STATISTICAL ANALYSIS PLAN

Protocol Number:	1620303
Title:	An Open-Label, Multi-Center Trial to Assess the Safety of Single and Repeat Treatments of DaxibotulinumtoxinA for Injection for Treatment of Moderate to Severe Glabellar Lines (SAKURA OPEN-LABEL SAFETY)
Study Phase:	3
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA 94560
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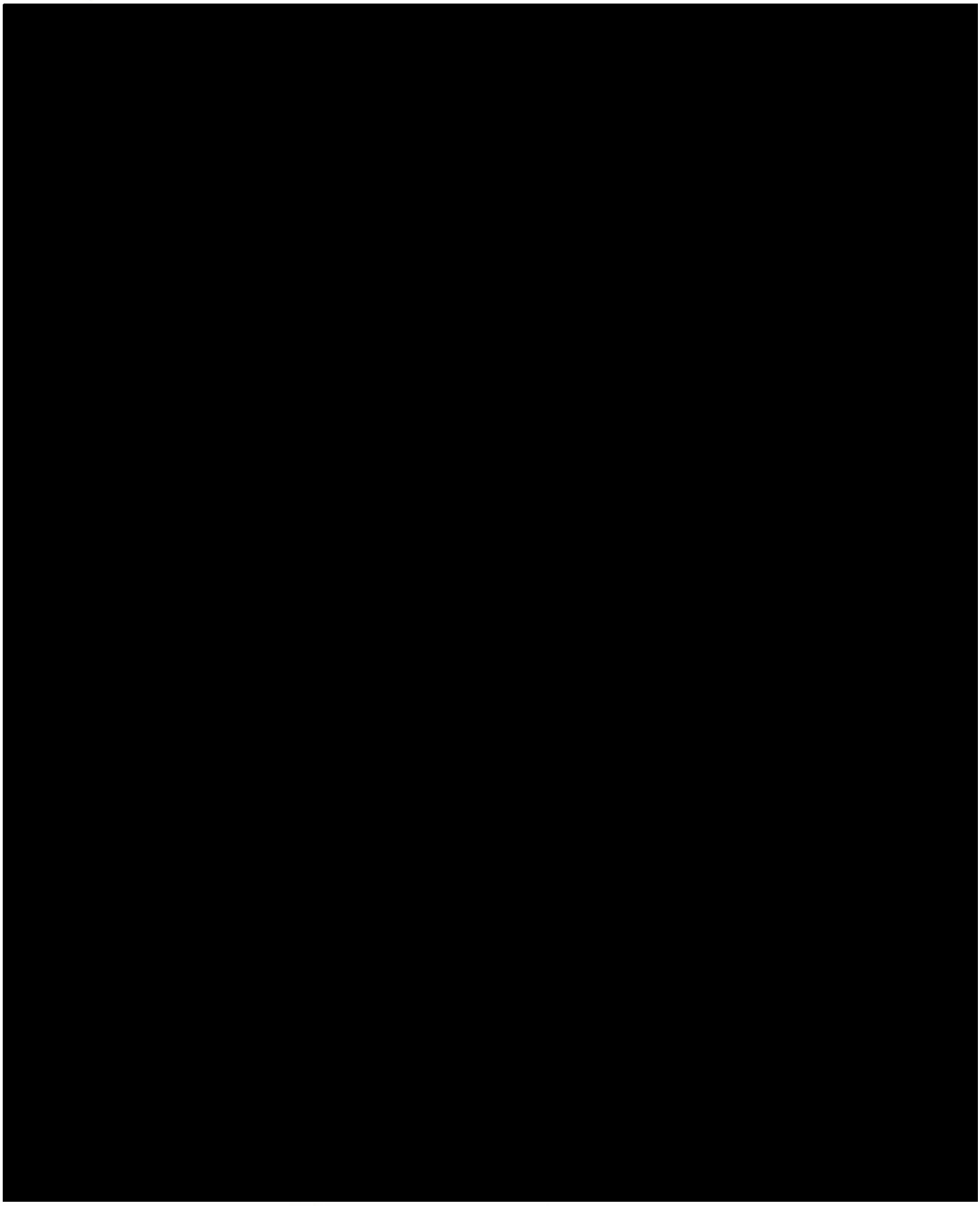
SAP Version Number:	Version 1.0
Protocol Version:	Amendment 1, 20 March 2017



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BoNTA	Botulinum neurotoxin type A
EOS	End of study
GAIS	Global Aesthetic Improvement Scale
IGA-FWS	Investigator Global Assessment-Facial Wrinkle Severity
kDa	kilodalton
MedDRA®	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRC	Medical Research Council
OLS	Open-label safety
PFWS	Patient Facial Wrinkle Severity
PP	Per-Protocol
Revance	Revance Therapeutics, Inc.
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical analysis system- software from SAS Institute Inc.
SD	Standard deviation
UPT	Urine pregnancy test
WOCBP	Women of childbearing potential
WHO	World Health Organization

1. INTRODUCTION

The safety and effectiveness of botulinum toxin type A to act on the neuromuscular junction and relieve muscle spasm and its clinical effects such as strabismus, pain, and facial wrinkles has been well established for over 20 years (Scott, 1981; Carruthers, 1992; Spencer, 2002).

This statistical analysis plan (SAP) describes the objectives of the study and the safety and effectiveness assessments that are collected. The safety endpoints and the effectiveness endpoints are defined, and the statistical methods used to analyze them are presented. Table shells for the planned end-of-text tables, figures, and listings are included in a separate document, but the titles are specified following the text of the SAP.

2. STUDY OBJECTIVES

2.1. Objectives

The study objective is to evaluate the long term safety of DaxibotulinumtoxinA for Injection for the treatment of moderate to severe glabellar lines following single and repeat administration.

2.2. Trial Endpoints

2.2.1. Safety Endpoints

The safety endpoints are:

- Incidence, severity and relationship to trial drug of treatment-emergent adverse events during each treatment and the trial overall
- Incidence, severity and relationship to trial drug of treatment-emergent serious adverse events during each treatment and the trial overall

2.2.2. Effectiveness Endpoints

Unless specified otherwise, all endpoints associated with Investigator Global Assessment Frown Wrinkle Severity (IGA-FWS), Patient Frown Wrinkle Severity (PFWS) or Global Aesthetic Improvement Scale (GAIS) henceforth will be based on assessments at maximum frown. When applicable, similar endpoints based on assessments at rest after maximum frown in those subjects with at least mild severity at baseline will be defined. Further details are provided in Section 4. The effectiveness endpoints are:

- Time to retreatment since the first DaxibotulinumtoxinA Injection (in Treatment-2 Evaluable only) and separately since the second DaxibotulinumtoxinA Injection (in Treatment-3 Evaluable only)
- Time to return to, or worse than, baseline on both IGA-FWS and PFWS (Treatments 1 and 2 only)
- Time to return to moderate or severe (2 or 3) on both IGA-FWS and PFWS (Treatments 1 and 2 only)
- Proportion of subjects with a ≥2 point improvement from baseline on both IGAFWS and PFWS at each visit over time
- Proportion of subjects with a score of none or mild (0 or 1) on IGA-FWS at each visit over time
- Proportion of subjects with a score of none or mild (0 or 1) on PFWS at each visit over time
- Proportion of subjects with a ≥1 point improvement from baseline on both IGA-FWS and PFWS at each visit over time
- Proportion of subjects with a ≥1 point improvement (i.e., improved, much improved, or very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)
- Proportion of subjects with a ≥2 point improvement (i.e., much improved, or very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)

- Proportion of subjects with a ≥3 point improvement (i.e., very much improved) on GAIS at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)
- Mean GAIS score at each visit over time (with investigator's assessment and subject's self-assessment summarized separately)

3. OVERALL STUDY DESIGN AND PLAN

3.1. Study Design

This is a phase 3, open label, multi-center trial to assess the safety of single and repeat administration of DAXI for Injection in subjects with moderate to severe glabellar lines. Subjects may enroll in this study by either rolling over from the SAKURA-1 or SAKURA-2 trials or by newly enrolling in this study. Approximately 1500 subjects will be newly enrolled in addition to approximately 600 roll over subjects from the SAKURA-1 and SAKURA-2 studies for a total of 2100 subjects. [redacted]

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3.1.1. Determination of Sample Size

This is a safety trial with all subjects treated with the same investigational product. The sample size of approximately 2,100 is considered to be adequate in assessing the safety based on several approaches. With approximately 2,100 subjects being treated in this trial, we can conclude [redacted]

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3.1.2. Treatments Administered

Approximately 1500 newly enrolled and 600 SAKURA-1/2 roll over adult subjects will be enrolled for a single treatment of DAXI for Injection. Subjects may have the opportunity of receiving up to one or two repeat treatments in this trial provided they meet the criteria for repeat treatment (see protocol section 3.4.4).

[redacted]

3.2. Safety and Effectiveness Assessments

3.2.1. Safety Assessments

Safety assessments include the physical examination; pregnancy testing for women of child-bearing potential (WOCBP); height, weight and other vital signs; 12-lead electrocardiograms; clinical laboratory evaluations; antibody evaluations; injection site evaluations, and assessments of adverse events.

