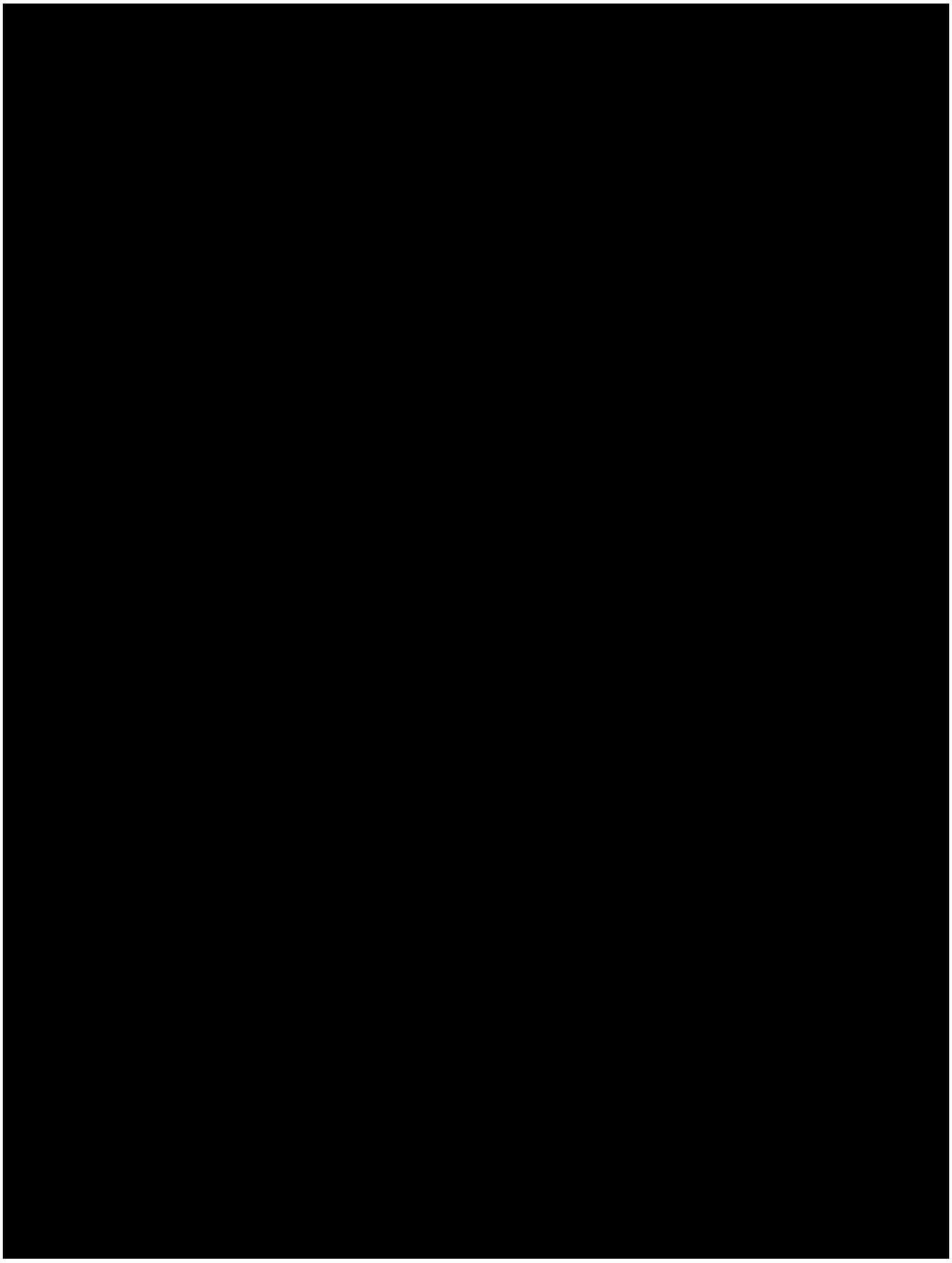
5.1.2 Analysis Methods

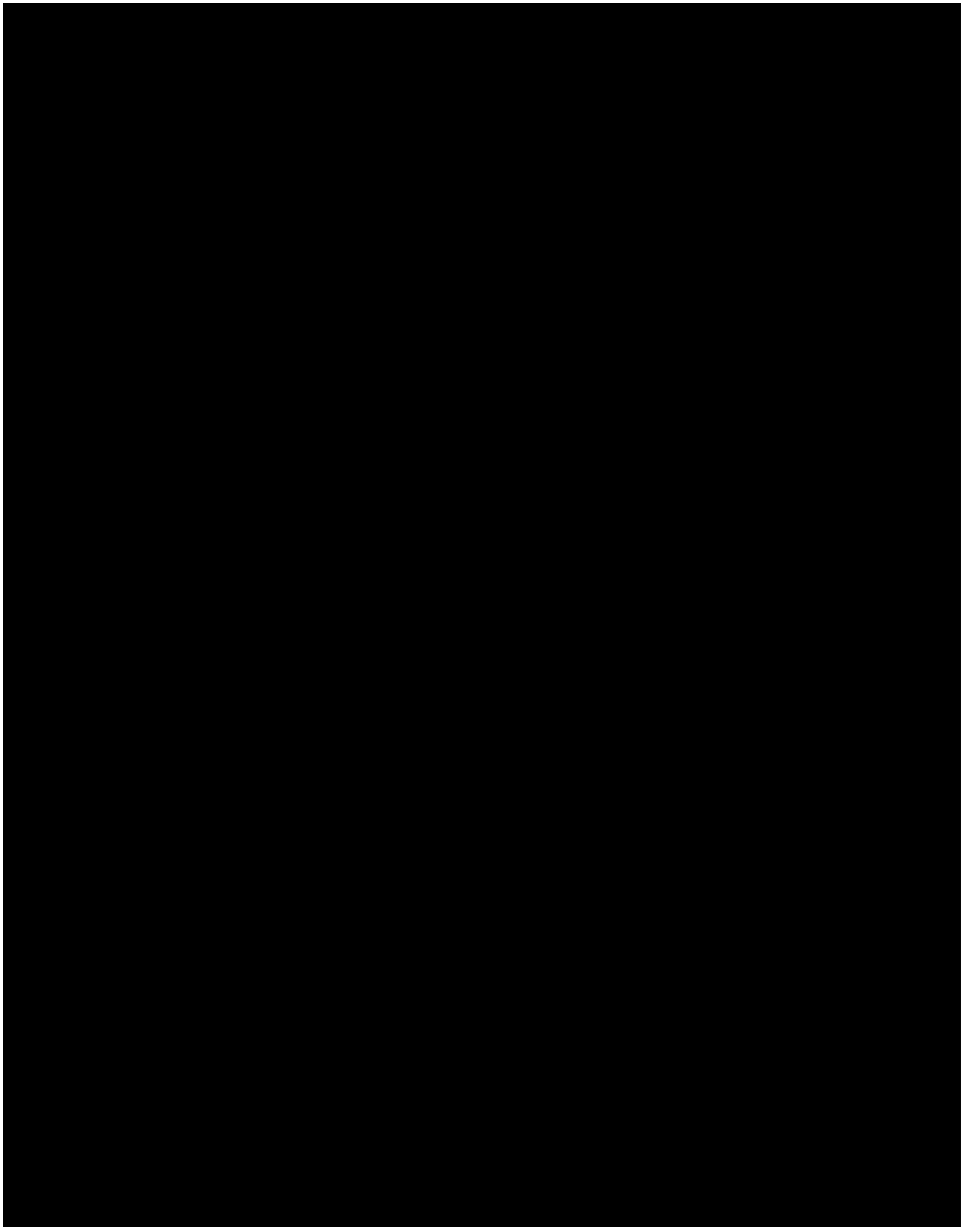
The FAS will be used for this analysis. The number and percentage of eyes meeting each of the primary effectiveness endpoints will be calculated. The effectiveness criteria will be considered to have been met if the percentage meets or exceeds the target rate at the time of refractive stability for all primary effectiveness endpoints. These analyses will be performed for the whole FAS [redacted]. An analysis will be performed once refractive stability is achieved; a final summary of these endpoints will be performed once the one year follow up is complete.

