CLINICAL PROTOCOL

Protocol No. C601

Title: A Randomized, Double-Blind, Placebo-Controlled Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients with Prader-Willi Syndrome
NCT03440814

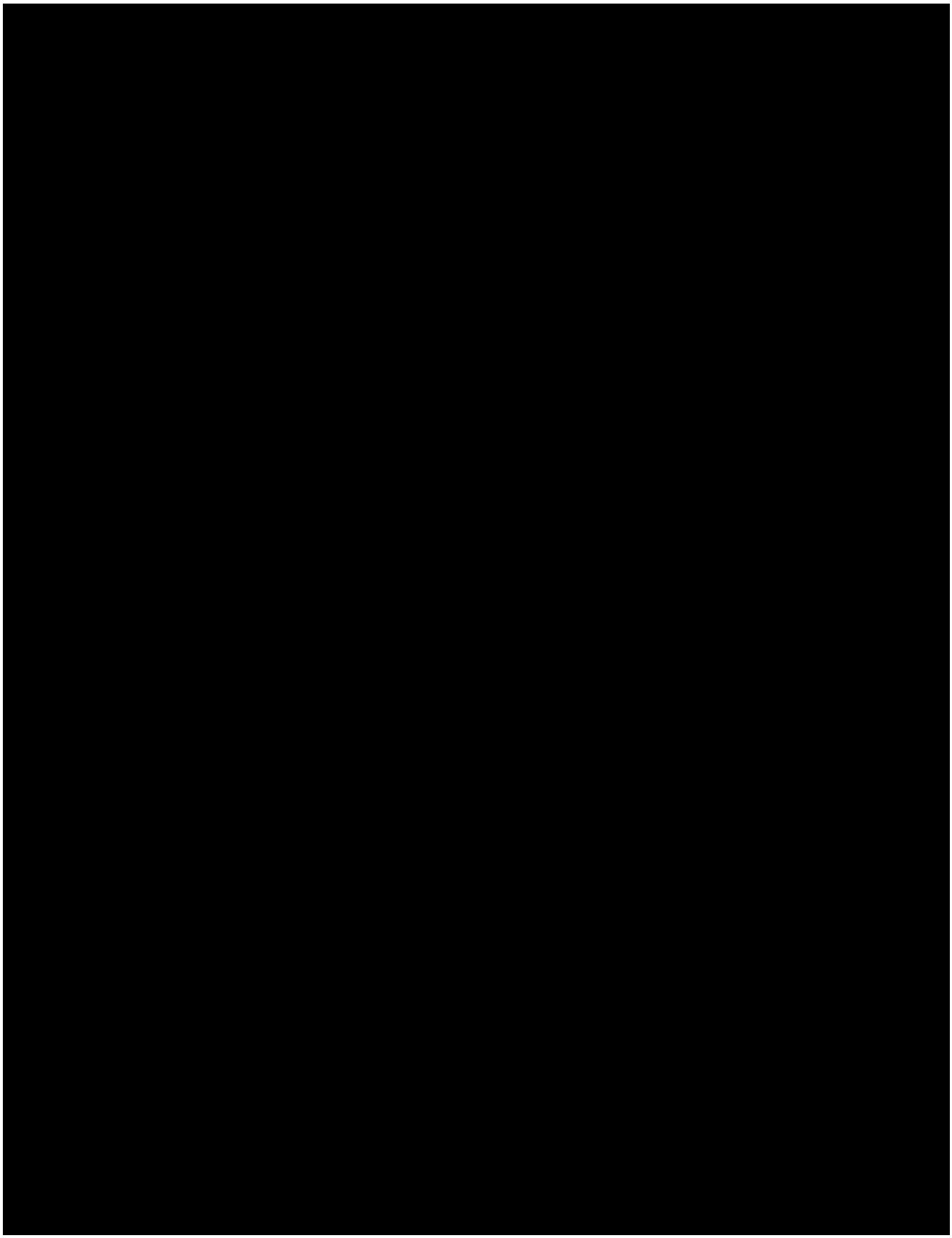
EudraCT No.: [redacted]

Version:

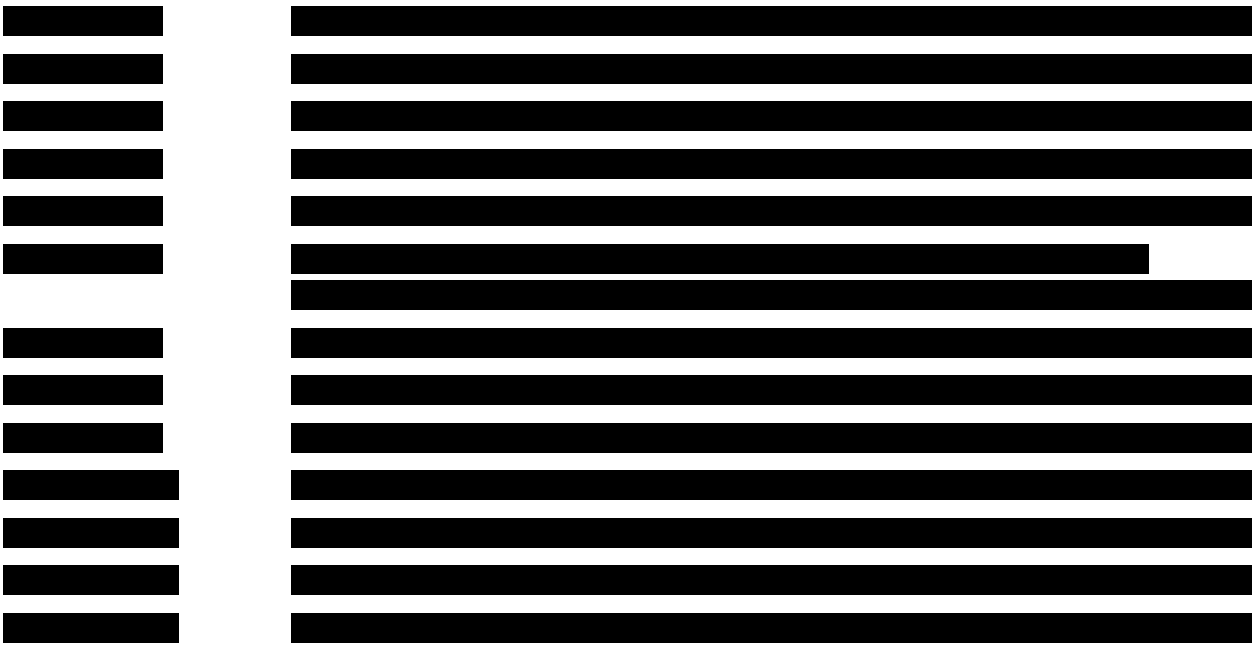
Original	28 November 2017
Amendment 1	20 February 2018
Amendment 2	19 July 2018
Amendment 3	12 November 2018
Amendment 4	26 April 2019
Amendment 4a	11 June 2019

Sponsor: Soleno Therapeutics, Inc.

[redacted]



1.0 TABLE OF CONTENTS



CHANGES FROM PREVIOUS VERSION

2.0 STUDY SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients with Prader-Willi Syndrome
Sponsor:	Soleno Therapeutics, Inc.
Phase of Development:	III
Objectives:	**Primary** The primary objective of this study is to evaluate the effects of diazoxide choline controlled-release (DCCR) tablet compared to placebo on hyperphagia in PWS patients. **Secondary** The secondary objectives of this study are to evaluate changes in body fat mass, Clinical Global Impression of Improvement (CGI-I), and Caregiver Global Impression of Change (GI-C) with DCCR compared to placebo in PWS patients. [redacted]
Study Design:	This is a multi-center, randomized, double-blind, placebo-controlled, parallel arm, phase III study comparing DCCR to placebo in approximately 105 PWS patients with hyperphagia. This study will be conducted at approximately 30 sites globally. Each subject's expected duration of study participation is approximately 105 days. [redacted]

Study Design (cont):	For subjects who are continuing on into clinical study C602, the open-label, long-term, safety extension study, C601 Visit 7 will also serve as Visit 1 in clinical study C602. For subjects who will not enroll into clinical study C602, this will be their final study visit, unless they are experiencing an adverse event at Visit 7 that requires a follow-up visit. [redacted] Randomized subjects will be titrated every two weeks with their assigned treatment, DCCR or placebo, until the target dose is achieved. The target dose is based on subject's weight.
Study Population:	Patients with genetically-confirmed Prader-Willi syndrome.
Screening Inclusion Criteria:	Potential subjects must meet all of the following inclusion criteria to be enrolled: [redacted]Provide voluntary, written informed consent (parent(s) / legal guardian(s) of subject); provide voluntary, written assent (subjects, as appropriate) [redacted]Male and female subjects, 4 years of age and older [redacted]Genetically-confirmed Prader-Willi syndrome. If confirmation by a method other than methylation analysis, subject and caregiver consent to methylation analysis. [redacted] [redacted]In a stable care setting for at least 6 months prior to Visit 1 and throughout the study [redacted]Caregiver must have been caring for the subject for at least 6 months prior to Visit 1 and will care for the subject throughout the study a minimum of 4 waking hours per day [redacted]

Screening Inclusion Criteria (continued):	[redacted]
Screening Exclusion Criteria:	Potential subjects must not meet any of the following exclusion criteria to be enrolled: [redacted] Have participated in an interventional clinical study (i.e., investigational drug or device, approved drugs or device evaluated for unapproved use) within 60 days prior to Visit 1 Entry of any subject's information or data into a non-interventional study and/or observational study (e.g., PATH for PWS) or PWS registry(ies) during the subject's participation in this study [redacted]

Screening Exclusion Criteria (continued):	[redacted] Positive urine pregnancy test (in females of child-bearing potential) Females who are pregnant or breastfeeding, and/or plan to become pregnant or to breast-feed during or within 90 days after study participation [redacted] Any other known disease and/or condition, which would prevent, in the opinion of the Investigator, the subject from completing all study visits and assessments required by the protocol
[redacted]	[redacted]
[redacted]	[redacted]

Efficacy Evaluation:	**Primary Endpoint** • Hyperphagia (HQ-CT) change from Baseline (Visit 2) to Visit 7 **Secondary Endpoints** • Body fat mass (DXA) change from Baseline to Visit 7 • Clinical Global Impression of Improvement at Visit 7 • Caregiver Global Impression of Change at Visit 7 [redacted]

Efficacy Evaluation (continued):	[redacted]
Safety Evaluation:	**Safety Endpoints** • Adverse events [redacted]

3.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AgRP	Agouti-Related Peptide
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
[redacted]	[redacted]
[redacted]	[redacted]
ATP	Adenosine triphosphate
[redacted]	[redacted]
C	Celsius
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CHI	Congenital Hyperinsulinism
Cmax	Maximum concentration
cm	Centimeters
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBC, DBC2-P	Developmental Behaviour Checklist, DBC Version 2 - Parent
DCCR	Diazoxide Choline Controlled-Release Tablet
DXA	Dual-Energy Absorptiometry
dL	Deciliter
DMF	N,N-Dimethylformamide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

Abbreviation or Term	Definition/Explanation
eGFR	Estimated glomerular filtration rate
EtOH	Ethanol
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
g	Gram
g/mol	Grams per mole
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GI-C	Global Impression of Change
GI-S	Global Impression of Severity
GLP	Good Laboratory Practices
HbA1c	Hemoglobin A1c or glycated hemoglobin test
HDL	High-Density Lipoprotein
hERG	Human Ether-a-go-go Related Gene
HFD	High-Fat Diet
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HSP	Hysterosalpingogram
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
ID	Imprinting Defect
IEC	Independent Ethics Committee
IGF-1	Insulin-Like Growth Factor
IM	Intramuscular
IPA	Isopropyl Alcohol
INR	International Normalized Ratio

Abbreviation or Term	Definition/Explanation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV, i.v.	Intravenous
IWRS	Interactive Web Response System
K^+	Potassium
K_{ATP}	ATP-Sensitive Potassium Channel
kg	Kilogram
LDL	Low-Density Lipoprotein
LFT	Liver Function Tests
MAGEL2	MAGE Family Member L2
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MeCN	Acetonitrile
MeOH	Methanol
MEK	Methyl Ethyl Ketone
mg	Milligram
min	Minute
MITT	Modified Intent-to-Treat
mL	Milliliter
µM	Micromolar
Mm	Millimeter
mrem	Millirem
msec	Millisecond
m^2	Meters Squared
NPY	Neuropeptide Y
OECD	Organisation for Economic Cooperation and Development
P	Placebo
pH	Hydrogen ion concentration

Abbreviation or Term	Definition/Explanation
PK	Pharmacokinetic(s)
PO	Pes Os, By Mouth
PP	Per Protocol
Pre	Before
PT	Prothrombin Time
PWS	Prader-Willi Syndrome
PWSP	Prader-Willi Syndrome Profile
QD	Once-a-day
QTcF	QT Interval corrected by Fridericia's Formula
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNORD	Small Nucleolar RNAs, C/D box
TdP	Torsades de Pointes
TEAE	Treatment-Emergent Adverse Events
ULN	Upper Limit of the Normal Range
UPD	Uniparental Disomy
US	United States
V	Visit
WBC	White Blood Cell

4.0 BACKGROUND

Diazoxide choline, a new chemical entity, is a benzothiadiazine that acts by stimulating ion flux through ATP-sensitive K+ channels (K_{ATP}). It is the choline salt of diazoxide, which is currently used as a treatment of infants, children and adults with hyperinsulinemic hypoglycemia. Diazoxide choline, formulated as a once-a-day extended-release tablet or DCCR (diazoxide choline controlled-release) tablets, has been studied in over 210 healthy volunteers and subjects with obesity, hypertriglyceridemia and Prader-Willi syndrome (PWS).

4.1 Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a complex neurobehavioral disorder, which is due to the absence of normally active, paternally expressed genes from the chromosome 15q11-q13 region.[1, 2] PWS is an imprinted condition with 70–75% of the cases due to a *de novo* deletion in the paternally inherited chromosome 15q11-q13 region, 20–30% from maternal uniparental disomy of chromosome 15 (UPD), and the remaining 2–5% from either microdeletions or epimutations of the imprinting center (i.e., imprinting defects; IDs).[3, 4] Prader-Willi syndrome has an has been estimated to afflict 350,000 to 400,000 individuals worldwide.[1]

There are no currently-approved products to treat hyperphagia in patients with PWS. Although growth hormone is approved in patients with PWS, it only addresses the short stature, and may reduce hypotonia, limit the accumulation of visceral fat, and reduce cognitive impairment.[5] A global patient survey conducted by the Foundation for Prader-Willi Research (n=779), found that 96.5% of respondents rated reducing hunger and 91.2% rated improving behavior around food as very important or most important symptom to be relieved by a new treatment. Physical function and body composition symptoms for which a high percentage of respondents indicated were very important or most important included: improving metabolic health (reduces fat / increases muscle 92.9%) and the related symptom of improves activity and stamina (81.3%). Behavioral and cognitive symptoms rated as very or most important were: reduces obsessive/compulsive behavior (85.2%), improves intellect/development (84.6%), and reduces temper outburst severity and frequency (83.2%).[6]

4.2 Investigational Agent

[redacted]

[redacted]

[redacted]

4.2.1 Mode of Action

The lack of expression of the SNORD116 gene is associated with the overexpression of neuropeptide Y (NPY) a potent appetite stimulatory neuropeptide.[7] Additionally, in PWS, leptin's regulatory control of hypothalamic neurons, particularly the NPY / agouti-regulated peptide (AgRP) neurons, is diminished. Diazoxide choline appears to be effective in the treatment of the resulting hyperphagia by agonizing the K_{ATP} channels in these dysregulated neurons, thereby amplifying the regulatory control of leptin. This leads to reduced secretion of NPY by these neurons, resulting in decreased hyperphagia.

4.3 Nonclinical and Clinical Data

Summaries of the studies in this section are included in the Investigator's Brochure for DCCR.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3.2 Summary of Clinical Data

[redacted]

[redacted]

[redacted]

4.3.2.2 Clinical Safety and Efficacy Studies

Clinical study PC025 in PWS was conducted using DCCR. This single-center, randomized withdrawal study consisted of 3 phases. The first phase of the study was open-label during which subjects were initiated on a DCCR dose [redacted] The second phase of the study was a double-blind, placebo-controlled phase. Any subject who showed [redacted] would be designated a Responder,

[redacted] The first dose of double-blind treatment was administered at the visit on Day 69. All subjects enrolled in the study were eligible to participate in an open-label treatment extension phase for 6 months.

PWS subjects treated with DCCR in this clinical study showed clinically relevant, statistically significant and dose dependent improvements in hyperphagia from Baseline to Day 69 (open-label phase). [redacted]

The adverse events associated with DCCR treatment and deemed related to DCCR by the Investigator in the prior PWS study in more than one subject include: peripheral edema, glucose tolerance impaired, and hyperglycemia.

In all of the studies with DCCR completed to date, two serious adverse events (SAEs) have been reported (neither of which were deemed to be related to DCCR): a case of pneumonia and an overnight hospitalization of a PWS subject with poorly controlled psychiatric disease. Adverse events (AE) reported in these studies were typically mild to moderate in severity, self-limiting and were consistent with the existing diazoxide product labels and the results of previously published clinical studies and case reports. DCCR [redacted] was well tolerated.

The available clinical data with DCCR as well as the nonclinical data with diazoxide choline and diazoxide indicate that DCCR could be used to treat multiple aspects of PWS including the characteristic hyperphagia, aggressive behaviors, and accumulation of excess body fat.

[redacted]

[redacted]

[redacted]

[redacted]

4.5 Dose Selection and Study Duration Rationale

4.5.1 Dose Selection Rationale

[redacted]

[redacted]

[redacted]

4.5.2 Study Duration Rationale

[redacted]

4.6 Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No change to the protocol will be implemented without the prior review and approval of the IRB/IEC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the change will be reported to the Sponsor and IRB/IEC as soon as possible.

4.7 Population

The population will consist of patients with genetically-confirmed Prader-Willi syndrome (PWS).

5.0 TRIAL OBJECTIVES

5.1 Primary

The primary objective of this study is to evaluate the effects of diazoxide choline controlled-release (DCCR) tablet compared to placebo on hyperphagia in PWS patients.

5.2 Secondary

The secondary objectives of this study are to evaluate changes in body fat mass, Clinical Global Impression of Improvement (CGI-I), and Caregiver Global Impression of Change (GI-C) with DCCR compared to placebo in PWS patients.

5.3 Additional Objectives

[redacted]

6.0 TRIAL DESIGN

6.1 Study Endpoints

6.1.1 Primary Study Endpoints

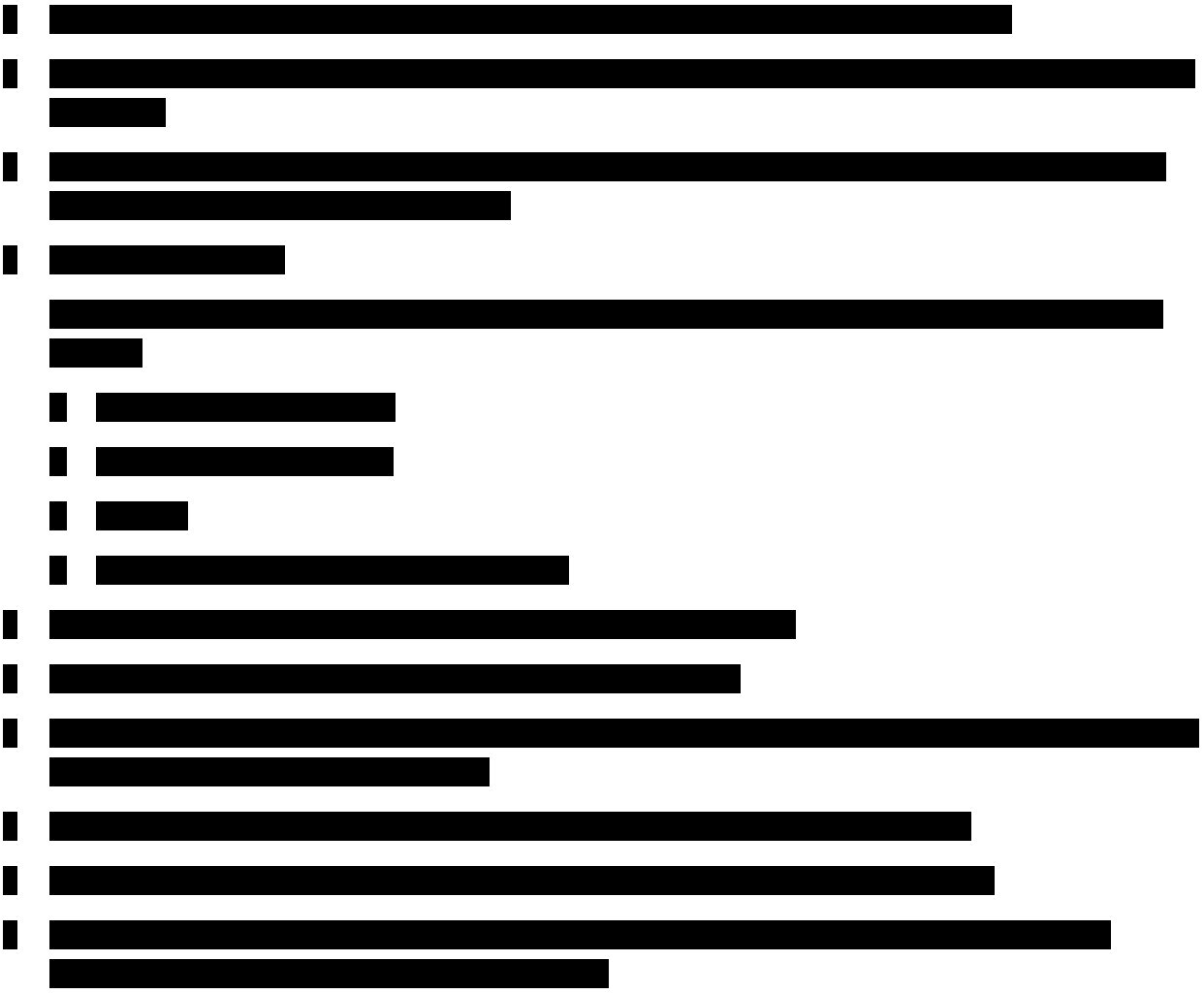
- Hyperphagia (HQ-CT) change from Baseline (Visit 2) to Visit 7

6.1.2 Secondary Study Endpoints

The following secondary endpoints, in order, are:

- Body fat mass (DXA) change from Baseline to Visit 7
- Clinical Global Impression of Improvement at Visit 7
- Caregiver Global Impression of Change at Visit 7

6.1.3 Additional Study Endpoints



[redacted]

6.1.4 Safety Endpoints

- Adverse events

[redacted]

[redacted]

6.2 Study Design/Type

This is a multi-center, randomized, double-blind, placebo-controlled, parallel arm, phase III study comparing DCCR to placebo in approximately 105 PWS subjects with hyperphagia. This study will be conducted at approximately 30 sites globally. [redacted]

Figure 1: Study Design Schematic

6.3 Randomization

[redacted]

The randomization code will be generated and maintained by an individual independent of the Sponsor, Soleno Therapeutics, Inc. (Soleno), and those related to the day-to-day conduct of the study and/or the management of the study.

6.3.1 Blinding

[redacted]

Study drug will be blinded. Placebo tablets matching the size, shape, and color of the respective DCCR tablet strengths will be used.

6.3.2 Additional Steps Taken to Minimize/Avoid Bias

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4 Maintenance of Randomization Code

The randomization code will be generated and maintained by an individual independent of the Sponsor and those related to the day-to-day conduct of the study and/or the management of the study.

In order to eliminate an immediate risk to a subject, Investigators will be able to obtain a specific subject's treatment group assignment.

6.5 Trial Treatment

6.5.1 Dose Description

Subjects will be randomized to one of two study treatments, diazoxide choline controlled-release (DCCR) or placebo. Diazoxide choline is formulated into an extended-release tablet. [redacted] Placebo tablets matching the size, shape, and color of the respective DCCR tablet strengths, but not containing any diazoxide choline, will be used.

6.5.2 Packaging and Labeling

[redacted]

The Interactive Web Response System (IWRS) will indicate which cards will be assigned to each subject.

6.5.3 Storage and Handling

[redacted]

The DCCR and placebo tablets are investigational drug products and must be stored, handled, and administered in accordance with this protocol, the Investigator's Brochure and labeling, as well as all applicable laws, regulations, and institution requirements.

6.6 Duration

Each subject's expected duration of study participation is approximately 105 days; visit windows are described in Section 9.0. [redacted] For subjects who are continuing on into clinical study C602, Visit 7 will also serve as Visit 1 in clinical study C602. For subjects who will not enroll into clinical study C602, this will be their final study visit, unless they are experiencing an adverse event at Visit 7 that requires a follow-up visit.

6.7 Discontinuation of the Study

Based on studies conducted with DCCR to date, it is not expected that serious safety issues will arise that would require a discontinuation of the study. The Data Safety Monitoring Board (DSMB) will minimally review unblinded safety data twice during the study:

- [redacted]
- [redacted]

Additional unblinded safety data reviews and/or ad hoc reviews of unblinded safety data by the DSMB if safety signals warrant more frequent scrutiny (i.e., similar CTCAE Grade 3 or higher suspected adverse reactions occurring in excess in the DCCR group compared to placebo) may be requested at the discretion of the DSMB.

