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VIFOR PHARMA

STATISTICAL ANALYSIS PLAN (SAP)

Investigational Drug:	VIT-2763
Treatment:	VIT-2763 in subjects with non-transfusion dependent beta-thalassaemia
Study Phase:	Phase 2a
Study Title:	A Phase 2a, Double-blind, Randomised, Placebo-controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non-transfusion Dependent Beta-thalassaemia
Protocol Number:	VIT-2763-THAL-201
Protocol Version:	4.0
Protocol Version date:	12 April 2021
Sponsor:	Vifor (International) Inc. Rechenstrasse 37 St. Gallen CH-9001 Switzerland [redacted]
SAP Version:	Final version V1.0
SAP Version Date:	29 November 2021
SAP Author:	[redacted]

[redacted]

[redacted]

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APPROVAL SIGNATURES FOR SAP

Study Title:	A Phase 2a, Double-blind, Randomised, Placebo-Controlled, Parallel Group, Multicentre Study on Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Multiple Doses of VIT-2763 in Subjects with Non-Transfusion Dependent Beta-thalassaemia
Protocol Number:	VIT-2763-THAL-201
Protocol Version/Amendment No. and Date (if applicable):	4.0/12 April 2021
New SAP Version and Date	Final version V1.0/29 November 2021
Superseded SAP Version and Date (if applicable):	

As signed below, I approved the Statistical Analysis Plan

[redacted]

Prepared by: [redacted]

_____

SAP Author (Name, title) — Signature

Approved by: [redacted]

_____

Trial Statistician (Name, title) — Signature

Approved by: Frank Richard

_____

Sponsor Medical Expert (Name, title) — Signature

Approved by: [redacted]

_____

Head of GCD (Name, title) — Signature — Date

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

[redacted]	[redacted]
%	Percentage
AE	Adverse event
ALP	Alkaline phosphatase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice daily
CI	Confidence interval
[redacted]	[redacted]
CRF	Case report form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EPO	Erythropoietin
[redacted]	[redacted]
FAS	Full analysis set
[redacted]	[redacted]
GCP	Good clinical practice
[redacted]	[redacted]
Hb	Haemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IVRS	Interactive voice response system
IWRS	Interactive Web Response System
[redacted]	[redacted]
MCH	Mean cell Hb
MCHC	Mean cell Hb concentration
MCV	Mean cell volume
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
N	Number
NOEL	No observed effect level
[redacted]	[redacted]
NTDT	Non-transfusion dependent thalassaemia
PPS	Per protocol set
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient reportedoutcome
PT	Preferred term
PV	Protocol violation
QD	Once daily
QoL	Quality of Life
[redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
SOC	System organ class
SOP	Standard operating procedure
SRT	Safety Review Team
SS	Safety set
sTFR	Soluble transferrin receptor
TDD	Total Daily Dose
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
TIBC	Total Iron Binding Capacity
TOC	Table of content
TSAT	Transferrin saturation
UIBC	Unsaturated Iron Binding Capacity

[redacted]

[redacted]

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SAP REVISION HISTORY

Version	Effective Date	Summary of Changes
0.1	11Sep2020	Initial version, based on protocol V2.0, 13Dec2019
0.2	10Nov2020	Second version, based on protocol V2.0, 13Dec2019
0.3	08Dec2021	Third version, based on protocol V3.0, 10Dec2020
0.4	10Jun2021	Fourth version, based on protocol V4.0, 12Apr2021
0.5	12Jul2021	Fifth version, based on protocol V4.0, 12Apr2021
1.0	29Nov2021	Final version, based on protocol V4.0, 12Apr2021

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under protocol VIT-2763-THAL-201 version 4.0 dated 12 April 2021.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 12 April 2021 and CRF dated 26 March 2021. Any further changes to the protocol or CRF may necessitate updates to the SAP. Statistical rationale and analysis methods specified in this document take precedence over those described in the protocol, should there be any differences.

1.1 Overall Study Design and Rationale

β-Thalassemia is a genetic anemia caused by partial or complete loss of b-globin synthesis, leading to ineffective erythropoiesis and Red Blood Cells (RBCs) with a short life span. Currently, there is no efficacious oral medication modifying anemia for patients with β-thalassemia.

The inappropriately low levels of the iron regulatory hormone hepcidin enable excessive iron absorption by ferroportin (FPN), the unique cellular iron exporter in mammals, leading to organ iron overload and associated morbidities. Correction of unbalanced iron absorption and recycling by induction of hepcidin synthesis or treatment with hepcidin mimetics ameliorates β-thalassemia. Hepcidin modulation or replacement strategies currently in clinical development all require parenteral drug administration [Siddique et al. 2012].

VIT-2763 is a small molecule with hepcidin-mimetic action and is developed by Vifor Pharma as a novel oral drug targeting FPN for the treatment of iron loading anemias. FPN is a key molecule in iron homeostasis as it is the only known transporter of iron into the blood stream in mammals. FPN is mainly expressed on intestinal enterocytes, macrophages of spleen and liver, and hepatocytes. On the basolateral membrane of intestinal enterocytes, FPN transfers dietary iron into the plasma; on spleen

[redacted]

and liver macrophages, it exports endogenous iron recycled from the Haemoglobin (Hb) of senescent RBCs, and on hepatocytes FPN exports iron that was released from liver stores [Ward et al. 2012].

Nonclinical studies with VIT-2763 showed improved anaemia, extended the life-span of RBCs, and prevention of iron loading. Additionally, amelioration of ineffective erythropoiesis, myelopoiesis and splenomegaly in th3/+ mice, a murine thalassaemia disease model, could be shown [Manolova et al. 2019].

The first-in-human study VIT-2763-101 in male and female healthy volunteers showed a temporary decrease in mean serum iron levels at single doses of 60 mg, 120 and 240 mg VIT-2763, and at all multiple dose levels. A temporary decrease in mean calculated % Transferrin saturation (TSAT) in serum was seen following all multiple VIT-2763 dose levels on both Day 1 and Day 7. The effect was accompanied by temporarily increased serum hepcidin levels following the highest single dose levels of 60 mg, 120 mg and 240 mg VIT-2763, and following all multiple dose levels of VIT-2763. Single and multiple oral VIT-2763 doses showed overall a favourable safety profile and were well tolerated by healthy male and female subjects.

Based on the requirement of regular blood transfusions needed for survival, beta thalassaemia has been recently classified into non-transfusion dependent thalassaemia (NTDT) (previously thalassaemia intermedia) and transfusion dependent thalassaemia (TDT) (previously thalassaemia major) [Viprakasit et al. 2018]. However, classification of NTDT or TDT only represents a patient's current clinical status, patients may shift clinically between NTDT or TDT over time. As such, NTDT patients may need transfusion therapy occasionally or for limited periods of time, especially during periods of growth and development, surgery, or pregnancy [Cappellini et al. 2018].

This is a phase 2a, double-blind, randomised, placebo-controlled, multiple dose, parallel group, multicentre study in adult and adolescent male and female subjects with NTDT.

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. Subjects who have met all eligibility criteria will be randomised according to their body weight.

The study comprises a non-treatment screening period of up to 4 weeks (28 days), a 12-week (84 days) treatment period and a safety follow-up period of 4 weeks (28±4 days).

Based on an anticipated drop-out rate of approximately 20%, it is estimated that approximately 6 subjects will be replaced or additionally randomised.

The study will commence with enrolment and treatment of adult NTDT subjects (Cohort I). It is planned to include NTDT adolescents (age ≥12 years up to 17 years, or deviating according to local country definitions, up to N=10, (Cohort II)). Enrolment of adolescent NTDT subjects will start only after relevant blinded safety and tolerability data, as well as blinded PK data in ≥10 adult NTDT subjects completed Week 8 of treatment has been received, including an initial benefit/risk review by a Safety Review Team (SRT). This will provide additional safety relevant information before treatment of adolescents will commence.

[redacted]

In addition, the preliminary efficacy of VIT-2763 by means of changes in iron related parameters and [redacted] will be assessed. Placebo treatment will be used in a minority of adult and adolescent NTDT patients in order to discriminate potential side-effects of active treatment from non-active treatment, and to investigate the natural variability of iron related markers [redacted]

1.2 Changes from Protocol

A modified FAS has been defined and added in the section 4.4. A sensitivity analysis for efficacy will be performed on the modified FAS if more than 3 subjects are excluded due to major Covid-19 related protocol deviation.

2 STUDY SUMMARY

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability of VIT-2763 versus placebo in adult and adolescent NTDT subjects over a 12-week treatment period.

2.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the preliminary efficacy of VIT-2763 versus placebo on iron markers in adult and adolescent NTDT subjects over a 12-week treatment period.
- To evaluate the PK of VIT-2763 in adult and adolescent NTDT subjects over a 12-week treatment period (using a population PK approach).