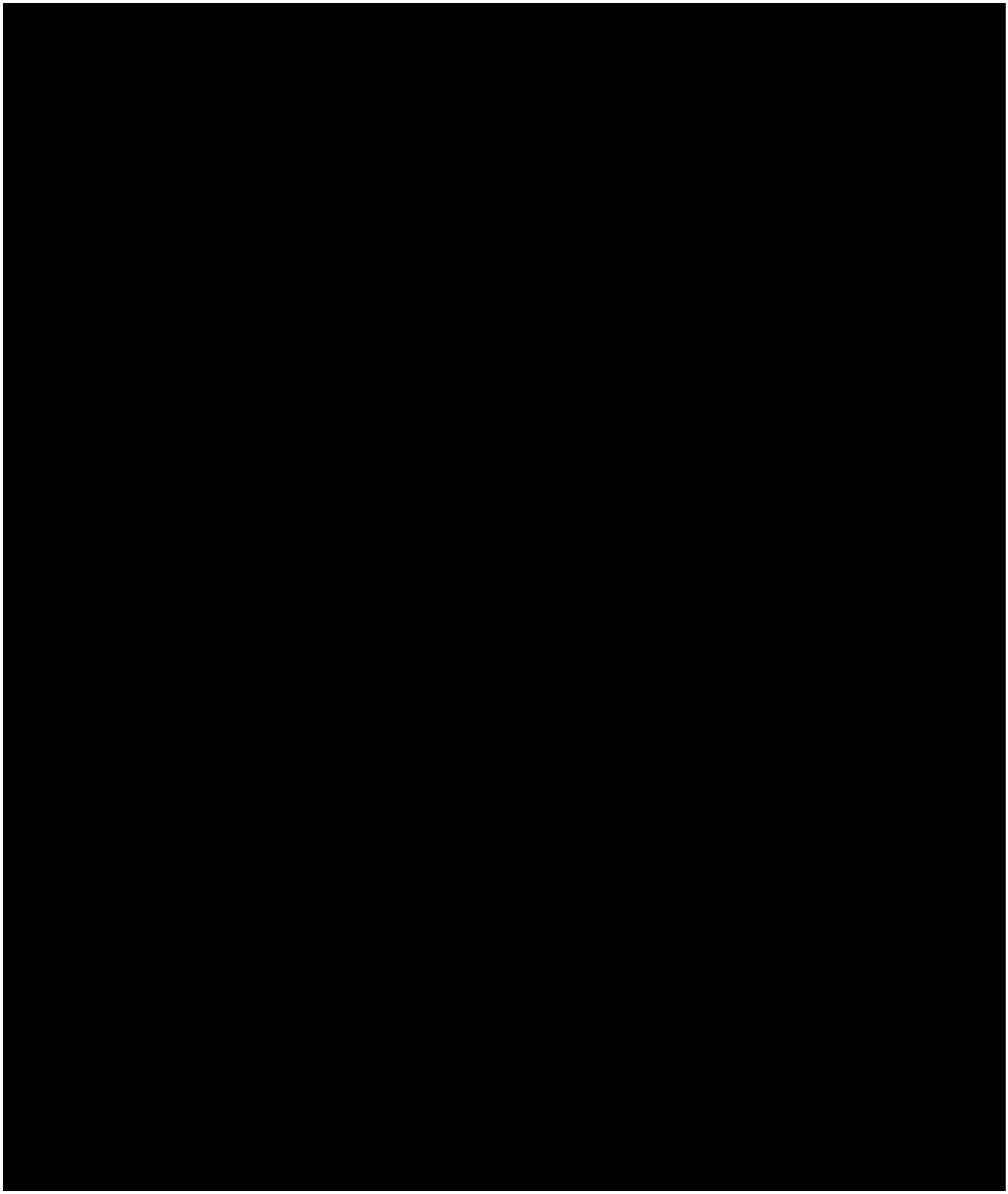


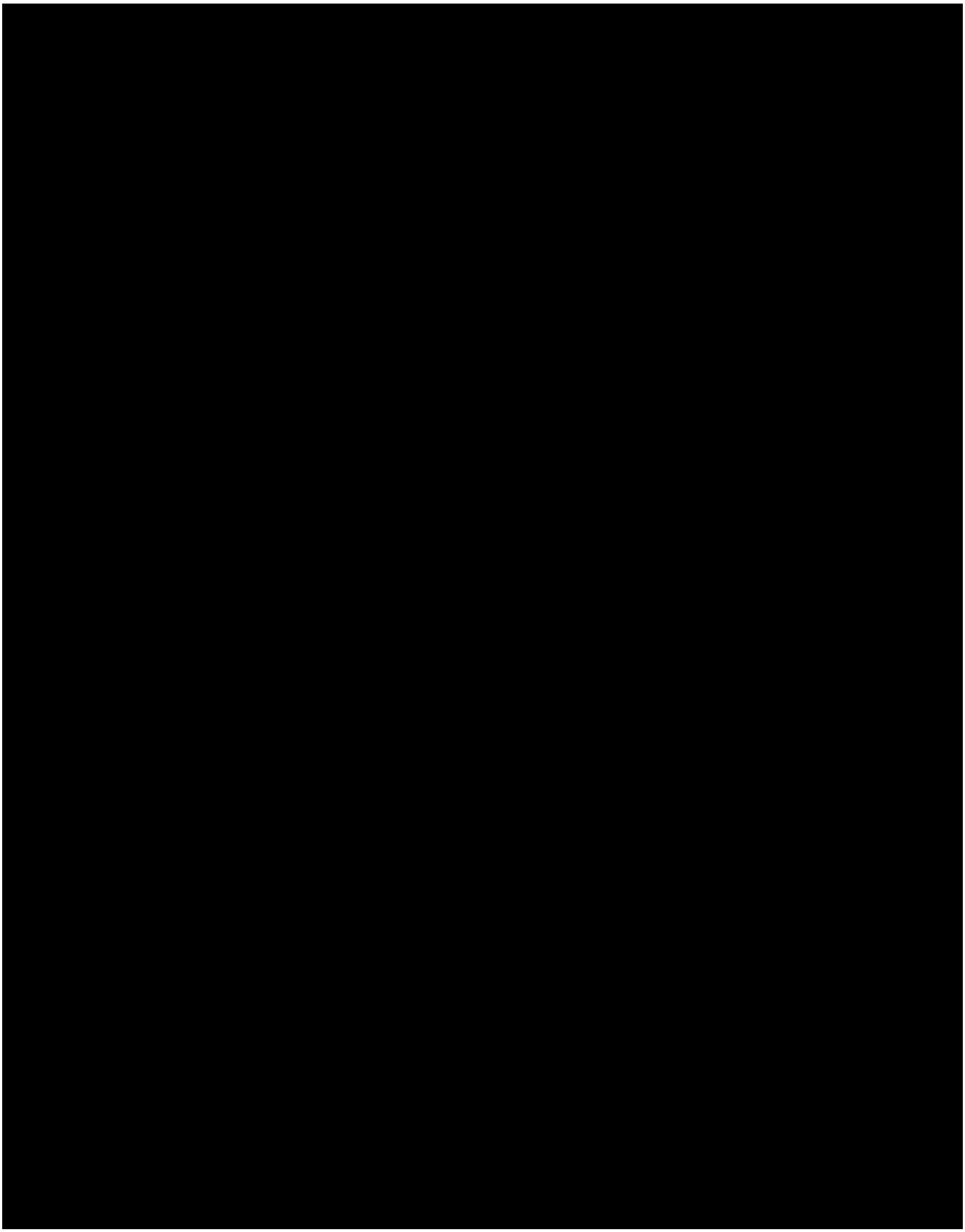


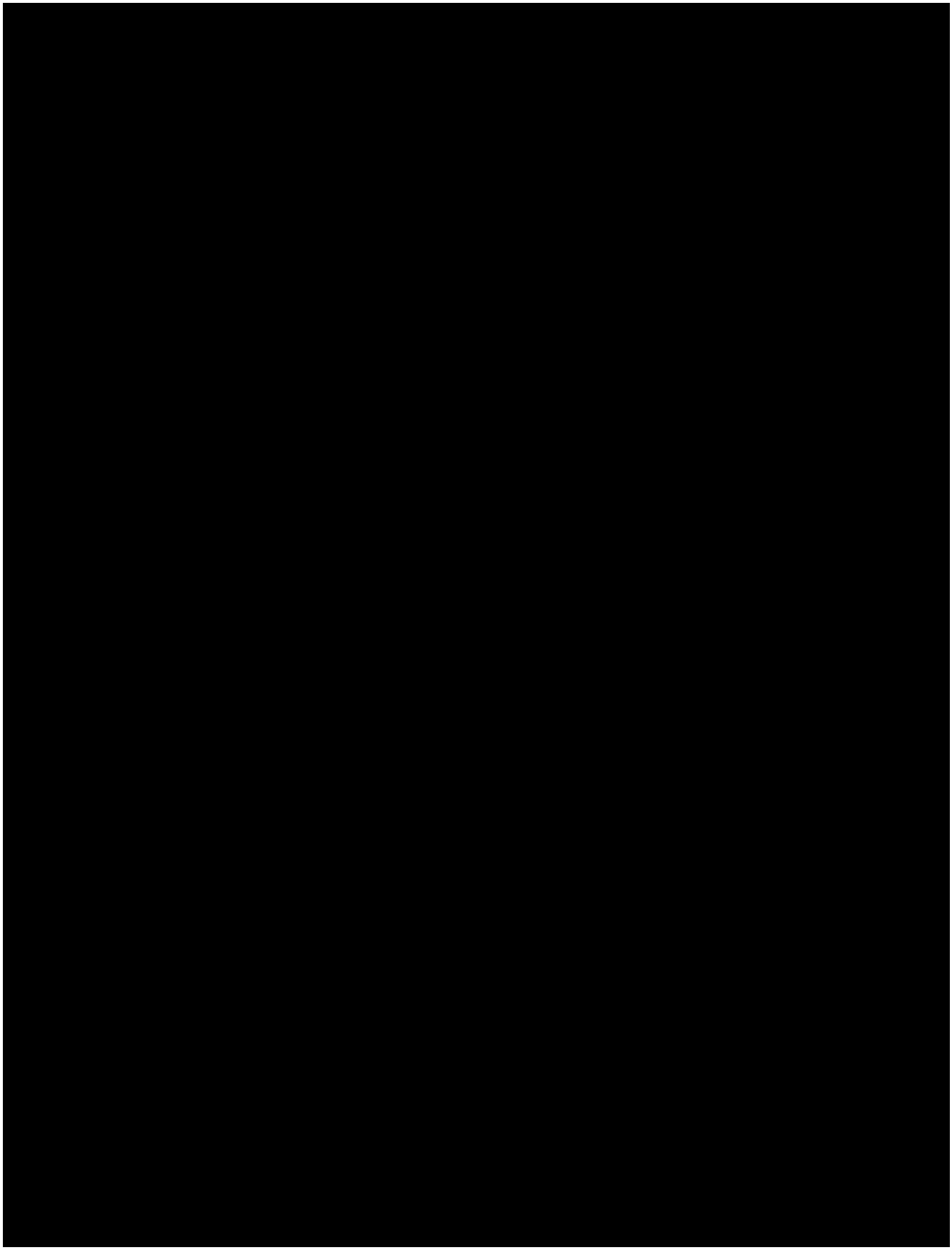


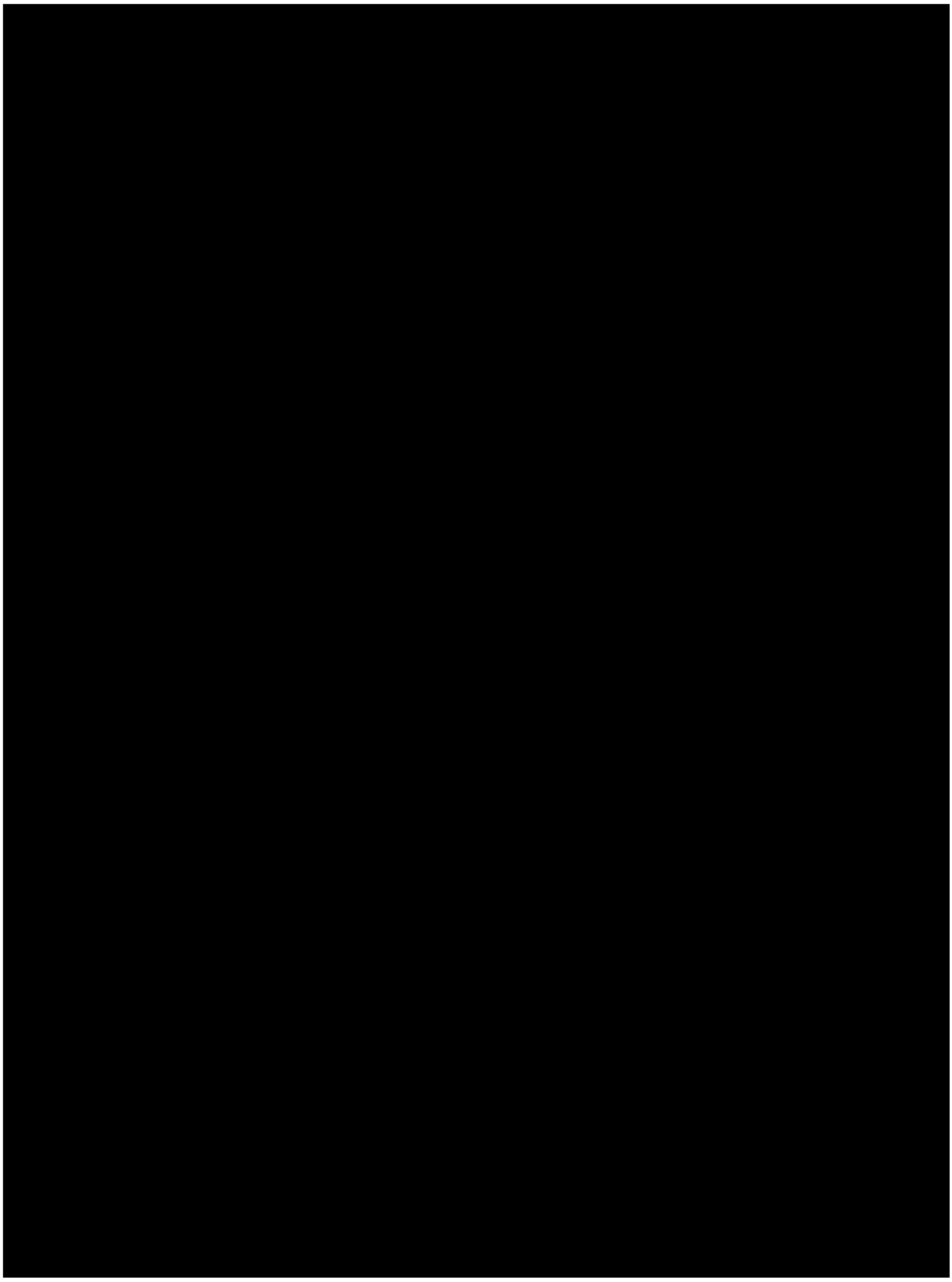


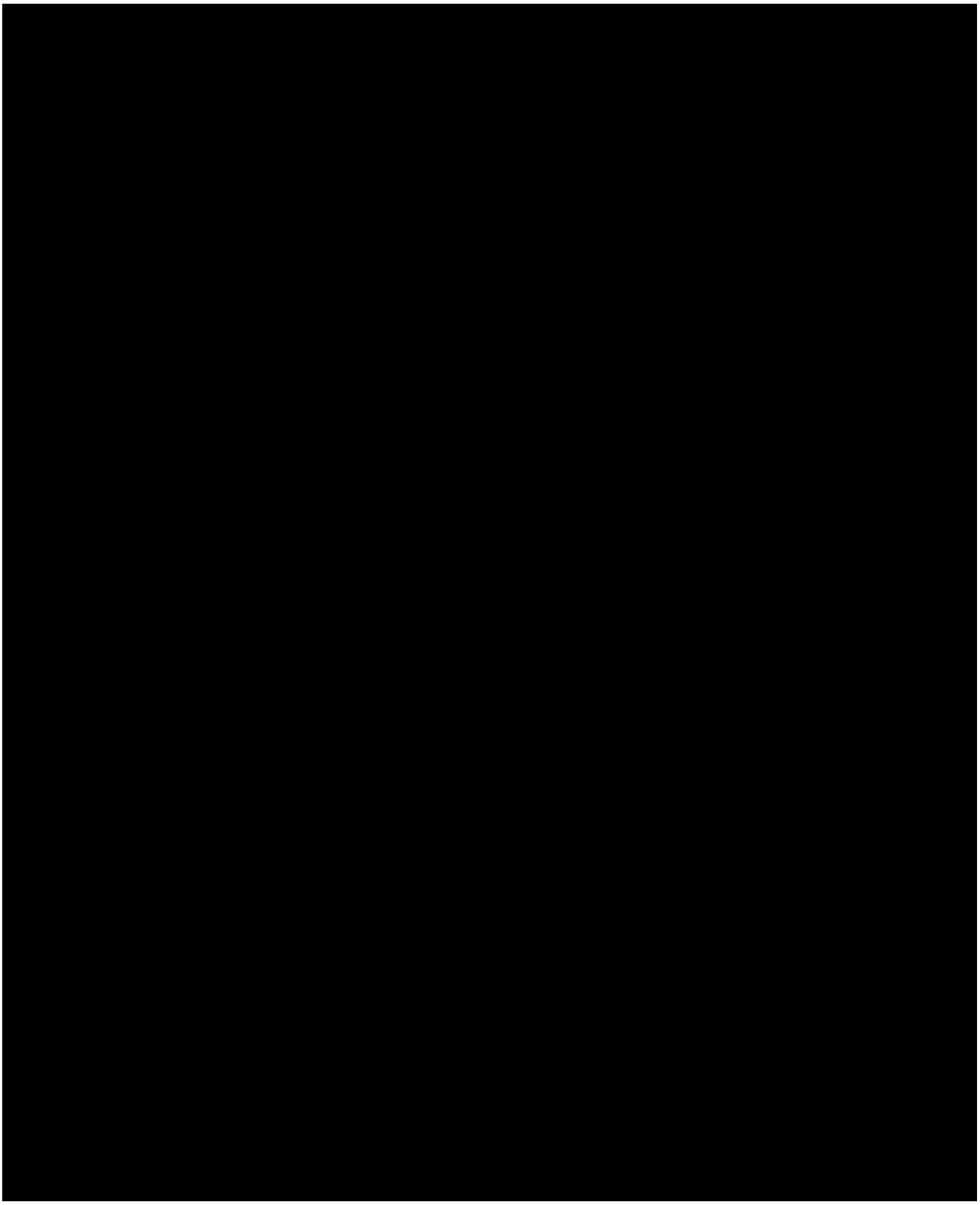












6 SAFETY ANALYSIS STRATEGY

All adverse events occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the SAF through descriptive summaries (counts and percentages) and listings. In addition, separate subject listings will be provided for AEs that occur in subjects:

- after signing informed consent but prior to exposure to IP (InnovEyes sightmap)

- exposed to IP (InnovEyes sightmap) but do not proceed to InnovEyes treatment (and thus are not included in the SAF)

Note: For analysis of refractive outcomes, the spherical component of the manifest and cycloplegic refractions (as tested at 4.0 m) will be adjusted for optical infinity by adding -0.25 D to the spherical magnitude for all post-operative assessments. Similarly, manifest refraction spherical equivalent (MRSE) will be calculated using the respective adjusted manifest and cycloplegic sphere values.

Unless otherwise specified, MRSE will be based on the subject's manifest refraction, not on the value collected by the sightmap device (measured refraction). Additionally, all visual acuity categories will be determined using logMAR values.

For analyses involving visual acuity, Snellen lines will be based on the conversion from logMAR line ± 2 letters (e.g., 20/20 Snellen = -0.04 to 0.04 logMAR).

6.1 Analysis of Primary Safety Endpoints

In order to establish safety of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap, the following four co-primary endpoints are defined:

- Percentage of eyes that lose 2 lines or more of BCDVA (Target at refractive stability ≤ 5%)
- Percentage of eyes with BCDVA worse than 20/40 (for eyes with BCDVA of 20/20 or better pre-op) (Target at refractive stability ≤ 1%)
- Percentage of eyes that have an increase of manifest refractive astigmatism of greater than 2.00 D of absolute cylinder as compared to the preoperative refraction (Target at refractive stability ≤ 5%)
- Percentage of eyes with a serious, non-flap related, ocular adverse event at the postoperative visits (Target per event type at refractive stability: ≤ 1%)

6.1.1 Statistical Hypotheses

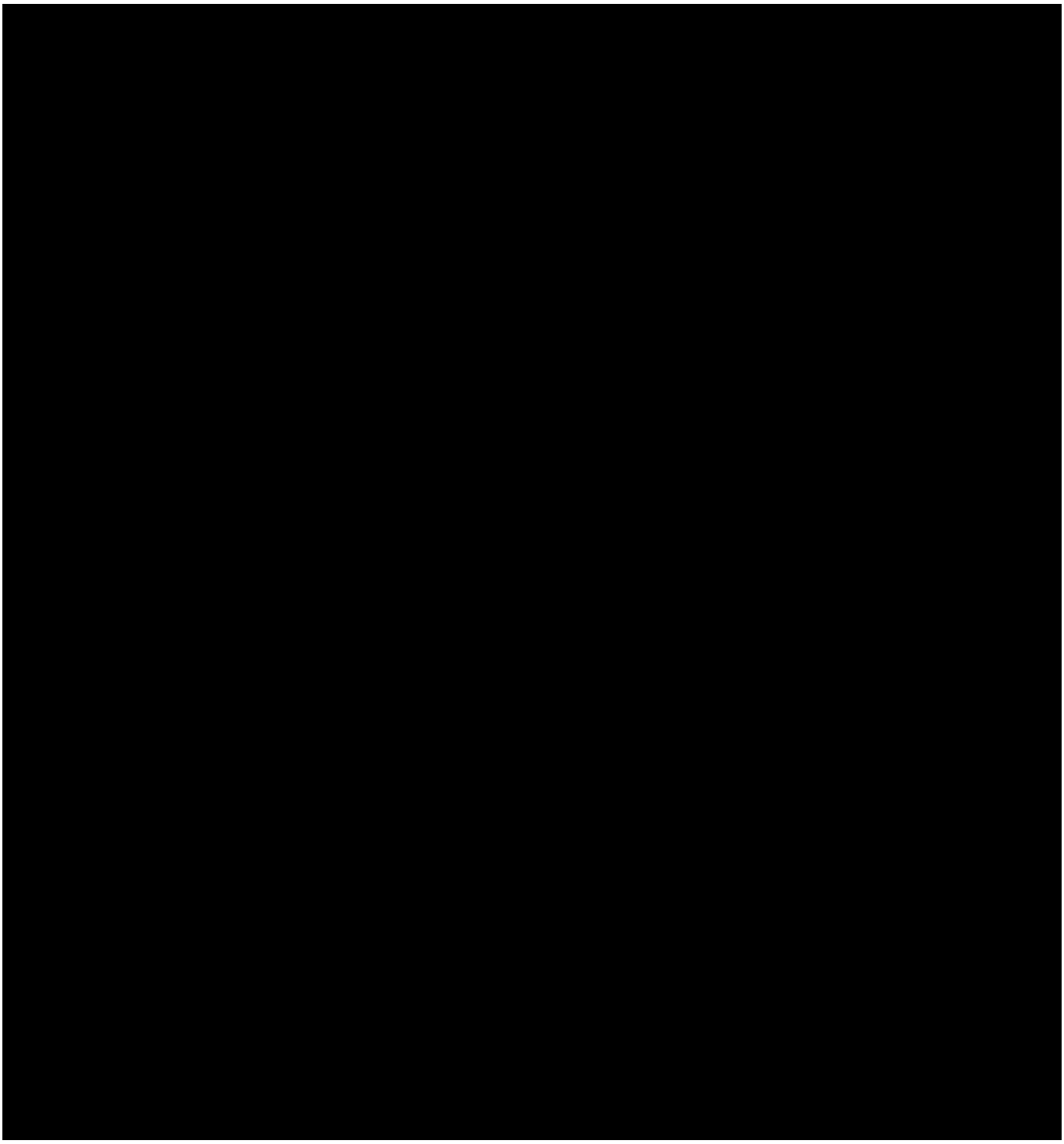
No hypothesis testing of the primary safety endpoints is planned.