Based on the DMSB's review of these unblinded data, study discontinuation reasons may include:

- The sponsor determines that it is unsafe to continue because of an unexpected safety signal not otherwise clinically anticipated in randomized subjects without relevant medical history
- Significant imbalance in rate of serious, unexpected adverse reactions that, independent of study drug, are not clinically anticipated in subjects randomized to DCCR versus placebo in subjects without relevant medical history
- Significant imbalance in rate of serious adverse reactions that, independent of study drug, are not clinically anticipated in subjects randomized to DCCR versus placebo in subjects without relevant medical history

[redacted]

[redacted]

6.8 Product Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain an inventory record to document the receipt, dispensation and return of each blinded treatment card.

[redacted]

[redacted]

6.9 Data Identification

[redacted]

[redacted]

Data that are entered directly into an electronic medium (e.g., EDC, tablet, etc.) together with the metadata, are considered eSource data and are kept together as an electronic record (eSource document) for capture, transmission and/or storage.

[redacted]

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Screening Assessments

Potential subjects must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for study enrollment. Assessments of the subject or reports the subject

and/or caregiver provide will be used to determine eligibility at the Screening Visit (Visit 1). If the subject does not meet these criteria, he/she will be considered a screen failure. The subject/caregiver must not be informed of the reason for failure to meet the screening criteria until the study is completed.

7.1.1 Screening Inclusion Criteria

Potential subjects must meet all of the following inclusion criteria to be enrolled:

- Provide voluntary, written informed consent (parent(s) / legal guardian(s) of subject); provide voluntary, written assent (subjects, as appropriate)
- [redacted]
- Genetically-confirmed Prader-Willi syndrome. If confirmation by a method other than methylation analysis, subject and caregiver consent to methylation analysis.
- [redacted]
- In a stable care setting for at least 6 months prior to Visit 1 and throughout the study
- Caregiver must have been caring for the subject for at least 6 months prior to Visit 1 and will care for the subject throughout the study a minimum of 4 waking hours per day
- [redacted]

7.1.2 Screening Exclusion Criteria

Potential subjects must not meet any of the following exclusion criteria to be enrolled:

- [redacted]

- Have participated in an interventional clinical study (i.e., investigational drug or device, approved drugs or device evaluated for unapproved use) within 60 days prior to Visit 1

- [redacted] Positive urine pregnancy test (in females of child-bearing potential)
- [redacted] Females who are pregnant or breastfeeding, and/or plan to become pregnant or to breast-feed during or within 90 days after study participation

[redacted]

- [redacted] Any other known disease and/or condition, which would prevent, in the opinion of the Investigator, the subject from completing all study visits and assessments required by the protocol

[redacted]

[redacted]

7.3 Subject Withdrawal

Subjects and/or parent (s) / legal guardian(s) are free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Female subjects who become pregnant will be withdrawn from the study. [redacted]

[redacted]

[redacted]

8.0 TREATMENT OF SUBJECTS

8.1 Treatments to be Administered

DCCR or placebo doses will be administered orally, once daily in the morning with water or other beverage. Tablets must be swallowed whole and should not be broken, crushed or chewed.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Drug product will be packaged for home administration.

[redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

8.3 Dose Maintenance

Once the target dose is reached, the subject will be maintained on that dose for the remainder of the treatment period.

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

8.6 Medication

All concomitant medications (i.e., pharmaceuticals, biologics, herbal preparation, homeopathy, nutraceuticals, or procedures [e.g., acupuncture, vagal stimulation]) will be approved by the Medical Monitor prior to Visit 2. Once the subject is randomized, any new, chronic, concomitant medication given to the subject should be discussed with the Medical Monitor.

8.6.1 Prohibited Medications and Procedures

The following medications are not permitted within 3 months prior to Screening (Visit 1) and during the study:

- Anti-obesity medications or other medications (including herbal preparations, over-the-counter products) or procedures for weight reduction
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Any investigational drugs or devices

[redacted]

8.7 Monitoring for Subject Compliance

[redacted] A member of the study site personnel will review the used study medication cards and assess the subject's compliance with the study drug administration. [redacted]

9.0 STUDY PROCEDURES

The following sections describe the procedures and assessments that will be performed during the study. The Schedule of Events, located in Section 9.2, indicates the frequency of these procedures and assessments.

[redacted]

[redacted]

[redacted]

9.1 Description of Study Procedures and Assessments

9.1.1 Informed Consent / Assent

At the beginning of the Screening Visit, potential participants and their parents(s) or legal guardian(s) will be given an IRB/IEC-approved informed consent form and an IRB/IEC-approved assent form by a member of the study site personnel (i.e., study coordinator, Investigator, or other study site personnel). Parent(s) / legal guardian(s) of potential participants and potential participants will be provided time to read the consent and assent forms as well as the opportunity to ask questions and have their questions answered prior to the initiation of any study-specific assessments. Parents / legal guardians of subjects must voluntarily provide written informed consent and subjects must voluntarily provide written consent or assent, as applicable, before any study-related assessments are performed. Once signed by the parent(s) / legal guardian(s), subject and the study site personnel performing the consent process, a copy of the consent form and assent form, as applicable, will be given to the parent(s) / legal guardian(s). The original forms will be stored in the study site's files. The subject's medical records/source documents must include documentation that written informed consent and written assent was obtained from parent(s) / legal guardian(s) and subject, and that the parent(s) / legal guardian(s) of subject received copies of the signed, fully-executed informed consent form and assent form. In the event that the caregiver is not the parent or legal guardian, the source documents will need to include documentation that the caregiver was designated by the parent / legal guardian to complete questionnaires for the subject. All of the applicable eligibility criteria for the designated caregiver must be met.

9.1.2 Medical History, Medications and Demographics

[redacted] subjects will be asked about subject's relevant medical history and any medication and supplements (e.g., homeopathy, natural health products, etc.) the subject is currently taking or has taken, or procedures performed within 3 months of the Screening Visit.

[redacted] In addition, the subject's demographic information (age, gender, race, and ethnicity) will be collected. Potential fertility should be assessed. Subjects who are considered

potentially fertile should receive contraception instruction as deemed necessary by the Investigator. Refer to Appendix 1 for additional information.

[redacted]

9.1.3 Physical Examination

A full physical examination (exam), including all major body systems, will be performed at each visit [redacted]

Any conditions or symptoms reported after the subject is enrolled at the Screening Visit will be recorded as an AE on the AE eCRF. This includes new events, conditions, disease-related signs or symptoms that have worsened in severity or increased in frequency, and any event or finding that the Investigator feels is clinically significant.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

9.1.4 Vital Signs

Vital signs will be measured at every visit [redacted] Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, and respiration. [redacted]

[redacted]

9.1.5 Weight

Body weight will be measured at every visit [redacted]

[redacted]

[redacted]

9.1.7 Height

Height will be measured at the Baseline Visit [redacted] and the End of Study Visit [redacted]

[redacted]

9.1.8 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed at the Screening Visit (Visit 1), Visit 6 and the End of Study Visit (Visit 7). It is not necessary for the subject to be fasting for any ECGs.

[redacted].

The ECG performed at the Screening Visit will serve as the baseline ECG to evaluate changes. Nurses or investigators experienced in performing ECGs will perform the ECGs.

[redacted]

A trained cardiologist at the study site will review the ECG output and provide an assessment of the intervals, segments, abnormalities of T-wave or U-wave morphology, and a diagnostic statement to the investigator.

9.1.9 Laboratory Tests

For the blood tests, subjects will need to fast overnight (at least 8, but preferably 10-12 hours prior to the collection of their blood). They must not have anything to eat or drink, except water. The following blood tests will be performed on blood collected, prior to study drug administration during the study at the Visits as defined in the Schedule of Events (Section 9.2).

- Fasting Plasma Glucose
- Fasting Plasma Insulin
- HbA1c
- IGF-1
- Chemistry Panel

- Total Bilirubin
- Direct Bilirubin
- Indirect Bilirubin (calculation)
- Alkaline Phosphatase
- Alanine Transaminase (ALT)
- Aspartate Aminotransferase (AST)
- Gamma-Glutamyl Transferase (GGT)
- Magnesium
- Chloride
- Calcium
- Phosphorus
- Total Protein
- Albumin
- Globulin (calculation)
- Uric Acid
- Creatine Kinase
- Blood Urea Nitrogen
- Creatinine
- Estimated glomerular filtration rate (calculated-screening only)
- Sodium
- Potassium
- Bicarbonate

- Hematology Panel
  - Hemoglobin
  - Hematocrit
  - WBC
  - RBC
  - RBC morphology
  - MCV
  - MCH
  - MCHC
  - Platelets
  - Neutrophils (abs, %)
  - Lymphocytes (abs, %)
  - Monocytes (abs, %)
  - Basophils (abs, %)
  - Eosinophils (abs, %)
- Coagulation Panel
  - APTT
  - PT
  - INR
- Lipid Panel
  - Triglycerides
  - Total Cholesterol
  - HDL Cholesterol
  - Non-HDL Cholesterol
  - LDL Cholesterol
- Urinalysis
  - Color and clarity
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Bilirubin
  - Urobilirubin
  - Blood
  - Nitrite
  - Leukocyte esterase
  - Microscopic

[redacted]

Instructions on sample collection, processing, storage, packaging and shipping will be provided in the laboratory manual.

9.1.9.1 Monitoring of Laboratory Results

Each subject's laboratory reports will be sent by the central laboratory to the Investigator, who will assess the results for clinical significance. [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted] [redacted]	[redacted] [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.12 Urine Pregnancy Test

At every visit [redacted], female subjects of childbearing potential will be given a urine pregnancy test at the clinic. Subjects with a positive urine pregnancy test will be excluded or withdrawn from the study if confirmed by a serum pregnancy test. [redacted]

9.1.13 Enrollment

At Visit 1, subjects who meet the screening eligibility criteria will be eligible for enrollment into the run-in period of the study. Subjects will be assigned a unique identification number.

9.1.14 Randomization

At Visit 2, subjects who meet the eligibility criteria for randomization will be eligible for randomization into the study.

9.1.15 Dual-Energy Absorptiometry (DXA)

[redacted] dual-energy absorptiometry (DXA) will be used to measure the subjects' body composition. Whole body (with head) scans will be performed. Reports should include a breakdown of the following regions: left arm, right arm, trunk, left leg, right leg, and head. Each region should be evaluated for body fat mass (g), lean body mass (g), total mass (g) and percent (%) body fat. If the DXA scan report includes Region % fat and Tissue %fat, then the Region % fat should be recorded on the eCRF for percent body fat.

[redacted]

9.1.16 Clinical Global Impression Scales

Two Clinical Global Impression (CGI) scales are completed by the Investigator: CGI of Severity and CGI of Improvement. For the these scales, it is important for the Investigator to establish the presence of relevant symptoms, their frequency, intensity or severity and their effect on the major areas of the subject's life such as work, home, school and relationships.

[redacted]

9.1.16.2 Clinical Global Impression of Improvement (CGI-I)

The Clinical Global Impression of Improvement (CGI-I) for Improvement is a single statement designed to assess the Investigator's overall perception of change in the subject's condition across the course of the clinical trial. The Investigator provides a response to "Compared to the subject's condition at enrollment, the subject's condition is:" by rating the subject's behavior using a 7-point response scale: Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, and Very much worse. The Investigator should only take into account the subject's PWS condition.

[redacted]

9.1.17 Caregiver-Completed Questionnaires

Caregiver questionnaires and interviews should be administered in a relaxed, informal setting. [redacted] The caregiver should consider all environments and situations including, but not limited to, school, work, and outside activities. In addition, nights and weekends should be considered.

[redacted]

9.1.17.1 Hyperphagia Questionnaire - Clinical Trials (HQ-CT)

Hyperphagia-related behaviors will be assessed by the validated hyperphagia questionnaire for clinical trials (HQ-CT), an instrument designed to measure symptoms of food related preoccupations and behaviors that will be completed by the caregiver [redacted] The HQ-CT

consists of nine items with responses ranging from 0–4 units each (possible total score range: 0−36). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.17.3 Caregiver Global Impression of Change (GI-C)

The Caregiver Global Impression of Change (GI-C) is a single statement designed to assess the caregiver's overall perception of change in the subject across the course of the clinical trial. The caregiver provides a response to "Please choose the response below that best describes the overall change in the person's PWS since they started taking the study medication" using a 7-point graded response scale: Very much better, Moderately better, A little better, No change, A little worse, Moderately worse, and Very much worse.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.18 Study Drug Dispensation

[redacted]

The subject will be provided a sufficient supply of study drug plus some overage for daily administration of the assigned dose until the subsequent visit.

[redacted]

9.1.19 Study Drug Administration

The study drug is to be administered by mouth (PO) once daily in the morning at approximately the same time, with water or another beverage. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.20 Study Drug Accountability

At Screening (Visit 1), the caregiver will be instructed on how to the record the date and time when the study drug is taken on the study medication cards. At each subsequent visit, a member of the study site personnel will review with the caregiver the recorded information on the study medication cards then document dosing compliance and note discrepancies, if any, in the source documents and on the appropriate eCRF.

[redacted]

9.1.21 Adverse Events

Subjects will be monitored for safety from the time they are enrolled at the Screening Visit (Visit 1) until the End of Study Visit (Visit 7). Any conditions or symptoms reported will be recorded as an AE in the subject's source documents and on the AE eCRF page. Subjects who have an ongoing AE related to study drug will be followed until resolution or stabilization of the event.

[redacted]

9.1.22 Concomitant Medications / Procedures

Medications taken and procedures performed [redacted] will be recorded in the subject's source document [redacted]

9.2 Schedule of Events

Visit Number	1	2		[redacted]	[redacted]	5[redacted]	6[redacted]	7†[redacted]
	Screening	Pre-Rand	Post-Rand					End of Study
Day[redacted]	-14	0		14	28	42	56	91
Week	-2	0		2	4	6	8	13
Informed Consent, Assent	X							
Demography	X							
Medical History	X	X*						
Screening Inclusion/Exclusion Criteria Review	X							
Enrollment	X							
Randomization Inclusion/Exclusion Criteria Review		X						
Randomization		X						
Physical Examination, [redacted] Vital Signs, Weight, Waist Circumference	X	X**		X[1]	X[1]	X[1]	X[1]	X**
Height		X						X
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]				[redacted]	[redacted]
Urine Pregnancy Test***	X	X		X	X	X	X	X
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hematology Panel including PT, APTT and INR, Chemistry Panel, LFTs	X	X		X	X	X	X	X
HbA1c	X							X
Lipid Panel		X			X		X	X
IGF-1		X						X
[redacted]		[redacted]						[redacted]
Urinalysis		X			X		X	X
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]							
DXA Scan			X					X
Hyperphagia Questionnaire (HQ-CT)	X	X			X		X	X
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CGI-I, [redacted]			X[#]		X		X	X
[redacted]			[redacted]					[redacted]
[redacted]			[redacted]					[redacted]
[redacted]			[redacted]		[redacted]		[redacted]	[redacted]
Study Drug Dispensation	X		X	X	X	X	X	
Study Drug Accountability		X		X	X	X	X	X

Visit Number	1	2		[redacted]	[redacted]	5[redacted]	6[redacted]	7†[redacted]
	Screening	Pre-Rand	Post-Rand					End of Study
Day[redacted]	-14	0		14	28	42	56	91
Week	-2	0		2	4	6	8	13
Study Drug Administration##	X		X	X	X	X	X	
Adverse Events[redacted]	X	X	X	X	X	X	X	X
Concomitant Medications[redacted]	X	X	X	X	X	X	X	X

† Visit 7 assessments will be used as the Visit 1 assessments for subjects who enroll in Study C602.

[redacted]

†† ECG performed at the Screening Visit will be used as the baseline ECG to evaluate changes.

[redacted]

Full physical examination to be conducted if needed.

*** For females of child-bearing potential only. A positive urine pregnancy test must be confirmed by serum pregnancy test.

[redacted]

At each visit, after the necessary procedures have been completed, the assigned dose of DCCR or placebo will be taken in the clinic with water or other beverage. All other doses will be taken daily in the morning as described in Section 8.1

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.0 ASSESSMENT OF EFFICACY

10.1 Efficacy Parameters

The efficacy parameters that will be assessed in this study are:

- HQ-CT score
- Body fat mass (DXA)
- Clinical Global Impression of Improvement
- [redacted]
- Caregiver Global Impression of Change
- [redacted]

[redacted]

11.0 ASSESSMENT OF SAFETY

11.1 Safety Parameters

The safety parameters that will be assessed in this study are:

- Adverse events

[redacted]

11.2 Definitions

The following definitions, developed in accordance with the International Committee on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, 21 CFR Part 312.32, and EU Directive 2005/28/EC and Regulation 536/2014 will be used for the purpose of identifying AEs in this clinical study.

11.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation patient, administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or increase in severity or frequency of a pre-existing abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

11.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is reasonable possibility that the drug caused the adverse event. Suspected adverse reactions will consist of the adverse events that are evaluated by the Investigator as possibly related or probably related to the study drug.

11.2.3 Serious Adverse Event

A serious adverse event (SAE) is any adverse experience occurring after enrollment at any dose that results in any of the following outcomes: death, life-threatening (at the time of the event), hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (in an offspring)

Medically significant events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2.3.1 Hospitalizations as Serious Adverse Events

All AEs requiring hospitalization or prolongation of hospitalization should be reported as SAEs.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate eCRF: short-term administrative hospitalization for procedures, tests

or treatments of conditions that would not otherwise constitute an SAE, or elective hospitalizations.

11.2.4 Unexpected Adverse Event

Any adverse event that is not listed in the Reference Safety Information section in the Investigator's Brochure or is not listed at the same specificity or severity that has been observed previously.

11.2.5 Expected Adverse Events

[redacted]

AEs reported as related to DCCR in at least 10% of subjects include peripheral edema and headache. AEs reported in 2-9% of subjects include decreased appetite, palpitations, hyperglycemia, fluid retention, dizziness, chest pain, fatigue, tachycardia, nausea, hirsutism, abdominal distension, and arthralgia.

11.3 Adverse Event Assessment

As defined above, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

AEs may include increases in intensity or frequency of conditions or diseases that were pre-existing prior to study participation. An example might include a subject in whom routine headaches become more severe or begin to occur more frequently.

Medical or surgical procedures are not in and of themselves considered AEs, but if a condition or disease led to the procedure, the condition or disease would be considered an AE unless it was present prior to entering the study and did not worsen after entering the study.

When possible, AEs will be graded according to CTCAE criteria (CTCAE, Version 5.0, which can be found online at https://evs.nci.nih.gov/ftp1/CTCAE).

Subjects entering the trial with ongoing baseline medical conditions should have their signs/symptoms graded according to CTCAE criteria. Increases in CTCAE grading from baseline conditions (e.g., Grade 1 to Grade 2) will be considered adverse events.

A non-serious AE is any AE that does not meet the definition of a serious adverse event.

11.3.1 Performing AE Assessments

11.3.1.1 Adverse Event Severity

AEs will be assessed for severity (intensity) according to the clinical description provided in the CTCAE Version 5.0 (Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5). If an AE cannot be classified using CTCAE terminology, severity will be assessed using the following definitions listed in Table 8.

Table 8: Adverse Event Severity

Grade 1	**Mild**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.[1]
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living.[2]
Grade 4	**Life-threatening**	Life-threatening consequences; urgent intervention indicated.
Grade 5	**Death**	Death related to the AE.

1 Examples of instrumental activities of daily living include: Watching television, using a computer, playing video games, attending school, playing outside, using the telephone, etc.

2 Examples of self-care activities of daily living are: bathing, dressing and undressing, feeding self, using the toilet, taking medications, etc.

11.3.1.2 Adverse Event Relationship

For each AE, the Investigator is required to assess the causal relationship (relatedness) between the administration of the study drug and the occurrence of the AE. The Investigator should use his or her clinical judgment and the following definitions to determine relatedness.

- **Not Related:** The AE is not related if exposure to the study drug has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the study drug, i.e., there are no facts (evidence) or arguments to suggest a causal relationship
- **Unlikely Related:** The AE is more or most likely explained by causes other than the study drug
- **Possibly Related:** The administration of the study drug and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the study drug

- **Probably Related:** Exposure to the study drug and AE are reasonably related in time **and** the study drug is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

11.3.1.3 Vital Signs, Physical Examination and Clinical Laboratory Adverse Events

Laboratory abnormalities and changes in vital signs or physical examination/findings are considered AEs only if they are determined to be clinically significant by the Investigator, result in withdrawal from the study, necessitate therapeutic intervention, or for some other reason the Investigator considers them clinically important. However, if any of these changes in laboratory, vital signs or physical examinations is attributable to a new disease or condition or a worsening of a condition pre-existing study enrollment, the disease or condition itself shall be the reported AE, not the change in laboratory, vital sign or physical examination.

11.3.2 Serious Adverse Event Reporting

All SAEs must be reported to Soleno within 24 hours of first knowledge of the event. All SAEs that occur from the time the subject is enrolled at Screening through the End of Study Visit are reportable within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of first knowledge of the event, the site must contact Soleno by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Initial reporting should not be delayed in order to obtain resolution or follow-up information.
- The site will fax an SAE report, or similar form, which includes the following information, as available:
  - Study subject number
  - Basic demographic information (age, gender, weight)
  - Relationship to study drug
  - The outcomes attributed to the event (death, life-threatening, hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
  - The onset date and severity of the event
  - A brief description of the event including frequency and severity of symptoms leading to diagnosis

- A list of relevant test results and lab data
- Any other relevant history
- Date of study drug administration
- Whether the study drug was discontinued prematurely
- Investigator's assessment of causality

The completed SAE report should be sent electronically as soon as possible (within 24 hours) to:

[redacted]

The Medical Monitor or another representative or designee of Soleno may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE eCRF. The same nomenclature should be used on both the SAE report and the AE eCRF.

The Investigator is responsible for the complete and timely reporting of all SAEs to Soleno, following up on resolution of the SAE, and expeditiously and simultaneously notifying the responsible IRB/IEC of the occurrence and details of the event according to institutional standard procedures. In the event there is a question as to whether the experience is serious, the event should be reported.

12.0 STATISTICAL PLAN

It is estimated that 105 subjects will be enrolled and randomized. In this multi-center study, each site is anticipated to enroll 3 or more subjects.

12.1 Sample Size Justification

[redacted]

[redacted]

12.3 Efficacy Analyses

All efficacy endpoints will be summarized at each visit by treatment group as well as by treatment group and strata in the ITT, MITT and PP Populations using summary statistics. Unless otherwise stated, subjects who are randomized to the wrong hyperphagia score group or growth hormone status will be analyzed in the stratum they belong in (vs. stratum randomized to if there are errors).

12.3.1 Primary Efficacy Analysis

The primary endpoint (change from Baseline to Visit 7 in the HQ-CT score) will be analyzed using a linear mixed model for repeated measurements in the ITT Population. All available data

from each subject will be used, with no imputation of missing data. The dependent variable will be the change from Baseline to Visit 7 and the model will include fixed effects for treatment group [redacted] time [redacted] the interaction between treatment and time, and the randomization stratification variable for baseline growth hormone use. The baseline value of the HQ-CT score will be included as a covariate and the unstructured covariance model will be used. This model will include 7 fixed effects [redacted] and 6 random effects. With a total sample size of 105 subjects randomized in a 2:1 ratio, this model is appropriate. The primary analysis will compare the two treatment groups at Visit 7 using a two-sided test at the alpha=0.05 level of significance.

12.3.1.1 Multiple Comparisons - Control of the Alpha Level

To control the alpha level for the primary and secondary efficacy analyses at 0.05, a hierarchical fixed sequence testing procedure will be used. [redacted]

12.3.2 Secondary Efficacy Analyses

Body fat mass will be analyzed using an ANCOVA model with change from baseline to Visit 7 as the response, baseline as a covariate, and treatment group and the randomization stratification variables as factors.

The Clinical Global Impression of Improvement and Caregiver Global Impression of Change will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) mean score test with modified ridit scores, stratified by the randomization stratification variables.

[redacted]

12.4 Subgroup Analyses

Analyses of the primary, selected secondary and/or selected exploratory endpoints may be performed using the following subgroups: gender, baseline HQ-CT score, PWS genetic subtype/subclass, [redacted] Other subgroup analyses may be conducted.

12.5 Safety Analyses

All safety analyses will be conducted in the Safety Population. Subjects who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses.

All safety data will be summarized by treatment group and also by treatment group and strata.

12.5.1 Adverse Events

Adverse events will be coded using MedDRA. A treatment-emergent AE (TEAE) is defined as an AE that starts or worsens at or during the time of or after the first study drug administration through the Visit 7.

12.5.2 Clinical Laboratory Evaluations

All numeric laboratory data including chemistry (including liver enzyme of ALT, AST, and GGT) and hematology tests will be summarized at each visit as well as changes from baseline using summary statistics. In addition, the maximum post-baseline and minimum post-baseline values will be summarized.

Laboratory values will be categorized as normal, high, and low, based on normal ranges. Shift from baseline will be summarized at each post-baseline visit.

[redacted]

[redacted]

12.5.4 ECG Parameters

Descriptive statistics for heart rate, RR interval, PR interval, QRS interval, QT interval, and QT interval corrected with Fridericia's (QTcF) formula and the change from baseline to each post-baseline visit will be presented. Changes in morphology will be captured in text.