3.2.1.1. Solicited AEs - Injection Site Evaluation

Injection sites will be evaluated at the Screening Visit, Treatment Visit pre- and post-treatment (to determine if there is an immediate reaction to the investigational product), Follow-up Visits, and Final Evaluation Visit or Early Discontinuation Visit, if applicable. The assessment will be done as a global evaluation of the five injection sites (Table 3.2-1).

Table 3.2-1 Injection Site Evaluation

	Present?	
Assessment Descriptor	**Yes**	**No**
Erythema		
Edema		
Burning or Stinging (sensation as described by subject)		
Itching (sensation as described by subject)		
Bruising		

3.2.1.2. Adverse Events

All adverse events (AEs) will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. AE severity will be graded as mild, moderate, or severe as

defined in Section 6.1.2 of the protocol. AEs with an onset on or after the date and time of study treatment will be considered Treatment-emergent.

[redacted]

3.2.1.4. Clinical Laboratory Data

As outlined in Table 3.2-2, non-fasting samples for hematology, chemistry, PT (Screening only) and urinalysis will be collected at Screening, Week 4 visits, prior to Retreatment (as applicable), and at the Final Evaluation Visit. [redacted]

Table 3.2-2 Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen	Hemoglobin Hematocrit Leukocyte Count (total) Leukocyte Count (differential) Red Blood Cell Count Platelet Count	Specific gravity pH Glucose Protein Blood Bilirubin Ketones	Prothrombin time (PT) (Screening only) Urine Pregnancy (WOCBP only)* [redacted]
WOCBP = Women of child-bearing potential *If positive at timepoints after trial treatment, confirm by serum pregnancy test.			

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[redacted]

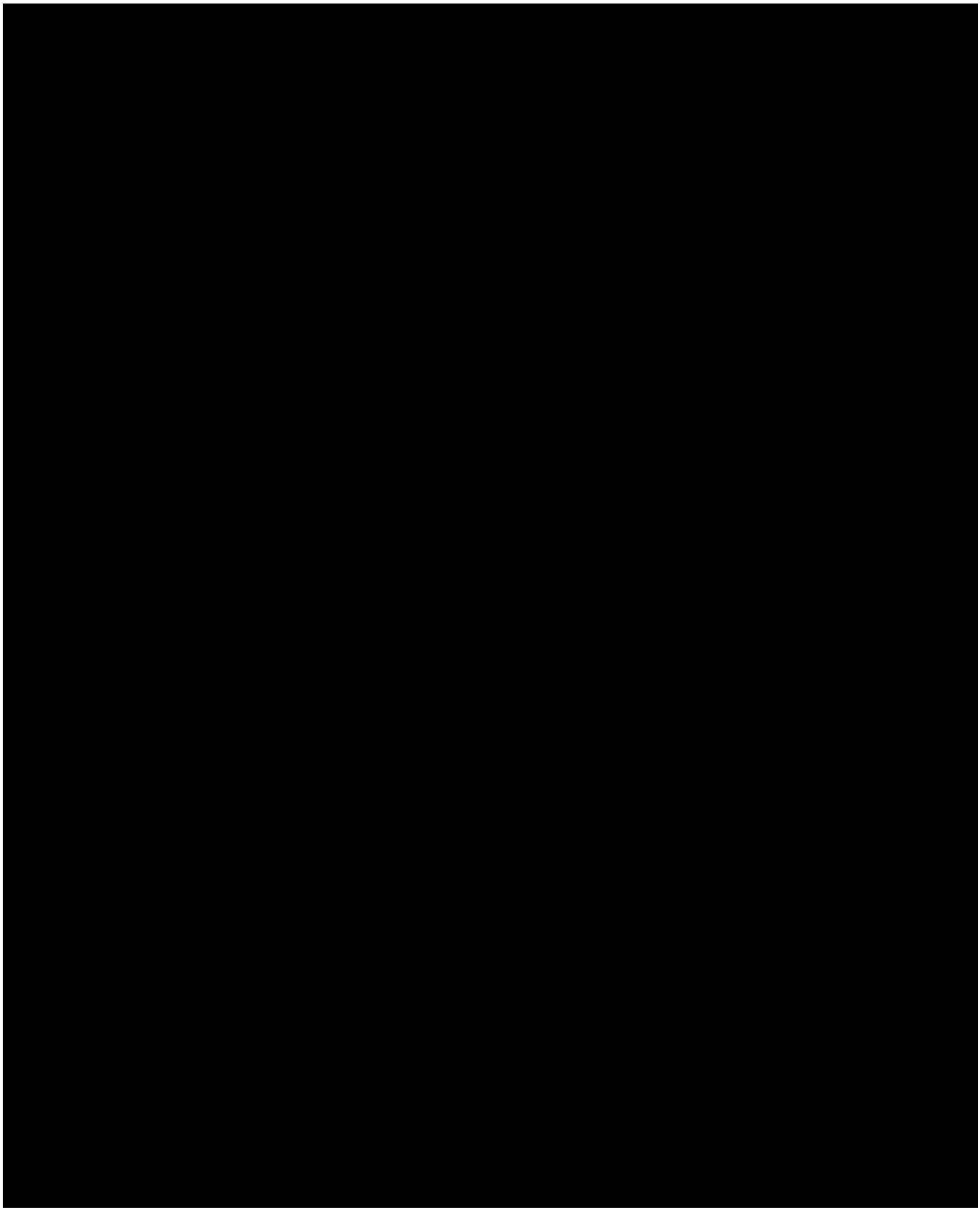
3.2.1.6. Vital Signs

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained at the Screening, Treatment Visit (pre- and post-treatment), Week 2, Final Evaluation or Early Discontinuation Visit, and at any visit where signs or symptoms of distant spread of toxin are reported.

3.2.1.7. Physical Examination

A physical examination, in addition to vital signs, including neurological examination of the face, general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities will be conducted at Screening, Week 2 and Final Evaluation or Early Discontinuation Visits. Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History page.

Significant physical examination findings which meet the definition of an adverse event will be recorded on the adverse event page post-treatment.



3.2.2. Effectiveness Assessments

Effectiveness assessments will include Investigator assessment of glabellar line severity and glabellar line improvement as well as subject assessment of glabellar line severity and improvement.

3.2.2.1. Frown Wrinkle Severity

Frown wrinkle severity is assessed by both the subject (Patient Frown Wrinkle Severity [PFWS]) and the investigator (Investigator Global Assessment Frown Wrinkle Severity [IGA-FWS]) using the same 4-point rating scale, as shown in Table 3.2-6.

The severity is assessed at maximum frown and at rest after maximum frown by both the subject and the investigator. The scores range from 0 = none to 3 = severe.

Table 3.2-6 Frown Wrinkle Severity

Rating Score	Frown Wrinkle Severity	Description
0	None	No wrinkles
1	Mild	Very shallow wrinkles
2	Moderate	Moderate wrinkles
3	Severe	Deep wrinkles

3.2.2.2. Global Aesthetic Improvement Scale

The Investigator and subject will assess the visual appearance (at maximum frown and at rest after maximum frown) of the glabellar line improvement from the baseline condition using the following 7 point severity Global Aesthetic Improvement Scale (GAIS, Table 3.2-7).

Table 3.2-7 Global Aesthetic Improvement Scale

Rating Score	Wrinkle Improvement
-3	Very Much Worse
-2	Much Worse
-1	Worse
0	No Change
1	Improved
2	Much Improved
3	Very Much Improved

[redacted]

4. STATISTICAL METHODS

All statistical programming will be performed using statistical analysis system (SAS) version 9.4 or higher.

[redacted]

4.1. Definition of Baseline

For subjects who completed participation in SAKURA-1 or SAKURA-2 and are participating in SAKURA-OLS, the Final Evaluation visit assessments/procedures of the previous trial, end of trial prothrombin time (PT), and the Week 12 serum antibody test of the previous trial will serve as the trial baseline for this trial.

For subjects who are newly enrolled into SAKURA-OLS, the trial baseline will be the last available value prior to the first treatment in the OLS study.

For summaries associated with a specific treatment, the baseline will be the last available value prior to the specific treatment (i.e., re-baselined or treatment baseline). For the effectiveness endpoints that are derived from a comparison with the baseline, two derivation rules using different reference time points as the baseline (i.e., trial baseline or treatment baseline) will be applied separately.

4.2. Analysis Populations and Summary Groups

4.2.1. Safety Evaluable Population

The Safety Evaluable population will include all subjects who are exposed to the investigational product and who provide any post-treatment safety information.

4.2.2. Treatment Evaluable Populations

Analyses specifically associated with each of the three treatment periods within the SAKURA-OLS trial will be performed on a subset of the safety Evaluable population, including only those subjects who receive trial treatment and have post-treatment safety information for the specific treatment. These safety Evaluable sub-populations will be respectively identified as:

- Treatment-1 Evaluable,
- Treatment-2 Evaluable, or
- Treatment-3 Evaluable

In addition to subjects who are directly enrolled into SAKURA-OLS, the trial also includes subjects rolling over from two pivotal phase 3 studies, SAKURA-1 and SAKURA-2. For the roll over subjects who are in the active treatment group in the prior trial, the first DAXI for Injection treatment in SAKURA-OLS will in fact be their second DAXI for Injection treatment; these subjects are excluded from the Treatment-1 Evaluable population but are included in Treatment-2 Evaluable and Treatment-3 Evaluable populations.