[redacted]

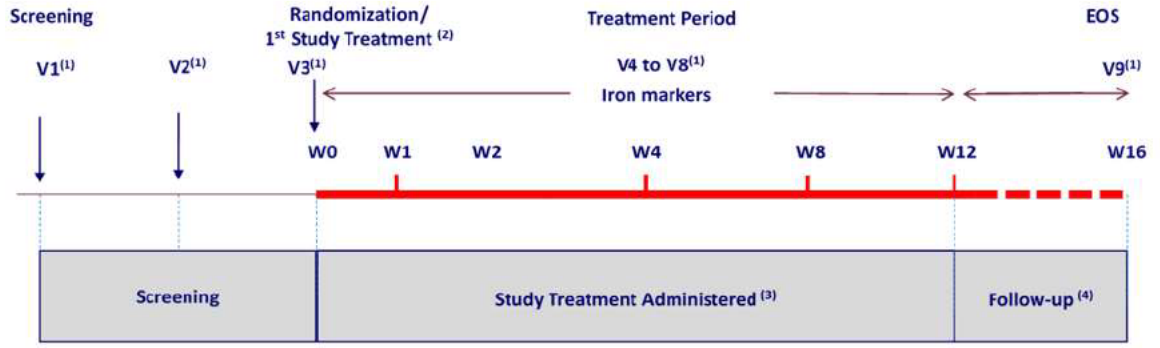
[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

2.2 Study Design

Figure 1 Flow Chart – Adults (Cohort I) and Adolescents (cohort II)



1 Performed in-hospital. Optional Visit 2 in order to determine the Hb level. If for logistical reasons the subject may not be able to attend Visit V2, the screening Hb value in conjunction with a historical Hb value obtained at maximum 2 weeks prior to screening, or an additional Hb value taken prior to randomisation can be assessed. V9 may be conducted by telephone call or as an in-clinic visit.
2 Randomisation: Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 QD or BID or placebo. Adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo. Allocation to dosing will be performed according to Table 1.
3 A first blinded interim analysis will be performed and the data reviewed by a SRT once ≥10 adult subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort I, the randomisation algorithm should ensure that the first 10 subjects in Cohort I will match a 4:4:2 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. A second blinded interim analysis will be performed and data reviewed by the SRT once ≥5 adolescent NTDT subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort II, randomisation algorithm should ensure that the first 5 subjects in Cohort II will match a 2:2:1 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo.
4 All subjects, whether completing the treatment or who have withdrawn prematurely, are asked to attend a follow-up visit 4 weeks (28±4 days) after their last administration of study treatment to collect any new AEs and concomitant medications. This visit may be conducted by telephone call or as an in-clinic visit.
Notes: AE=Adverse event; BID=Twice daily; EOS=End of study; Hb=Haemoglobin; NTDT=Non-transfusion dependent thalassaemia; QD=Once daily; SRT=Safety Review Team.

The study will commence with enrolment and treatment of adult NTDT subjects (Cohort I). Adult subjects will be randomised in an 8:8:4 ratio to receive either VIT-2763 QD or BID or placebo at a dose of 120 mg for subjects with a body weight ≥60 kg or at a dose of 60 mg for subjects with a body weight <60 kg.

A blinded interim analysis will be performed and the data reviewed by an SRT once ≥10 subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort I, the randomisation algorithm should ensure that the first 10 subjects in Cohort I will match a 4:4:2 distribution to receive either 60/120 mg VIT-2763 QD or BID or matching placebo. Enrolment and treatment of adult NTDT subjects into Cohort I will continue during the study up to 30 adults and/or adolescent subjects completed the study Week 12 visit. Remaining adult NTDT subjects will be randomised to either 60 mg or 120 mg VIT-2763 or placebo according to the body weight assessed at screening.

The SRT will make recommendations whether to enrol adolescent NTDT subjects into Cohort II.

Adolescent subjects will be randomised in a 4:4:2 ratio to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥ 60 kg or at dose of 60 mg for subjects with a body weight <60 kg, as shown in Table 1.

[redacted]

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Table 1 Dose Regimens Based on Body Weight at Screening

Subject body weight at screening (kg)	Dose schedule (mg VIT-2763 or placebo)			
	Adults (morning – evening dose)	Adolescents (morning-evening dose)	Total daily dose	TDD/kg body weight (1)
40-59	60-placebo	60-placebo	60	1.0-1.5
	60-60	60-60	120	2.0-3.0
	placebo-placebo	placebo-placebo	N/A	N/A
60-100	120-placebo	120-placebo	120	1.2-2
	120-120	120-120	240	2.4-4.0
	placebo-placebo	placebo-placebo	N/A	N/A

1 Estimated total daily dose/kg body weight range based on individual plasma PK parameters versus dose level/body weight obtained from human Phase 1 study.

Notes: N/A=Not applicable; PK=Pharmacokinetic; TDD=Total Daily Dose

A blinded interim analysis will be performed and data reviewed by the SRT once ≥5 adolescent NTDT subjects have completed the study Week 8 visit. For the purpose of the safety review in Cohort II, the randomisation algorithm should ensure that the first 5 subjects in Cohort II will match a 2:2:1 distribution to receive either 60 mg or 120 mg VIT-2763 QD or BID or matching placebo. Remaining adolescent NTDT subjects who have been screened and/or enrolled into Cohort II at the time of the interim analysis will continue in the study, whilst the enrolment of new adolescent subjects in the study will be suspended until after the SRT has reviewed the blinded safety and tolerability data of the first 5 adolescent subjects and has been given the recommendation to continue the enrolment of adolescent subjects (enrolment hold).

The SRT may also make recommendations to reduce the dose level at any given interim steps, or to unblind any subject due to safety concerns, or to stop the trial. The SRT consists at a minimum of the Co-ordinating investigator, 2 independent haematologists, the Vifor medical monitor, and the Vifor drug safety representative or their designee.

[redacted]

[redacted]

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2.3 Schedule of Events

Table 2 Schedule of Events

Visit	Screen V1	Screen V2	Baseline V3	V4 Week 1	V5 Week 2	V6 Week 4	V7 Week 8	V8 Week 12/ EOT	FUP V9 Week16/ EOS
Study Day	-28 to -1	-15 (Optional) [16]	1	7	14	28	56	84	112
Visit Windows	N/A	±3	N/A	±1	±2	±3	±3	±3	±4
Informed consent	X[17]								
(Review of) eligibility criteria	X	X	X[1]						
Demographics	X								
Medical/medication history	X	X	X						
Physical examination[2]	X		X					X	
Body weight and height	X							X (weight)	
Vital signs (blood pressure, pulse rate)	X		X	X	X	X	X	X	
Single 12-lead ECG	X		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	
Safety and Haematology Laboratory									
Haematology[4], biochemistry[4]	X		X	X	X	X	X	X	
Coagulation	X		X			X		X	
Serum ferritin, TSAT[4]	X								

[redacted]

[redacted]

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Visit	Screen V1	Screen V2	Baseline V3	V4 Week 1	V5 Week 2	V6 Week 4	V7 Week 8	V8 Week 12/ EOT	FUP V9 Week16/ EOS
Study Day	-28 to -1	-15 (Optional) [16]	1	7	14	28	56	84	112
Visit Windows	N/A	±3	N/A	±1	±2	±3	±3	±3	±4
Urinalysis (pH, protein, glucose, ketone, blood, spot urine for protein/ creatinine and albumin/creatinine ratio)	X		X	X	X	X	X	X	
Urine drug screen, alcohol	X								
Pregnancy test[5]	X[5]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	
Serology (HBsAg, HBV, HCV, HIV)	X								
PD iron [redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]		[redacted]		[redacted]	[redacted]	
Haemoglobin local[9]		X	X	X	X	X	X	X	
VIT-2763 PK[10]			X			X	X	X	
[redacted]			[redacted]					[redacted]	
Adverse events	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Study drug dispensation			X	X	X	X	X		
Study drug administration[12]			X	X	X	X	X	X	

[redacted]

[redacted]

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Visit	Screen V1	Screen V2	Baseline V3	V4 Week 1	V5 Week 2	V6 Week 4	V7 Week 8	V8 Week 12/ EOT	FUP V9 Week16/ EOS
Study Day	**-28 to -1**	**-15 (Optional)** [16]	**1**	**7**	**14**	**28**	**56**	**84**	**112**
Visit Windows	**N/A**	**±3**	**N/A**	**±1**	**±2**	**±3**	**±3**	**±3**	**±4**
Study drug accountability				X	X	X	X	X	
[redacted]			[redacted]			[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]					[redacted]	

1 Any outstanding criteria not available on Day -15 (screening Visit 2) to be available before randomisation.
2 Body systems to be assessed include general appearance, head (eyes, ears, nose and throat), cardiovascular, respiratory, abdominal, musculoskeletal, neurological, lymph nodes and skin.
3 At 2-3 hours post-administration post-morning dose.
4 [redacted] Biochemistry sample including electrolyte status (sodium, potassium, magnesium, calcium, chloride), total bilirubin, urea, uric acid, creatinine, total protein, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, glutamate dehydrogenase, lactate dehydrogenase, haptoglobin, amylase, bicarbonate, unconjugated bilirubin, creatine phosphokinase, folic acid, Vitamin B_{12}, albumin, glucose, total cholesterol, and triglycerides. Clotting: prothrombin time, activated partial thromboplastin time, thrombin time. Serum ferritin, serum iron, unsaturated iron binding capacity, calculated transferrin saturation (screening visit only); all parameters will be assessed centrally.
5 For female subjects only; beta-human chorionic gonadotropin in serum at screening and V8 (Samples will be derived from serum biochemistry tube); in urine at baseline and all other visits.
6 PD measurements include serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated transferrin saturation, [redacted] will be assessed centrally. Samples will be collected on Visits 3 to 8 approximately 2 hours post-dose.
7 [redacted]
9 Haematology sample to assess Hb will be taken locally at study site and results must be available at day of dosing (sample at optional Visit V2).
10 PK samples will be collected on Visit 3 and Visit 7 at pre-dose trough and at approximately 1 hour and 4 hours post-dose, and on Visits 6 and 8 at pre-dose trough and approximately at 1 hour and 3 hours post-dose.
11 [redacted]
12 Administered in the morning approximately between 08:00 a.m. and 10:00 a.m., first morning dose administered in the hospital on Day 1, and at all Visits V4-V8; self-administration (morning and evening) at home for the whole study period at non-study visits, from Day 2 to Day 84. Food intake, except for water, to be avoided for at least 1 hour prior to and post dosing. Study drug accountability will be performed at V4-V8.
13 [redacted]
14 Liver iron concentration (mg/g dry weight) in adult NTDT subjects to be assessed, in subjects who have given their informed consent. [redacted]
15 [redacted]