[redacted]

12.5.5 Vital Signs

Descriptive statistics for resting heart rate, diastolic blood pressure, systolic blood pressure, temperature and the change from baseline to each post-baseline visit. The change from baseline to the minimum and maximum post-baseline values will also be summarized by treatment group. Shift tables may also be presented. Clinically significant vital signs will be identified in the eCRF and will be listed.

[redacted]

[redacted]

12.7 Termination Criteria

The DSMB may recommend stopping or modifying the study based on safety concerns identified based on its review of unblinded safety data (See Section 6.7). Potential study discontinuation reasons include:

- The sponsor determines that it is unsafe to continue because of an unexpected safety signal not otherwise clinically anticipated in randomized subjects without relevant medical history
- Significant imbalance in rate of serious, unexpected adverse reactions that, independent of study drug, are not clinically anticipated in subjects randomized to DCCR versus placebo in subjects without relevant medical history
- Significant imbalance in rate of serious adverse reactions that, independent of study drug, are not clinically anticipated in subjects randomized to DCCR versus placebo in subjects without relevant medical history

If such issues arise, Soleno will, in consultation with the DSMB, Investigators, appropriate regulatory authority(ies), and/or IRBs/IECs, take the steps necessary to modify or discontinue the study.

12.8 Deviation Reporting

Changes made to the Statistical Analysis Plan (SAP) after it has been signed but prior to database lock will be documented in an amendment to the Statistical Analysis Plan. Any important changes made to the analysis after database lock will be described in the clinical study report (CSR).

12.9 Interim Analysis

There is no interim analysis planned in this study.

13.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Site visits will be conducted by authorized representative(s) of Soleno to inspect study data, subject's medical records, and eCRFs in accordance with current GCPs and respective national and local government regulations and guidelines (if applicable). The Investigator and Institution will permit authorized representatives of Soleno, its designees, the national health authorities, local authorities, and IRB/IEC direct access to source data/documents, with the exception of the responses to the HQ-CT and Global Impression Questions during the course of the study as described in Section 6.3.2, to conduct study-related monitoring, audits, IRB/IEC review, and regulatory inspections.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

Soleno will ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Quality control will be applied at each stage of data handling to ensure that all data are reliable and have been processed (e.g., monitoring to review source documents/subject's charts against eCRFs, development of a monitoring plan, data management system with appropriate logic checks, quality control review of the database prior to database lock, quality control procedures to confirm accurate table, listings, etc.).

Audits may be performed as part of implementing quality assurance. Audits will evaluate study conduct, data/record integrity, and/or compliance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements.

The study will be registered on ClinicalTrials.gov by Soleno.

15.0 ETHICAL CONSIDERATIONS

This study will be conducted according to applicable national standards for protection of human subjects and Good Clinical Practice including but not limited to US regulations 21 CFR 50, 56, 312, Regulation EU 536/2014, Directive 2005/28/EC, Regulation EU 2016/679, and ICH Topics E2A, E2B(R3), E6(R2), and E11(R1).

IRB/IEC approval will be obtained for the protocol, informed consent form, assent form, and all information provided to the caregiver / subject prior to their use in the study. No study site will receive study drug prior to obtaining IRB/IEC approval for the study.

All parent(s) / legal guardian(s) of prospective subjects for this study will be provided an informed consent form that describes this study and provides sufficient information for them to make an informed decision about their child's participation in this study. As applicable, prospective subjects will be provided an assent form that describes this study and provides sufficient information for them to provide assent to participate in the study. The informed consent form and assent form will be submitted with the protocol for review and approval by the IRB/IEC. The formal consent and assent, as applicable, of a subject's participation, using the IRB/IEC-approved informed consent form, will be obtained before that subject is submitted to any study procedure. The parent(s) / legal guardian(s) and subject will be given adequate time to review the patient information and informed consent form, given the opportunity to ask questions, and understand that if they decline to participate in the study, the future care of the subject will not change. The informed consent form must be signed by the parent(s) / legal guardian(s) and the assent form must be signed by the subject. The investigator-designated research professional obtaining the consent and assent must also sign the informed consent form and assent form. Copies of the signed informed consent and assent forms will be provided to the parent / legal guardian.

16.0 DATA HANDLING AND RECORD KEEPING

The Investigator must maintain adequate records for the study including completed eCRFs, data correction forms, original source documents including certified copies of original source documents, signed ICFs, drug accountability records, AE reports, screening and enrollment logs, correspondence with the IRB/IEC and Soleno or designee and other pertinent data and information. Essential documents must be retained for 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of a clinical development of the study drug, whichever is longer. These documents should be retained for a longer period if specified through written agreement with Soleno. Following study closure, the Investigator must inform Soleno if the location for study record storage is changed (e.g. the Investigator leaves the institution where the study was conducted). In order to ensure that documents are not inadvertently destroyed prematurely, please contact Soleno prior to destruction of any study-related documents.

Data obtained from this study, including subject identity information, will be handled, processed, stored, and retained in accordance with applicable laws, regulations, and guidances.

17.0 PUBLICATION PLAN

The results of this clinical study may be used by Soleno in registration documents for regulatory authorization in the countries and/or regions participating in this study, or other countries or regions, or for public dissemination in the form of papers, abstracts, posters, or other information

materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an Investigator. Institution may publish the results relating solely to work performed at the institution for this study only after the clinical trial has been completed, the data have been unblinded, final data analyses have been completed. In all cases, in order to avoid disclosures that could jeopardize proprietary rights, to ensure accuracy of the study data, and to ensure integrity is maintained, all manuscripts, abstracts, and presentations related to this study must be submitted to Soleno for review at least 45 days before their submission or release or as specified in separate written agreements.

18.0 REFERENCES

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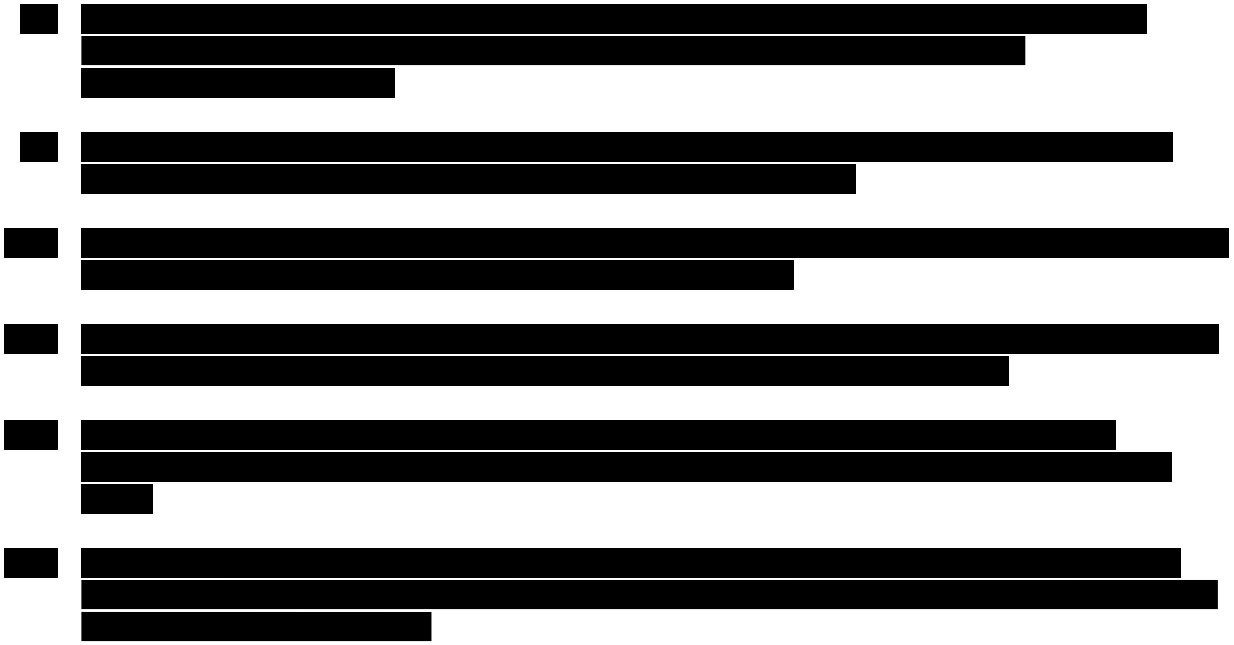

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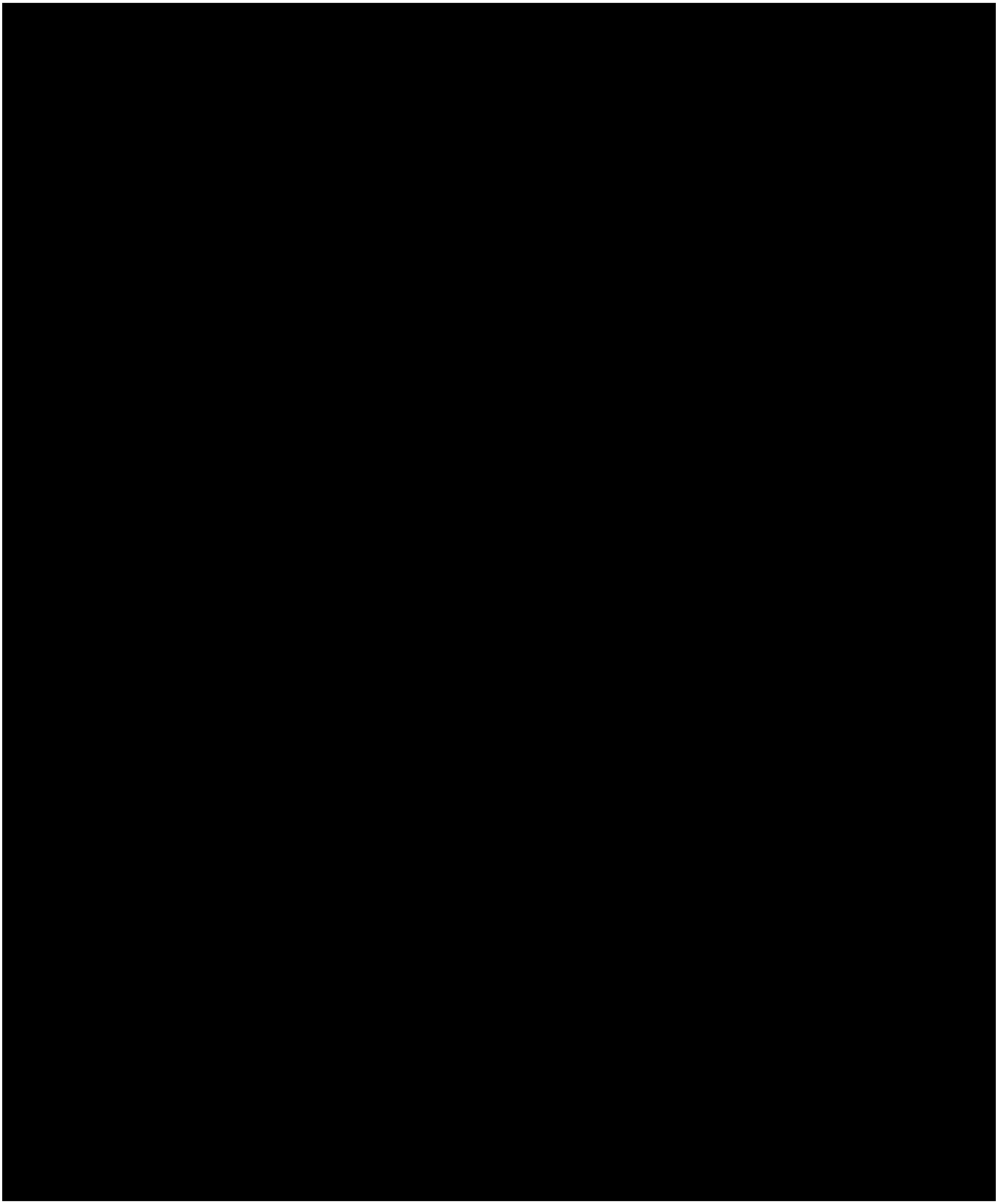

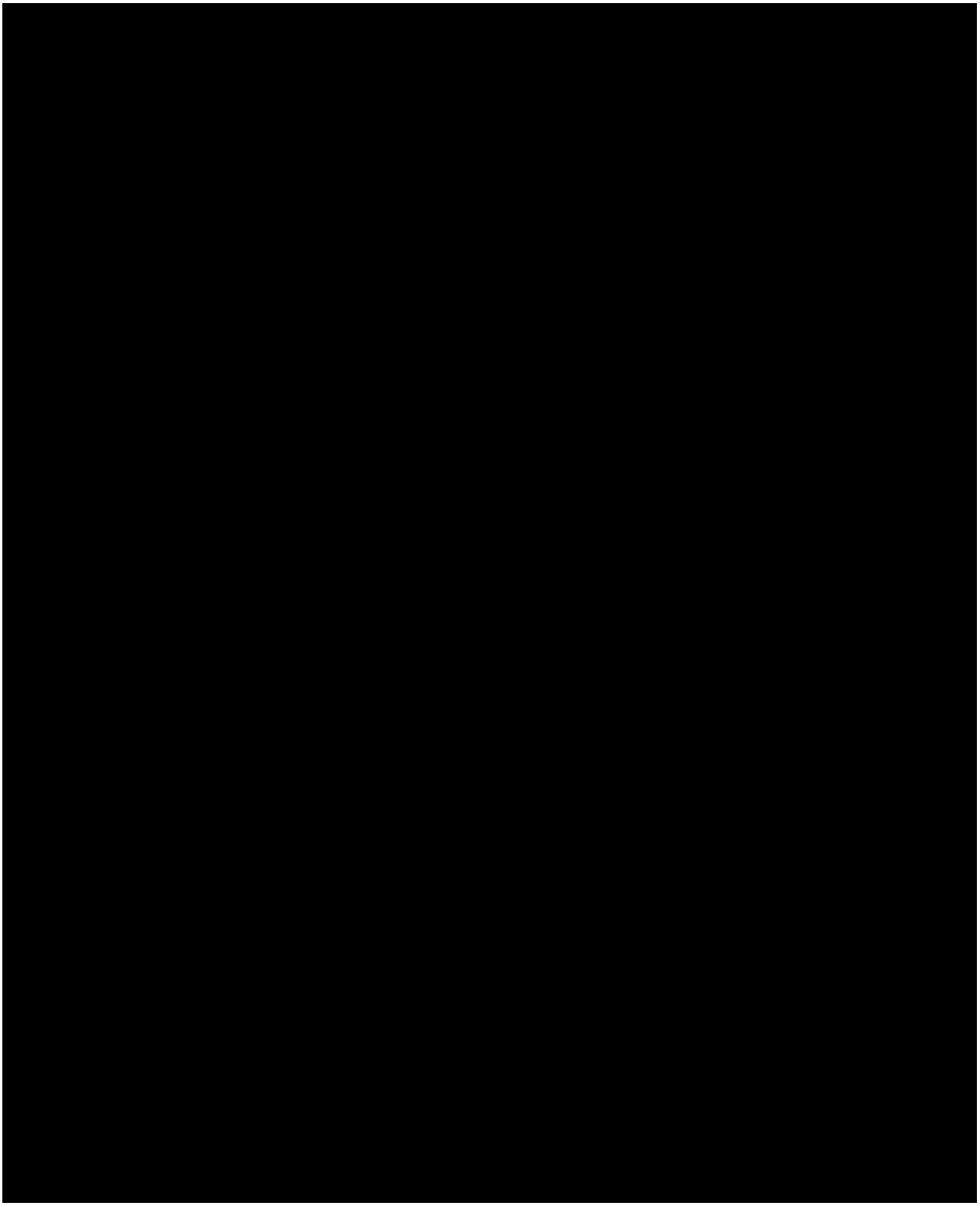

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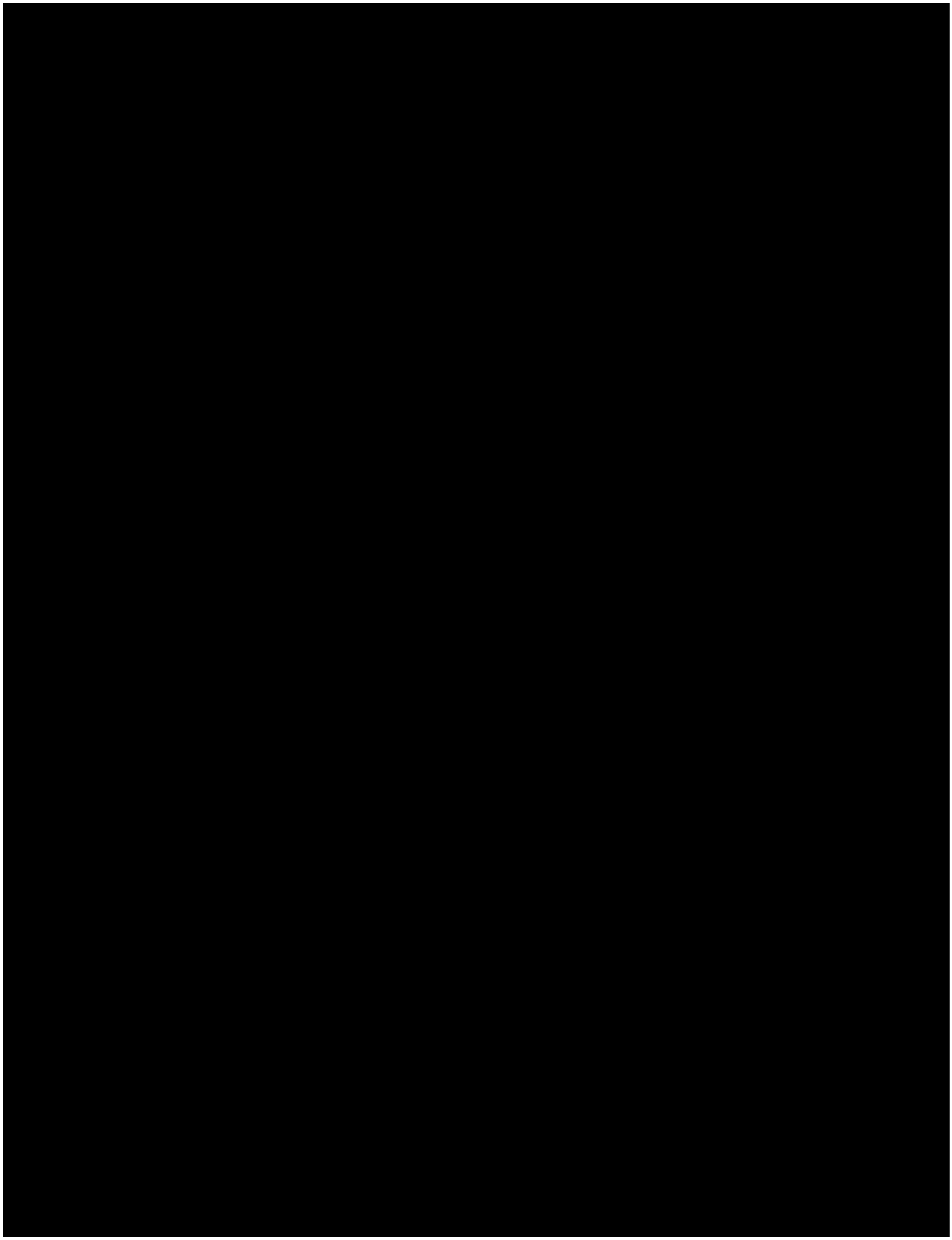