4.2.3. Per-Protocol Population

Although not explicitly required by the protocol, a Per-Protocol (PP) population will be defined and will include subjects who are enrolled, are exposed to the investigational product, and who complete the first 12 weeks of the study without a major protocol violation.

4.2.4. Analysis Summary Groups

Based on the subject's prior exposure to DAXI for Injection, the following two summary groups will be defined for analyses:

- Group A: all subjects who have received DAXI for Injection in SAKURA-1 or SAKURA-2
- Group B: all subjects in SAKURA-OLS who are not in Group A and are receiving DAXI for Injection for the first time

4.3. Subject Disposition

The number and percentage of subjects who have signed informed consent, received treatment, and completed key visits will be tabulated by summary group (Group A and Group B) and overall and by trial center and included in a listing. Reasons for not completing the study will also be tabulated by summary group and overall and by trial center using numbers and percentages; this data will also be included in a

listing. For those subjects who are considered to have failed screening, the reason(s) for failure will be provided in a listing.

The number and percentage of subjects included and excluded from the analysis populations (Safety Evaluable, Treatment-1 Evaluable, Treatment-2 Evaluable, Treatment-3 Evaluable, and Per-Protocol) will be tabulated overall and for each summary group (Group A and Group B). Reason(s) for exclusion from each population will be summarized and listed.

[redacted]

Major protocol deviations will be listed and summarized by summary group.

4.4. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics by summary group and overall. Continuous variables will be summarized using the number of non-missing observations, mean, standard deviation, median, minimum and maximum. Categorical data will be summarized using the number and percentage of subjects in each category.

Demographic data include age, sex, race and ethnicity. Age in years will be categorized as 18 to 45, >45 to 55, and >55 as well as into groups defined as <65 and ≥65 for inclusion in summaries. Baseline characteristics include prior Botulinum toxin Type A, time since last prior Botulinum toxin Type A Injection, and Fitzpatrick skin type, as well as the baseline assessment of the efficacy questionnaires, PFWS and IGA-FWS. Summaries will be produced for the Safety Evaluable, Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable by summary group and overall.

4.5. Medical History

Medical history will be classified on the basis of MedDRA terminology, using the latest terminology at the time of database finalization. Medical history will be summarized for the Safety Evaluable population by summary group, system organ class, and preferred term, and will be listed.

4.6. Prior and Concomitant Medications

Prior and concomitant therapies/medications used at Screening and during the trial will be coded using the World Health Organization (WHO) drug dictionary and summarized by summary group, Anatomic Therapeutic Chemical (ATC) second level term, and preferred name for the Safety Evaluable population. Prior and concomitant medications will be summarized separately.

4.7. Safety Analyses

Safety summaries and analyses will be performed on the Safety Evaluable, Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations. Descriptive statistics will be presented to summarize the safety data.

4.7.1. Extent of Exposure

All subjects receive a minimum of one administration of investigational product, and potentially up to three administrations. The dosage of investigational product injected and the dose of investigational product injected at each of the five injection sites will be summarized by summary group overall and for each administration using descriptive statistics (number of non-missing observations, mean, median, minimum, maximum, and standard deviation).

4.7.2. Injection Site Evaluations

The injection site evaluations will be summarized using number and percentage of subjects reporting the presence of each item (Erythema, Edema, Burning or Stinging, Itching and Bruising) by summary group and visit for Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable, as well as the number and percentage of subjects with an event at any post-treatment visit. In addition, the number and percentage of subjects reporting any injection site item will be summarized by summary group for Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable, and by visit as well as at any post-treatment visit. Additionally, the number and percentages of subjects with the specified item will be summarized according to the first visit at which the event was present.

4.7.3. Adverse Events

All AEs will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent AEs are those AEs with an onset on or after the date and time of trial treatment or events which were present before treatment and which worsened after treatment. All treatment-emergent AEs will be summarized by summary group, system organ class, preferred term, severity, relationship, and seriousness. When summarizing events by causality and severity by subject, each subject will be counted only once within a

system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification.

All information pertaining to AEs noted during the trial will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding trial drug, corrective treatment, outcome, and drug relatedness. The event onset relative (in number of days) to the date of first treatment administration in the SAKURA-OLS trial, as well as to the date of last trial treatment administration prior to the event, will be provided. In addition, a list of adverse events that lead to the subject's premature discontinuation of the trial will also be provided.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by summary group and severity and relationship to trial treatment. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

The summaries of AEs and SAEs will be performed for the trial overall, and for each of the three treatment periods. Furthermore, the summaries of AEs will be performed for the trial overall by gender. For SAEs and AEs of special interest (see Section 4.5.10 of the protocol), rate-per-injection and rate-per-subject-year will be calculated and summarized by summary group. A 95% confidence interval will also be provided for the rate.

4.7.4. Laboratory Tests

4.7.4.1. Clinical Safety Laboratory Parameters

Laboratory test results will be summarized with descriptive statistics by visit. Change from OLS trial baseline to Final Evaluation Visit will be summarized for continuous test results.

Shift tables will be presented to summarize laboratory test results at Baseline and Final Evaluation Visit. Normal ranges established by the central laboratory will be used to determine shifts. A listing of all out-of-range laboratory test results at any evaluation will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

4.7.4.2. Pregnancy Tests

Urine pregnancy tests (UPTs) will be summarized for all treated subjects in the category of WOCBP and presented in the data listings.

[redacted]

4.7.6. Vital Signs and Physical Examination

Vital signs will be summarized with descriptive statistics for each summary group by visit for Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable. The actual value as well as the change from baseline for each visit will be summarized using the number of non-missing observations, mean, median, minimum, maximum and standard deviation.

Abnormal findings from the physical examination will be summarized by body system and summary group for Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable using number and percentage of subjects with a normal, abnormal and clinically significant, or abnormal and not clinically significant result.

4.8. Effectiveness Analyses

Effectiveness data will be summarized as observed with no imputation for missing data. Descriptive statistics will be provided for all effectiveness variables at all timepoints by summary group. 95% confidence intervals and/or p-values for comparing the difference between subgroups of interest (e.g., females vs males) will be provided as appropriate.

All analyses will be performed for endpoints assessed at both maximum frown and at rest after maximum frown.

For the endpoints that are derived from a comparison with the baseline, two derivation rules using different reference timepoints as the baseline will be applied separately. The first reference timepoint is the OLS trial baseline. The second is the treatment-specific baseline (eg, the last value before treatment 2 for the Treatment-2 Evaluable population).

4.8.1. Time to Retreatment

The time to retreatment assessments will be summarized with point estimates of median duration and 2-sided, 95% CIs, using the log-log transformation by summary group. Estimates of survival rates and the 2-sided, 95% CI, using the log-log transformation will also be provided. Kaplan-Meier survival curves will be plotted by summary group. The time to retreatment from the first DAXI for Injection will be performed on the Treatment-2 Evaluable population only (Group B only). The time to retreatment from the second DAXI for Injection will be performed on the Treatment-3 Evaluable population only.

4.8.2. Time to Return to a Given State

The time to return to, or worse than, baseline on both the IGA-FWS and PFWS is defined as:

- Relative to OLS trial baseline:
  - For subjects with no decrease from OLS trial baseline through Week 4 of the first trial treatment for both the IGA-FWS and the PFWS at the same visit, set time to return to a given state to zero.
  - For subjects with a decrease from OLS trial baseline through Week 4 of the first trial treatment for both the IGA-FWS and the PFWS at the same visit, set time to return to a given state to the first visit at which both the IFA-FWS and the PFWS are at or worse than the OLS trial baseline value (Change ≥ 0) minus the OLS trial baseline visit.
  - For subjects that do not return to, or worse than, OLS trial baseline, the final evaluation visit will be used as the end time of the event; and, the observation will be considered censored.

- Relative to treatment-specific baseline:
  - For subjects with no decrease from treatment-specific baseline through Week 4 of the given treatment for both the IGA-FWS and the PFWS at the same visit, set time to return to a given state to zero.
  - For subjects with a decrease from treatment-specific baseline through Week 4 of the given treatment for both the IGA-FWS and the PFWS at the same visit, set time to return to a given state to the first visit at which both the IFA-FWS and the PFWS are at or worse than the treatment-specific baseline value (Change ≥ 0) minus the treatment-specific baseline visit.
  - For subjects that do not return to, or worse than, treatment-specific baseline, the final evaluation visit will be used as the end time of the event; and, the observation will be considered censored.

The time to return to 2 (moderate) or 3 (severe) on both the IGA-FWS and PFWS is defined as:

- Relative to OLS trial baseline:
  - For subjects with no visit from OLS trial baseline through Week 4 of the first treatment that has a score below 2 on both the IGA-FWS and the PFWS at the same visit, set time to return to a score of 2 or 3 to zero.
  - For subjects with a visit from OLS trial baseline through Week 4 of the first treatment that has a score below 2 on both the IGA-FWS and the PFWS at the same visit, set time to return to a score of 2 or 3 to the first visit at which both the IFA-FWS and the PFWS have a score of 2 or higher minus the OLS trial baseline visit.
  - For subjects that do not have both the IGA-FWS and the PFWS above 2 at the final evaluation visit, this visit will be used as the end time of the event; and, the observation will be considered censored.