[redacted]

[redacted]

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16 In case there is no retrospective Hb value, it is allowed to schedule optional screening visit V2 and baseline V3 the same day providing that local Hb result can be obtained on the day of combined V2/V3 visit and that there should be at least 1 week between screening Visit V1 and the combined V2/V3 visit. If V2 and V3 are done the same day, site should only complete V3 in EDC.

17 In case of extraordinary events (e.g., COVID-19 pandemic) it is acceptable to have the informed consent via e-mail, SMS or a verbal consent (a witness is required), if allowed per local country guidance. Written consent has to be provided as soon as possible and must be properly recorded in the source documentation.

Notes: ECG=Electrocardiogram; EDC=Electronic data capture; EOS=End of study; EOT=End of treatment; [redacted] FUP=Follow-up; [redacted] Hb=Haemoglobin; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; [redacted] bound iron; NTDT=Non-transfusion dependent thalassaemia; PD=Pharmacodynamic; PK=Pharmacokinetic; [redacted]

[redacted]

2.4 Sample Size Determination

No specific sample size calculations have been performed for this study.

It is planned to randomise at least 20 subjects in Cohort I and up to 10 subjects in Cohort II.

2.5 Randomisation and Blinding

Subjects will be allocated one of the following treatments: VIT-2763 QD or VIT-2763 BID or placebo. The randomisation allocation ratio will be 8:8:4 for Cohort 1 (adult NTDT subjects) and 4:4:2 for Cohort 2 (adolescent subjects) and the randomisation method will be interactive web response system (IWRS) RTSM from Medidata RAVE. The randomisation schedule was generated and maintained by Covance according to SOP number ST-SOP-001 version 06. The schedule and the seed will be sequestered until the study database is locked and the study is unblinded.

Table 3 presents the treatment group labels and table 4 presents the visit labels that will be used in all output.

Table 3 Study Treatments

Studied Treatment	Treatment Label
Active treatment 1	VIT-2763 QD
Active treatment 2	VIT-2763 BID
Placebo	Placebo

Adult and adolescent subjects will be randomised to receive either VIT-2763 QD or BID or placebo, at a dose of 120 mg for subjects with a body weight ≥60 kg or at dose of 60 mg for subjects with a body weight <60 kg.

Table 4 Study Visits

Visit Number (Title)	Visit Label
Visit 1 (Screening)	Screening
Visit 2 (Optional Screening)	Screening 2
Visit 3 (Day 1)	Baseline *
Visit 3 (Day 1)	Baseline 2h post-dose **
Visit 4 (Week 1)	Week 1
Visit 5 (Week 2)	Week 2
Visit 6 (Week 4)	Week 4
Visit 7 (Week 8)	Week 8
Visit 8 (Week 12)	EOT Week 12

Visit 9 (Week 16)	EOT Week 16

* Baseline is defined in section 5.1.2.
** For ECG, baseline value will be defined during Screening visit and assessment recorded at the Visit 3 (Day 1) will be presented as "Baseline 2h post-dose".

2.5.1 Interim Analysis

No formal interim analysis is planned.

A SRT will be instituted for this study in order to ensure ongoing safety of study subjects in this study.

2.5.2 Safety Review Team

For each cohort, blinded data of the first 10 subjects in Cohort I and the first 5 subjects in Cohort II will be reviewed by an SRT.

Data to be reviewed by the SRT are defined in the SRT charter version 1.0 date 16 March 2020. Tabulations and listings will be run on blinded data by Vifor Biostatistics Department (or other Vendors) and sent only to the SRT members.

For PK concentrations, dummy aliases will be used instead of subject identifiers. Timepoints where any subject has missing sample(s) will be removed entirely to prevent unblinding.

2.6 Study Endpoints

2.6.1 Primary Safety Endpoint(s)

- Reported or observed adverse events (AEs): by system organ class (SOC) and preferred term (PT) (MedDRA coded term), by severity and relation to study product in each treatment group.
- Reported or observed serious AEs (SAEs): by SOC and PT (MedDRA coded term), by severity and relation to study product in each treatment group.
- Changes in vital signs (supine systolic and diastolic blood pressure and pulse rate), clinical laboratory safety tests (haematology, serum biochemistry, coagulation, and urinalysis), 12-lead ECG, and physical examination findings.

2.6.2 Secondary Endpoint(s)

- Assessment of iron parameters (total serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated TSAT, from baseline over a 12-week period (absolute and change from baseline)).
- PK parameters: individual estimates of Cmax, clearance, distribution volume, AUC will be obtained using a population PK approach in adult and adolescent subjects combined with suitable mathematical/statistical analysis, using nonlinear mixed-effects modelling. Sparse sampling for determination of VIT-2763 plasma concentration following multiple dosing will be obtained from pre-dose trough to 3 or 4 hours post-dose at selected study visits.

[redacted]

2.6.3 [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Only in subjects who consent in writing to provide blood samples for biomarkers and genotyping, whole blood samples will be taken and stored for later determination of biomarkers and genotyping. The biomarker and pharmacogenetic endpoints will be defined at a later time point, taking into account further scientific and clinical data.
- [redacted]

3 HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No statistical hypotheses have been done since no formal sample size has been calculated.

3.2 Statistical Decision Rules

There is no formal statistical decision rule for this study, and all analyses are considered descriptive.

4 ANALYSIS SETS

In accordance with ICH E3 [1] and E9 [2] guidelines, the analysis sets are defined as follows:

4.1 Safety set

The safety set (SS) consists of all randomised subjects who have taken at least one dose of study medication. The subjects in the SS will be analysed based on the treatment they received, regardless of randomisation.

[redacted]

4.2 Full analysis set

The full analysis set (FAS) consists of all subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least one dose of randomised treatment
- Had at least 1 post-baseline PD assessment

The FAS will be created in accordance with the Intent-To-Treat principles. The subjects in the FAS will be analysed based on the treatment that they were randomised to.

Subjects who received blood transfusion will be censored from their first transfusion date for the FAS. All efficacy and PK data considered as censored data will not be part of summary tables and figures but will be listed as other data and identified with a censor flag.

4.3 Per-protocol set

The per-protocol set (PPS) consists of all subjects who, in addition to the FAS criteria, had no major protocol deviation (as defined in the section 4.5 and finalised during the blind data review meeting).

The subjects in the PPS will be analysed based on the treatment that they were randomised to.

Subjects who received blood transfusion will be censored from their first transfusion date for the PPS. All efficacy and PK data considered as censored data will not be part of summary tables and figures but will be listed as other data and identified with a censor flag.

4.4 Other Analysis Sets

For the purposes of tables and listings further four analysis population are defined:

- **Screened population** (all screened subjects)
- **All randomised subjects** (all randomised subjects)
- **Modified full analysis set (optional)**: The modified FAS will consist of all subjects of FAS with no major Covid-19 related protocol deviation. The population will be defined depending of the number of covid-19 subjects and the impact on the analyses. The subjects in the modified FAS will be analysed based on the treatment that they were randomised to.

4.5 Protocol Deviations

The protocol deviations, classified as major by Vifor in the Project Specific Protocol Deviation List version 7.0 dated 26 November 2021 will be identified for all subjects by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Population	Category	Sub category	Description	Vifor's

[redacted]

				classification
PPS	2. Study Conduct/ Procedures	A. Inclusion/ Exclusion Criteria	Failure to complete inclusion criteria #1	Major
PPS	2. Study Conduct/ Procedures	B. Screening	8. Safety and Haematology Laboratory samples not taken at screening and baseline visit prior to first dosing	Major
PPS	2. Study Conduct/ Procedures	B. Screening	9. Safety and Haematology Laboratory samples: results needed for eligibilty confirmation missing at screening and baseline visit prior to first dosing.	Major
PPS	2. Study Conduct/ Procedures	B. Screening	21. Randomization errors (e.g. incorrect randomization process interaction with IVRS system) resulting in incorrect allocation of the study therapy	Major
PPS	2. Study Conduct/ Procedures	D. Study Restrictions/ Withdrawal Criteria	1. Non-compliance with protocol restrictions (e.g. use of prohibited medication or prohibited treatment therapy)	Major
PPS	2. Study Conduct/ Procedures	D. Study Restrictions/ Withdrawal Criteria	2. Non-compliance with subject withdrawal criteria defined in the protocol (i.e. subject continued in study but should have been withdrawn).	Major
PPS	2. Study Conduct/ Procedures	E. Dose Formulation/ Dose Administration	2. Incorrect IMP dose intake: Patient took less than 80% of prescribed doses or took more than 105% of prescribed doses. To be assessed during the course of the study (V3 to V8)	Major
PPS	2. Study Conduct/ Procedures	E. Dose Formulation/ Dose Administration	3. Incorrect subject IMP kit given OR wrong dose regimen (total daily dose) assigned based on screening body weigth	Major

All protocol deviations will be presented in the data listings, including the nature of the protocol deviation, non-important or important.