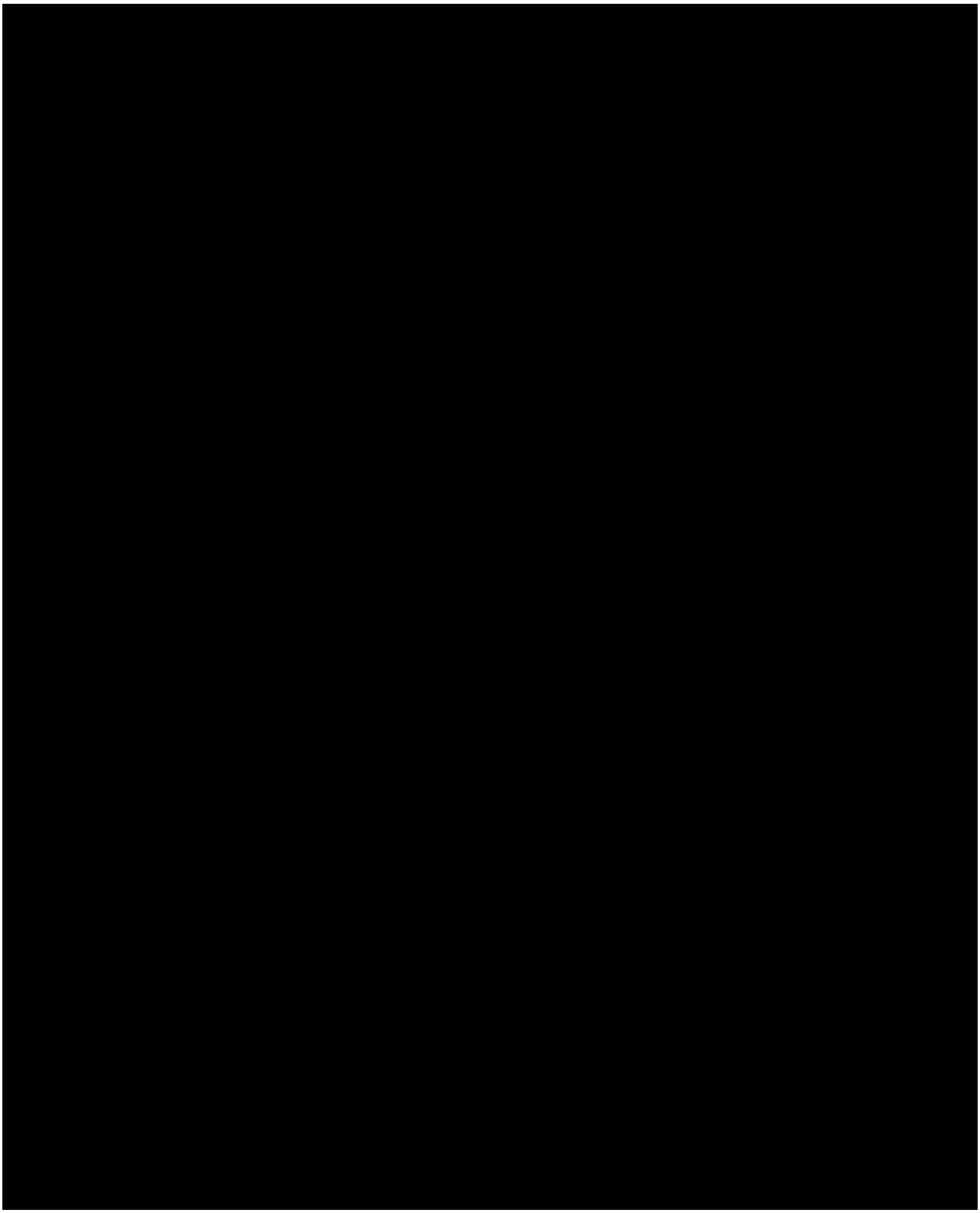

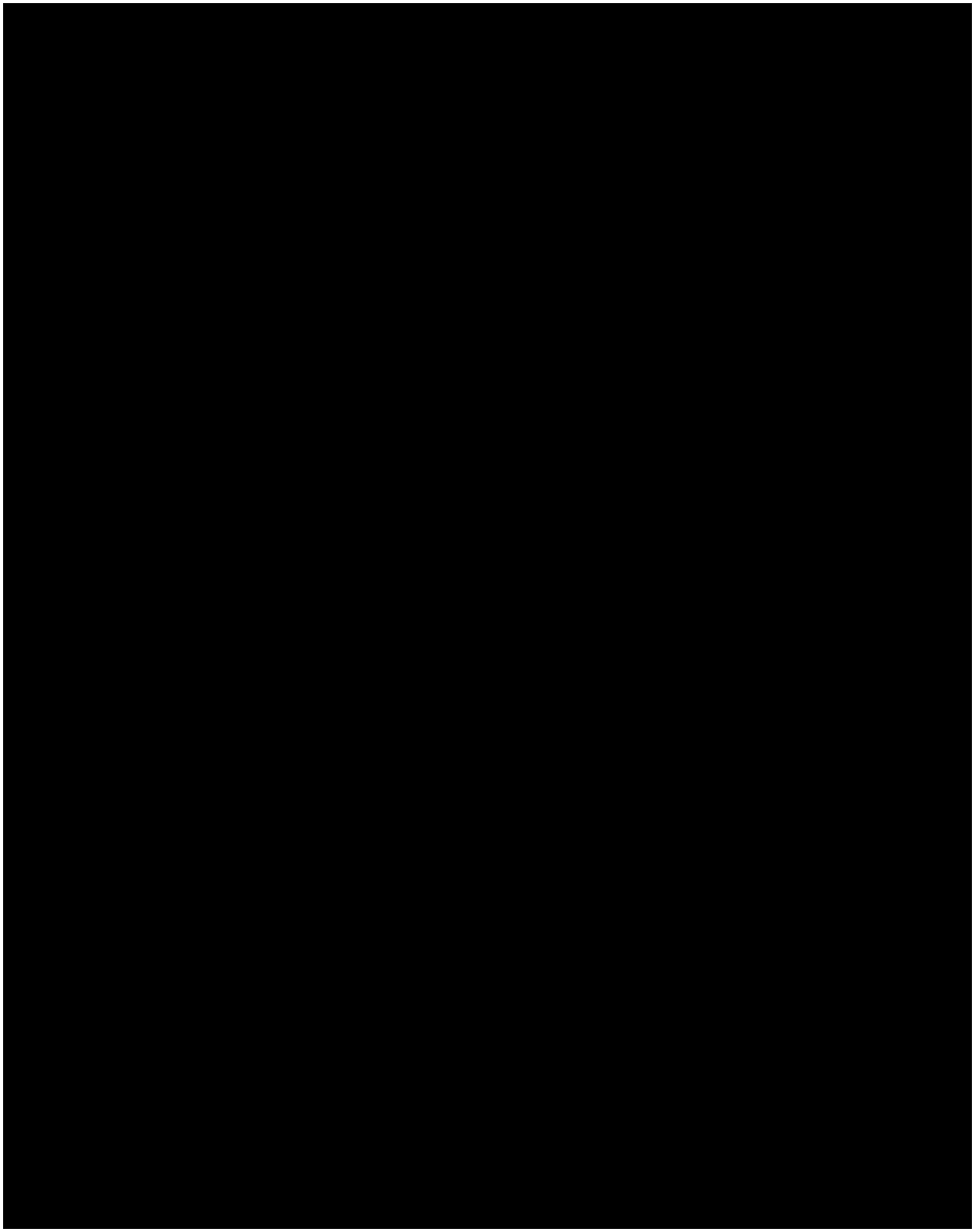

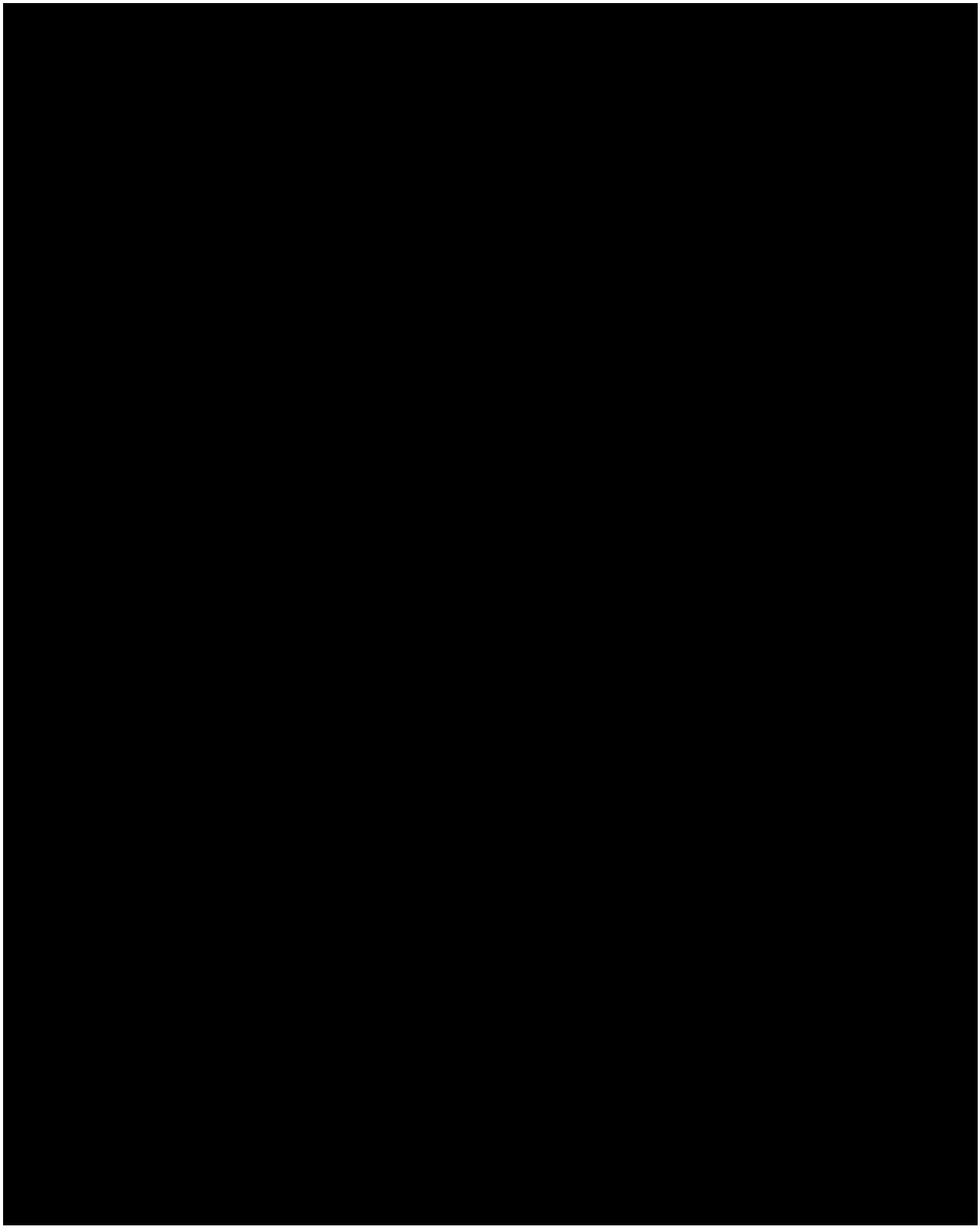

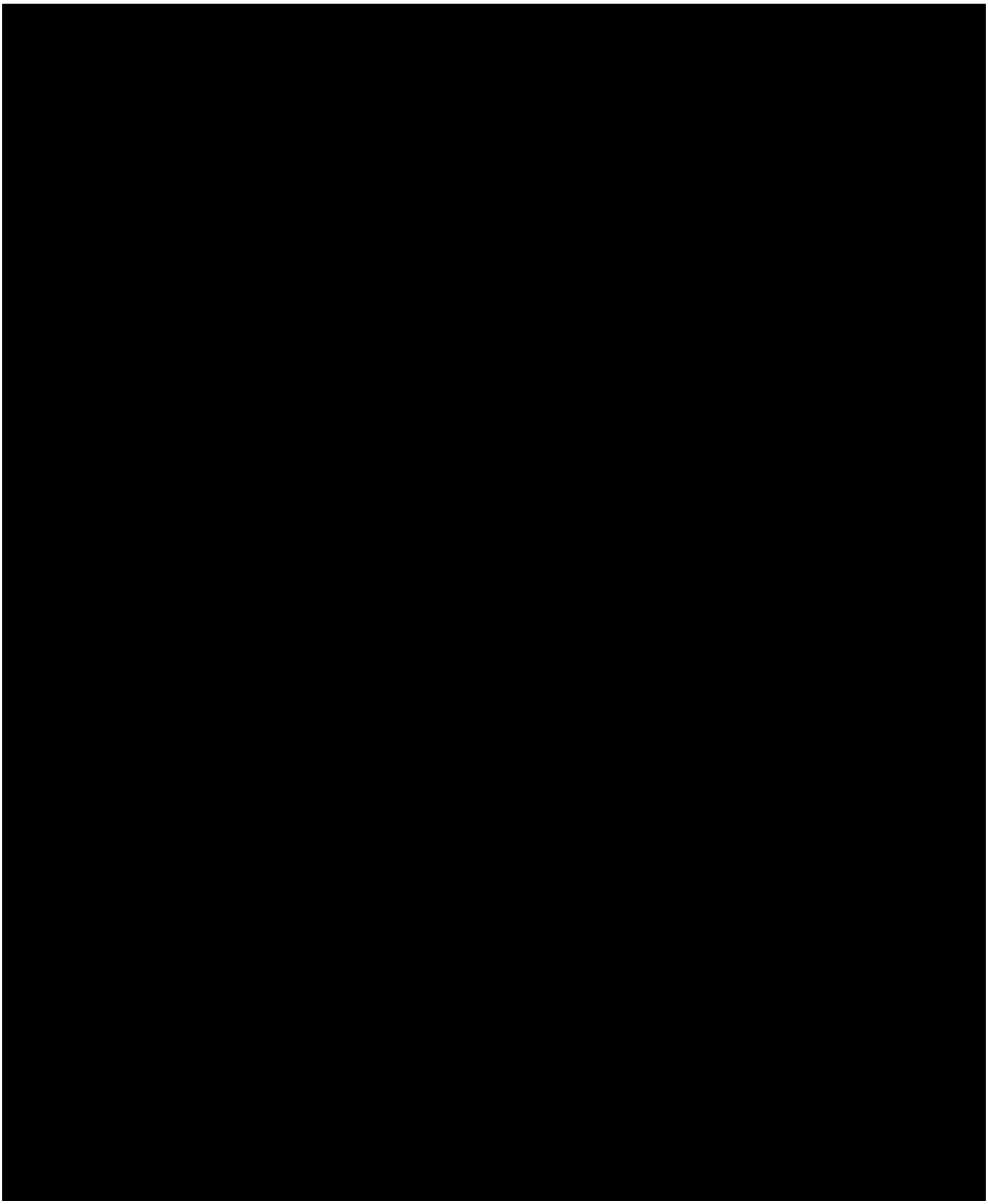

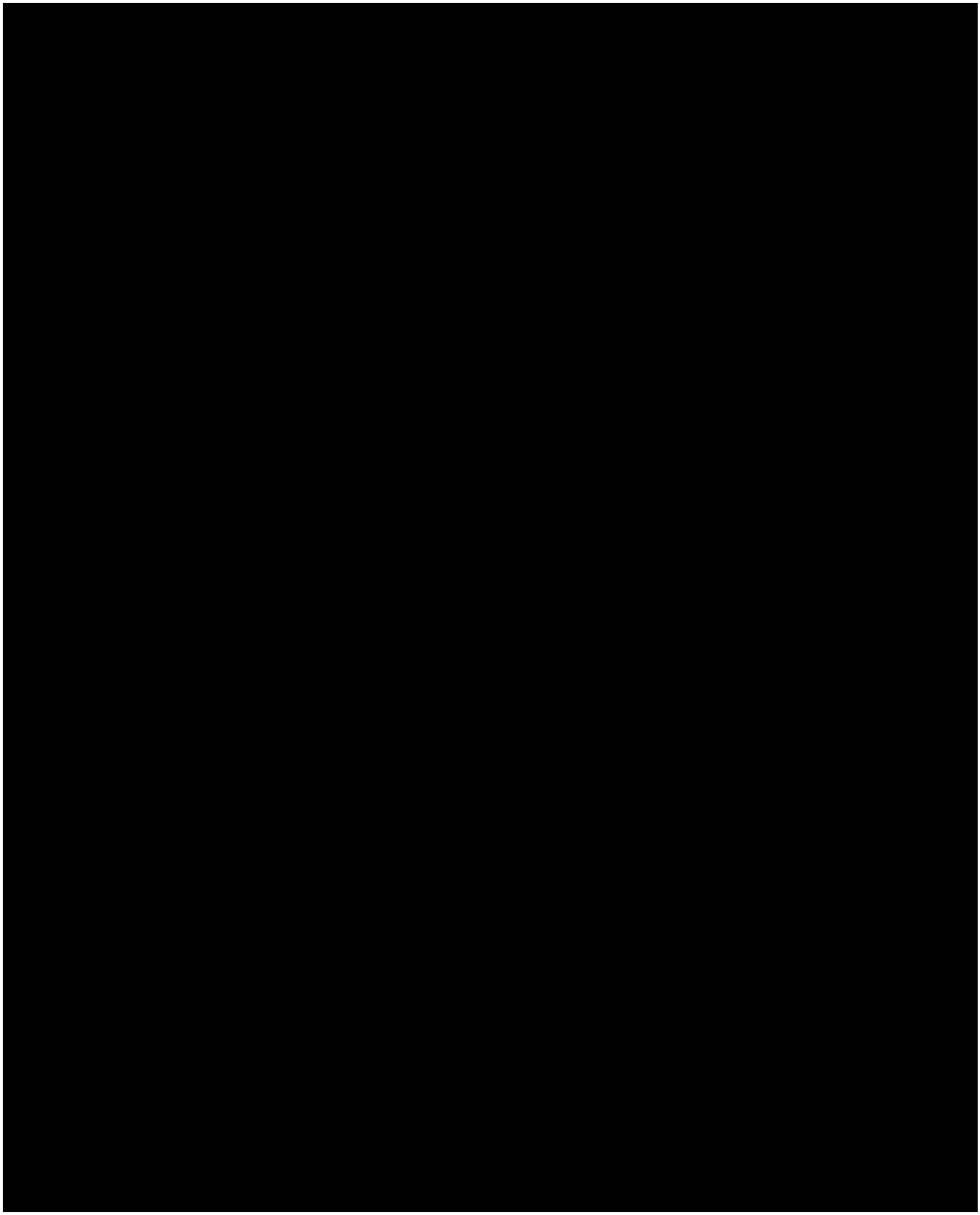

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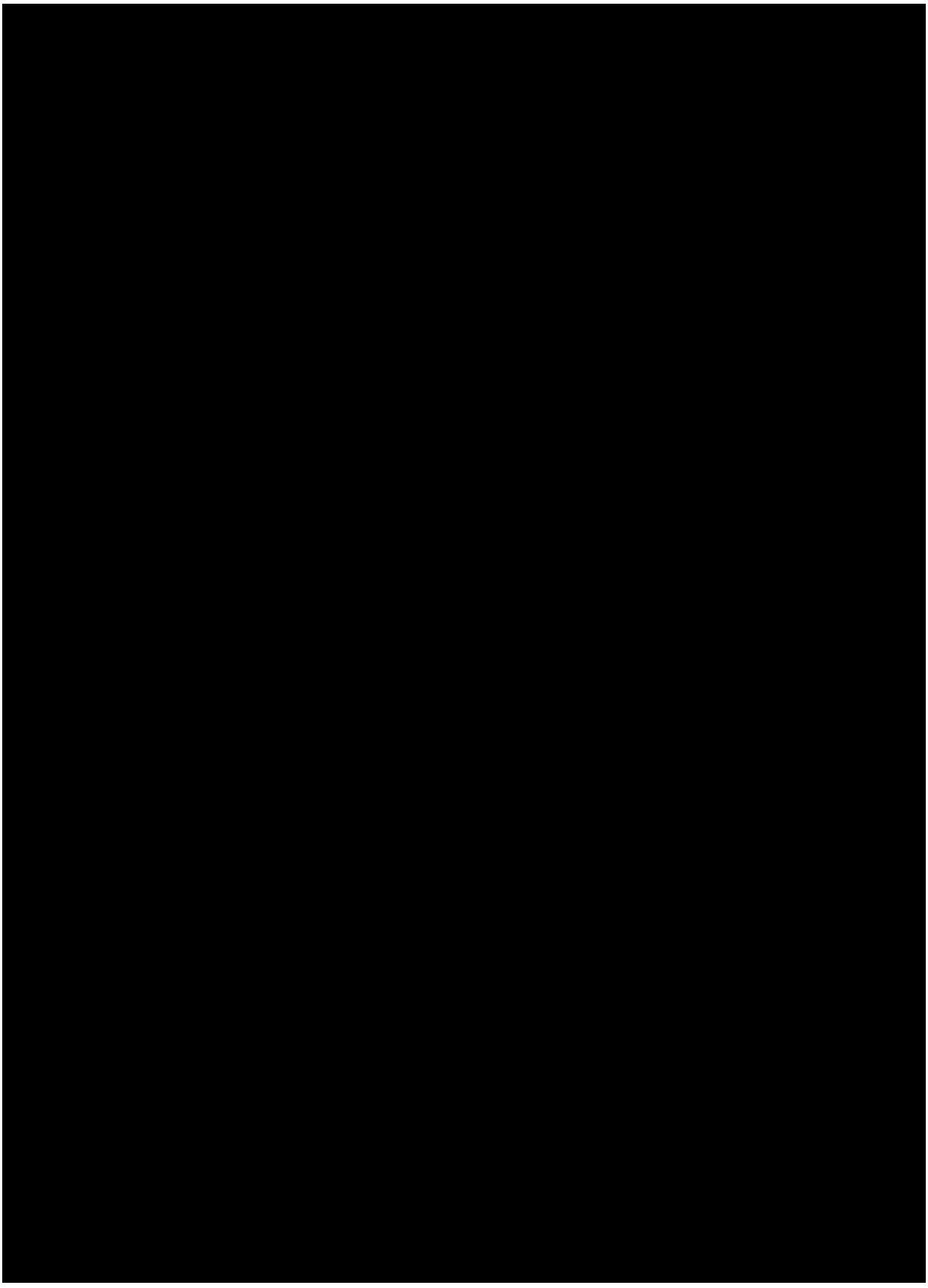