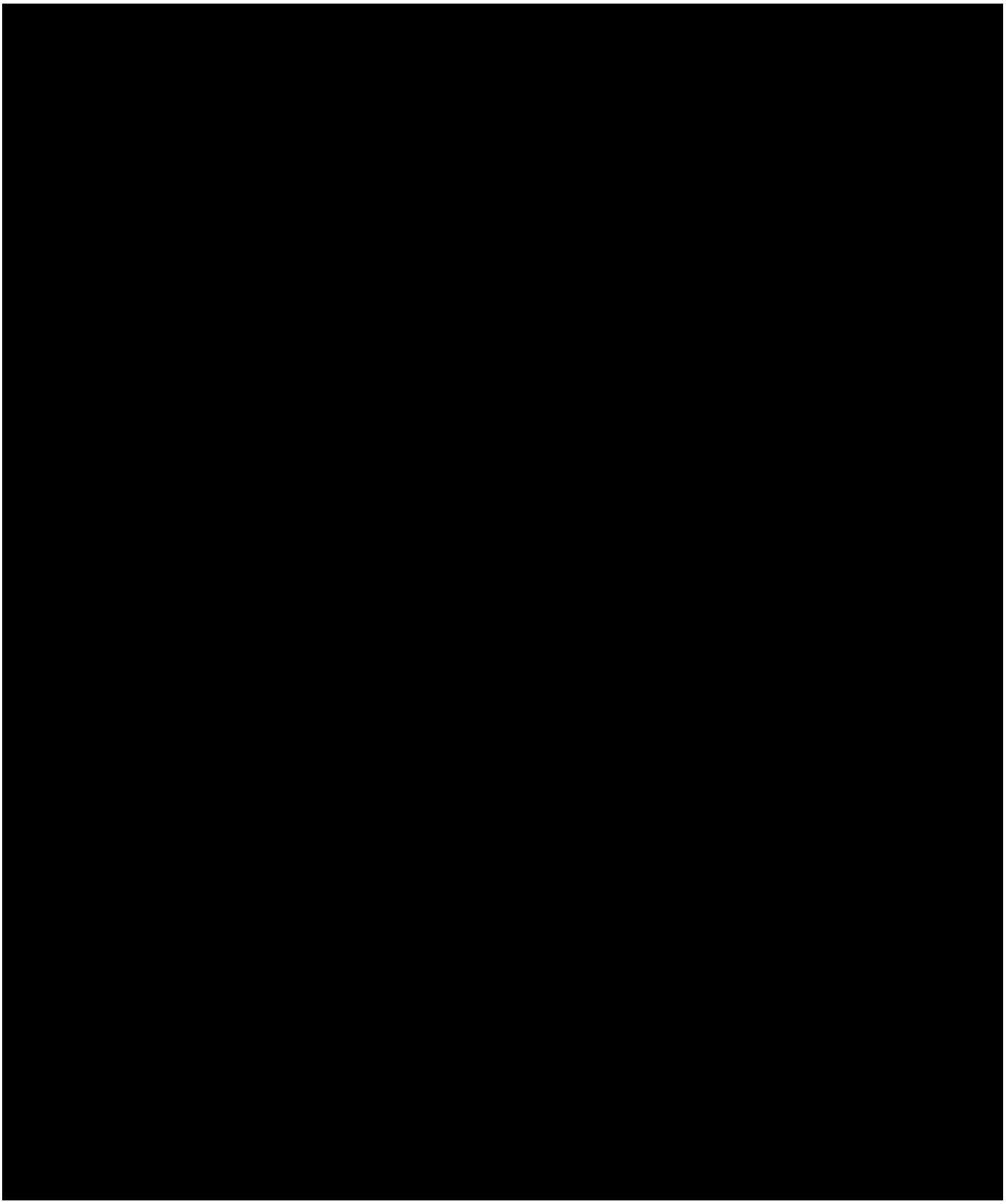
6.1.2 Analysis Methods

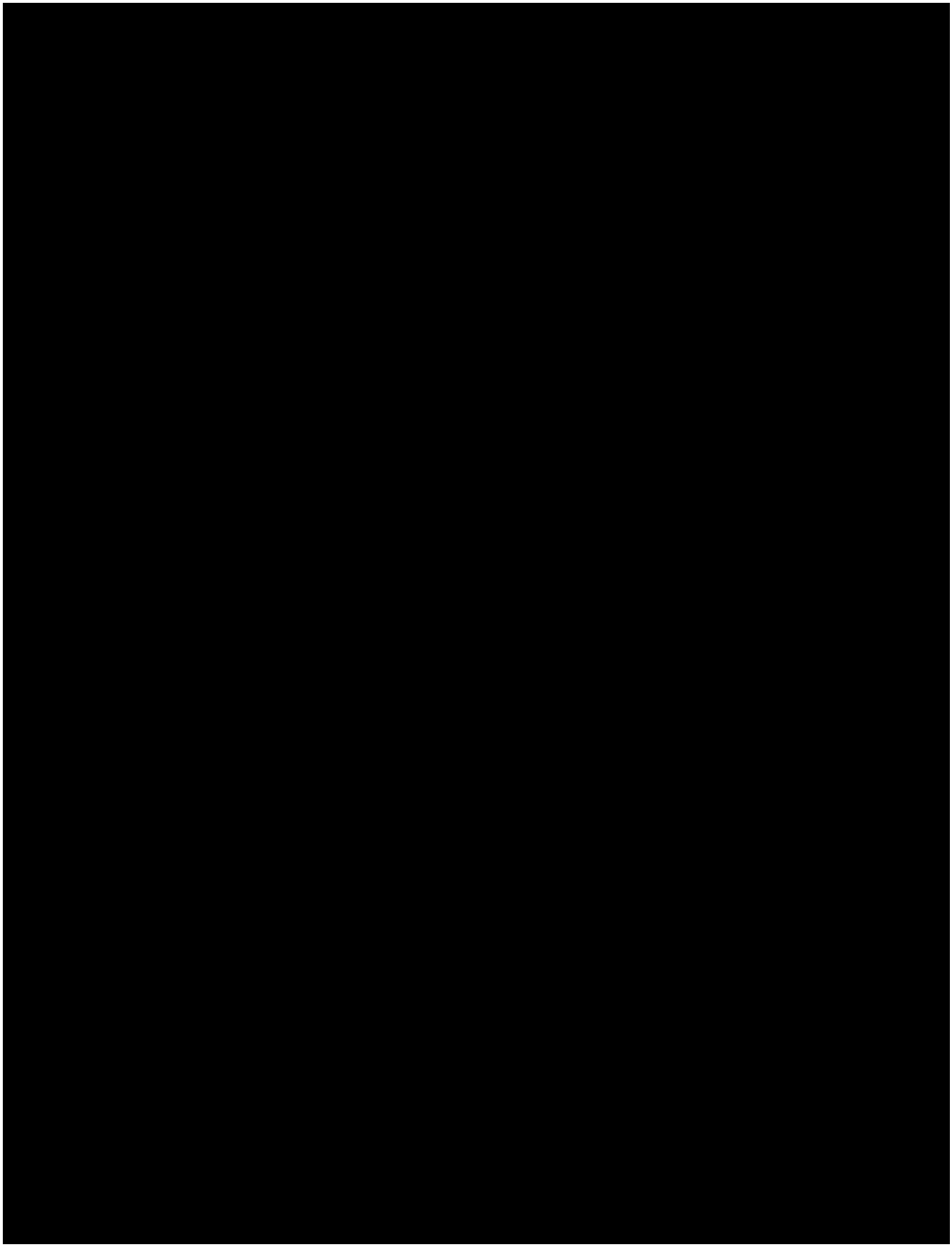
The SAF will be used for this analysis. The number and percentage of eyes experiencing each of the primary safety endpoints will also be calculated. The safety criteria will be considered to have been met if the percentage is less than the target rate at the time of refractive stability

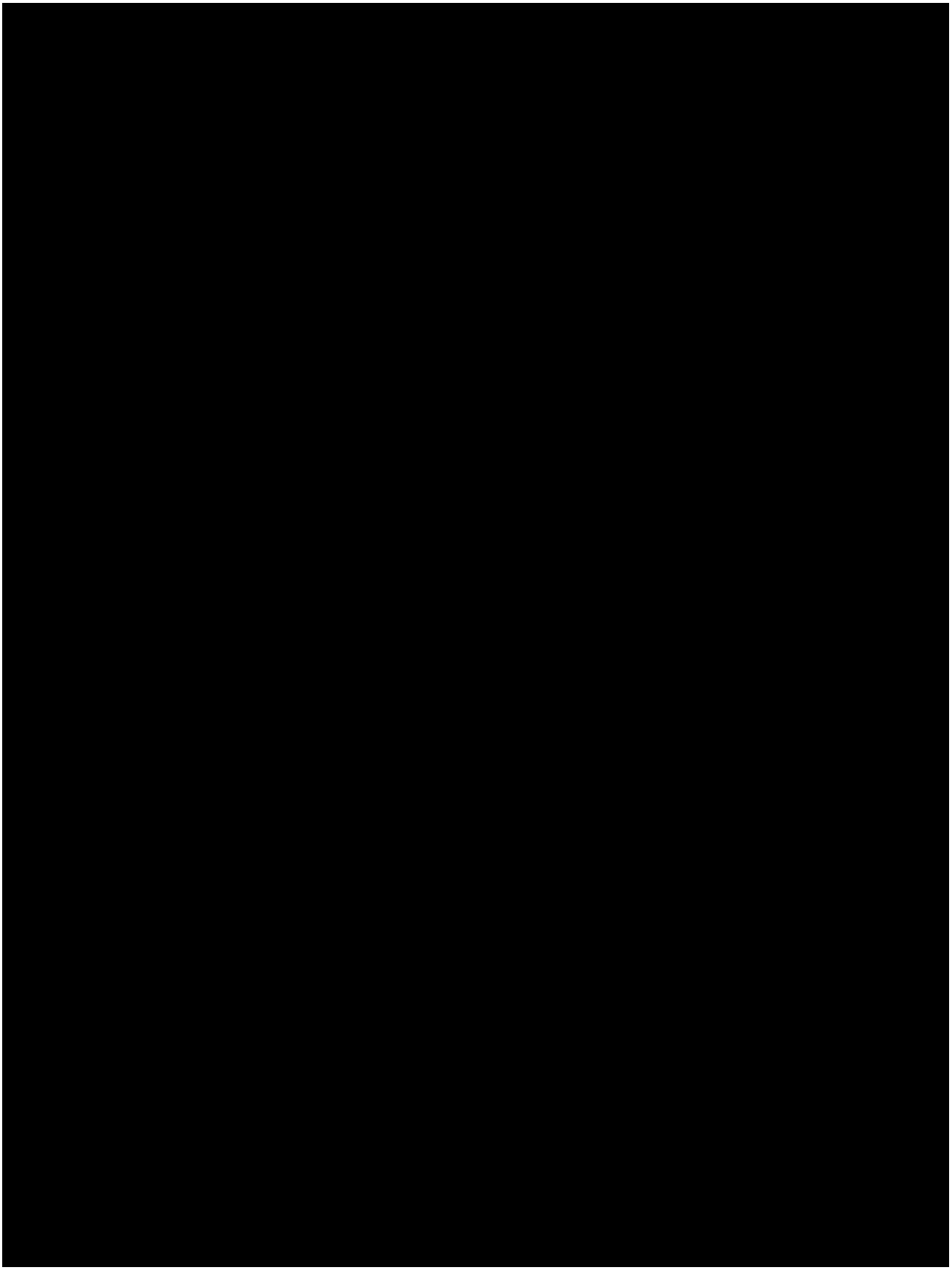
for all of the primary safety endpoints. Adverse events that are non-flap related will be indicated as such on the adverse event CRF. It should be noted that the percentage of eyes with a serious, non-flap related, ocular adverse event will be compared to the 1% target by adverse event type (not for all ocular adverse event types combined).

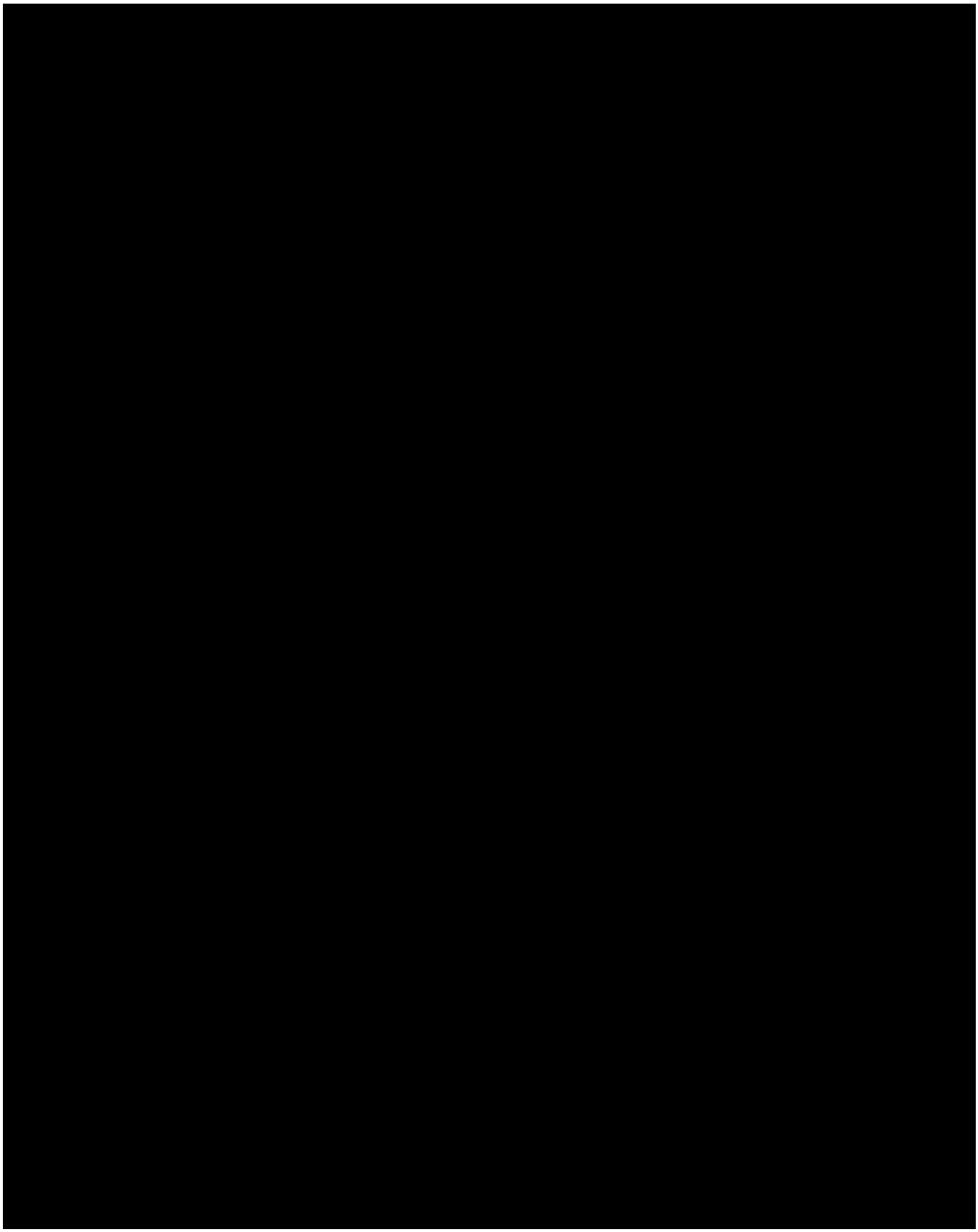
Summary statistics for the primary safety endpoints will be presented by site, race and ethnicity, age (> 21 years old vs. ≤ 21 years old), and by gender.











6.3 Interim Analysis for Safety

An analysis will be performed once refractive stability is achieved; a final analysis will be performed once the one year follow up is complete.

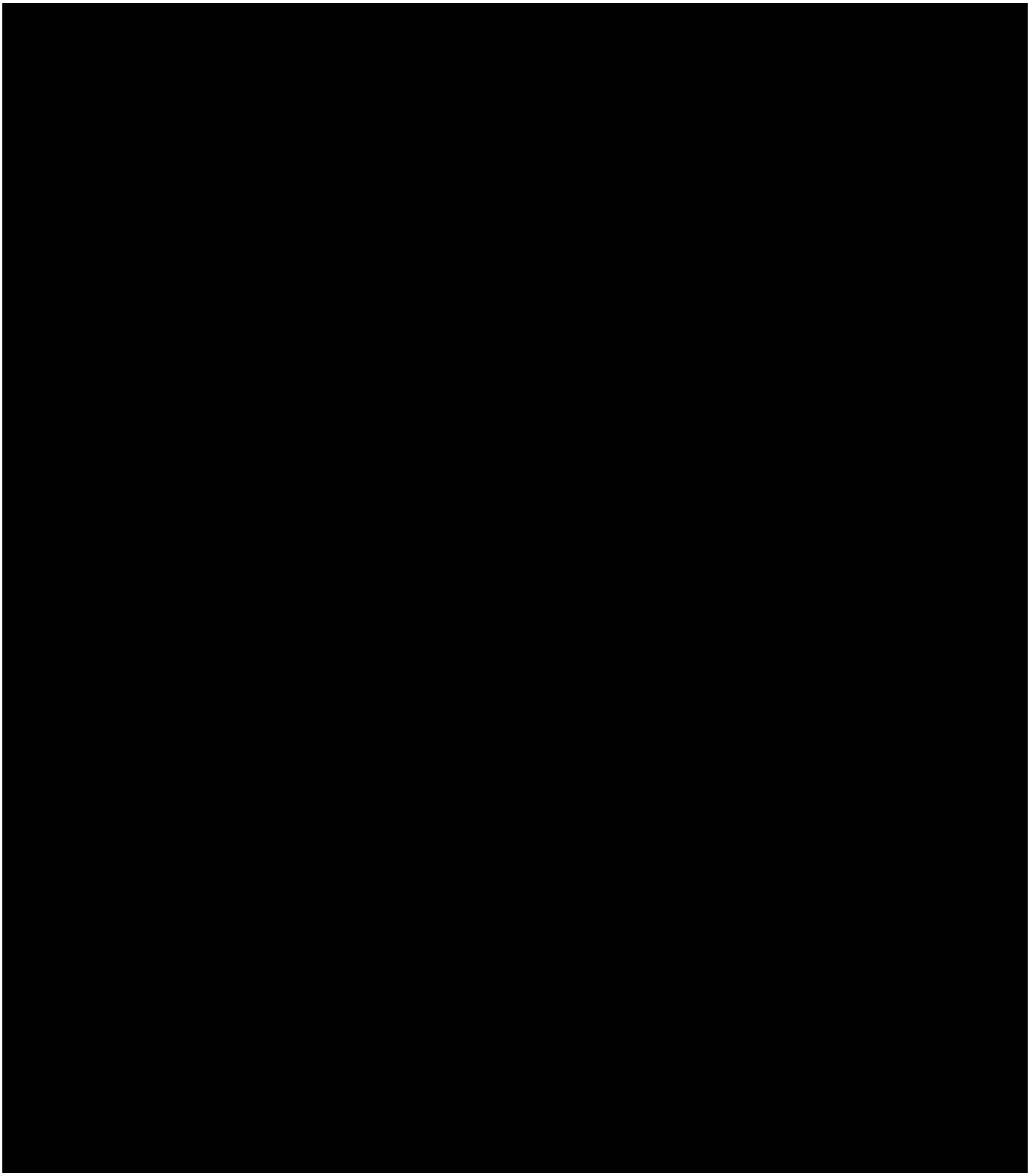
7 SAMPLE SIZE AND POWER CALCULATIONS

Up to 374 eyes will be treated in this study. With 374 eyes treated, any ocular serious adverse event type that occurs in at least 1% of the population undergoing the procedure will be observed in this study at least one time, with approximately 95% probability. This is in accordance with ANSI Z80.11-2012(R2017).