[redacted]

[redacted]

5 DESCRIPTION OF THE STATISTICAL ANALYSIS

This section describes the statistical analyses, presentation of the results, and the study endpoints/measures that will be collected and/or derived during the study at the time points specified in the Schedule of Events (see section 2.2).

5.1 General Considerations

The software used for all summary statistics and statistical analyses will be SAS® Version 9.4 or later (SAS Institute, Inc.).

Derived datasets will be generated by the Biostatistics Department from the Clinical Interchange Standard Consortium (CDISC) Study Data Tabulation Model (SDTM [version 3.2]) datasets in accordance with CDISC ADaM version 2.1 and the ADaM Implementation Guide v1.1.

The two cohorts (adults/adolescents) will be analysed the same way into 2 separated analyses, if 5 or more adolescents are randomised into the study. Otherwise, a pooled analysis of adult and adolescent subjects will be performed [redacted]).

The treatment groups will be displayed as:

1. VIT-2763 QD
2. VIT-2763 BID
3. Placebo

If at least 1 subject is randomised in each body weight category, summary statistics will be repeated in each body weight category.

There is no formal statistical level for this study, and all analyses are considered descriptive.

5.1.1 Standard Descriptive Statistics

Continuous Variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be obtained for continuous variables: number, mean, standard deviation, median, inter-quartile range and range. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. Mean, median, inter-quartile range will be displayed to one more decimal place than collected value and standard deviation will be displayed to two more decimal place than collected value.

Categorical Variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be presented for categorical values: total number of available values and missing values, number of values

[redacted]

[redacted]

in each category and the corresponding percentage of the total number of values available will be calculated. The percentage will be displayed using two decimals.

Percentages will be calculated using the total subjects per randomised treatment group, except for outputs in the SAF, where percentages are based on the total subjects per actual treatment group.

5.1.2 Definition of Baseline, Visits and Visit Windows

The baseline will be defined as the last available (non-missing) value before the first administration of study drug except for parameters listed below:

- PD measurements (serum iron, serum ferritin, unsaturated iron binding capacity, calculated transferrin saturation). Baseline will be collected during screening period within the biochemistry sample.
- For following parameters, the baseline will be defined as the value at Visit 3 2h post-dose:
  - [redacted]
  - [redacted]
  - [redacted]
  - PD measurements (serum transferrin).

Study day 1 is defined as the day of the first study drug administration. For analysis relative day, if considered date less than first study drug administration date, then analysis relative day will be considered date minus first study drug administration date, otherwise, it will be considered date minus first study drug administration date + 1.

5.1.3 Analysis Assessment Windows

Table 5 describes the Analysis Assessment Windows that will be used in all analyses.

Table 5 Analysis Assessment Windows

Visit Label	Planned visits (Protocol Specified)	Analysis Assessent Window	Target Day
Baseline*	--	<=1 Day*	1
Baseline 2h post-dose **	± 1 days	Day 1	1
Week 1	± 1 days	From Day 2 to Day 10	7
Week 2	± 2 days	From Day 11 to Day 21	14
Week 4	± 3 days	From Day 22 to Day 42	28

[redacted]

[redacted]

Week 8	± 3 days	From Day 43 to Day 70	56
EOT Week 12	± 3 days	From Day 71 to Day 98	84
EOS Week 16	± 4 days	>= Day 99	112

* For ECG, baseline value (<1 Day) will be defined during Screening visit and assessment recorded at the Visit 3 (Day 1) will be presented as "Baseline 2h post-dose".

** For [redacted] and serum transferrin, baseline value will be defined as the value at Visit 3 2h post-dose and will be labelled "Baseline 2h post-dose". Changes from baseline in summaries will be calculated using the baseline 2h post-dose value.

All assessments (planned and unscheduled) will be re-mapped into the analysis windows. For a parameter, if several assessments fall into the same analysis window, the closest to the target day will be considered for the analysis. When there are 2 assessments closest to the target day, the latest one will be considered for the analysis (i.e. if there are 2 visits which fall on Day 13, Day 15, the visit from Day 15 will be considered for analysis.). If in case there are 2 records with valid results which fall on same date/visit, then the average of the 2 results will be taken and an additional record will be added to be considered for analysis and flagged.

5.1.4 Treatment Start/Stop Dates

If there are no treatment dates available in the administration page of the CRF, date of randomisation will be imputed as the start of treatment date, if it is known that the subject received study drug (information recorded in the administration page of the CRF or any information from monitoring).

If the end of treatment date is missing in the treatment termination page of the CRF, the earliest date between the returned date from supply accountability log page and the latest date from administration page (with no return recorded) would be imputed.

5.1.5 Tables and Listings Presentation

The listings will display all the data contained in the CRF, including the screen failure patients collected information if appropriate. The listings will be ordered by cohort, treatment groups, body weight and subject number.

There will be no statistical tests performed. If confidence is mentioned, the level will be 95% unless otherwise specified.

5.1.6 Analysis Populations

The safety set will be used for all safety analyses.

The FAS will be used for [redacted] and PK concentration. The PPS will be also used

[redacted]

[redacted]

in case of any difference with FAS. The modified FAS may be used depending of the number of covid-19 subjects and the impact on analyses.

Demographics and baseline characteristics, medical history and concurrent medical conditions, prior and concomitant medications and procedure and study drug exposure and compliance will be computed on the FAS, PPS and the SS. Only sets with different attribute will be presented.

5.1.7 Pooling of Sites/Country

Not applicable for this study

5.1.8 Analysis of Subgroups

The following subgroups will be considered:

- Body weight at screening: <60 kg/ ≥ 60 kg
- Gender: Male/Female
- Race: American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/Other. Each race category will be part of subgroup analysis only if there is at least one subject in.

In case of imbalance between treatment groups regarding baseline characteristics, other subgroup analyses may be performed.

Following outputs will be repeated in each subgroup:

- Table 14.2.1.1.1 Summary statistics of other iron related parameters over time
- Table 14.2.1.5.1 Summary Statistics of Increase from Baseline in Haemoglobin by Visit
- Table 14.3.1.1.1 Overall Summary of Adverse Events
- Table 14.3.1.2.1 Treatment-emergent Adverse Events by System Organ Class and Preferred Term
- Table 14.3.1.3.1 Serious TEAEs by System Organ Class and Preferred Term
- Table 14.3.1.5.1 Serious TEAEs related to study medication by System Organ Class and Preferred Term

5.1.9 Methods for Handling and imputation of Missing Data

For medications and procedures, imputation of missing or partial dates will be done to identify concomitant medications and procedures as follows:

- If the start date of the medication/procedure is unknown (i.e. complete missing date), the worst-case scenario will be assumed. The medication/procedure will be considered as both a prior medication/procedure and a concomitant medication/procedure.

[redacted]

[redacted]

- If the month and the day of the start date of the medication/procedure are missing, the month and the day will be imputed to January, 1st of the year specified.
- If the day of the start date of the medication/procedure is missing, the day will be imputed to the first day of the month specified.
- If the end date is unknown (i.e. missing), the date will be kept as missing however the medication/procedure will be considered concomitant.
- If the month and the day of the end date of the medication/procedure are missing, the month and the day will be imputed to December, 31st of the year specified.
- If the day of the end date of the medication/procedure is missing, the day will be imputed to the last day of the month specified.

The original incomplete, missing or partial dates and corresponding imputed dates will be presented in the listings.

Subject Disposition

Subject disposition data will be collected on the CRF when a subject completed or discontinued from the study. The patient disposition data will be summarized. The following data will also be presented in the listings:

- Date of informed consent or assent.
- Date of randomisation.
- Date of completion/or withdrawal

For diagnosis, imputation of partial dates will be done as follows:

- If the date of the diagnosis is unknown (i.e. complete missing date), the date will not be imputed.
- If the month and the day of the date of the diagnosis are missing, the month and the day will be imputed to January, 1st of the year specified.
- If the day of the date of the diagnosis is missing, the day will be imputed to the first day of the month specified.

[redacted]

[redacted]

Adverse events

Missing and/or incomplete dates/times for AEs are imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking additionally into account that the start

[redacted]

[redacted]

date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing. This will be done as follows:

For a missing/incomplete start date/time the minimum of the following will be imputed:

- The maximum of the earliest possible start date/time and the date/time of first study medication administration.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the maximum of the following will be imputed:

- The minimum of the latest possible stop date/time and the date/time of last study medication administration.
- The earliest possible stop date/time.
- The earliest possible start date/time.