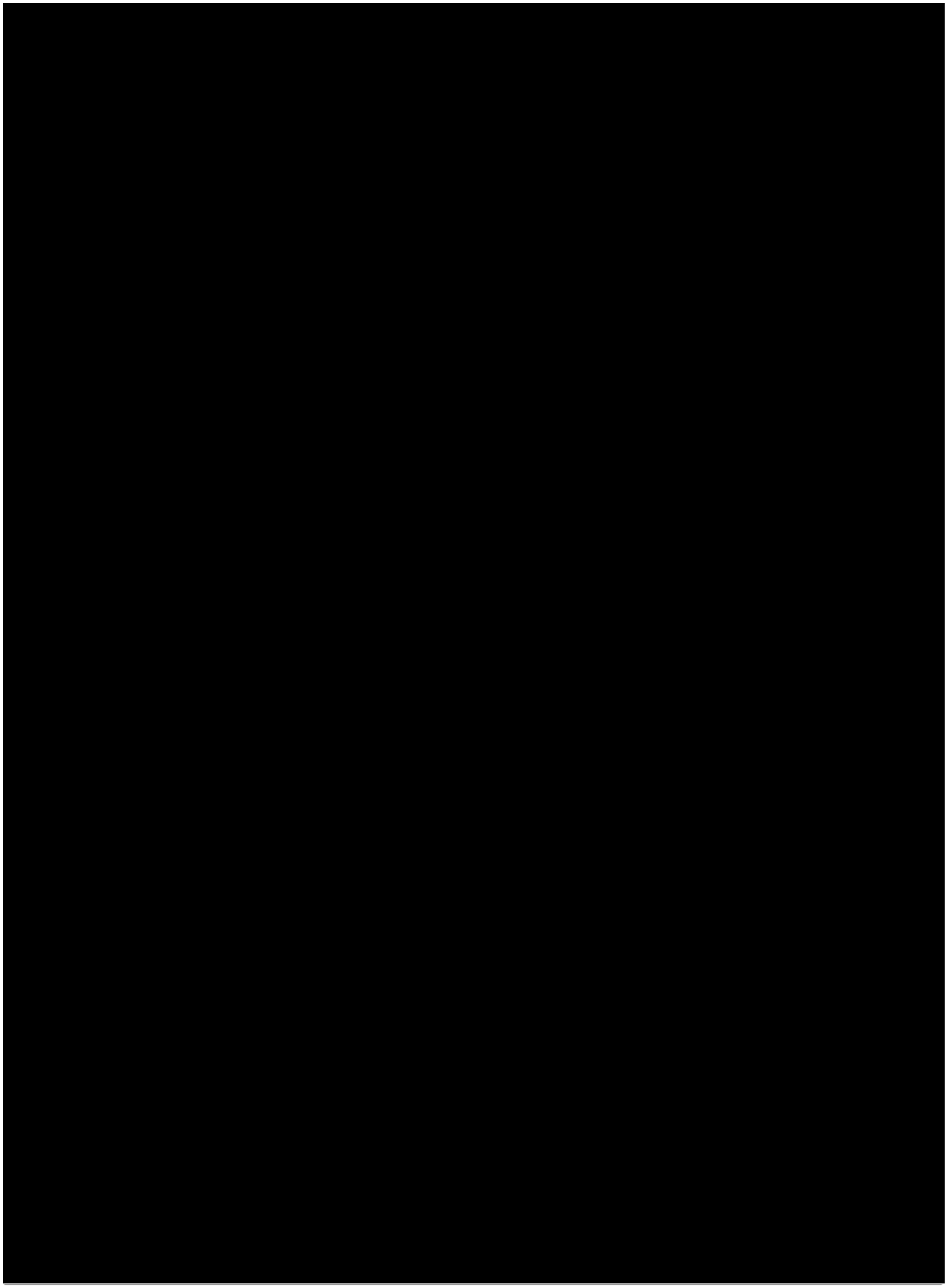

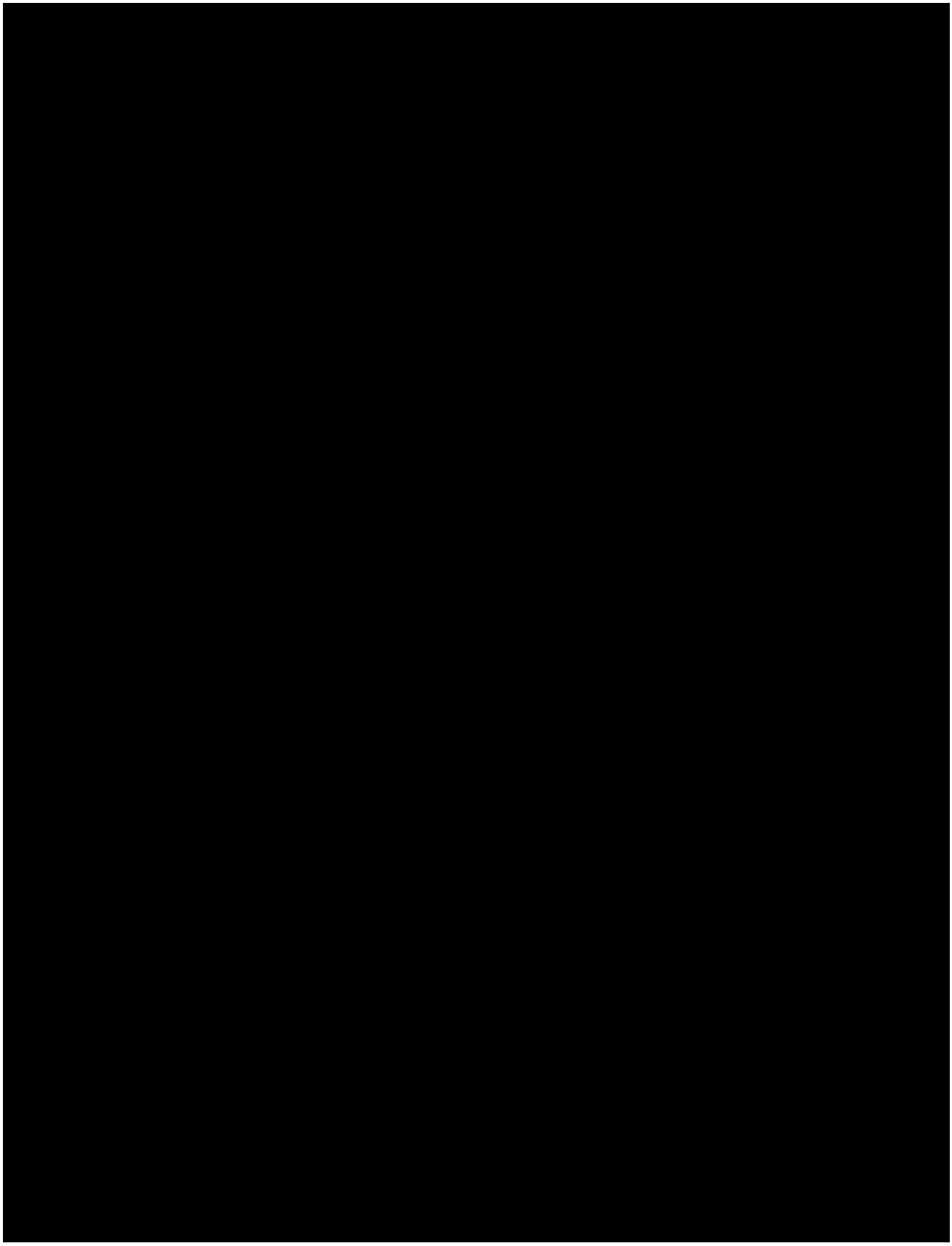

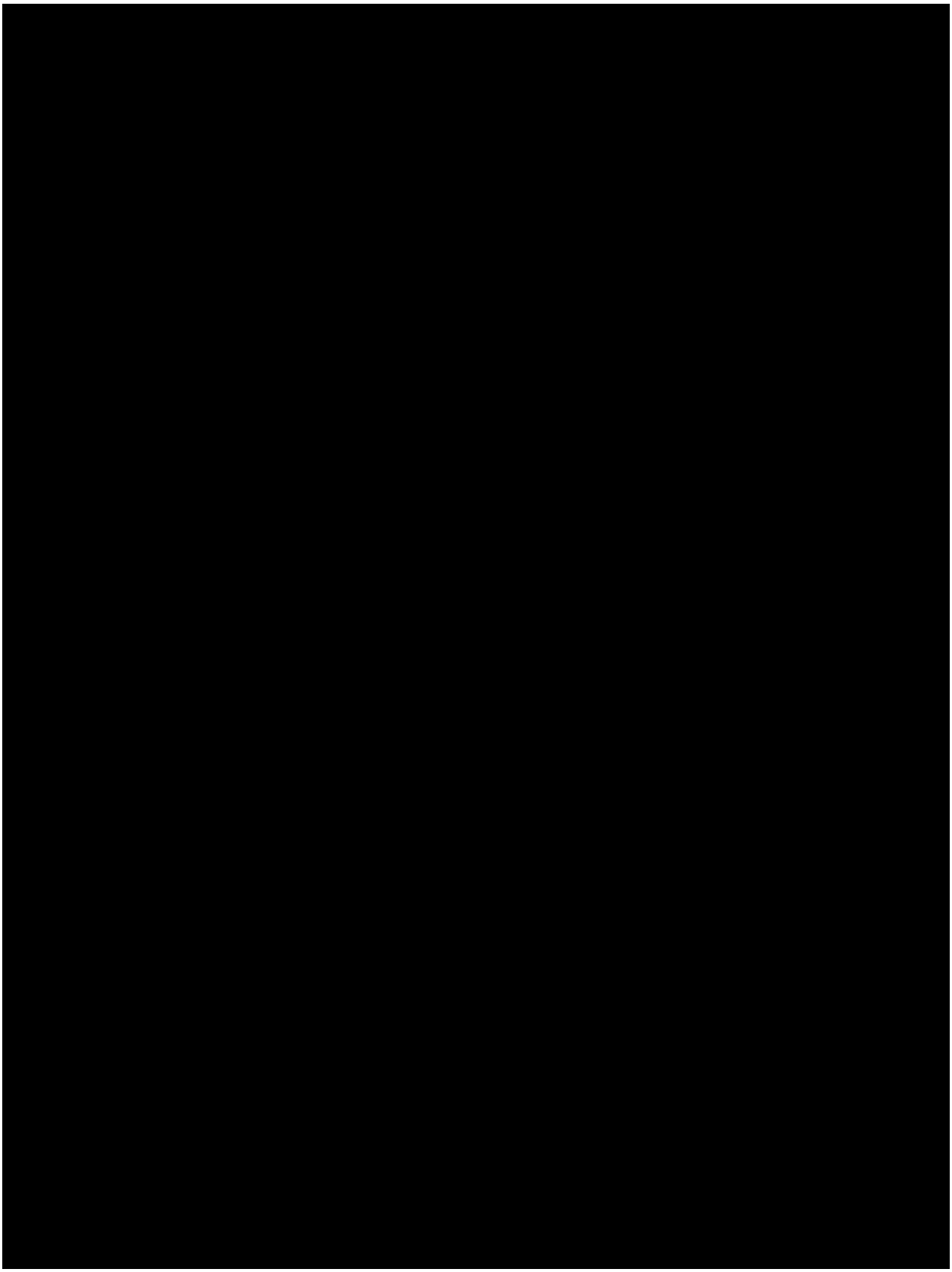

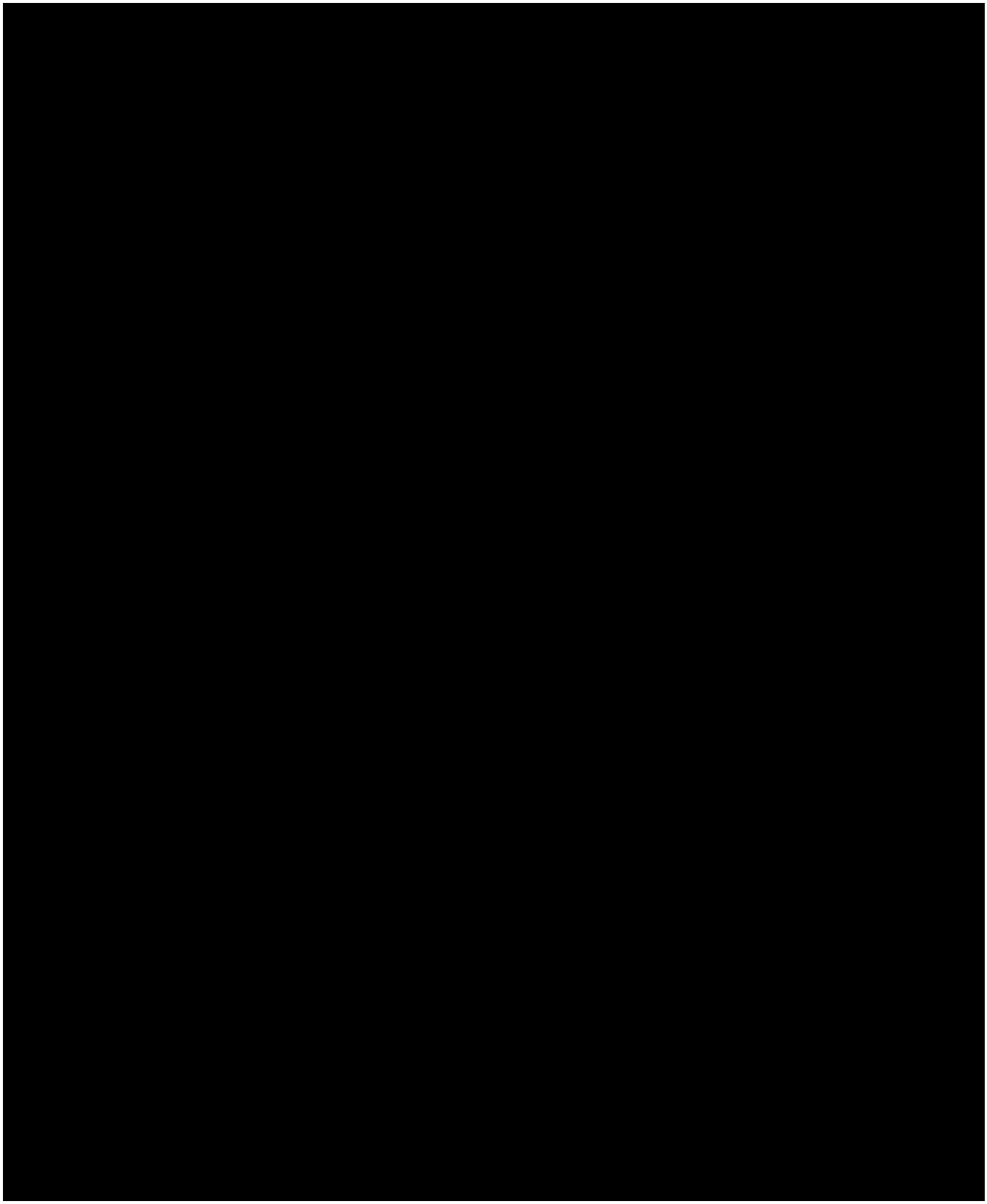

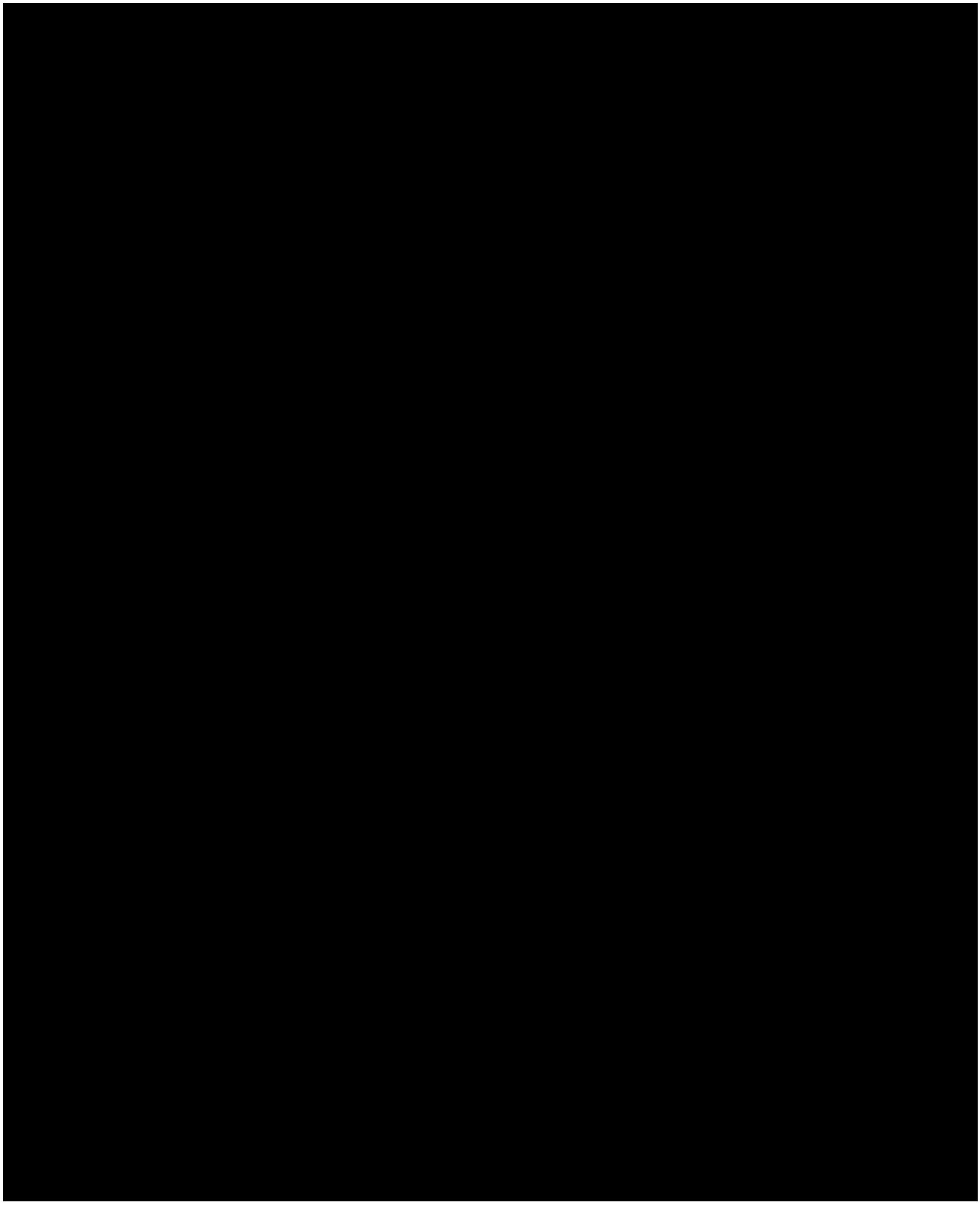

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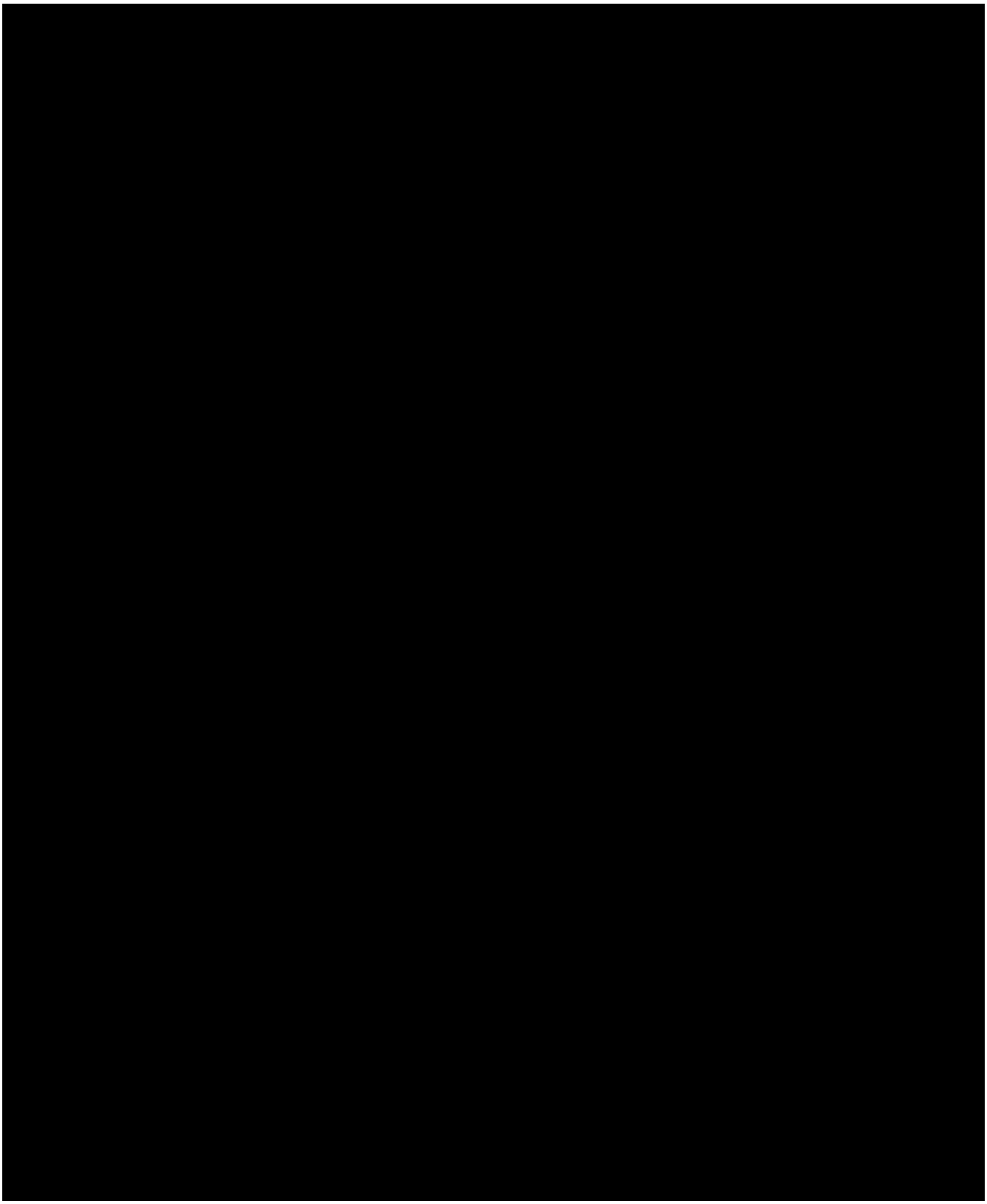

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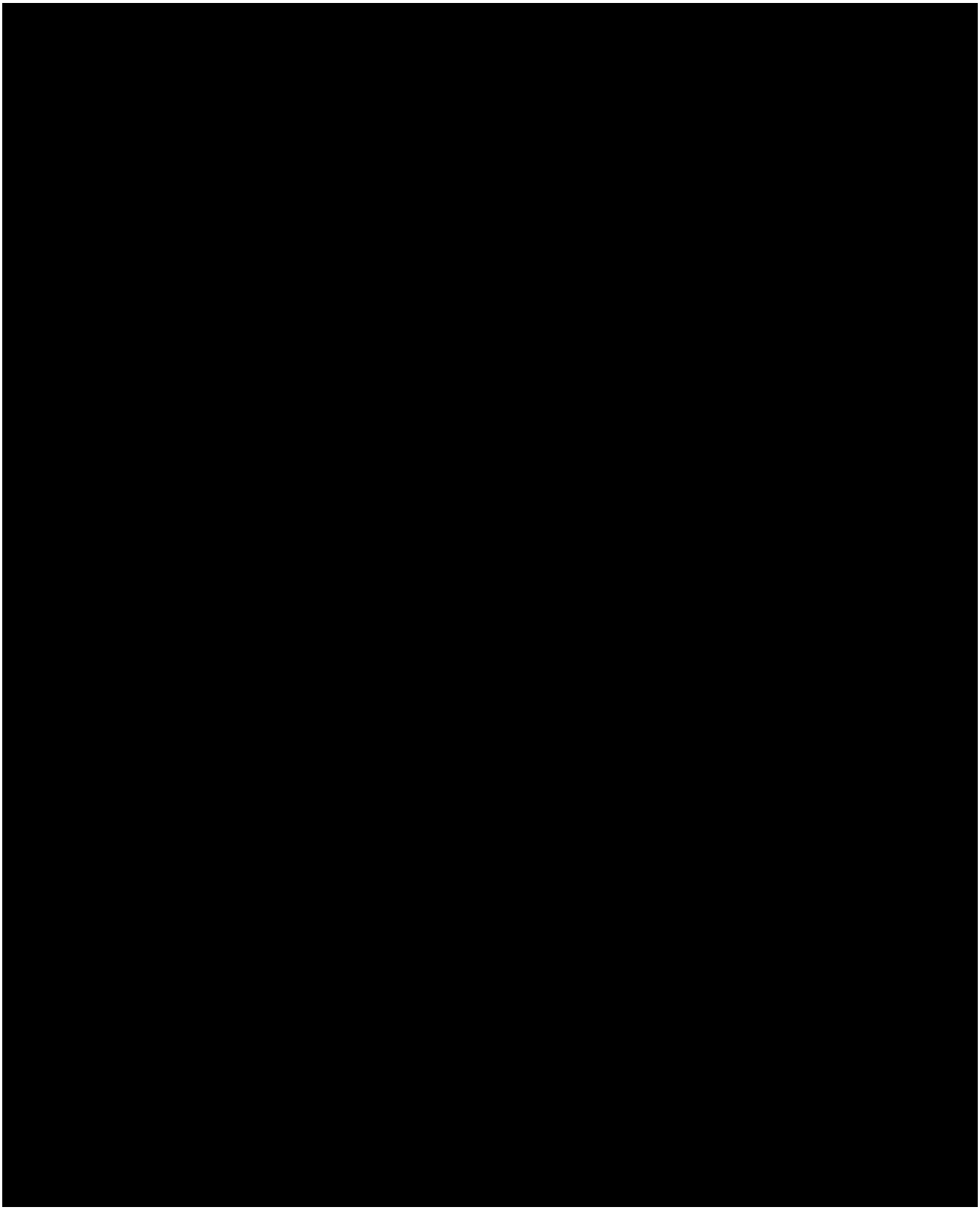

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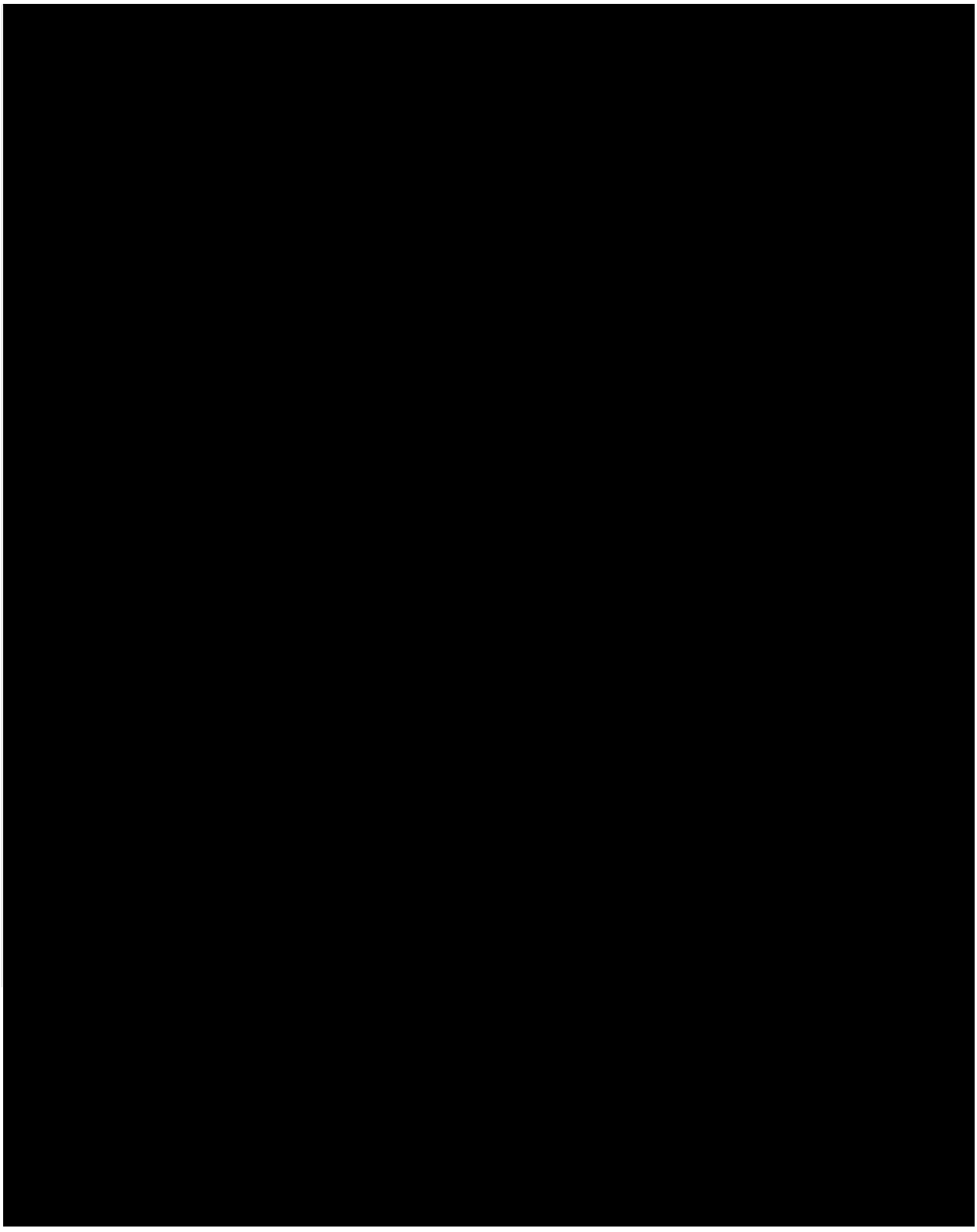

