TITLE PAGE

Protocol Number:	812P306
Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Flexible-Dose Study of the Efficacy and Safety of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Avenue Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
IND number:	108,864
Investigational Medicinal Product:	Viloxazine extended-release capsule
Indication:	Attention-deficit/hyperactivity disorder (ADHD)
Contract Research Organization (CRO):	[redacted]
CRO Medical Monitor	[redacted]
Supernus Medical Advisor	[redacted]
Phase:	3
Protocol Version:	4.0
Date:	06Mar2020
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

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INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature Date

Print Name

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SUPERNUS PHARMACEUTICALS, INC. PROTOCOL APPROVAL PAGE

Authors:

[redacted]

Reviewers:

[redacted]

Approvers:

[redacted]

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CLINICAL PROTOCOL SYNOPSIS

Sponsor: Supernus Pharmaceuticals, Inc.	
Name of Product: SPN-812 (viloxazine extended-release capsule)	**Name of Active Ingredient:** Viloxazine hydrochloride
Protocol Number: 812P306	**Phase of Development:** 3
Full Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Flexible-Dose Study of the Efficacy and Safety of SPN-812 in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)	
Number of Study Sites: Up to 40 study sites	
Number of Subjects: Approximately 366 subjects will be randomized to one of two treatment arms (1:1 ratio; 183 subjects per arm).	
Indication: Attention-deficit/hyperactivity disorder (ADHD)	

Objectives:

Primary Objective:

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo for the treatment of ADHD in adults as measured by the adult ADHD Investigator Symptom Rating Scale (AISRS) total score.

Key Secondary Objective:

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo on the global assessment of severity for ADHD as measured by the Clinical Global Impression - Severity of Illness (CGI-S) scale.

Additional Secondary Objectives:

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo on:
    1) Clinical response rate of severity of illness as measured by the categorical CGI-S Responder Rate (CGI-S score 1 or 2).
    2) Global assessment of improvement as measured by the Clinical Global Impression - Improvement scale (CGI-I) for ADHD.
    3) Clinical response rate of improvement as measured categorical CGI-I Responder Rate (CGI-I score 1 or 2).
    4) Anxiety symptoms as measured by the Generalized Anxiety Disorder 7-Item scale (GAD-7).
    5) Clinician-rated ADHD symptoms as measured by the AISRS subscales of Inattention and Hyperactivity/Impulsivity.
    6) Clinician response rate of ADHD symptom reduction as measured by the 50% responder rate in AISRS total score.
    7) Clinician response rate of ADHD symptom reduction as measured by the 30% responder rate in AISRS total score.
    8) Executive functioning as measured by Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A; Self Report).
    9) Aspects of executive function and problems of self-regulation as measured by the BRIEF-A Summary Index Scales and BRIEF-A scales.

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Safety Objective:

- To evaluate the safety and tolerability of SPN-812 200 mg to 600 mg in adult subjects with ADHD.

[redacted]

Efficacy Endpoints:

Primary Endpoint:

- The primary efficacy endpoint is the change from baseline (CFB) at end of study (EOS) in the AISRS total score.

Key Secondary Endpoints:

- The key secondary efficacy endpoint is the CFB at EOS in the CGI-S score.

Additional Secondary Endpoints:

Additional secondary efficacy endpoints are:

1) Percentage of subjects with a CGI-S score of 1 or 2 at EOS.
2) CGI-I score at EOS.
3) Percentage of subjects with a CGI-I score of 1 or 2 at EOS.
4) CFB at EOS in the GAD-7 total score.
5) CFB at EOS in the AISRS Inattention subscale score and the Hyperactivity/Impulsivity subscale score.
6) AISRS 50% responder rate (defined as the percentage of subjects with a ≥ 50% reduction in the CFB AISRS total score) at EOS.
7) AISRS 30% responder rate (defined as the percentage of subjects with a ≥ 30% reduction in the CFB AISRS total score) at EOS.
8) CFB at EOS in the BRIEF-A Global Executive Composite (GEC) T-score.
9) CFB at EOS in the BRIEF-A T-score by each Summary Index Scale and by individual BRIEF-A scale.

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Safety Endpoints:

- Safety endpoints are adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).

[redacted]

Study Design:

This is a randomized, double-blind, placebo-controlled, multicenter, parallel group, flexible dose study of SPN-812 in adults diagnosed with ADHD per Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5™) criteria. Approximately 366 subjects will be randomized in a 1:1 ratio (183 subjects per arm): SPN-812 (200 mg to 600 mg) or placebo. Following up to 5 weeks of screening, subjects will be treated with study medication (SM) for 6 weeks.

At the Screening Visit (Visit 1), after informed consent is obtained, subjects will undergo initial screening evaluations/scales, and inclusion/exclusion criteria will be reviewed to confirm the subject's eligibility. Subjects taking ADHD medication at screening will undergo a washout of at least 1 week (or 5 half-lives of the medication, whichever is longer) before the Baseline Visit (Visit 2; Day 1). At the Baseline Visit, subjects who meet inclusion/exclusion criteria will be randomized. The Treatment Period will consist of 6 weeks of treatment with dosing starting Day 2 (morning after Visit 2) until Day 43 (Visit 7; end of study, EOS) (Section 4.2). Subjects will undergo efficacy and safety evaluations, return the previous dosing card, and receive the next card.

Subjects who complete the study may enroll in a separate open-label extension (OLE) safety study. Those subjects who do not enroll in OLE safety study will receive a phone call 1 week following EOS visit for safety.

Duration of Subject's Participation:

Following up to 5 weeks of screening, subjects will be treated with SM for 6 weeks. The total study duration from the Screening Visit to the end of the treatment period is up to 11 weeks.

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Investigational Medicinal Products, Reference Therapy, Doses and Mode of Administration

Study Medication: SPN-812 (viloxazine extended-release capsule)

Dose levels: 200 mg to 600 mg once daily (QD)

Reference Therapy: Matching placebo

Mode of Administration: Orally as intact capsules, each containing 200 mg of SPN-812

Treatment Arm	Number and Identity of Capsules to be Taken QD During the Treatment Period		
	Week 1	**Week 2**	**Week 3 to Week 6**
A: Placebo	2 Placebo	2 Placebo	1-3 Placebo
B: SPN-812	1 Placebo 1 SPN-812	2 SPN-812	1-3 SPN-812

QD = once daily
Each SPN-812 capsule contains 200 mg SPN-812.

Statistical Methodology

Sample Size:

Assuming an effect size of 0.407, 128 subjects per treatment group (256 total subjects for 2 arms) in the Full Analysis Set (FAS) will yield 90% power at a significance level of 0.05 (two-sided) to reject the equality of treatment means between the placebo and the SPN-812 treatment group. Assuming approximately 30% of subjects drop out before the completion of the study, an adjusted sample size of 366 subjects (183 per arm) will be randomized to obtain 128 subjects per arm in the FAS at the completion of the study.

Analysis Populations:

The **Randomized Population** is all subjects who complete the Baseline Period, meet the inclusion/exclusion criteria and are randomized.

The **Full Analysis Set (FAS)** is a subset of subjects in the Randomized Population who took at least one dose of study medication, and had a Baseline and at least one post-Baseline assessment of AISRS. Subjects in the FAS will be analyzed according to the treatment to which they were randomized. The efficacy analyses will be conducted using the FAS.

The **Per Protocol (PP) Population** is a subset of subjects in the FAS who complete all 7 visits through EOS with no missing AISRS assessments and no major protocol violations. Subjects in the PP Population will be analyzed according to the treatment received.

The **Safety Population** is all subjects randomized into the study who receive at least one dose of SM. Subjects in the Safety Population will be analyzed according to the treatment received.

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Statistical Methods:

Efficacy

- The primary efficacy variable, change from baseline in AISRS total score to Week 6 (EOS), will be analyzed using mixed model for repeated measures (MMRM), which assumes that missing data are missing at random (MAR). The model will include fixed effect terms for baseline AISRS total score, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood (REML) method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance-covariance matrix, the first (co)variance structure that does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry. The adjusted mean (least square mean [LS mean]) of CFB at EOS for AISRS total score for each treatment arm (placebo and SPN-812) will be presented, along with the corresponding standard error. The SPN-812 treatment arm will be compared with placebo. The LS means of the treatment groups, differences between the LS treatment means and placebo, and 95% confidence intervals (CIs) for the treatment differences with p-values will be computed.
- The sensitivity analysis assumes that missing AISRS total scores are missing not at random (MNAR). Placebo-based multiple imputation will be used to fill-in missing values. This approach may be considered “worst-case” sensitivity analyses as it assumes that after discontinuation, subjects from the SPN-812 treatment arm would adopt the outcome model estimated from the placebo arm. The placebo-based imputation will be implemented as described in the statistical analysis plan.
- The secondary analyses will be based on the FAS with missing values imputed using multiple imputation assuming MAR. All secondary analyses will use analysis of covariance (ANCOVA) (except categorical CGI, 50% responder and 30% responder which uses Pearson’s Chi-squared test or Fisher exact test on the absolute value at Week 6 (EOS)) on the change from baseline at Week 6 (EOS) (except CGI-I which uses the absolute value) with treatment and baseline (baseline CGI-S will be used for CGI-I) as fixed effect. The SPN-812 treatment arm will be compared with the placebo arm. The LS means of the treatment groups, differences between the LS treatment mean and placebo (SPN-812 minus placebo), and 95% CIs for the treatment differences with p-values will be computed.
- The primary and key secondary analyses will be repeated for the PP Population as supplemental analyses.

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Safety

- The incidence rate of AEs will be calculated by treatment arm using the Medical Dictionary for Regulatory Activities for each system organ class and preferred term.
- Clinical laboratory values, vital signs, and ECG results will be summarized using descriptive statistics. C-SSRS outcomes will also be summarized.

[redacted]

Inclusion Criteria:

1. Is male or female, aged 18 to ≤ 65 years at screening.
2. Is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained from the subject (a signed ICF).
4. Weight within the normal or overweight ranges according to accepted values of the Body Mass Index Chart (18.0 to 35 kg/m^2).
5. Is able to swallow capsules whole, without crushing, chewing or cutting.
6. Is willing and able to attend study appointments within the specified time windows.
7. Has a primary diagnosis of ADHD according to the DSM-5 classification, with diagnosis made at least 6 months prior to screening and confirmed with Structured Clinical Interview for DSM-5 Clinical Trials version (SCID-5-CT).
8. Has an AISRS total score of ≥ 26 at the Screening Visit and at the Baseline Visit (V2, Day 1).
9. Has a CGI-S score of ≥ 4 (moderately ill or worse) at the Screening Visit (V1) and Baseline Visit (V2, Day 1).
10. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning 30 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone (FSH) level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to screening).

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11. Males must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of SM, or
    b. Have been surgically sterilized prior to the Screening Visit.

Exclusion Criteria:

1. Has previously enrolled in a SPN-812 study.
2. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior to the first Screening Visit.
3. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
4. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
5. Has history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication or excipients.
6. Has history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. A current diagnosis of a major neurological disorder; or
    b. Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or
    c. Encephalopathy
7. Has any history of schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, autism, post-traumatic stress disorder or obsessive-compulsive disorder.
8. Has any current psychiatric disorder (per DSM-5 criteria) other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias, and subject is not receiving pharmacological treatment for the comorbidity/secondary diagnoses (e.g., antidepressant for MDD) at time of screening nor for the duration of study.
9. Has a Symptoms of Depression Questionnaire (SDQ) mean score >3.0 at screening.
10. Has a Hamilton Anxiety Rating Scale (HAM-A) score of > 21 at screening.
11. Has organic mental disorders, or mental disorders due to a general medical condition (per DSM-5 criteria).
12. Has a current diagnosis or history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) (per DSM-5 criteria) within the 12 months prior to screening; or is assessed by the Investigator as having regularly consumed alcohol exceeding 21 units for males and 14 units for females per week (1 unit

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equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within the 12 months prior to screening.

13. Is currently using, or has a positive result on the drug screening at the Screening Visit for drugs of abuse (alcohol, opiates, methadone, cocaine, methamphetamine [including ecstasy], phencyclidine, propoxyphene, methylphenidate, barbiturates, and benzodiazepines). If subject's serum drug screen for ethanol is positive at Screening (V1) and the investigator determines subject does not have alcohol use disorder, then the subject may have a repeat serum drug screen for ethanol performed before baseline within the allotted screening period (results must be received prior to V2 baseline). If second serum drug screen for ethanol is positive, subject is excluded from participating in the study, however, if second serum drug screen for ethanol is negative, subject may proceed to V2.
14. Is a (known or self-identified) current habitual/chronic cannabis user (medicinal or recreational); or
    - Has a positive urine drug screen for cannabis at the Screening Visit and is considered, per the Investigator's judgement, to be a habitual/chronic cannabis user; or
    - Has a positive urine drug screen for cannabis at both the screening and follow-up drug screen at the Baseline Visit, even though the subject is not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user.

    Note: Subjects who have a positive urine drug screen for cannabis at the Screening Visit but who are not considered to be a habitual/chronic cannabis user per the Investigator's judgement may, with Sponsor approval, undergo an additional urine drug screen at least 4 weeks after the original urine drug screen at Baseline Visit, prior to randomization. Subjects must agree to refrain from cannabis use throughout study.
15. Has treatment-resistant ADHD based on a history of receipt of >2 approved ADHD medications that failed to adequately improve the subject's symptoms. A subject who is naïve to ADHD treatment is not excluded from study participation.
16. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
17. Has history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin that has not been in remission for > 5 years prior to the first dose of SM.
18. Has or has had one or more of the following conditions considered clinically significant/relevant by the Investigator in the context of the study:
    - cardiovascular disease
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse < 50 bpm)
    - tachycardia (pulse > 100 bpm)
    - respiratory disease

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- hepatic impairment or renal insufficiency
- metabolic disorder
- endocrine disorder
- gastrointestinal disorder
- hematological disorder
- infectious disorder
- any clinically significant immunological condition
- dermatological disorder

19. Exhibits clinically significant abnormal vital signs at screening (see Note below).
20. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
    - Serum creatinine > 1.5 times the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 times ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase > 2 times ULN.
21. Has any of the following cardiology findings at screening (see Note below):
    - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
    - PR interval > 220 ms;
    - QRS interval > 130 ms;
    - QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia's method);
    - Second- or third-degree atrioventricular block;
    - Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.
22. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
23. Evidence of infection with hepatitis B or C, or human immunodeficiency virus (HIV)-1 or HIV-2, as determined by results of testing at screening.
24. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
25. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 30 days or 5 half-lives prior to Baseline Visit (Day 1) (whichever is longer) during the screening period or anticipated for the duration of the study.
26. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.
27. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS within the 6 months prior to screening.
28. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

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LIST OF TABLES AND FIGURES

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-IV/5	ADHD Rating Scale IV/5
ADR	adverse drug reaction
AE	adverse event
AISRS	ADHD Investigator Symptom Rating Scale
ANCOVA	analysis of covariance
ATC	Anatomical-Therapeutic-Chemical (code)
BMI	body mass index
BRI	Behavioral Regulation Index
BRIEF-A	Behavior Rating Inventory of Executive Function–Adult version
CAARS	Conners Adult ADHD Rating Scale
CFB	change from baseline
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CI	confidence interval
CL/F	apparent clearance
CRA	clinical research associate
CRO	clinical research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders – 4^{th}/5^{th} Edition
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ER	extended release
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCP	females of childbearing potential
FSH	follicle stimulating hormone
FPC	follow-up phone call
GAD-7	Generalized Anxiety Disorder 7-Item scale
GCP	Good Clinical Practice
GEC	Global Executive Composite
HAM-A	Hamilton Anxiety Rating Scale
HIV	human immunodeficiency virus
HRQL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IR	immediate release
IRB	institutional review board

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IWRS	interactive web response system
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Metacognitive Index
MMRM	mixed model for repeated measures
MNAR	missing not at random
OLE	open-label extension
PFC	prefrontal cortex
PGx	pharmacogenomics
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
QD	once daily
QTcF	QT corrected using Fridericia's method
REML	restricted maximum likelihood
SADR	suspected adverse drug reaction
SCID-5-CT	Structured Clinical Interview for DSM-5 Clinical Trials version
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDQ	Symptoms of Depression Questionnaire
SM	study medication
SNMA	serotonin norepinephrine modulating agent
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UDS	urine drug screen
Vd/F	apparent volume of distribution
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

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1 INTRODUCTION

1.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric condition characterized by inattention, hyperactivity and impulsivity. Epidemiological data suggest that ADHD affects up to 8% of children in the United States, while the estimated prevalence in the adult population is between 0.3% and 5% (**McCann and Roy-Byrne, 2004**). The standard pharmaceutical treatments for ADHD include psychostimulants, non-stimulants, and antidepressants. Stimulants (e.g., methylphenidate, amphetamine) are the first-line pharmacotherapies for the treatment of ADHD. However, 10% to 30% of patients do not adequately respond to stimulants or experience intolerable adverse events (AEs; e.g., decreased appetite, sleep problems, headaches) (**Briars and Todd, 2016**).

SPN-812 (extended-release viloxazine) is a structurally distinct, bicyclic, Serotonin Norepinephrine Modulating Agent (SNMA). The active substance in SPN-812 is viloxazine, whose mechanism of action is multimodal with antagonistic activity observed at 5-HT2B and agonistic activity at 5-HT2C receptors, as well as weaker antagonistic effects at ADRα1B, ADRβ2 and 5-HT7 receptors. Additionally, SPN-812 acts as a modulator with inhibitory effects at the norepinephrine reuptake transporter. Viloxazine was previously marketed in several European countries as an antidepressant as an immediate-release (IR) product. An extended-release (ER) formulation of viloxazine, SPN-812, has been developed by Supernus to prolong the release and absorption of viloxazine post-administration, thereby minimizing fluctuations in plasma drug levels and allowing longer dosing intervals for a drug with a relatively short half-life. SPN-812 was developed for potential use in the treatment of subjects with ADHD, based on the pharmacological properties and favorable safety profile and the current unmet medical need for effective long-acting, nonstimulant ADHD treatment in children and adolescents. SPN-812 is being evaluated in the current study for potential use in the treatment of ADHD in adults based on the pharmacological properties and favorable safety profile of viloxazine.

1.2 Clinical Information

The safety, pharmacokinetics (PK) and drug-drug interactions for the IR and ER formulations of SPN-812 have been evaluated in multiple Phase 1 studies in healthy adults. As of April 2019, a number of studies evaluating the efficacy and safety of SPN-812 treatment for ADHD in pediatric and adult populations have been completed, including one Phase 2 study in adults (18 to 65 years of age; 812P201), one pediatric Phase 2 in children (6 to 12 years of age; 812P202), and four pediatric Phase 3 studies, two in children (6 to 11 years of age; 812P301 and 812P303) and two in adolescents (12 to 17 years of age; 812P302 and 812P304). In addition, there is an ongoing pediatric open-label extension (OLE) safety study in children and adolescents (6 to 17 years of age; 812P310). Key findings from the completed Phase 2 and Phase 3 studies are summarized below. Additional details are provided in the SPN-812 Investigator's Brochure.

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Phase 1 Studies

Phase 1 studies include comparison of single and two-bead SPN-812 extended release (ER) formulations to an SPN-812 immediate release (IR) formulation at single and multiple doses (812P102 and 812P103, respectively), evaluation of food and sprinkling effects (812P105), drug-drug interactions (DDIs) on CYP1A2, 2D6, and 3A4 substrates with evaluation of SPN-812 ER metabolism in CYP2D6 poor metabolizers vs. CYP2D6 extensive metabolizers (812P113.1), DDI with d-amphetamine (812P113.2), DDI with methylphenidate (812P113.3), evaluation of the effect of alcohol on SPN-812 metabolism (812P115), evaluation of the effect of renal impairment on SPN-812 metabolism (812P112.1), evaluation of multiple dose SPN-812 on QT Interval (812P117), evaluation of maximum tolerable doses and cardiac safety in a single and multiple-ascending dose study (812P120) have also been evaluated. In addition, a [14C]-labelled oral IR solution was used to examine human absorption, metabolism, and excretion (812P111).

Results from these studies demonstrated that 200 mg single dose of an extended release SPN-812 formulation resulted in a mean maximum plasma concentration (Cmax) of 1.33 µg/mL, area under the plasma concentration-time curve extrapolated to infinity (AUCinf) of 27.3 hr*µg/mL, median time to maximum concentration (tmax) of 5 hours, and a half-life of approximately 7 hours (812P103). Lower mean Cmax was observed for SPN-812 as compared to SPN-812 IR and by 48 hours overall viloxazine exposure was comparable between the two formulations. The rate of absorption of viloxazine was formulation dependent; SPN-812 exhibited a slower absorption rate than SPN-812 IR. Following multiple-dose administration of SPN-812 on consecutive days, steady-state was achieved by the second day of multiple dosing. Little systemic accumulation of viloxazine was observed as no major increase in pharmacokinetic (PK) parameters was observed following multiple administration of SPN-812 compared to single dose administration, during the same time interval.

Food and sprinkling did not affect the relative bioavailability of viloxazine following administration of SPN-812 capsules (812P105). SPN-812 interacted as a strong inhibitor of CYP1A2, a weak inhibitor of CYP2D6, a weak inhibitor of CYP3A4; and displayed no significant differences in metabolism within CYP2D6 poor metabolizers and CYP2D6 extensive metabolizers (812P113.1). There was no DDI between SPN-812 and d-amphetamine (812P113.2) nor SPN-812 and methylphenidate (812P113.3). In addition, there was no dose dumping observed with co-administration of alcohol with SPN-812 (812P115). Renal impairment resulted in a 1.09-fold, 1.3-fold, and 1.9-fold increase in AUC for mild, moderate, and severe renal impairment subjects receiving 400 mg SPN-812 as compared to healthy subjects (812P112.1). Multiple doses of 1800 mg (supratherapeutic) SPN-812 did not affect cardiac repolarization as measured by QTcI and QTcF or other electrocardiographic parameters (812P117). In the single ascending/multiple ascending dose study, SPN-812 was well tolerated up to 2100 mg/day as a single dose and up to 1800 mg/day as multiple doses given once daily for 5 consecutive days. Intolerable adverse events (AEs) were not observed at doses of up to

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1800 mg/day. SPN-812 at a single supratherapeutic dose had no effect on cardiac repolarization or other electrocardiographic parameters, other than slight increase in heart rate consistent with the known anticholinergic effect of viloxazine (812P120).

In the human absorption, metabolism, and excretion study, absorption of the isomers, R- and S-viloxazine, was rapid with a median Tmax of 1.0 hour and showed a 2:1 concentration ratio, respectively. Nearly 100% of the radioactive dose was recovered with approximately 90% being recovered within 24 hours of administration, demonstrating complete absorption of the drug followed by rapid elimination. The primary circulating form was SPN 812; the only metabolite found above 10% total radioactivity was de-activated hydroxylated glucuronide.

The most common AEs in the Phase 1 studies in healthy adults were somnolence and headache. Most AEs were mild; none were severe or serious. No clinically significant, study medication-related findings were observed for laboratory or electrocardiogram (ECG) tests in any study. In general, SPN 812 is considered to be well tolerated with no safety events observed that would be unexpected for viloxazine.

Phase 2 Studies

The randomized, blinded, proof-of-concept Phase 1/2 study 812P201 compared an IR formulation of SPN-812 and placebo administered three times a daily in a dose range of 150 to 300 mg/day in 52 adults (26 per treatment) with ADHD. In addition to assessing the safety and tolerability of SPN-812 IR, scores of both the Investigator-rated and patient-rated Conners Adult ADHD Rating Scale (CAARS) were collected at weekly intervals during the 6-week treatment period. Treatment with SPN-812 IR showed a statistically significant reduction in median CAARS total ADHD symptom score compared to placebo. Treatment-emergent AEs were reported in 23 (88.5%) subjects in the SPN-812 IR group and in 18 (72.0%) subjects in the placebo group. The most common AEs in SPN-812 IR group were nausea, decreased appetite, headache, and insomnia. There were no clinically significant ECGs, clinical laboratory test results, vital signs, or physical examination findings in either group during the study. No serious adverse events (SAEs) or deaths occurred during the study.

The 812P202 study in children with ADHD assessed the effect of SPN-812 in reducing the symptoms of ADHD as measured by the ADHD Rating Scale IV (ADHD-RS-IV). Subjects aged 6 to 12 years were randomized in a 1:2:2:2:2 ratio of placebo or active treatment (SPN-812 100, 200, 300, or 400 mg) and received 3 weeks of titration at 100 mg/week followed by 5 weeks of maintenance dosing for a total of 8 weeks of treatment. Mean ADHD-RS-IV Total Scores improved throughout treatment in all groups. Differences in change from baseline to end of study between SPN-812 and placebo were statistically significant at the three higher SPN-812 doses ($p \leq 0.0310$) but not at the 100-mg dose. The treatment effect compared to placebo increased with the dose; however, pairwise comparisons among the four active treatment groups showed no statistically significant differences among the SPN-812 doses. All doses of SPN-812 were well tolerated with no serious or severe AEs and no clinically significant effect on

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laboratory values of common hematology and chemistry tests. The most common AEs were somnolence, decreased appetite, and headache.

Phase 3 Studies

Four pivotal Phase 3 studies of SPN-812 for the treatment of ADHD have been completed in the pediatric population: two studies in children 6 to 11 years of age (evaluating 100 mg, 200 mg, and 400 mg) and two studies in adolescents 12 to 17 years of age (evaluating 200 mg, 400 mg, and 600 mg). As of April 2019, preliminary results are available for all four studies.

Children (6 to 11 years of age)

Study 812P301 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 100 mg/day and 200 mg/day for the treatment of ADHD in children 6 to 11 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) with SPN-812 100 mg/day or 200 mg/day led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (29.6%), 74 (48.1%), and 77 (47.8%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, and headache. AEs were considered to be at least possibly treatment related in 16 (10.1%), 41 (26.6%), and 56 (34.8%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 2 (1.3%), 5 (3.2%), and 2 (1.2%) subjects in the placebo, SPN-812 100 mg/day, and SPN-812 200 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 2 in the SPN-812 100 mg/day treatment group and 1 in the SPN-812 200 mg/day treatment group. All SAEs were considered unlikely related or not related to study medication. No deaths occurred during the study.

Study 812P303 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in children 6 to 11 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 8 weeks (3 weeks of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 47 (45.6%), 56 (52.3%), and 58 (58.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, headache, decreased appetite, and fatigue. AEs were considered to be at least possibly treatment related in 22 (21.4%), 42 (39.3%), and 51 (51.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. AEs

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led to permanent study medication discontinuation (and study withdrawal) in 3 (2.9%), 6 (5.6%), and 4 (4.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. SAEs were reported in 3 subjects: 1 in the SPN-812 200 mg/day treatment group and 2 in the SPN-812 400 mg/day treatment group. No deaths occurred during the study.

Adolescents (12 to 17 years of age)

Study 812P302 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 200 mg/day and 400 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 200 mg/day or 400 mg/day for 6 weeks (1 week of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo.

Throughout treatment, AEs were reported in 38 (36.5%), 43 (43.4%), and 56 (53.3%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, decreased appetite, headache, fatigue and nausea. AEs were considered to be at least possibly treatment related in 20 (19.2%), 32 (32.3%), and 41 (39.0%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 0, 4 (4.0%), and 2 (1.9%) subjects in the placebo, SPN-812 200 mg/day, and SPN-812 400 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812 200 mg/day treatment group. No deaths occurred during the study.

Study 812P304 was a randomized, double-blind, placebo-controlled study of the efficacy and safety of SPN-812 at 400 mg/day and 600 mg/day for the treatment of ADHD in adolescents 12 to 17 years of age. The primary endpoint of the study was the change from baseline in ADHD-RS-5 Total Score at end of study. Treatment with SPN-812 400 mg/day for 7 weeks (2 weeks of titration followed by 5 weeks of maintenance at a fixed dose) led to a statistically significant improvement in ADHD-RS-5 Total Score compared to placebo; however, ADHD-RS-5 Total Score during treatment with SPN-812 600 mg/day did not showed a statistically significant improvement compared to placebo.

Throughout treatment, AEs were reported in 39 (40.2 %), 58 (58.0%), and 55 (55.6%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. The most frequently reported AEs were somnolence, fatigue, headache, decreased appetite, and nausea. AEs were considered to be at least possibly treatment related in 18 (18.6%), 44 (44.0 %), and 45 (45.5%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. AEs led to permanent study medication discontinuation (and study withdrawal) in 1 (1.0%), 4 (4.0%), and 5 (5.1%) subjects in the placebo, SPN-812 400 mg/day, and SPN-812 600 mg/day treatment groups, respectively. SAEs were reported in 2 subjects, both in the SPN-812 400 mg/day treatment group. No deaths occurred during the study.

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1.3 Study Rationale

In the 812P201 study, the change from baseline in CAARS total score at end of study (EOS) was significantly reduced with SPN-812 IR 150 to 300 mg/day compared to placebo in adults (ages ≥ 18 years of age) with ADHD. The efficacy and safety of SPN-812 showed positive results in three separate trials assessing efficacy of 200 mg/day and two separate trials assessing efficacy of 400 mg/day SPN-812. The proposed doses of SPN-812 200 to 600 mg/day in the current adult study are expected to provide similar exposure in adults compared to that provided by 200 to 400 mg/day in children and adolescents. These doses fall well within the range of doses where a low number of AEs to no AEs were observed in Phase 1 trials (single and multiple dose), and those AEs that were observed were mild to moderate in severity. In addition, the current study is intended to expand the indication of SPN-812 treatment of ADHD in children/adolescents (6 to 17 years of age) to also include treatment of ADHD in adults (18 to 65 years of age).

In addition to assessing the effect of SPN-812 treatment on ADHD symptom in adults (AISRS), the study aims to explore treatment response within other domains of the disorder, including functional impairment and executive functioning (**Becker et al., 2011**; **Wiener et al., 2016**). The prefrontal cortex (PFC) is critical for regulating so-called executive functions and for controlling attention and behavior. Regulation of behavior is accomplished through networks of interconnected pyramidal cells, which serve to store goals and rules guiding an individual's actions. These networks interact with each other and are highly dependent on their neurochemical environment. A change in the neurochemical environment can affect these networks and result in PFC dysfunction (**Arnsten, 2006**; **Arnsten, 2009**). ADHD is a chronic, debilitating disorder that affects many aspects of daily life and has a substantial burden on personal and professional functioning. A person with ADHD can exhibit a number of functional impairments, and the motivation in seeking medical treatment typically stems from the need to address dysfunction in social, emotional, academic, and/or familial domains (**Epstein and Weiss, 2012**). Optimal medical and behavioral management should ideally incorporate treatments that do not just improve symptoms of ADHD, but improve the broader functioning of a patient, especially in the areas of self-esteem, educational achievement, executive function and relationships with peers, teachers, and family. In addition, the impact of reducing ADHD symptoms and improving executive function may have an impact on the presence and severity of anxiety [redacted] in adults, [redacted]
Therefore, executive function (BRIEF-A), the presence and severity of anxiety symptoms (GAD-7), [redacted]) will be also assessed during the current study.

In summary, the rationale for studying adult ADHD with SPN-812 is the efficacy and tolerability observed in the results from the four Phase 3 pediatric studies and the encouraging results in the Phase 2 adult ADHD study.

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2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo for the treatment of ADHD in adults as measured by the adult ADHD Investigator Symptom Rating Scale (AISRS) total score.

2.2 Key Secondary Objectives

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo on the global assessment of severity for ADHD as measured by the Clinical Global Impression - Severity of Illness (CGI-S) scale.

2.3 Additional Secondary Objectives

- To evaluate the efficacy of SPN-812 200 mg to 600 mg compared to placebo on:
    1) Clinical response rate of severity of illness as measured by the categorical CGI-S Responder Rate (CGI-S score 1 or 2).
    2) Global assessment of improvement as measured by the Clinical Global Impression - Improvement (CGI-I) scale for ADHD.
    3) Clinical response rate of improvement as measured by the categorical CGI-I Responder Rate (CGI-I score of 1 or 2).
    4) Anxiety symptoms as measured by the Generalized Anxiety Disorder 7-Item scale (GAD-7).
    5) Clinician-rated ADHD symptoms as measured by the AISRS subscales of Inattention and Hyperactivity/Impulsivity.
    6) Clinician response rate of ADHD symptom reduction as measured by the 50% responder rate in AISRS total score.
    7) Clinician response rate of ADHD symptom reduction as measured by the 30% responder rate in AISRS total score.
    8) Executive functioning as measured by the Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A; Self Report).
    9) Aspects of executive function and problems with self-regulation as measured by the BRIEF-A Summary Index Scales and BRIEF-A scales.

2.4 Safety Objective

- To evaluate the safety and tolerability of SPN-812 200 mg to 600 mg in adult subjects with ADHD.

[redacted]

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2.6 Primary Endpoint

- The primary efficacy endpoint is change from baseline (CFB) at end of study (EOS) in the AISRS total score.

2.7 Key Secondary Endpoints

- The key secondary efficacy endpoint is the CFB at EOS in the CGI-S score.

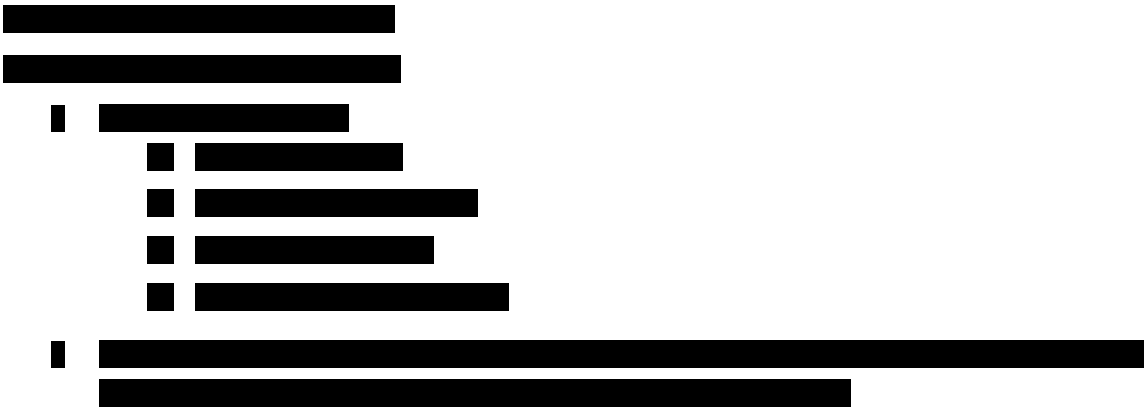
2.8 Additional Secondary Endpoints

Additional secondary efficacy endpoints are:

1) Percentage of subjects with a CGI-S score of 1 or 2 at EOS.
2) CGI-I score at EOS.
3) Percentage of subjects with a CGI-I score of 1 or 2 at EOS.
4) CFB at EOS in the GAD-7 total score.
5) CFB at EOS in the AISRS Inattention subscale score and the Hyperactivity/Impulsivity subscale score.
6) AISRS 50% responder rate (defined as the percentage of subjects with a ≥ 50% reduction in the CFB AISRS total score) at EOS.
7) AISRS 30% responder rate (defined as the percentage of subjects with a ≥ 30% reduction in the CFB AISRS total score) at EOS.
8) CFB at EOS in the BRIEF-A Global Executive Composite (GEC) T-score.
9) CFB at EOS in the T-score by each BRIEF-A Summary Index Scale and by individual BRIEF-A scale.

2.9 Safety Endpoints

The safety endpoints are adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), physical examination, and the Columbia Suicide Severity Rating Scale (C-SSRS).



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3 INVESTIGATIONAL STUDY PLAN

3.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, parallel group, flexible dose study of SPN-812 in adults diagnosed with ADHD per Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5™) criteria. Approximately 366 subjects will be randomized in a 1:1 ratio (183 subjects per arm): SPN-812 (200 mg to 600 mg) or placebo. Following up to 5 weeks of screening, subjects will be treated with study medication (SM) for 6 weeks. Upon completion of the 6-week treatment period, subjects will be either enrolled in a separate OLE study or followed for 1 week after EOS for safety. The total study duration from the screening visit to the end of the treatment period is up to 11 weeks.

Screening Period (Visit 1): The screening period is a minimum of 7 days and a maximum of 35 days. After informed consent is obtained, subjects will undergo initial screening evaluations and be administered the screening scales, and inclusion/exclusion criteria will be reviewed to confirm the subject's eligibility. Subjects taking ADHD medication at screening will undergo a washout of at least 1 week (or 5 half-lives of the medication, whichever is longer) before the Baseline Visit (Day 1).

Baseline and Randomization (Visit 2): At the Baseline Visit, inclusion/exclusion criteria will be reviewed to confirm eligibility, including pregnancy testing for females of childbearing potential (FOCP) and urine drug screen. Subjects with positive drug screen will be excluded. Subjects will also be administered the AISRS scale and CGI-S. Those with a Visit 2 AISRS total score of ≥ 26 and a CGI-S score of ≥ 4 will be eligible for randomization, and those with an AISRS total score of < 26 or a CGI-S score of < 4 will be excluded from study participation. On Day 1, eligible subjects will be randomized 1:1 to SPN-812 200 mg to 600 mg or matching placebo; initial dose should be taken Day 2.

Treatment Period (Visits 3 to 7): This period of the study will consist of 6 weeks of treatment with dosing starting Day 2 (morning after Visit 2) until Day 43 (Visit 7/EOS). The subject's SM compliance will be assessed throughout the Treatment Period, and subjects who are noncompliant may be discontinued.

Study Medication Treatment (Visits 3 to 7):

All subjects should dose for 6 weeks starting on Day 2 (morning after Visit 2) through Day 43 (Visit 7/EOS) (Section 4.2). All subjects will take 2 capsules (SPN-812 200 mg/day and/or matching placebo) daily starting on Day 1 for the first week (Week 1) and 2 capsules (SPN-812 400 mg/day or matching placebo) daily for the second week (Week 2). From Week 3 through Week 6 per the discretion of the Investigator, the subject's dose may be titrated up (maximum 600 mg/day) or tapered down (minimum of 200 mg/day) in increments of 200 mg based on the subject's clinical response and tolerability to SM. Subjects will return to the clinical site for weekly visits during this period of the study (except between Visits 6 and 7) to undergo efficacy and safety evaluations, return the previous dosing card, and receive the next card. For AEs or risks that cannot be managed using permitted concomitant medications (Section 4.6)

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or other protocol-specified management (Section 6.3), SM dosing should be discontinued (Section 3.4) and an Early Termination (ET) Visit conducted. SM dosing will otherwise continue until Visit 7 (Week 6).

End of Study (Visit 7):

Subjects will return for final study assessments. Subjects terminated from the study prior to Visit 7 will also undergo safety evaluations at the time of study withdrawal at ET visit, however, if subject's Early Termination (ET) visit occurs:

- >7 days after the date of subject's last dose, efficacy assessments **should not** be performed/collected at ET visit
- ≤7 days after the date of subject's last dose, efficacy assessments should be performed/collected at ET visit;

[redacted]

Unscheduled visits may be conducted at the discretion of the Investigator throughout the study. AEs will be assessed at all scheduled and unscheduled visits.

Follow-up/Open-label Extension Period: Subjects who complete the 6-week treatment period may be eligible for an OLE safety trial. Subjects who do not enter the OLE trial will be contacted by telephone for safety follow-up 1 week after the EOS Visit.

3.2 Rationale for Study Design

A randomized, placebo-controlled trial is the gold standard for evaluating the efficacy of an investigational product.

Dose levels of SPN-812 200 to 600 mg were selected based on the efficacy results from the Phase 3 pediatric trials, as well as the low number and low intensity (mild or moderate) of AEs observed at doses from 300 to 900 mg in Phase 1 single dose and multiple dose studies.

The AISRS is a validated, robust tool that measures ADHD symptoms and demonstrates responsiveness to change with medication in adults (**Spencer et al., 2010**). Change in AISRS total score was selected as the primary outcome measure because AISRS is a clinician/investigator structured interview assessing the existence and severity of ADHD symptoms per the DSM-IV criteria. The CGI-S was selected as a key secondary outcome measure because it is commonly used as a reliable measure of severity of a disease/disorder in clinical research, as well as a measure of change in severity over time during an experimental treatment.

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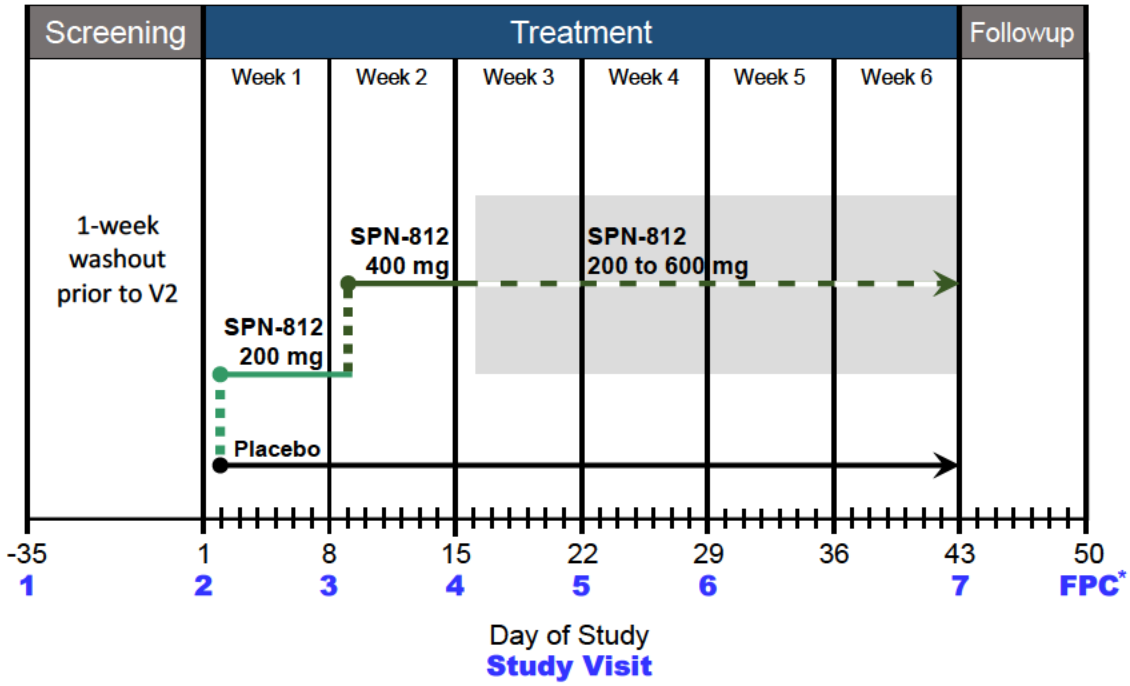
Figure 1 Study Schematic



*A safety follow-up phone call will be performed 1 week after EOS Visit only for those subjects who do not enroll/rollover into the Open-Label Extension study

3.3 Study Population

3.3.1 Number of Subjects

Approximately 366 subjects (183 per treatment arm) will be randomized in this clinical study.

3.3.2 Inclusion Criteria

1. Is male or female, aged 18 to ≤ 65 years at screening.
2. Is able to read and understand the Informed Consent Form (ICF).
3. Written informed consent obtained from the subject (a signed ICF).
4. Weight within the normal or overweight ranges according to accepted values of the Body Mass Index (BMI) Chart (18.0 to 35.0 kg/m^2).
5. Is able to swallow capsules whole, without crushing, chewing or cutting.
6. Is willing and able to attend study appointments within the specified time windows.
7. Has a primary diagnosis of ADHD according to the DSM-5 classification, with diagnosis made at least 6 months prior to screening and confirmed with Structured Clinical Interview for DSM-5 Clinical Trials version (SCID-5-CT).
8. Has an AISRS total score of ≥ 26 at the Screening Visit and at the Baseline Visit (V2, Day 1).

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9. Has a CGI-S score of ≥ 4 (moderately ill or worse) at the Screening Visit (V1) and Baseline Visit (V2, Day 1).
10. Females of childbearing potential (FOCP) must be either sexually inactive (abstinent) or, if sexually active, must agree to use one of the following acceptable birth control methods beginning at least 30 days prior to the first dose of SM and throughout the study:
    a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to first SM administration
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide
    d. Established hormonal contraceptive

    Females are considered not to be of childbearing potential if they are either post-menopausal (amenorrhea for at least 2 years and serum follicle stimulating hormone [FSH] level of >40 IU/L) or permanently sterilized (e.g., bilateral tubal ligation, hysterectomy, bilateral oophorectomy for 6 months minimum prior to screening).
11. Males must:
    a. Use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥ 1 month after the last dose of SM; or
    b. Have been surgically sterilized prior to the Screening Visit.

3.3.3 Exclusion Criteria

1. Has previously enrolled in a SPN-812 study.
2. Is currently participating in another clinical trial or has participated in a clinical trial within 60 days prior to the first Screening Visit.
3. Is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
4. Female subjects who are pregnant, lactating and/or sexually active and not agreeing to use one of the acceptable birth control methods throughout the study.
5. Has a history of severe drug allergy or hypersensitivity, or known hypersensitivity, to the study medication or excipients.
6. Has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that, in the Investigator's opinion, is likely to affect central nervous system functioning. This would include subjects with:
    a. A current diagnosis of a major neurological disorder; or
    b. Seizures, seizure disorder or seizure-like events; or a history of seizure disorder within the immediate family (siblings, parents); or
    c. Encephalopathy

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7. Has any history of schizophrenia, schizoaffective disorder, bipolar disorder, borderline personality disorder, antisocial personality disorder, narcissistic personality disorder, autism, post-traumatic stress disorder or obsessive-compulsive disorder.
8. Has any current psychiatric disorder (per DSM-5 criteria) other than ADHD with the following exceptions: ADHD is primary diagnoses with comorbidity/secondary diagnoses of major depression disorder (MDD), nicotine dependence, social anxiety disorder, generalized anxiety disorder, or phobias, and subject is not receiving pharmacological treatment for the comorbidity/secondary diagnoses (e.g., antidepressant for MDD) at time of screening nor for the duration of study.
9. Has a Symptoms of Depression Questionnaire (SDQ) mean score of >3.0 at screening.
10. Has a Hamilton Anxiety Rating Scale (HAM-A) score of >21 at screening.
11. Has organic mental disorders, or mental disorders due to a general medical condition (per DSM-5 criteria).
12. Has a current diagnosis or history of substance use disorder including alcohol use disorder (excluding nicotine and caffeine) (per DSM-5 criteria) within the 12 months prior to screening; or is assessed by the Investigator as having regularly consumed alcohol exceeding 21 units for males and 14 units for females per week (1 unit equals 340 mL of beer, 115 mL of wine, or 43 mL of spirits) within the 12 months prior to screening.
13. Is currently using, or has a positive result on the drug screening at the Screening Visit for drugs of abuse (alcohol, opiates, methadone, cocaine, methamphetamine [including ecstasy], phencyclidine, propoxyphene, methylphenidate, barbiturates, and benzodiazepines). If subject's serum drug screen for ethanol is positive at Screening (V1) and the investigator determines subject does not have alcohol use disorder, then the subject may have a repeat serum drug screen for ethanol performed before baseline within the allotted screening period (results must be received prior to V2 baseline). If second serum drug screen for ethanol is positive, subject is excluded from participating in the study, however, if second serum drug screen for ethanol is negative, subject may proceed to V2.
14. Is a (known or self-identified) current habitual/chronic cannabis user (medicinal or recreational); or
    - Has a positive urine drug screen for cannabis at the Screening Visit and is considered, per the Investigator's judgement, to be a habitual/chronic cannabis user; or
    - Has a positive urine drug screen for cannabis at both the screening and follow-up drug screen at the Baseline Visit, even though the subject is not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user.

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Note: Subjects who have a positive urine drug screen for cannabis at the Screening Visit but who are not considered, per the Investigator's judgement, to be a habitual/chronic cannabis user may, with Sponsor approval, undergo an additional urine drug screen at least 4 weeks after the initial urine drug screen at Baseline Visit, prior to randomization. Subjects must agree to refrain from cannabis use throughout study.

15. Has treatment-resistant ADHD based on a history of receipt of >2 approved ADHD medications that failed to adequately improve the subject's symptoms. A subject who is naïve to ADHD treatment is not excluded from study participation.
16. Has any other disorder for which its treatment takes priority over treatment of ADHD or is likely to interfere with study treatment, impair treatment compliance, or interfere with interpretation of study results.
17. Has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin that has not been in remission for > 5 years prior to the first dose of SM.
18. Has or has had one or more of the following conditions considered clinically significant/relevant by the Investigator in the context of the study:
    - cardiovascular disease
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse < 50 bpm)
    - tachycardia (pulse > 100 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrine disorder
    - gastrointestinal disorder
    - hematological disorder
    - infectious disorder
    - any clinically significant immunological condition
    - dermatological disorder
19. Exhibits clinically significant abnormal vital signs at screening (see Note below).
20. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following (see Note below):
    - Serum creatinine > 1.5 × the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 × ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase > 2 × ULN.
21. Has any of the following cardiology findings at screening (see Note below):
    - Abnormal ECG that is, in the Investigator's opinion, clinically significant;
    - PR interval > 220 ms;

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- QRS interval > 130 ms;
- QTcF interval > 450 ms (for men) or > 470 ms (for women) (QT corrected using Fridericia's method);
- Second- or third-degree atrioventricular block;
- Any rhythm, other than sinus rhythm, that is interpreted by the Investigator to be clinically significant.