8 REFERENCES

Eydelman MB, Drum B, Holladay J, Hilmantel G, Kezirian G, Durrie D, Stulting RD, Sanders D, Wong B. “Standardized analyses of correction of astigmatism by laser systems that reshape the cornea”. J Refract Surg. 2006 Jan-Feb; 22(1):81-95.

Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., & Hays, R. D. “Development of the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25)”. Archives of Ophthalmology 2001, 119, 1050-1058.



10 APPENDIX- SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS

Table 10-1 Schedule of Study Procedures and Assessments

		Screening[1]	Surgery	Postoperative							Other	
		Visit 0	Visit 00 / Visit 00A[2]	Visit 1 / Visit 1A	Visit 2 / Visit 2A	Visit 3 / Visit 3A	Visit 4 / Visit 4A	Visit 5 / Visit 5A	Visit 6 / Visit 6A	Visit 7 / Visit 7A	Early Exit	USV[3]
Procedure/ Assessment		**Day -30 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
Informed Consent		X										
Inclusion/Exclusion		X	X[4]									
Demographics		X										
Medical History		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[5]*		X										
Cycloplegic Refraction		X						X				
Mesopic pupil size		X				X	X	X	X	X	X	
InnovEyes sightmap	Aberrometry	X[6]				X	X	X	X	X	X	
	Biometry	X[6]				X	X	X	X	X	X	
	Keratometry	X[6]				X	X	X	X	X	X	
	Pachymetry (Corneal	X[6]				X	X	X	X	X	X	
	Topography*	X[6]				X	X	X	X	X	X	

	Screening[1]	Surgery	Postoperative							Other	
	Visit 0	Visit 00 / Visit 00A[2]	Visit 1 / Visit 1A	Visit 2 / Visit 2A	Visit 3 / Visit 3A	Visit 4 / Visit 4A	Visit 5 / Visit 5A	Visit 6 / Visit 6A	Visit 7 / Visit 7A	Early Exit	USV[3]
Procedure/ Assessment	**Day -30 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
Wavefront Refraction	X[6]				X	X	X	X	X	X	
UCDVA	X		X	X	X	X	X	X	X	X	X
Manifest/Subjective Refraction[7]	X			X	X	X	X	X	X	X	
BCDVA	X			X	X	X	X	X	X	X	
UCNVA	X						X				
[redacted]											
IOP	X				X	X	X	X	X	X	X
Slit Lamp Examination	X		X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X						X			X	X
InnovEyes LASIK Planning	X										
InnovEyes LASIK		X									
[redacted]											
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

	Screening[1]	Surgery	Postoperative							Other	
	Visit 0	Visit 00 / Visit 00A[2]	Visit 1 / Visit 1A	Visit 2 / Visit 2A	Visit 3 / Visit 3A	Visit 4 / Visit 4A	Visit 5 / Visit 5A	Visit 6 / Visit 6A	Visit 7 / Visit 7A	Early Exit	USV[3]
Procedure/ Assessment	**Day -30 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
Device Deficiencies	X	X	X	X	X	X	X	X	X	X	X

[1] Screening should cover evaluation of both eyes with intent for bilateral treatment on the same surgery day

[2] 'A' denotes visit for 2nd eye treated

[3] Unscheduled visit - other study assessments may be performed per the Investigator's discretion

[4] Confirm inclusion/exclusion criteria as needed

[5] Required only for women of child-bearing age, not postmenopausal or surgically sterile

[6] Measured twice, once with cycloplegia and once for treatment planning

[7] Subjective Refraction to assess for inclusion stability at Screening (Visit 0) should be performed on the site's chart; subjective refraction for VA testing for VA testing will be refraction on sponsor provided electronic chart

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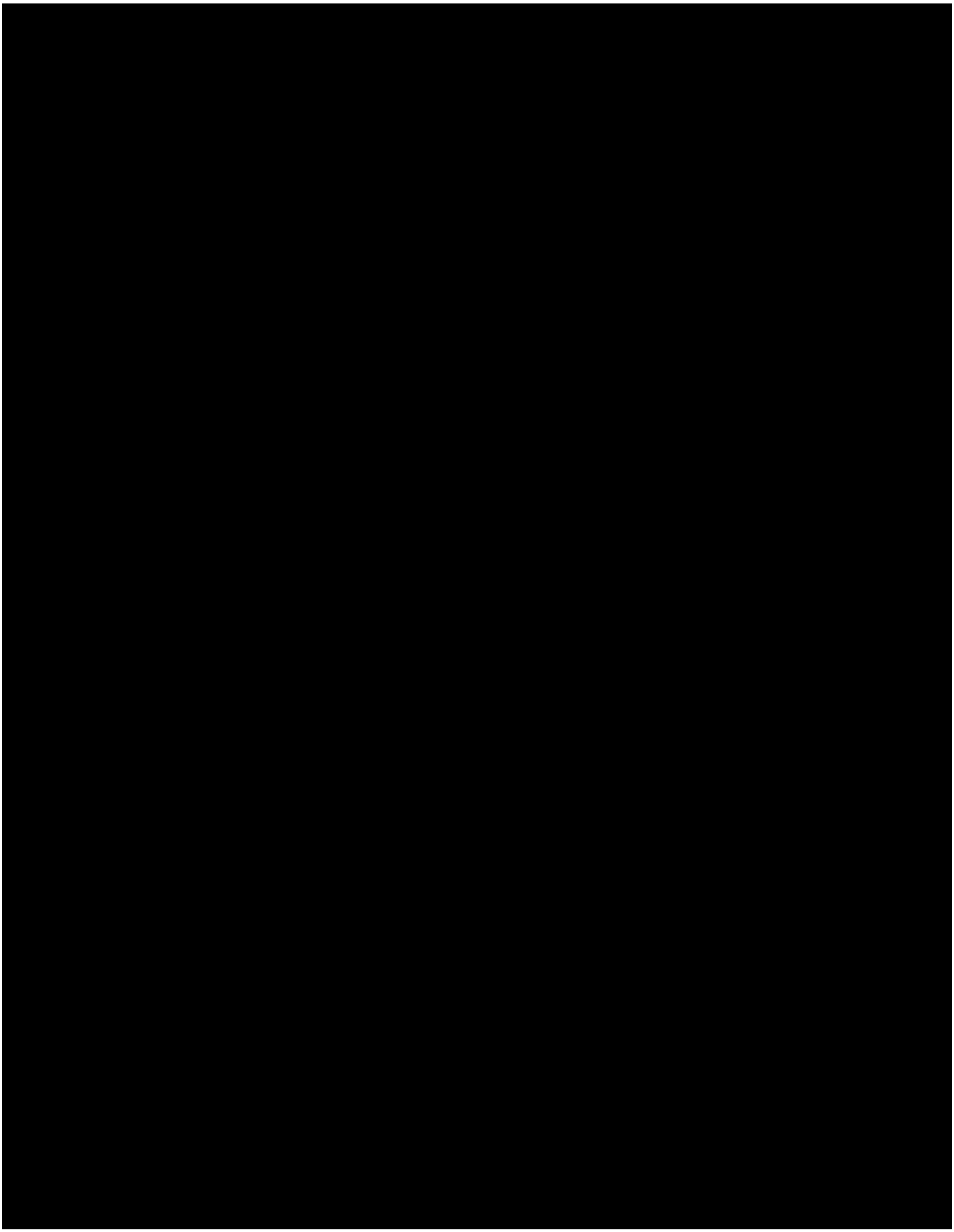
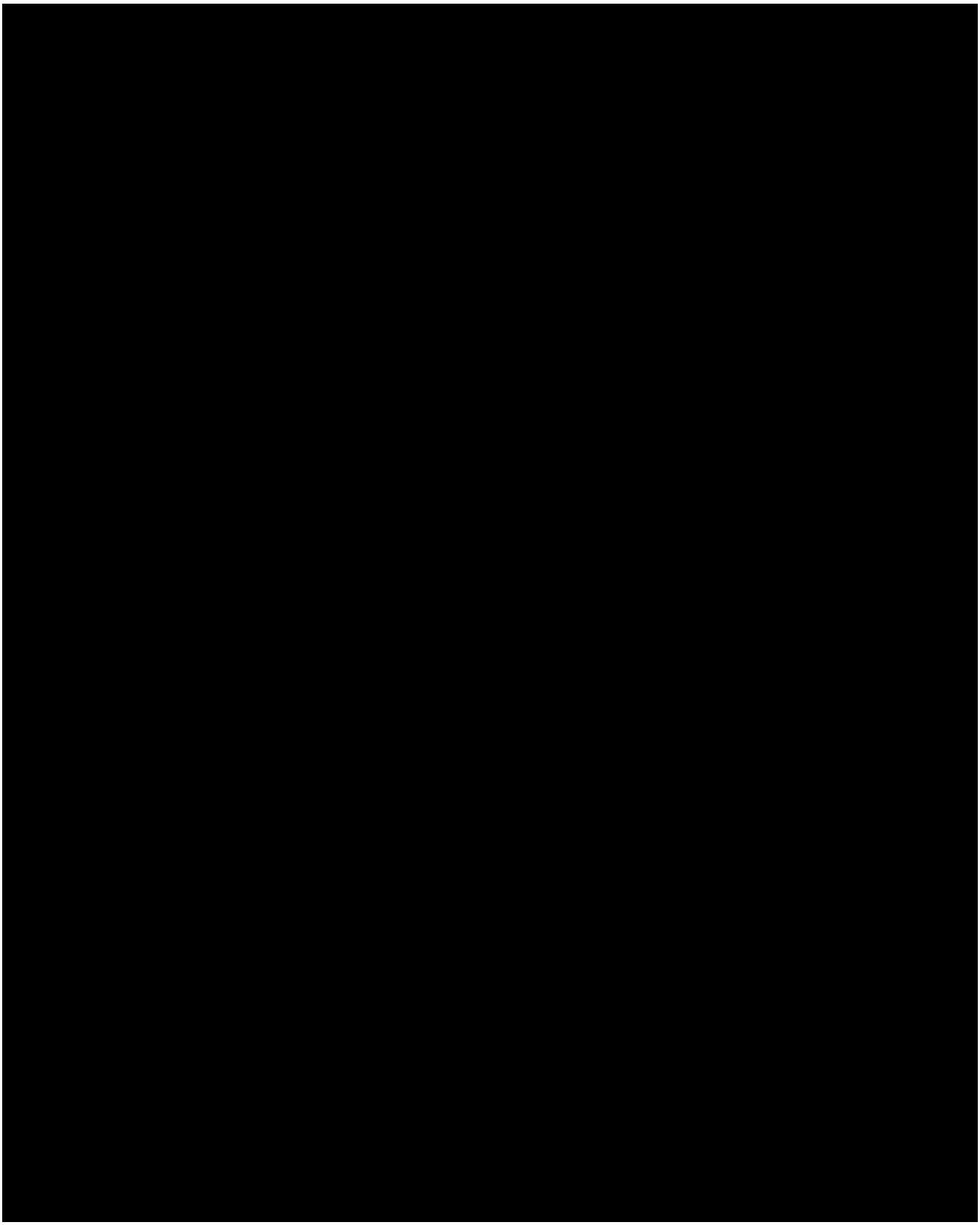
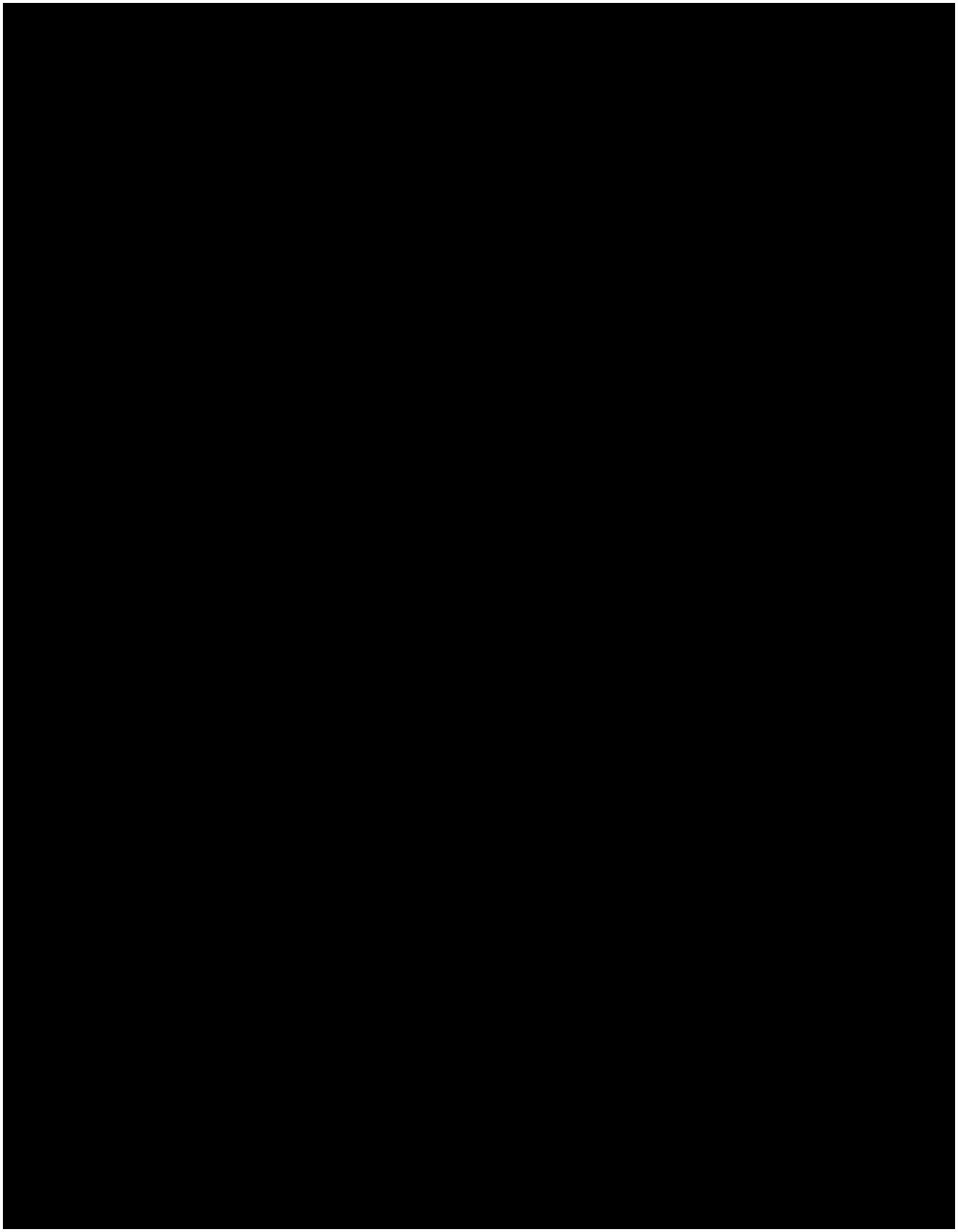
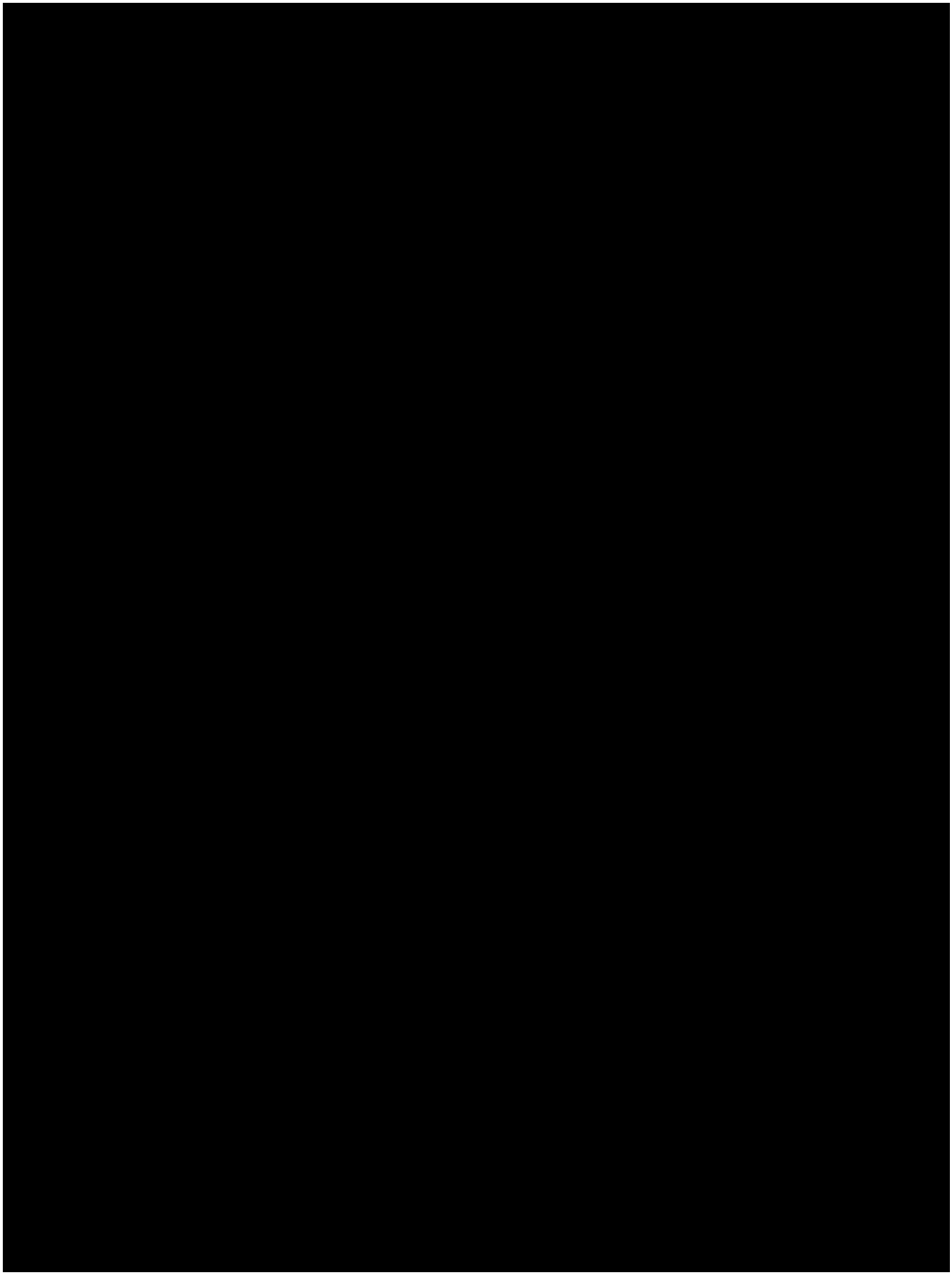
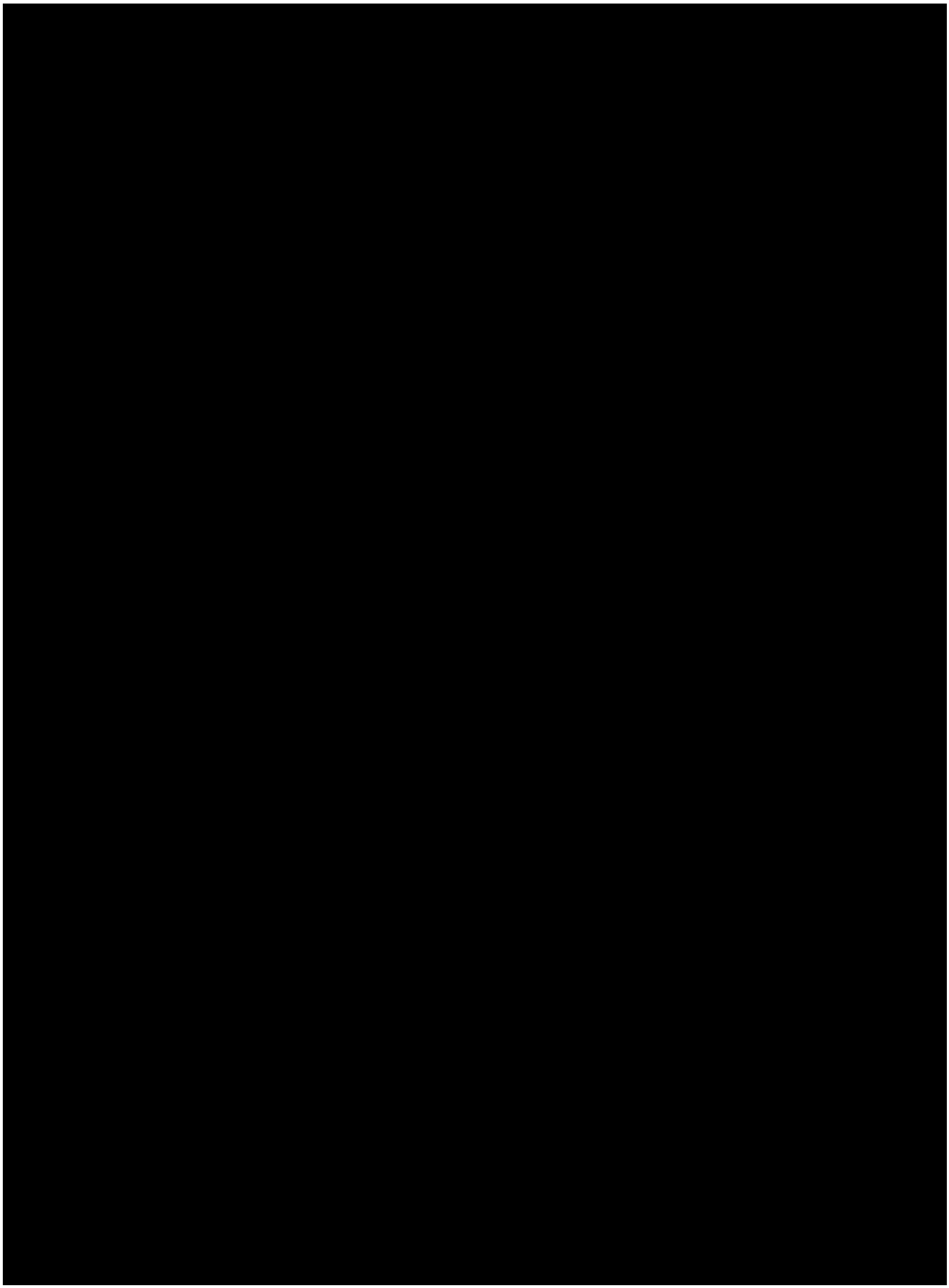
* Data collected in source only