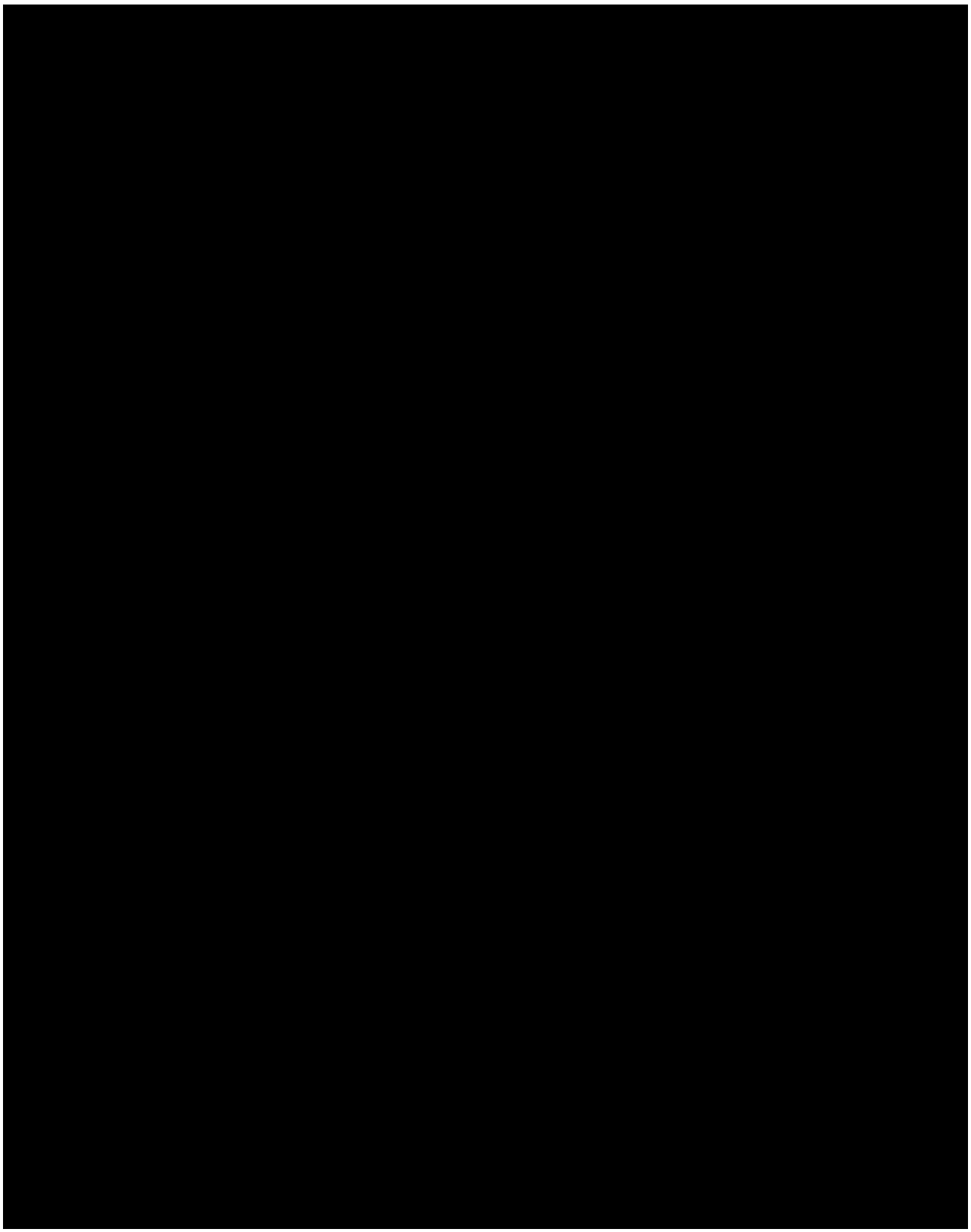

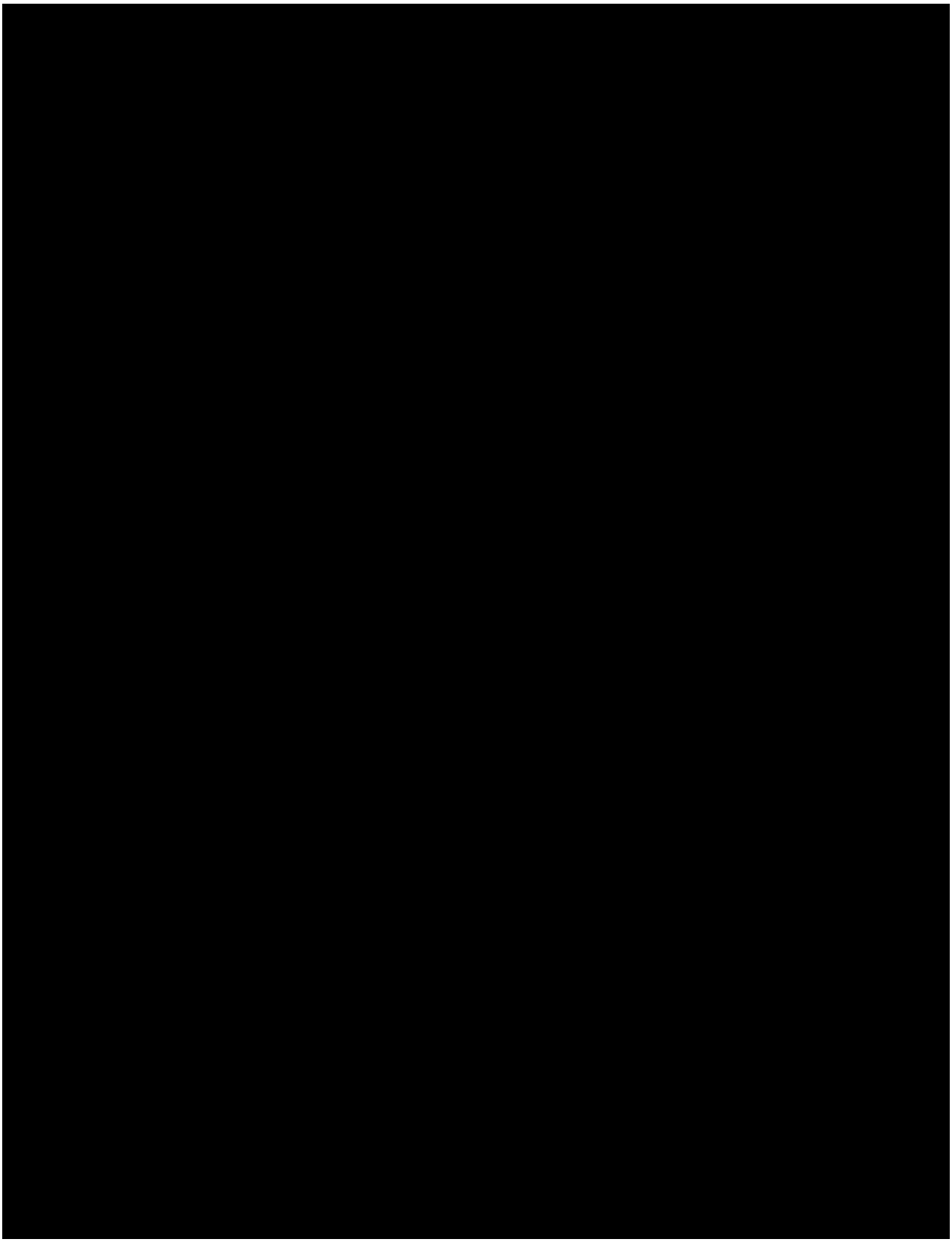

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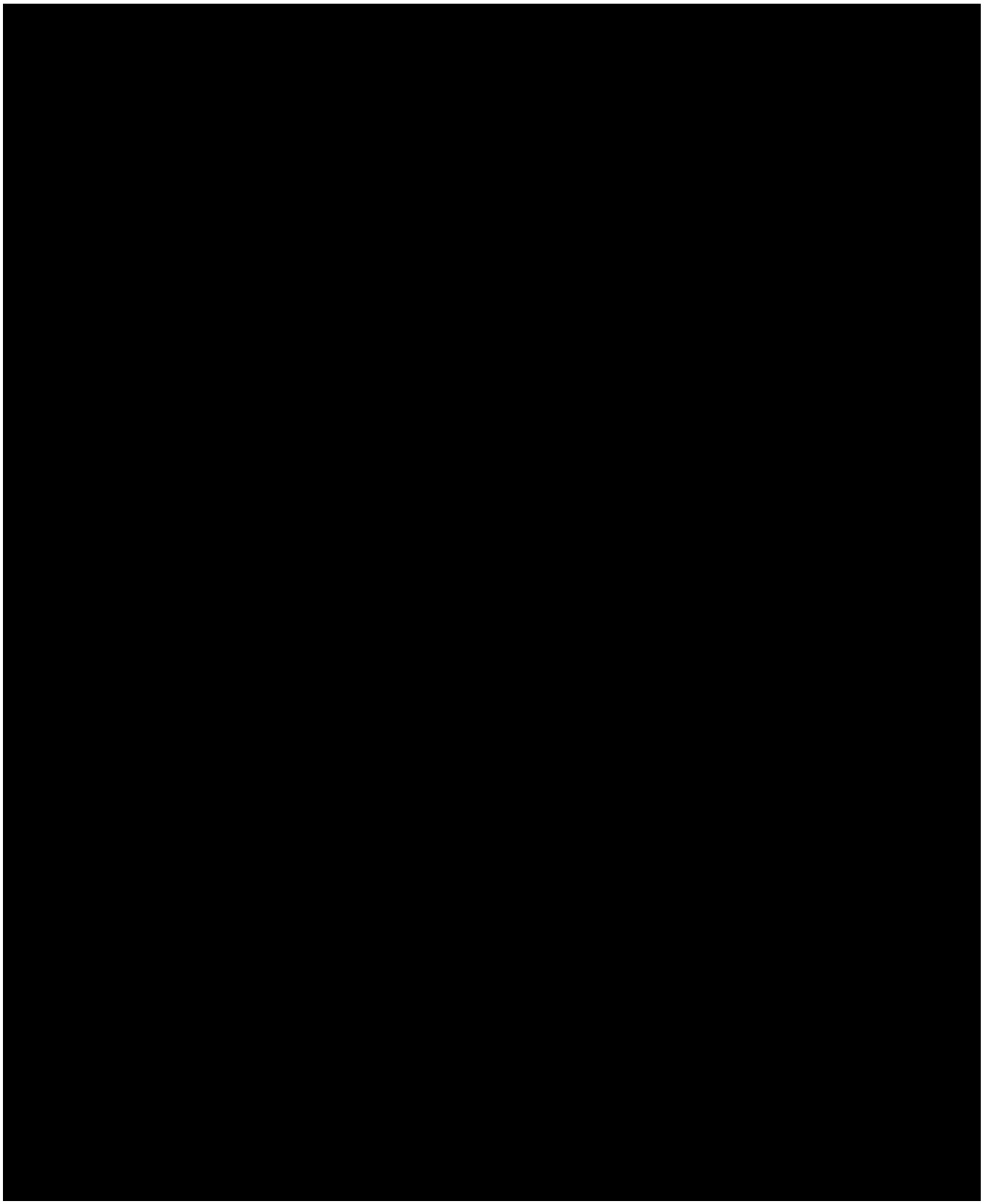

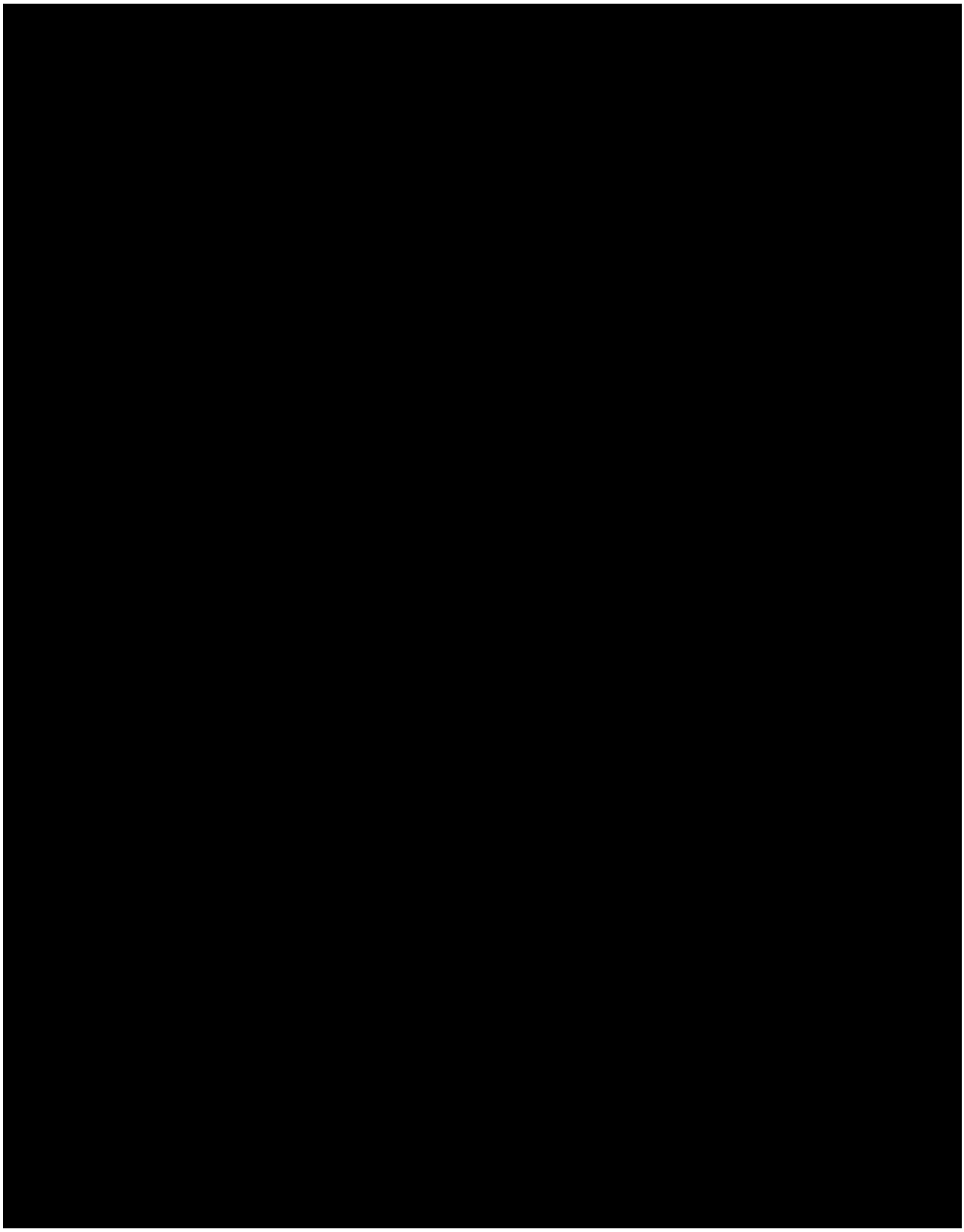

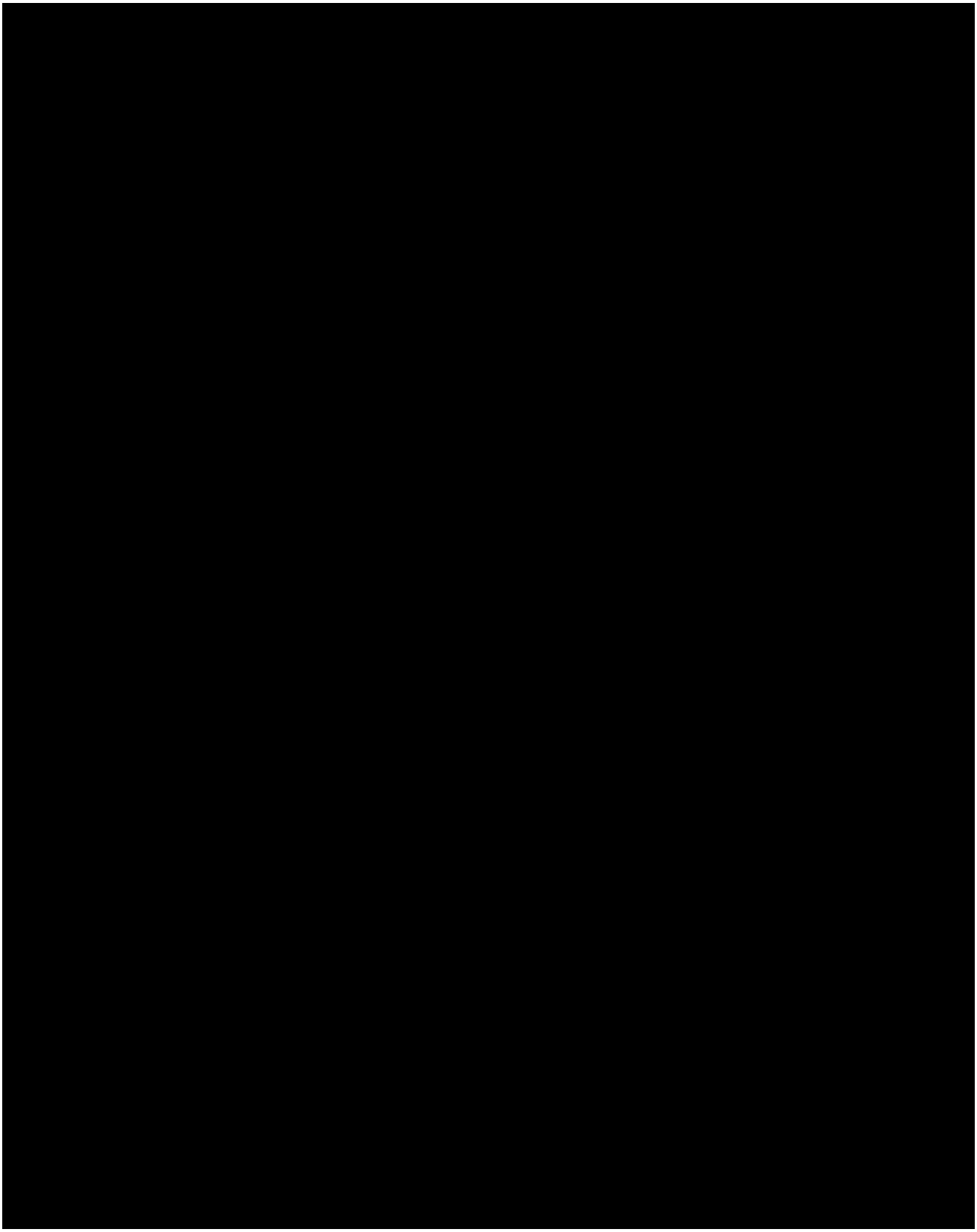

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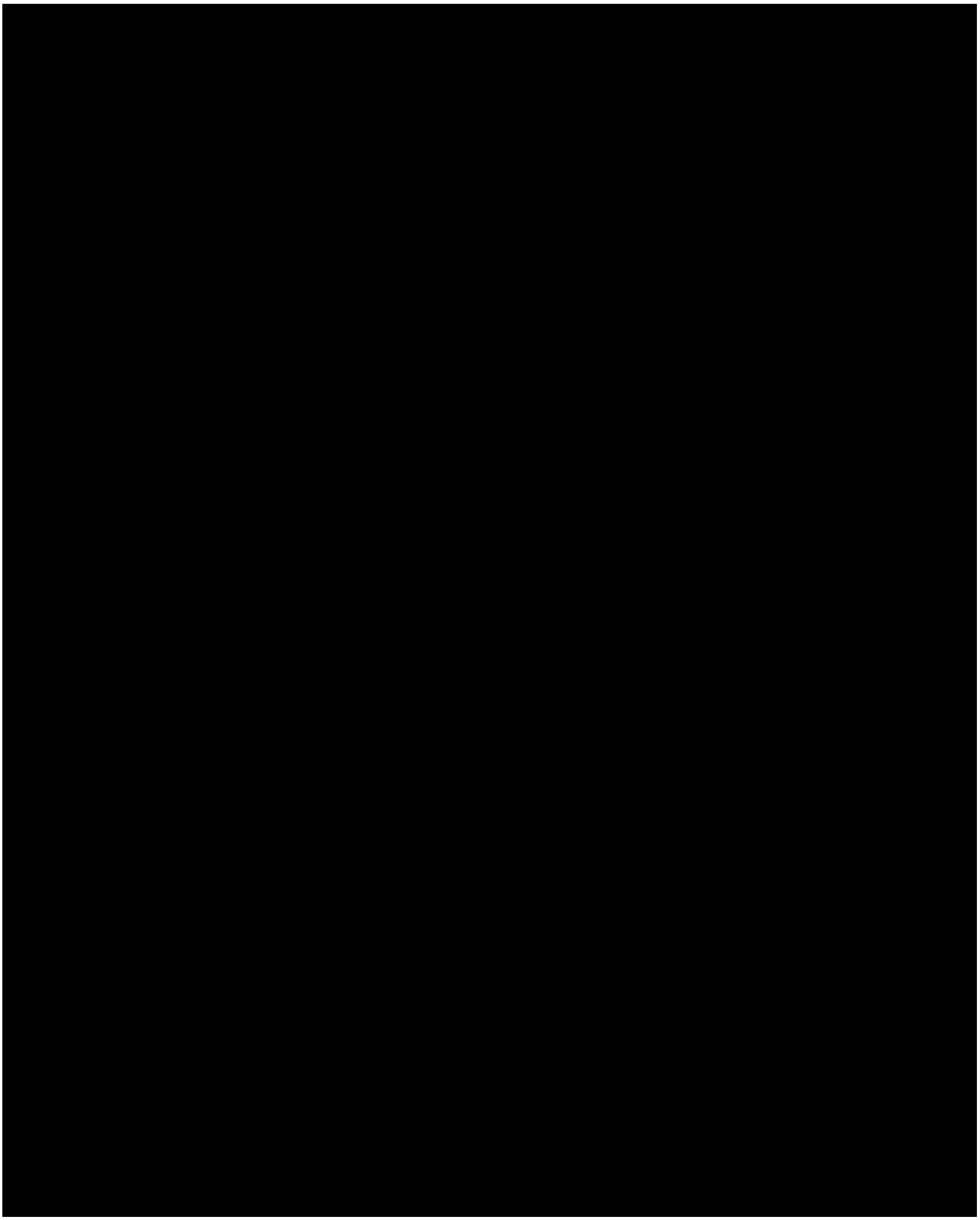