22. Has any disease or medication that could, in the Investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with study conduct or interpretation of results.
23. Evidence of infection with hepatitis B or C, or human immunodeficiency virus (HIV)-1 or HIV-2, as determined by results of testing at screening.
24. Lost or donated more than 450 mL of blood during the 30 days prior to screening.
25. Use of any investigational drug or prohibited concomitant medications including known CYP1A2 substrates (e.g., theophylline, melatonin) within 30 days or 5 half-lives prior to Baseline Visit (Day 1) (whichever is longer) during the screening period or anticipated for the duration of the study.
26. History of unexplained loss of consciousness, unexplained syncope, unexplained irregular heartbeats or palpitations or near drowning with hospital admission.
27. Has attempted suicide within the 6 months prior to screening, or is at significant risk of suicide, either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale (C-SSRS) within the 6 months prior to screening.
28. In the Investigator's opinion, is unlikely to comply with the protocol or is unsuitable for any other reason.

Note: Repeat testing for clinical laboratory tests, vital signs, and ECG parameters is permitted one time for each test, at the discretion of the Investigator, as long as the repeat test result is available within the 35-day screening period to determine eligibility.

3.4 Completion of Study and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 7.

Subjects who are randomized and dosed with SM, but who withdraw or are withdrawn from participation in the study by the Investigator before he/she finishes the study (i.e., after Visit 2 but to prior Visit 7), should complete an ET Visit. Procedures listed for Visit 7 (see Table 2) should be completed at ET visit, with the following exception:

If subject's Early Termination (ET) visit occurs:

- >7 days after the date of subject's last dose, efficacy assessments **should not** be performed/collected at ET visit.
- ≤7 days after the date of subject's last dose, efficacy assessments should be performed/collected at ET visit;

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All reasons for screening failure will be recorded. If the subject passes screening but fails eligibility at Visit 2 (Baseline Visit), the reason(s) will also be recorded.

The Site Investigator(s) or subjects themselves may stop SM treatment at any time for safety or personal reasons. A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Sponsor may also withdraw the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and Clinical Research Associate (CRA) before the subject stops SM. Subjects removed from the study for any reason will not be replaced.

Reasons for a subject's early discontinuation may include:

- Withdrawal of consent
- Noncompliance
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

The primary reason for the subject's early discontinuation, including specific reason why subject withdrew consent or PI ended subject's study, must be recorded in the subject's medical record and on the electronic case report form (eCRF). If the subject withdraws consent or the Investigator discontinues the subject's participation in the study, the reason for the subject's withdrawal or Investigator's discontinuation of the subject should also be documented and captured on the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

If a subject misses doses of SM during this study, the Investigator shall counsel the subject on the importance of compliance. If the subject has consistently missed doses, he or she may be discontinued from the study at the discretion of the Investigator and in consultation with the Medical Monitor; all procedures for discontinuation will be followed.

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4 STUDY TREATMENT

4.1 Study Medication Identity, Packaging and Labeling

Study medication is supplied as capsules packaged in a double-blind configuration and supplied by the Sponsor in labeled blister cards. Each SM blister card will include identical-looking capsules that contain 200 mg of SPN-812 or matching placebo to provide daily dose levels of 0 mg, 200 mg, 400 mg, or 600 mg of SPN-812.

Each blister card will supply a subject with 7 days of dosing plus 2 extra days if needed. Each card will be labeled with the protocol number, at a minimum.

4.2 Study Medication Administration

Study medication will be administered orally once daily (QD) as intact capsules, with or without food. Daily dosing should occur in the morning. Splitting the daily dose (e.g., taking part of the daily dose in the morning and the remainder of the daily dose in the evening) is not permitted. Study medication will be dispensed to subject following randomization on Day 1 (Visit 2), however, subject should take initial dose of study medication the next morning on Day 2. During the first 2 weeks of the Treatment Period, regardless of treatment arm, subjects will take 2 capsules QD. During the remaining 4 weeks of the Treatment Period, subjects may take a minimum of 1 capsule daily up to a maximum of 3 capsules QD as follows: per the Investigator's discretion based on the subject's clinical response and tolerability, the dose of SPN-812 can be titrated up or tapered down in increments of 200 mg/day per week to a target dose within the range between 200 and 600 mg/day (Table 1). However, it is recommended that subjects continue to take 2 capsules during Week 3.

Table 1 Study Medication Administration

Treatment Arm	Number and Identity of Capsules to be Taken QD During the Treatment Period		
	Week 1	Week 2	Week 3 to Week 6
A: Placebo	2 Placebo	2 Placebo	1 to 3 Placebo
B: SPN-812	1 Placebo 1 SPN-812	2 SPN-812	1 to 3 SPN-812

QD = once daily
Each SPN-812 capsule contains 200 mg SPN-812.

4.3 Method of Assigning Subjects to Treatment Arm

Eligible subjects will be randomized in a 1:1 ratio at Visit 2 (Baseline) to receive placebo or active SPN-812.

Treatment A: Placebo
Treatment B: SPN-812 (200 mg to 600 mg)

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Allocation of study treatment will occur centrally via an interactive web response system (IWRS) using a randomization schedule to determine the SM assignment for each subject being randomized. A dosing card(s) will be given to the subject at each study visit starting at Visit 2.

4.4 Blinding

The subject and all personnel involved with the conduct and interpretation of the study, including the Investigators, study site personnel, the Sponsor and contract research organization (CRO) clinical staff, including the Medical Monitor, will be blinded to study medication. [redacted] Randomization schedule data will be kept strictly confidential, filed securely by the IWRS vendor, and accessible only to authorized persons until the time of unblinding.

4.5 Study Medication Handling and Accountability

All SM will be supplied by the Sponsor to the Investigator. SM supplies must be stored in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with International Conference on Harmonisation (ICH) E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping) in a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject; collection of unused supplies; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or a representative of the Food and Drug Administration (FDA). The assigned CRA will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies, including

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empty containers, are to be returned to the Sponsor at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form.

4.6 Concomitant Medications

Subjects may not be on any prohibited medication as indicated in the inclusion/exclusion criteria. SPN-812 is a strong CYP1A2 inhibitor. Substrates with a narrow therapeutic window are prohibited during the study. Specific prohibited concomitant medications for this study include known CYP1A2 substrates (e.g., theophylline, melatonin). Subjects receiving prior ADHD medication at screening will undergo a washout period of at least 1 week (or 5 half-lives of the medication, whichever is longer) before the Baseline Visit (Day 1).

No concomitant medications are allowed during the study, with the following exceptions:

- Nutritional supplements (e.g., multivitamins, fish oil) (herbal supplements are prohibited)
- EMLA® or other numbing cream for venipuncture
- Common over-the-counter therapies for minor transient ailments (e.g., acetaminophen for headache, ibuprofen for fever).

Additional concomitant medications are allowable on a case-by-case basis at the discretion of the Investigator and sponsor approval.

All concomitant medications will be recorded in the eCRF.

Caffeine use is permitted during the study and will be recorded in the eCRF.

5 STUDY METHODS

5.1 Study Visits and Procedures

All subjects who are randomized and take the initial dose of SM will be followed according to the protocol regardless of the number of doses of SM taken, unless consent for follow-up is withdrawn. The Sponsor or Sponsor's designee must be notified of all deviations from the protocol visit or procedures, except as noted, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. Subjects will be instructed to call study personnel to report any abnormalities during the intervals in between study visits and to come to the study site if medical evaluation is needed and as the urgency of the situation indicates. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up.

The Schedule of Events and Assessments for the study is shown in Table 2.

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Table 2 Schedule of Events and Assessments

Study Period	Screening	Baseline	Treatment				EOS/ET	Follow-up[a] (phone call)
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**FPC[a]**
Day of Study	**-35 to -1**	**1**	**8**	**15**	**22**	**29**	**43**	**50**
Week of Study	**-5 to -1**	**–**	**1**	**2**	**3**	**4**	**6**	**–**
Study Visit Window	**–**	**–**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Signed informed consent	√							
SCID-5-CT	√							
HAM-A	√							
Relevant histories (social, medical, psychiatric, family psychiatric, neurological)	√							
Demographics	√							
Smoking, alcohol consumption use/history	√							
Physical examination	√						√	
Height	√							
Blood sample for FSH (Post-menopausal females only)	√							
Serum pregnancy test (FOCP only)	√							
Serology	√							
Subject training video module	√	√		√		√		
Review eligibility criteria	√	√						
Randomize		√						
Review adverse events			√	√	√	√	√	√
Review concomitant medications and caffeine use	√	√	√	√	√	√	√	√
Hematology/serum chemistry	√	√					√	
Urinalysis	√	√					√	
ECG	√	√					√	
Serum drug screen	√							
Urine drug screen [c, g]	√ [c, g]	√ [h]	√ [h]	√ [h]	√ [h]	√ [h]	√ [h]	
Urine pregnancy test (FOCP)		√	√	√	√	√	√	
Orthostatic BP/HR [b]	√	√	√	√	√	√	√	
Vital signs [d] and weight	√	√	√	√	√	√	√	
C-SSRS	√	√	√	√	√	√	√	

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Study Period	Screening	Baseline	Treatment				EOS/ET	Follow-up[a] (phone call)
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**FPC[a]**
Day of Study	**-35 to -1**	**1**	**8**	**15**	**22**	**29**	**43**	**50**
Week of Study	**-5 to -1**	**–**	**1**	**2**	**3**	**4**	**6**	**–**
Study Visit Window	**–**	**–**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
AISRS[f]	√	√	√	√	√	√	√[e]	
CGI-S[f]	√	√	√	√	√	√	√[e]	
CGI-I[f]			√	√	√	√	√[e]	
GAD-7		√		√		√	√[e]	
BRIEF-A		√					√[e]	
SDQ	√	[redacted]						
[redacted]								
[redacted]								
Blood sample for PGx (optional)		√						
SM dispensed		√	√	√	√	√		
SM returned and accountability			√	√	√	√	√	

[redacted] ADHD = attention deficit/hyperactivity disorder; AISRS = Adult ADHD Investigator Symptom Rating Scale; BP = blood pressure; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version (Self)=; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity of Illness scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; FOCP = females of childbearing potential; FPC = follow-up phone call; FSH = follicle stimulating hormone; GAD-7 = Generalized Anxiety Disorder 7-item scale; HAM-A = Hamilton Anxiety Rating Scale; HR = heart rate; PGx = pharmacogenomics; [redacted]; POC = "Point of Care'; SCID-5-CT = Structured Clinical Interview for DSM-5 Clinical Trials version; SDQ = Symptoms of Depression Questionnaire; SM = study medication; UDS = urine drug screen.

a. Follow-up assessments (via phone calls) are only required for subjects who do not enroll in the open-label extension study.
b. Orthostatic blood pressure and heart rate should be measured after the subject has been seated for at least 5 minutes and within 3 minutes of standing.
c. With sponsor approval, subjects who exhibit a positive urine drug screen for cannabis at the Screening Visit and, per Investigator judgement, are not considered a habitual/chronic cannabis user, may undergo an additional urine drug screen at the Baseline Visit to determine eligibility; see Exclusion Criterion 14 in Section 3.3.3 for details.
d. Blood pressure, heart rate, respiratory rate, and oral temperature.
e. If subject's ET visit is conducted >7 days after the date of subject's last dose, do not perform/collect efficacy assessments at ET visit[redacted]
f. Investigator-rated efficacy assessments should be performed/conducted/collected prior to administering any self-report efficacy assessments to subjects.
g. Perform Standard UDS and Point of Care UDS Test 2 only (V1; Table 3).
h. Perform Point of Care UDS both Test 1 and Test 2 (V2-V7; Table 3).

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5.1.1 Visit 1 – Screening

The following assessments will be conducted:

- ICF signed
- SCID-5-CT, HAM-A and SDQ
- Social, medical, psychiatric, family psychiatric, and neurological histories
- Demographics
- Smoking and alcohol consumption use/history
- Physical examination and height
- Blood sample for:
  - FSH (post-menopausal females only)
  - Serum pregnancy test (FOCP only)
  - Hematology and serum chemistry (non-fasted sample allowed)
  - Serology (HIV, Hepatitis B and Hepatitis C)
  - Serum drug screen (ethanol)
- Urine sample for:
  - Urinalysis
  - 'Standard' UDS and Point of Care UDS Test 2 (**Table 3**)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- ECG
- C-SSRS
- Subject training video module
- AISRS and CGI-S
- Eligibility criteria
- Concomitant medications and caffeine use

5.1.2 Visit 2 – Baseline (Randomization)

The following assessments will be conducted:

- Blood sample for hematology and serum chemistry (non-fasted sample allowed)
- Urine sample for:
  - Urinalysis
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)*
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- ECG
- C-SSRS
- Subject training video module
- AISRS, CGI-S, GAD-7, BRIEF-A, [redacted]
- Eligibility criteria
- Concomitant medications and caffeine use
- Blood sample for pharmacogenomics (PGx; optional)
- Randomization
- SM dispensed

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5.1.3 Visits 3 to 7 – Treatment Period Including End of Study

Visit 3 – Week 1

The following assessments will be conducted:

- Urine sample for:
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)**
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- C-SSRS
- AISRS, CGI-S, and CGI-I
- AEs
- Concomitant medications and caffeine use
- SM dispensed
- SM return and accountability

Visit 4 – Week 2

The following assessments will be conducted:

- Urine sample for:
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)**
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- C-SSRS
- Subject training video module
- AISRS, CGI-S, CGI-I, and GAD-7
- AEs
- Concomitant medications and caffeine use
- SM dispensed
- SM return and accountability

Visit 5 – Week 3

The following assessments will be conducted:

- Urine sample for:
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)**
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- C-SSRS
- AISRS, CGI-S, and CGI-I
- AEs
- Concomitant medications and caffeine use
- [redacted]
- SM dispensed
- SM return and accountability

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Visit 6 – Week 4

The following assessments will be conducted:

- Urine sample for:
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)**
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- C-SSRS
- Subject training video module
- AISRS, CGI-S, CGI-I, and GAD-7
- AEs
- Concomitant medications and caffeine use
- [redacted]
- SM dispensed
- SM return and accountability

Visit 7 – Week 6/EOS

The following assessments will be conducted:

- Physical examination
- Blood sample for hematology and serum chemistry (non-fasted sample allowed)
- Urine sample for:
  - Urinalysis
  - Point of Care UDS Test 1 and Test 2 (**Table 3**)**
  - Urine pregnancy test (FOCP only)
- Orthostatic blood pressure/heart rate
- Vital signs and weight
- ECG
- C-SSRS
- AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, [redacted]
- AEs
- Concomitant medications and caffeine use
- [redacted]
- SM return and accountability

* At the baseline visit (Visit 2), the Point of Care urine drug screen should be completed and results known first before randomizing subject or performing any efficacy assessments. If a subject has a positive drug screen at the baseline visit, he/she is excluded from participating in the study.

** At all post-baseline study visits (Visit 3-7/EOS), the Point of Care urine drug screen should be completed and results known first before any efficacy assessments are conducted. If a subject has a positive drug screen at any post-baseline visit (V3-V7), then the subject's participation in the study should be ended/terminated and no efficacy assessments (AISRS, CG-S, CGI-I, GAD-7, BRIEF-A, [redacted]) should be performed at that visit (ET); all safety assessments should still be

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performed/completed at the visit. A follow-up phone call with the subject should also be performed 1 week following discontinuation of SM/study.

NOTE: At each study visit, Investigator-rated efficacy assessments (AISRS, CGI-S, CGI-I) should be performed/conducted/collected prior to administering any self-report efficacy assessments to subjects.

NOTE: When training video module is scheduled, the subject must view the training video module prior to administering any efficacy assessments (AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A, [redacted]).

NOTE: For subjects who discontinue/terminate early (ET Visit), EOS assessments will be performed at ET visit, however, efficacy assessments (AISRS, CGI-S, CGI-I, GAD-7, BRIEF-A[redacted] **should not** be collected if the ET visit occurs >7 days after date of subject's last dose of SM.

5.1.4 FPC – Follow-up Phone Call (Not for Subjects Who Enter OLE Study)

Those subjects who do not enter the OLE study will be contacted via telephone for the following assessments approximately 1 week after the EOS Visit:

- AEs
- Concomitant medications and caffeine use

5.1.5 Unscheduled Visits

At the discretion of the investigator throughout the study, unscheduled visits may be conducted to perform or repeat assessments, including record ECG, measure vital signs and weight (orthostatic blood pressure/heart rate), draw blood sample for hematology and/or serum chemistry or serum pregnancy test (FOCP) or ethanol drug screen, obtain urine sample for urine pregnancy test and/or drug screen, administer C-SSRS, perform physical examination. AEs and concomitant medications should also be assessed at all unscheduled visits. SM may also be dispensed and/or returned at unscheduled visits if needed.

[redacted]

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[redacted]

[redacted]

[redacted]

5.1.7 Future Research

If the subject consents to have samples used for future research, including but not limited to PGx testing, this additional research may not start immediately and may start at any time during the sample storage period.

Subjects who have provided consent for PGx testing will have a blood sample taken at baseline. If PGx testing is performed, results from individual tests will be used for research purposes only, and a report separate from the clinical study report will be generated. Samples will be identified only by the study subject number to maintain confidentiality. If a given subject's [redacted] safety data warrant evaluation of PGx, DNA will be extracted from that subject's PGx blood sample and tested for any genetic variations associated with CYP2D6 enzyme. This enzyme is involved in the metabolism of viloxazine and genetic variation may affect the PK of SPN-812. Samples will be stored for up to 10 years for potential future research purposes such as possible testing of genes involved in the efficacy of the drug and possible association with particular adverse events of the drug (i.e., to facilitate an understanding of non-responders to treatment and/or individuals who show an unusual safety profile). The DNA analysis will not be used for individual genetic characterization, and the subject's identity will be kept confidential.

Data from samples will not have diagnostic value and will not be used for individual genetic characterization or development of a commercial product. At the end of testing or 10 years, any remaining samples will be destroyed. The subject may withdraw consent for PGx testing at any time; if consent is withdrawn, the subject's sample will be destroyed.

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6 STUDY VARIABLES AND ASSESSMENTS

6.1 Efficacy Assessments

6.1.1 Adult ADHD Investigator Symptom Rating Scale (AISRS)

The adult ADHD Investigator Symptom Rating Scale (AISRS) was developed to better measure the presence and severity of ADHD symptoms based on DSM-IV diagnostic criteria in adult patients (**Spencer et al., 2010**; Appendix 11.1.1). It is a semi-structured clinical interview with suggested prompts for each item to improve interrater reliability. The scale consists of 18 items that directly correspond to the 18 symptoms of ADHD and are further subdivided into two subscales: Inattention (9 items) and Hyperactivity/Impulsivity (9 items). During the interview with the subject, the clinician/investigator rates the frequency and severity of each symptom on a 4-point Likert-type scale, where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe, with a maximum total score of 54 points and maximum subscale score of 27 points. The scale allows the assessment of functional impairments linked to each symptom dimension. The AISRS total score is the sum of the Inattention and Hyperactivity/Impulsivity subscale scores.

The AISRS is used to assess drug efficacy in the treatment of ADHD in adults, and the AISRS total score is the primary outcome measure for this study.

6.1.2 Clinical Global Impression – Severity of Illness (CGI-S)

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (**Guy, 1976**). The Clinical Global Impression – Severity of Illness scale (CGI-S; Appendix 11.1.2) is a single item clinician rating of the clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with patients with ADHD. The CGI-S is evaluated on a 7-point scale, where 1 = Normal, not at all ill, asymptomatic, 2 = Borderline Ill, 3 = Mildly Ill, 4 = Moderately Ill, 5 = Markedly Ill, 6 = Severely Ill, and 7 = Extremely Ill. Successful therapy is indicated by a lower overall score in subsequent testing.

6.1.3 Generalized Anxiety Disorder 7-item Scale (GAD-7)

Generalized Anxiety Disorder 7 scale (GAD-7) is a self-reported 7-item questionnaire for screening and measuring the severity of generalized anxiety disorder (**Spitzer et al., 2006**; Appendix 11.1.4). The GAD-7 measures the severity of various symptoms of generalized anxiety disorder over the past 2 weeks according to reported response categories with assigned points. The patient scores each GAD-7 item on 4-point Likert scale, where 0 = Not at all, 1 = Several days, 2 = Over half the days, and 3 = Nearly every day. The clinician/investigator can obtain the total score by summating all 7 items. GAD-7 total scores range from 0 to 21, where a total score of 1 to 4 = None/Minimal anxiety, 5 to 9 = Mild anxiety, 10 to 14 = Moderate anxiety, and ≥ 15 = Severe anxiety. It takes less than 5 minutes to complete the GAD-7.

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6.1.4 Clinical Global Impression – Improvement (CGI-I)

The CGI scale was developed to provide a brief, stand-alone assessment of the clinician's view of a subject's global functioning prior to and after administration of SM (**Guy, 1976**). The Clinical Global Impression – Improvement scale (CGI-I; Appendix 11.1.3) is an assessment of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of treatment. The CGI-I is evaluated by the investigator at each post-baseline study visit during treatment relative to the subject's condition at baseline on a 7-point scale where 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse. Successful therapy is indicated by a lower overall score in subsequent testing. The CGI-S assessment obtained at the baseline visit should serve as a basis for the investigator's CGI-I assessment of improvement in the subject's conditions at each post-baseline study visit during the treatment period.

6.1.5 Behavior Rating Inventory of Executive Function–Adult (BRIEF-A)

The Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A; Self report) is a standardized rating scale that captures views of an individual's executive functions into everyday behaviors in adults ages 18 to 90 years (**Roth et al., 2005**; **Roth et al., 2013**; Appendix 11.1.5). It has been utilized in clinical trials to assess changes in executive function with treatment for neurological and psychiatric disorders, including ADHD (**Adler et al 2014**). The BRIEF-A is 75-item in nine non overlapping scales and two summary index scales that assesses aspects of executive function and problems with self-regulation from the perspective of the individual. The subject rates each item on a 3-point Likert scale (Never, Sometimes, or Often) based on their experienced within the last month. Higher scores indicate poorer executive function. The BRIEF-A takes 15-20 minutes to complete. The self-report provides the insight of the individual's viewpoint of their own difficulties in self-regulation.

Description of the nine BRIEF-A scales (**Roth et al., 2013**) by summary index scale:

1. The Behavioral Regulation Index (BRI) captures the ability to maintain appropriate regulatory control of one's own behavior and emotional responses. The BRI is broken down into the following four scales within the BRIEF-A:
    - Inhibit: Control impulses; appropriately stop verbal, attentional, physical behavior at the proper time
    - Shift: Move freely from one situation, activity, or aspect of a problem to another as the situation demands; think flexibly to aid problem-solving
    - Emotional control: Modulate one's emotional responses appropriately
    - Self-Monitor: Recognize the effect of one's own behavior on others
2. The Metacognitive Index (MI) reflects the individual's ability to initiate activity and generate problem-solving ideas, to sustain working memory, to plan and organize problem-solving approaches, to monitor success and failure in problem

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solving, and to organize one's materials and environment. The MI is broken down into the following four scales within the BRIEF-A:

- Initiate: Begin a task or activity without external prompting; independently generate ideas
- Working memory: Hold information in mind in order to complete a task; stay with, or stick to, an activity
- Plan/organize: Anticipate future events; set goals; develop steps ahead of time to carry out a task; organize information and behavior to achieve and objective; carry out tasks in a systematic manner
- Task Monitor: Assess performance during or after finishing a task for mistakes
- Organization of Materials: Keep workspace and living areas in an orderly manner; keep track of materials needed for tasks

6.1.6 Symptoms of Depression Questionnaire (SDQ)

The Symptoms of Depression Questionnaire (SDQ) is designed to measure the severity of symptoms across several subtypes of depression and was developed (items chosen) on the basis of the most current knowledge of depressive symptoms and Major Depressive Disorder (MDD) subtypes (**Pedrelli et al., 2014**; Appendix 11.1.6). The SDQ is a 44-item self-report depression scale that inquires about an extensive number of depressive symptoms. Items reflect a broad and heterogeneous collection of depression related symptom features, and it includes several items that inquire about anxiety symptoms. The SDQ has been utilized in clinical trials along with other commonly used scales like the Montogmery Asberg Depression Rating Scale (MADRS) assessing potential treatments in patients with depression (**Fava et al., 2016**; **Papakostas et al., 2019**). The subject self-rates/scores each item on a 6-point scale (1-6) as it pertains to the past month. Each item is rated based on a subject's perception of what is normal for the individual (score = 2), what is better than normal (score = 1), and what is worse than normal (scores = 3–6). A SDQ average (mean) score greater than 3.5, which is equivalent to a Montgomery-Asberg Depression Rating Scale (MADRS) score of 25, is consistent with severe depression (**Fava et al., 2016**). The clinician/investigator generates a total score (SDQ-T) by summated all 44 scores. SDQ total scores can range from 44-264. SDQ-T refers to the total score of the SDQ. SDQ-1 subscale includes items related to lassitude, mood, and cognitive functioning; SDQ-2 subscale includes items related to anxiety, agitation, irritability, and anger; SDQ-3 subscale includes items related to suicidal ideation. SDQ-4 subscale assesses disruptions in sleep quality. SDQ-5 subscale includes items on changes in appetite and weight. The SDQ takes less than 10 minutes to complete.

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[redacted]

6.2 Safety Variables and Assessments

Safety assessments include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs and 12-lead ECGs, C-SSRS, and the performance of physical examinations as detailed in the Schedule of Events and Assessments.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Supernus or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subjects.

6.2.1 Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (GCP), an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

An AE can be, for example:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent injuries, or exacerbation of an existing disease.

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- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

6.2.2 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) are defined as seizure or AEs that might represent a seizure. This includes, but is not limited to syncope/syncopal episode, pseudoseizure, myoclonus, and severe muscle spasms.

6.2.3 Causality

Adverse events may be categorized as either Adverse Drug Reactions or Suspected Adverse Drug Reactions based on their relationship to SM and the degree of certainty about causality.

Suspected adverse drug reactions (SADRs) are a subset of adverse events for which there is evidence to suggest a causal relationship between the drug and the AE, i.e., there is a reasonable possibility that the drug caused the adverse event.

Adverse drug reactions (ADRs) are a subset of all SADRs for which there is reason to conclude that the drug caused the event.

6.2.4 Recording and Evaluation of Adverse Events

All subjects who are screened (Visit 1) will be questioned regarding any current and prior medical health status or diagnoses, which will be documented as medical history. At each contact with the subject following first dose of SM (post-Visit 2), the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate adverse event module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated WBC, cough, abnormal chest X-ray, etc., can all be reported as “pneumonia”.

All AEs occurring after Visit 2 and throughout the study period must be recorded. A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first dose of study medication is taken, or that worsened following first administration of study medication. All AEs in this study will be recorded after administration of SM, therefore all will be treatment-emergent. The clinical course of each AE should be followed for at least 30 days following the date of last dose of SM (either due to EOS or ET) or until resolution, or until, in the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

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The Investigator is responsible for evaluating AEs and determining the following:

- Serious vs. Non-serious: Is the event a Serious Adverse Event (SAE)?
- Causality: Was AE related or possibly related to the SM?
- Severity: How pronounced is the incapacity/discomfort caused by an AE?

6.2.5 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

6.2.6 Criteria for Assessing Causality

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a causal relationship unlikely, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- Not related: Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- Unlikely related: Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on drug withdrawal may be lacking or unclear. This will be reported as a **Suspected Adverse Drug Reaction (SADR)**.
- **Definitely related**: Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the medication (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **Adverse Drug Reaction (ADR)**.

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6.2.7 Serious Adverse Events

Adverse events are classified as serious or non-serious. An AE or ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

6.2.8 Investigator Responsibilities for Reporting SAEs

The Investigator must immediately report to the Sponsor all SAEs, regardless of whether the Investigator believes they are drug related.

All SAEs must be reported to the Drug Safety Contact within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE Form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents). The Investigator will keep a copy of this SAE Report form on file at the study site.

The Investigator or study physician, after thorough consideration of all facts that are available, must include an assessment of causality of an AE to SM in the report to the Sponsor.

SAEs should be followed until resolution or until no further/additional information can be obtained regarding the event. Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor, as it becomes available, using the SAE Report Form.

The Drug Safety Contact for SAE reporting is:

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6.2.9 Other Events Requiring Immediate Reporting

The Investigator must report a pregnancy that occurs in a subject during a clinical study to the Drug Safety Contact within 24 hours of first becoming aware of the event. Subjects who become pregnant during the study should be discontinued from study medication immediately. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the Investigator must follow any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

Acute suicidal crisis or clinically significant suicidal behavior or ideation should be reported to the Drug Safety Contact within 24 hours of first becoming aware of the event.

6.2.10 Sponsor Responsibilities for Reporting SAEs

The Sponsor will inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study sites submit SAE information to the Sponsor in the manner described above.

Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB). Investigators must also submit the safety information provided by the Sponsor to the IRB unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB.

It is the responsibility of the Sponsor to notify all participating Investigators, in a written IND safety report, of any SADR that is both serious and unexpected. The Sponsor will also notify participating Investigators of any findings from other sources (other studies, animal and in vitro testing, etc.) that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

6.3 Treatment-Emergent Suicidal Ideation

Prospective assessment of suicidal ideation and suicidal behavior is a mandatory part of the safety evaluations for any drug developed for a psychiatric indication (**FDA, 2012**). In this study, the initial evaluation of subjects will be conducted prior to enrollment to assess lifetime suicidal ideation and to identify subjects who must not participate in the trial due to pre-existing suicidality risk. The assessment will then be repeated at each subsequent study visit to monitor the occurrence of new suicidal and self-injurious tendencies.

6.3.1 Columbia Suicide Severity Rating Scale (C-SSRS)

Assessment of suicidal ideation and behavior will be conducted using the Columbia-Suicide Severity Rating Scale (C-SSRS) (**Posner et al., 2011**; [Baseline] Appendix 11.1.10; [Since Last Visit] Appendix 11.1.11). The C-SSRS is an FDA-recommended prospective assessment instrument that directly classifies suicidal ideation and behavior

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events into 11 preferred categories, including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent.

The instrument has been validated used successfully in adult patients with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating.

6.3.2 Suicide Risk Management Plan

The protocol procedures related to clinical care of patients with treatment-emergent suicidal ideation and behavior must be implemented to ensure proper management of the event and protection of subject's safety. If a disclosure of suicidal ideation is revealed as part of the C-SSRS questionnaire or when a subject spontaneously expresses that he/she may be a threat to him/herself, the study team should be prepared to quickly evaluate the event and to determine the appropriate course of action.

6.3.2.1 Assessment of Suicide Risk

Any indication of suicidal ideation should be evaluated as soon as possible by appropriately trained staff. The Investigator is responsible for making the final judgment regarding potential suicide risk and need subsequent action.

6.3.2.2 Acute Suicidal Crisis

A person evaluated as being at high risk should be transferred to an immediate care facility. The Investigator will guide intervention as clinically indicated and follow up with the subject within 1 week and/or refer him/her to a qualified mental health professional.

6.3.2.3 Non-acute Suicidal Risk

The Investigator will conduct safety planning with the subject and will follow up within 1 week.

Reference materials for subjects and caregivers should include lists of mental health organizations and professionals, outpatient behavioral services, local crisis and peer support groups and Suicide/Crisis Hotlines.

6.4 Clinical Measurements

6.4.1 Screening and Clinical Safety Laboratory Assessments

All clinical laboratory tests will be performed by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 2) shows the time points at which blood and urine samples will be collected. Table 3 presents the clinical laboratory tests to be performed. At Screening

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(Visit 1) perform the serum drug screen (ethanol), the 'Standard' urine drug screen (UDS) and 'Point of Care' UDS (Test 2 only). Perform the 'Point of Care' drug screen (Test 1 and Test 2) at baseline (Visit 2) and at every subsequent study visit during treatment period (Visit 3-7).

Table 3 Clinical Laboratory Tests

Category	Parameters
Serology	Human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B, hepatitis C
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, and WBC count with differential
Chemistry	**Electrolytes**: Chloride, phosphate, potassium, sodium
	Liver function tests: Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin
	Renal function parameters: Blood urea nitrogen, creatinine
	Other: Glucose, Ca^{+2}, albumin, total protein, bicarbonate **FSH:** Post-menopausal females only
Urinalysis	Macroscopic examination[a], pH, specific gravity, protein, glucose, ketone, occult blood, WBC, nitrites, bilirubin, urobilinogen
Serum Drug Screen	Ethanol
'Standard' Urine Drug Screen (UDS)	amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressant, THC (cannabinoids)
'Point of Care' Urine Drug Screen (UDS)	Test 1: amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, ecstasy, methadone, methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressant, THC (cannabinoids). Test 2: methylphenidate
Pregnancy test (blood sample at screening, urine sample at other time points)	FOCP only

FOCP = females of childbearing potential; FSH = follicle stimulating hormone; WBC = white blood cell
[a] A microscopic examination will be performed on abnormal findings unless otherwise specified.

6.4.2 Vital Signs and Weight

Vital signs measurements (includes orthostatic blood pressure/heart rate, respiratory rate and body [oral] temperature) and body weight will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). Orthostatic blood pressure and heart rate should be measured after the subject has been sitting for 5 minutes and again within 3 minutes of subject standing. Vital signs may be taken at any other time, as deemed necessary by the Site Investigator.

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6.4.3 Physical Examinations and Height

Physical examinations and measurement of height will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). The physical examination conducted at screening will include assessments of all body systems except genitourinary. Any findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical examination, only changes from baseline (Screening Visit) will be noted.

6.4.4 Electrocardiograms (ECGs)

A 12-lead ECG will be obtained at the time points shown in the Schedule of Events and Assessments (Table 2). Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position for at least 10 minutes. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 hours by the Investigator or qualified Sub-investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

[redacted]

6.6 Screening Scales and Assessment Tools

6.6.1 Structured Clinical Interview for DSM-5 - Clinical Trials (SCID-5-CT)

The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide for making the major DSM-5 diagnoses (**Spitzer et al., 1992**; **First et al., 2015**; Appendix 11.1.8). It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The Clinical Trials version (SCID-5-CT) is an adaptation of the Research version (SCID-5-RV) that has been reformatted, streamlined, and optimized for use in clinical trials that incorporate typical inclusion and exclusion criteria. The SCID is broken down into separate modules corresponding to categories of diagnoses, including ADHD. Most sections begin with an entry question that would allow the interviewer to "skip" the associated questions if not met. For all diagnoses, symptoms are coded as present, subthreshold, or absent. A diagnosis of ADHD is made following the post-traumatic stress disorder diagnostic algorithm.

6.6.2 Hamilton Anxiety Rating Scale (HAM-A)

The Hamilton Anxiety Rating Scale (HAM-A) is a rating scale developed to assess/measure the severity of an individual's anxiety (**Hamilton, 1959**; Appendix 11.1.9). The HAM-A is used to assess severity of anxiety in children, adolescents and

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adults in both clinical and research settings (**Hamilton, 1959**; **Maier et al., 1988**; **Borkovec et al., 1993**). The HAM-A consists of 14 items or parameters, each defined by a series of symptoms. It measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The HAM-A does not provide any standardized probe questions. The HAM-A is a clinician-rated evaluation. Each item on the HAM-A is rated/scored on a 5-point Likert scale, where 0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Very severe. The ratings/scores of all 14 items are summated to yield a total score (ranging from 0 to 56), where ≤ 17 indicates “mild anxiety severity,” 18 to 24 indicates “moderate anxiety severity,” 25 to 30 indicates “moderate to severe anxiety severity,” and ≥ 31 indicates “severe anxiety.” It take 5 to 10 minutes to complete the HAM-A.

6.6.3 Symptoms of Depression Questionnaire (SDQ)

See Section 6.1.6; Appendix 11.1.6

6.7 Subject training video module

Study subject perceptions of clinical research can affect response to study treatments, including placebo (**Leuchter et al., 2014**). In order to provide education and thereby reduce aspects of placebo response which may be associated with expectation of therapeutic benefit, all participants will view a brief training module which reviews key topics including (a) their role in the trial, (b) the difference between medical care and research, (c) the use of placebo and (d) the importance of accurate reporting of symptoms throughout the trial. These will be organized into short segments of ~2-3 minutes each and will be delivered in non-technical language to help encourage comprehension. Site personnel will help facilitate viewing throughout the trial at the screening and baseline visits and predetermined study visits thereafter (see Schedule of Events; Table 2) in an appropriate location and be available to answer any questions that the study participant may have.

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7 STATISTICAL METHODS

7.1 General Considerations

All statistical analysis will be performed using SAS version 9.2 or higher either by Supernus or a designated CRO. A unique program will be developed for each created TLF report. All corresponding programs will be delivered to Supernus at the completion of the study if a designated CRO is used.

All tabulations of analysis results will include summaries for treatment arms of SPN-812 and placebo.

In this study, estimands will be estimated using appropriate statistical methods appropriate model (MMRM, ANCOVA, etc.) as described Section 7.8 for the efficacy analyses.

Where appropriate, variables will be summarized descriptively (frequency count and percentage for categorical variables; number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables).

Categorical variables will be analyzed using categorical response methods such as Pearson's Chi-square test. If expected frequencies are too small for asymptotic assumptions, exact testing techniques will be used.

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the eCRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Complete details of the statistical analysis will be provided in a separate statistical analysis plan (SAP). The statistical analysis methods described in the SAP will supersede the statistical methods described in this protocol.

7.2 Handling of Missing Data

With respect to the primary analysis, missing AISRS Total Scores will be assumed to be missing at random (MAR), that is, given the observed data, the reason for the missing data does not depend on the unseen data. The mixed model for repeated measures (MMRM) method, implemented via SAS® PROC MIXED (SAS/STAT Software), will be used for handling missing AISRS Total Scores under MAR assumption. Under MAR, the propensity for a data point to be missing is not related to the missing data, but is related to some of the observed data.

The sensitivity analysis for the primary endpoint will be performed by assuming that missing AISRS Total Scores are missing not at random (MNAR) meaning that the probability that an observation is missing may depend on its underlying unobserved value.

For analysis of secondary endpoints, missing values will be assumed as MAR.

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For safety analyses, missing dates for AEs and non-study medication use will be imputed as described in the SAP. Missing data for all other safety endpoints will not be imputed.

7.3 Analysis Populations

The **Randomized Population** is all subjects who complete the Baseline Period, meet the inclusion/exclusion criteria and are randomized.

The **Full Analysis Set (FAS)** is a subset of subjects in the Randomized Population who took at least one dose of study medication, and had a Baseline and at least one post-Baseline assessment of AISRS. Subjects in the FAS will be analyzed according to the treatment to which they were randomized. The efficacy analyses will be conducted using the FAS.

The **Per Protocol (PP) Population** is a subset of subjects in the FAS who complete all 7 visits through EOS with no missing AISRS assessments and no major protocol violations. Subjects in the PP Population will be analyzed according to the treatment received.

The **Safety Population** is all subjects randomized into the study who receive at least one dose of SM. Subjects in the Safety Population will be analyzed according to the treatment received.

[redacted]

7.4 Demographics and Baseline Analysis

Demographic/baseline variables including age, age group, sex, ethnicity, race, height and weight at screening, and BMI will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables. The descriptive summary will be presented by treatment group for the Randomized Population, FAS, and Safety Population.

Baseline comparability among the treatment groups will be summarized using a chi-square test for categorical variables and F-test for continuous variables. P-values will be used for descriptive purposes only.

7.5 Subject Disposition

A disposition of subjects will include the number and percentage of subjects in each of the following categories:

- Subjects in the Randomized Population
- Subjects in the FAS
- Subjects in the PP Population
- Subjects in the Safety Population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized. The reason for early discontinuation may include any of the following:

- Withdrawal of consent

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- Noncompliance
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

7.6 Study Medication Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to any SM. This will be calculated for each subject by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1).

Duration of treatment exposure will be summarized by duration category and will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of SM compliance is defined as {(number of capsules dispensed minus number of capsules returned) / X × (date of last dose minus date of first dose + 1)}* 100%, where 'X' is equal to 1 (200 mg) or 2 (2X200 mg), or 3 (3x 200 mg) (the number of capsules that the subject was instructed to take daily during the treatment period (i.e, between visits)).

$$\%\ SM\ compliance = \left[\frac{(\text{no. of capsules dispensed}) - (\text{no. of capsules returned})}{\text{X} \times [(\text{date of last dose}) - (\text{date of first dose}) + 1]}\right] \times 100$$

For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment.

7.7 Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHODD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the Safety Population.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Analysis

The primary efficacy variable, change from baseline in AISRS total score to Week 6 (EOS), will be analyzed using MMRM, which assumes that missing data are MAR. The model will include fixed effect terms for baseline AISRS total score, treatment, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood (REML) method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator

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degrees of freedom. In case there is a convergence problem in the MMRM model with the unstructured variance-covariance matrix, the first (co)variance structure that does not have convergence problem will be used for the analysis from the following ordered list: 1) Toeplitz, 2) Autoregressive of order 1, and 3) Compound symmetry. The adjusted mean (least square mean [LS mean]) of change from baseline to EOS for AISRS total score for each treatment arm (placebo and SPN-812) will be presented, along with the corresponding standard error. The SPN-812 treatment arm will be compared with placebo. The LS means of the treatment groups, differences between the LS treatment mean and placebo, and 95% confidence intervals (CIs) for the treatment differences with p-values will be computed.

7.8.1.1 Sensitivity Analysis

The sensitivity analysis assumes that missing AISRS total scores are MNAR. Placebo-based multiple imputation will be used to fill-in missing values. This approach may be considered “worst-case” sensitivity analyses as it assumes that after discontinuation, subjects from the SPN-812 treatment arm would adopt the outcome model estimated from the placebo arm. The placebo-based imputation will be implemented, which will be described in the SAP.

7.8.2 Secondary Efficacy Analyses

The secondary analyses will be based on the FAS with missing values imputed using multiple imputation assuming MAR.

All secondary analyses will use analysis of covariance (ANCOVA) [except categorical CGI, 50% responder and 30% responder, which use Pearson’s Chi-squared test or Fisher exact test on the absolute value at Week 6 (EOS)] on the change from baseline at Week 6 (EOS) (except CGI-I, which uses the absolute value) with treatment and baseline (baseline CGI-S will be used for CGI-I) as fixed effect. The SPN-812 treatment arm will be compared with the placebo arm. The LS means of the treatment groups, differences between the LS treatment means and placebo (SPN-812 minus placebo), and 95% CIs for the treatment differences with p-values will be computed.

7.8.2.1 Key Secondary Efficacy Analyses

The analysis of the key secondary objective will be conducted on the CFB at EOS in the CGI-S score

To preserve the overall type I error rate at 0.05 for the key secondary endpoint, a sequential testing procedure will be used with the following features. The key secondary endpoint will only be tested if SPN-812 treatment is significantly different from placebo for the primary endpoint.

7.8.2.2 Additional Secondary Analyses

Additional secondary analyses of the secondary efficacy variables will include:

1. Percentage of subjects with a CGI-S score of 1 or 2 weekly and at EOS.

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- The proportion (%) of responders (CGI-S score of 1 or 2) will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 minus placebo) and the p-value from Pearson's Chi squared Test or Fisher's Exact Test will be presented.

2. CGI-I score at EOS
   - The absolute value of CGI-I weekly and at EOS (Week 6) will be analyzed using ANCOVA with treatment as a fixed classification variable and baseline CGI-S as a covariate. To compare the treatment groups, the difference in LS means (SPN-812 minus placebo) will be presented along with the 95% CI around the difference and p-value.

3. Percentage of subjects with a CGI-I score of 1 or 2 weekly and at EOS
   - The proportion (%) of responders (CGI-I score of 1 or 2) will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 minus placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.

4. CFB biweekly and at EOS (Week 6) in the GAD-7 total score

5. CFB weekly (Week 6) in the AISRS Inattention subscale score and the Hyperactivity/Impulsivity subscale score at EOS

6. AISRS 50% Responder (defined a subject with a ≥ 50% reduction in the CFB AISRS total score) weekly and at EOS
   - The proportion (%) of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 minus placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.

7. AISRS 30% Responder (defined as a subject with a ≥ 30% reduction in the CFB AISRS total score) weekly and at EOS
   - The proportion (%) of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-812 minus placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.

8. CFB at EOS in the BRIEF-A Global Executive Composite (GEC) T-score.

9. CFB at EOS in the BRIEF-A T-score by each Summary Index Scale and by each individual BRIEF-A scale.

[redacted]

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[redacted]

7.9 Sample Size and Power Considerations

Assuming an effect size of 0.407, 128 subjects per treatment arm (256 total subjects for 2 arms) in the FAS will yield 90% power at a significance level of 0.05 (two-sided) to reject the equality of treatment means between the placebo and the SPN-812 treatment group.

Assuming approximately 30% of subjects drop out before the completion of the study, an adjusted sample size of 366 subjects (183 per arm) will be randomized to obtain 128 subjects per arm in the FAS at the completion of the study.

7.10 Interim Analysis

No interim analysis will be performed.

[redacted]

7.12 Safety Analysis

Safety analyses will be performed by treatment arm based on the Safety Population.

The incidence rate of AEs will be calculated by treatment arm for each system organ class (SOC) and preferred term (PT). The severity of the AEs and the relationship to SM will be summarized by treatment arm for each SOC and PT.

AEs will be summarized using discrete summaries at the subject and event level by SOC and PT, and by severity and relationship separately for each treatment arm. Verbatim description and Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for all AEs will be contained in the subject data listings.

Clinical laboratory values will be summarized by visit by treatment arm using descriptive statistics. For quantitative laboratory parameters, both actual values and change from screening values will be summarized.

Vital signs will be summarized by visit by treatment arm using descriptive statistics. Both actual values and change from baseline will be summarized.

ECG results will be summarized by visit by treatment arm using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The summary will be presented by treatment arm.

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8 DOCUMENTATION

8.1 Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

8.2 Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor, and IRB must be notified promptly.

Changes to the protocol which are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor or CRO will send a letter to the IRB detailing such changes.

8.3 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor's Quality Assurance team or qualified designee, which is an independent function from the study conduct team.

8.3.1 Data Collection

The primary source document will be the subject's medical record. If separate research records are maintained by the Investigator(s), both the medical record and the research

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record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF Completion Instructions that are provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of GCP.

8.3.2 Clinical Data Management

Data from eCRFs and other external data (e.g., laboratory data) will be entered into or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

8.3.3 Database Quality Assurance

In accordance with the vendor’s procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. The procedure for handling missing data will be addressed in the Statistical Analysis Plan (SAP). Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

8.3.4 Bioanalytical Sample Handling

Viloxazine and 5-hydroxy-viloxazine glucuronide concentrations in plasma samples will be determined using a validated chromatographic method. Viloxazine concentrations will be reported as viloxazine free base. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report.

8.4 Retention of Records

The Investigator has the responsibility to retain all study “essential documents”, as described in ICH E6 for at least two years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB correspondence). The Investigator must obtain written permission from Supernus prior to the destruction of any study document.

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8.5 Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor and the CRO immediately that this request has been made.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 Code of Federal Regulation (CFR) 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

8.6 Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until all Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

8.7 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

8.8 Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

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8.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

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9 ETHICS

9.1 Institutional Review Boards

The IRB that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the ICF will be reviewed and approved by the appropriate IRB before subjects are enrolled. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

9.2 Ethical Conduct of the Study

This study will be conducted in accordance with SOPs from both the Sponsor and the CRO. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent/Assent and IRB regulations).
- Local, national legal guidelines.

9.3 Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor).

Contact persons at the Sponsor and the CROs are listed in the reference binder provided to each investigational site. The study will be monitored by qualified personnel from the Sponsor or their designees, such as the CROs, for their respective sites. Medical writing, data management, and statistical analyses will be performed by the CROs. Laboratory tests will be conducted by a central laboratory as designated in the reference binder.

The study will be monitored by qualified personnel from Supernus. Data management and statistical analyses will be the responsibility of the CRO data management and biostatistics groups.

9.4 Subject Information and Consent

The Investigator (or designee) will inform the subject of all aspects pertaining to the subject’s participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

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The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and subject must sign and date the ICF before the subject can participate in the study. The subject will be given a copy of the signed and dated ICF and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject that consent, regarding study participation, may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use the amended ICF (including ongoing subjects).