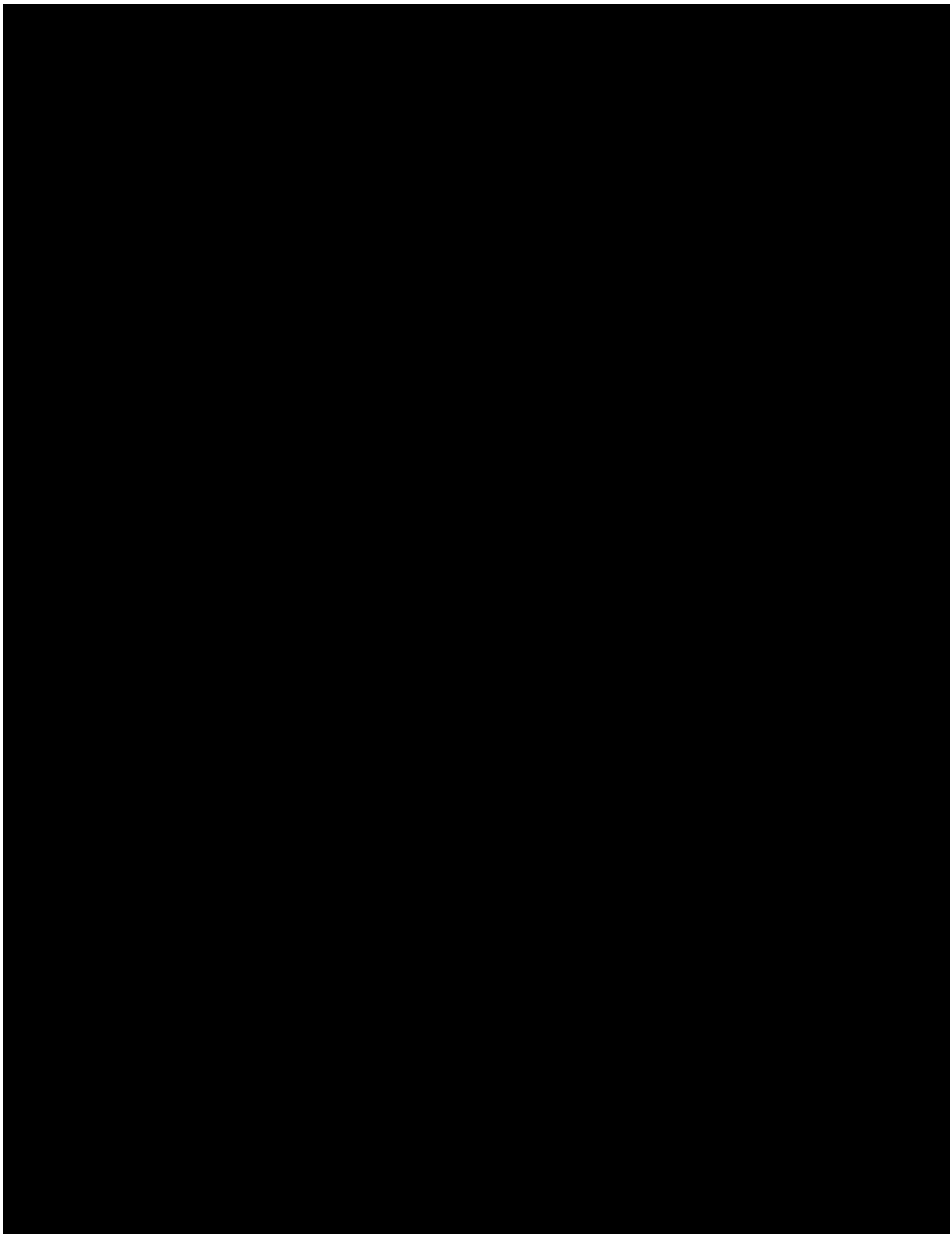


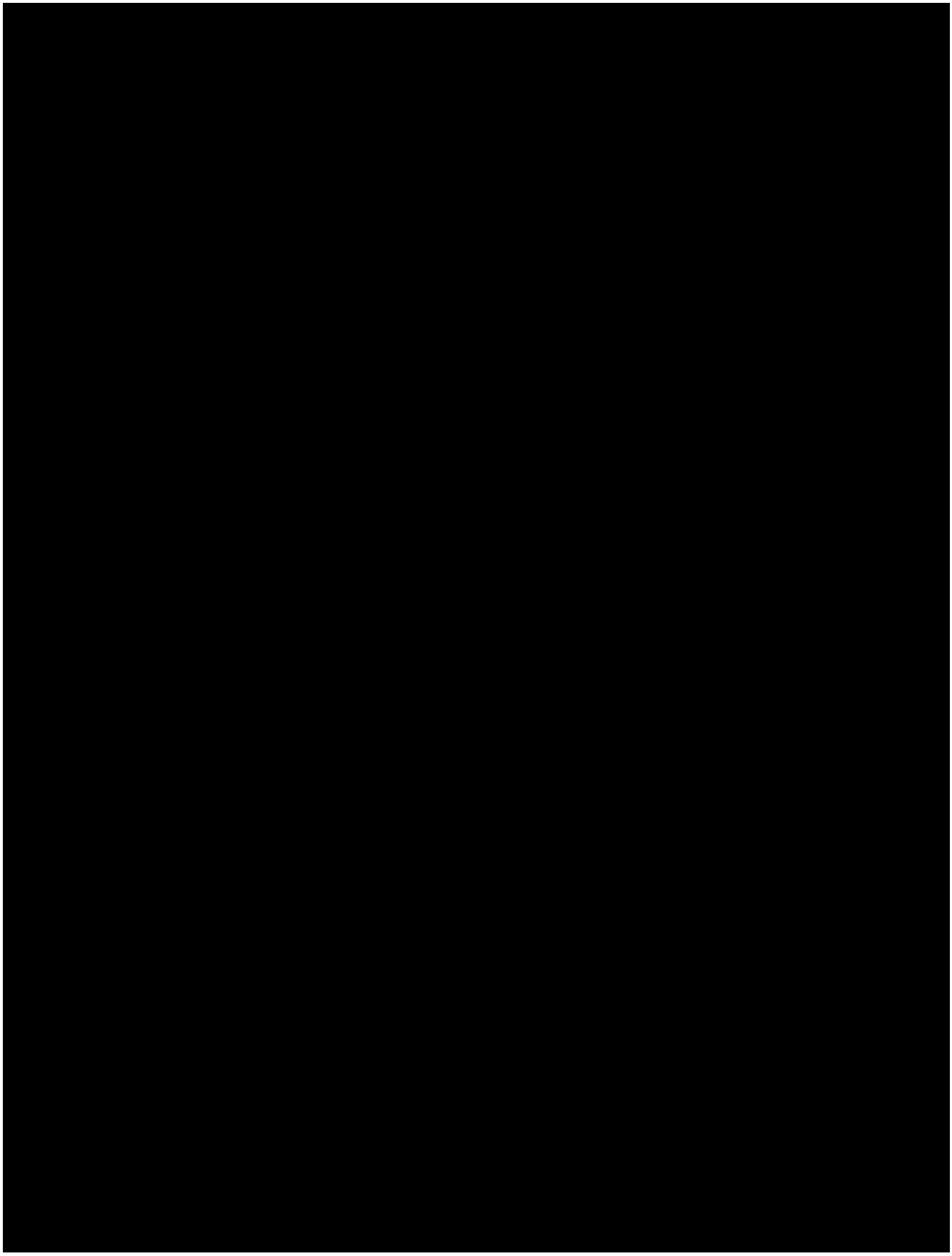


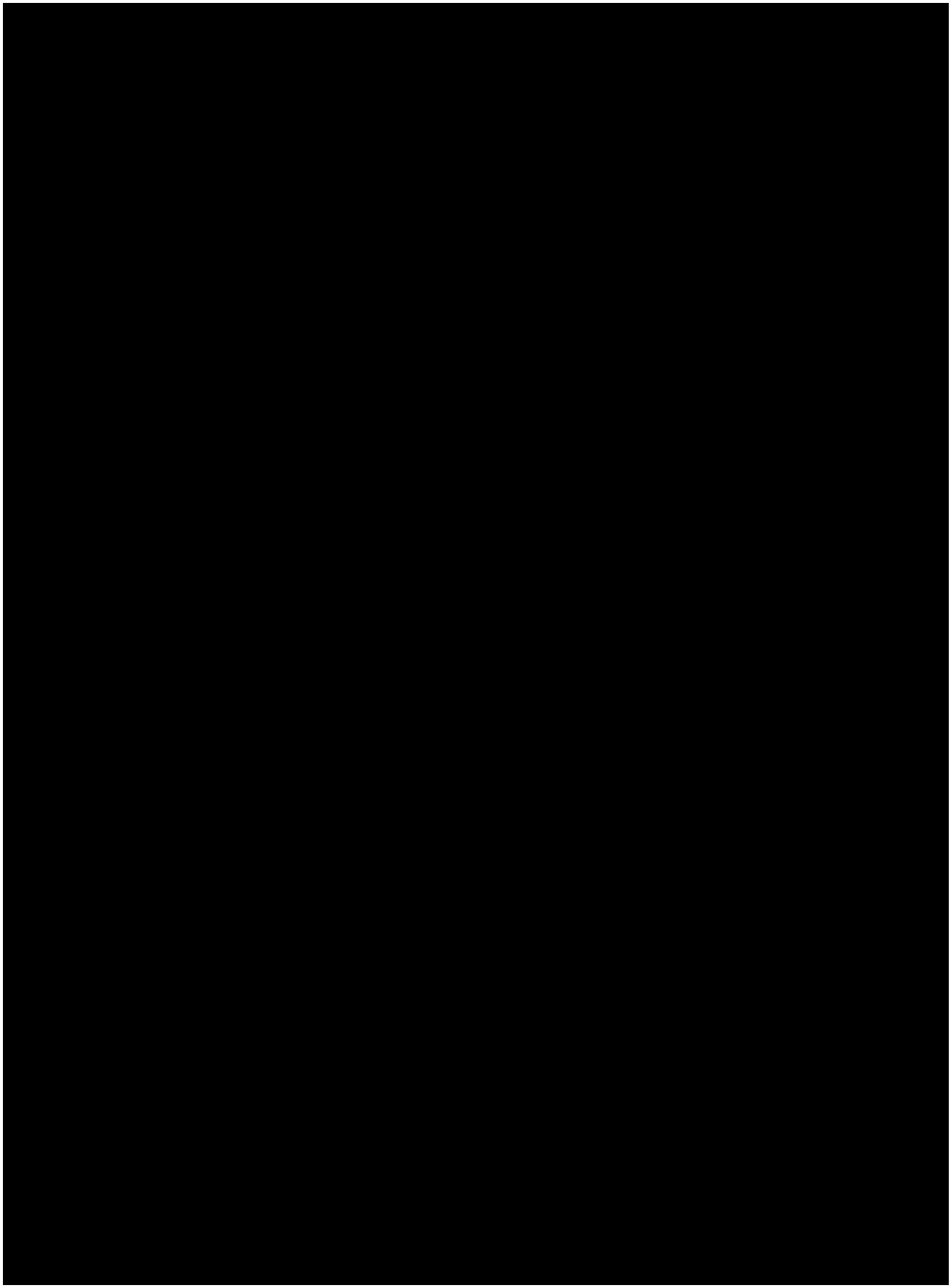


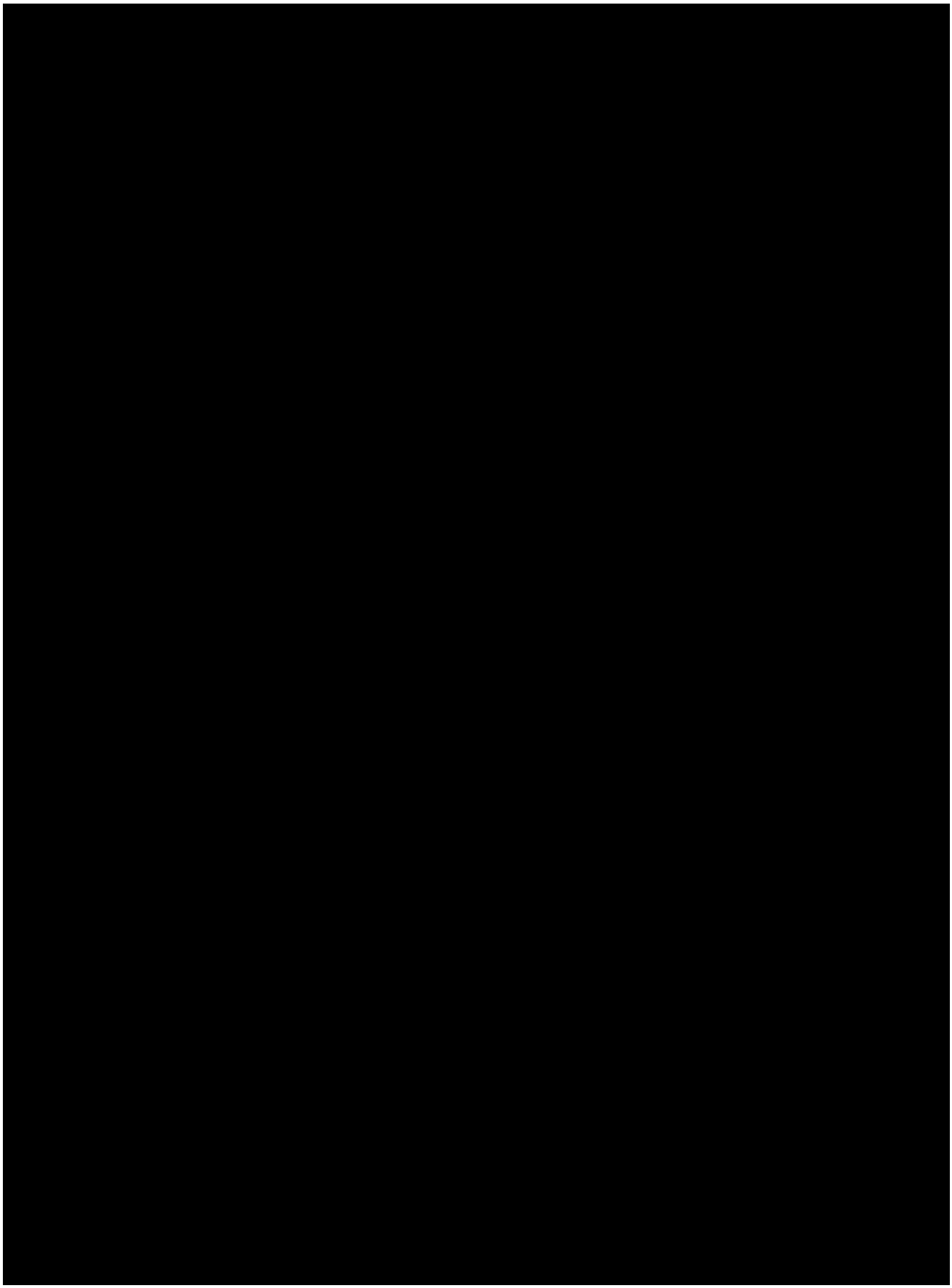


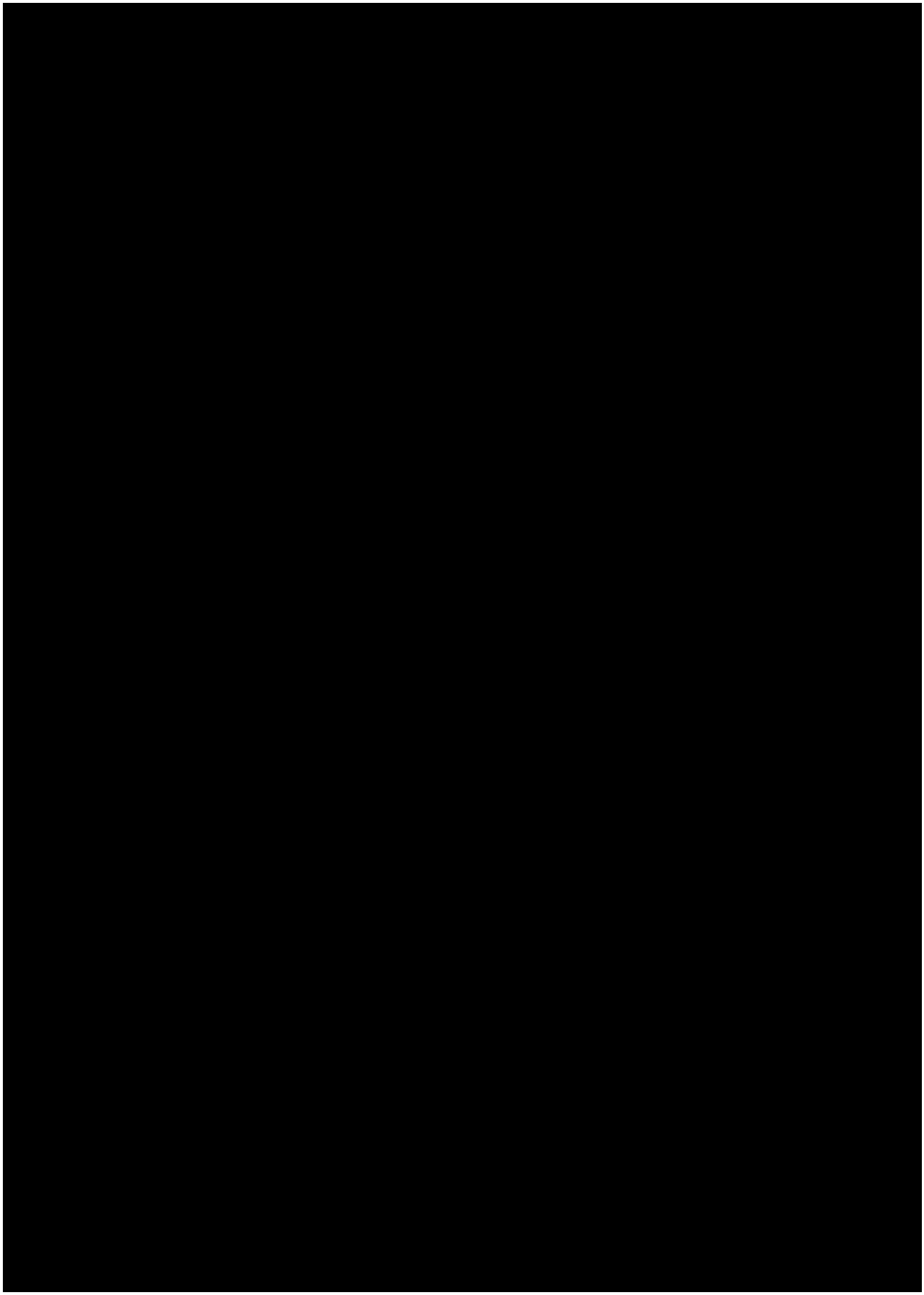