- Relative to treatment-specific baseline:
  - For subjects with no visit from treatment-specific baseline through Week 4 of the given treatment that has a score below 2 on both the IGA-FWS and the PFWS at the same visit, set time to return to a score of 2 or 3 to zero.
  - For subjects with a visit from treatment-specific baseline through Week 4 of the given treatment that has a score below 2 on both the IGA-FWS and the PFWS at the same visit, set time to return to a score of 2 or 3 to the first visit at which both the IFA-FWS and the PFWS have a score of 2 or higher minus the treatment-specific baseline visit.
  - For subjects that do not have both the IGA-FWS and the PFWS above 2 at the final evaluation visit, this visit will be used as the end time of the event; and, the observation will be considered censored.

The time to return to, or worse than, baseline, and time to return to moderate or severe (2 or 3), on both IGA-FWS and PFWS assessments will be summarized with point estimates of median duration and 2-sided, 95% CIs, using the log-log transformation by summary group. Estimates of survival rates and the 2-sided, 95% CI, using the log-log transformation will also be provided. Kaplan-Meier survival curves will be plotted by summary group.

Analyses will be performed relative to OLS trial baseline for the Safety Evaluable population. Analyses will also be performed relative to the treatment-specific baseline for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations.

4.8.3. Proportions of Subjects Meeting a Given Criterion

The assessments of the proportion of subjects meeting a given criterion will be summarized by summary group and visit. The proportion of responders will also be graphically displayed in a plot with time on the x-axis and the proportion of subjects responding on the y-axis.

The proportion of subjects with a ≥2 point improvement, and separately a ≥1 point improvement, from baseline on both the IGA-FWS and the PFWS will be determined relative to OLS trial baseline for the Safety Evaluable subjects and relative to the treatment-specific baseline for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations. The definition for a ≥2 point improvement from baseline in both assessments is defined as:

- Relative to OLS trial baseline:
  - For any visit at which the value for either IGA-FWS or PFWS or both is missing, the visit will be considered to not show at least a 2-point improvement.
  - For any visit at which the change from OLS trial baseline is less than 2 for either the IGA-FWS or PFWS, the visit will be considered to not show at least a 2-point improvement
  - For any visit at which the change from OLS trial baseline is 2 or greater for both the IGA-FWS and PFWS, the visit will be considered to show at least a 2-point improvement.

- Relative to treatment-specific baseline:
  - For any visit at which the value for either IGA-FWS or PFWS or both is missing, the visit will be considered to not show at least a 2-point improvement.
  - For any visit at which the change from treatment-specific baseline is less than 2 for either the IGA-FWS or PFWS, the visit will be considered to not show at least a 2-point improvement
  - For any visit at which the change from treatment-specific baseline is 2 or greater for both the IGA-FWS and PFWS, the visit will be considered to show at least a 2-point improvement.

Similar rules apply for the other endpoints.

The proportion of subjects with a score of none or mild (0 or 1) on the IGA-FWS, and separately on the PFWS, will be summarized by summary group and visit for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations. Furthermore, the proportion of subjects with a score of 2 (moderate) on the IGA-FWS, and separately on the PFWS, will be summarized by summary group and visit for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations.

For the endpoints derived from the GAIS assessment, the number and percentage of subjects who achieve scores of ≥1, will be summarized by summary group and visit for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations. The number and percentage of subjects who achieve scores of ≥2, and separately ≥3, will be summarized in a similar manner.

For the GAIS score, the mean score will be summarized using descriptive statistics by summary group and visit for the Treatment-1 Evaluable, Treatment-2 Evaluable, and Treatment-3 Evaluable populations. The investigator and subject assessments will be summarized separately for both the assessment performed at maximum frown and the assessment performed at rest after maximum frown.

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4.11. Statistical/Analytical Issues

4.11.1. Adjustments for Covariates

No adjustments for covariates are planned.

[redacted]

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[redacted]

4.11.5. Data Handling Conventions

For all analyses, the protocol specified Treatment Day 0 will be referred to as Study Day 1.

4.12. Interim Analyses and Data Monitoring

No interim analysis is planned.

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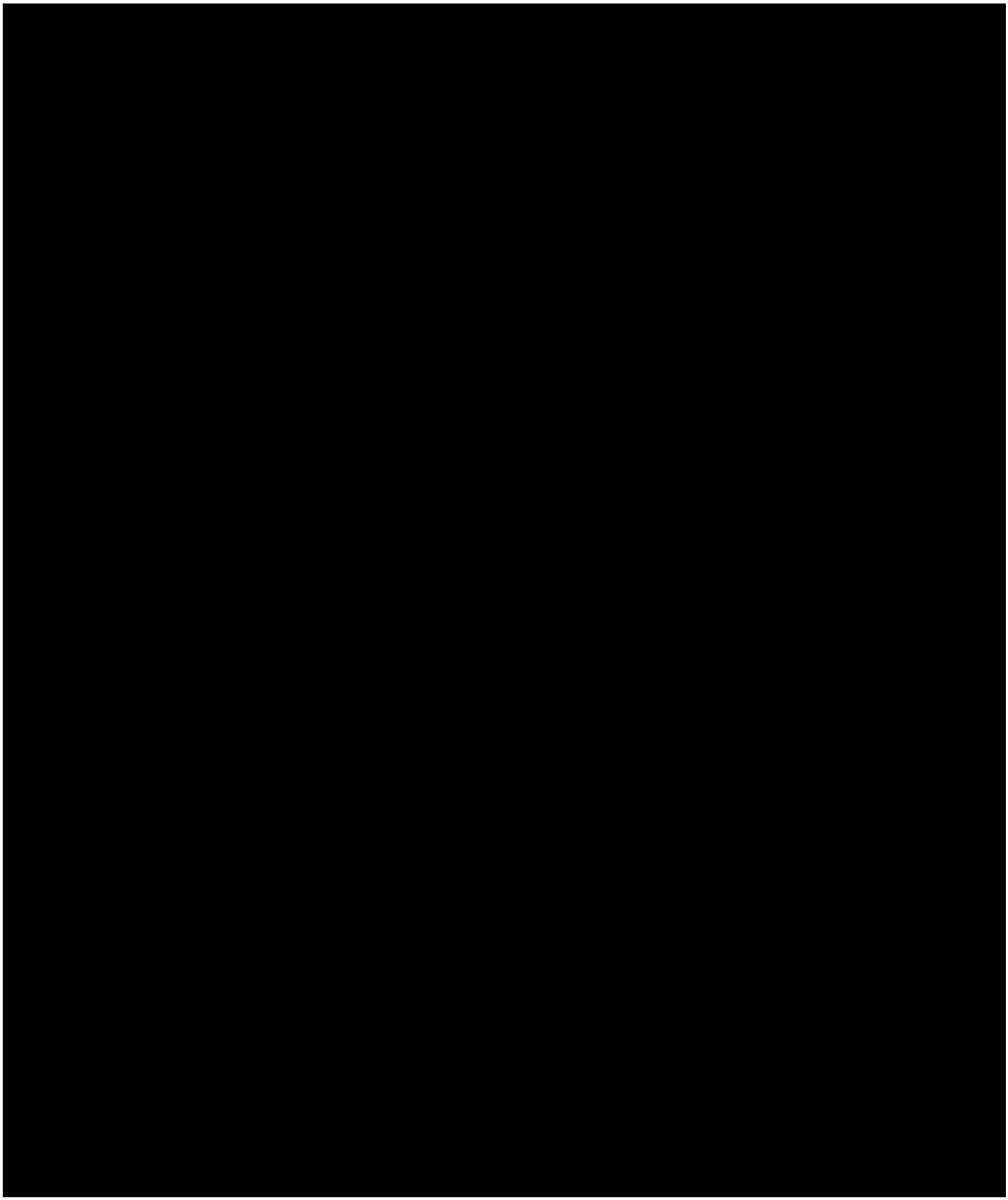