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11 APPENDIX:

11.1 Screening, Efficacy and Safety Scales and Questionnaires

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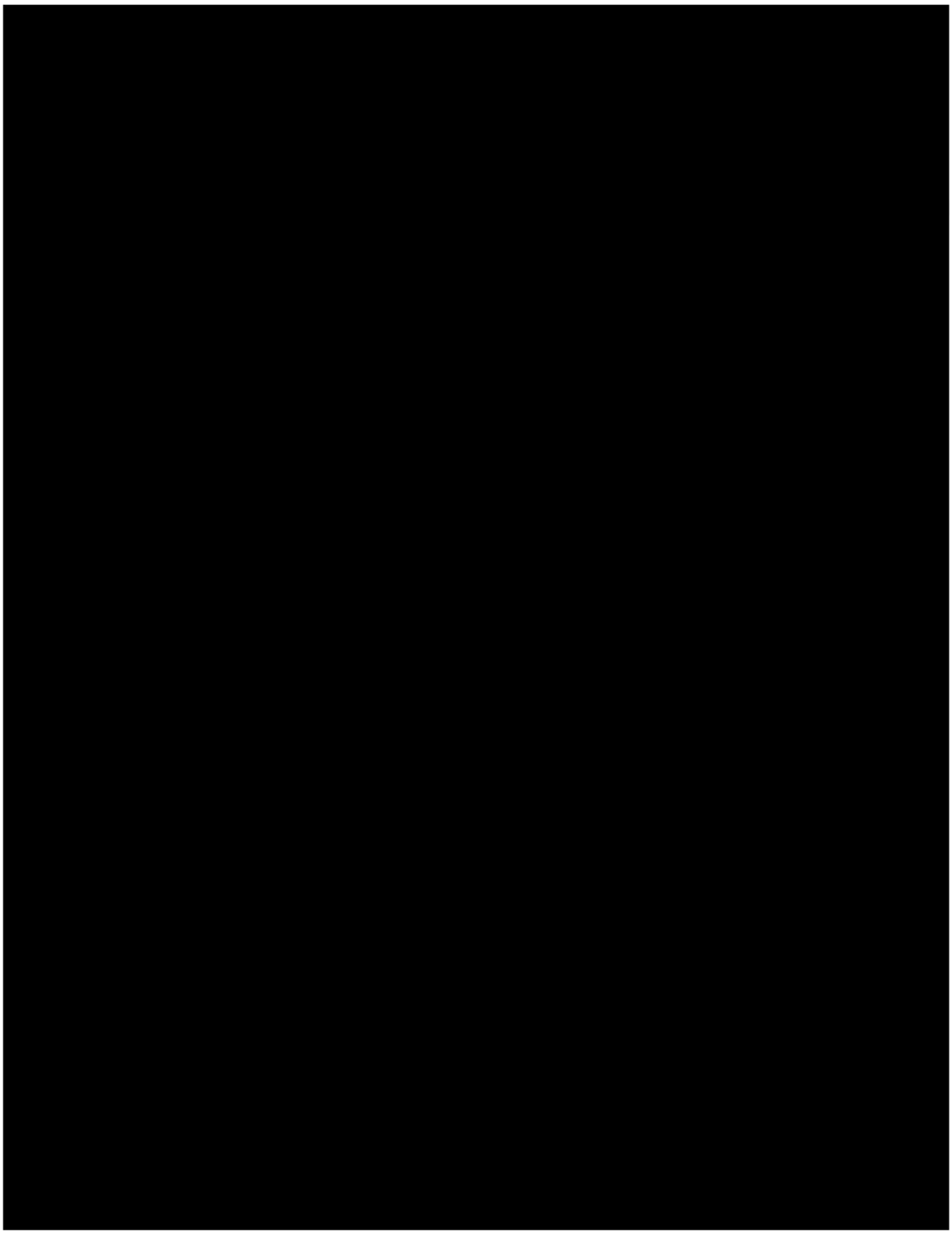
11.1.1 AISRS: Adult ADHD Investigator Symptom Rating Scale



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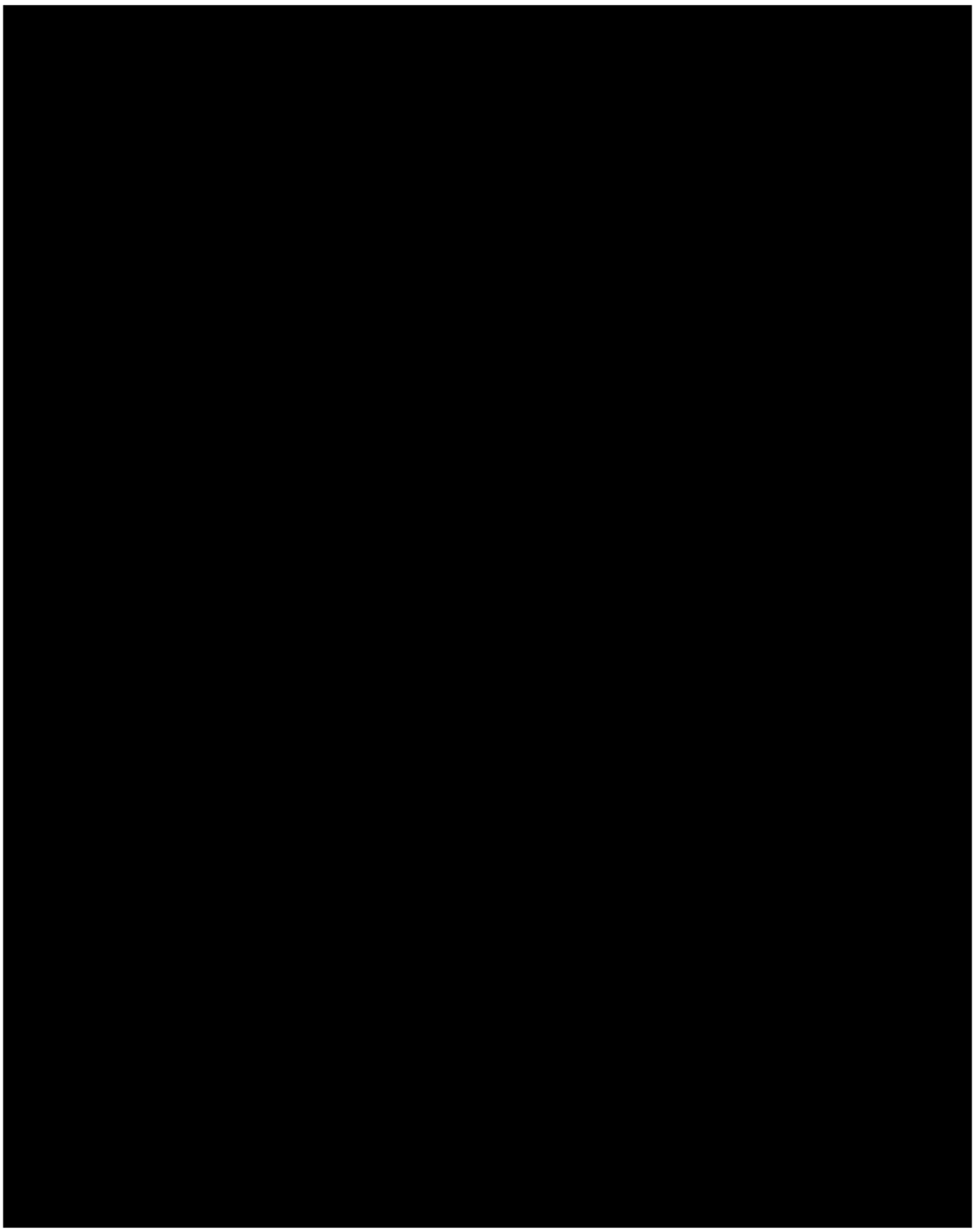

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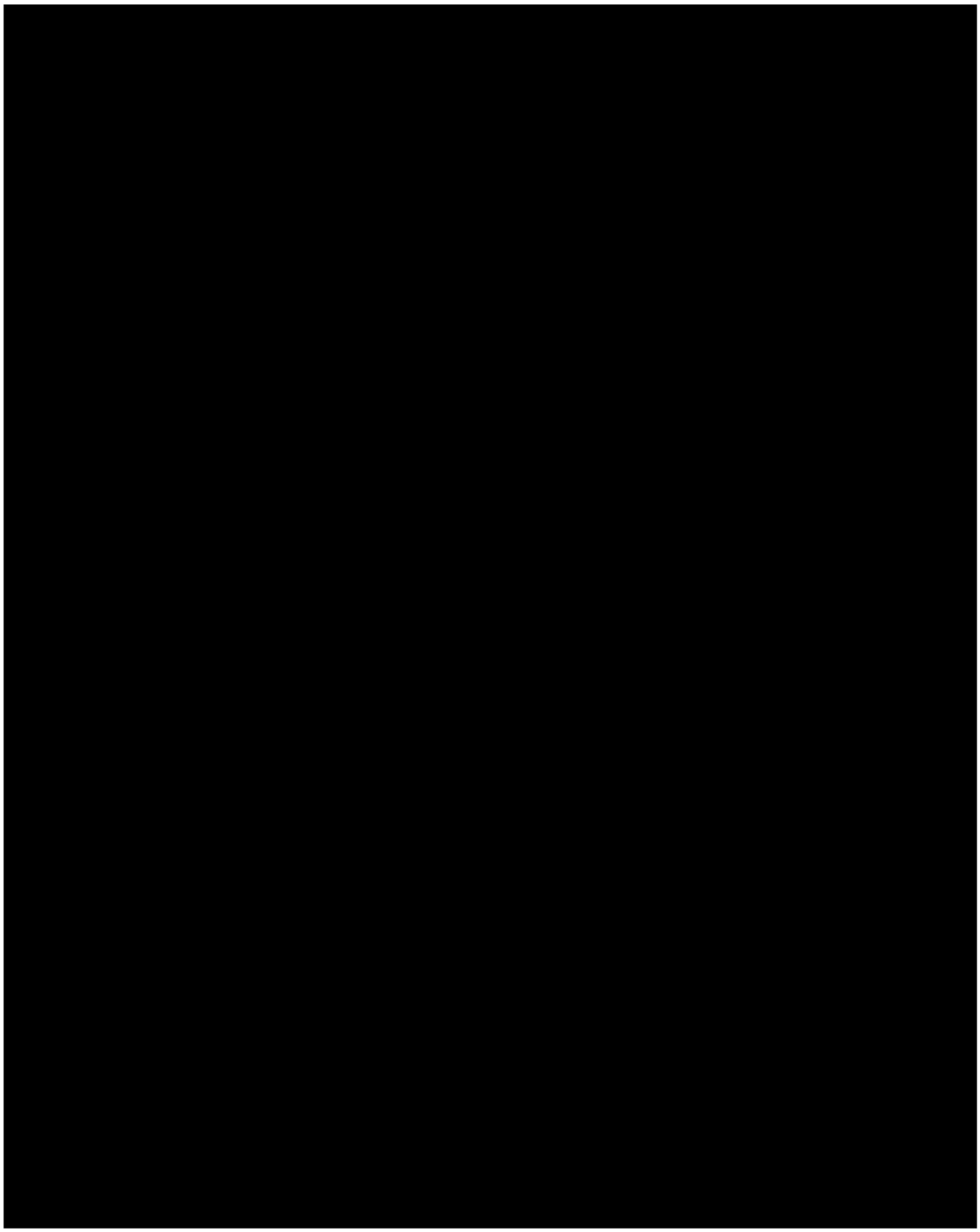

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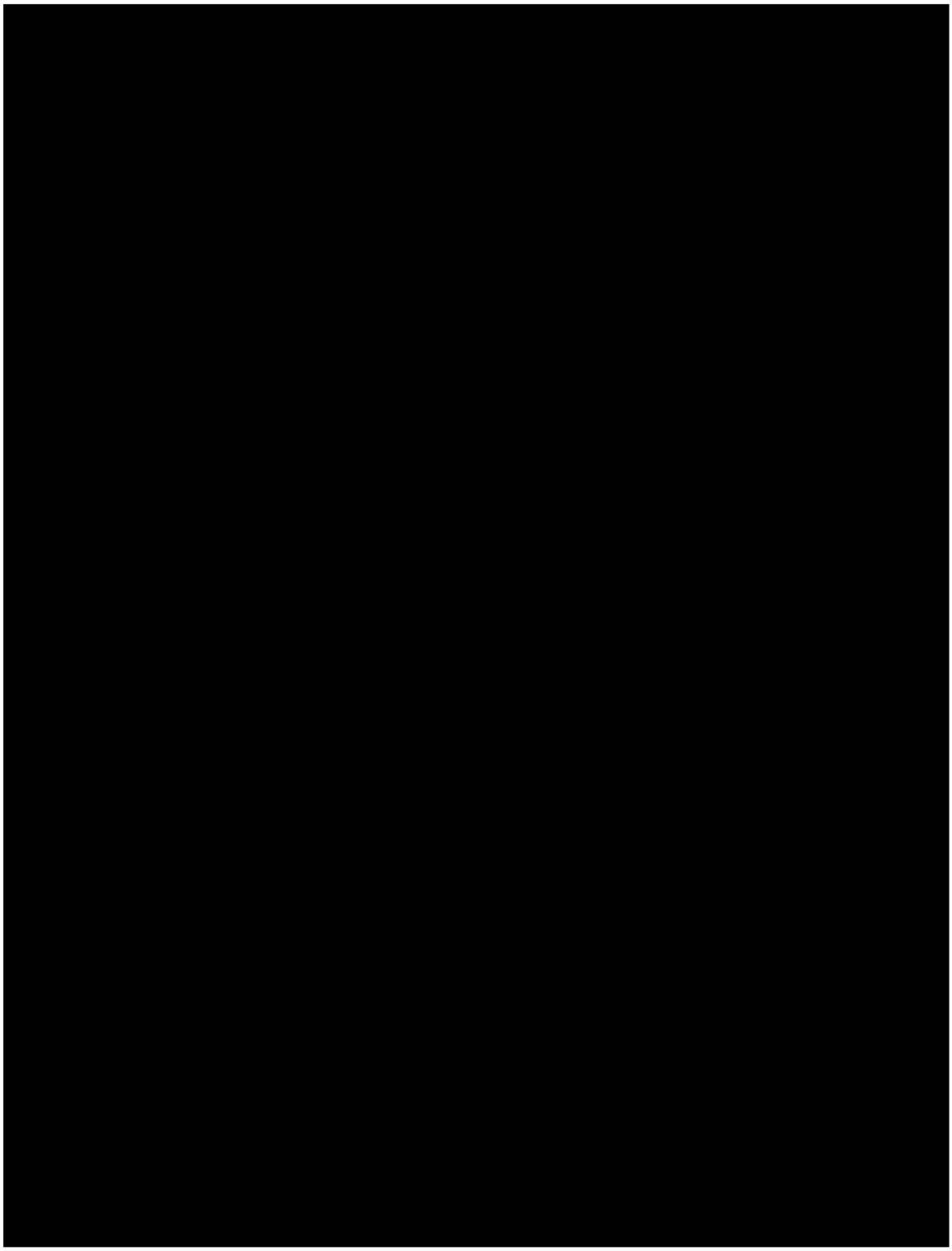

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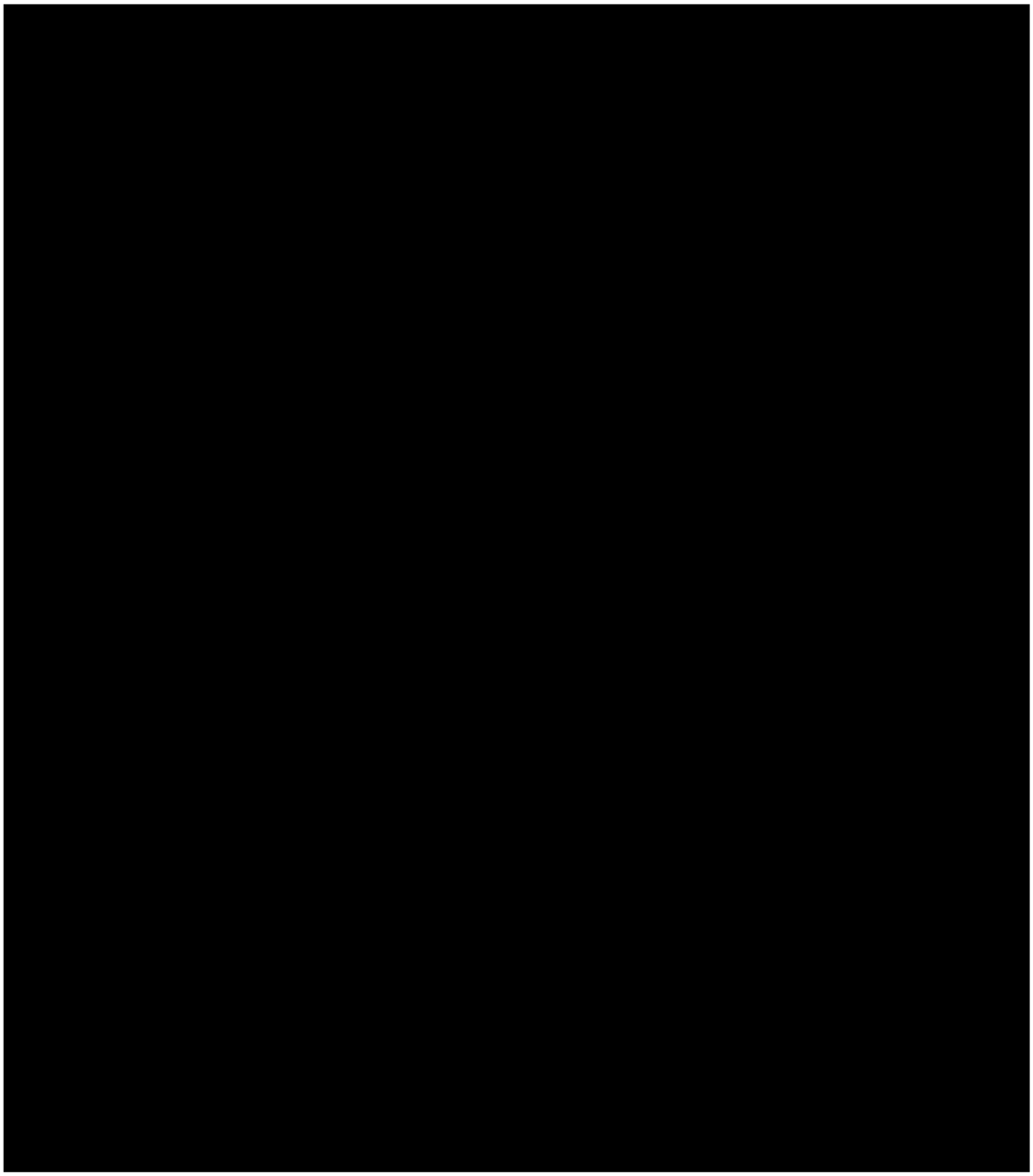
11.1.2 CGI-S: Clinical Global Impression – Severity of Illness



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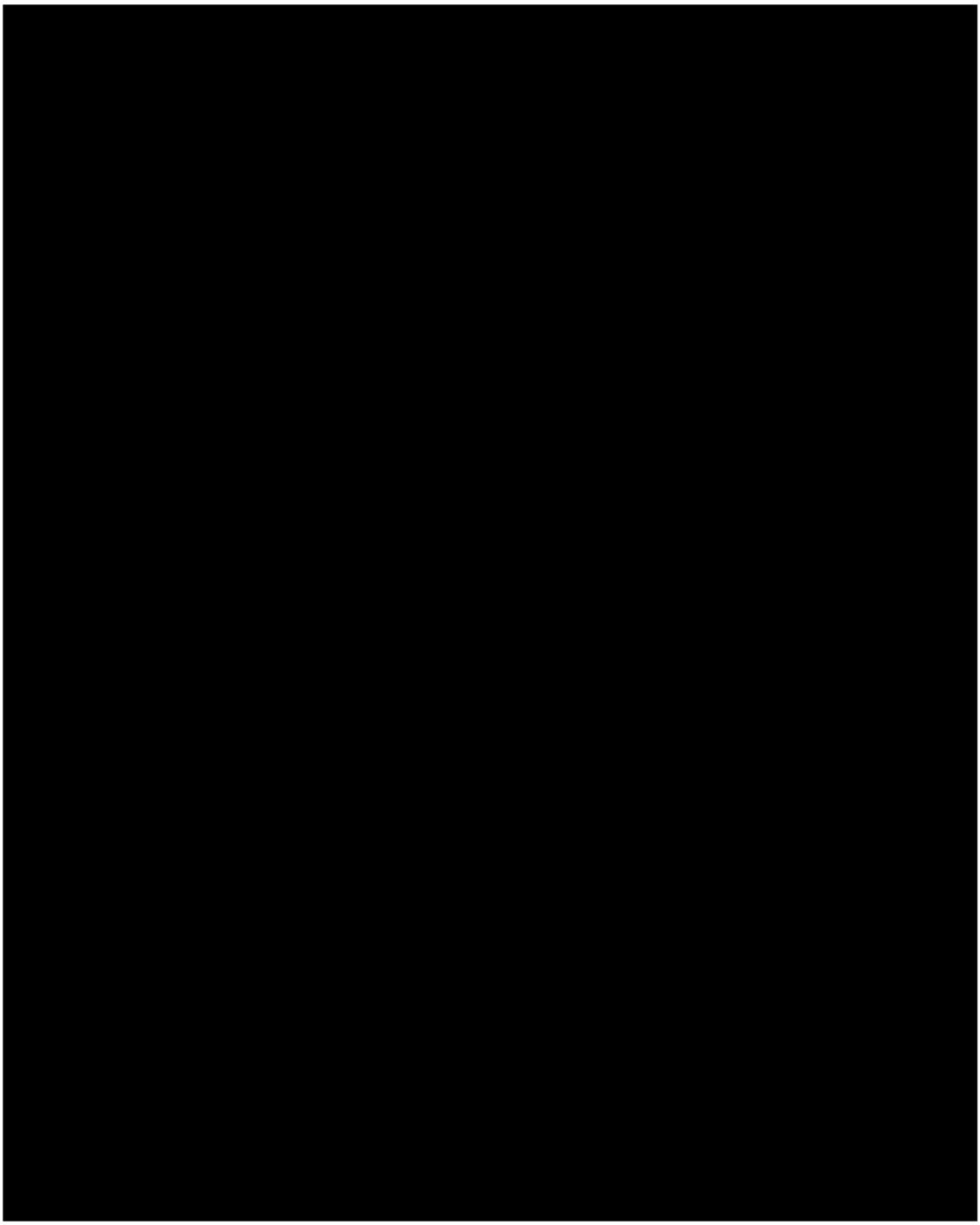
11.1.3 CGI-I: Clinical Global Impression – Improvement



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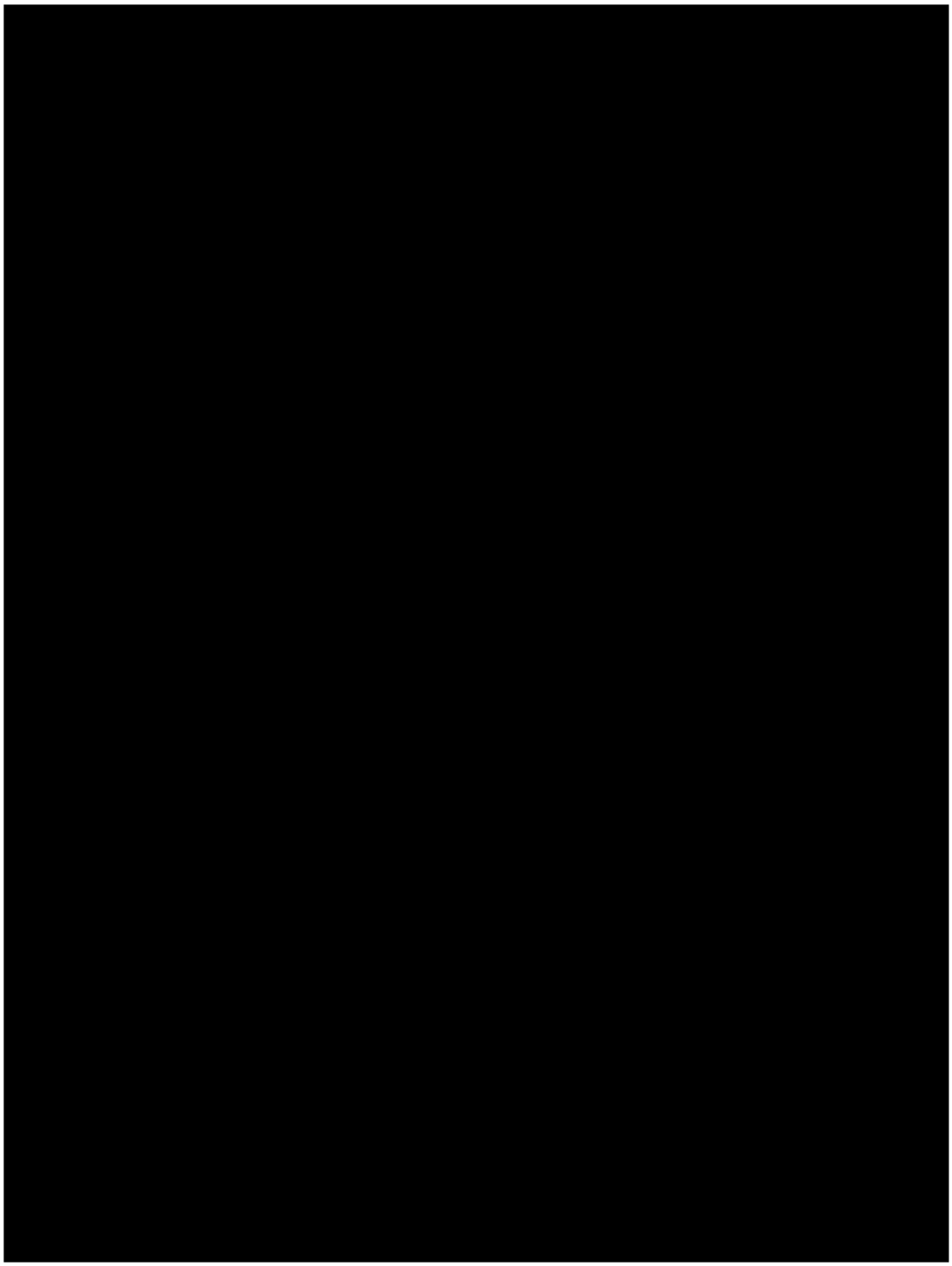
11.1.4 GAD-7: Adult ADHD Investigator Symptom Rating Scale



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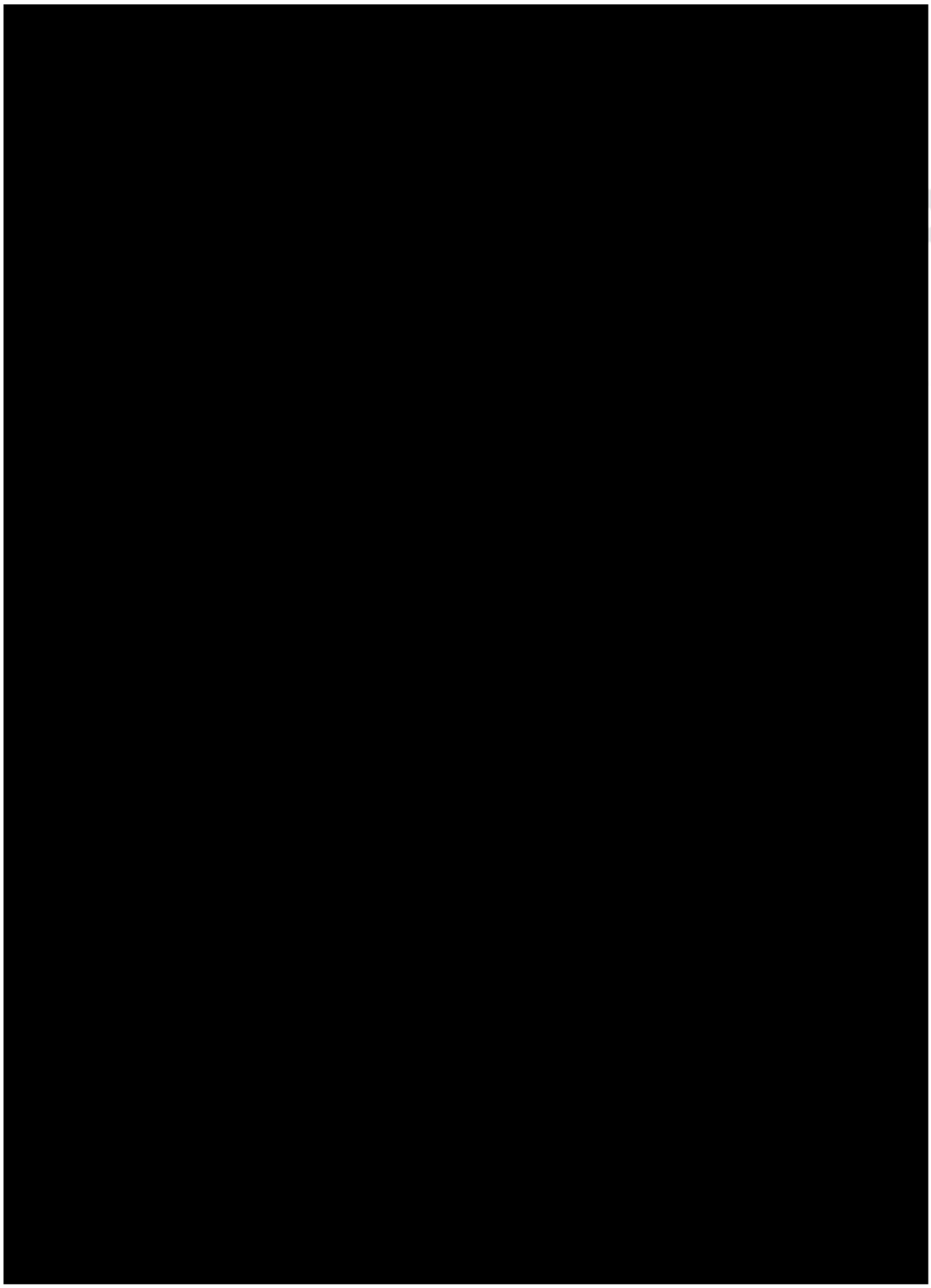
11.1.5 BRIEF-A: Behavioral Rating Inventory of Executive Functioning-Adult



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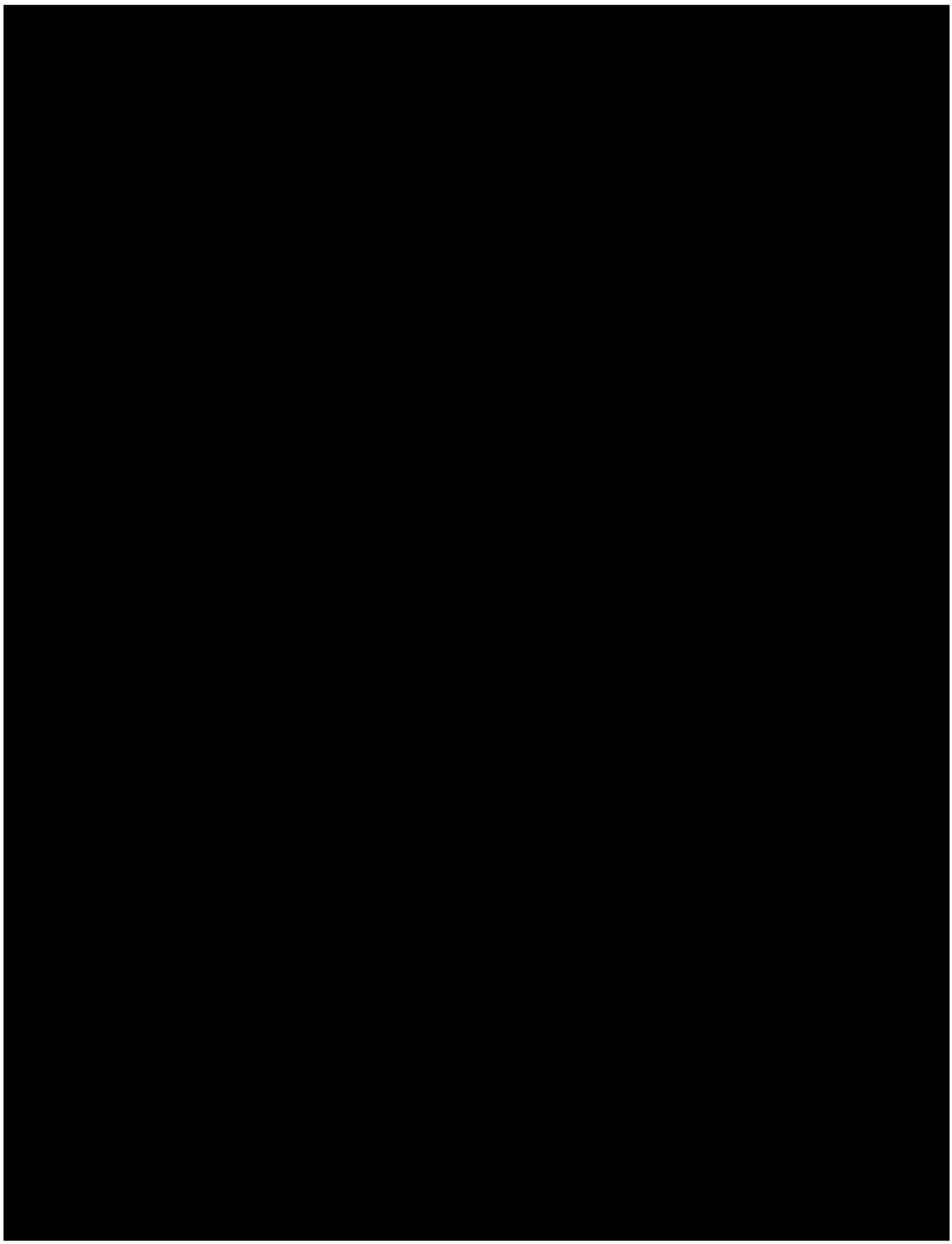

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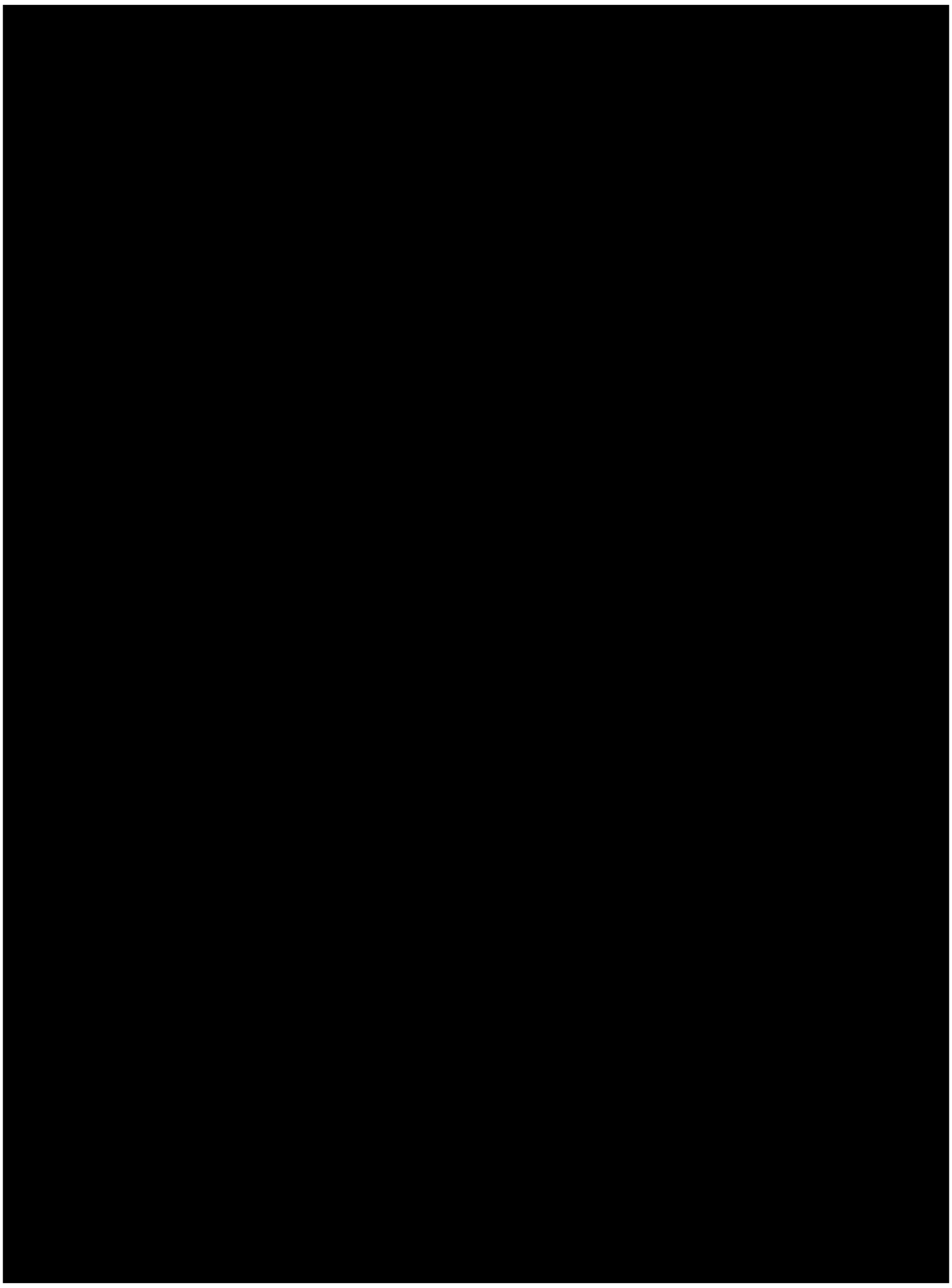

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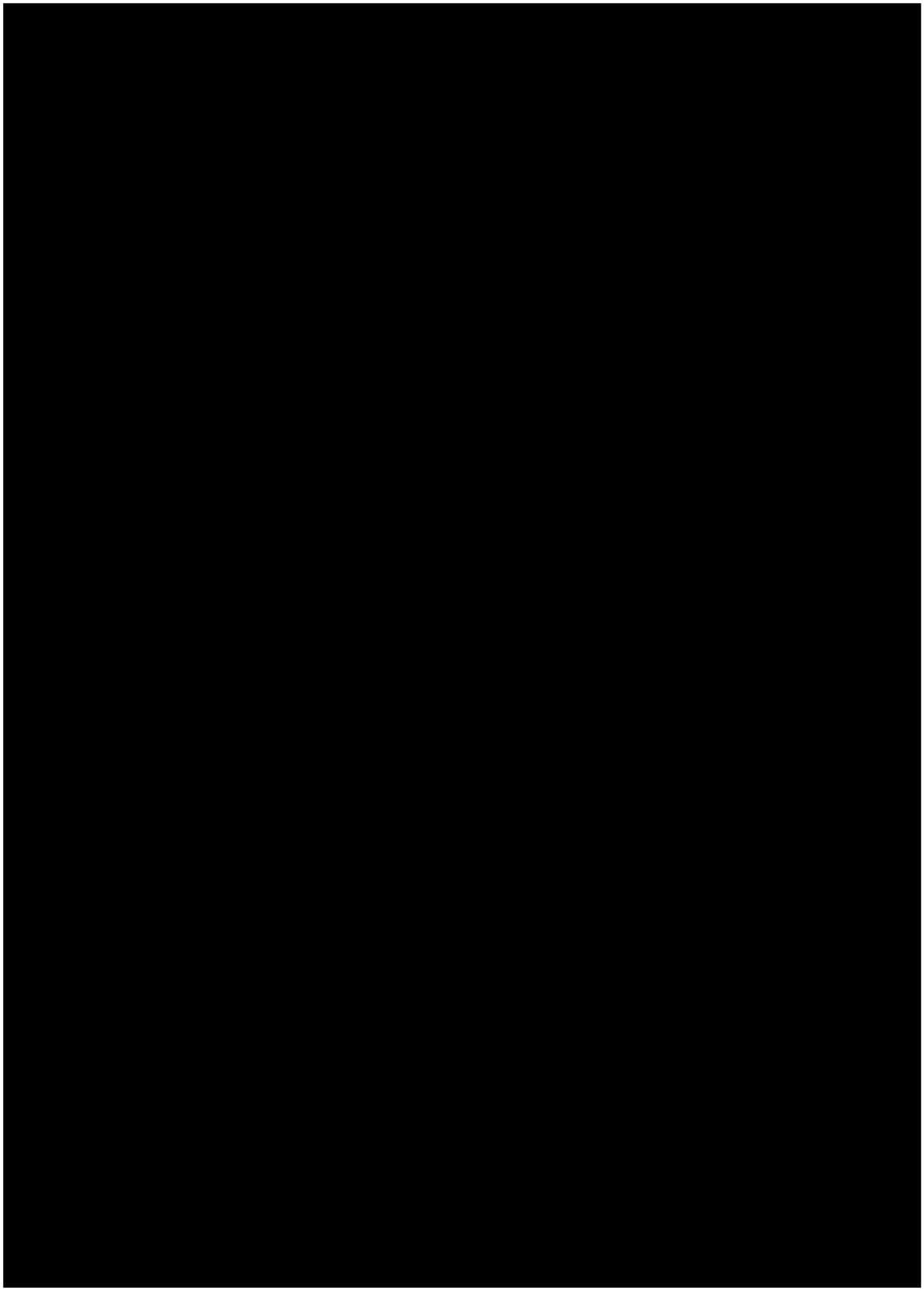
11.1.6 SDQ: Symptoms of Depression Questionnaire



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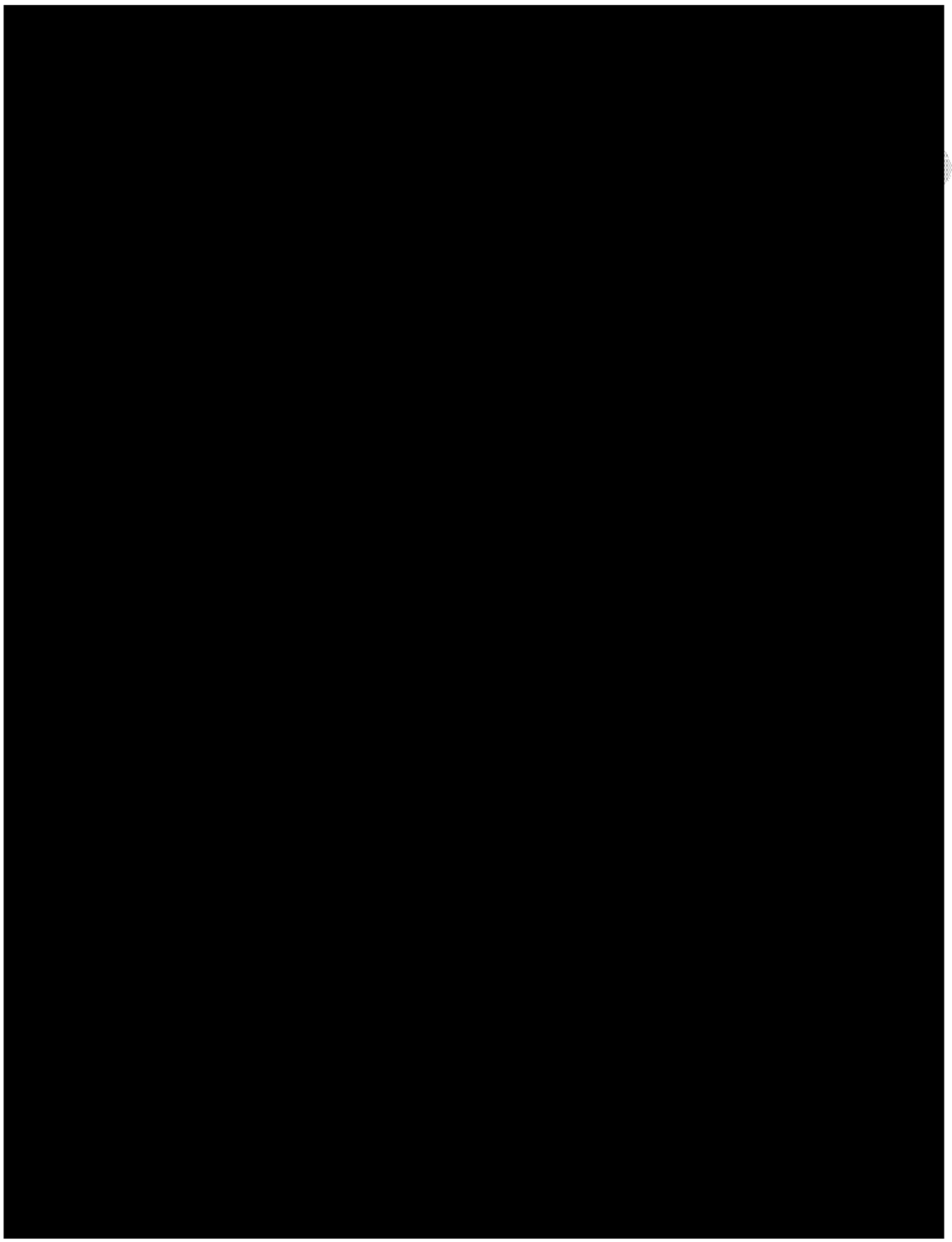

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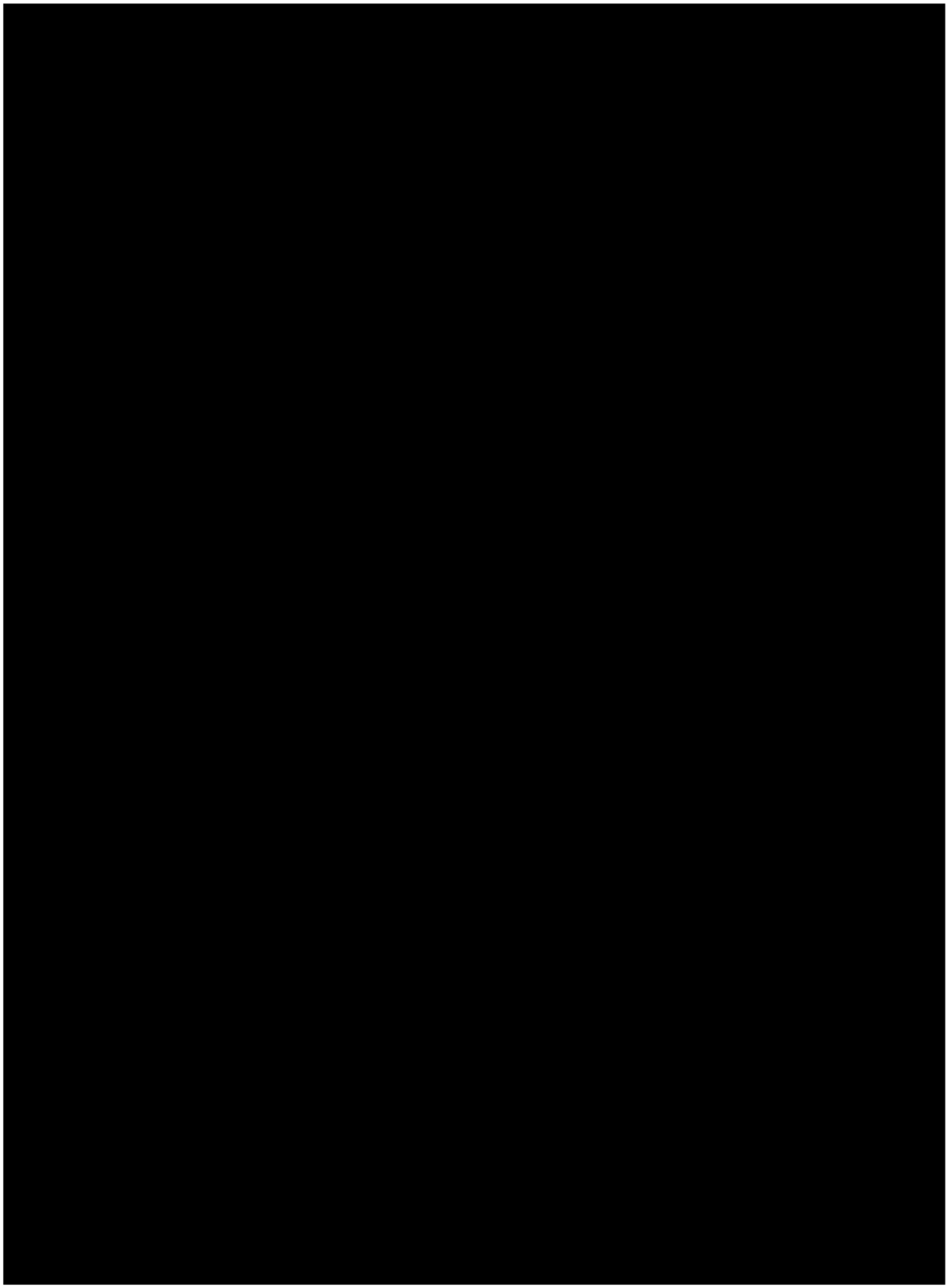