The earliest/latest possible date is defined as:

- The date itself if it is complete.
- The date of the first/last day of the month, if month and year are available but day is missing.
- The date of the first/last day of the year, if year is available but day and month are missing.
- A very early/late date, e.g., 01JAN2000 (01JAN2100), if the date is completely missing.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study medication. A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, 'Severe' will be imputed. If causality data is missing, 'Related to study medication' will be imputed. In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in summary tables.

Clinical Laboratory Evaluations

TSAT should be calculated as Total Iron /Total Iron Binding Capacity (TIBC) X 100 as per current SSW, while TIBC is calculated as sum of Total Iron and Unsaturated Iron Binding Capacity (UIBC).

UIBC values reported below the lower level of quantification (LLOQ) i.e. "< 5.0 µmol/L" should be imputed to zero, to avoid that TSAT values will be reported as "Unable to calculate".

[redacted]

[redacted]

5.2 Demographics and Baseline Subject Characteristics

Number of subjects screened will be summarised by treatment group and number and percents of subjects randomised and/or re-screened will be also summarised. Data of subjects included and excluded in FAS, PPS, and Safety Set with the reason of exclusion of any analysis set will be summarised and listed.

Reasons of exclusion from the Safety Set will be presented as follows:

- Not randomised,
- No treatment received.

Reasons of exclusion from the FAS will be presented as follows:

- Not randomised,
- No treatment received,
- No post-baseline assessment.

Subject demographic: sex, age, age in categories for adults: 18-29/30-49/50-65 years, race: American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/Other/Not Reported/Unknown, ethnicity: Hispanic or Latino/Not Hispanic or Latino/Not Reported/Unknown will be collected on the Demographics CRF page.

Baseline characteristics data at screening or at baseline (see section 5.1.2. for definition of the baseline):

- body weight, body weight in categories (<60, ≥60 kg), body mass index (BMI), BMI in categories for adults: <18.5,18.5-25/25-30/≥30 kg/m² will be collected on the Vital Signs CRF page
- iron parameters (total serum iron, ferritin, transferrin, calculated TSAT) will be collected from Central Lab.
- aetiology of beta-thalassemia (i.e. beta-thal Genotype if available and/or Beta-thal diagnosis) and the time to first treatment intake from the date of the diagnosis (in years), blood transfusion history (Yes/No) will be collected with time of last transfusion (in months) at treatment start for subjects with blood transfusion history on the Aetiology and Clinical Presentation, Transfusion CRF page.
- haemoglobin value will be collected via central review assessment.
- prior or ongoing at baseline iron chelation therapy (Anatomical Therapeutic Chemical (ATC) code = V03AC) will be collected in Prior or Concomitant Medication CRF page.
- prior or ongoing at baseline Hydroxyurea therapy (ATC code = L01XX) will be collected in Prior or Concomitant Medication CRF page.
- prior splenectomy (yes, no) subjects with at least one splenectomy recorded will be presented as splenectomy = yes.
- MRI Liver iron content (mg/g dry weight) will be collected from MRI central reading.

The Demographics and baseline Characteristics will be summarized and listed.

[redacted]

[redacted]

5.3 Medical History and Concurrent Medical Conditions

Medical history will consist of significant conditions or diseases that stopped at or before Screening. Ongoing conditions will be considered as concurrent medical conditions. Medical history and concurrent medical conditions will be coded using MedDRA [Version 23.0 or higher]. All medical history and associated concurrent medication condition will be listed, and the number and percentage of subjects with any medical history as well as number of events will be summarized by SOC and preferred term for each treatment group.

5.4 Prior and Concomitant Medications and Procedures

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) dictionary [Mar2020 B3G].

Prior medications will be defined as all medications taken before the first dose of study drug with a stop date prior to the first dose of study drug.

Concomitant medications will be defined as all medications with a start date before, on or after the first dose of study drug and with a stop date on or after the first dose of study drug or with a missing stop date.

Prior and concomitant medication will be summarized by number and percentage of subjects. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of treatment group and decreasing frequency of drug in a given drug class (therapeutic subgroup [2nd level of the ATC classification], chemical subgroup [4th level of the ATC classification] and Preferred Name). In case of equal frequency regarding drug, alphabetical order will be used. A same medication or procedure during the study for one subject will be counted once.

Prior procedures will be defined as all procedures performed before the first dose of study drug with a stop date prior to the first dose of study drug.

Concomitant procedures will be defined as all procedures with a start date before, on or after the first dose of study drug and with a stop date on or after the first dose of study drug or with a missing stop date.

Prior and concomitant procedures will be summarized by displaying the counts and percentages of subjects with at least 1 prior procedures, 1 concomitant procedures and the number of prior and concomitant procedures.

Listings with all prior and concomitant medications and procedures will be provided including the flag for prior, concomitant. Study days will be displayed with start and stop dates.

[redacted]

[redacted]

5.5 Study Drug Exposure and Compliance

The total amount of study drug taken will be calculated for each subject from the difference between the amount of drug given and the amount of drug returned. It will be compared to the amount expected to be taken by subject to calculate the percentage compliance to treatment.

Duration of study drug (in days) = Date of last intake of study medication – Start date of treatment +1

Total amount of study drug (number of capsules) = Number of capsules dispensed - Number of capsules returned

Expected amount of study drug (number of capsules) will be defined depending of body weight at screening as follows:

- if body weight at screening < 60 kg, (study day of date of visit Week 12/EOT - 1) x 2 +1
- if body weight at screening >= 60 kg, (study day of date of visit Week 12/EOT-1) x 4 +2

Overall compliance (%) = (Total amount of study drug / Expected amount of study drug)*100.

Morning dose compliance will be calculated and described after study unblinding. Indeed, identification of the kit numbers to the Morning doses or Evening doses will be needed for the calculation.

Total morning amount of study drug (number of capsules) = Number of morning capsules dispensed - Number of morning capsules returned

Expected morning amount of study drug (number of capsules) will be defined depending of body weight at screening as follows:

- if body weight at screening < 60 kg, (study day of date of visit Week 12/EOT-1) +1
- if body weight at screening >= 60 kg, (study day of date of visit week 12/EOT-1) x 2 + 2

Morning compliance (%) = (Total morning amount of study drug / Expected morning amount of study drug)*100.

The duration of study participation (Date of last assessment – Date of first dose of study drug +1) will be also calculated for each subject and described in summary table. Date of last assessment will be defined as the latest date out of: last contact date, laboratory assessment date, concomitant medication/concomitant procedure/adverse event start date or end date, physical examination date, vital sign assessment date, ECG assessment date, etc..

Study days will be displayed with dispensation, interruption and end dates in listings.

[redacted]

[redacted]

VIFOR PHARMA

5.6 Efficacy Analyses

5.6.1 Primary Efficacy Analysis

Not applicable for this study.

5.6.2 Secondary Efficacy Analysis

Not applicable for this study.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7 Safety Analyses

Safety evaluations will be performed using the safety set and analyzed according to the analysis methods described in 5.1.1 unless specified otherwise. Missing values will not be imputed unless stated otherwise.

5.7.1 Adverse Events

Adverse events data was collected from the time that first day of treatment for the duration of the trial.

Serious adverse events reported from the time of informed consent up to 4 weeks (28±4 days) after their last administration of study treatment will be recorded as part of the study. A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity after the first dose of study medication was taken. AEs occurring or increasing in severity up to 4 weeks (28±4 days) after their last administration of study treatment, will also be classified as treatment-emergent.

[redacted]

[redacted]

A treatment-emergent serious adverse event (TESAE) is defined as a SAE occurring or increasing in severity after the first dose of study medication was taken, and including SAEs occurring up to 4 weeks (28±4 days) after their last administration of study treatment. An AE will be classified as related to study medication if the relationship to study medication was recorded as certain, probable/likely and possible. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as unlikely and unrelated.

An AE leading to study discontinuation will be defined as an AE where the reason for study withdrawal was recorded as being due to an AE on the Study Termination CRF page and the response to Other Action taken on the Adverse Events CRF page, was recorded as early study termination.

An AE leading to treatment discontinuation is defined as an AE where the action taken with study drug of the event was recorded as drug withdrawn on the 'Adverse Events' CRF page.

Adverse events will be reported on a per-subject basis and per-event. On a per-subject basis this means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst severity and the strongest relationship to the study medication. The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

The relative day of start/stop date of AE will be calculated as follows:

- Start/Stop date of AE - date of first study medication administration +1 (if start/stop date of AE is completely known);
- Imputed start/stop date of AE - date of first study medication administration +1 (if start/stop date of AE is incomplete);
- missing (if start/stop date of AE is unknown).

The duration of an AE will be calculated as follows:

- date of last study medication administration – Start date of AE + 1 (when both dates are completely known);
- Date of completion/discontinuation – Start date of AE + 1 (when the Start date of AE is fully known but the AE is not resolved at the end of the study): in this case the duration will be presented as ">x days" in the listing rather than "x days";
- missing (when the Start date of AE is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date, or when the Start date of AE is > date of completion/discontinuation and the AE is not resolved).