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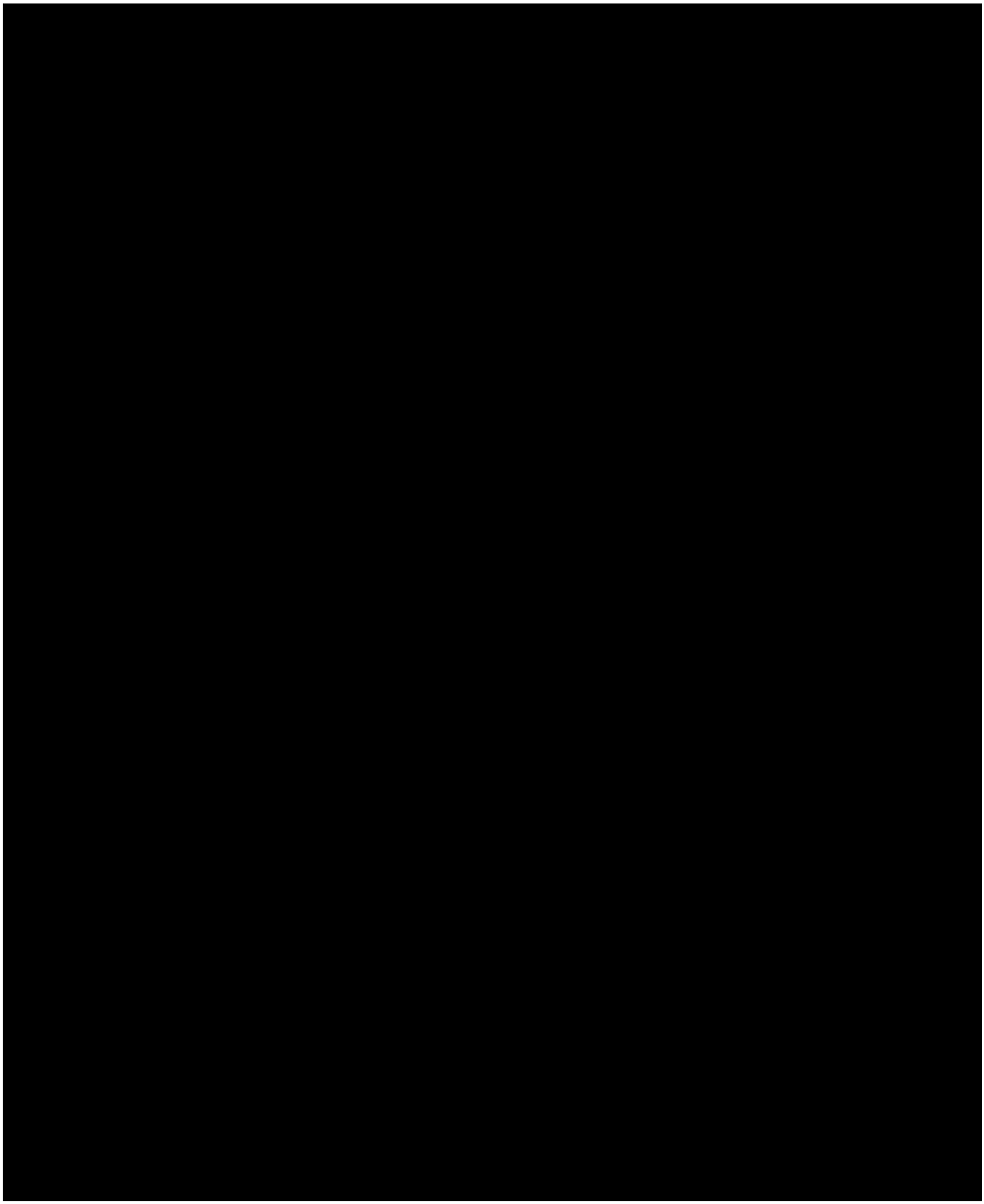