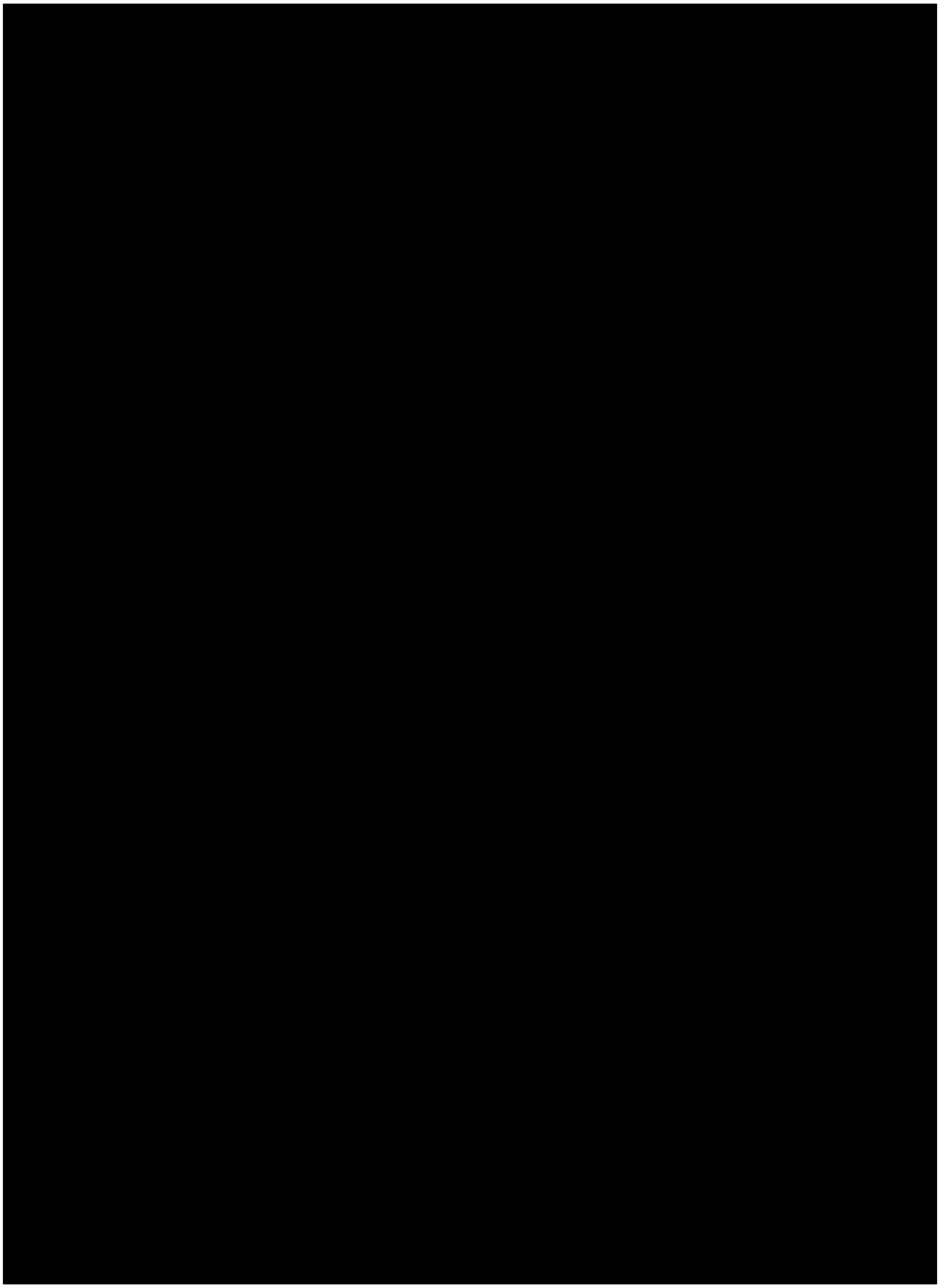


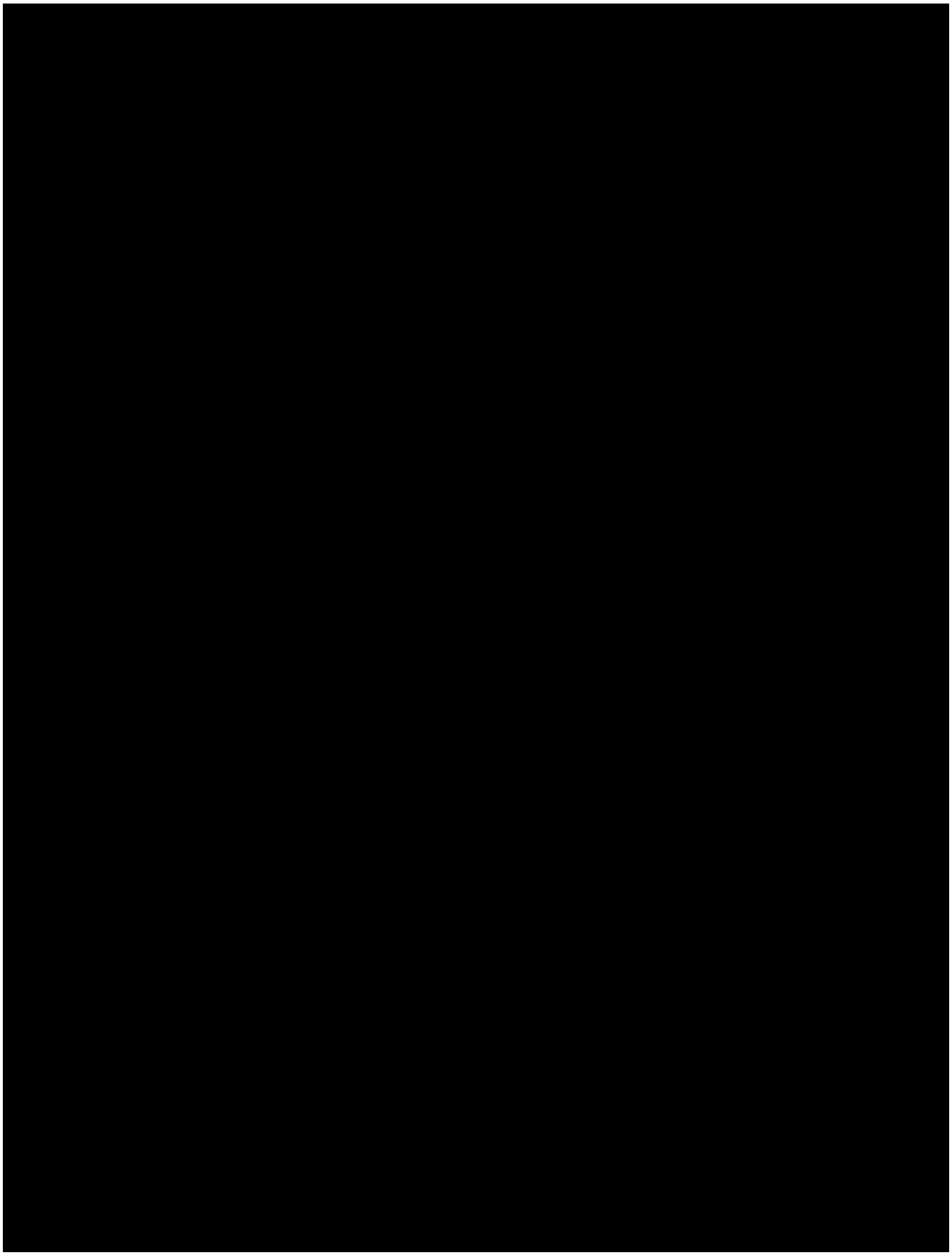


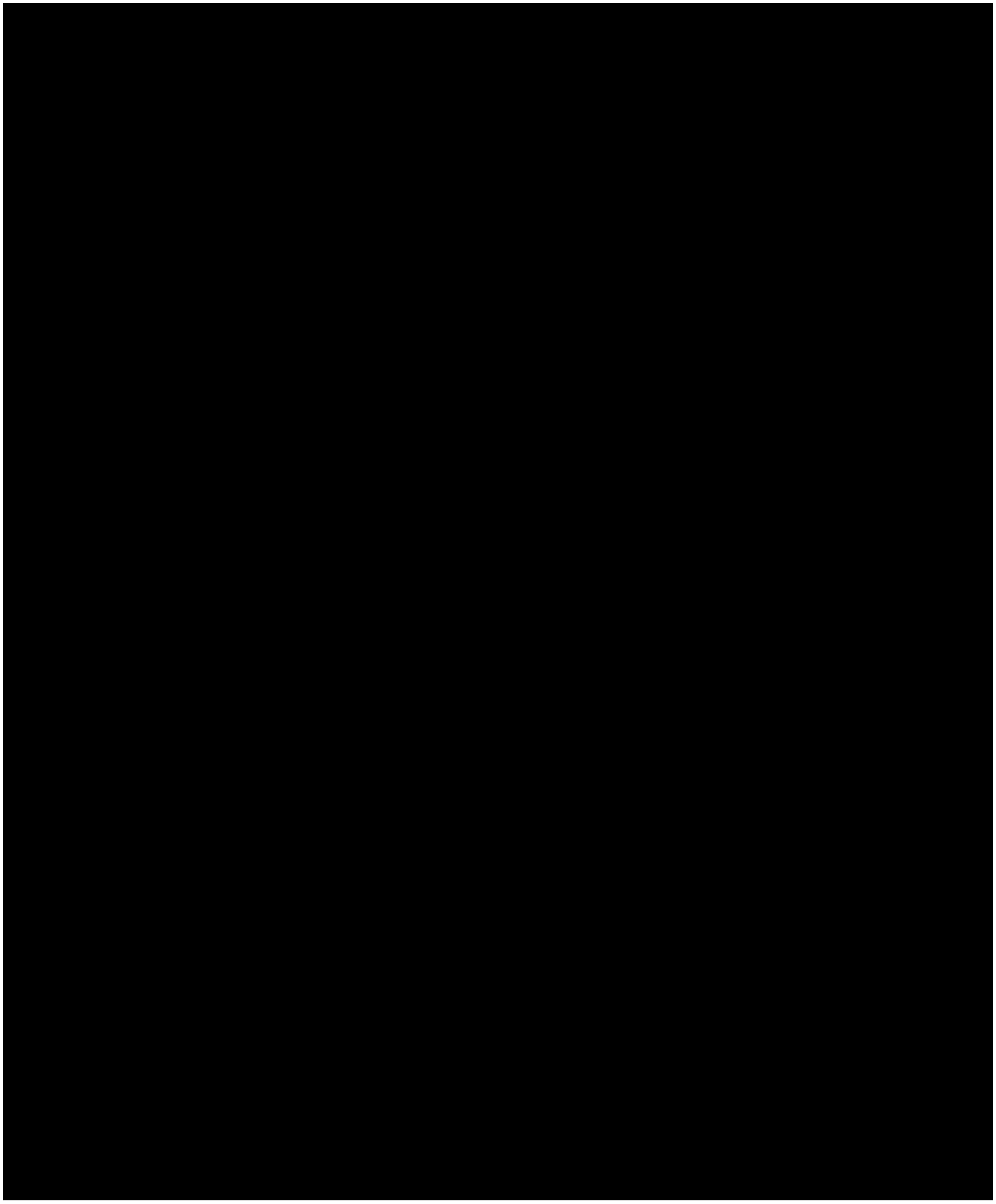


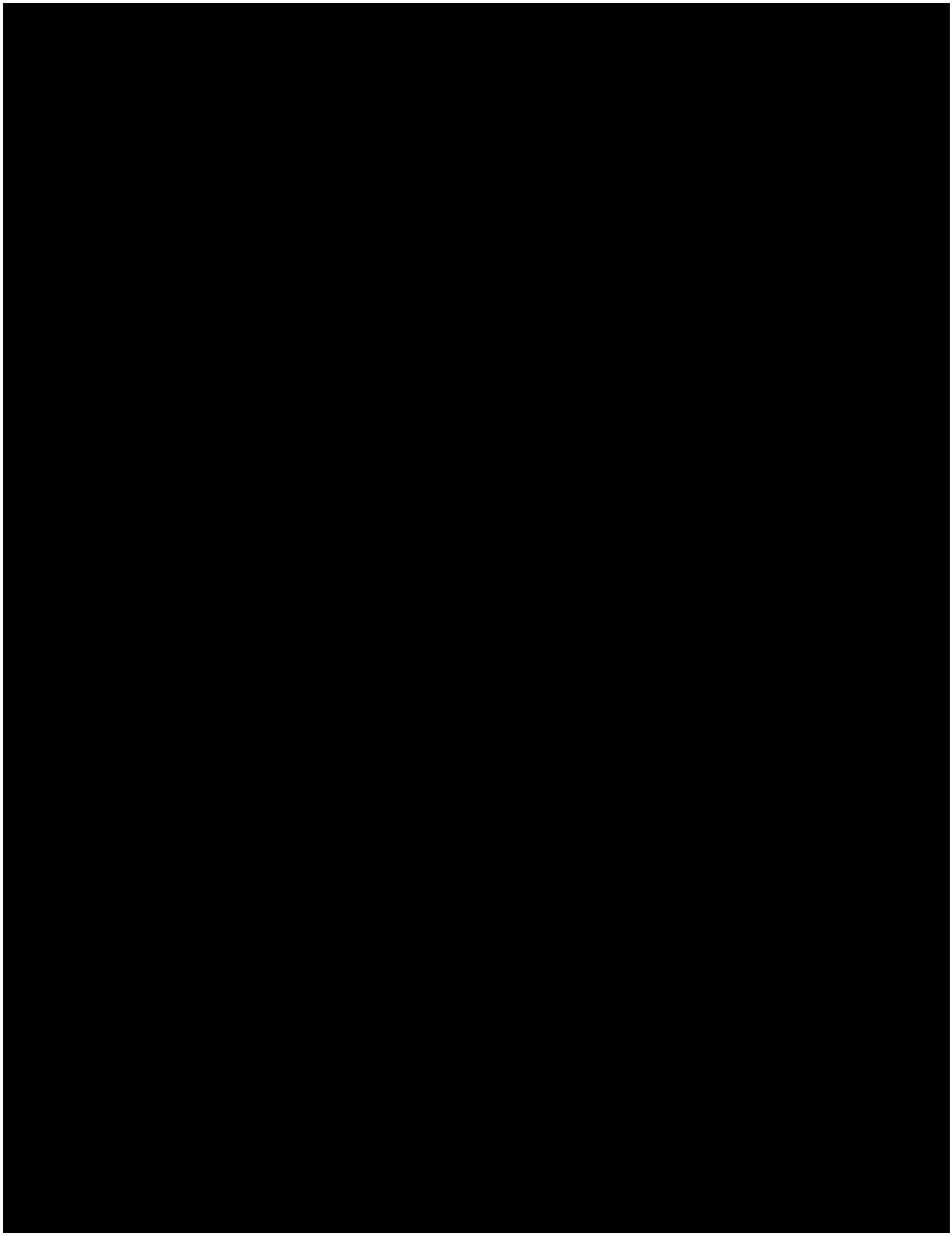