[redacted]

The overall summary of AEs table will include the counts and percentage of subjects with at least 1 TEAE and the number of events with each of the following, tabulated by overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on all subjects receiving placebo within each cohort:

- Any TEAEs
- Any severe TEAEs
- Any TEAEs related to study medication
- Any severe TEAEs related to study medication
- Any TEAEs leading to treatment discontinuation
- Any TEAEs leading to study discontinuation
- Any serious TEAEs
- Any serious TEAEs related to study medication
- Any TEAEs leading to death (outcome "fatal")
- Any TEAEs leading to death related to study medication

All TEAEs / serious TEAEs / TEAEs related to study medication / serious TEAEs related to study medication / severe TEAEs / moderate TEAEs / mild TEAEs / severe TEAEs related to study medication / TEAEs excluding SAEs (Clinical trial.gov and EudraCT -requirement) / TEAEs leading to treatment discontinuation / TEAEs leading to study discontinuation / TEAES leading to death will be tabulated by treatment group and overall including the number of subjects, percentage of subject with at least 1 TEAE and number of TEAEs by SOC and PT (both sorted alphabetically).

A listing of all AEs, all SAEs and all AEs leading to death with flag for AE onset outside of the on-treatment period will be provided including relative day and duration of AE.

A listing of TEAEs leading to treatment discontinuation and dose interruption will be also computed.

5.7.2 Clinical Laboratory Evaluations

A list of all protocol specified clinical laboratory tests are given in Appendix A and will be performed at screening, baseline, week 1, week 2, week 4, week 8 and week 12 for haematology, biochemistry and urinalysis and at screening, baseline, week 4 and week 12 for coagulation in accordance with the Schedule of Events in section 2.3. For analyses, Planned Assessment Windows (see Section 2.2.3) are defined for each visit.

Descriptive statistics will be performed for laboratory parameters on a continuous scale for the scores and change from baseline for each visit split by treatment group.

If multiple tests were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple tests at post-baseline visits occurring during the same visit window, the closest measurement will be used for the analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables. Laboratory values expressed as 'less than" or "greater than" will be imputed using the next numerical value (i.e. '<2.00' imputed as 1.99, ">0.3" imputed as 0.4).

Shift tables for the haematology and biochemistry laboratory parameters comparing values low, normal and high using the standard reference ranges will be presented for the baseline laboratory measurement versus the endpoint measurement for each subject. The number and percentage of subjects with abnormal values for each analyte will be summarized at each analysis visit. Abnormal values for each analyte will be determined using normal ranges provided by the central laboratory. The descriptive analysis by visit will also include an overall summary. If any of the subject's post-baseline measurements are abnormal (low or high), then the subject is classified as abnormal in the overall summary.

All laboratory results (local and central values) will be listed, including all unscheduled visits.

Only central laboratory parameters will be analysed.

eGFR formula: 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black)

Measurements of Alkaline Phosphatase (ALP) performed before the 1st of December 2020 will be recalibrated before being described with the ones recorded on or after this date. For this, those old measurements will be multiplied by 1.071 to be described with the new calibrated ALP measurements.

5.7.3 Electrocardiogram (ECG) Evaluations

Ventricular rate (bpm), PR interval (ms), QRS duration (ms), QT interval (ms), RR interval (ms), and QTcF (ms) interval will be evaluated at baseline, baseline 2h post-dose, week 1, week 2, week 4, week 8 and week 12.

A summary of abnormal clinically significant and not clinically significant electrocardiogram (ECG) results will be presented by treatment and visit. All ECG tests and results will be listed.

If multiple ECG evaluations were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple ECG evaluations at post-baseline visits occurring during the same visit window, the closets measurement to

the actual visit date will be used for the analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables.

QT corrected using Fridericia formula is defined as :

$$QTcF\,(ms) = QT\,(ms) \times \sqrt[3]{\frac{HR(bpm)}{60}}$$

Values by visit from baseline and changes from baseline by post-baseline visit for PR interval, QRS duration, QT interval and QTcF interval will be summarised on overall subjects receiving VIT-2763, subjects receiving VIT-2763 by dose daily frequency and on subjects receiving placebo.

Shift tables from baseline to maximal on treatment status (Normal/Abnormal/Missing) will be also provided.

5.7.4 Vital Signs Evaluations

The values and change from baseline results of Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg), pulse rate (bpm) and body weight (kg) will be summarised by visit split by treatment group.

For each vital signs variable, the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Baseline visit.

Vital signs will be presented for individual subjects in data listings.

If multiple vital signs evaluations were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple Vital signs evaluations at post-baseline visits occurring during the same visit window, the closest measurement to the actual visit date will be used for the analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables.

5.8 Physical Examinations

Physical examinations, including significant abnormalities, will be listed.

5.9 Other Analyses

5.9.1 Iron Pharmacodynamics Analyses

The values and change from baseline results of iron pharmadynamic parameters (serum iron, serum ferritin, serum transferrin, unsaturated iron binding capacity, calculated transferrin saturation) will be summarized and listed by treatment group and timepoints. No formal statistical tests are planned.

For each iron pharmadynamic parameters, the Baseline value is defined as the last non-missing measurement collected/during screening period.

[redacted]

5.9.2 Pharmacokinetics Analyses

The Pharmacokinetic endpoint is the plasma concentrations of VIT-2763 on Baseline, Week4, Week 8 and Week 12.

The population pharmacokinetic analysis will be described in a separate analysis plan.

Pharmacokinetic plasma concentration of VIT-2763 will be summarized and listed by treatment group and timepoints using descriptive statistics (including arithmetic mean, SD, arithmetic CV%, median, observed maximum, minimum, N and for back-transformed data geometric mean and geometric SD). No formal statistical tests are planned.

The following rules will be applied if there are values that are below the limit of quantification (BLQ) or if there are missing values (eg, no result [NR]) in a plasma concentration data sets to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If values are obtained from more than or equal to 3 subjects by dose group, the summary statistics will be calculated.
- If values are obtained from less than 3 subjects by dose group, all arithmetic and geometric summary statistics will be denoted as NC (except min and max values).

[redacted]

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APPENDICES

APPENDIX A: LABORATORY PARAMETERS

Haematology parameters:

Test Description	Conventional Units	SI Units	Number of decimal places
Haemoglobin	g/dL	g/L	1
Fetal Haemoglobin,EDTAwb,335	%	%	1
Hematocrit	%		0
RBC	x10^6/uL	TI/L	1
Mean cell volume (MCV)	fL	fL	0
mean cell Hb (MCH)	pg	pg	0
mean cell Hb concentration (MCHC)	g/dL	g/L	0
Reticulocyte Count %-CL	%	%	1
Reticulocyte Count WBEDTA-CL	x10^6/uL	TI/L	3
red cell distribution width (RDW)	%	%	1

WBC	x10^3/uL	GI/L	2
Platelets	x10^3/uL	GI/L	0

Biochemistry parameters:

Test Description	Conventional Units	SI Units	Number of decimal places
Serum Sodium	mEq/L	mmol/L	0
Serum Potassium	mEq/L	mmol/L	1
Magnesium	mg/dL	mmol/L	1
Calcium (EDTA)	mg/dL	mmol/L	1
Serum Chloride	mEq/L	mmol/L	0
Total Bilirubin	mg/dL	umol/L	1
Urea Nitrogen	mg/dL	mmol/L	0
Serum Uric Acid	mg/dL	umol/L	1
Creatinine(Rate Blanked)-2dp	mg/dL	umol/L	2
Total Protein	g/dL	g/L	1
Alkaline Phosphatase	U/L	U/L	0
AST (SGOT)	U/L	U/L	0
ALT (SGPT)	U/L	U/L	0
GGT	U/L	U/L	0
Glutamate Dehydrogenase-RUO	U/L	U/L	0
LDH	U/L	U/L	0
Haptoglobin	mg/dL	g/L	0
Serum Amylase	U/L	U/L	0
Serum Bicarbonate	mEq/L	mmol/L	1
eGFR (CKD-EPI GFR)	mL/min/1.73m^2	mL/min/1.73m^2	0
Unconjugated bilirubin (indirect bilirubin)	mg/dL	umol/L	0
Creatine Kinase	U/L	U/L	0
Folic acid (folate)	ng/mL	nmol/L	1
Vitamin B12	pg/mL	pmol/L	0
Albumin-BCG	g/dL	g/L	1

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Serum Glucose	mg/dL	mmol/L	0
Cholesterol (High Performance)	mg/dL	mmol/L	0
Triglycerides (GPO)	mg/dL	mmol/L	0
Total Iron, Serum	ug/dL	umol/L	0
Ferritin	ng/mL	ug/L	1
Unsaturated Iron Binding Capacity	ug/dL	umol/L	0
Transferrin-CL	mg/dL	g/L	3

Coagulation parameters:

Test Description	Conventional Units	SI Units	Number of decimal places
Prothrombin Time	sec	Sec	1
APTT-FSL	sec	Sec	1
Thrombin Time, Na Cit pl-CL	sec	sec	1