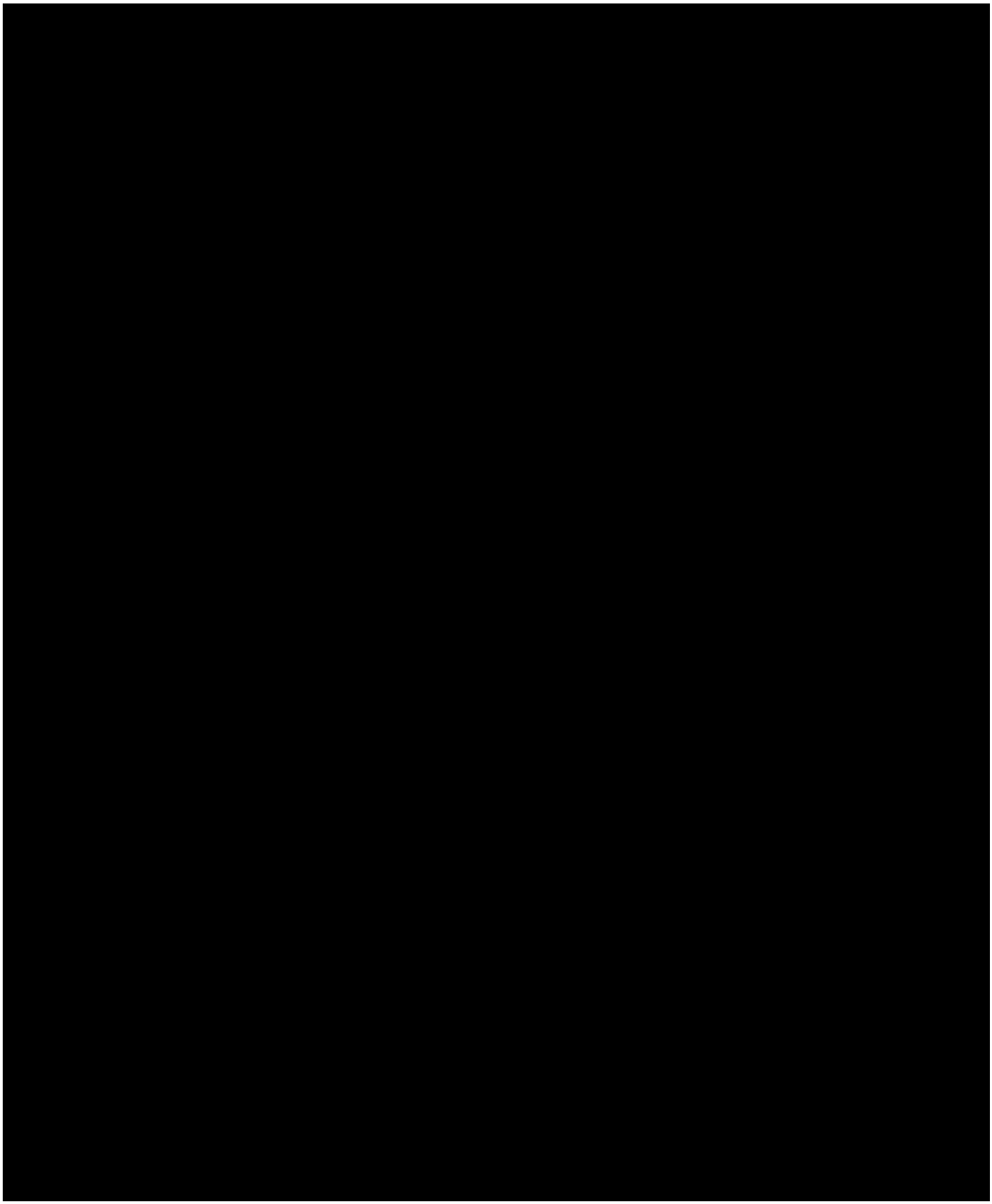

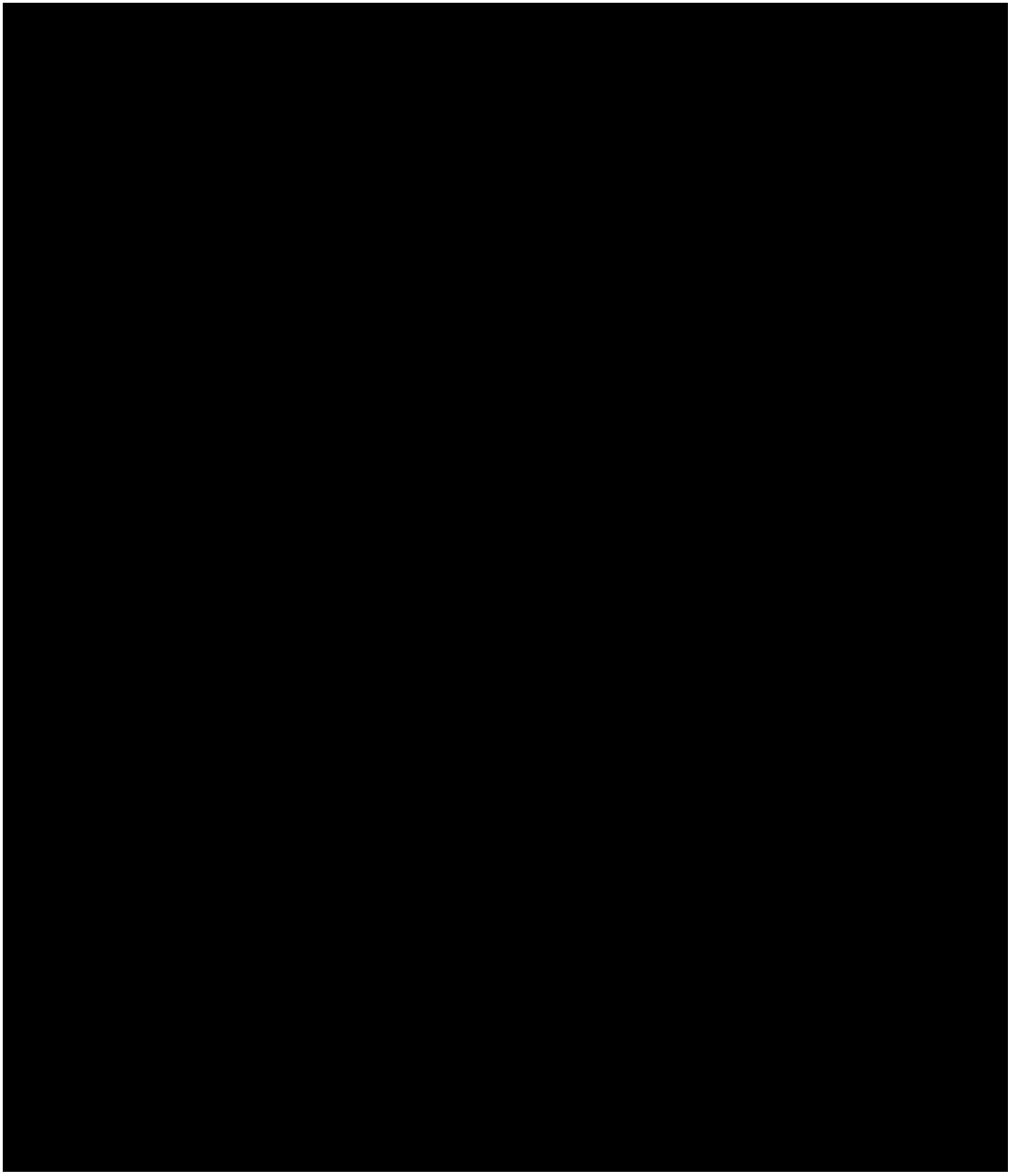

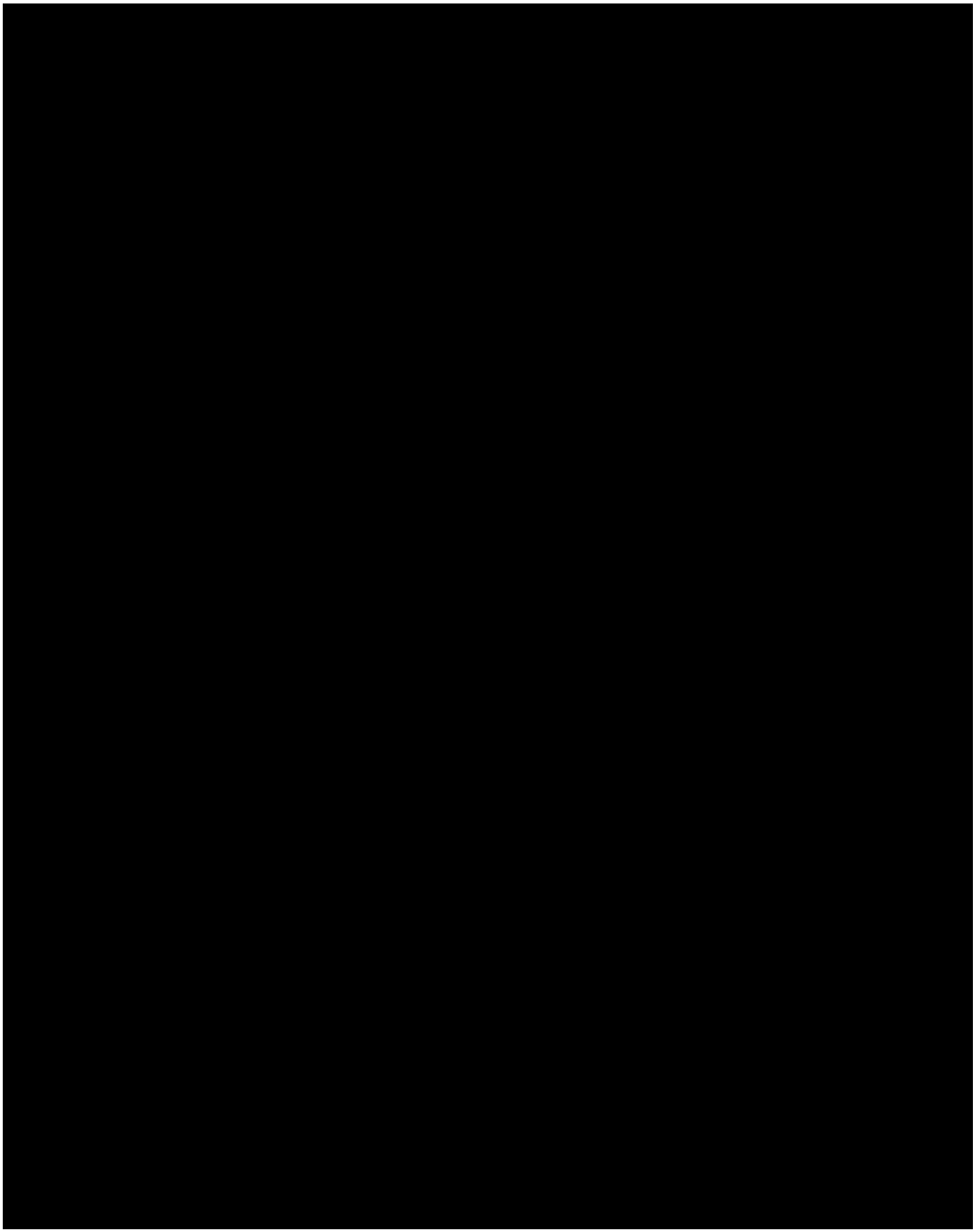

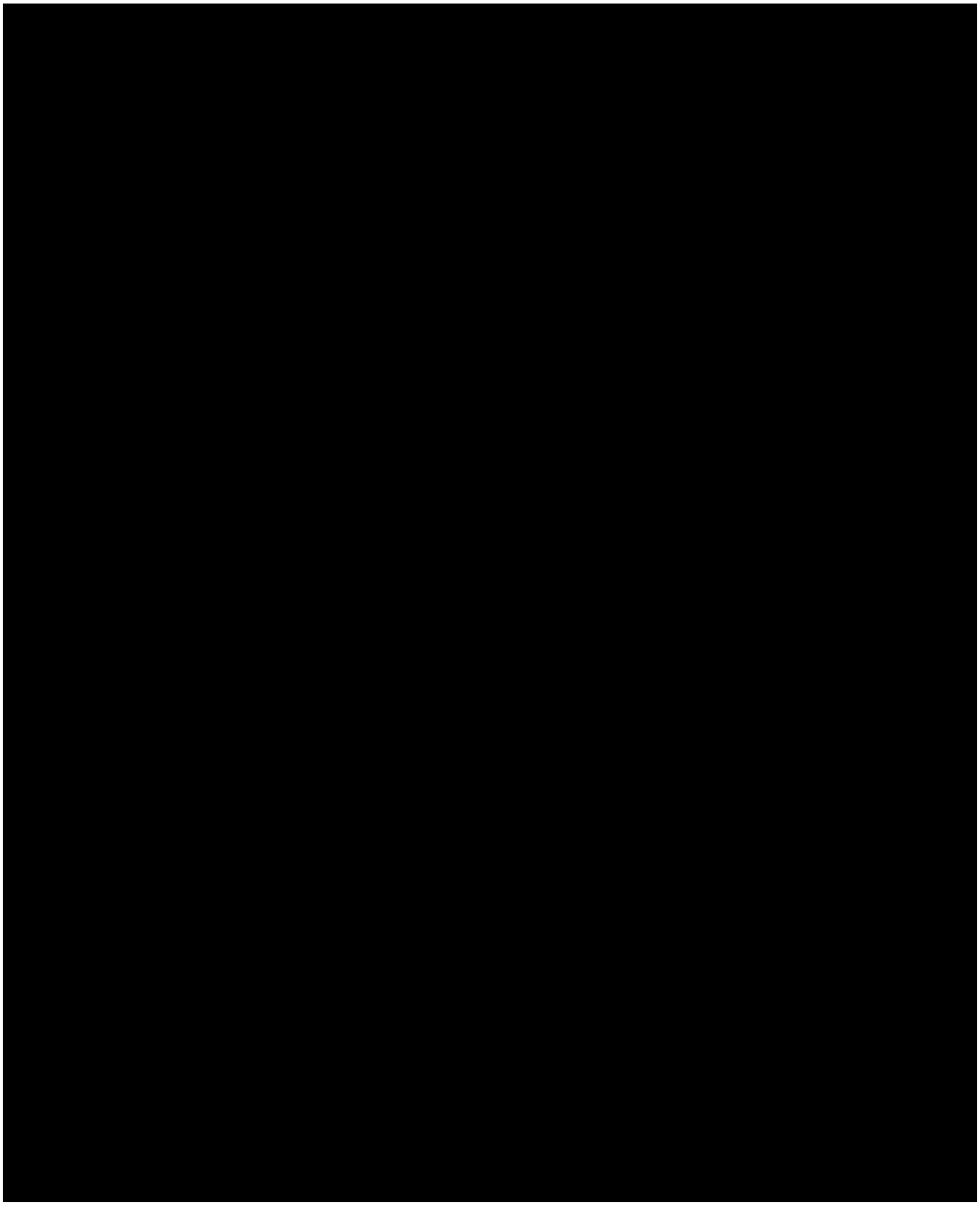