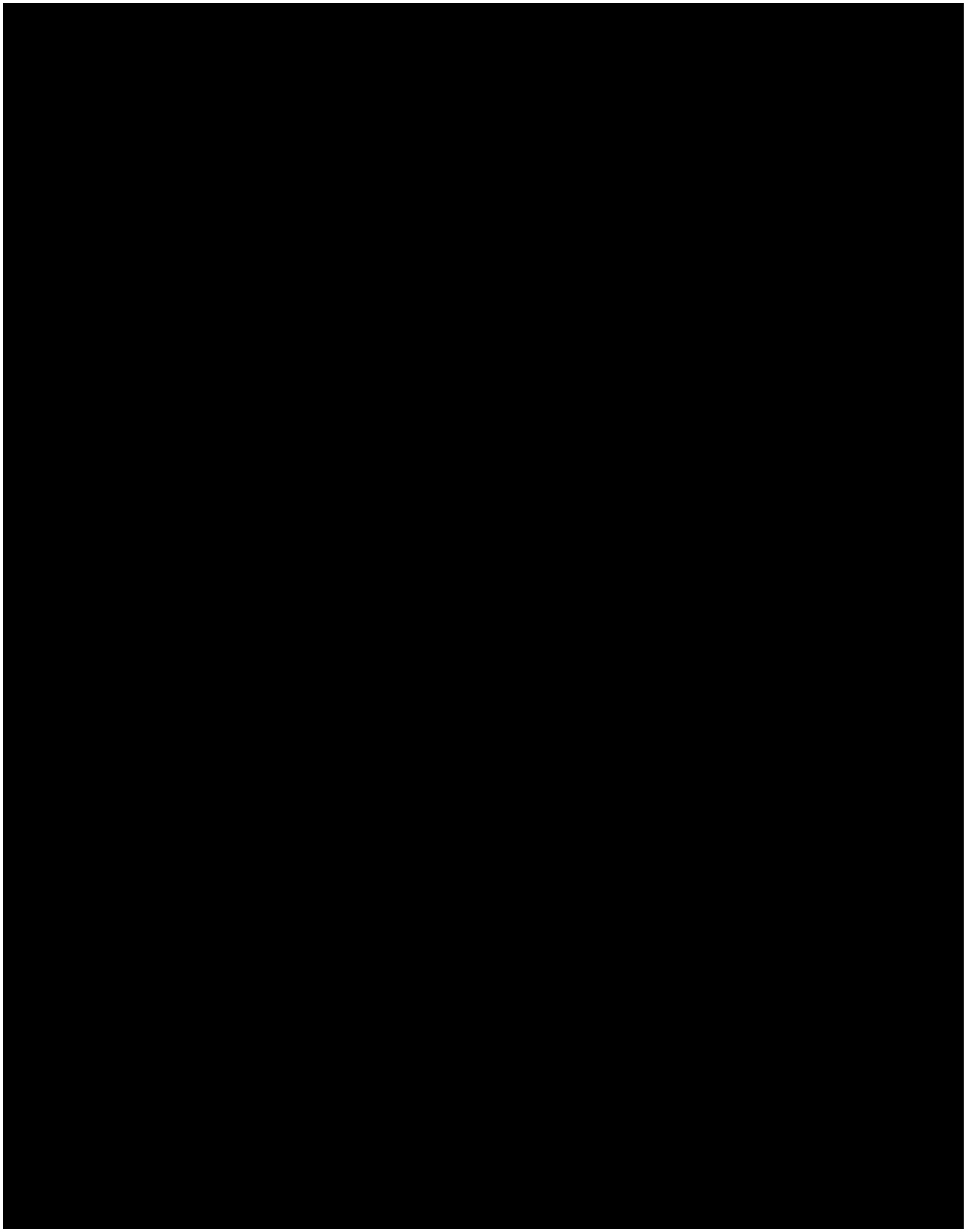

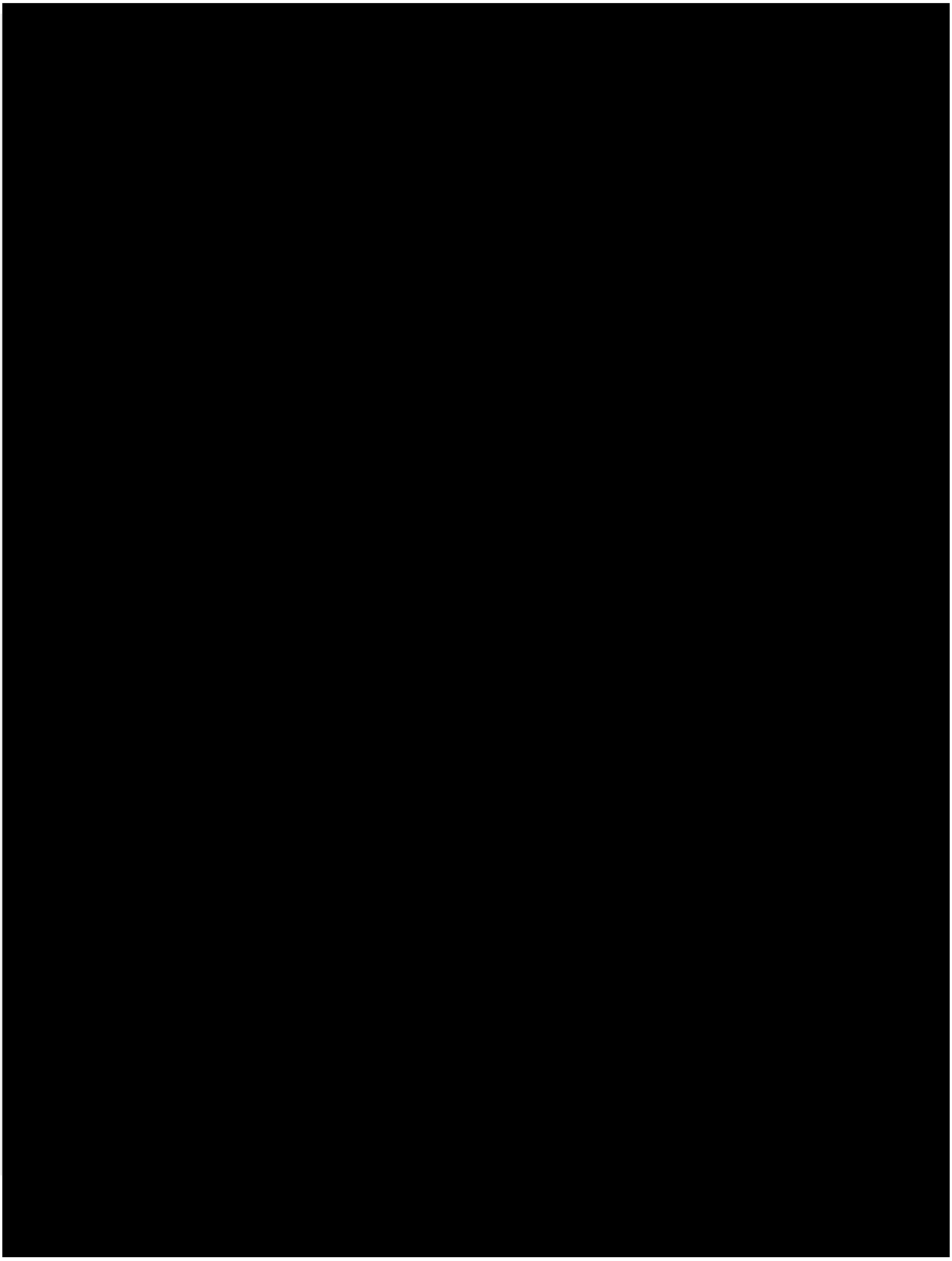

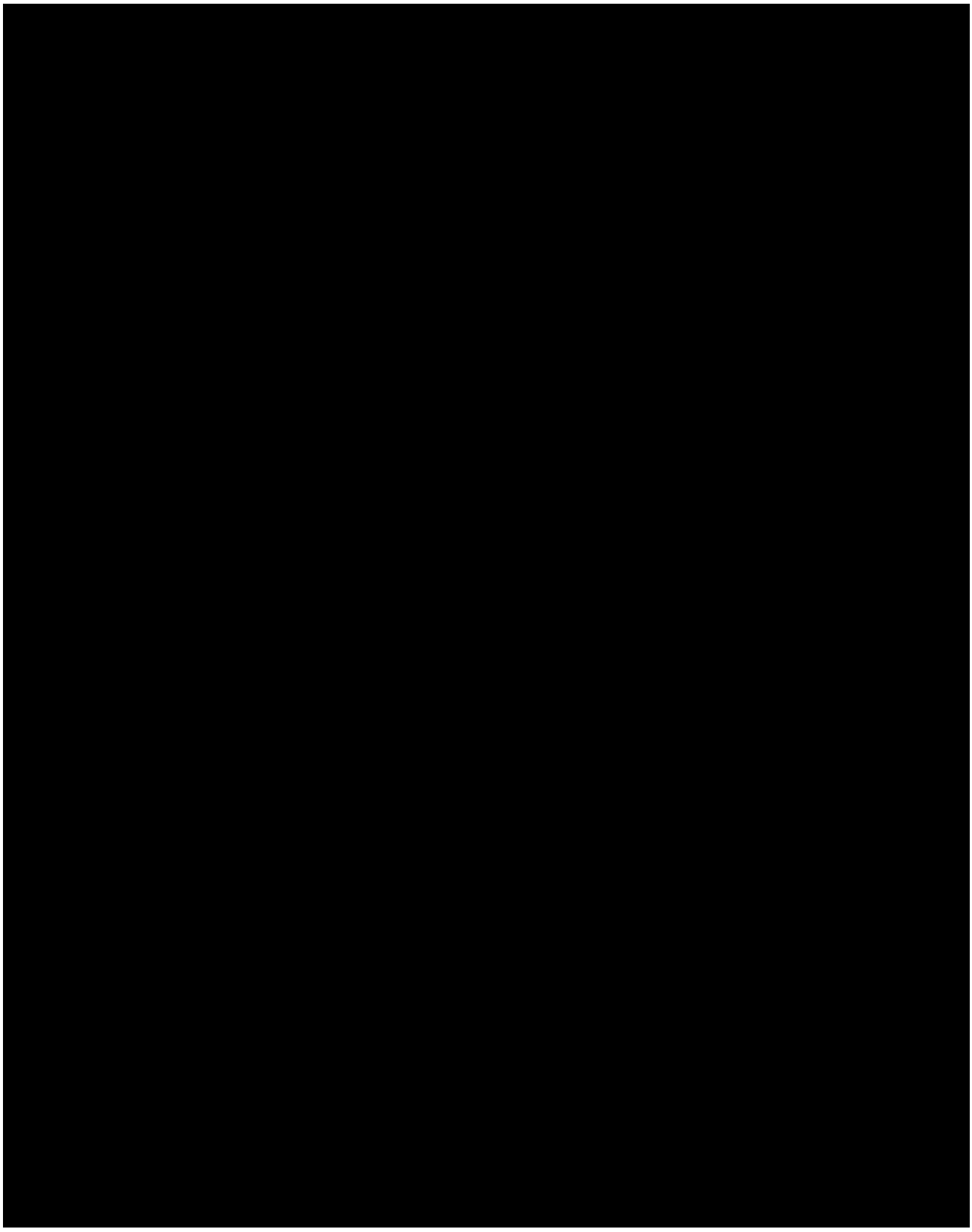

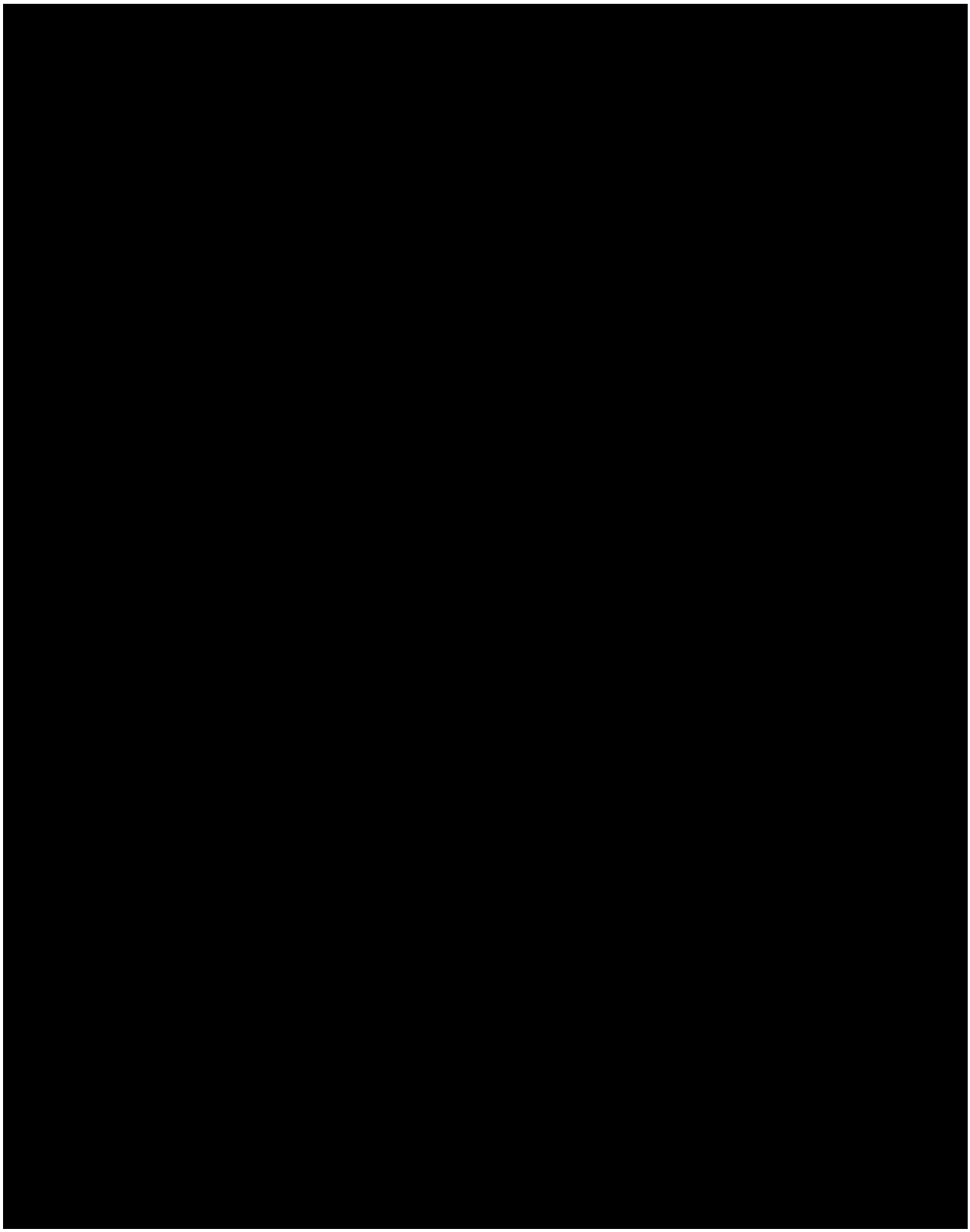

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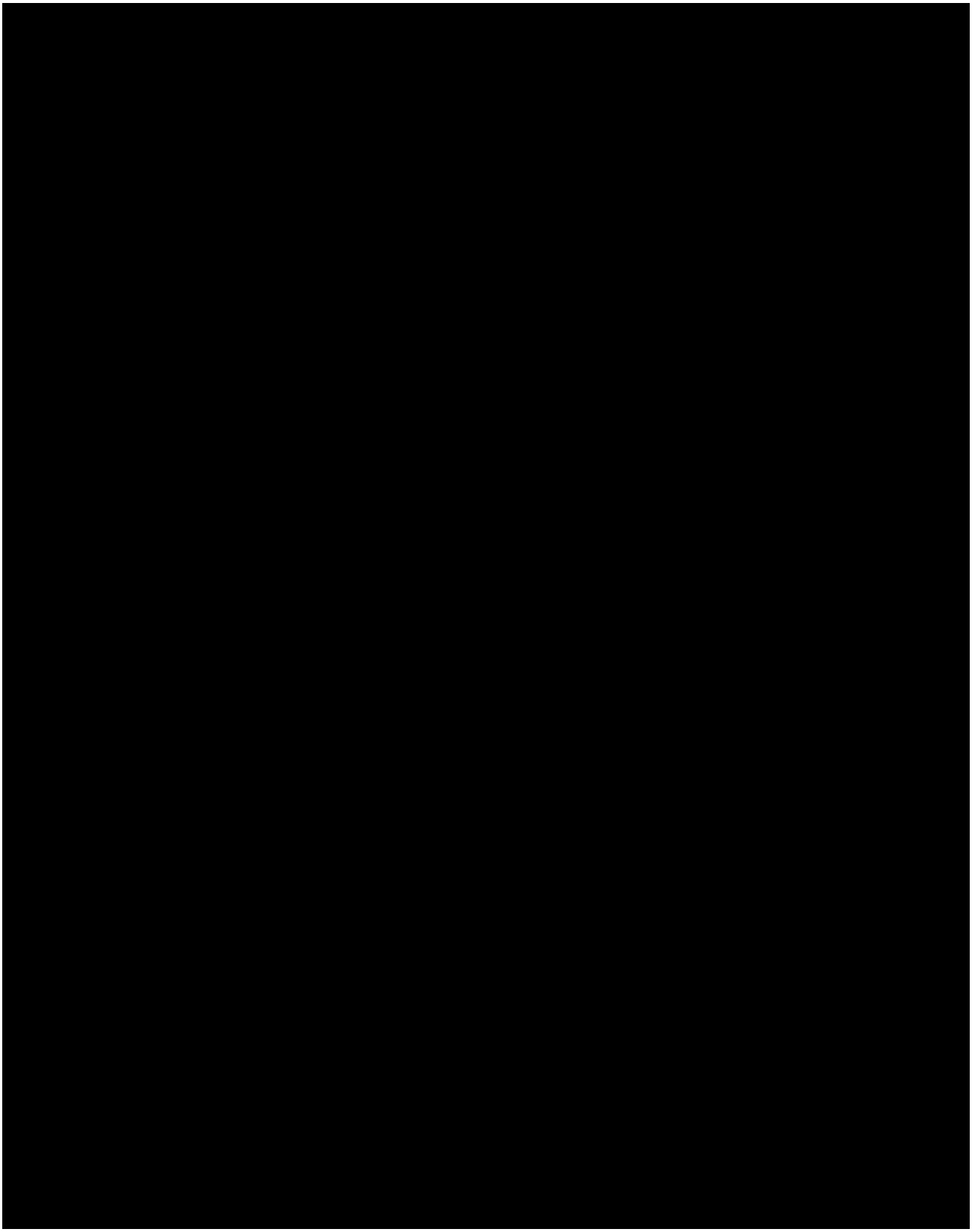