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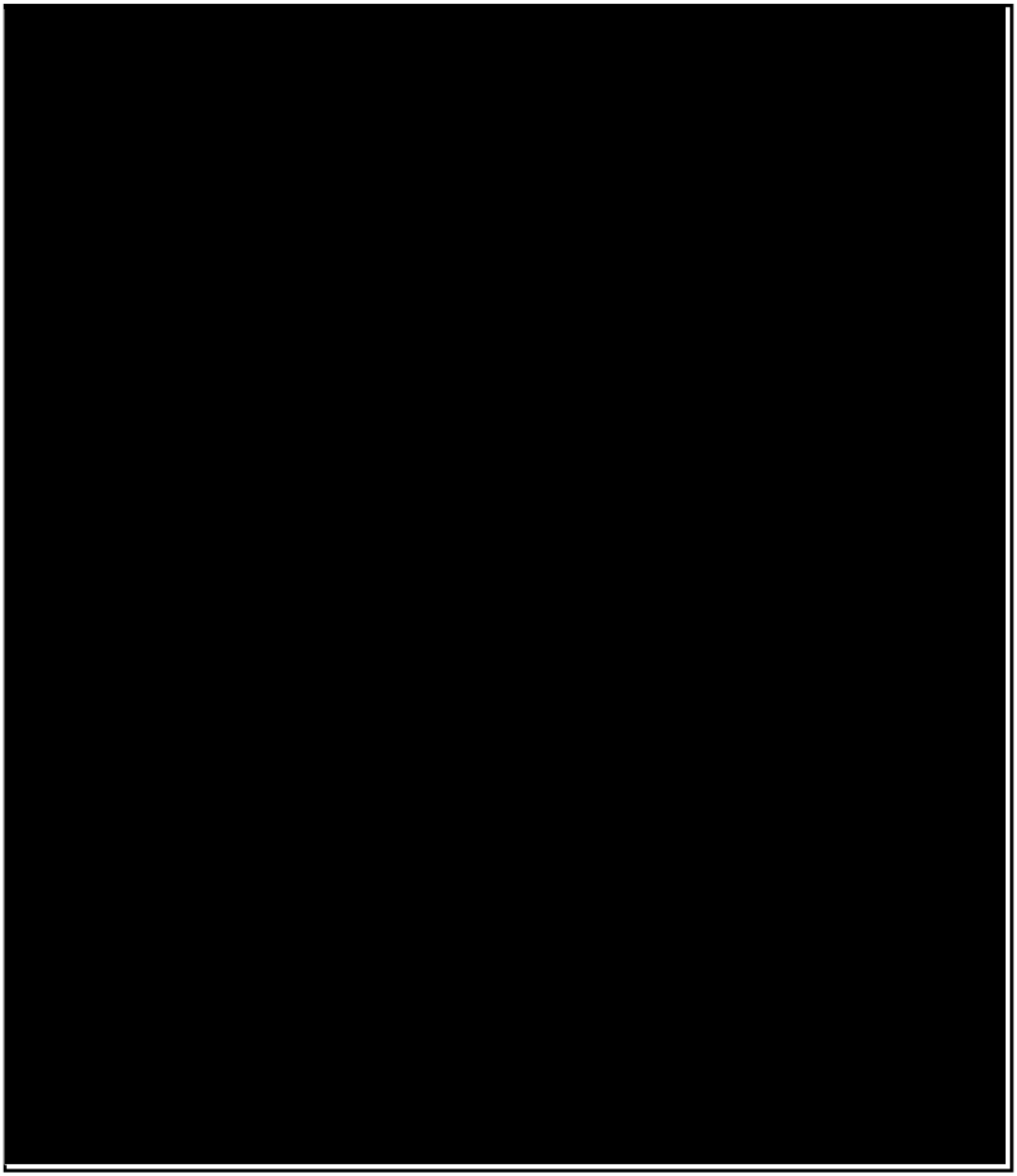

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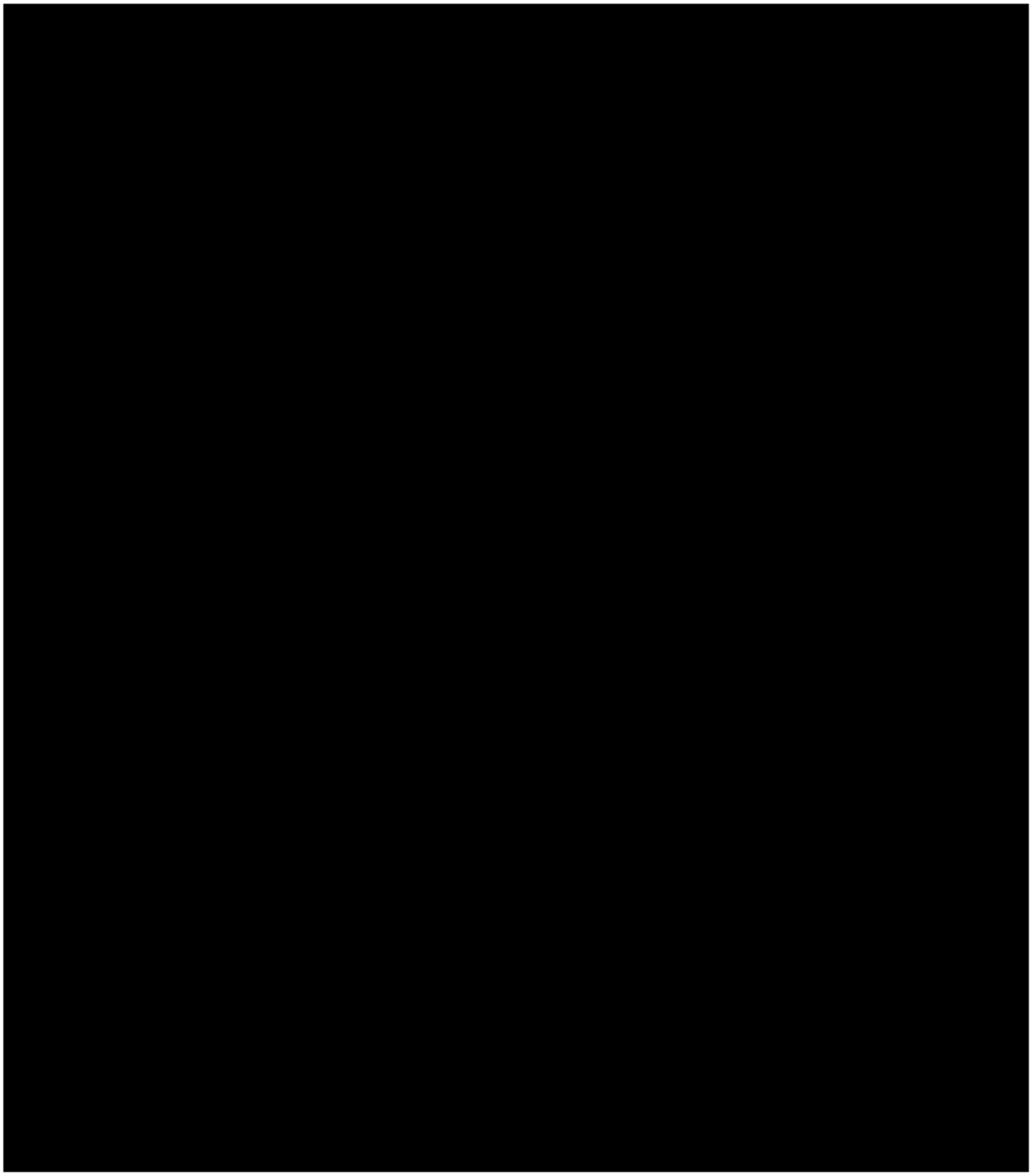

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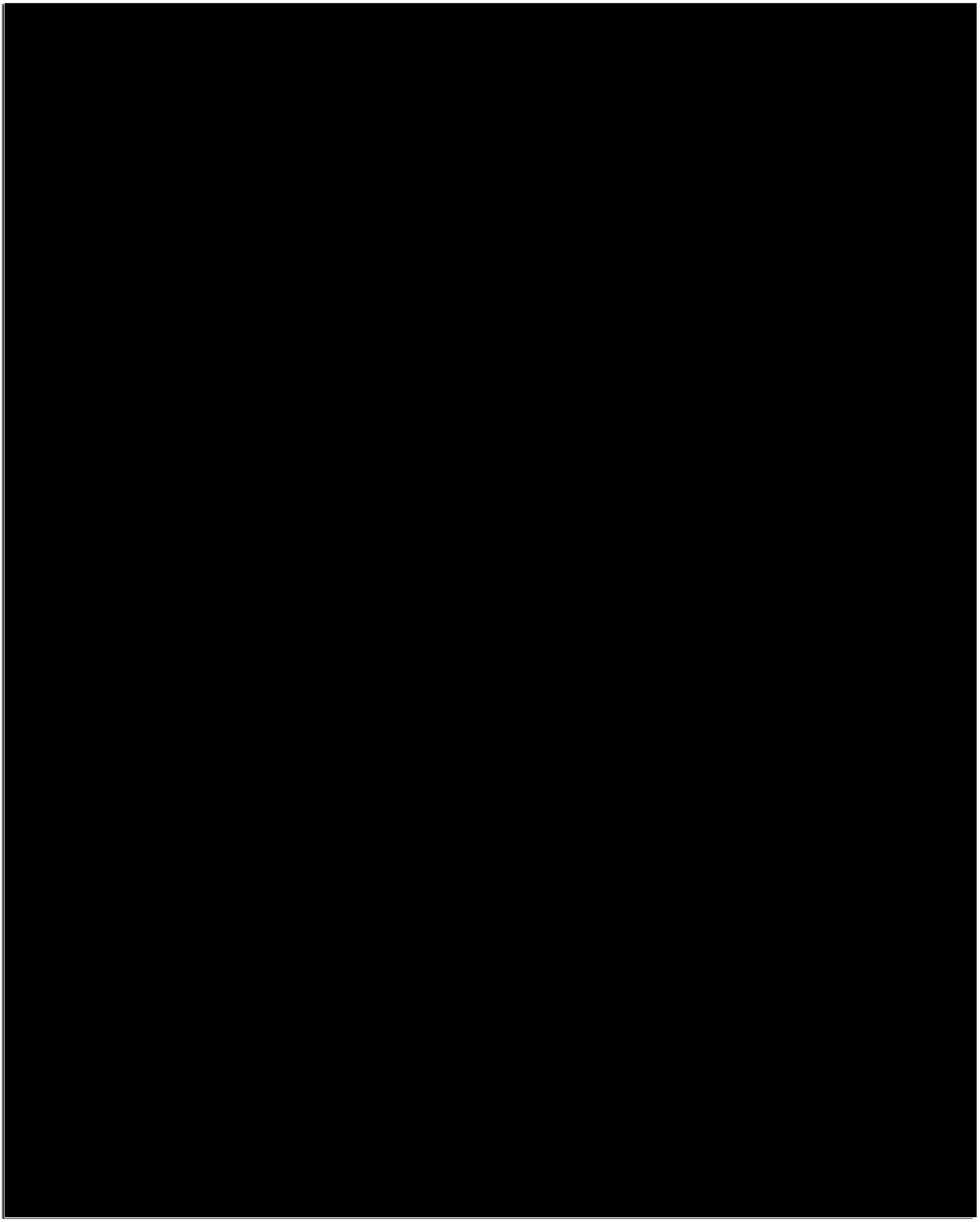