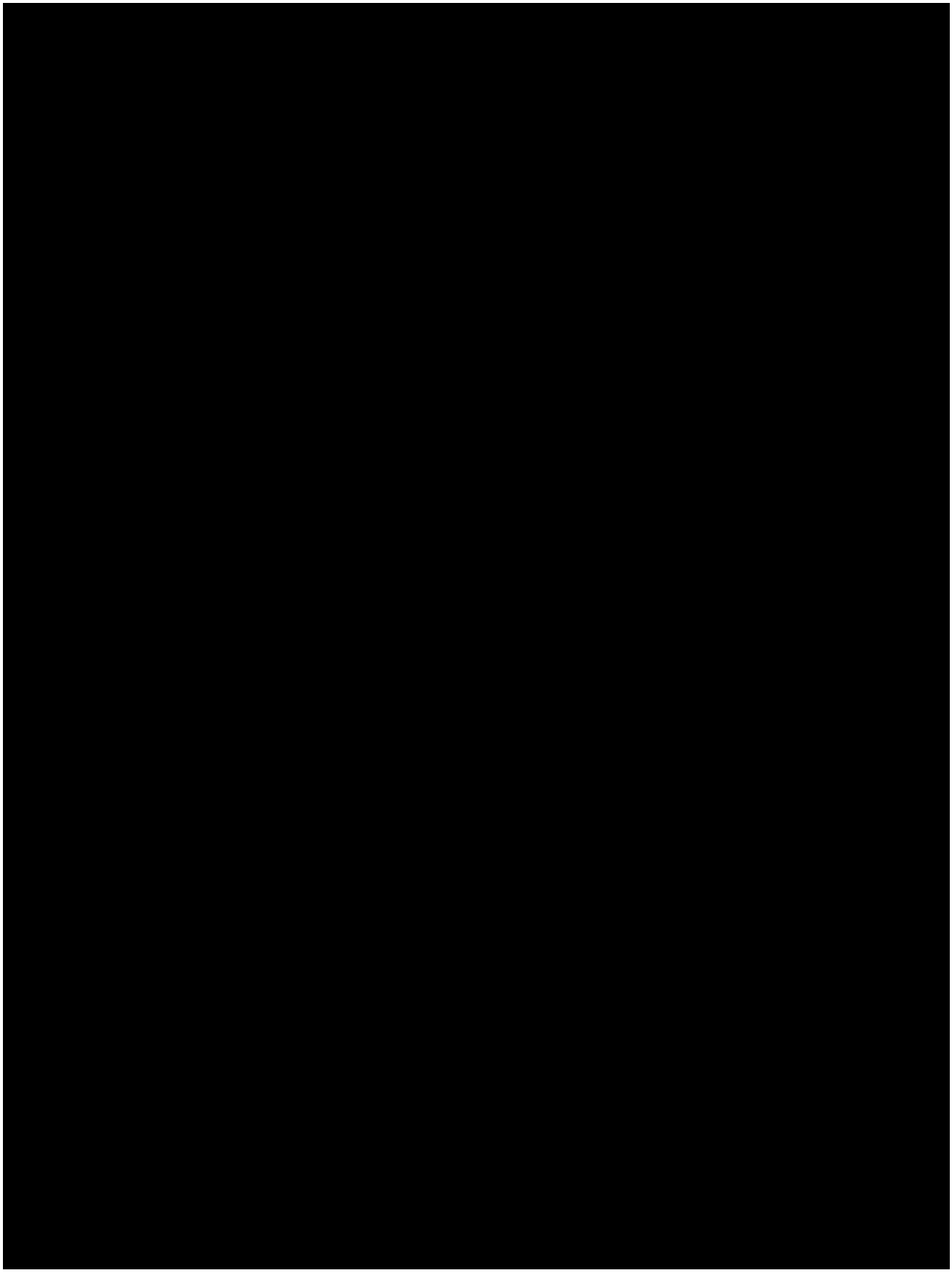


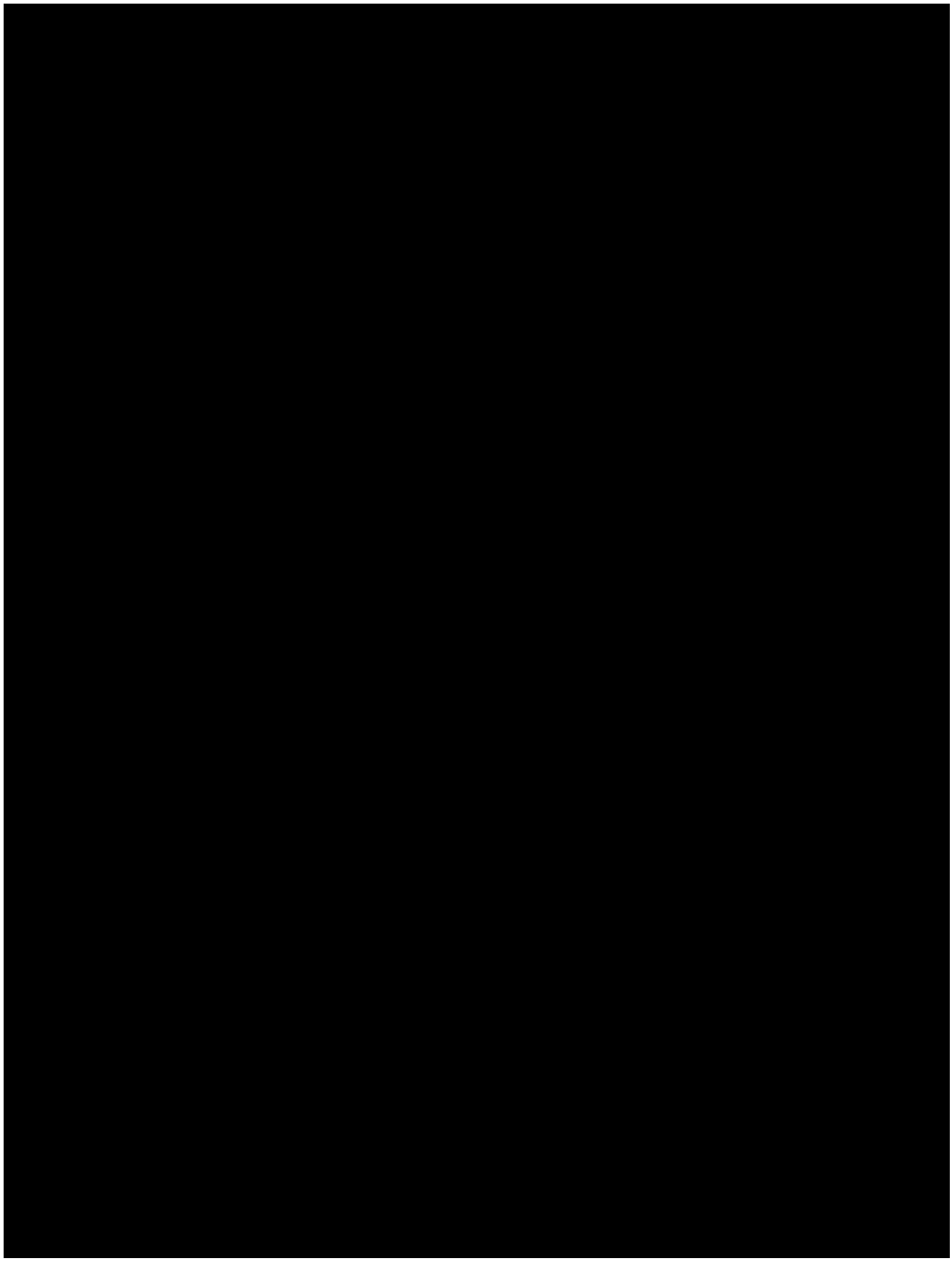


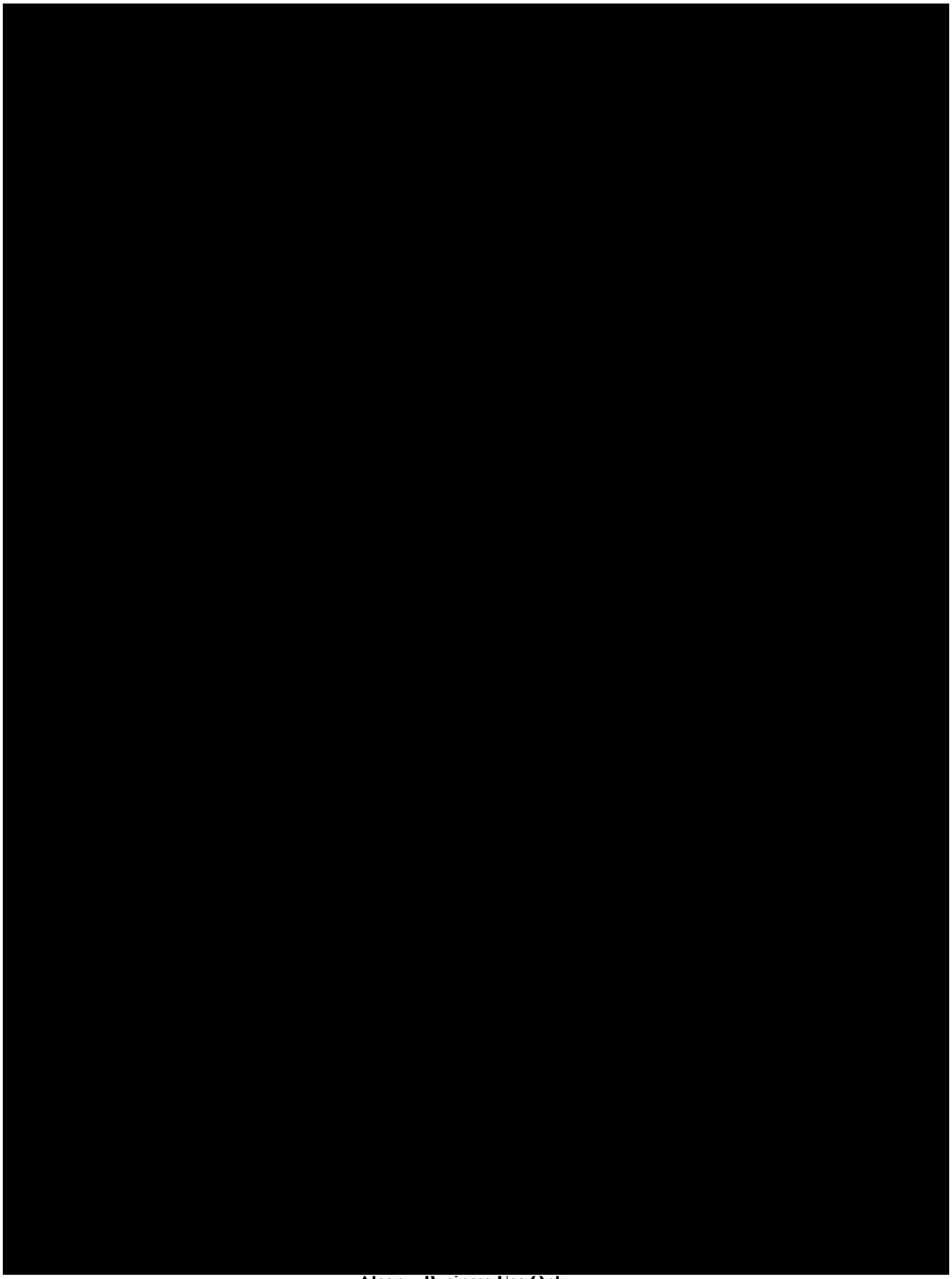


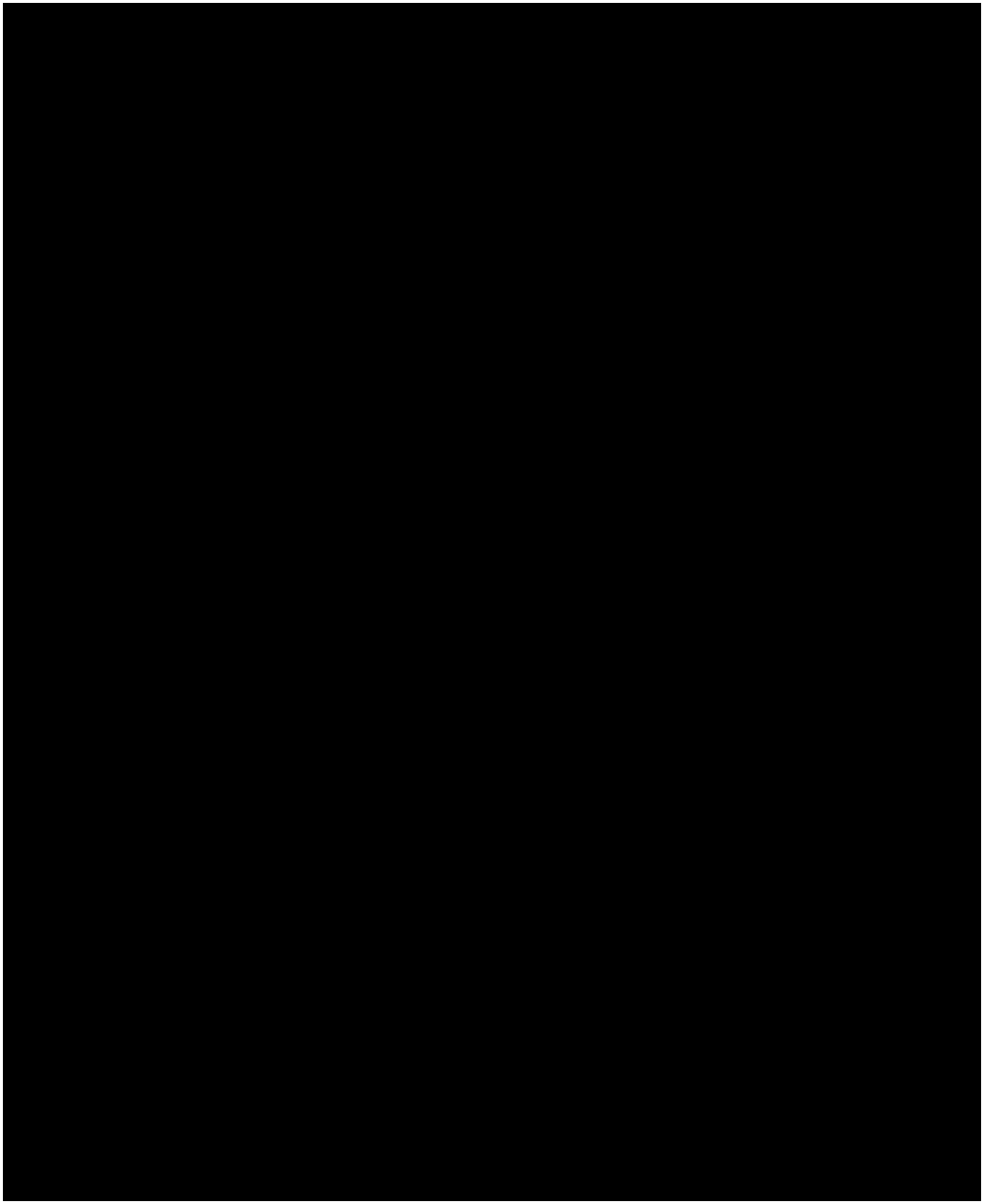


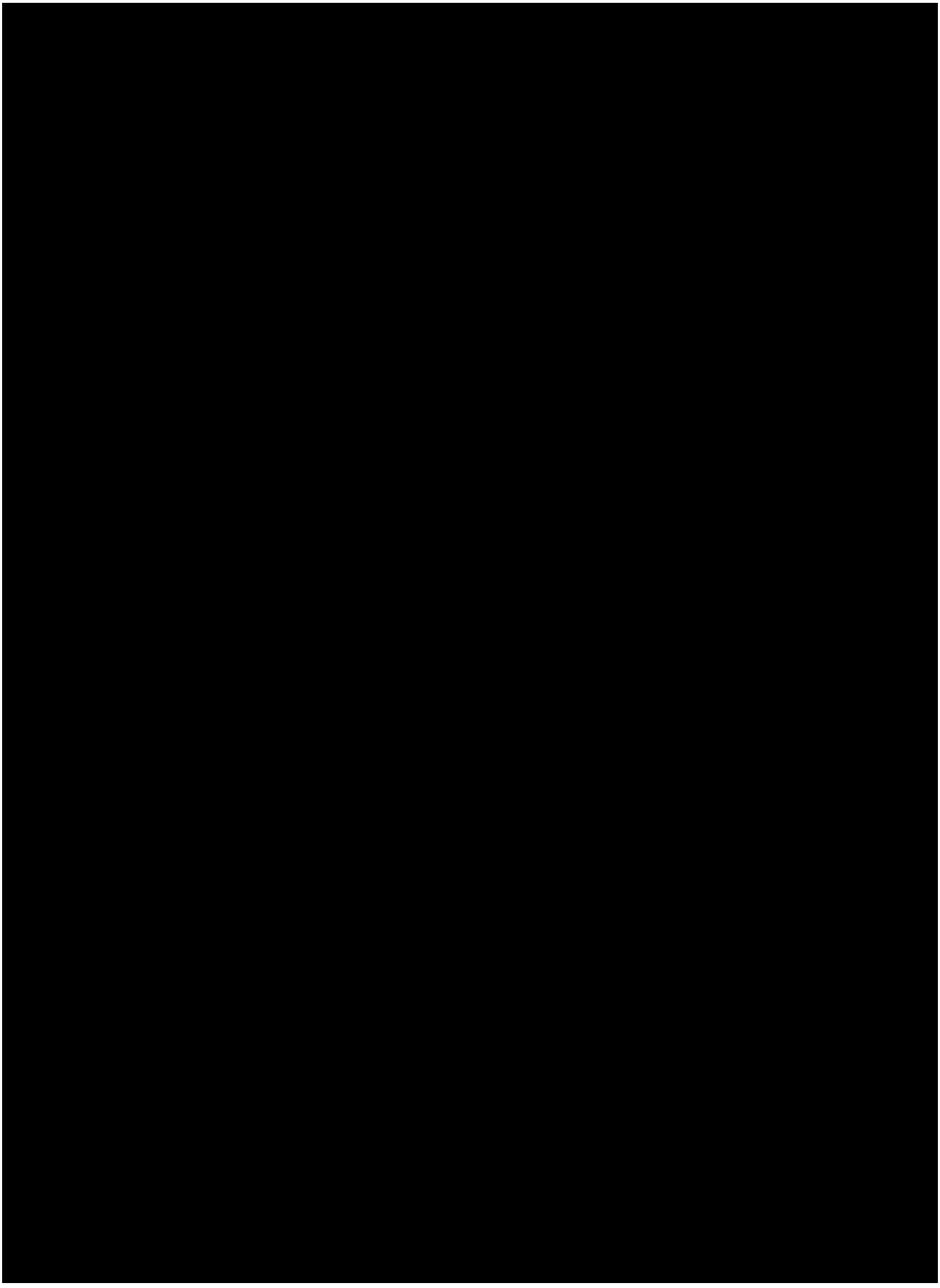