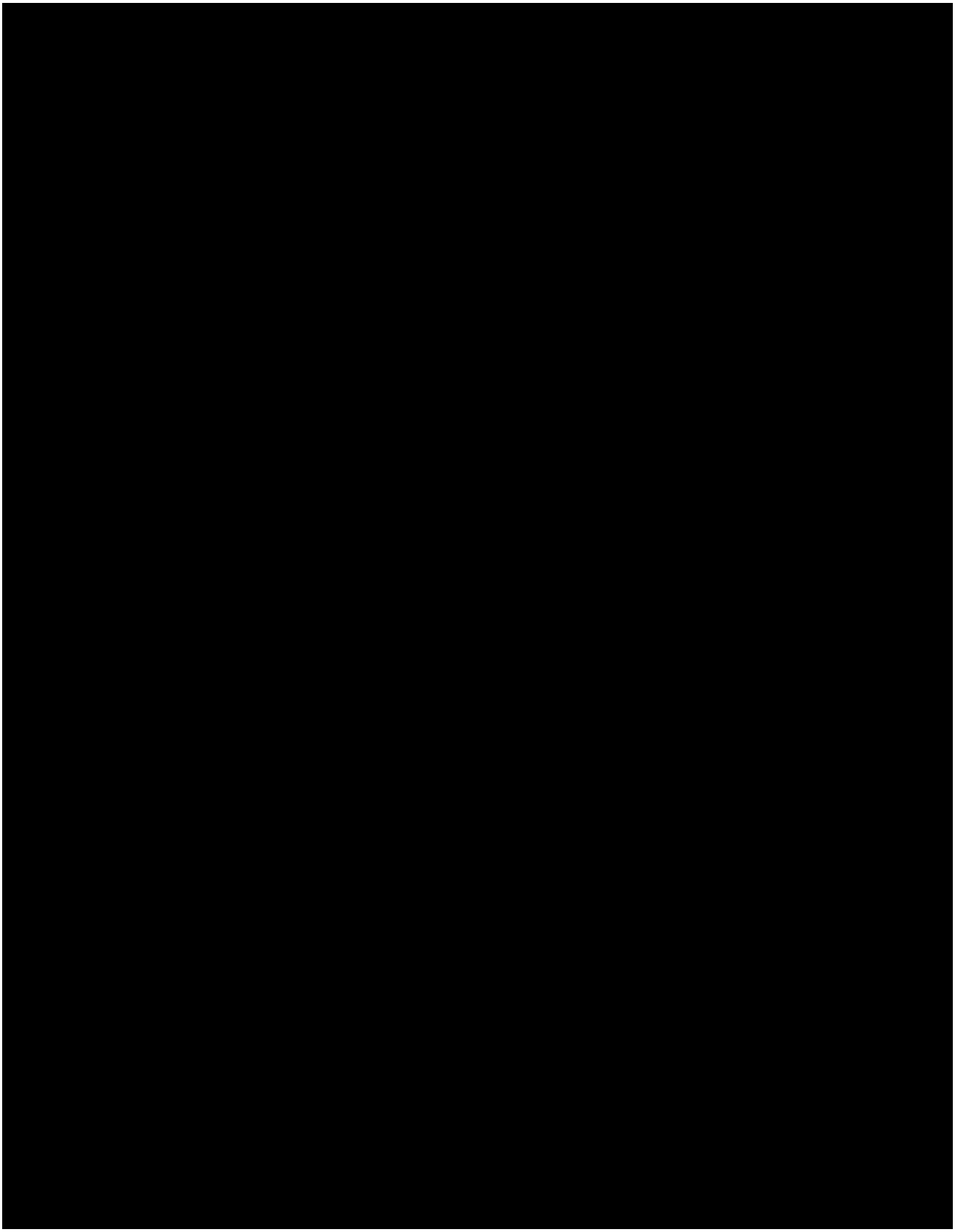

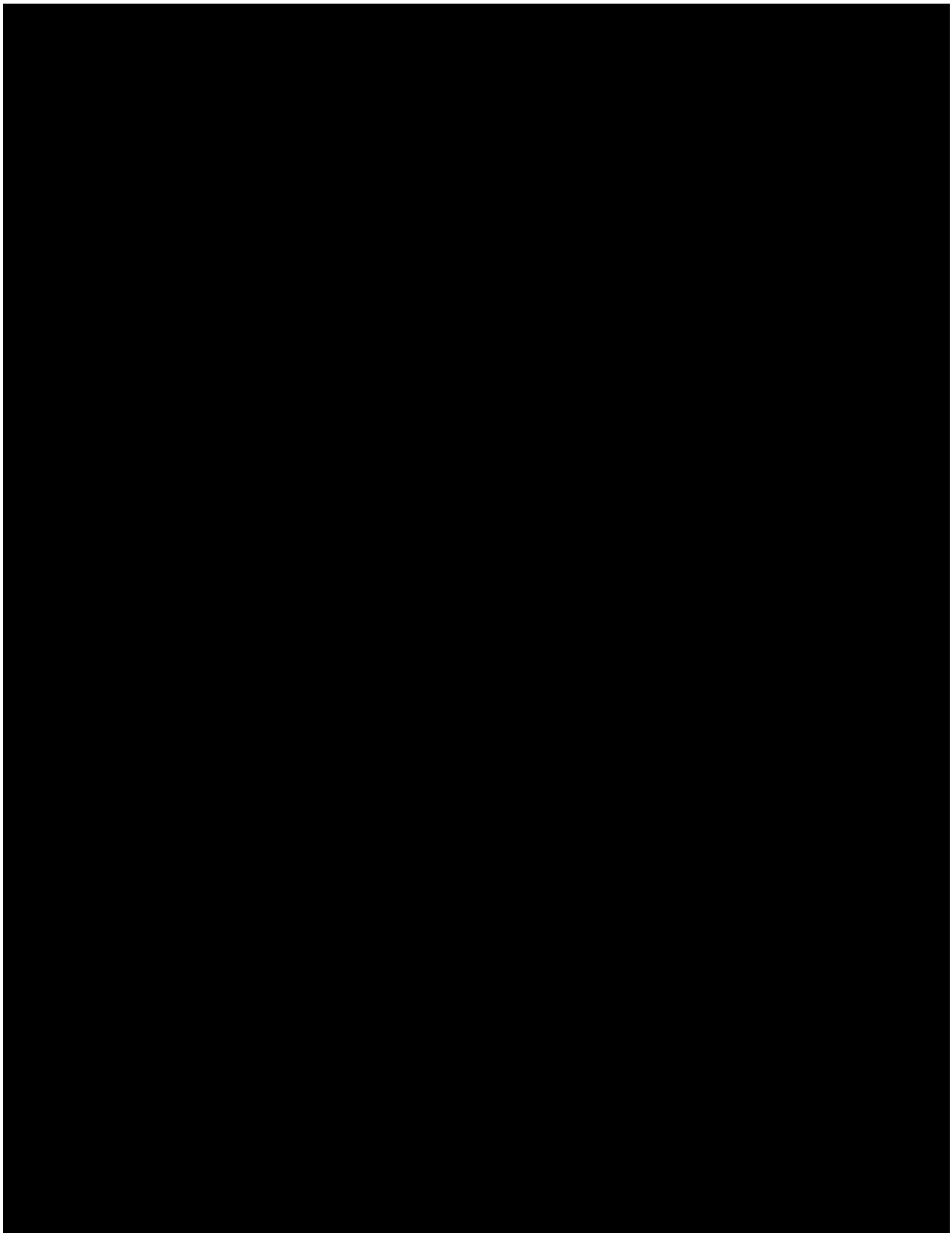

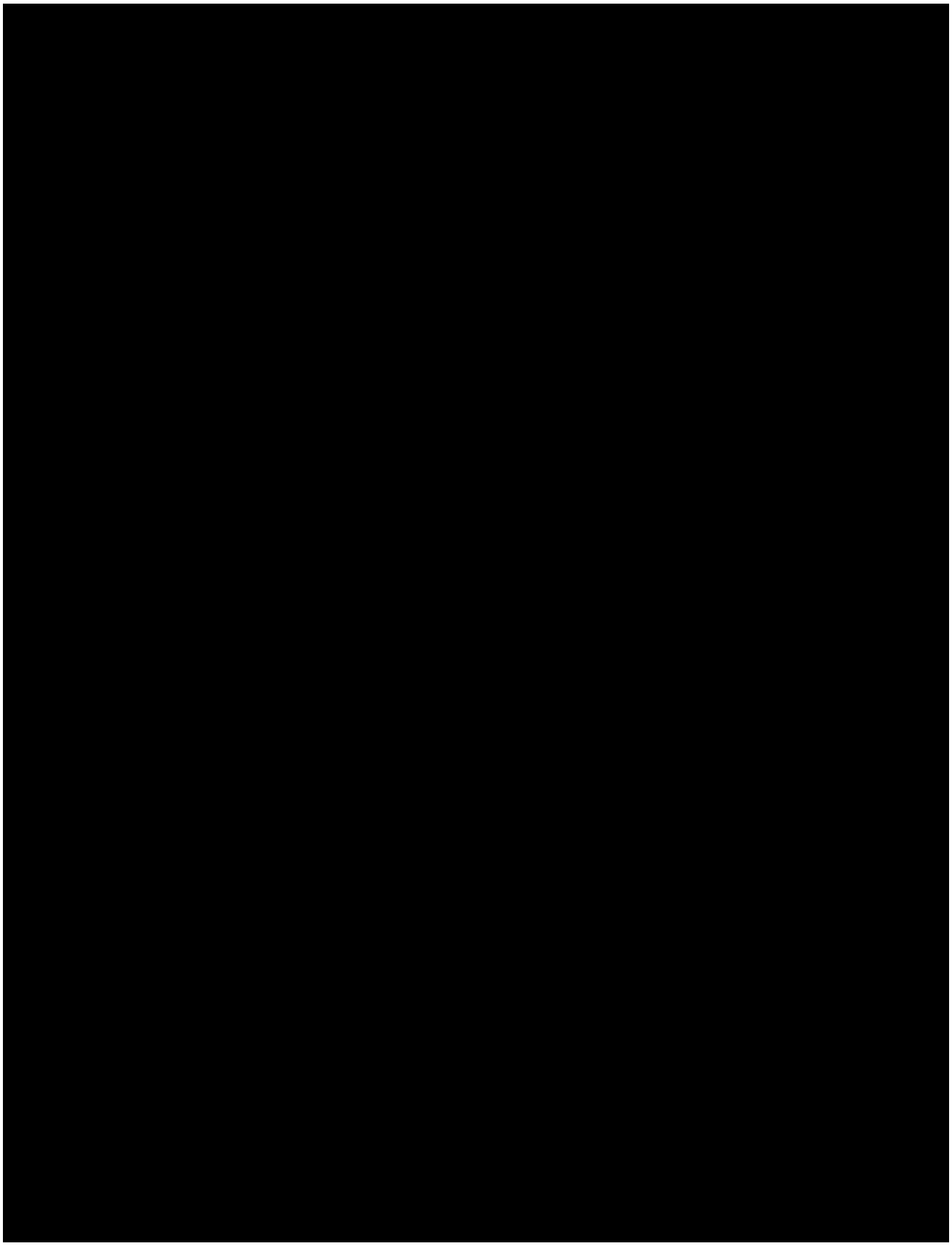

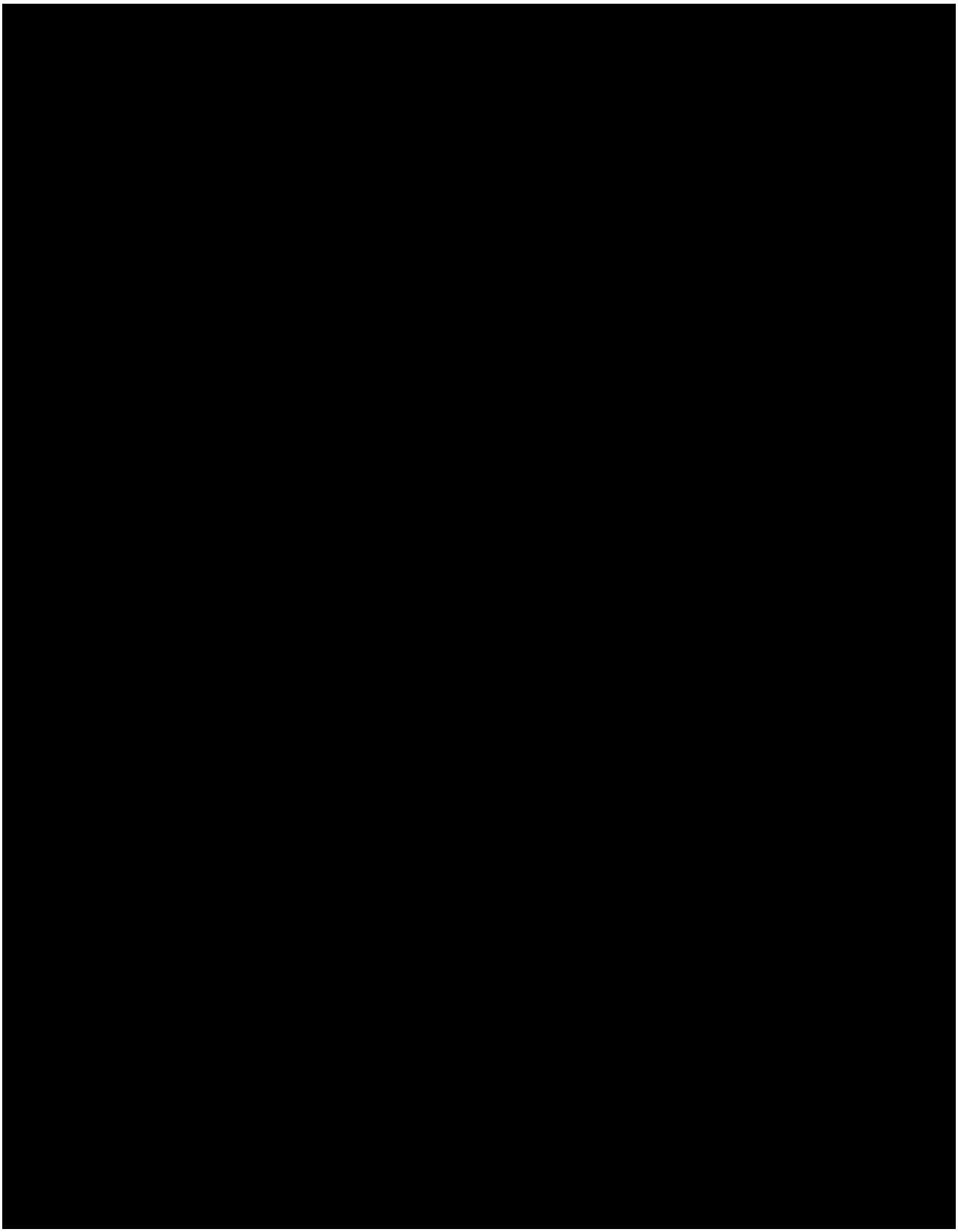

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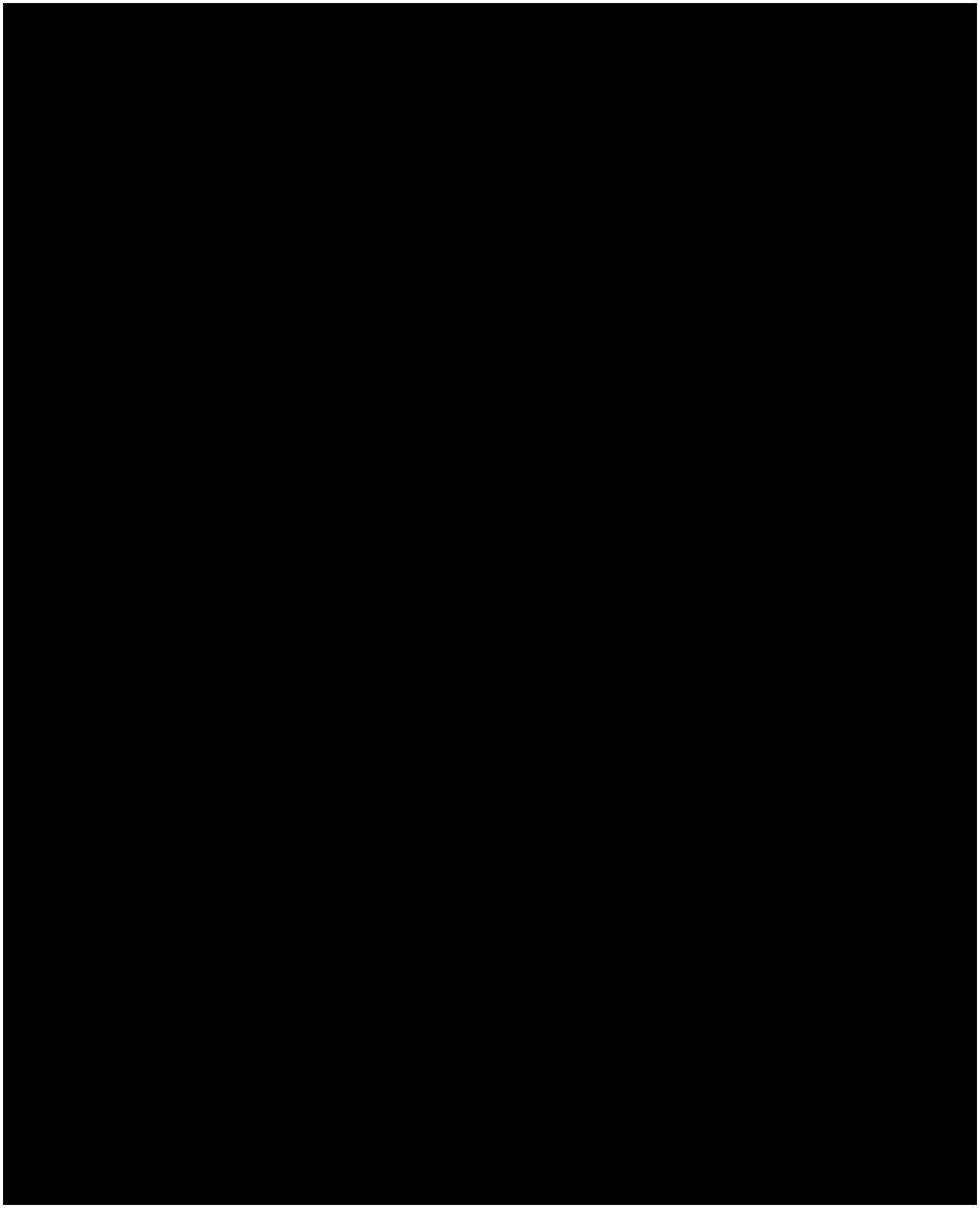

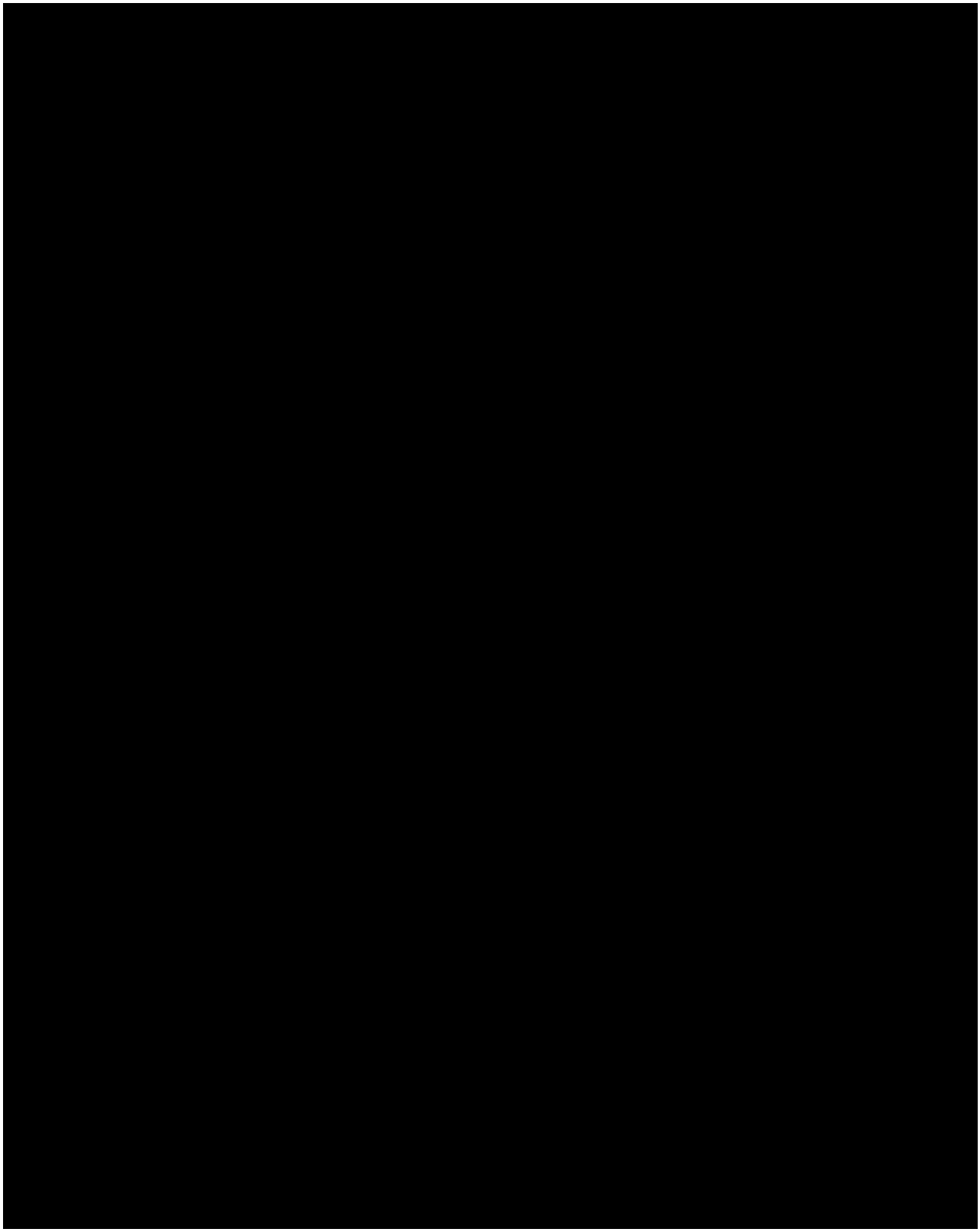

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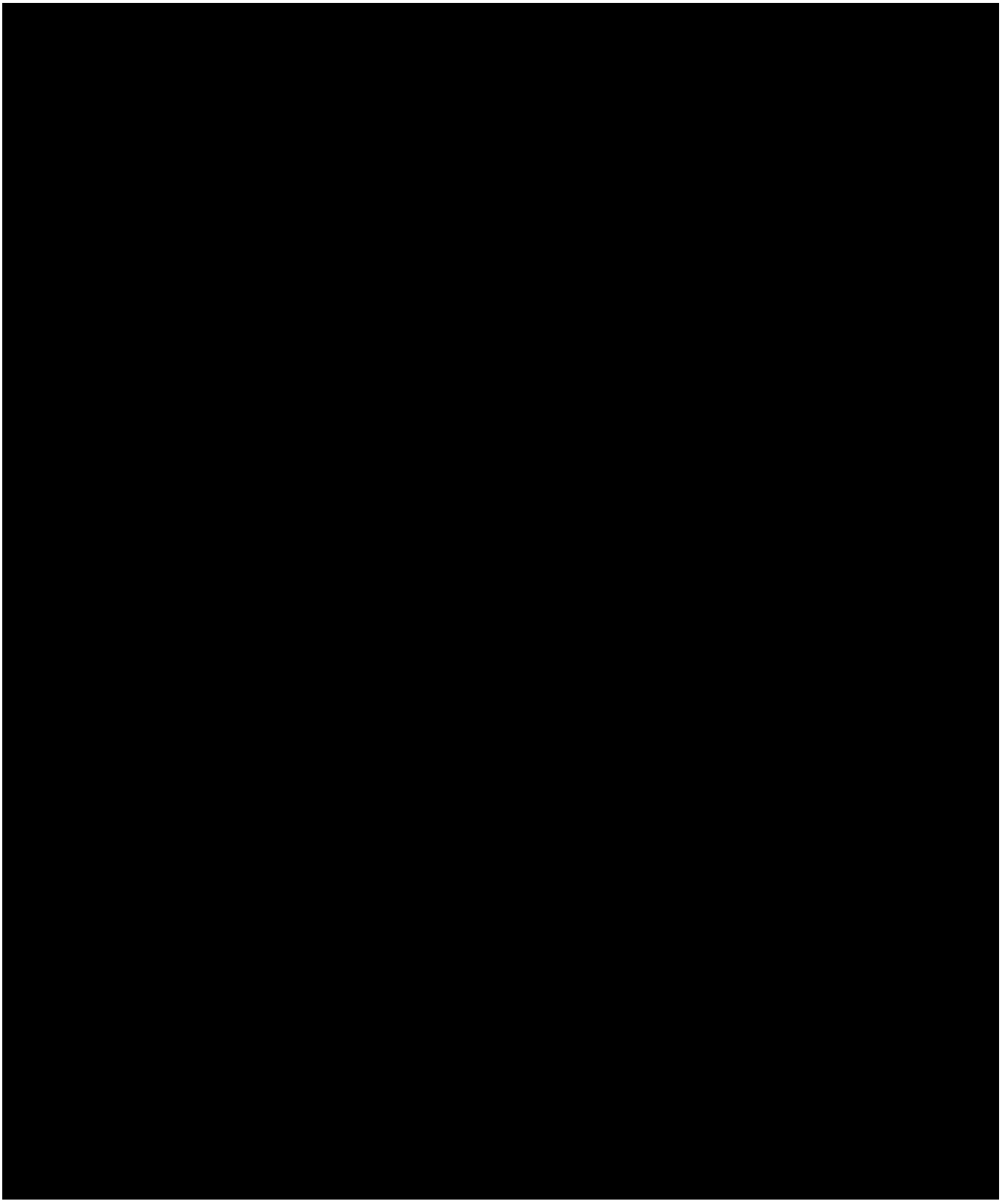

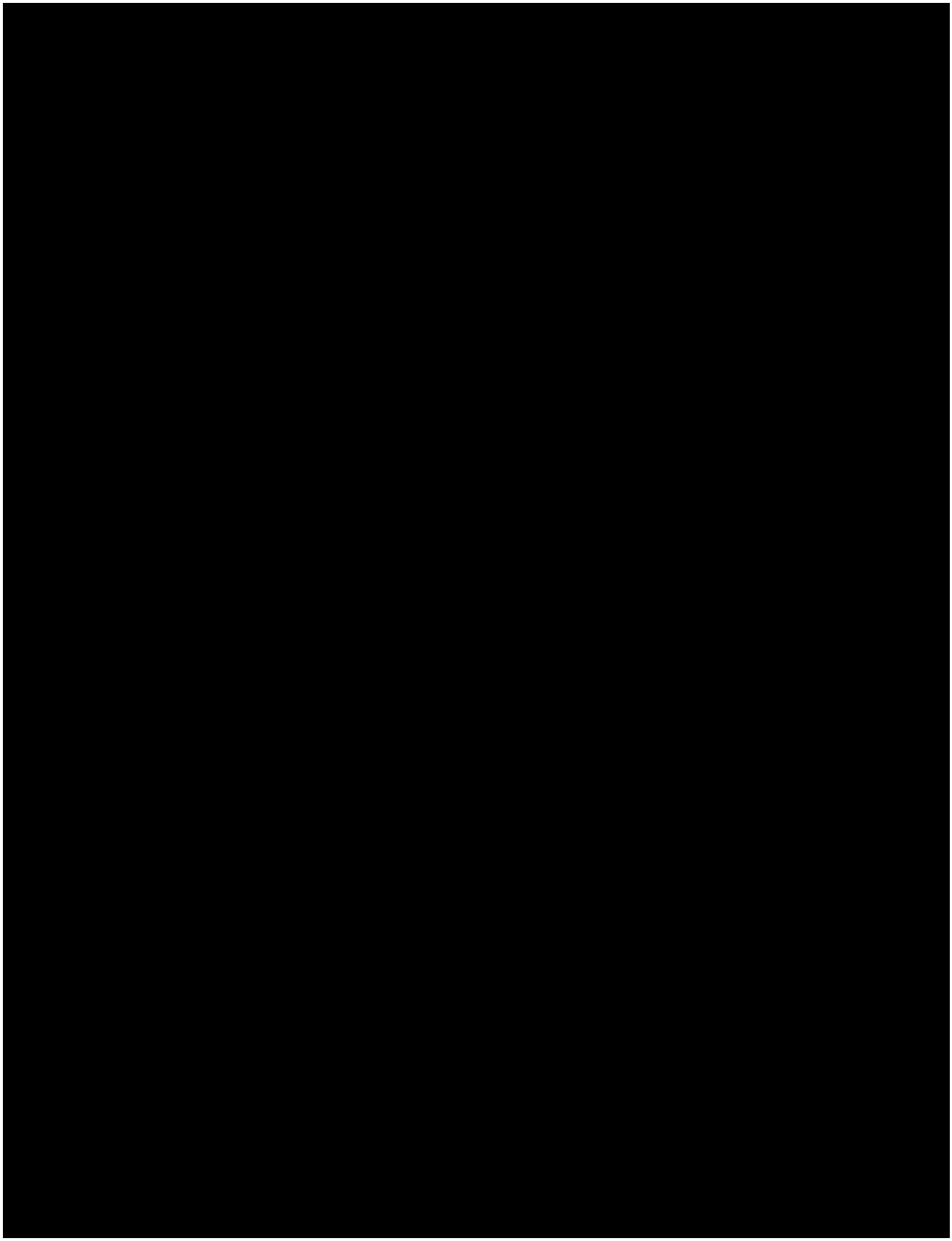

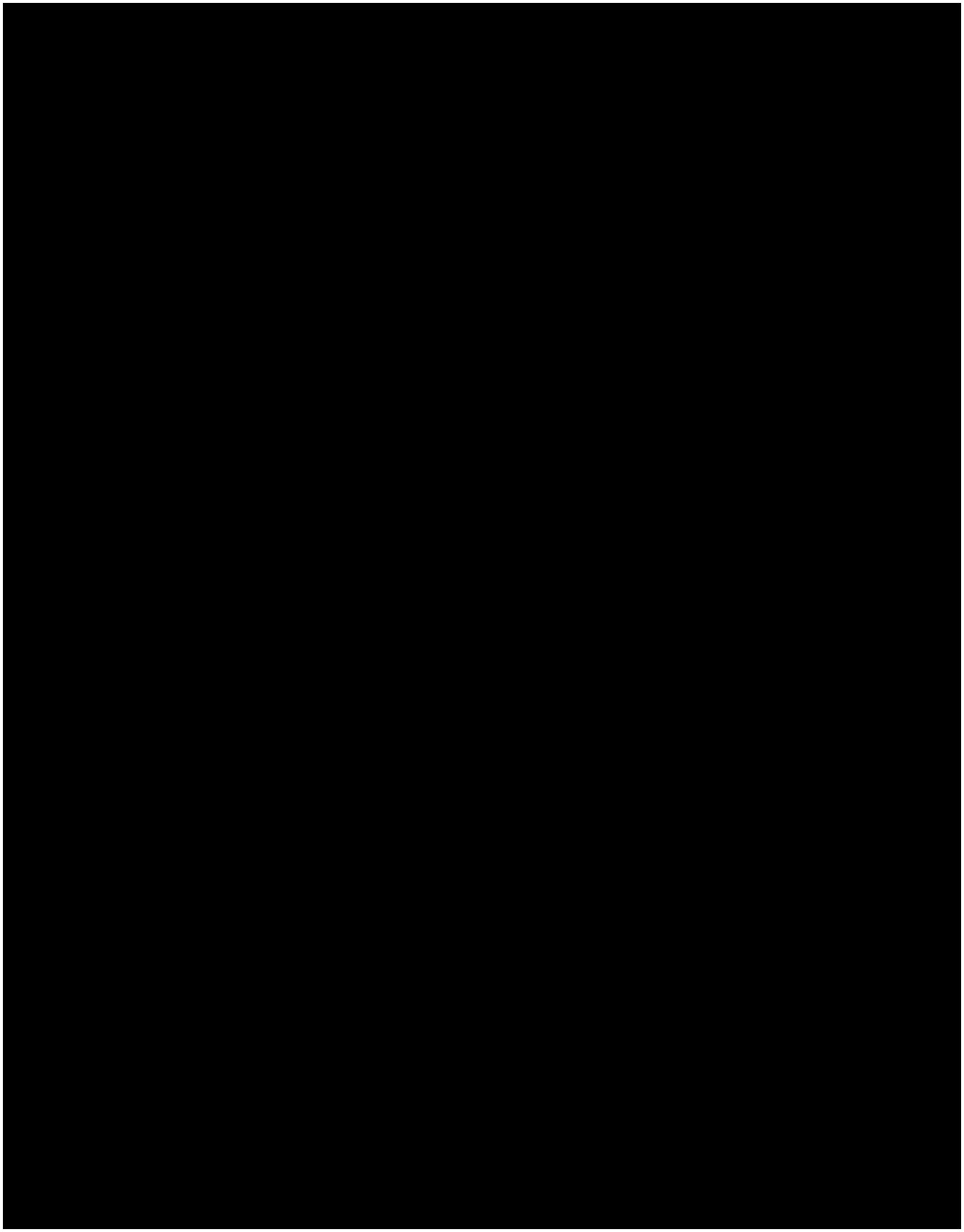

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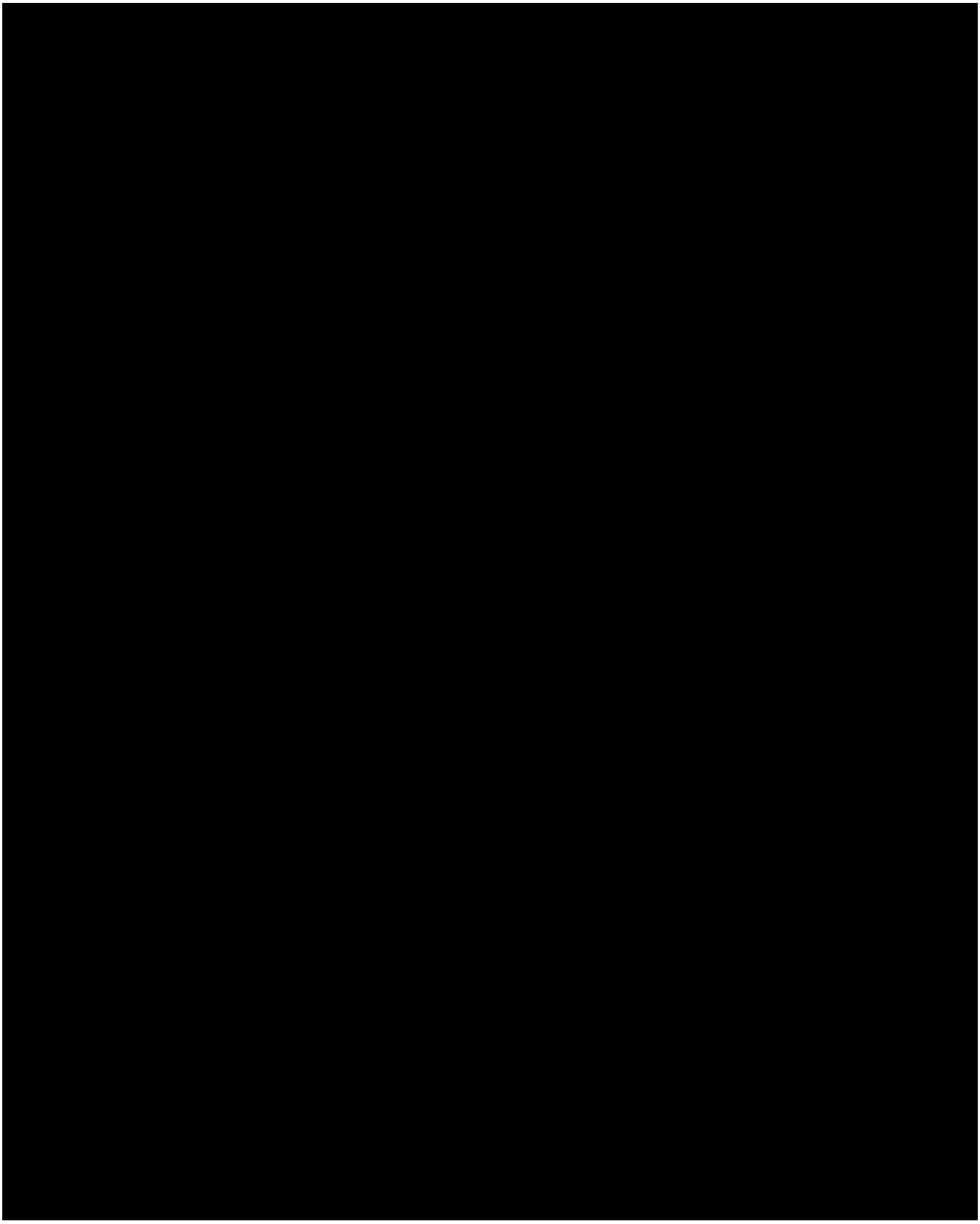

A Randomized, Double-Blind, Placebo-Controlled Study of

Diazoxide Choline Controlled-Release Tablet (DCCR) in

Patients with Prader-Willi Syndrome

Protocol: C601

Final, [redacted] Addendum

[redacted]

STATISTICAL ANALYSIS PLAN

This document provides clarification on the populations used for analysis in study C601.

In the Statistical Analysis Plan (SAP) [redacted] for study C601, "A Randomized, Double-Blind, Placebo-Controlled Study of Diazoxide Choline Controlled-Release Tablet (DCCR) in Patients with Prader-Willi Syndrome," the intent-to-treat (ITT) population [redacted] is being revised to consist of all randomized subjects who have a Baseline HQ-CT value and at least one post-Baseline HQ-CT value.

[redacted]

Justification: The primary efficacy analysis uses a linear mixed model for repeated measurements in the ITT population to model changes from Baseline in the Hyperphagia Questionnaire (HQ-CT) without imputed data. To be included in the primary efficacy analysis model, a subject must have at least one post-Baseline HQ-CT value. [redacted]

STATISTICAL ANALYSIS PLAN APPROVAL

Protocol: C601

[redacted] **ADDENDUM**

[redacted]