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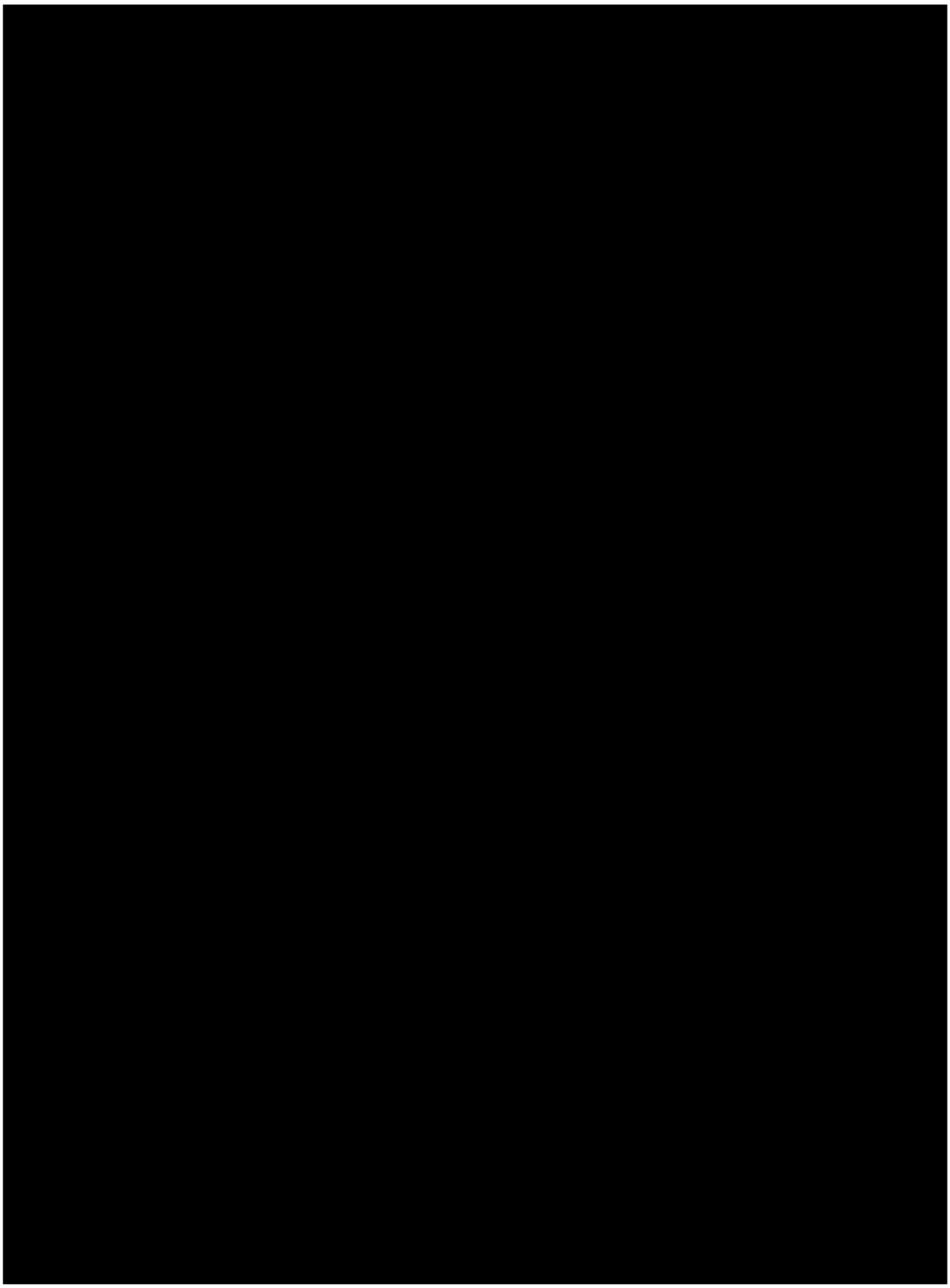

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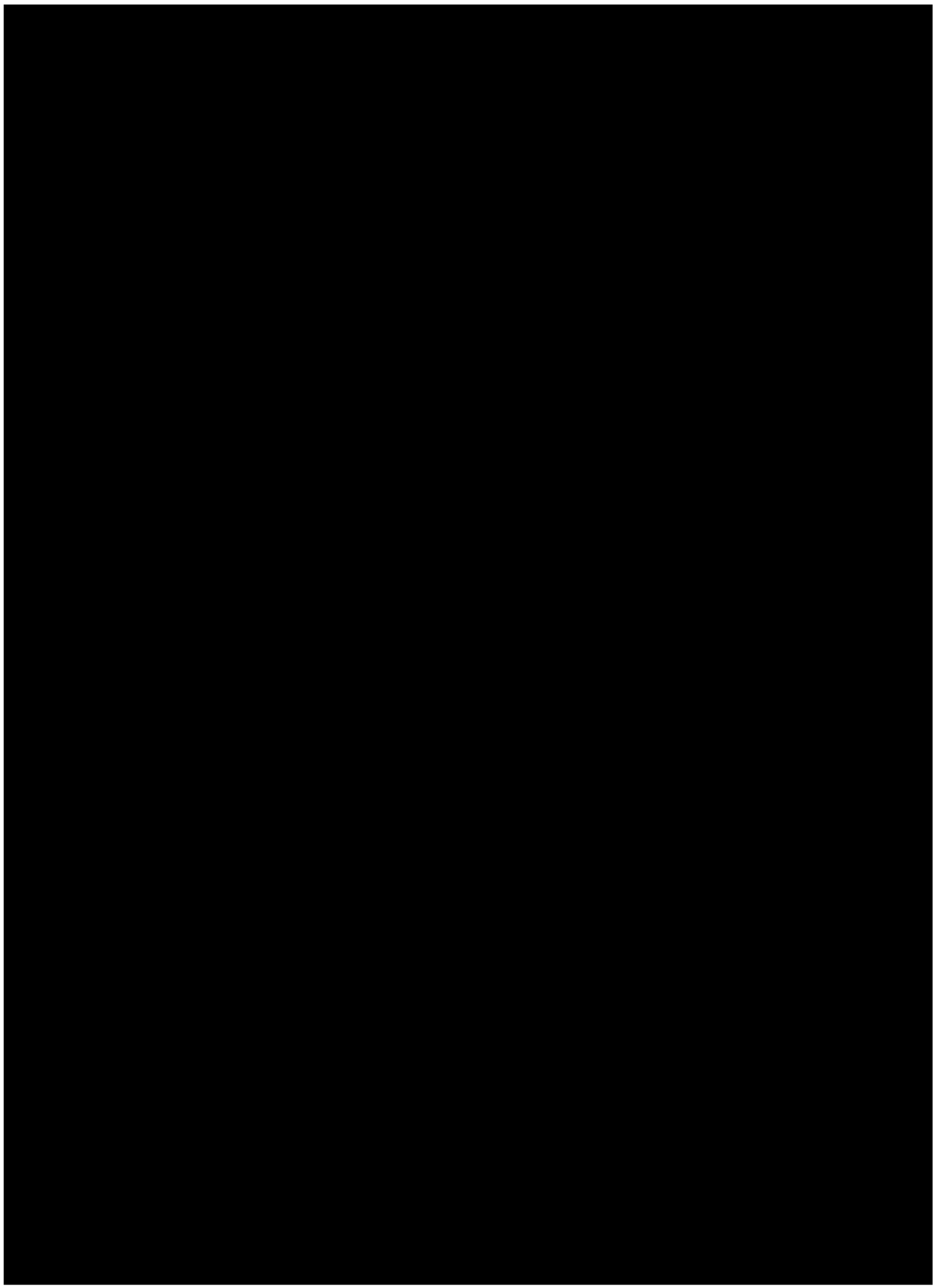

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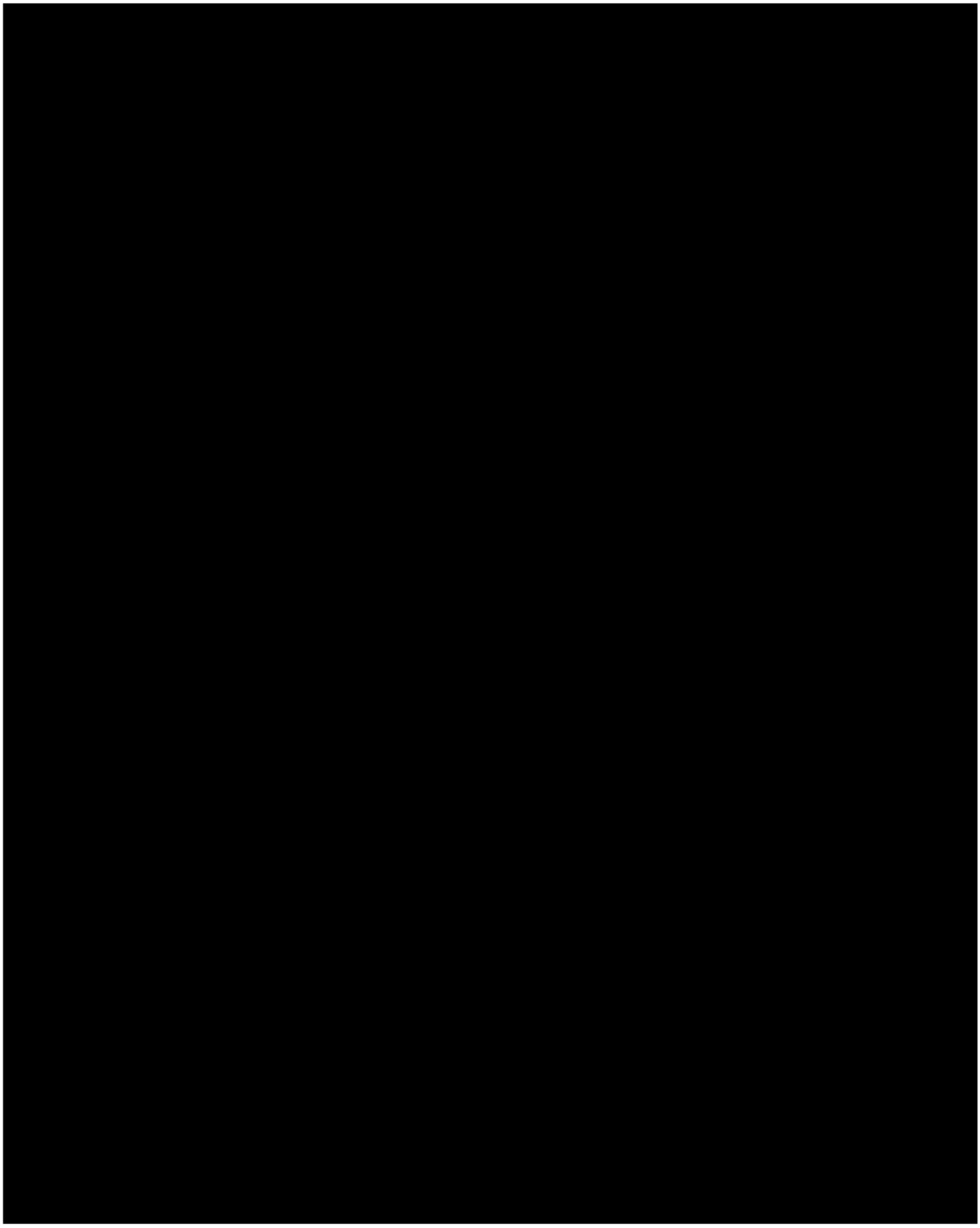

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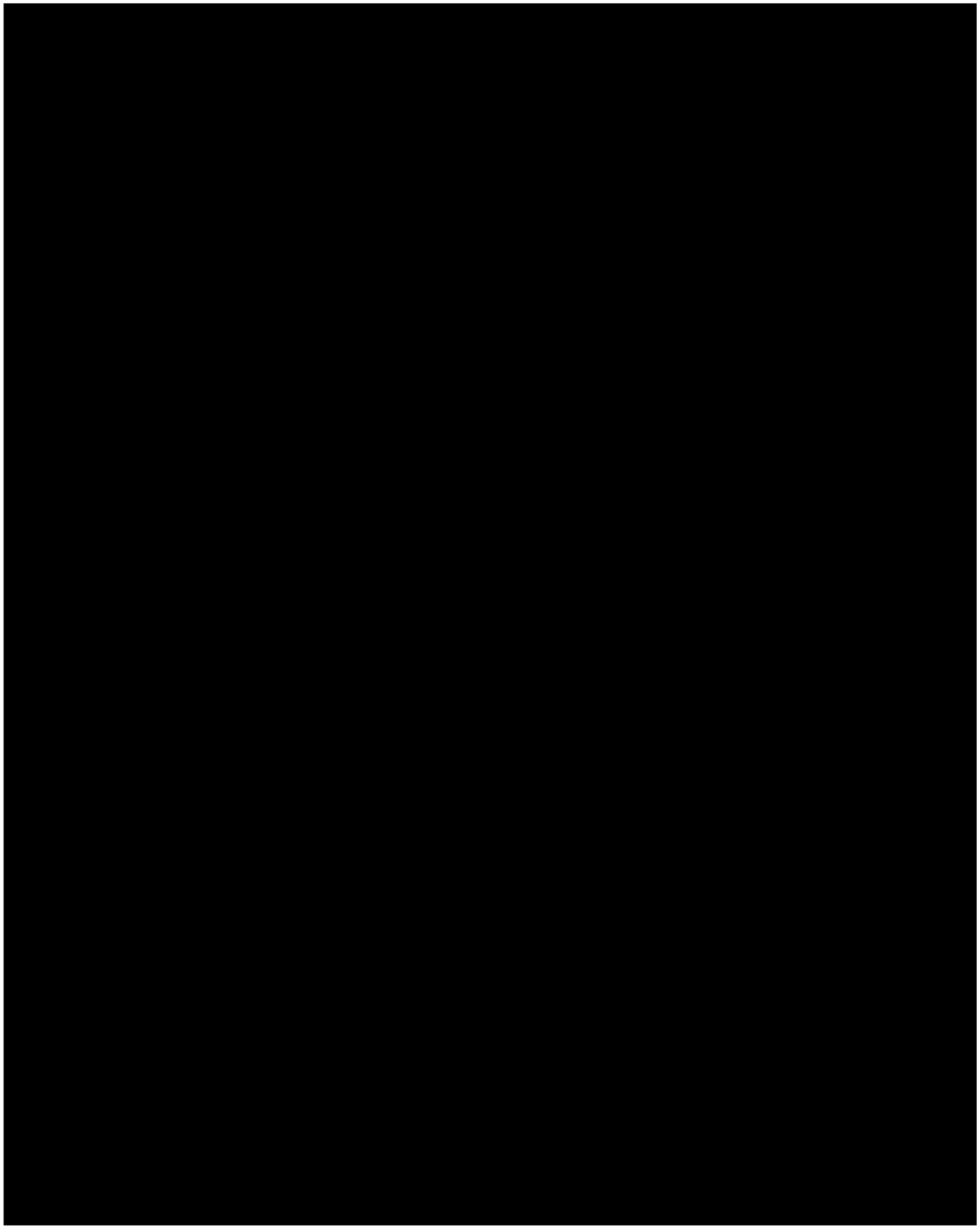

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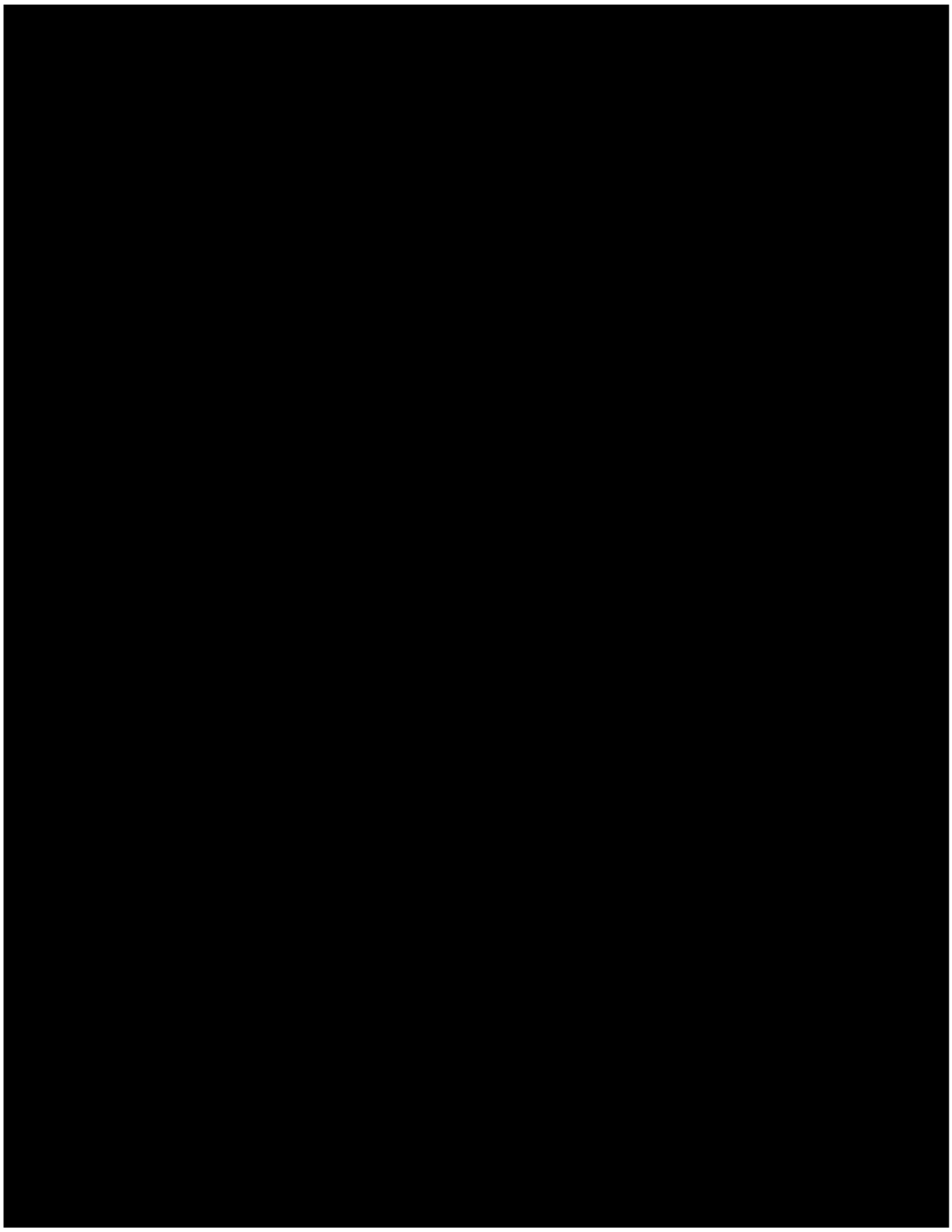

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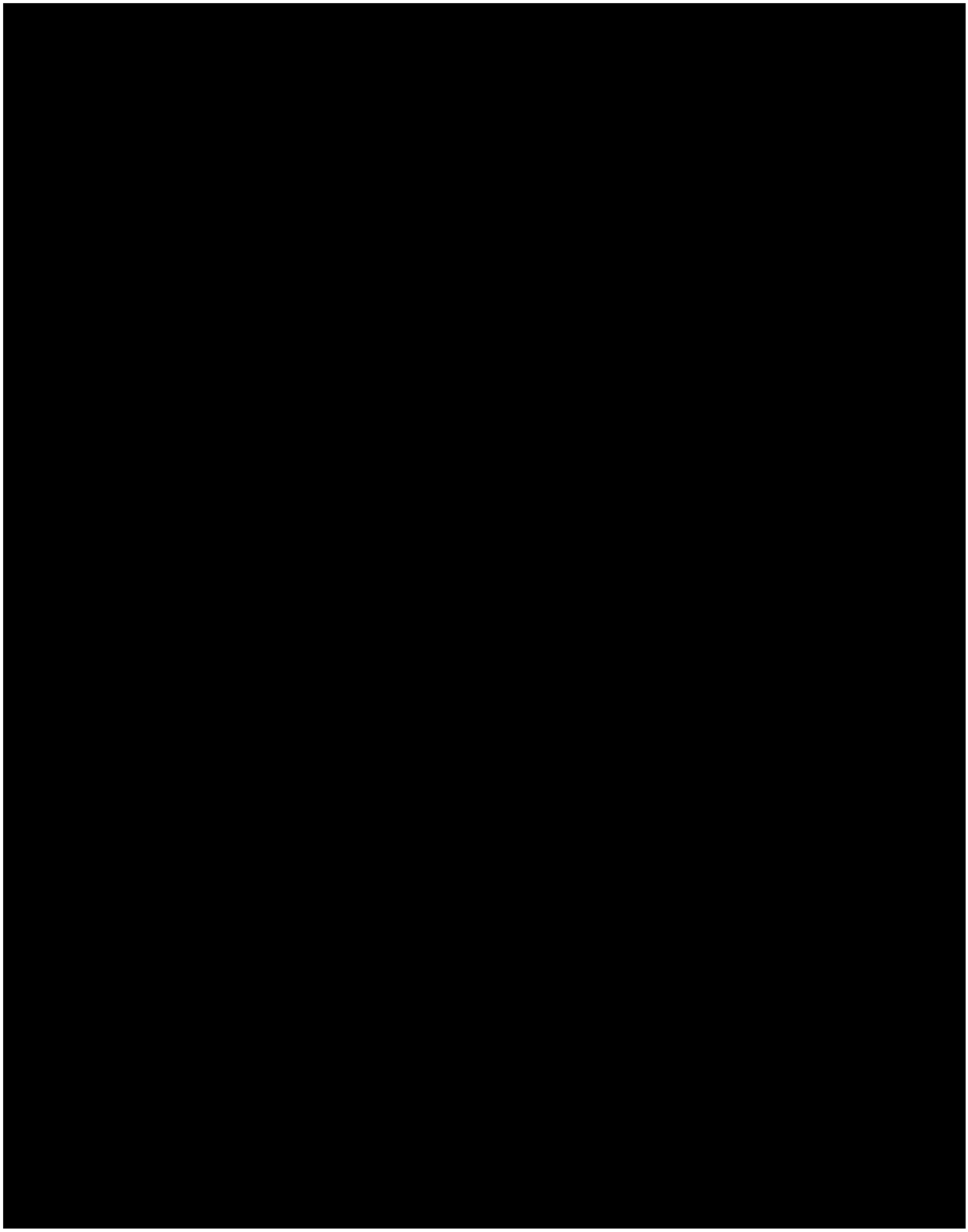

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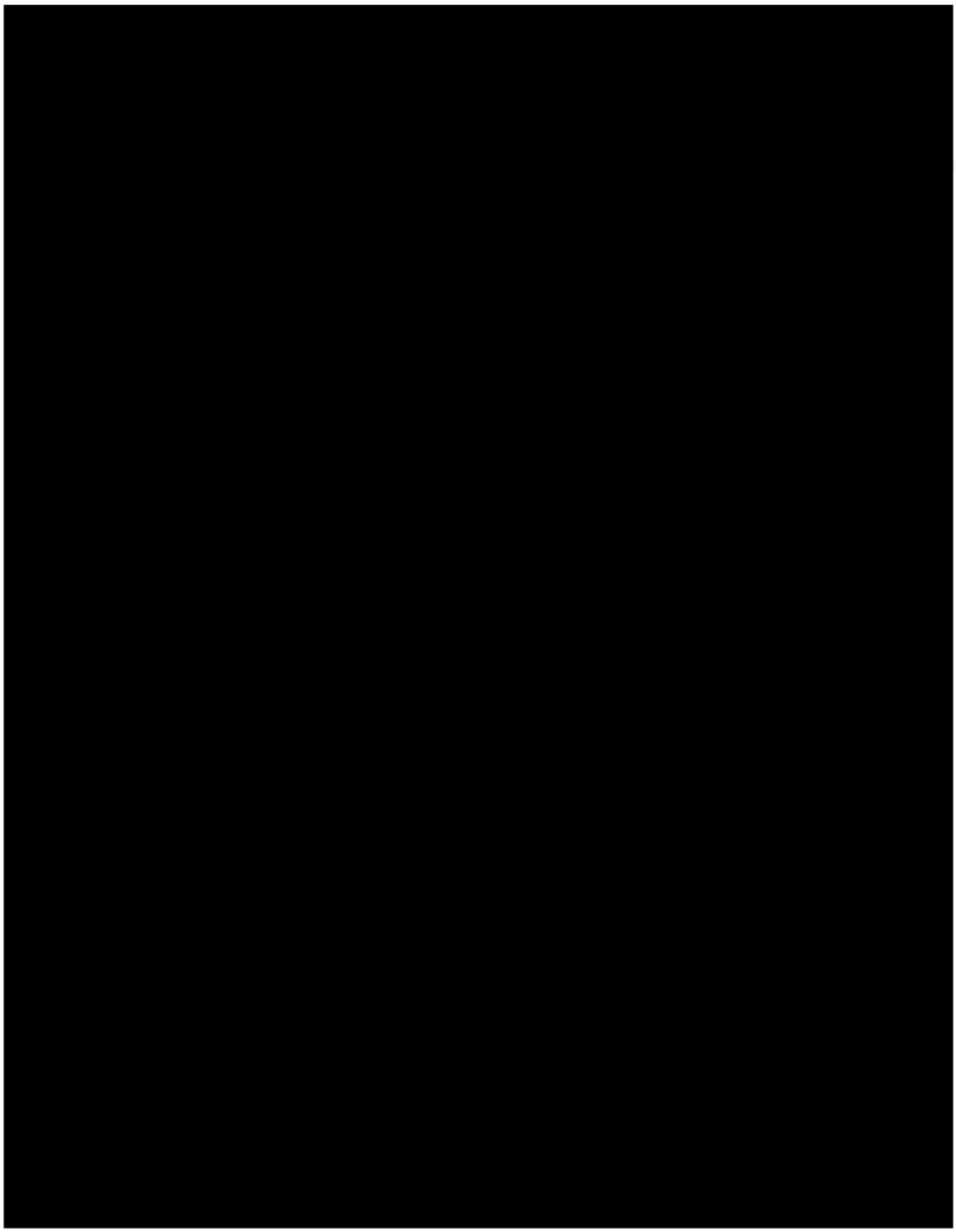

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11.1.8 SCID-5-CT: Structured Clinical Interview for DSM-5: Clinical Trial

[redacted]

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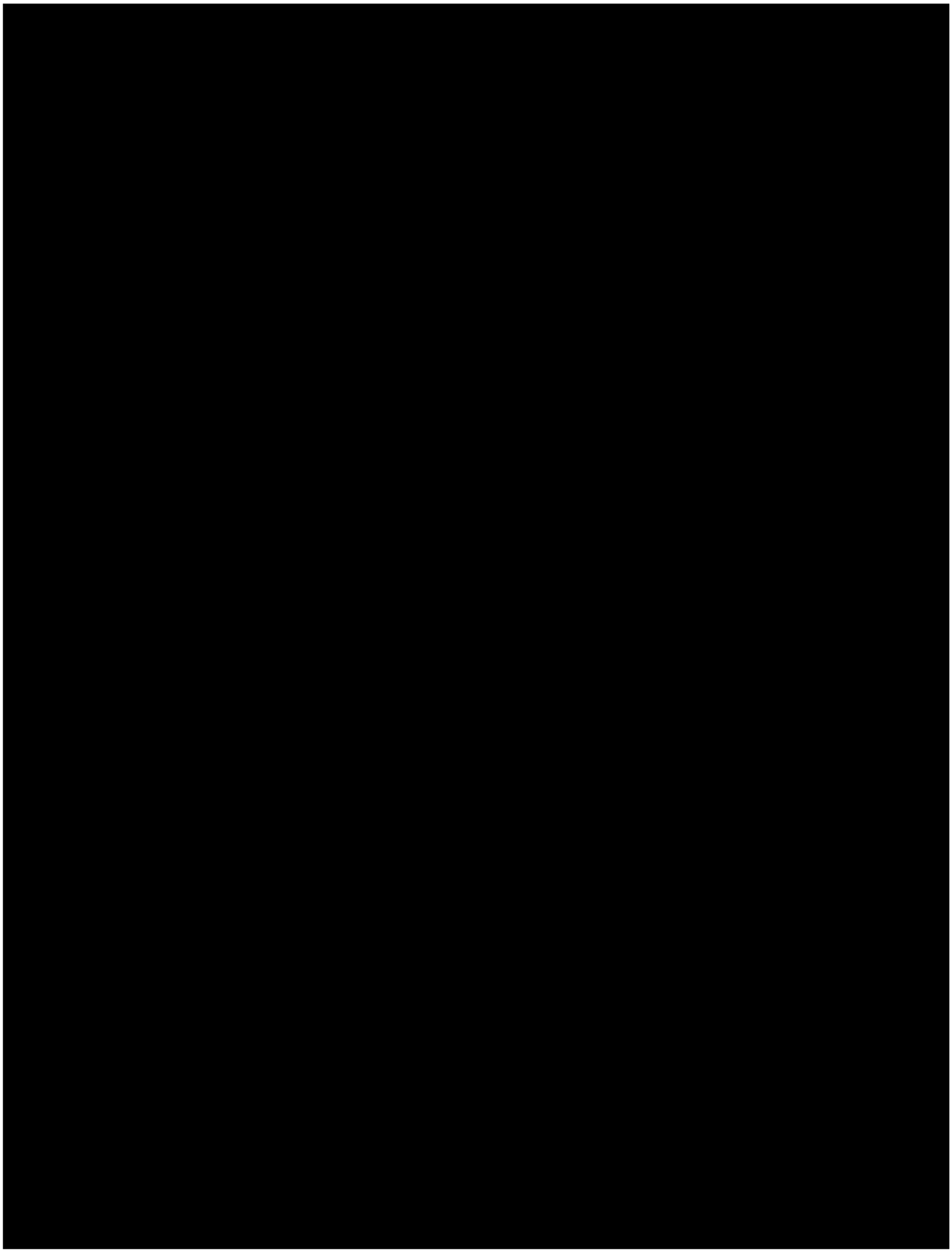

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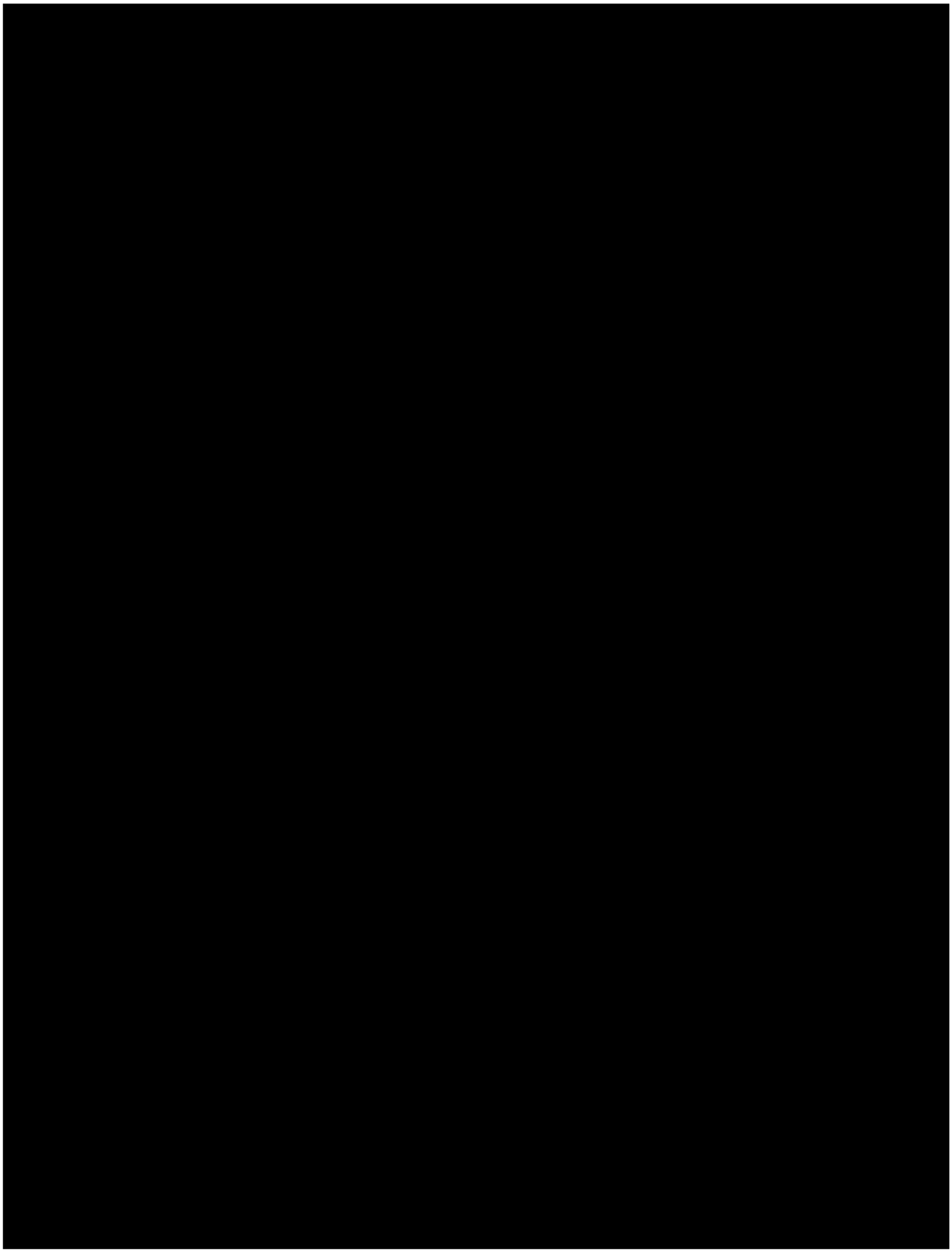

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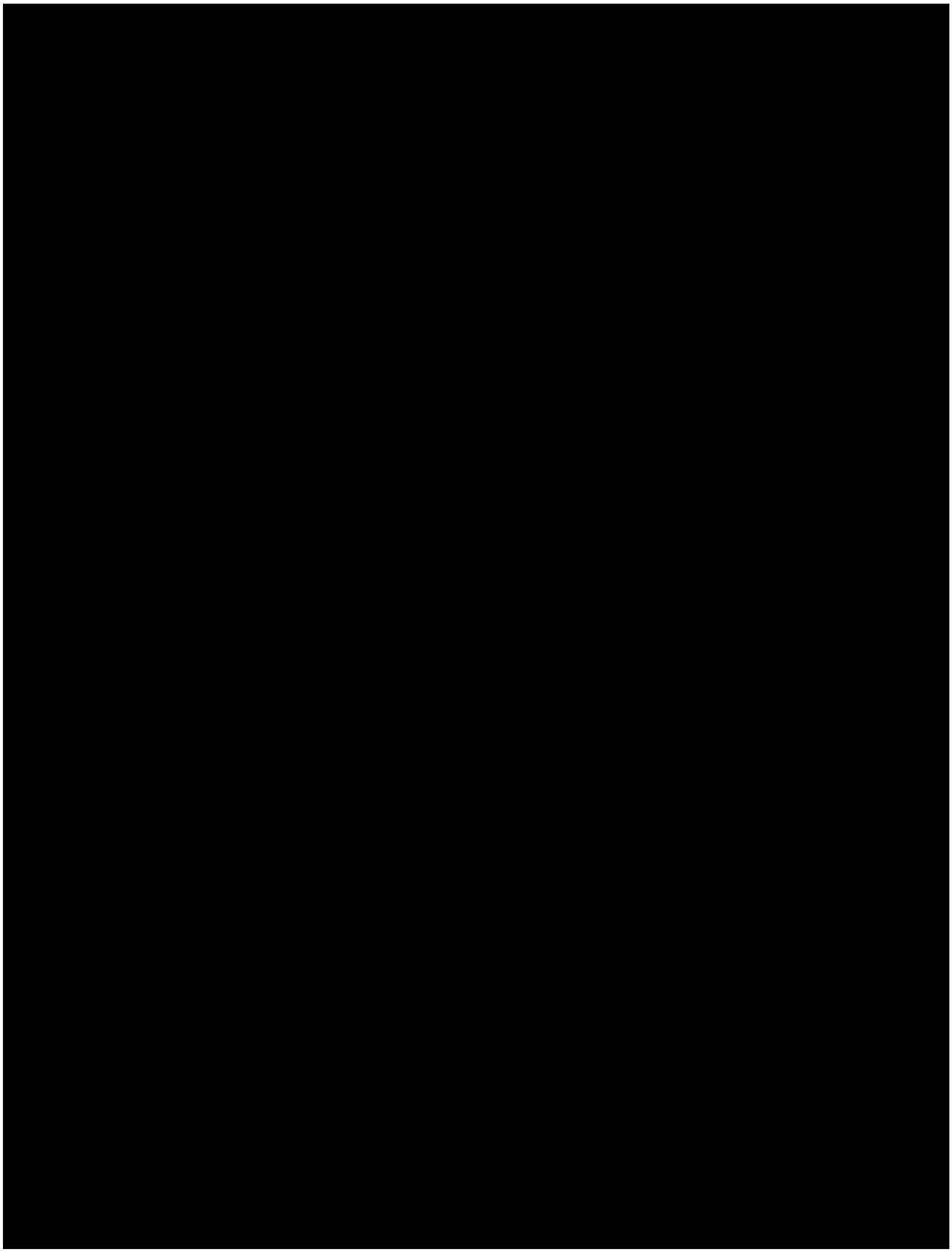

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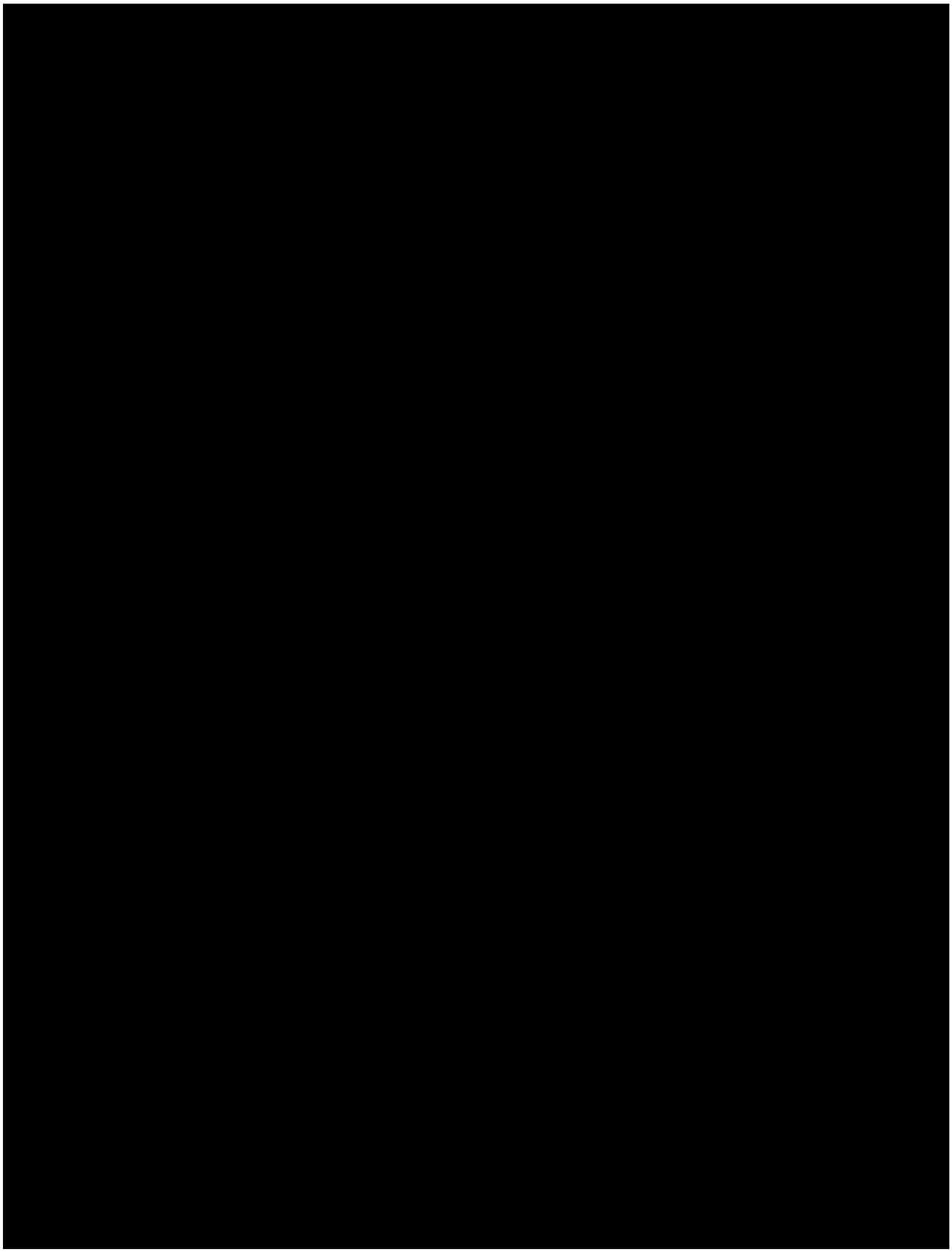

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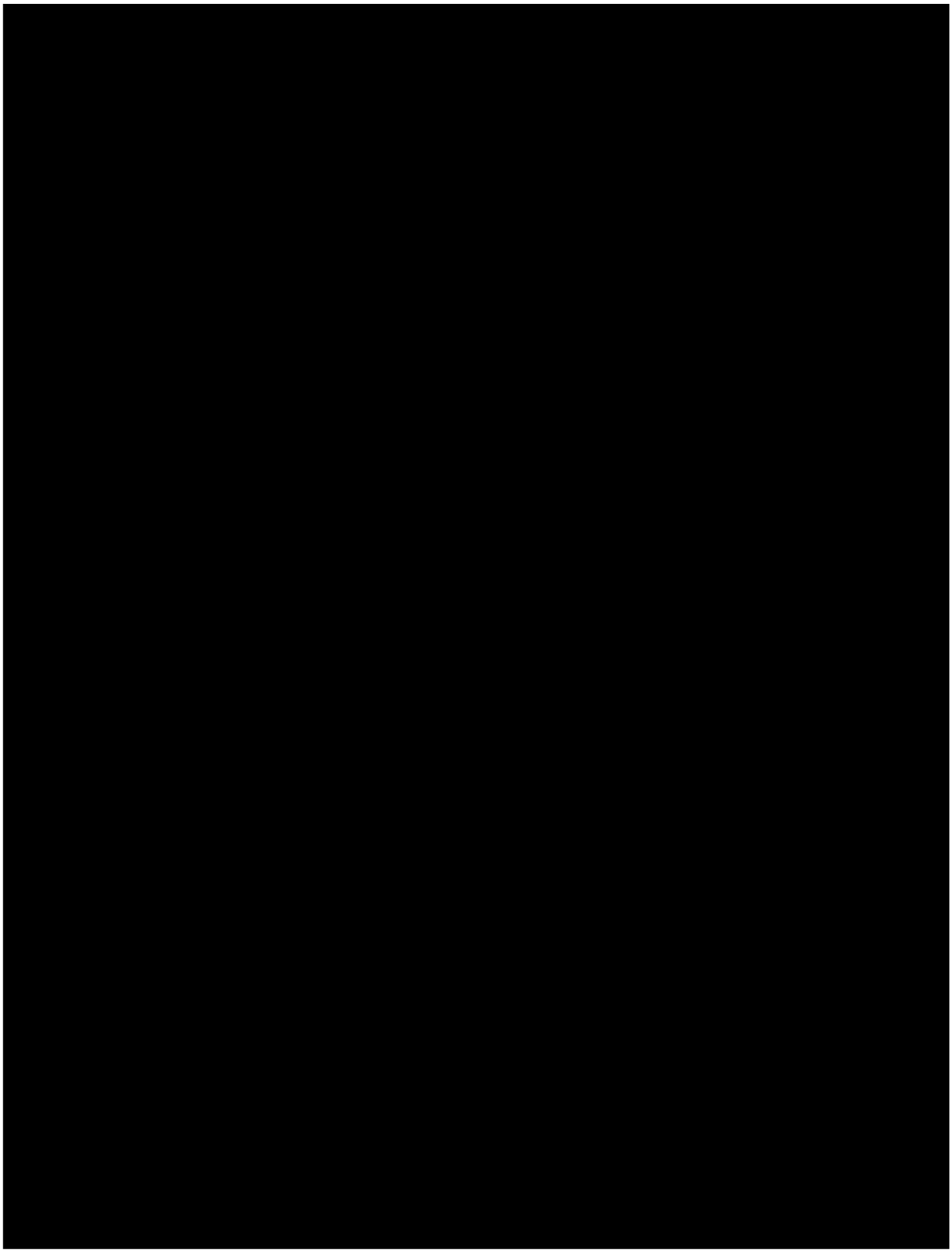

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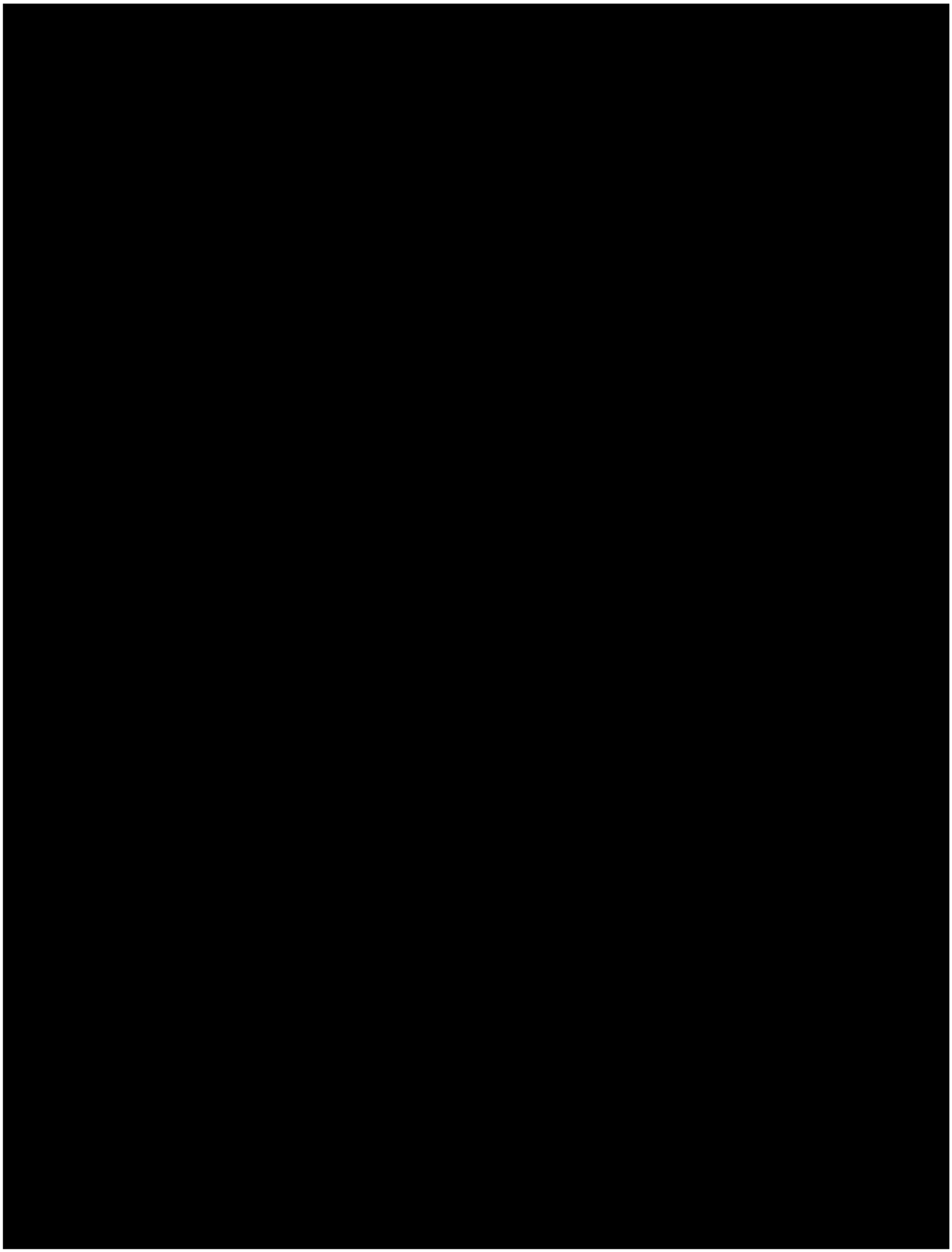