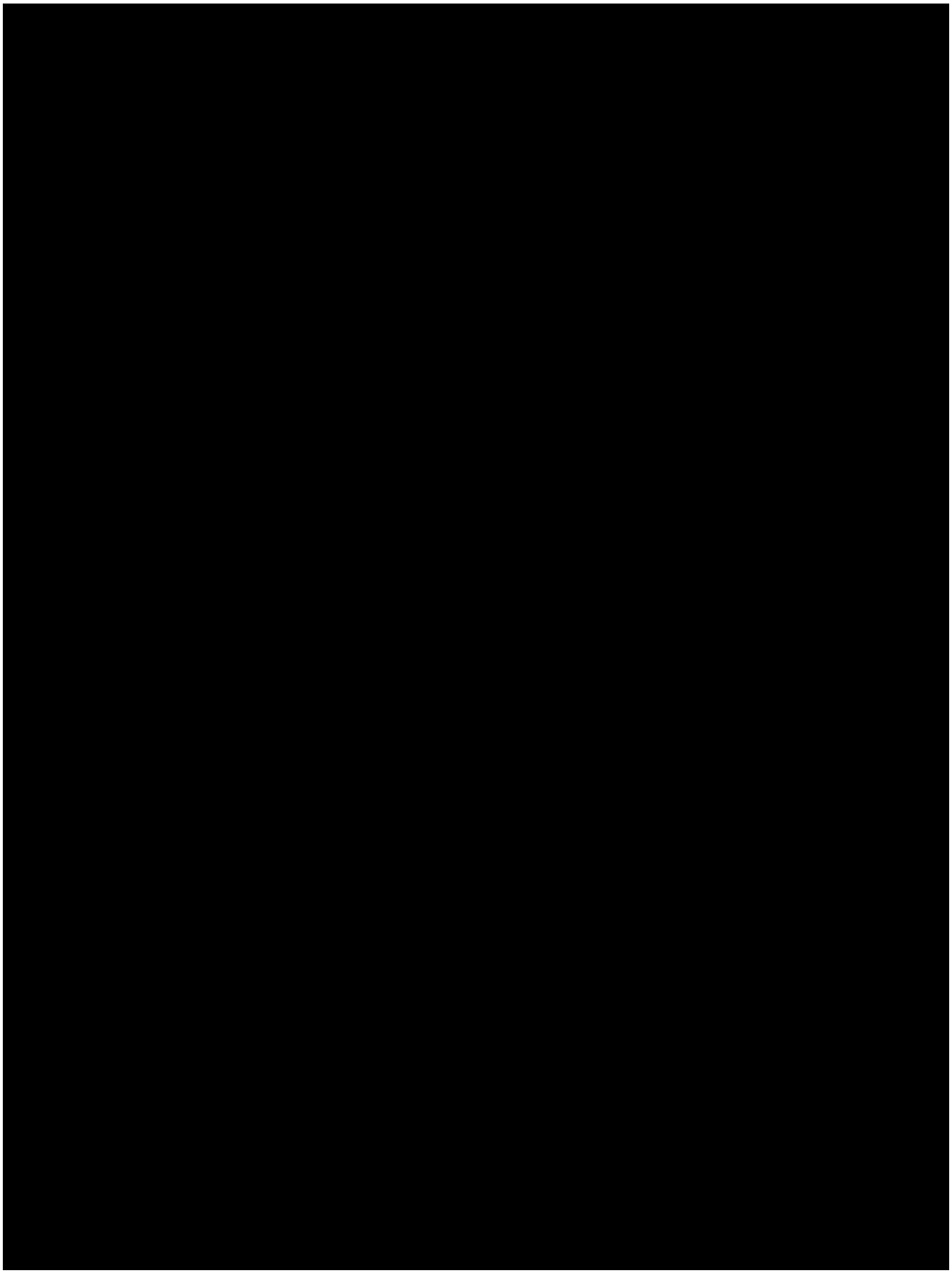

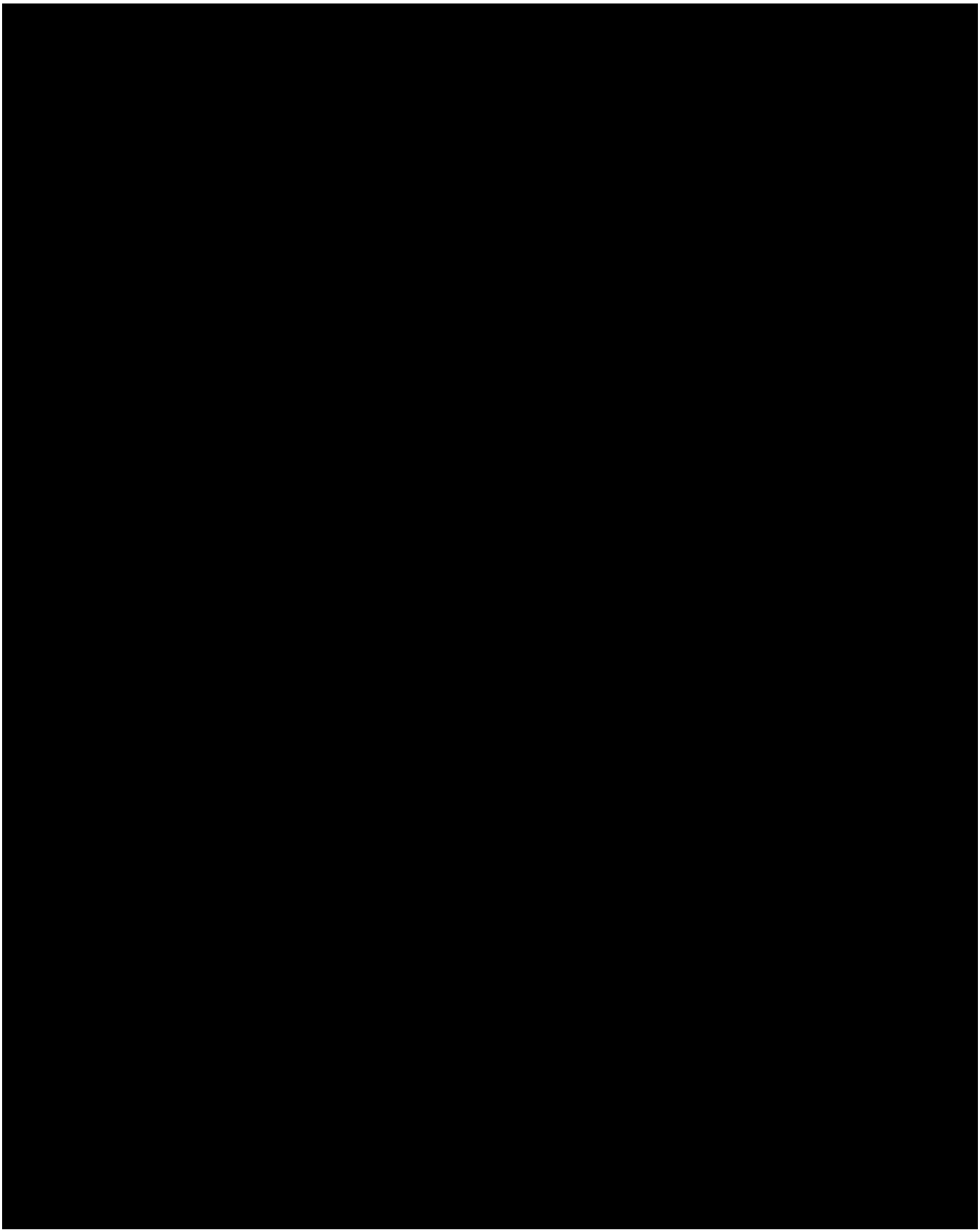

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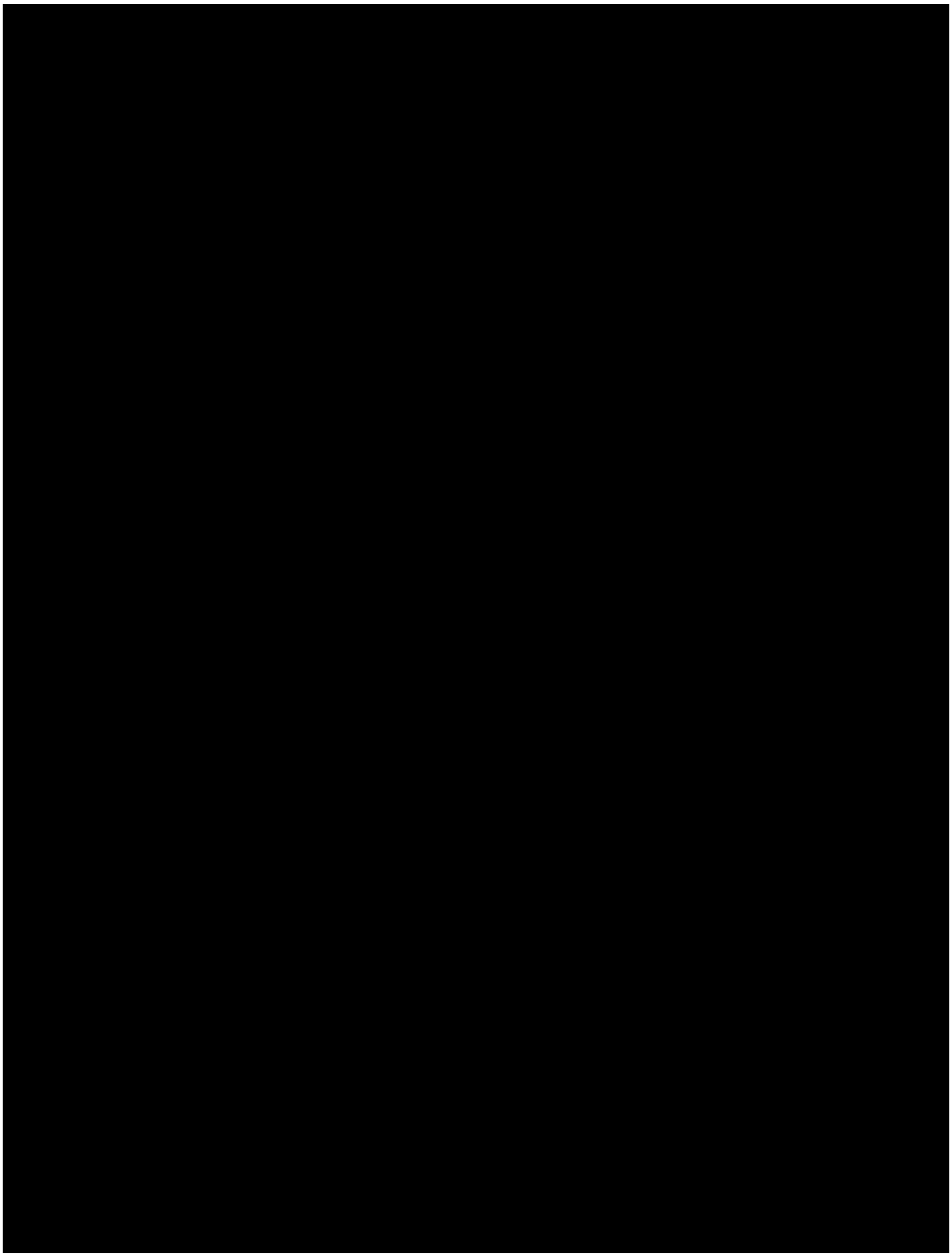