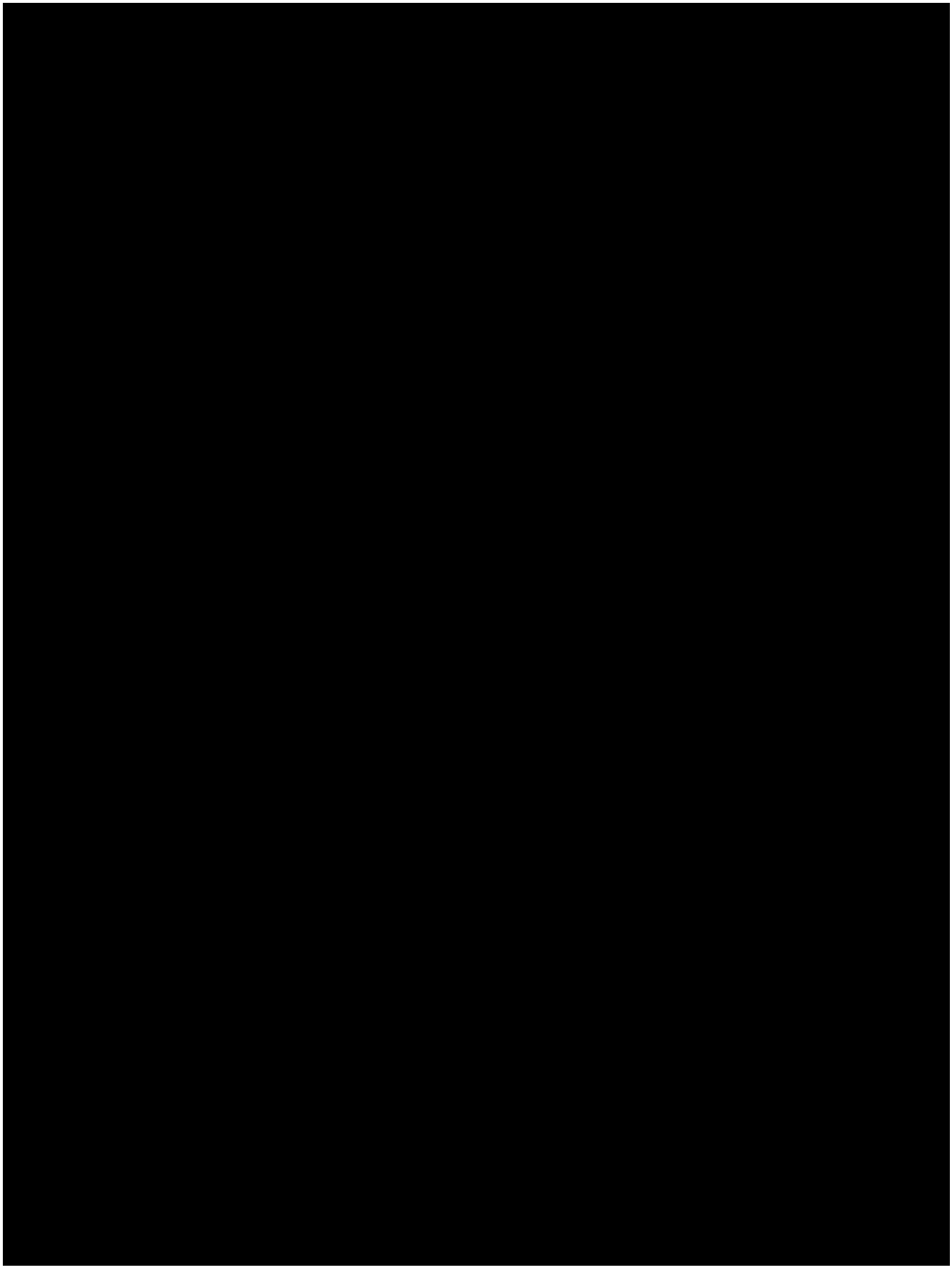


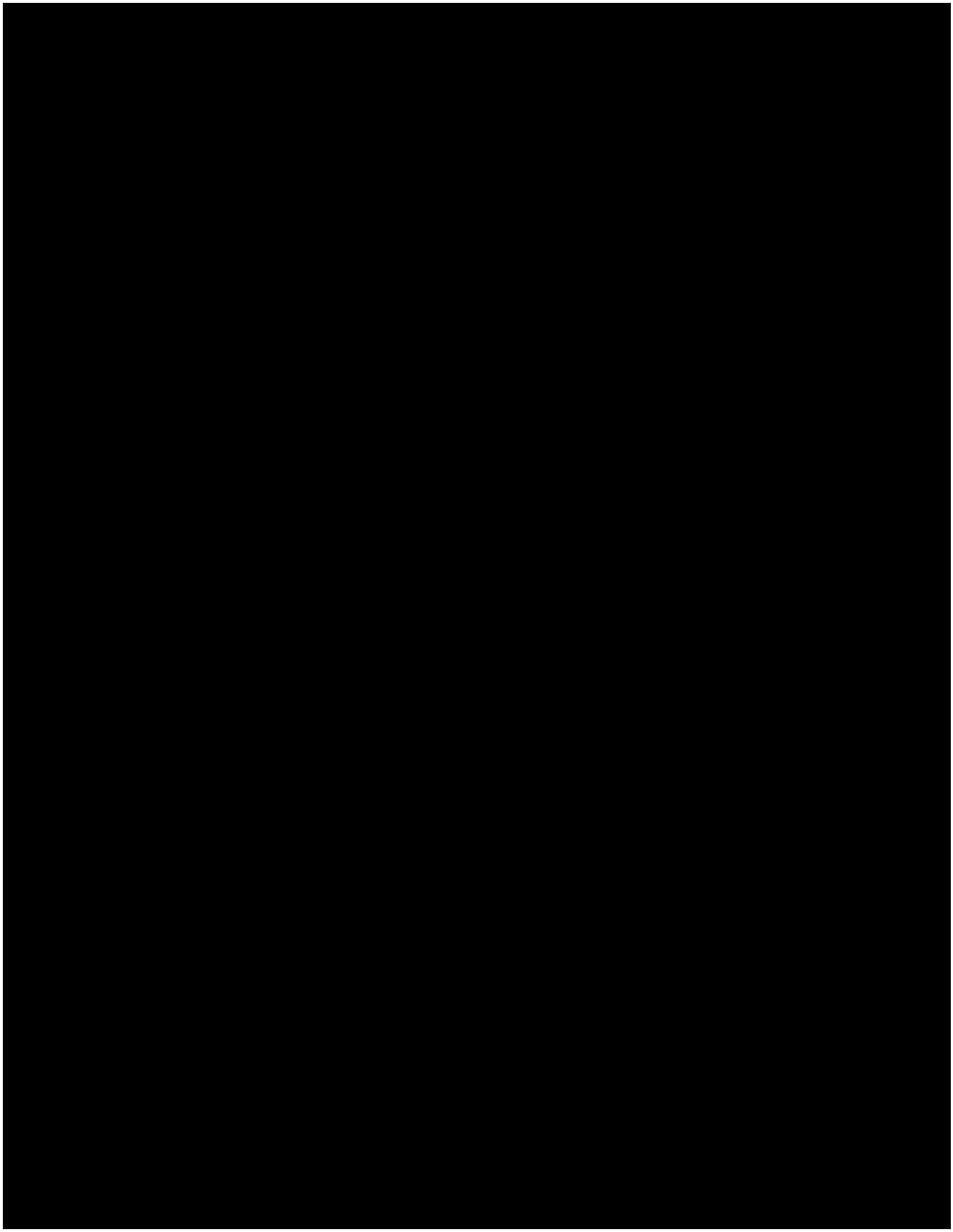


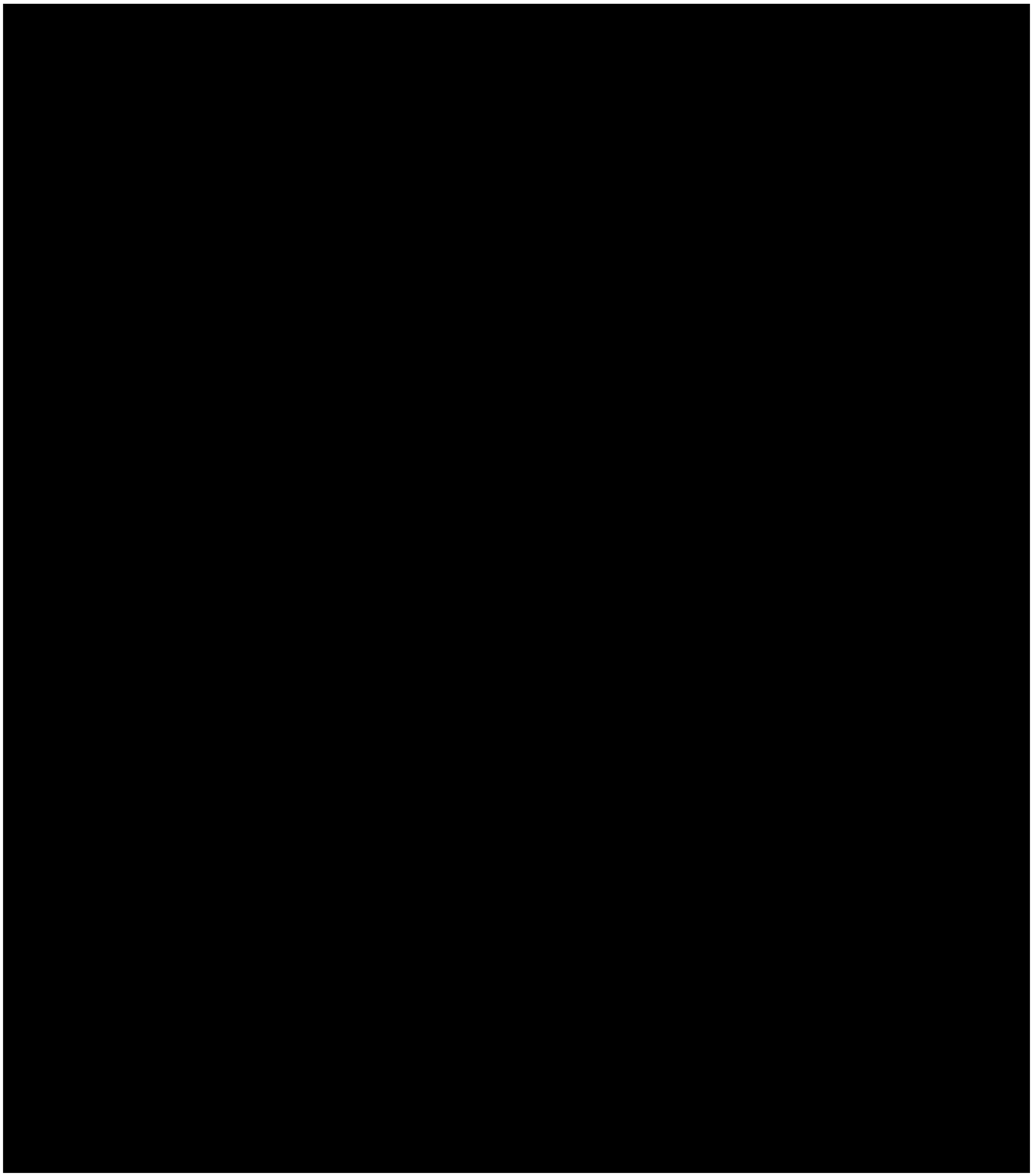












Signature Page for V-CLN-0000922 v4.0