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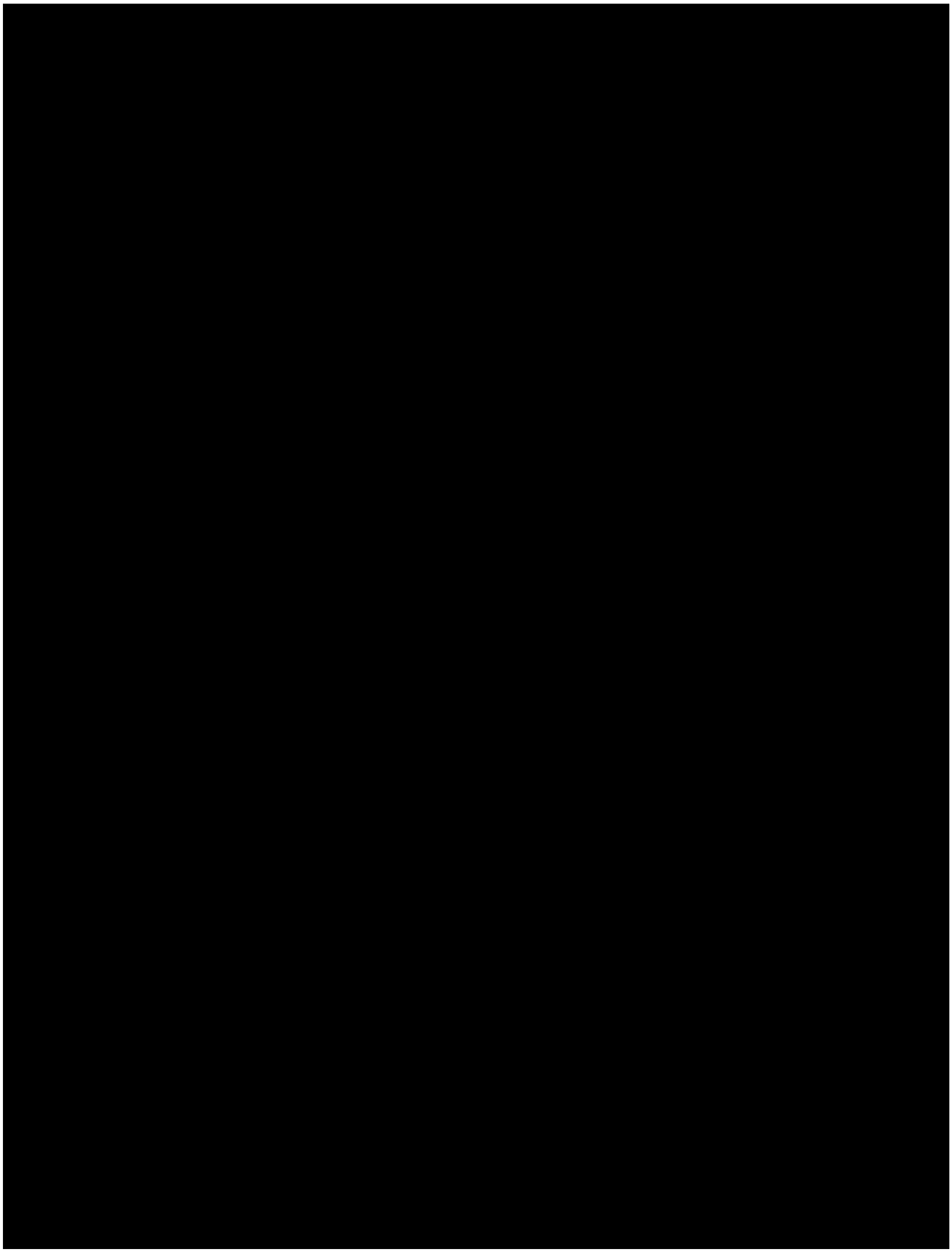

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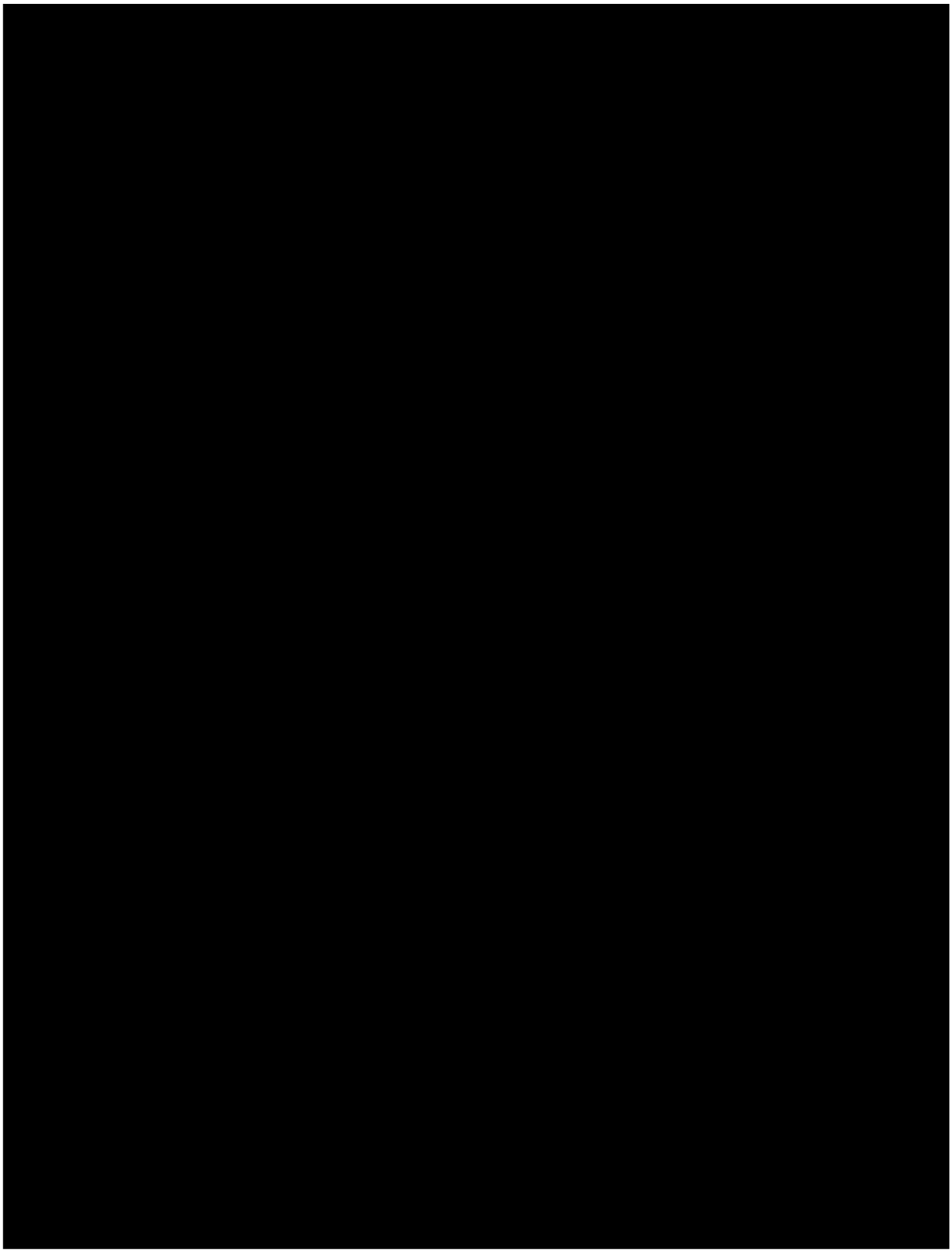

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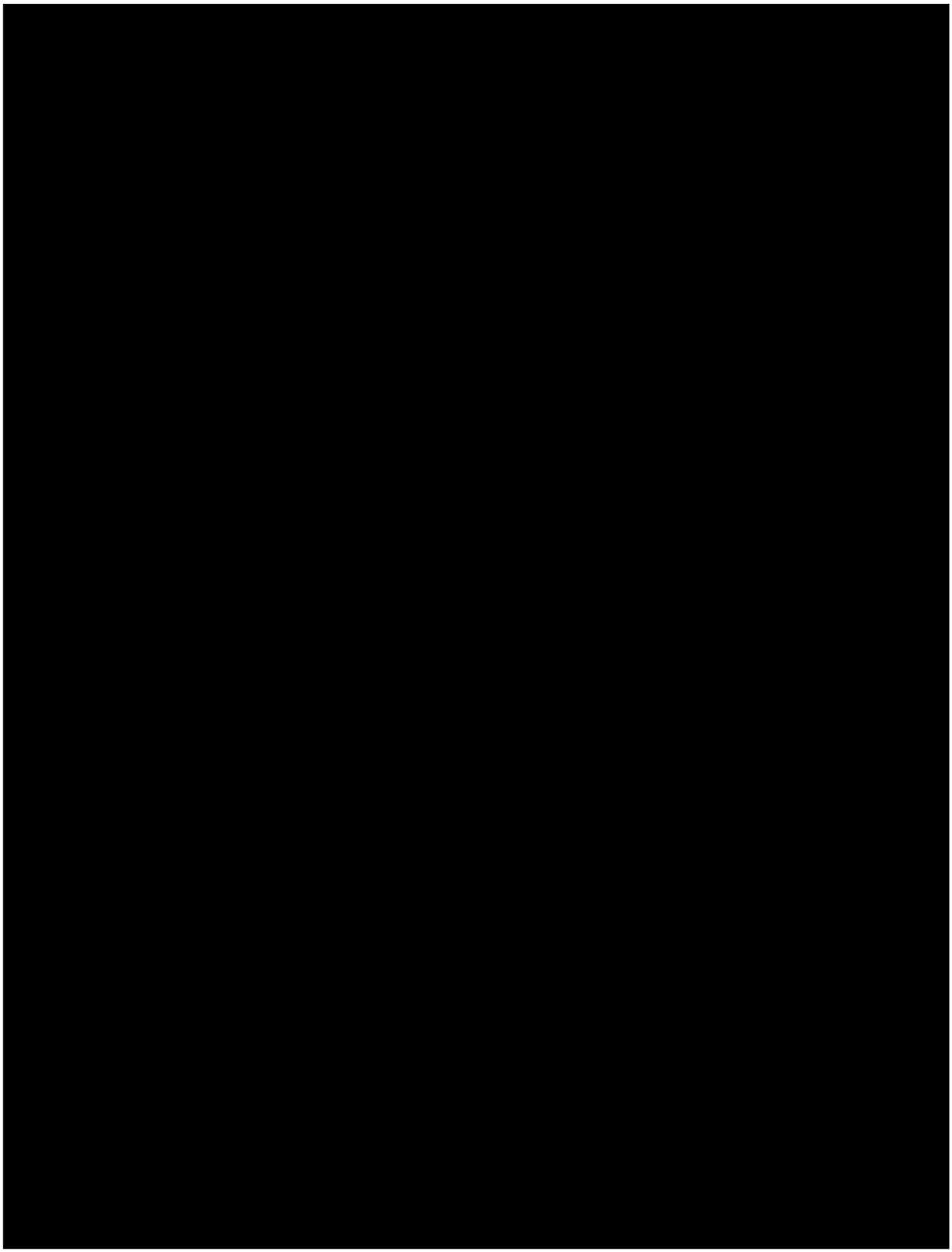

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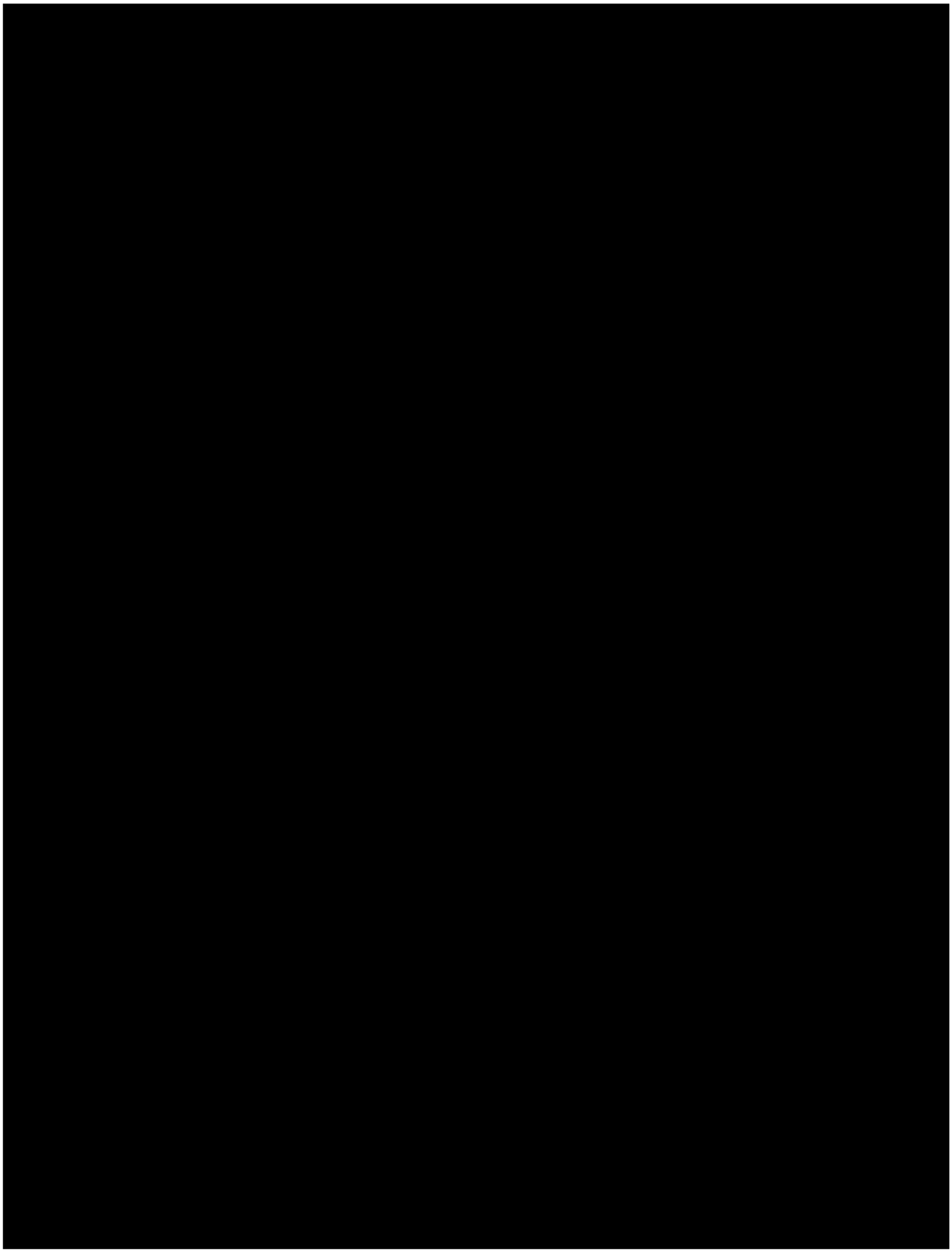

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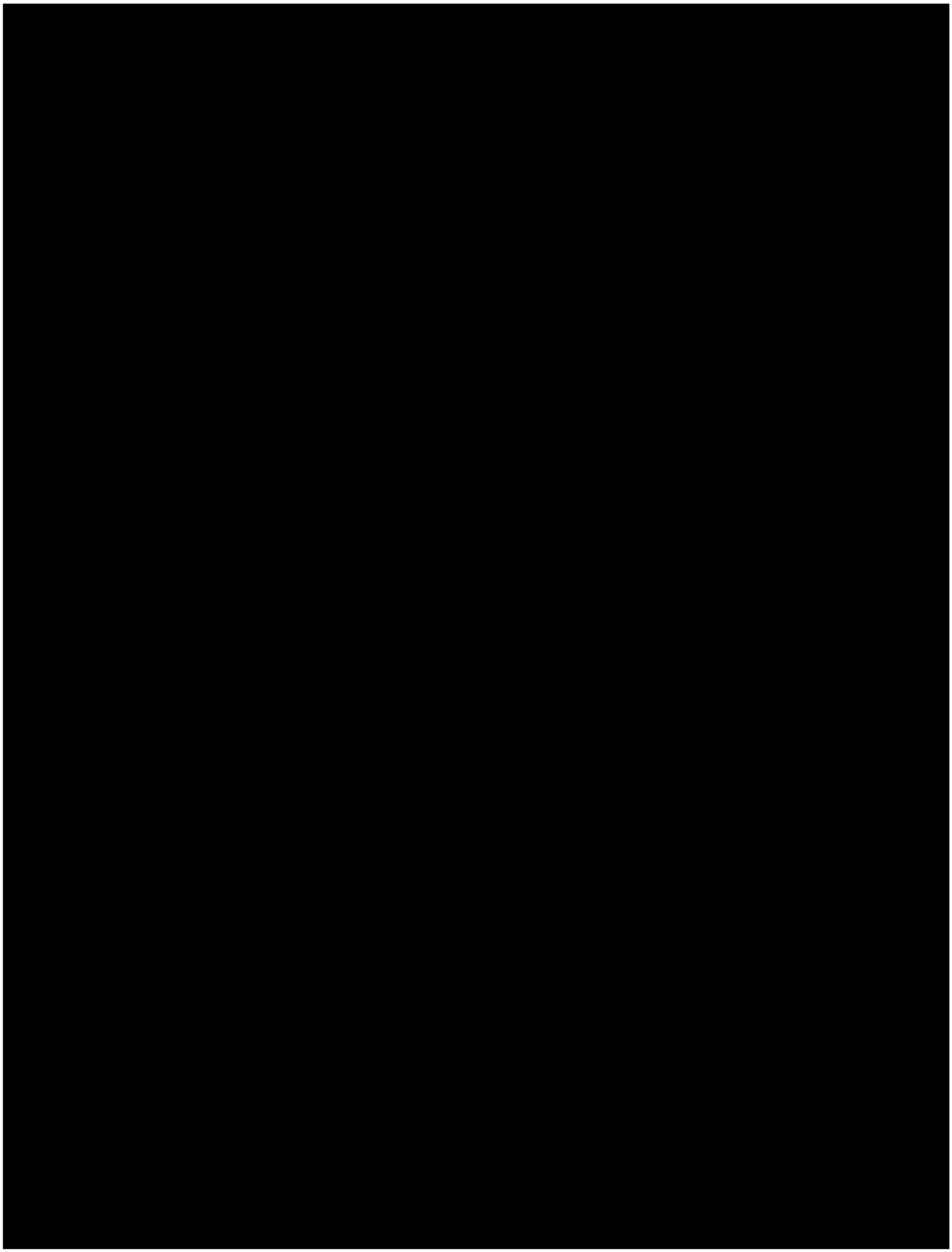

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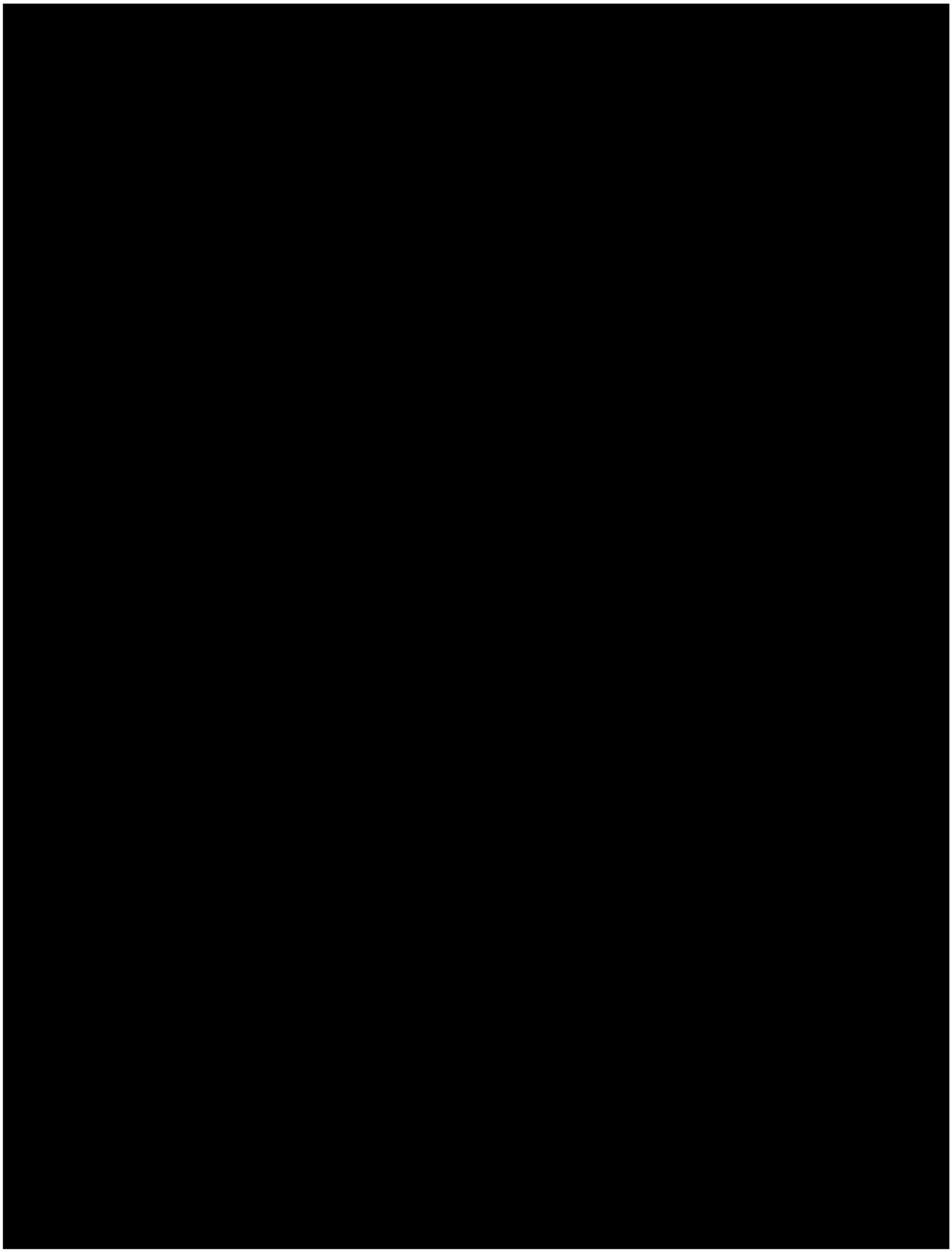

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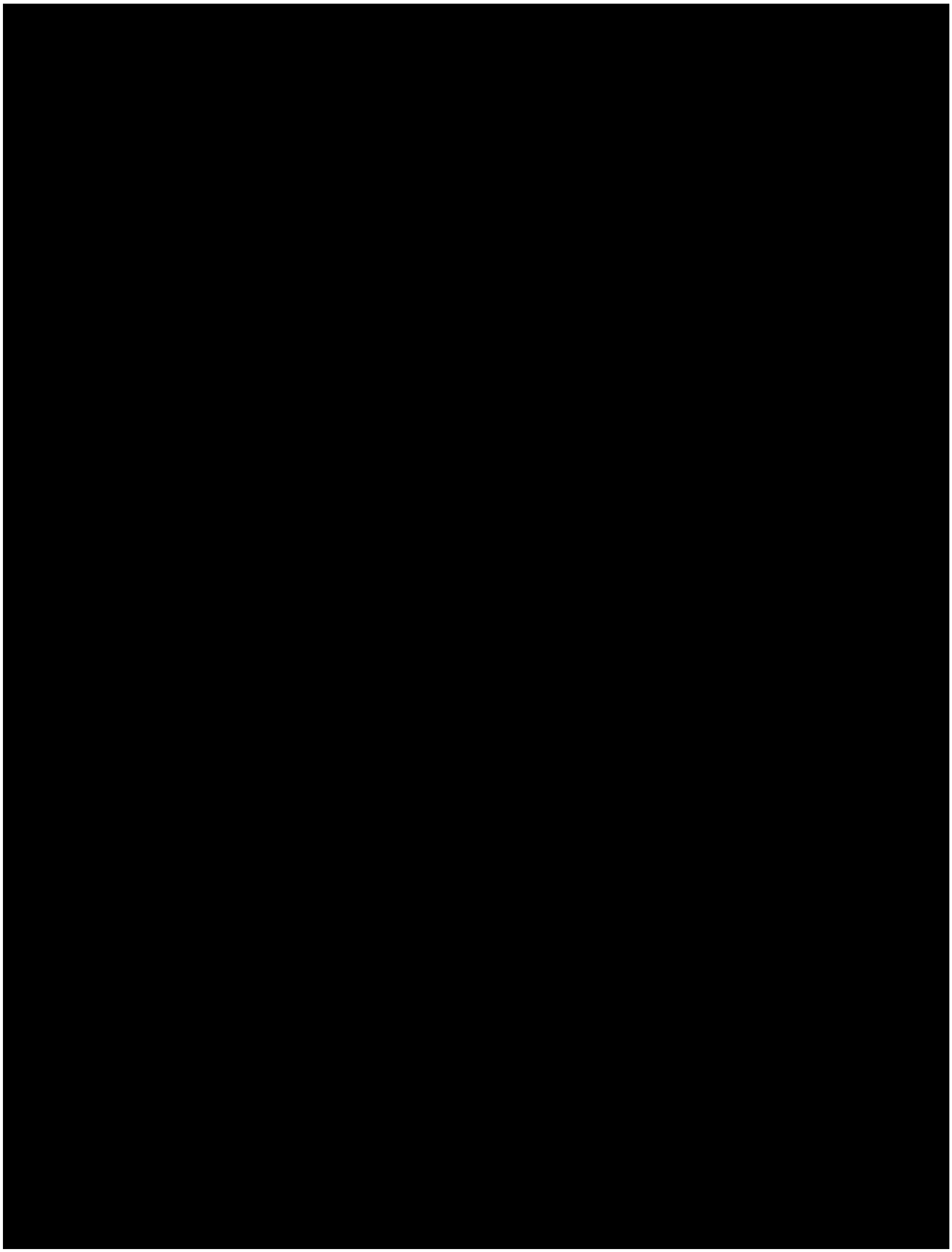

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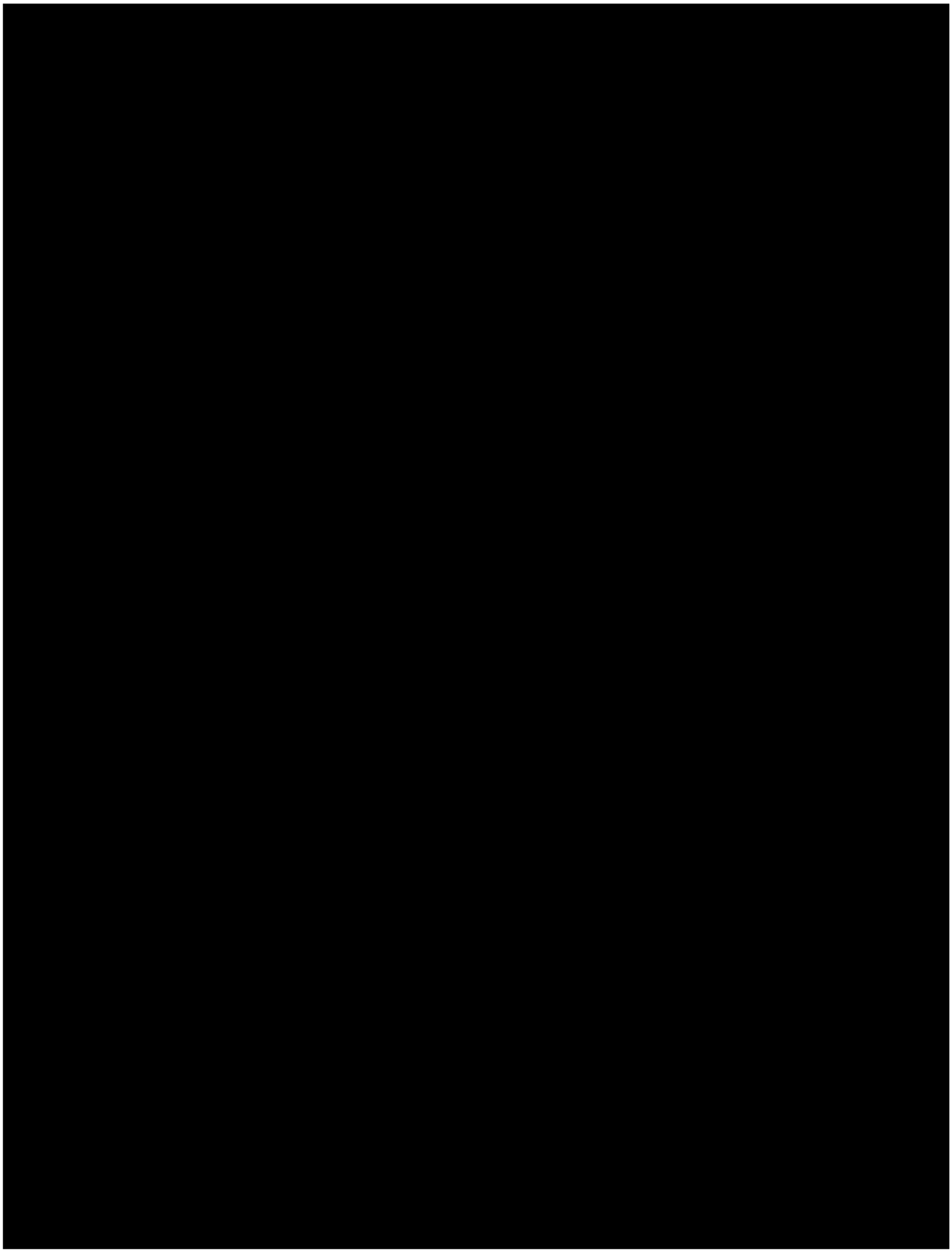

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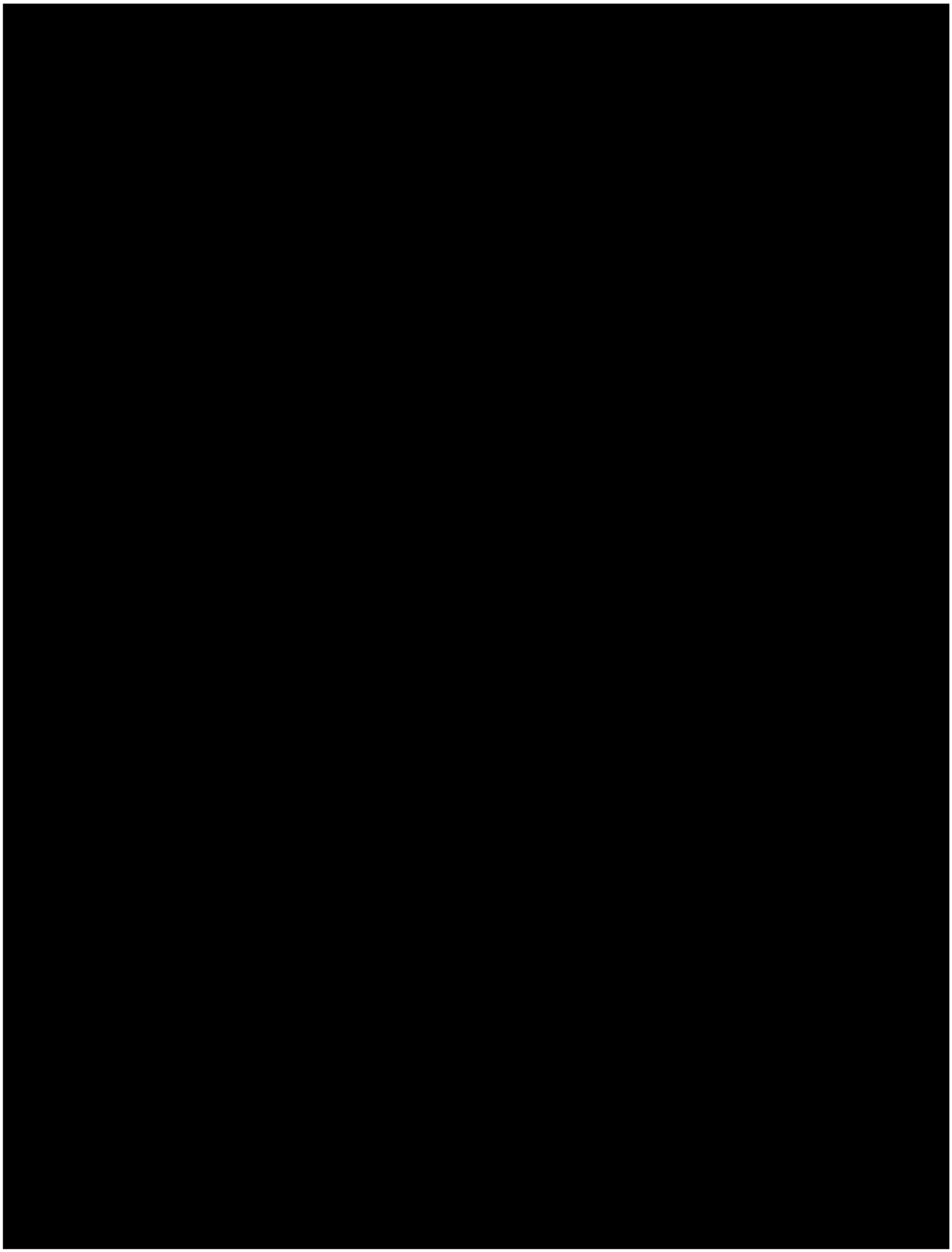

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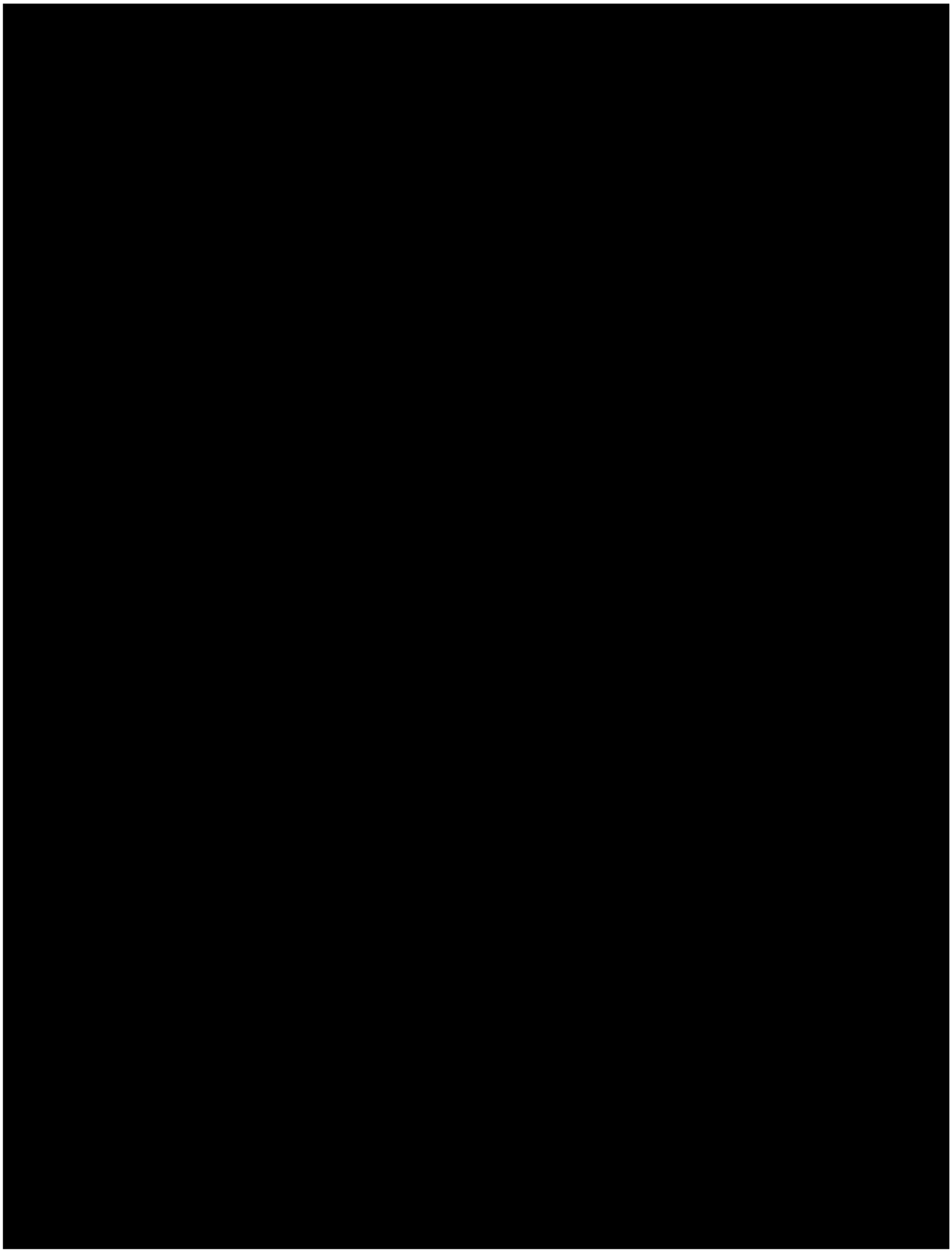

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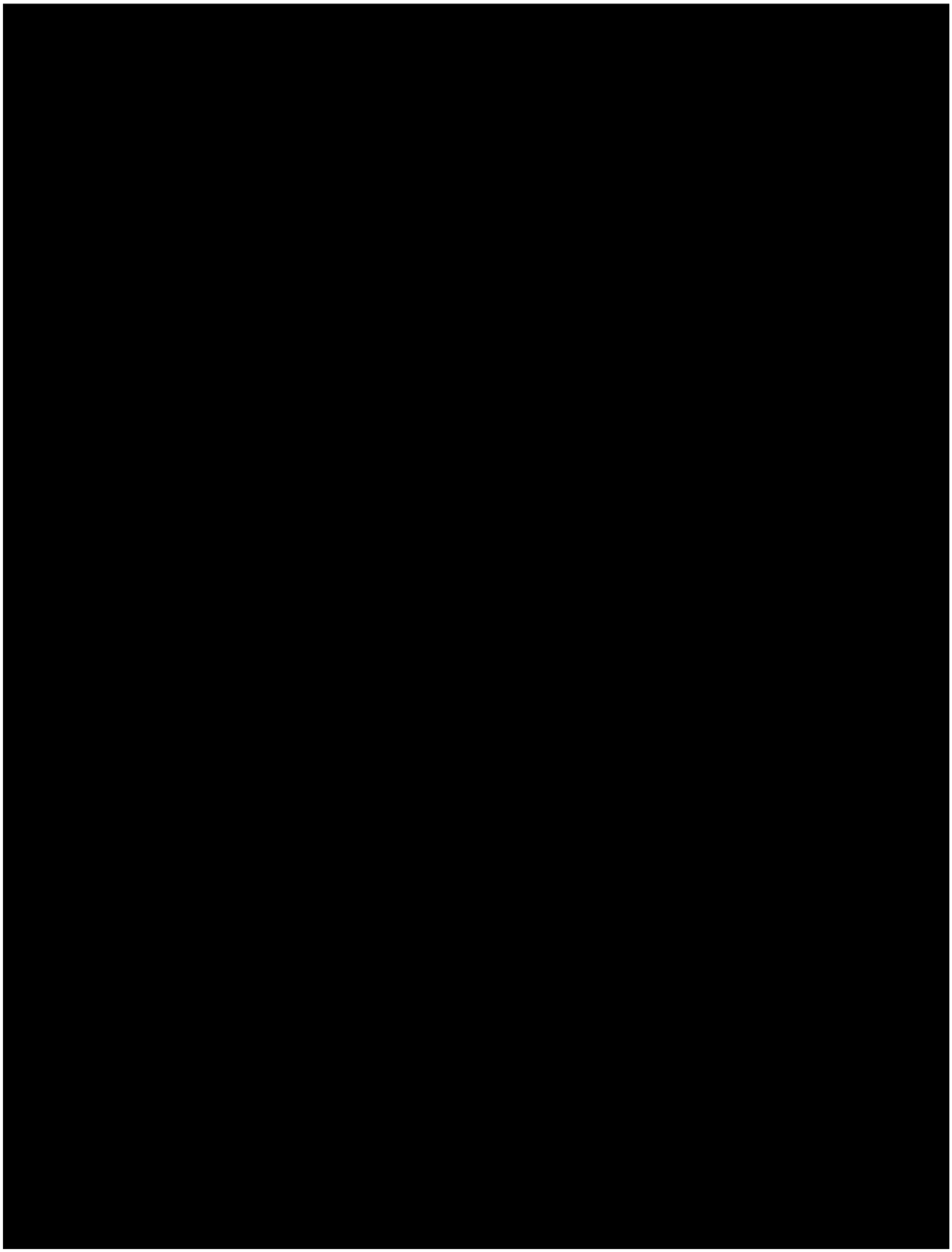

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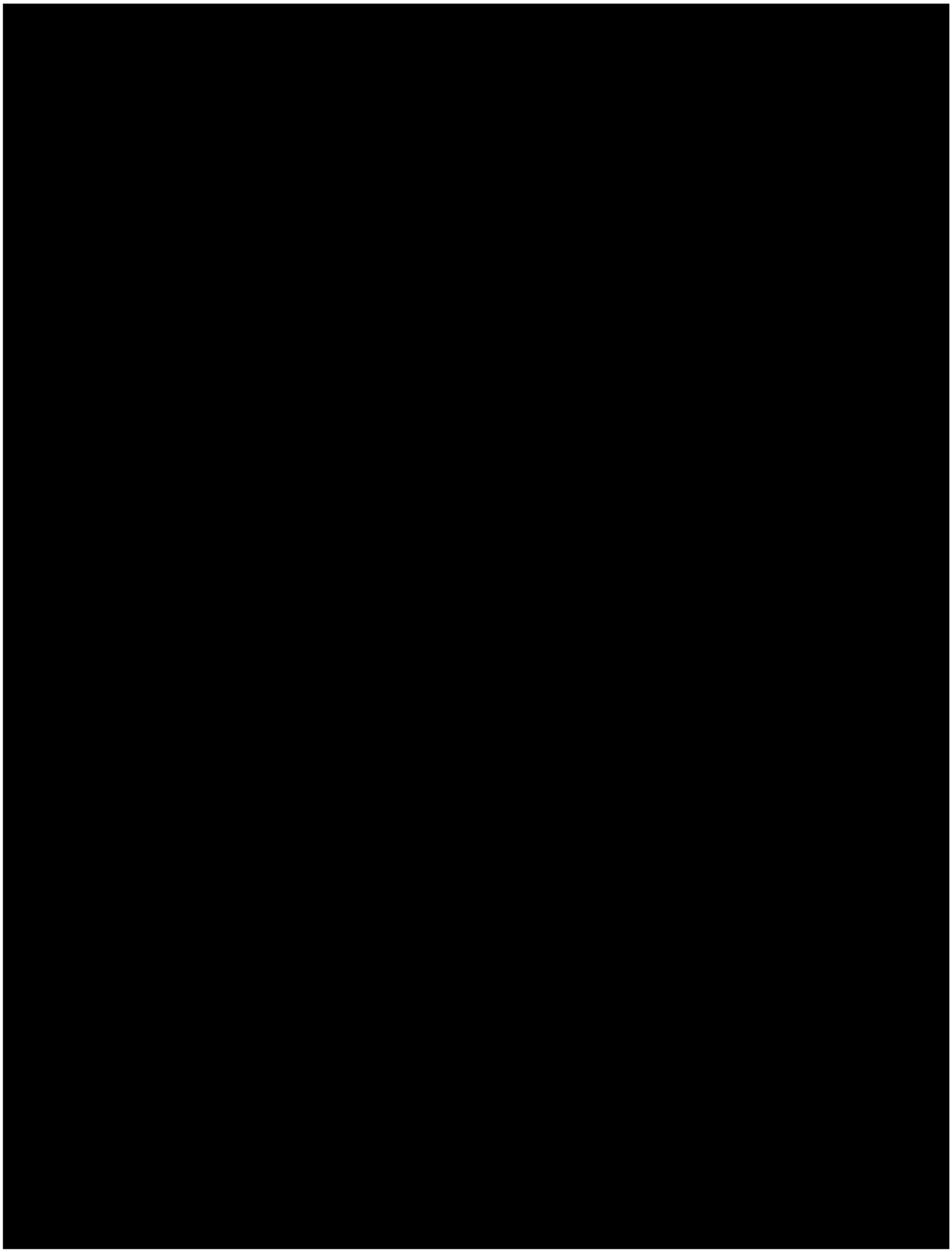

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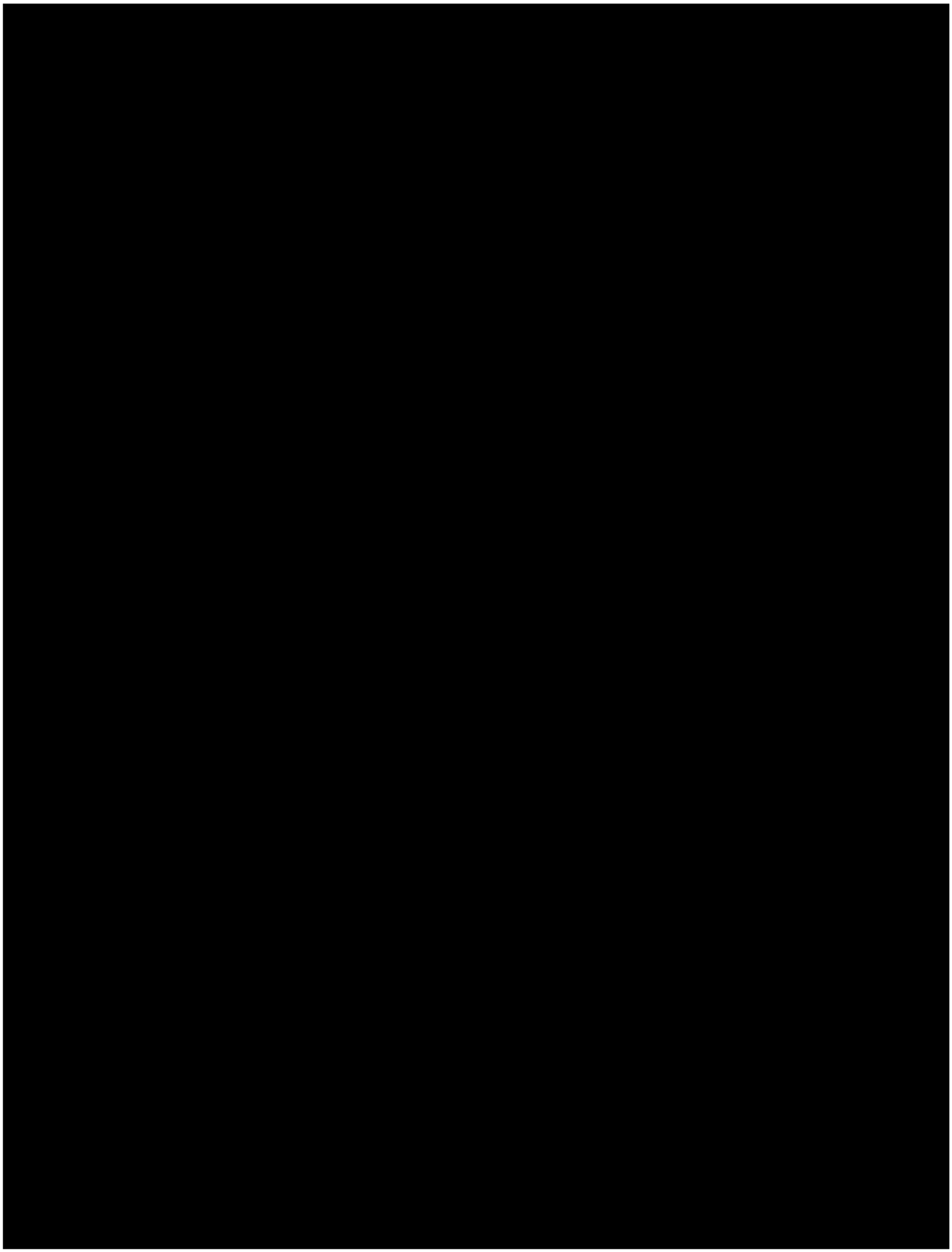