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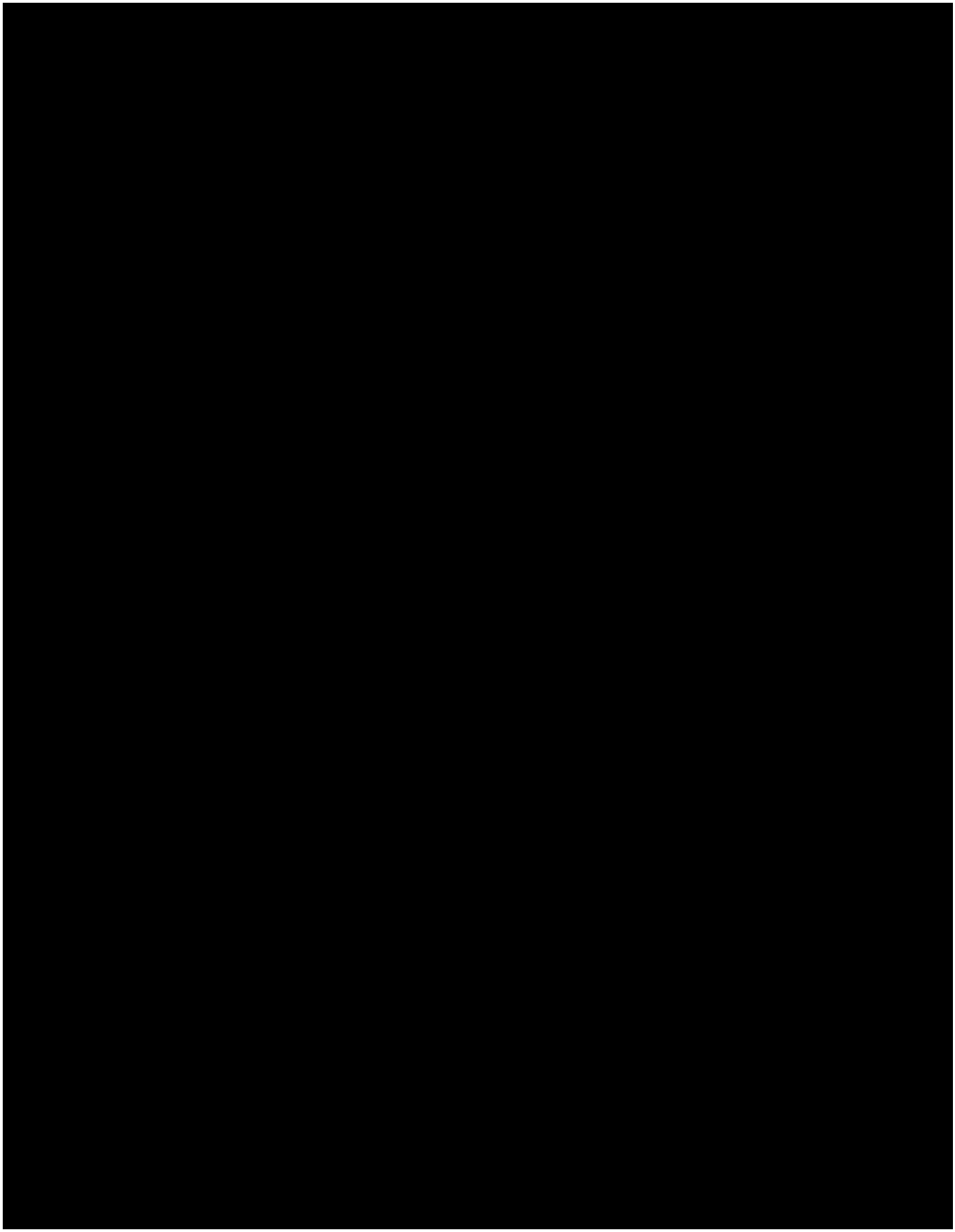

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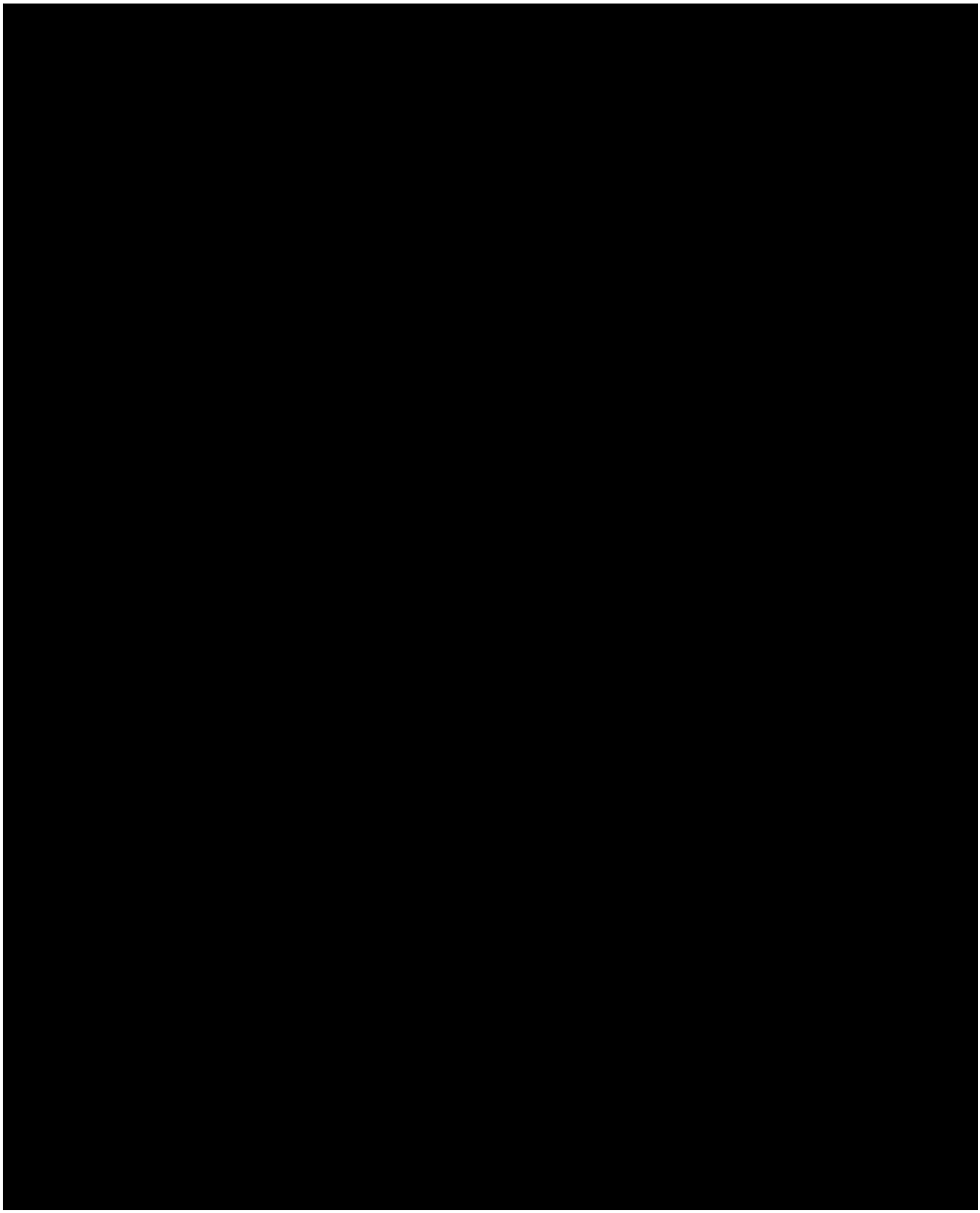

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