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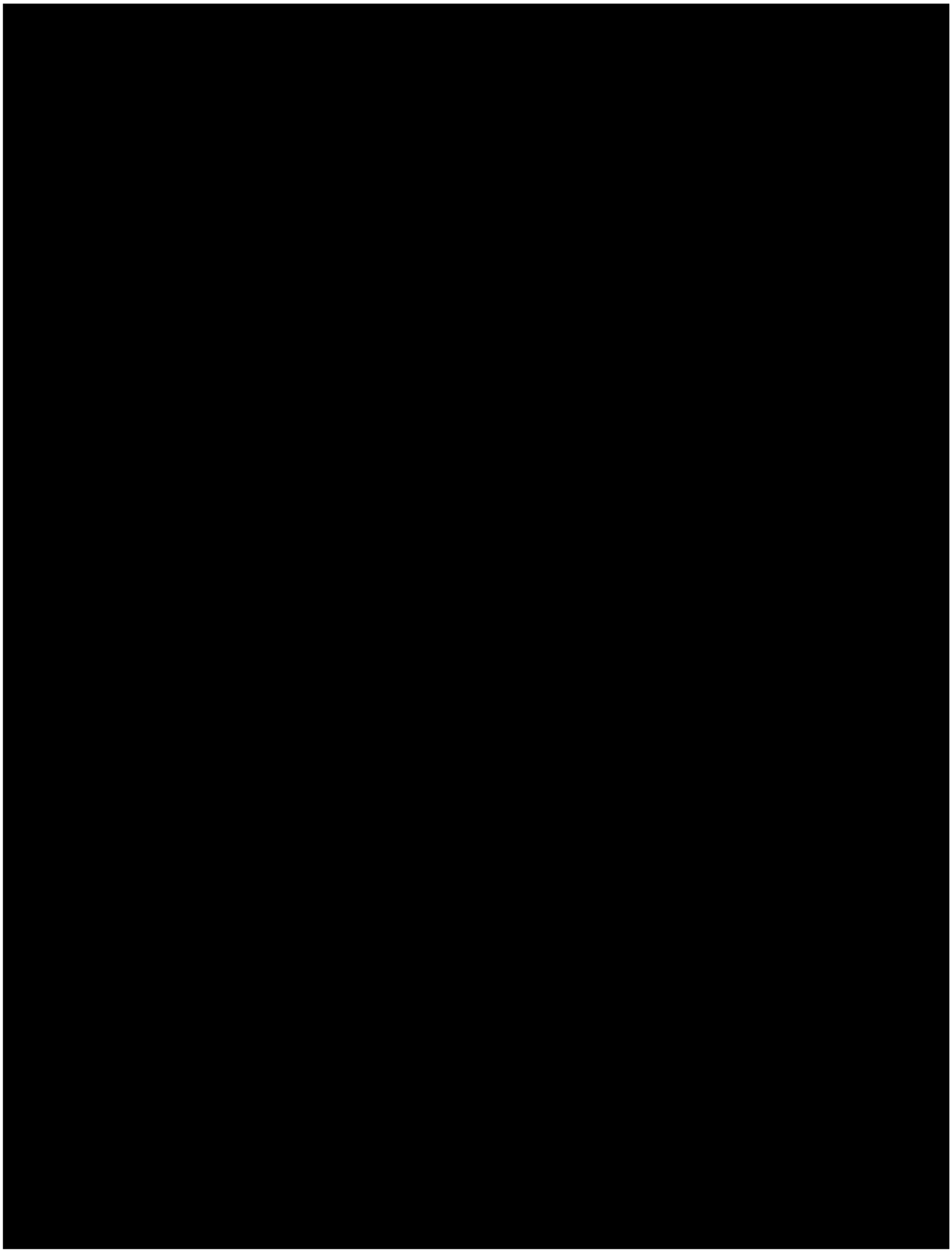

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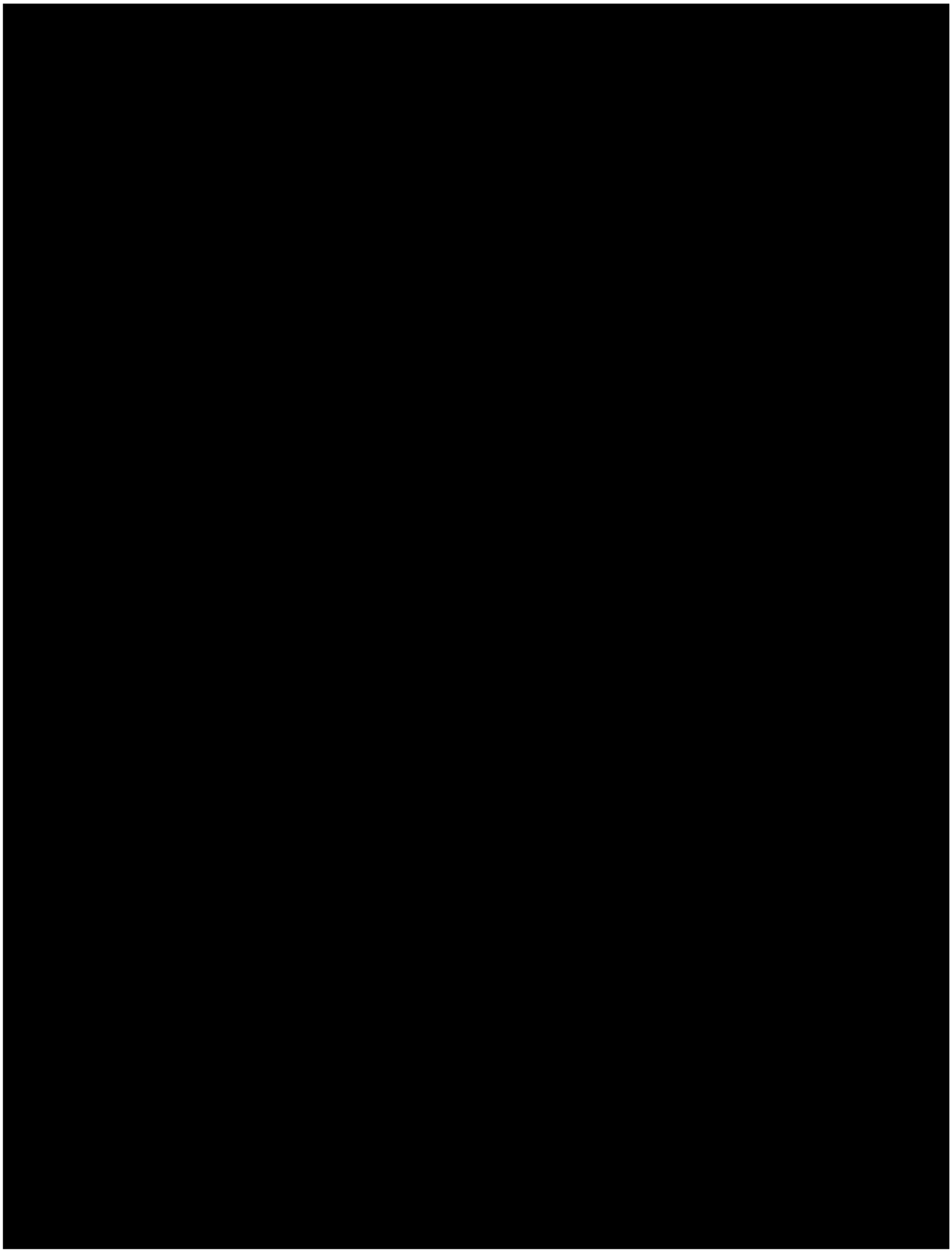

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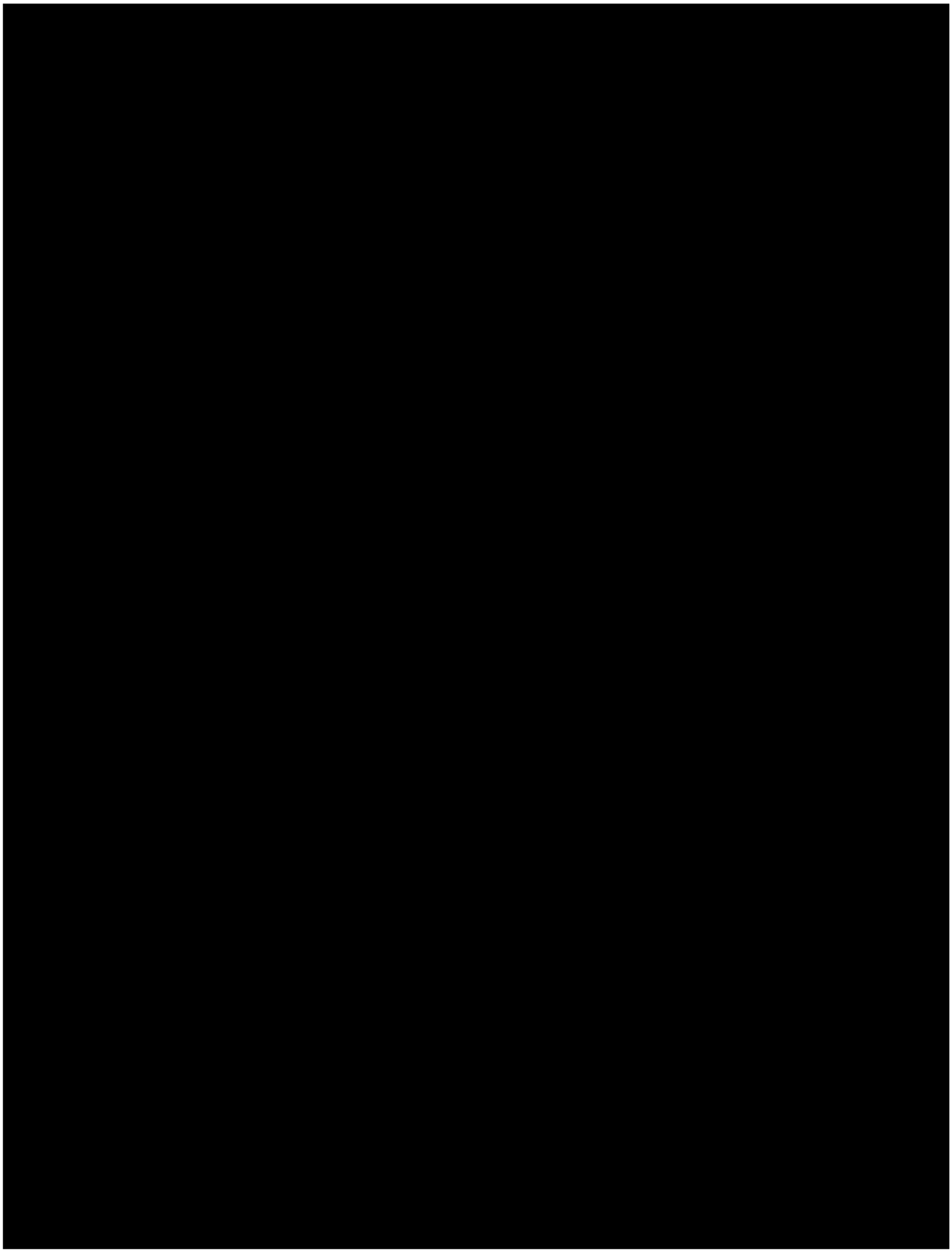

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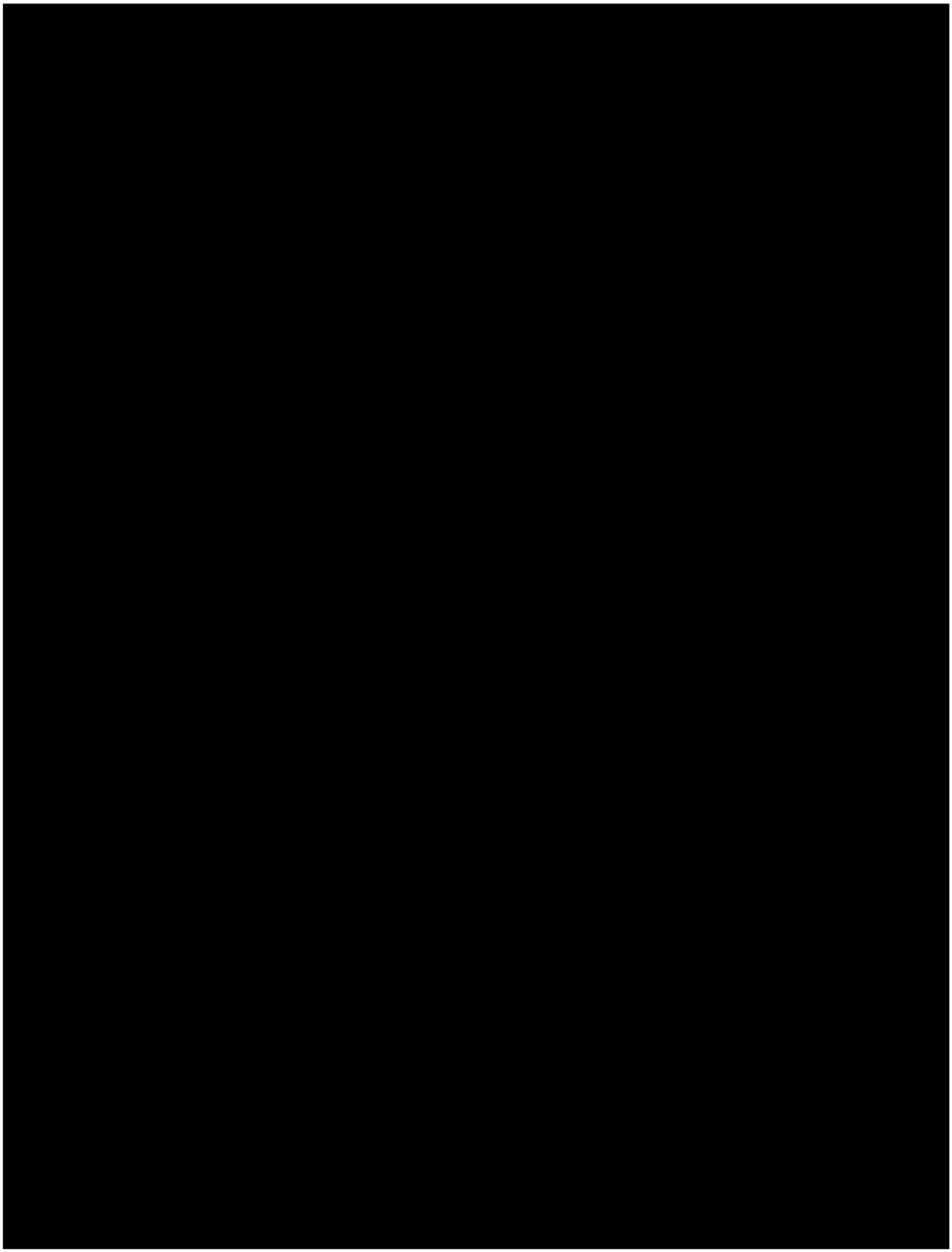

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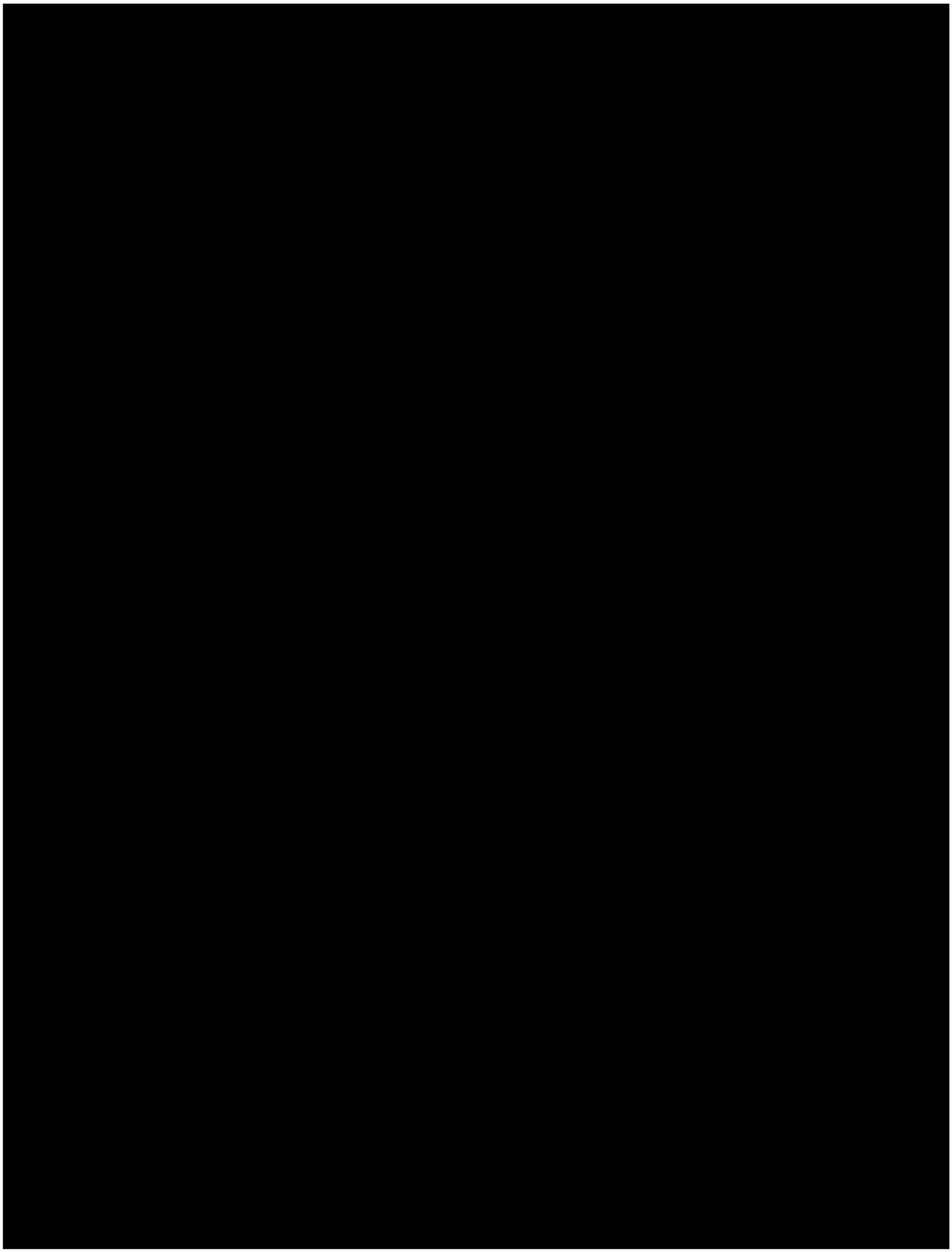

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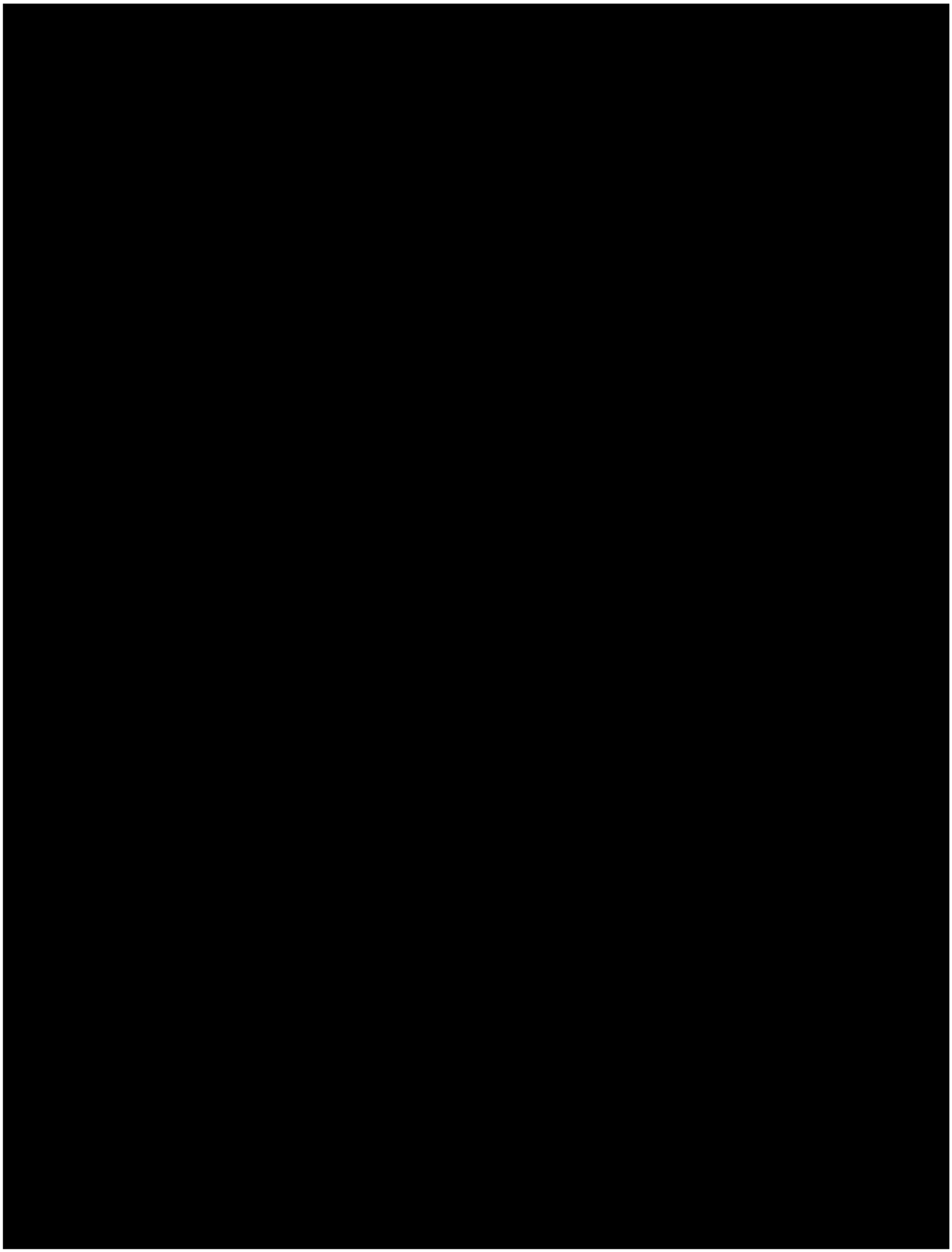

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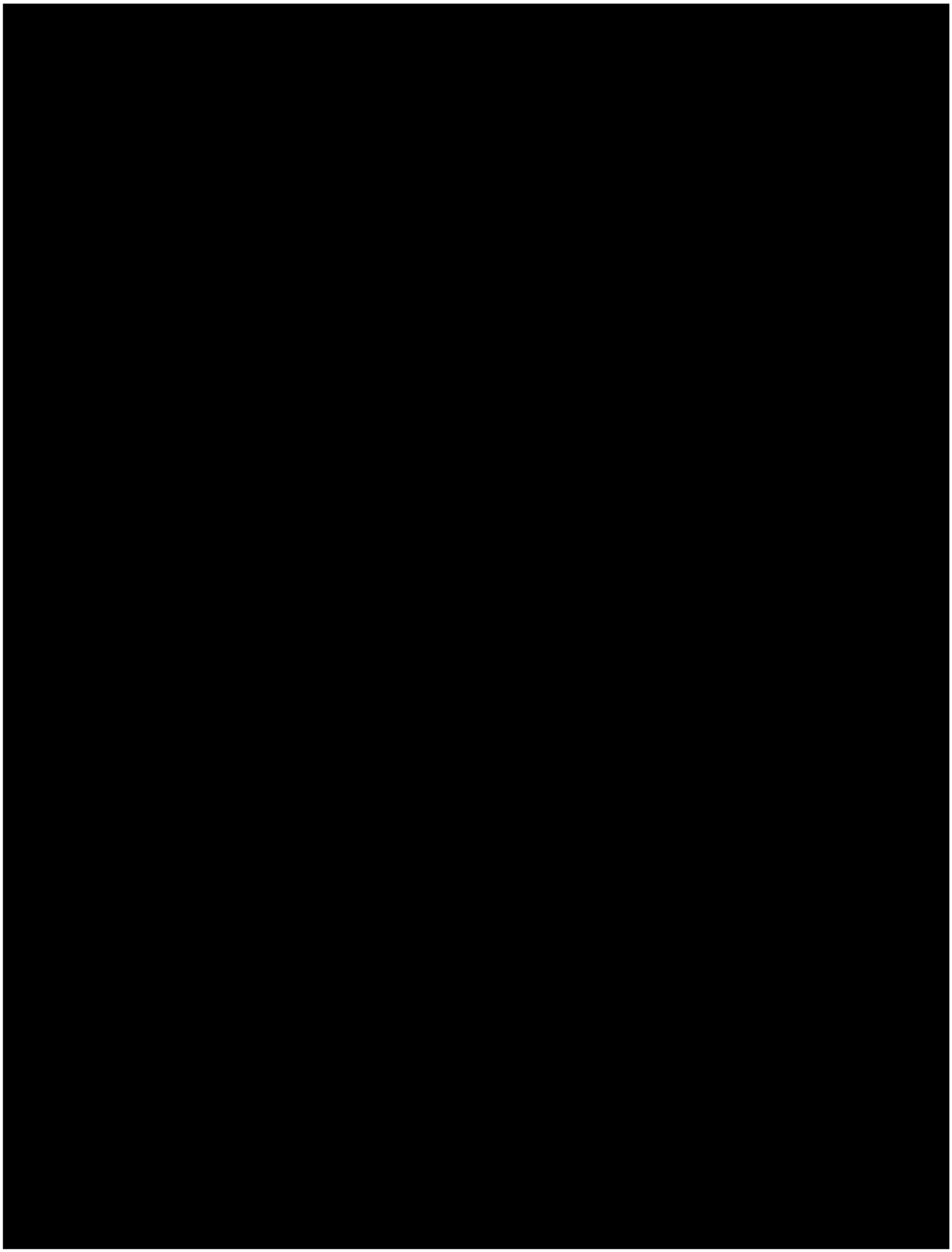

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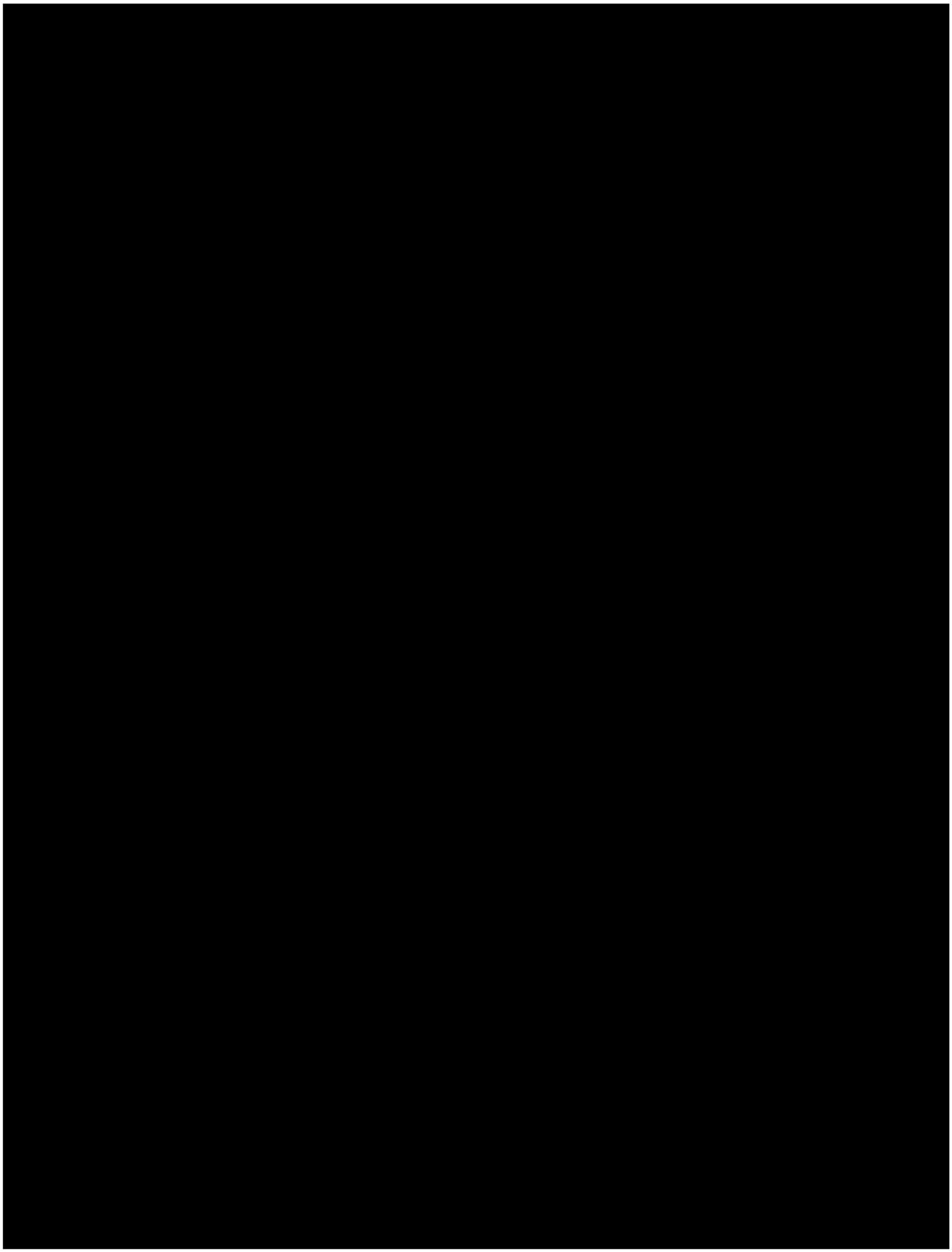

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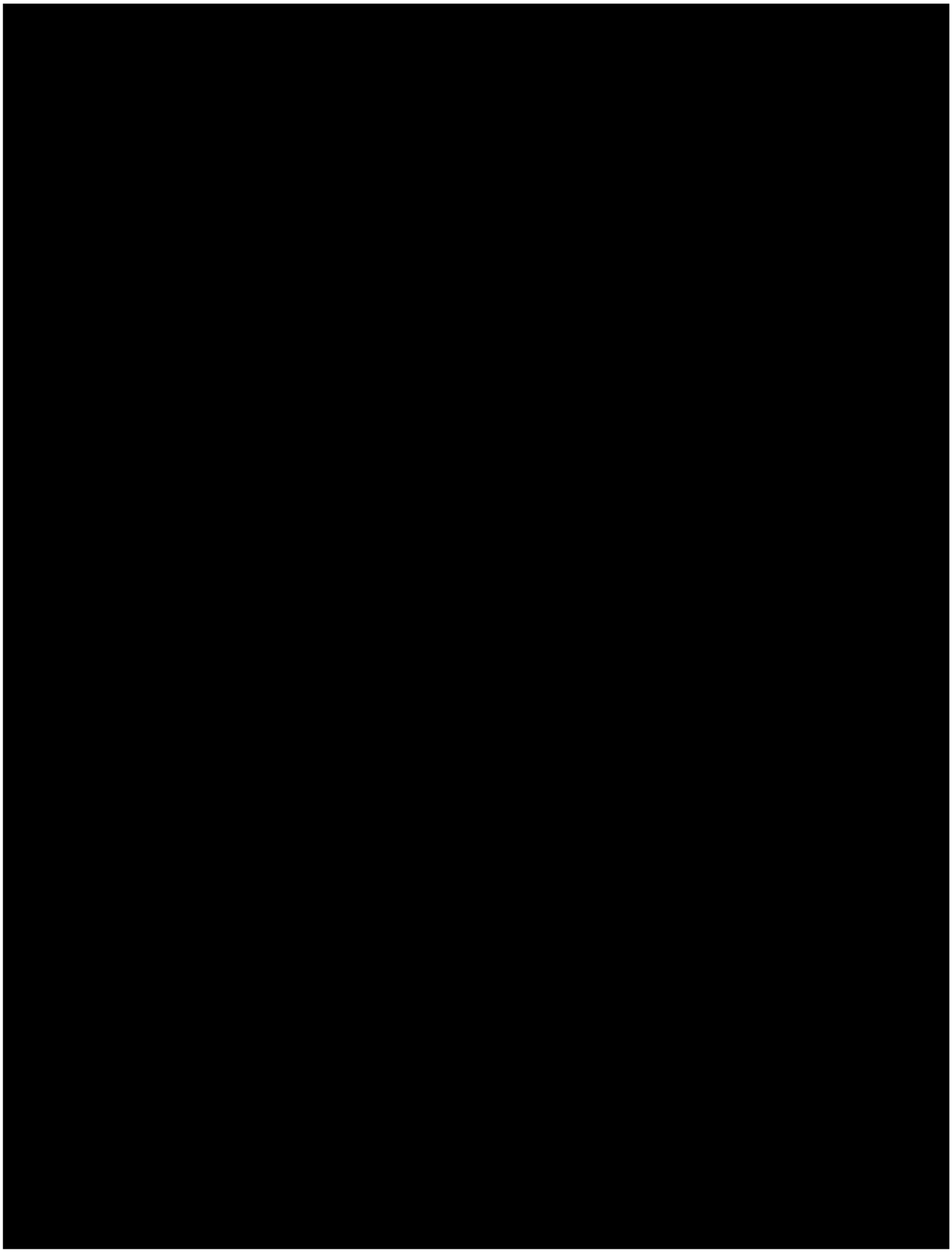

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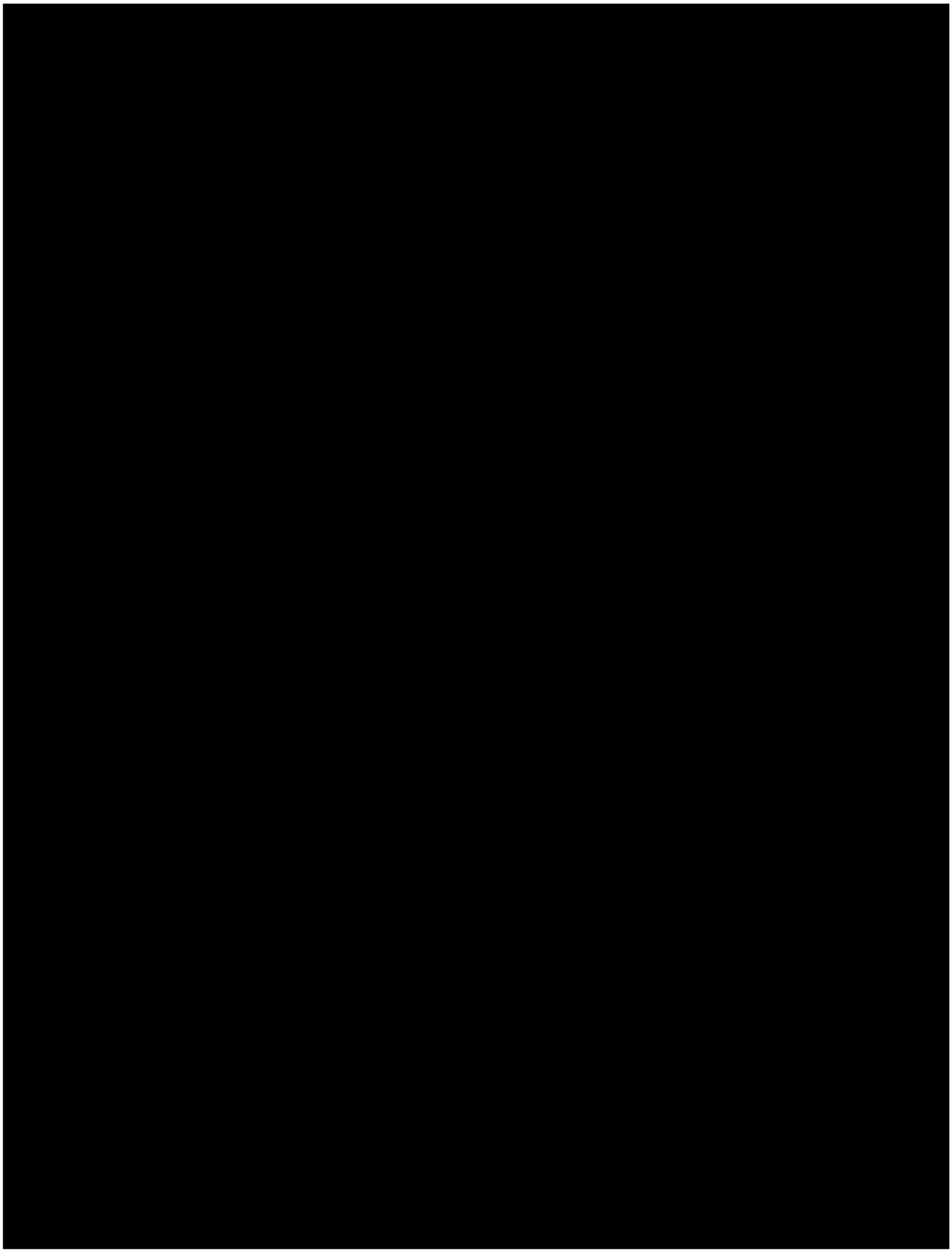

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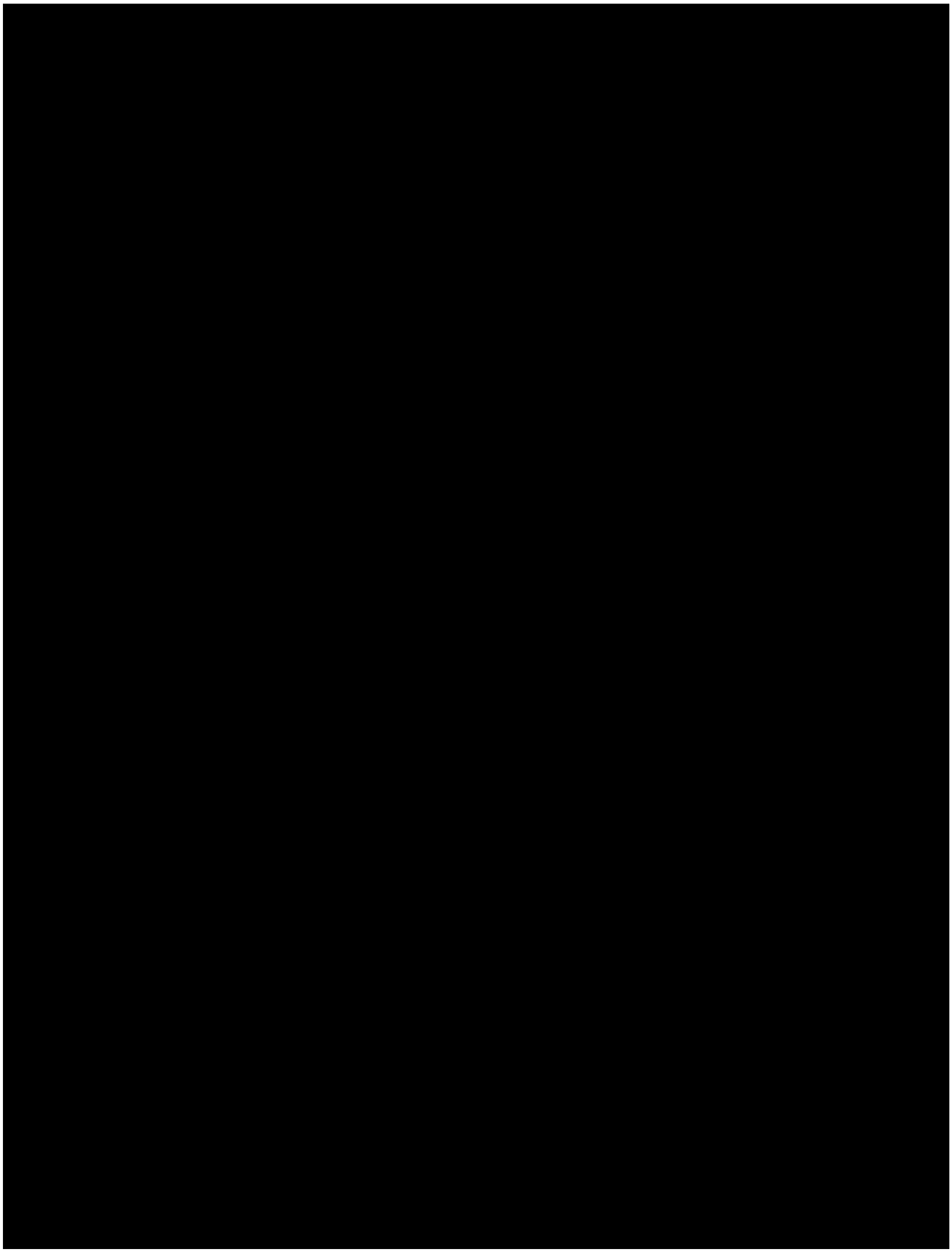

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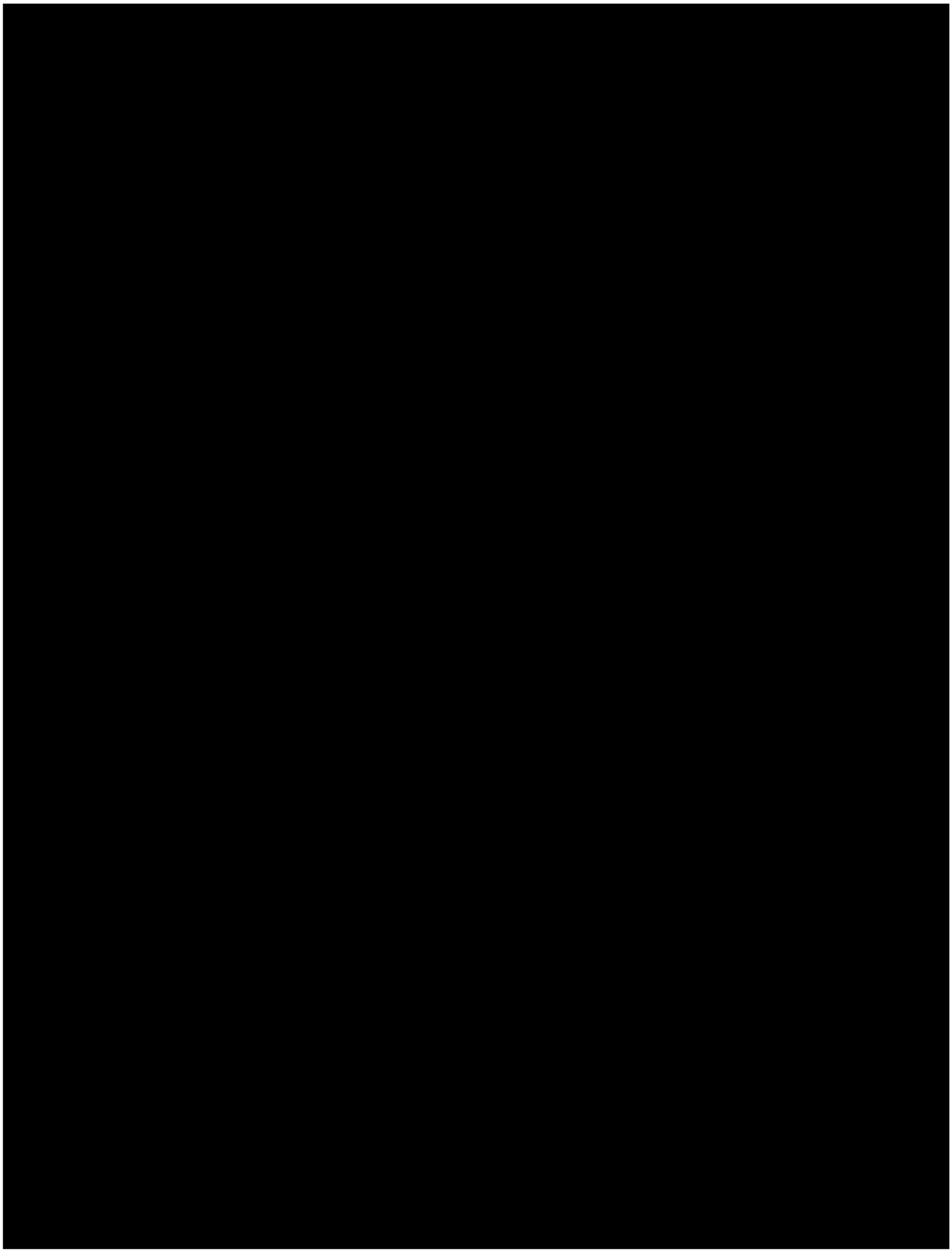

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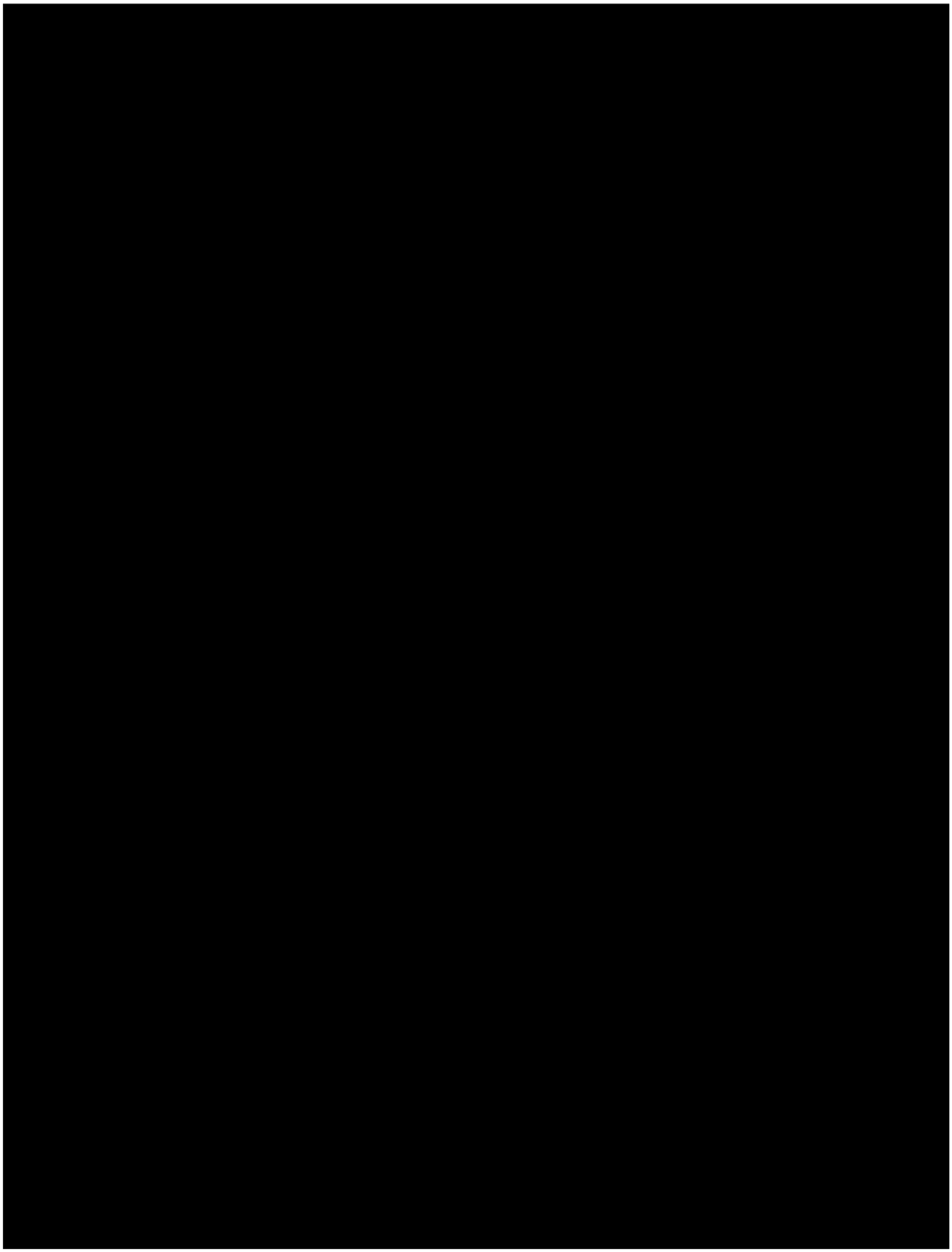

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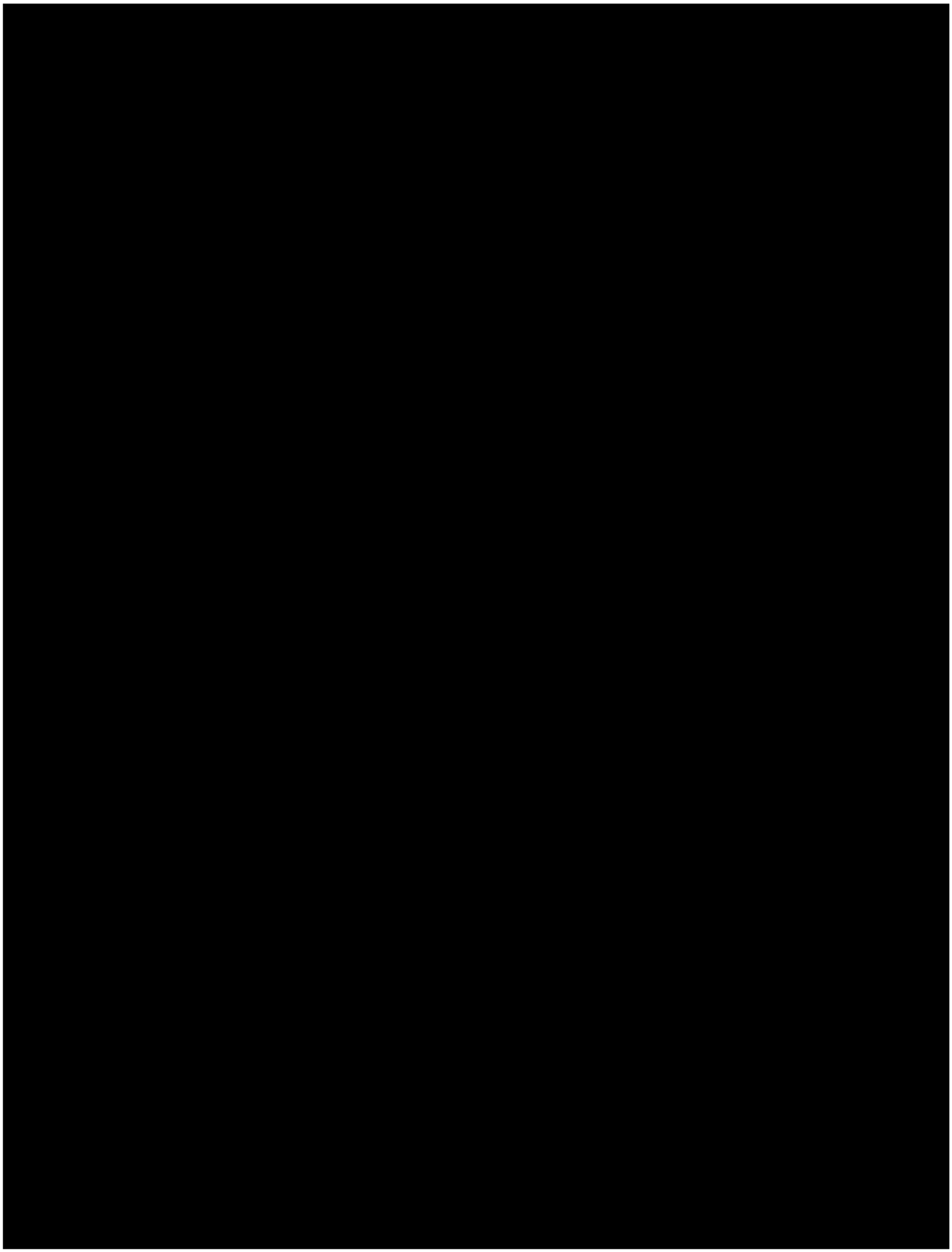

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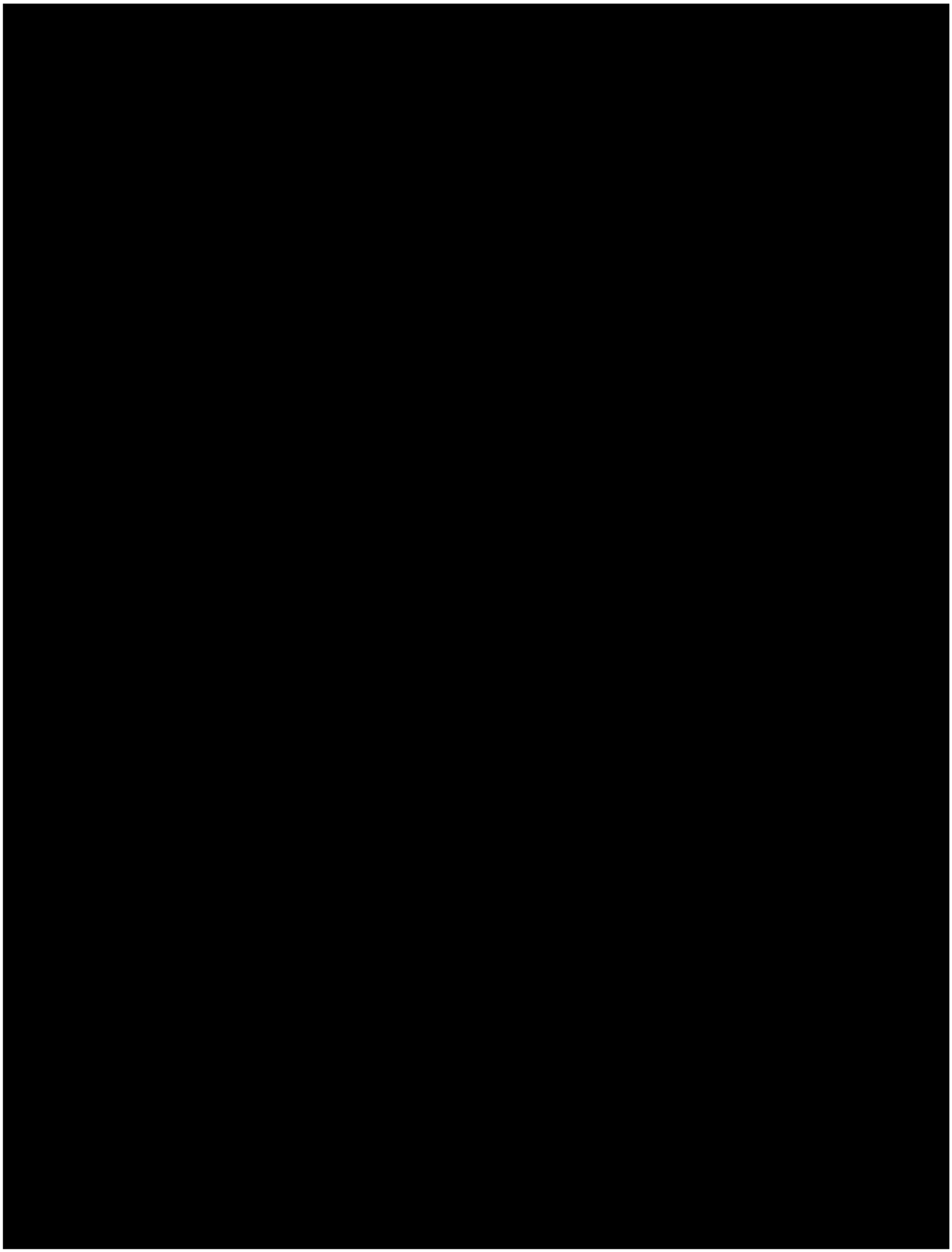

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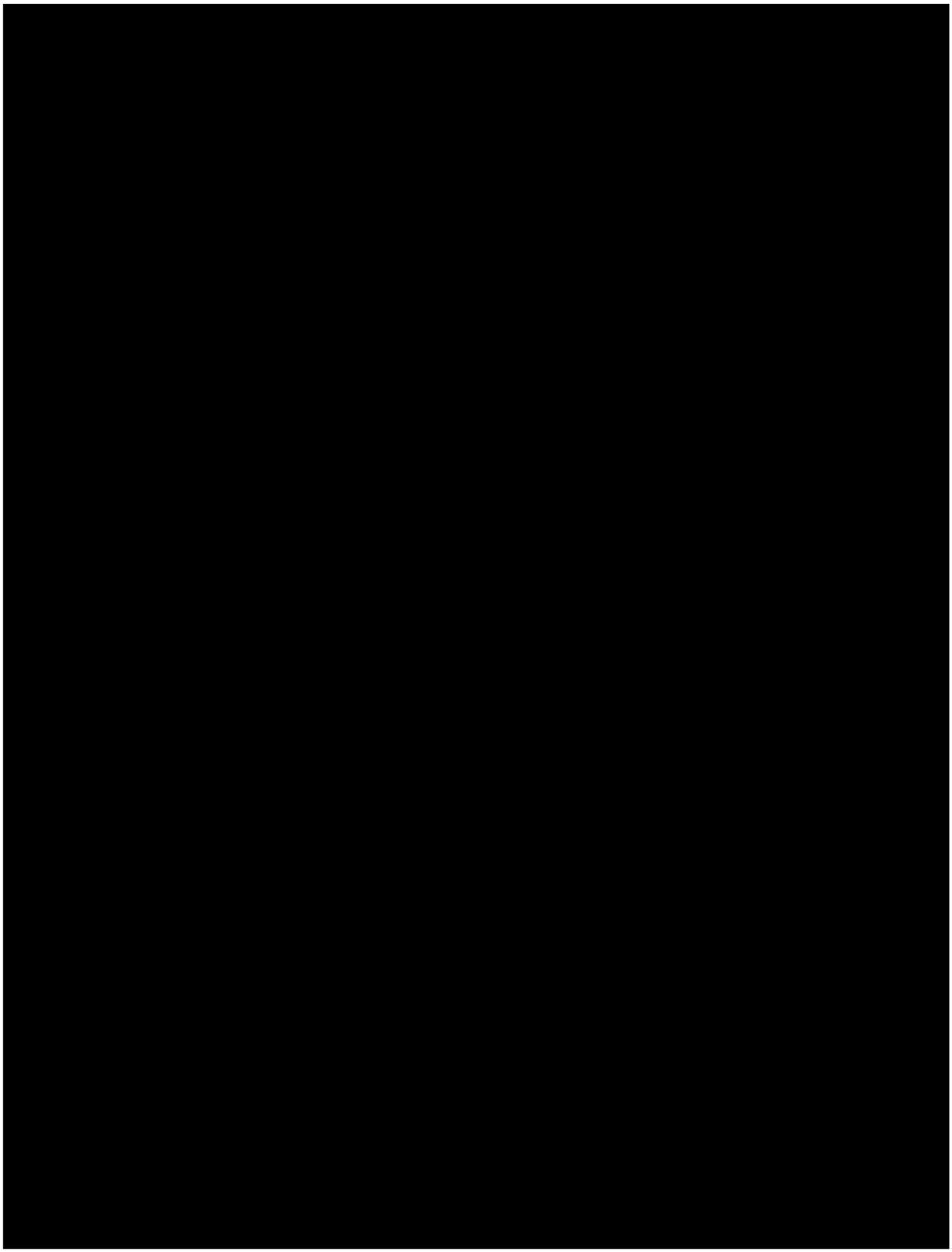

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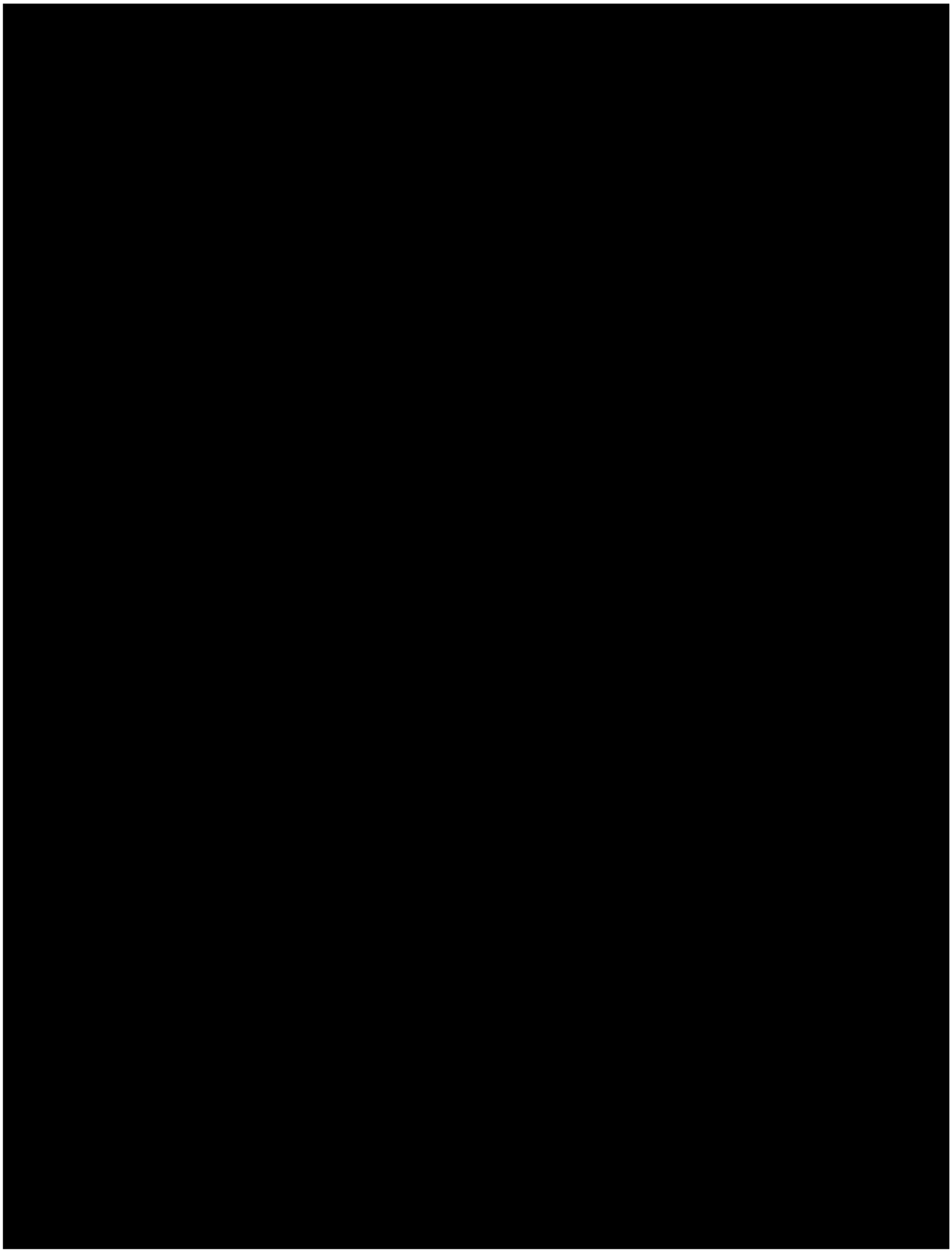

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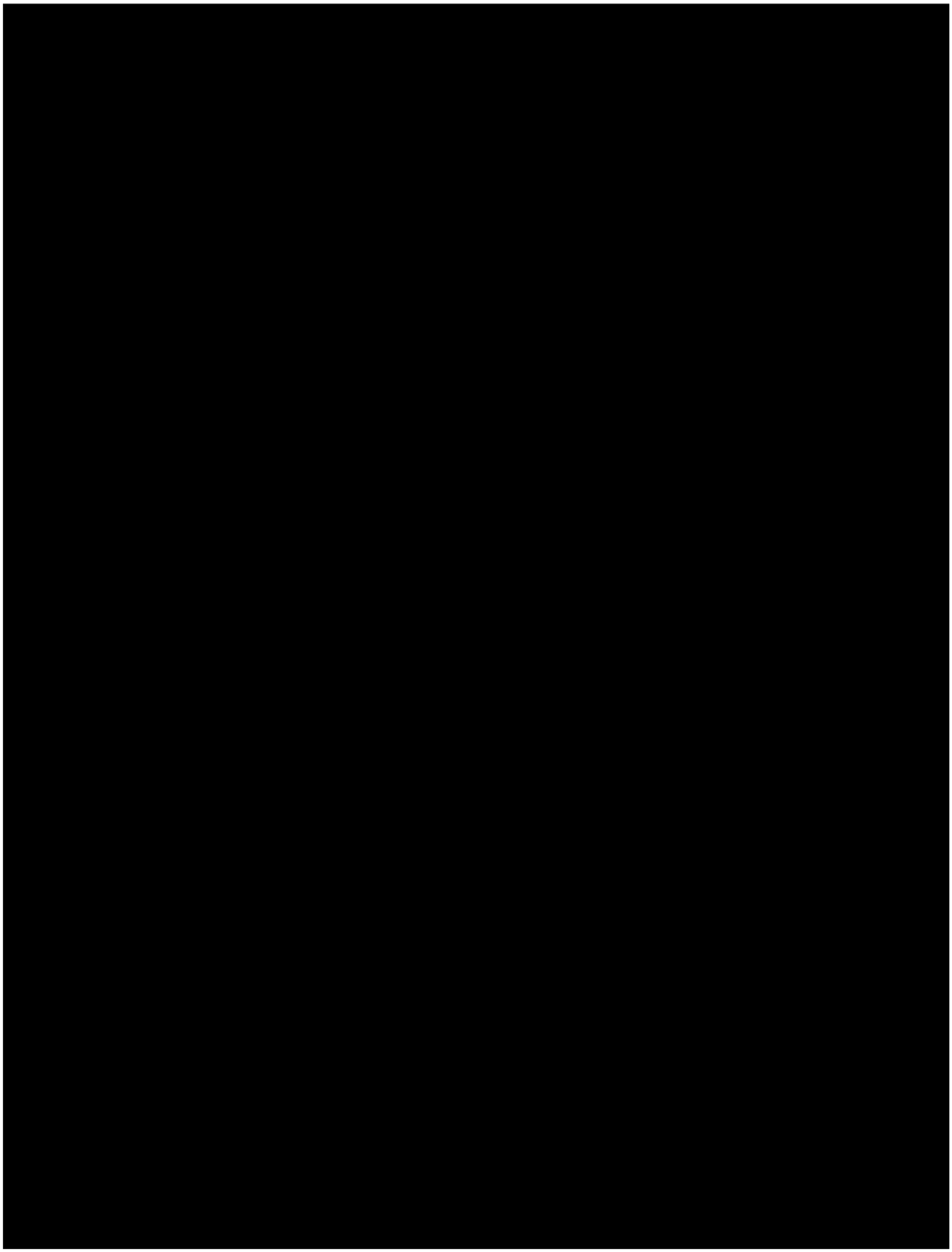

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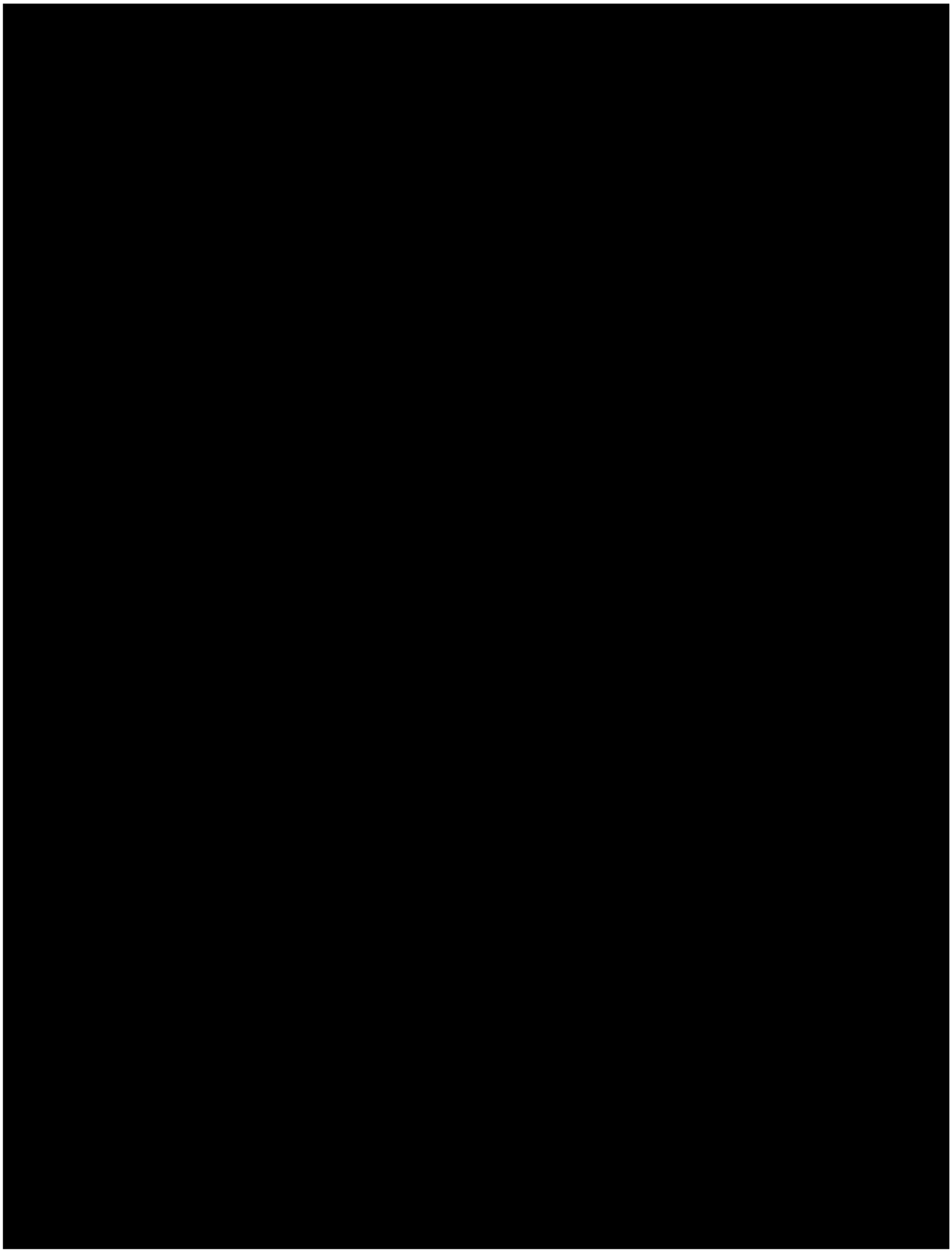

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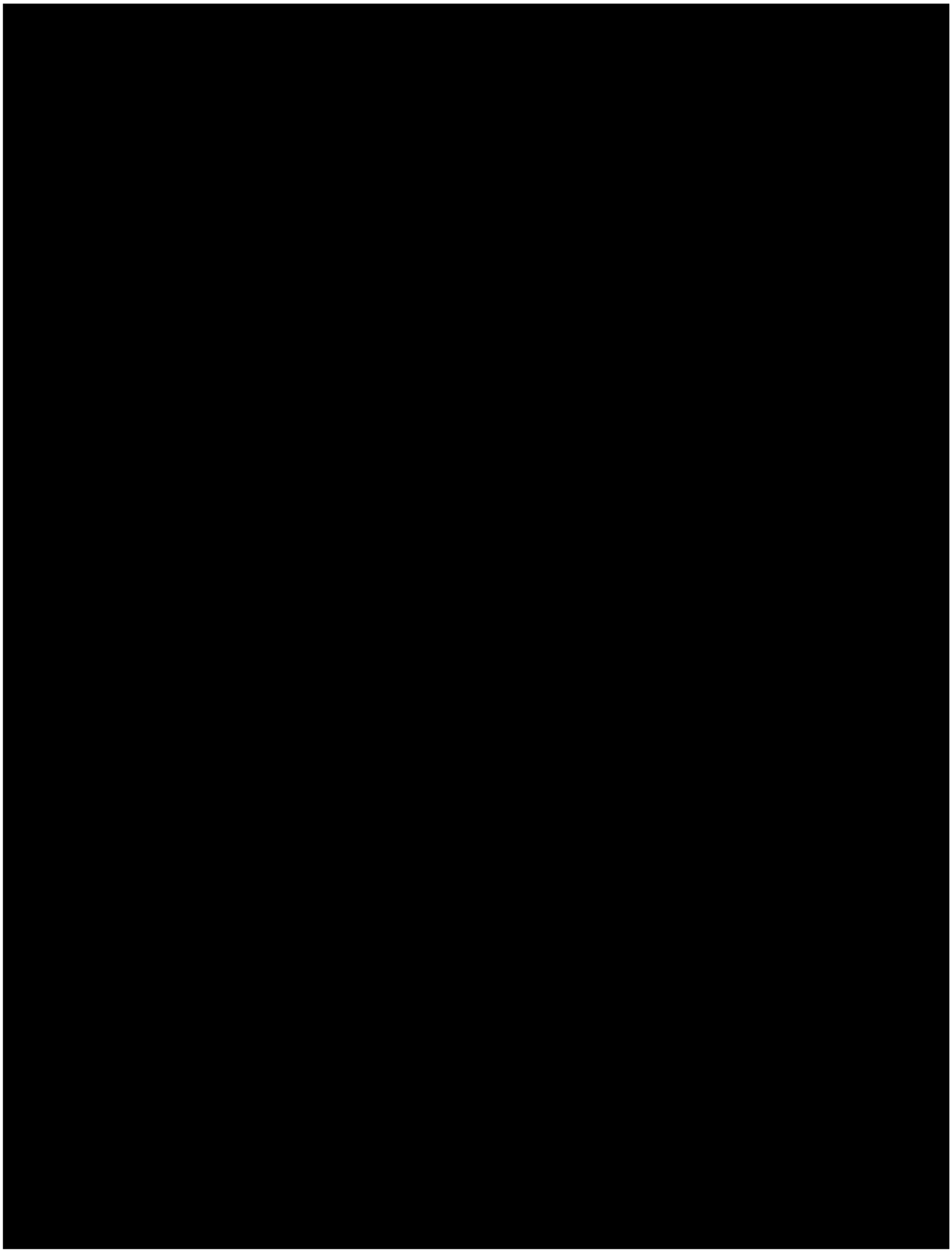

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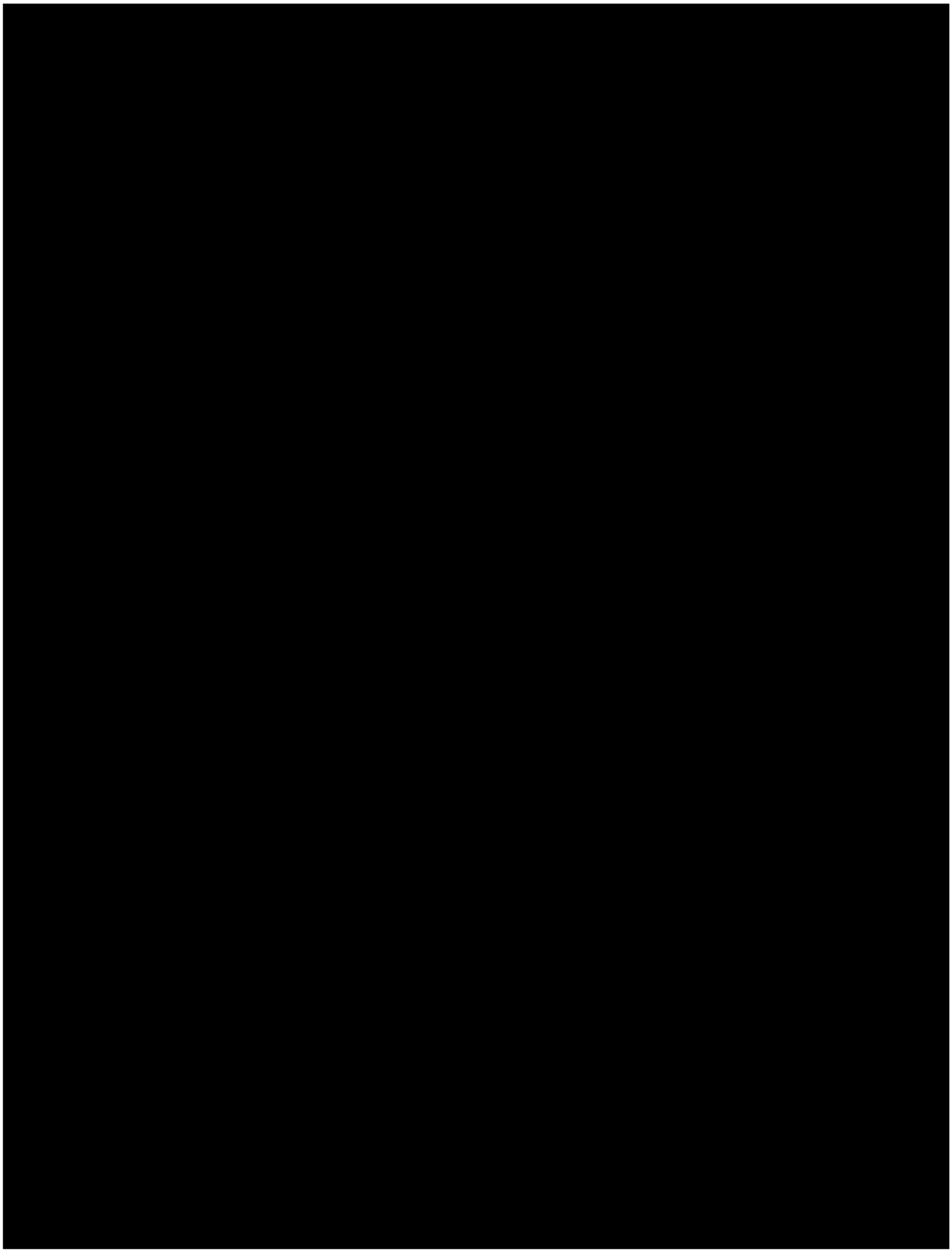

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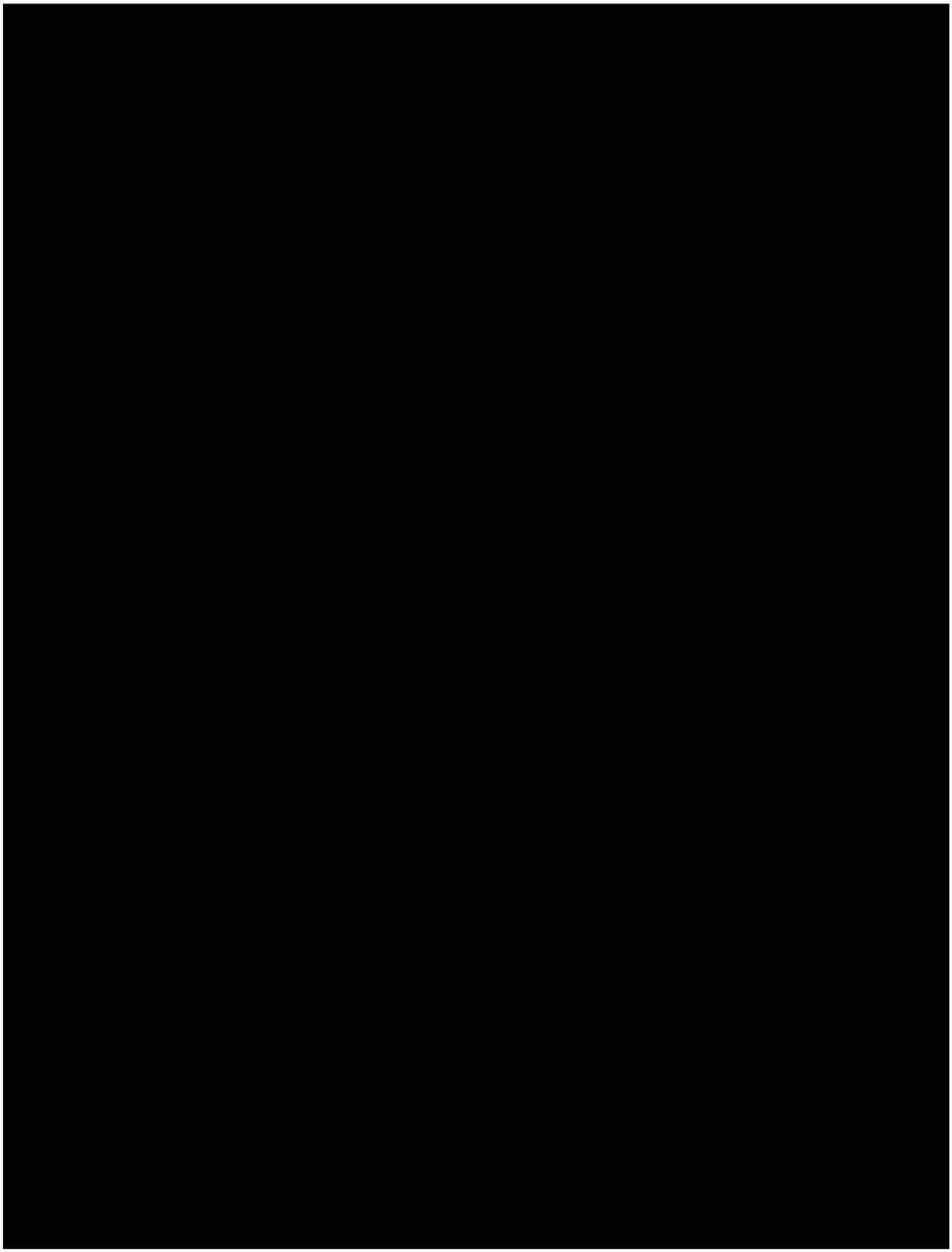

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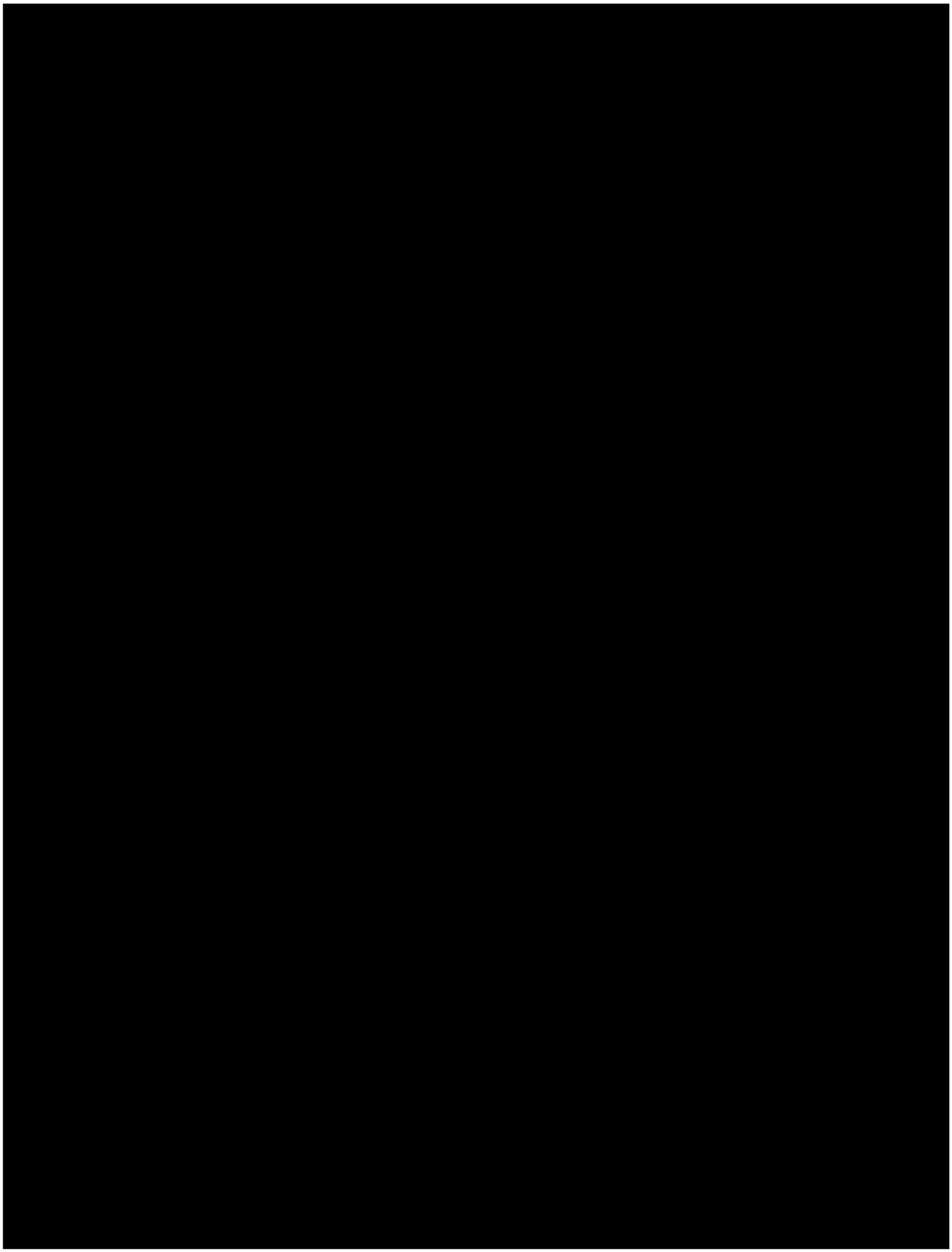

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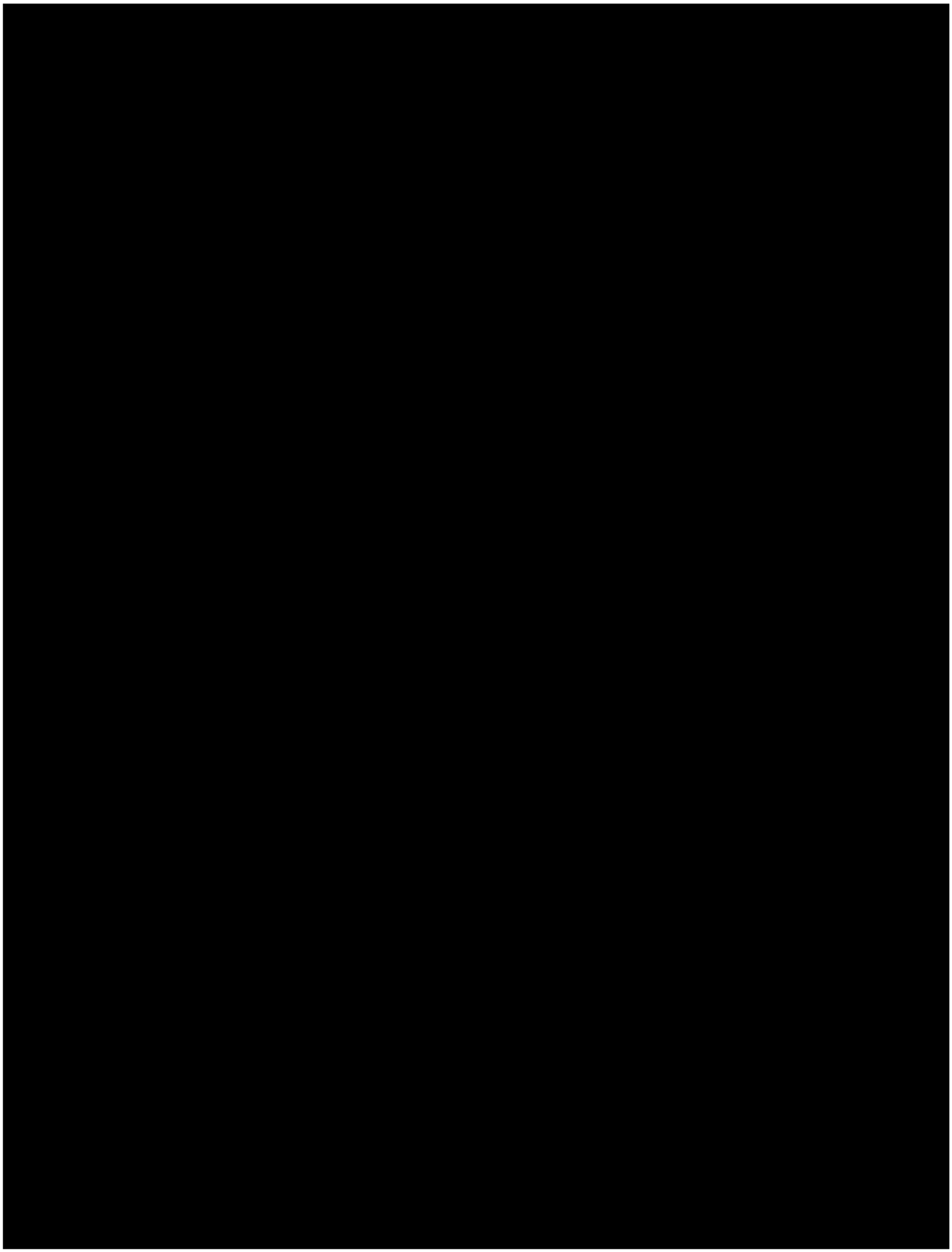

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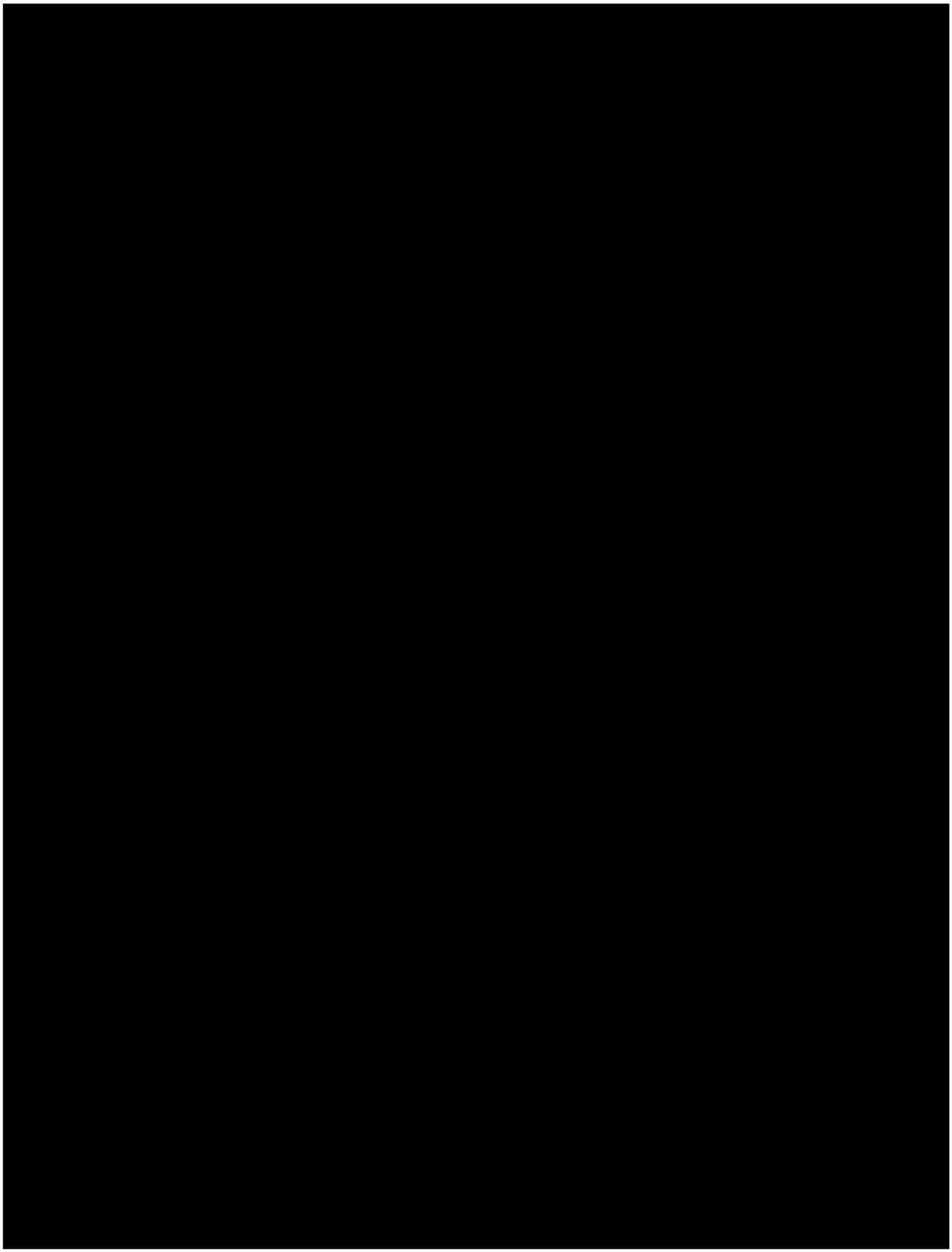

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11.1.9 HAM-A: Hamilton Anxiety Scale

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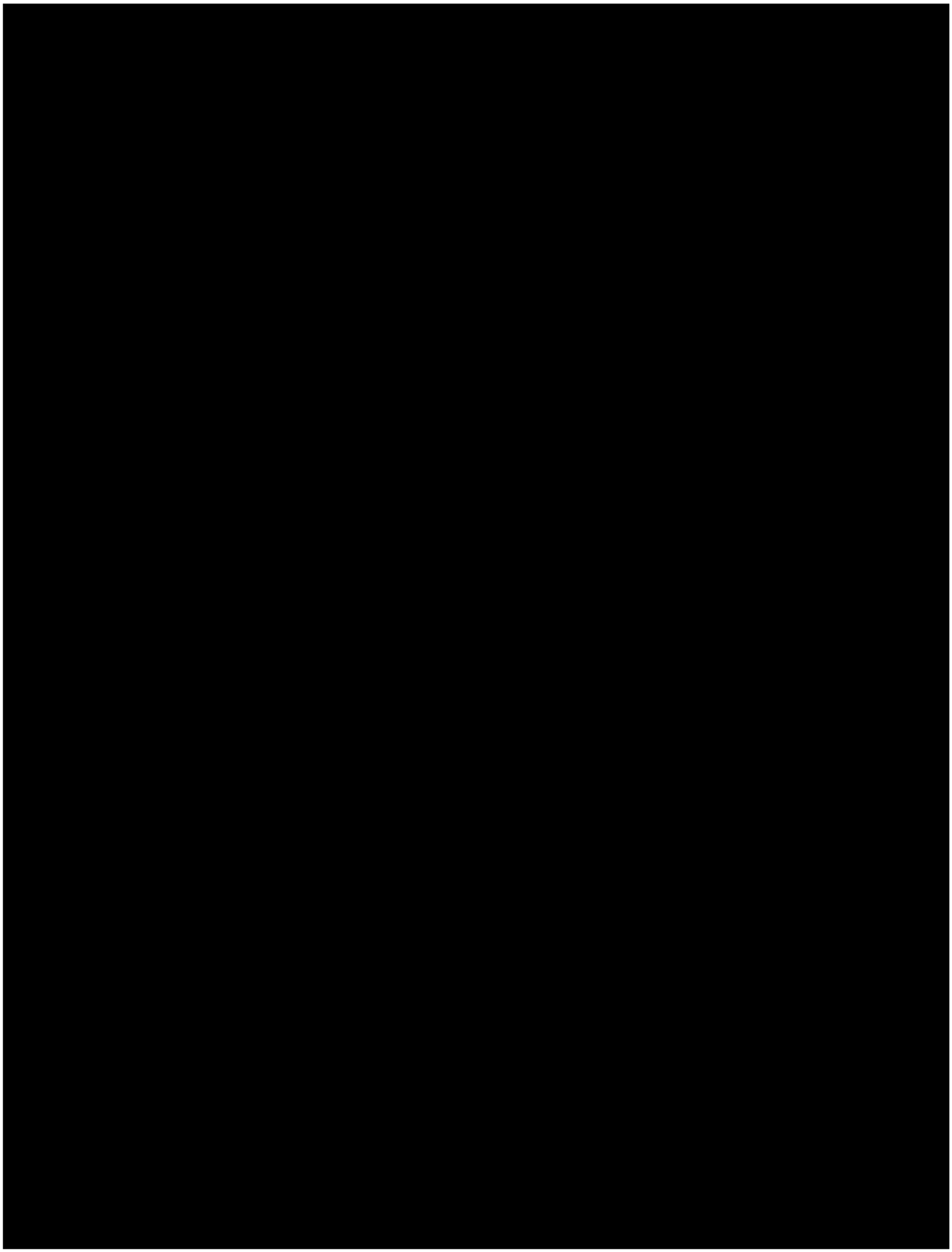

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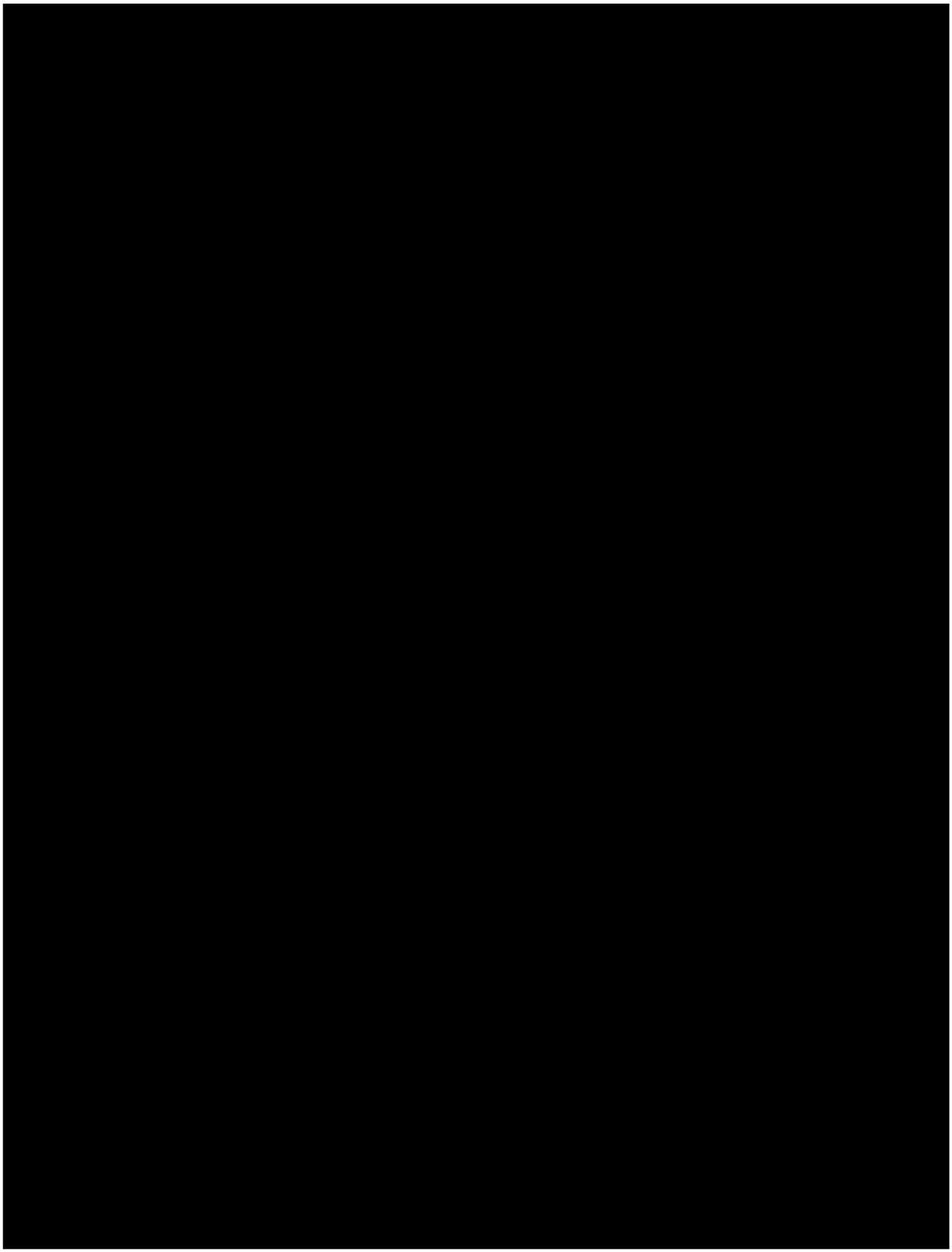

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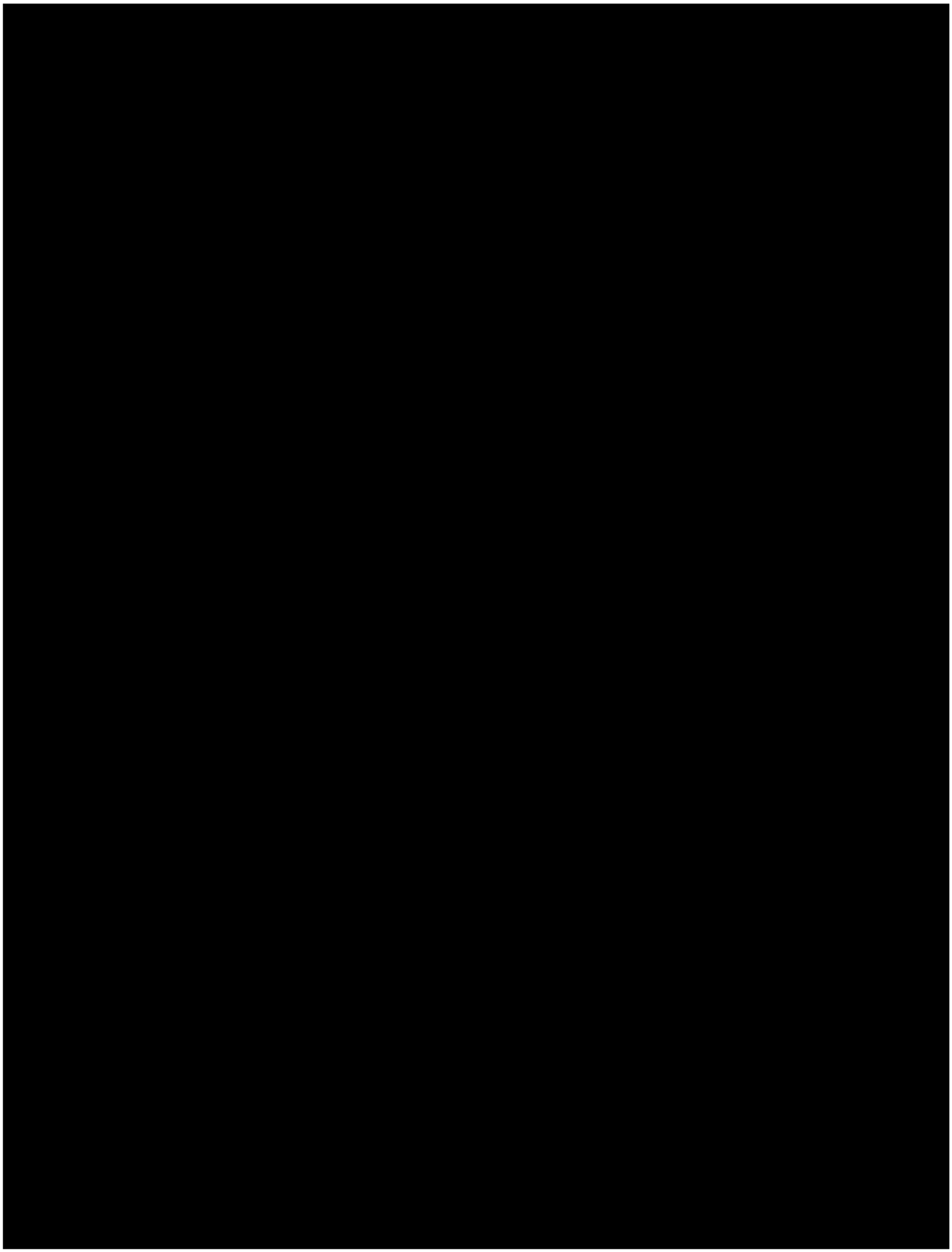

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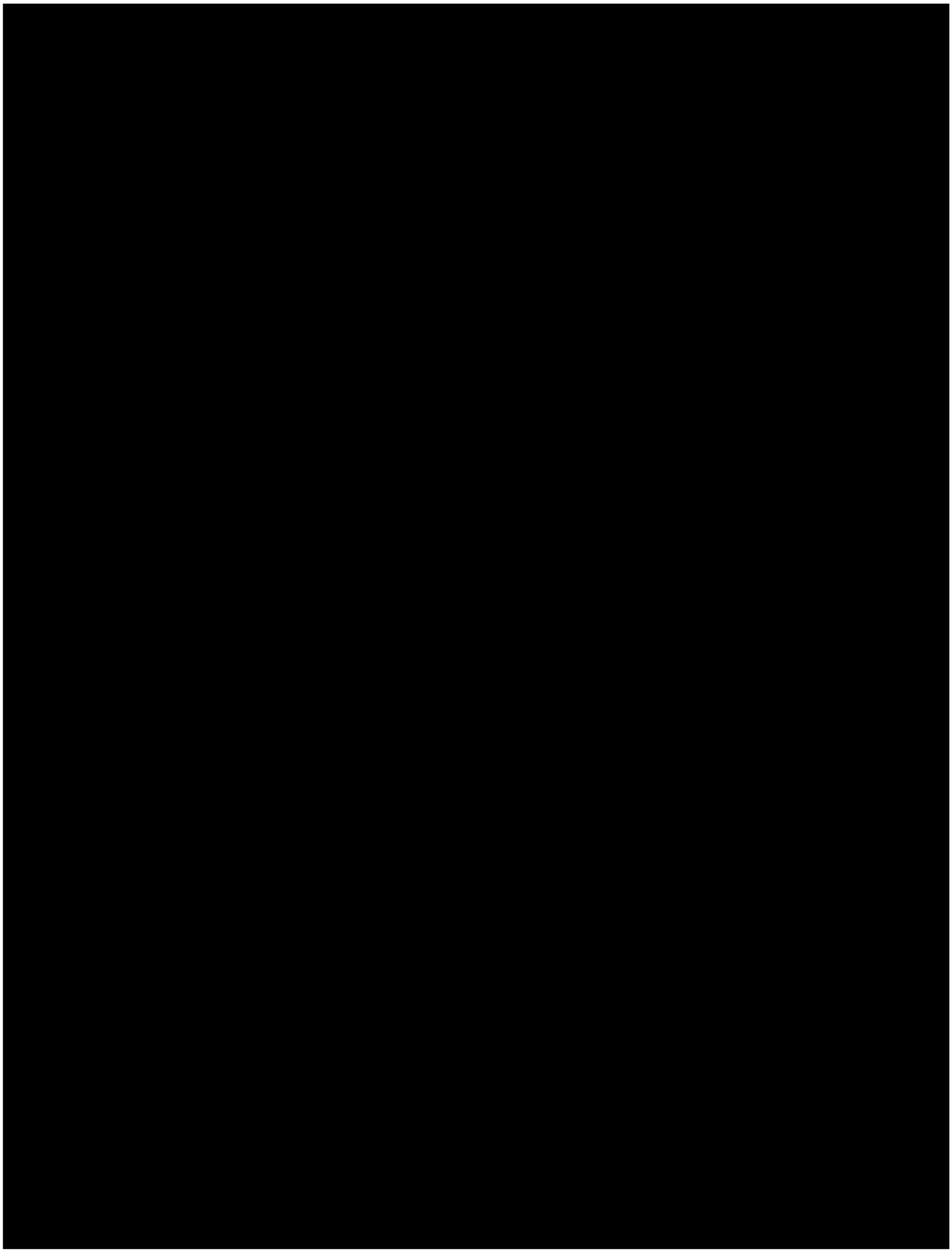

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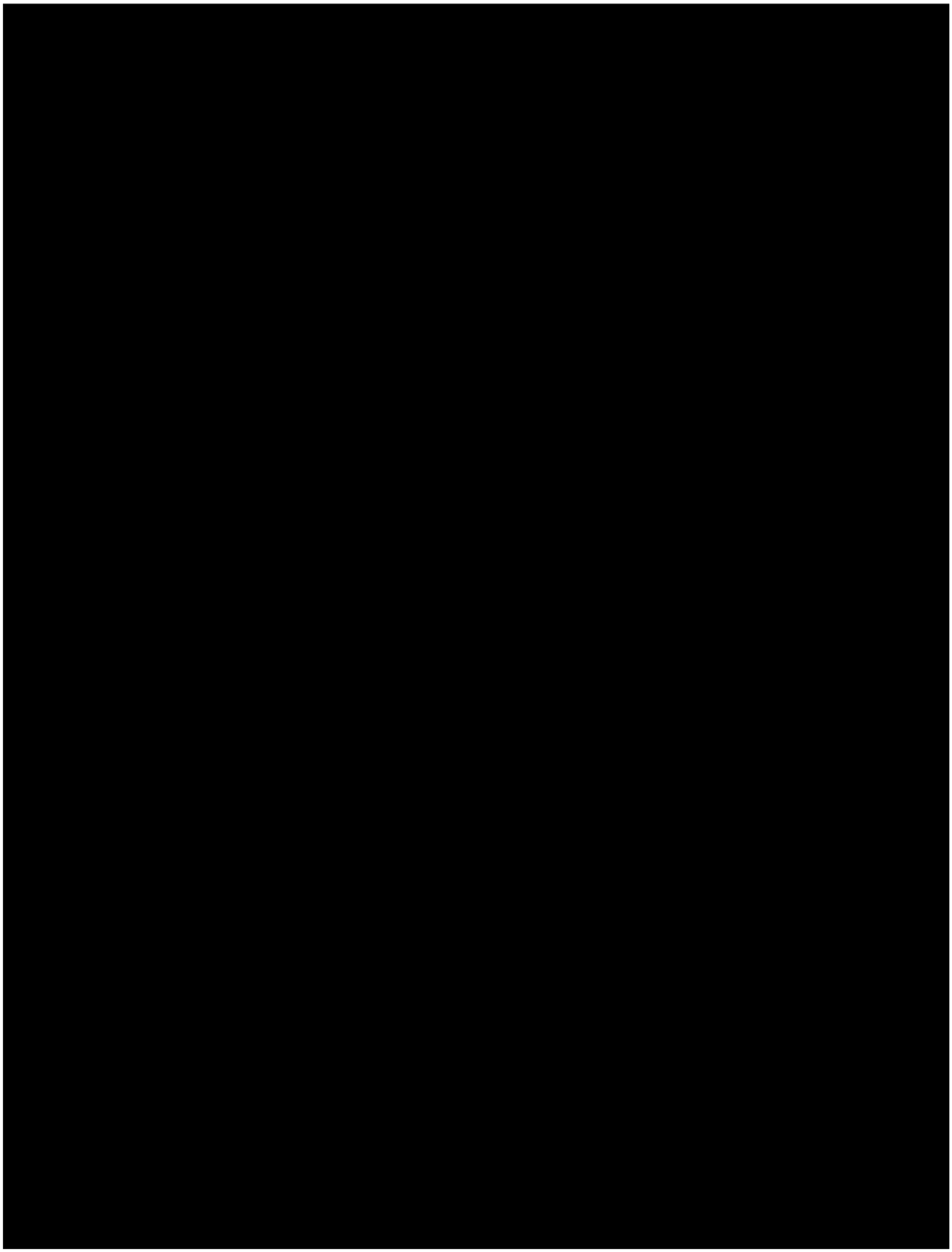

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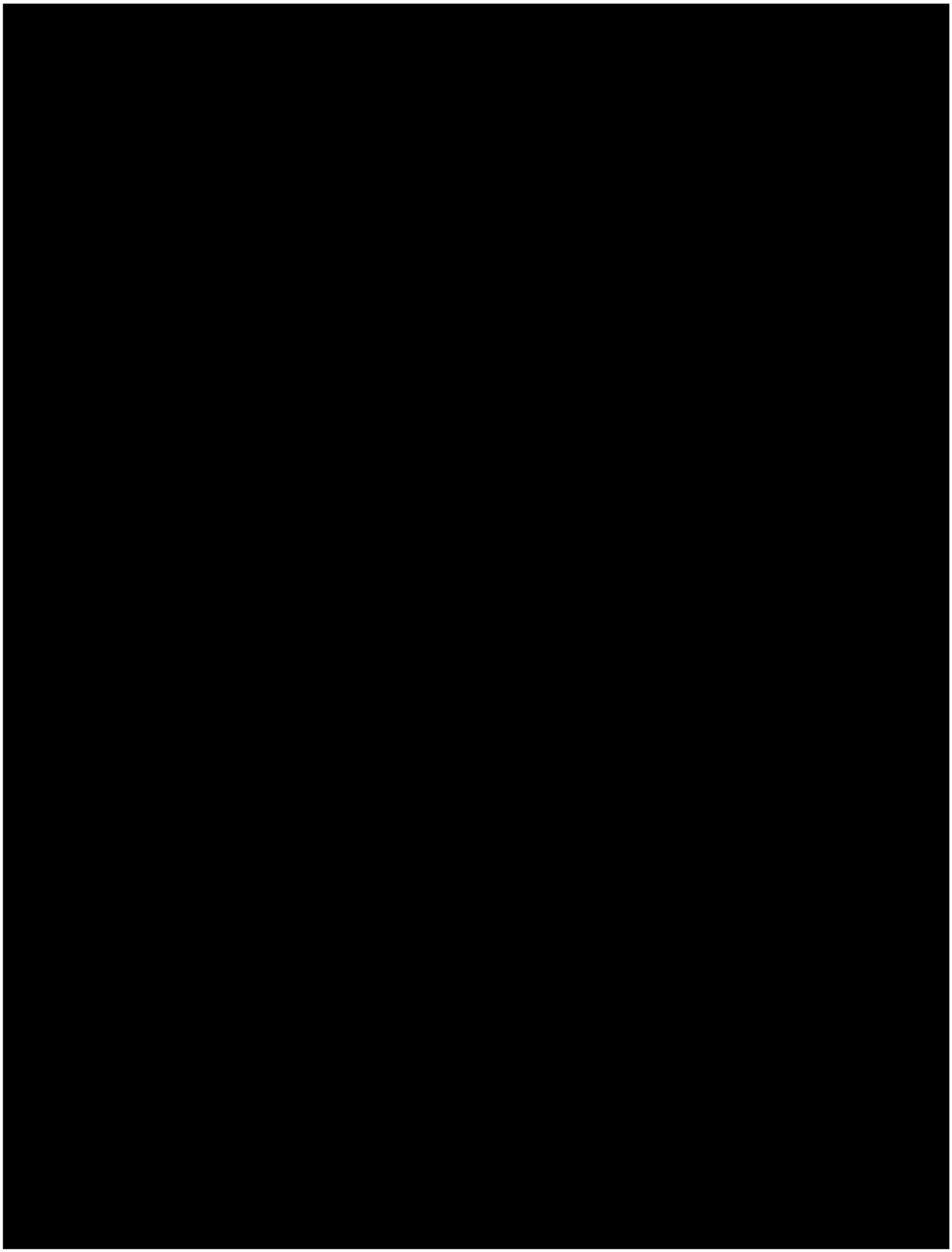

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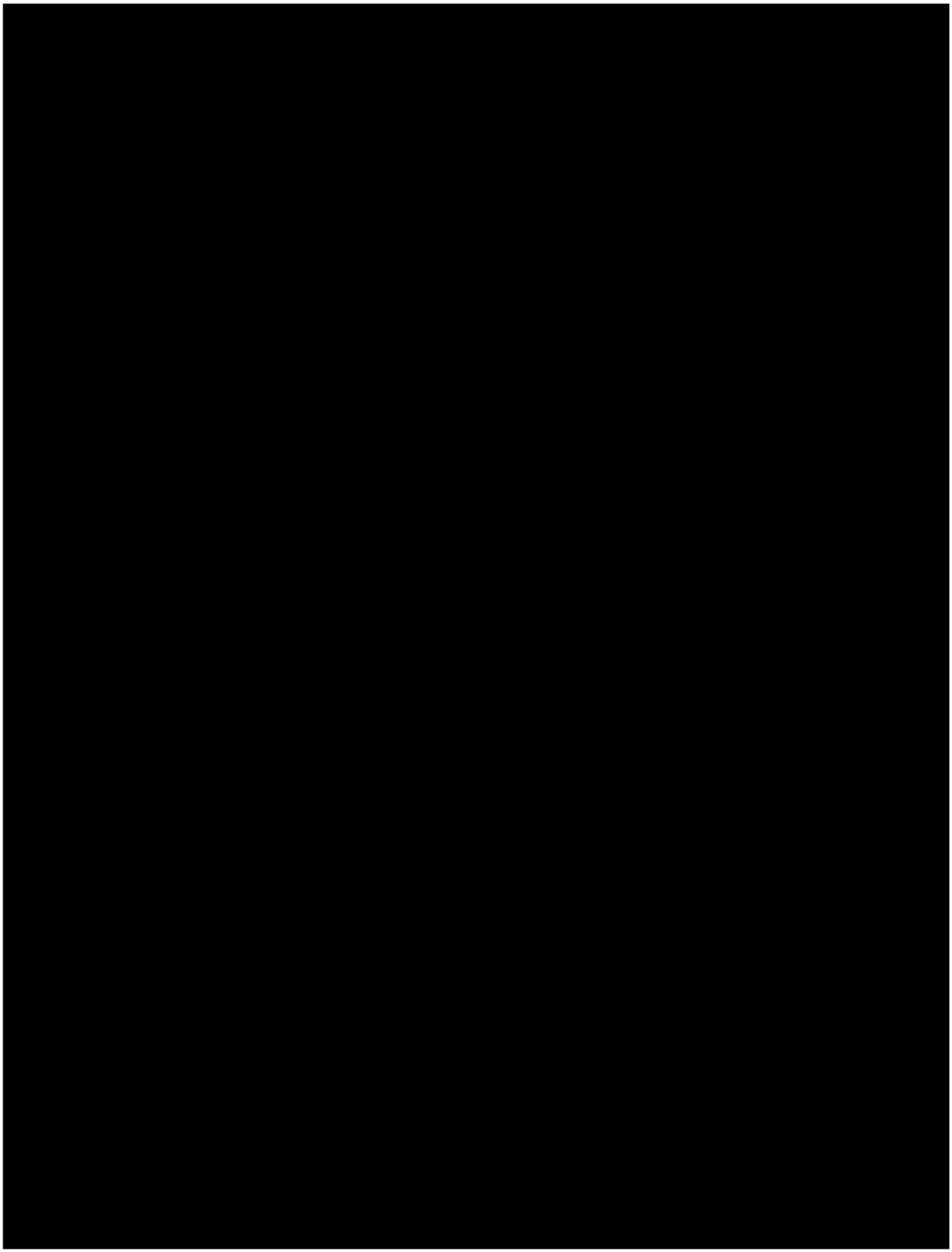

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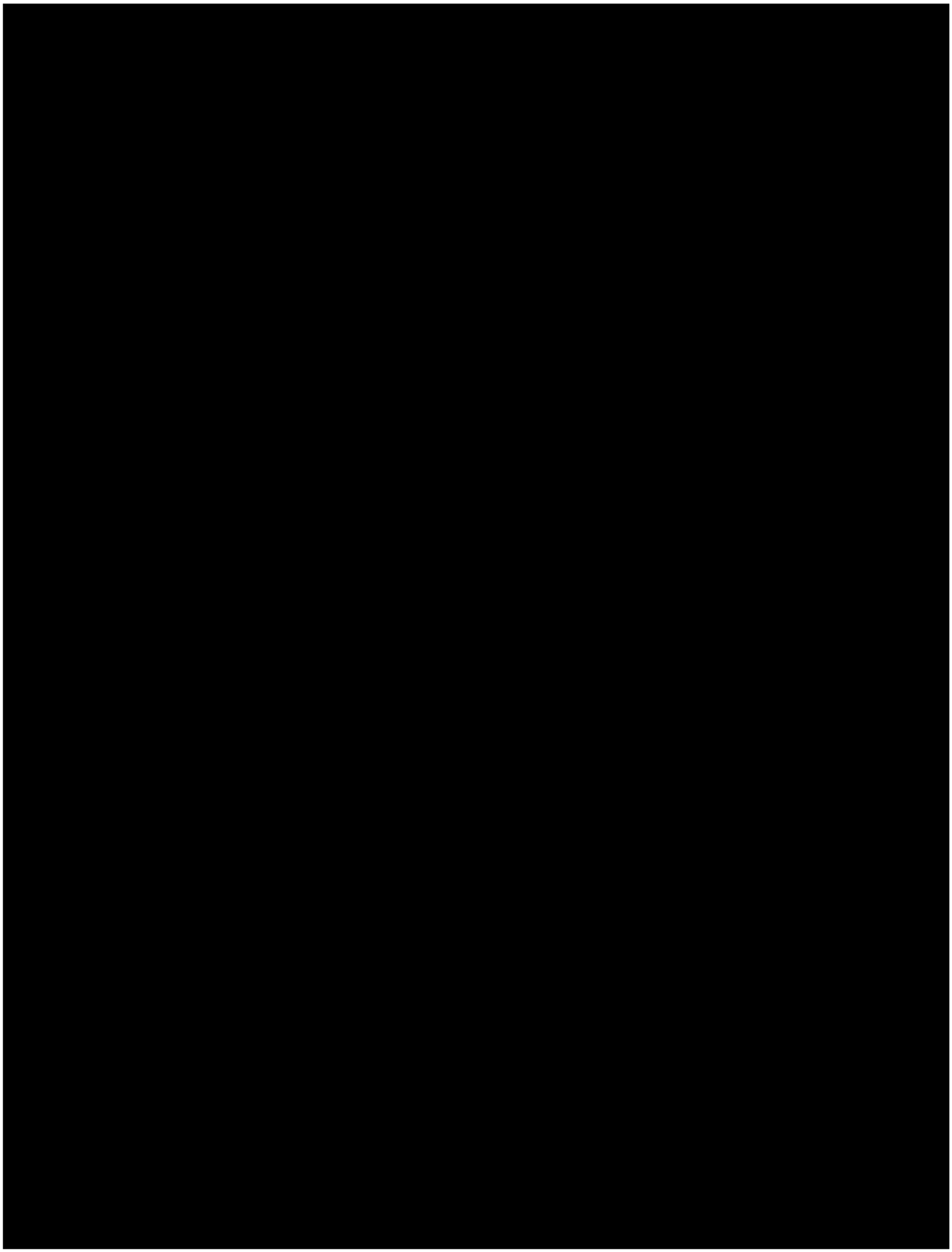

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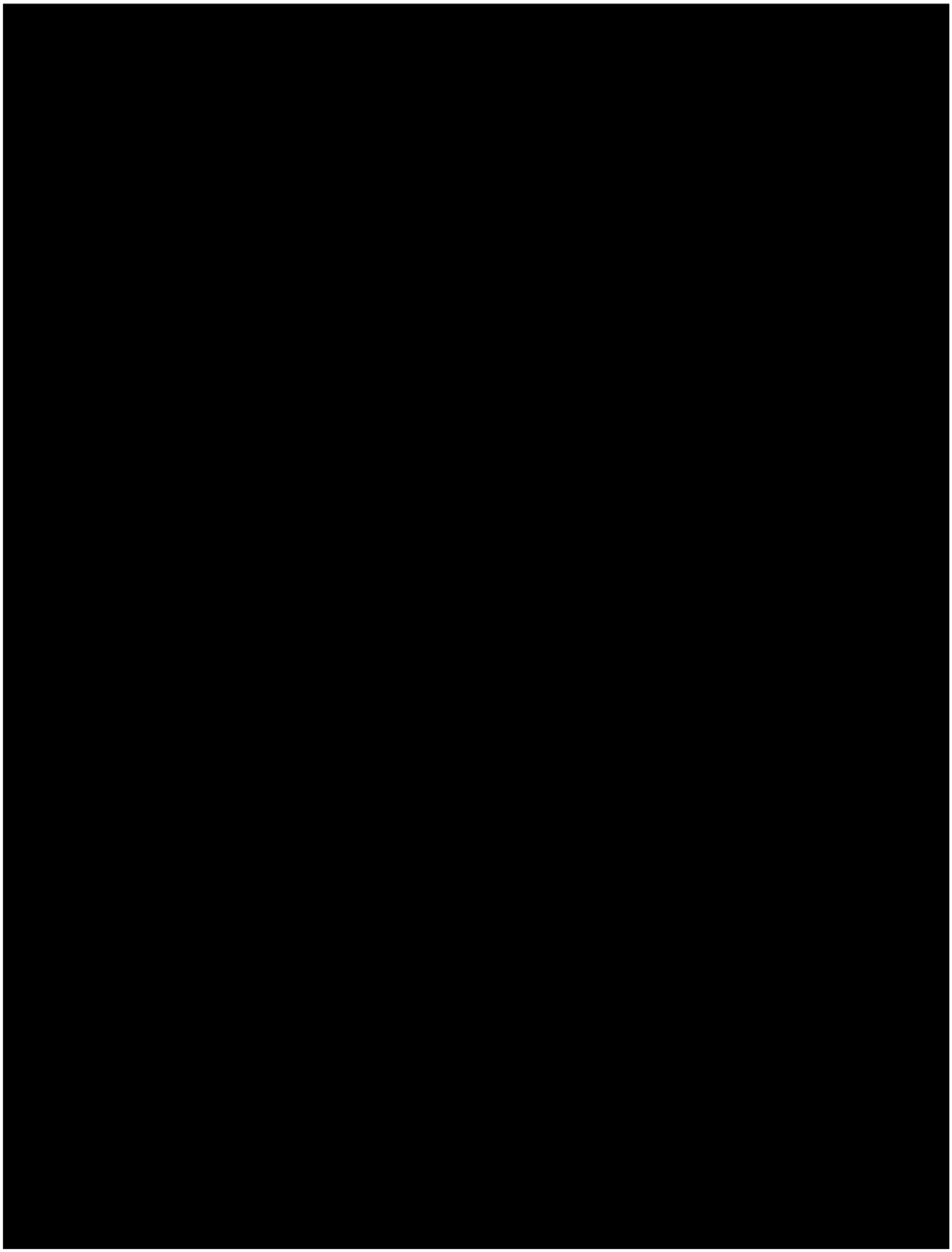

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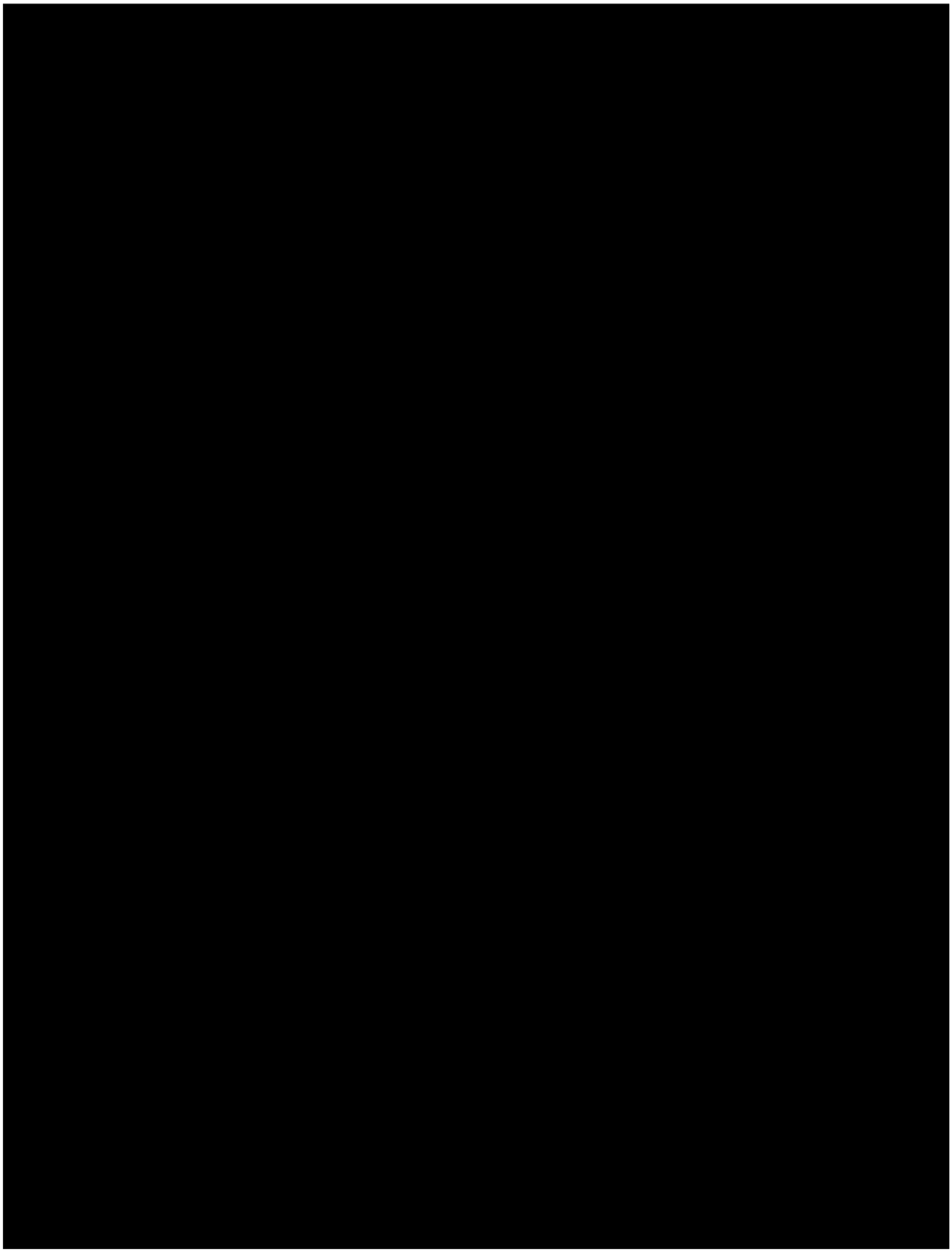

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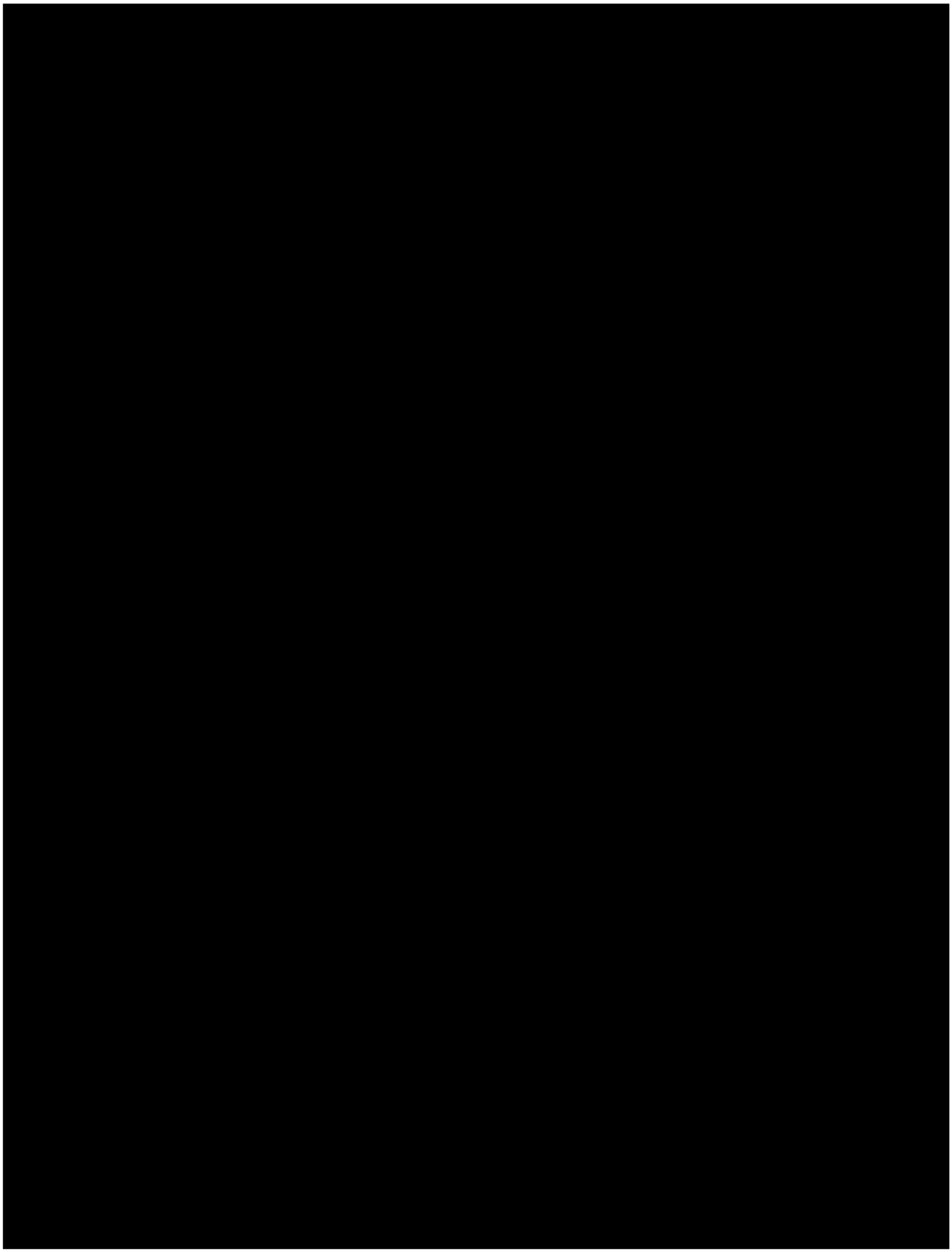

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11.1.10 C-SSRS: Columbia-Suicide Severity Rating Scale: Baseline

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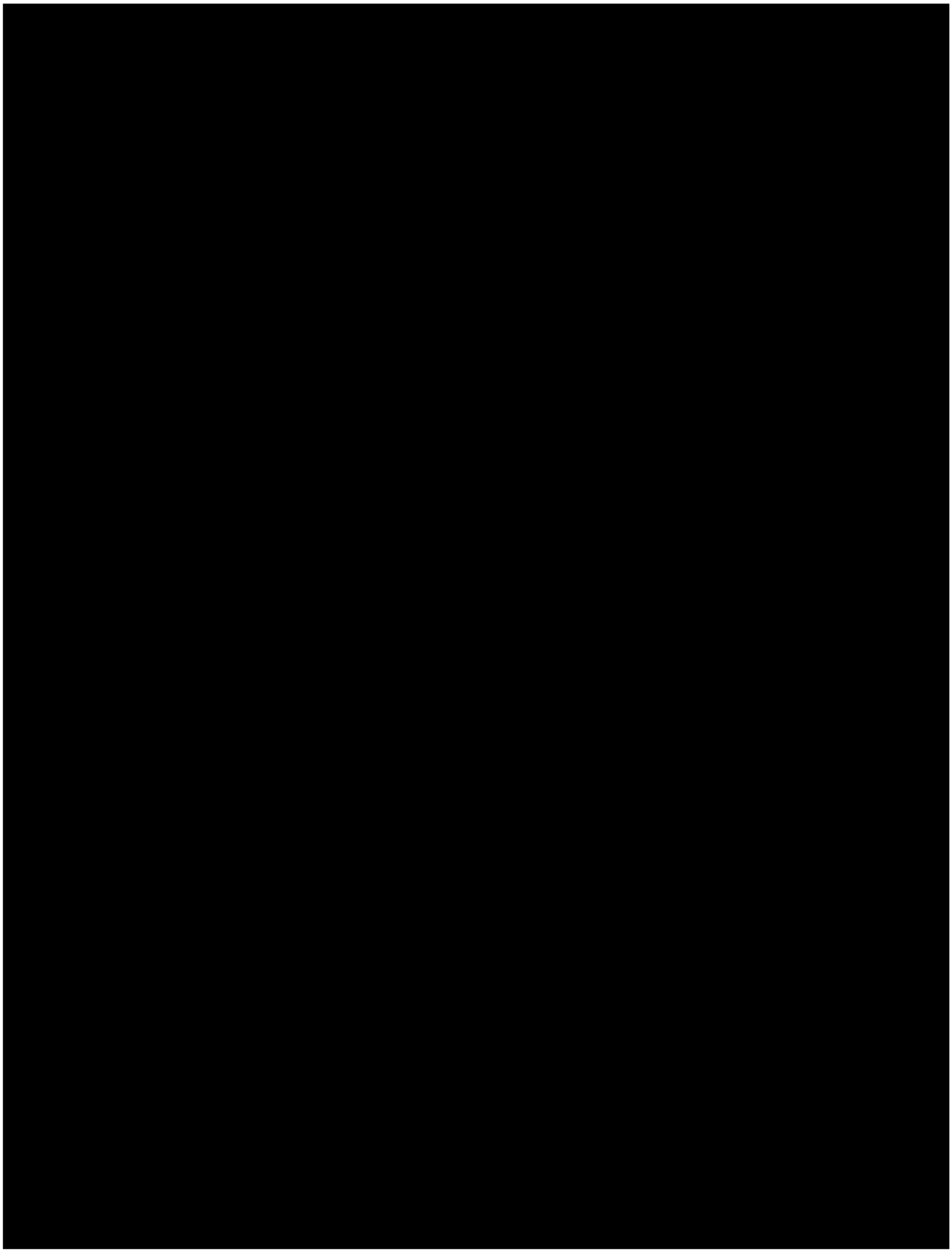

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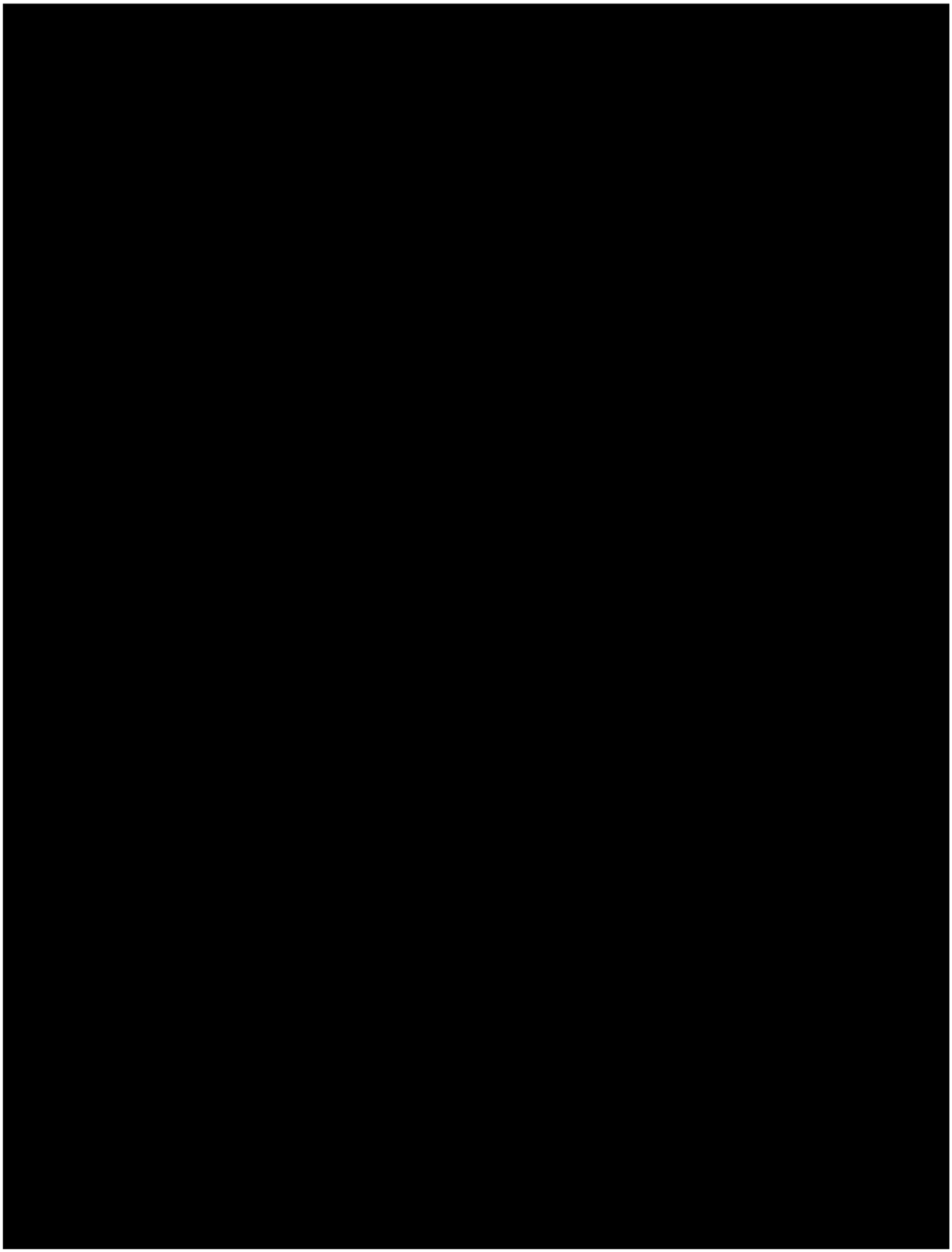

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11.1.11 C-SSRS: Columbia-Suicide Severity Rating Scale: Since Last Visit

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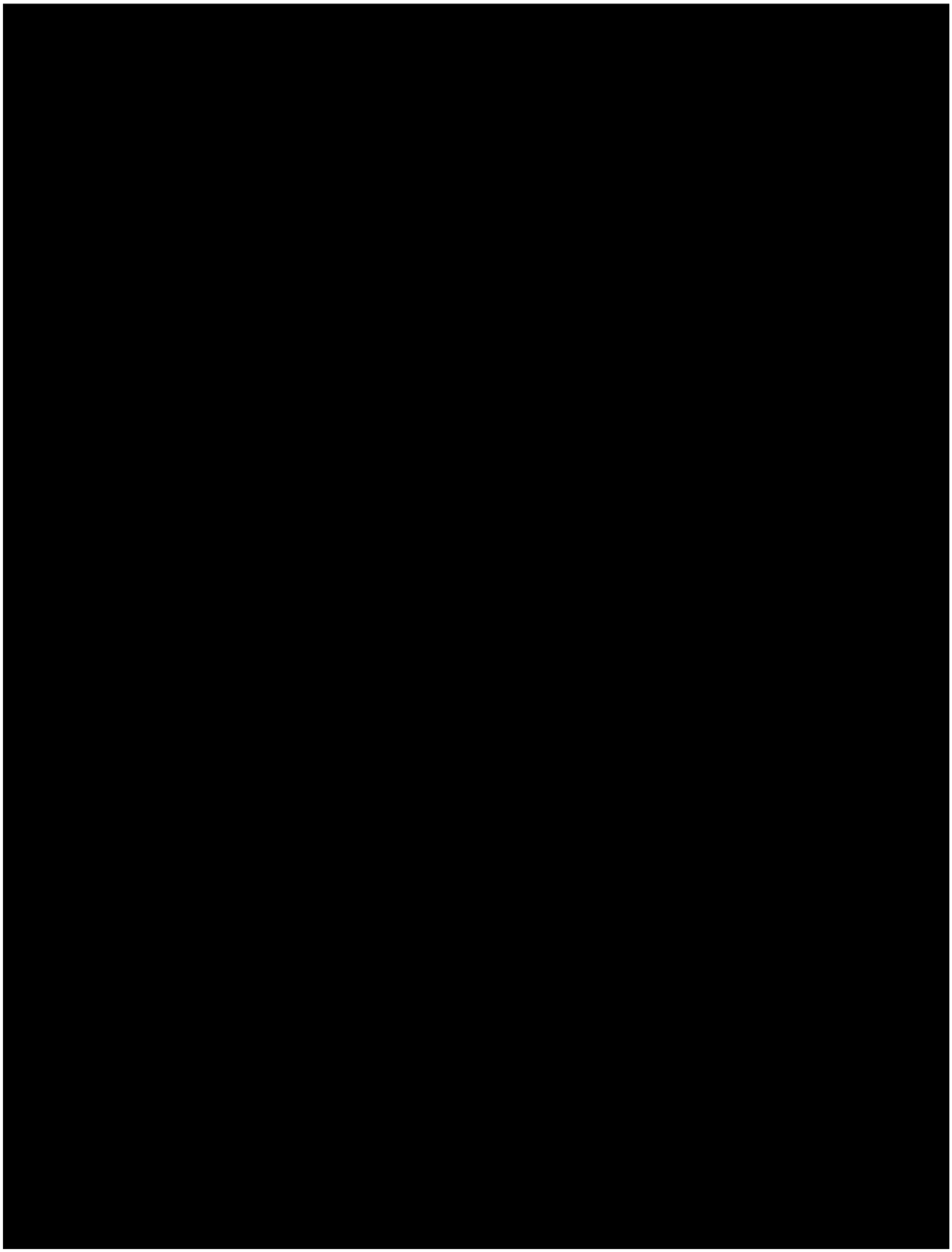

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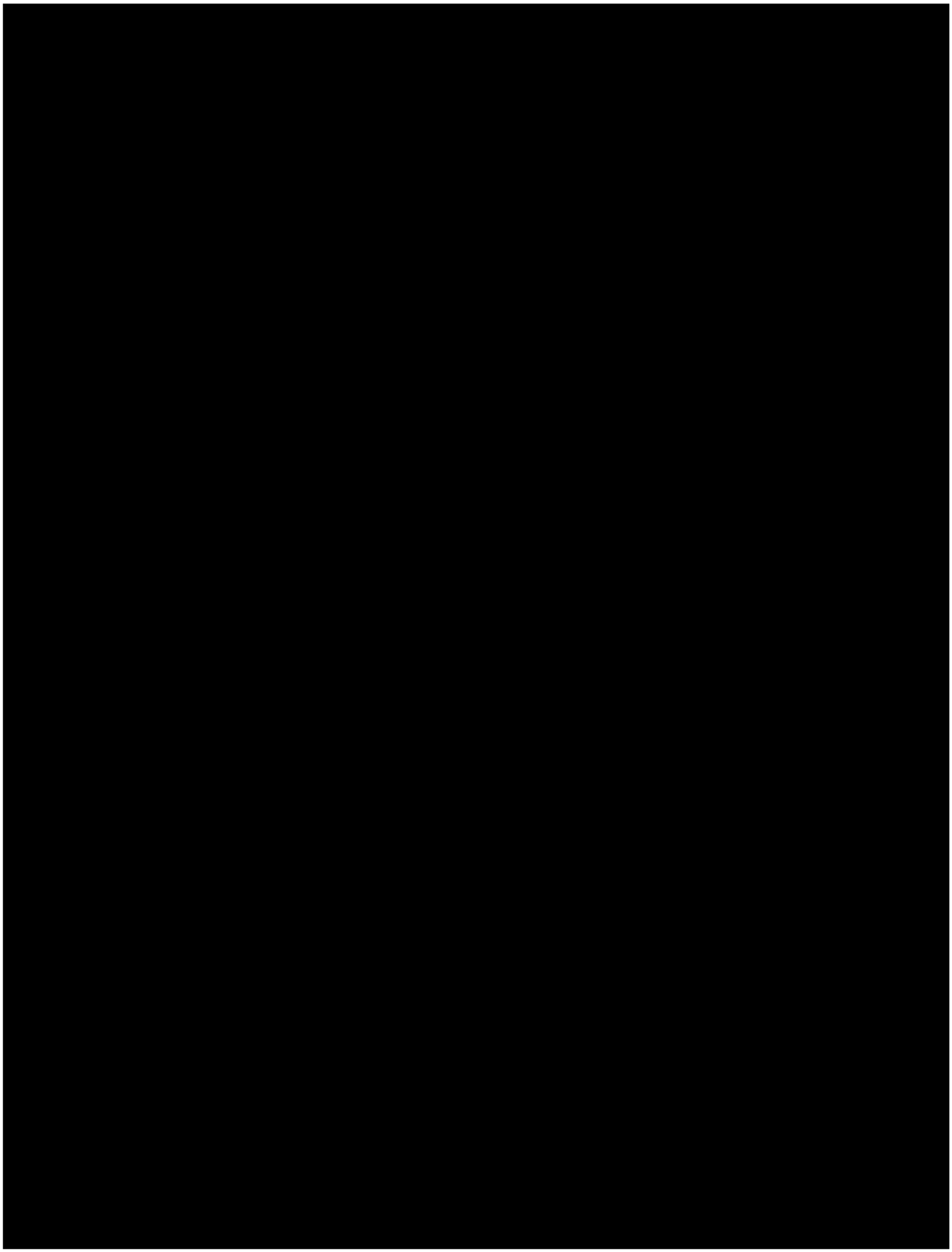

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