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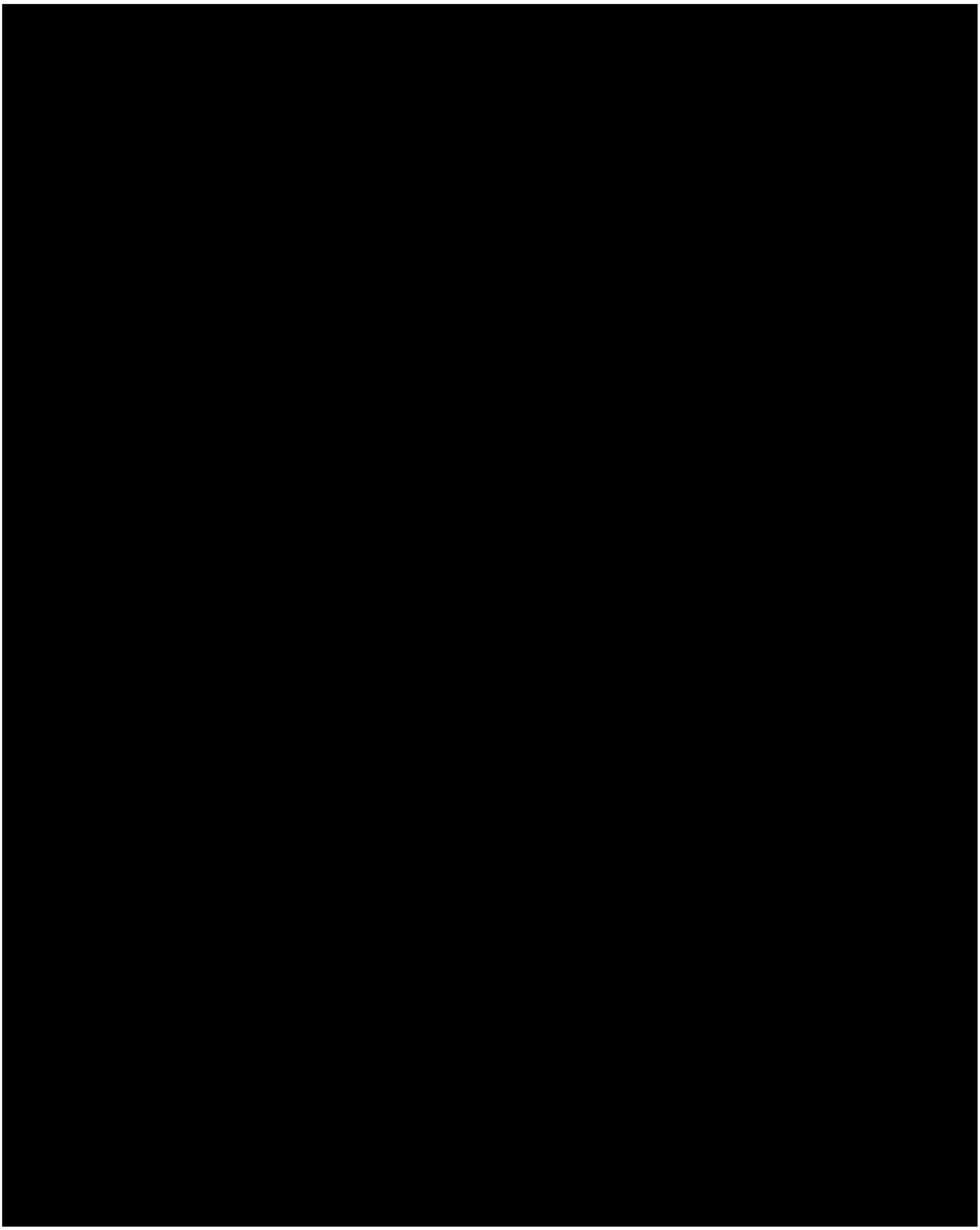

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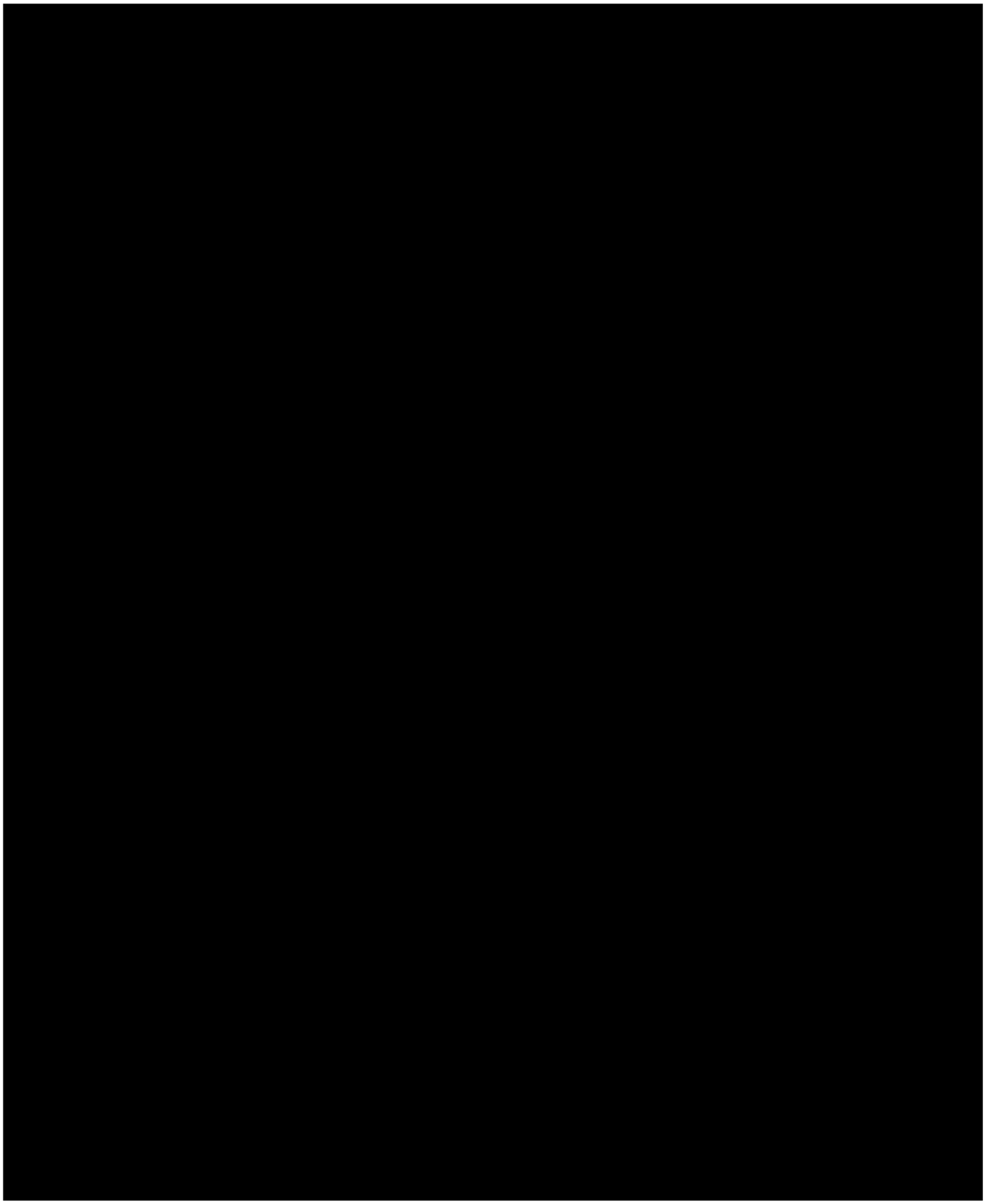

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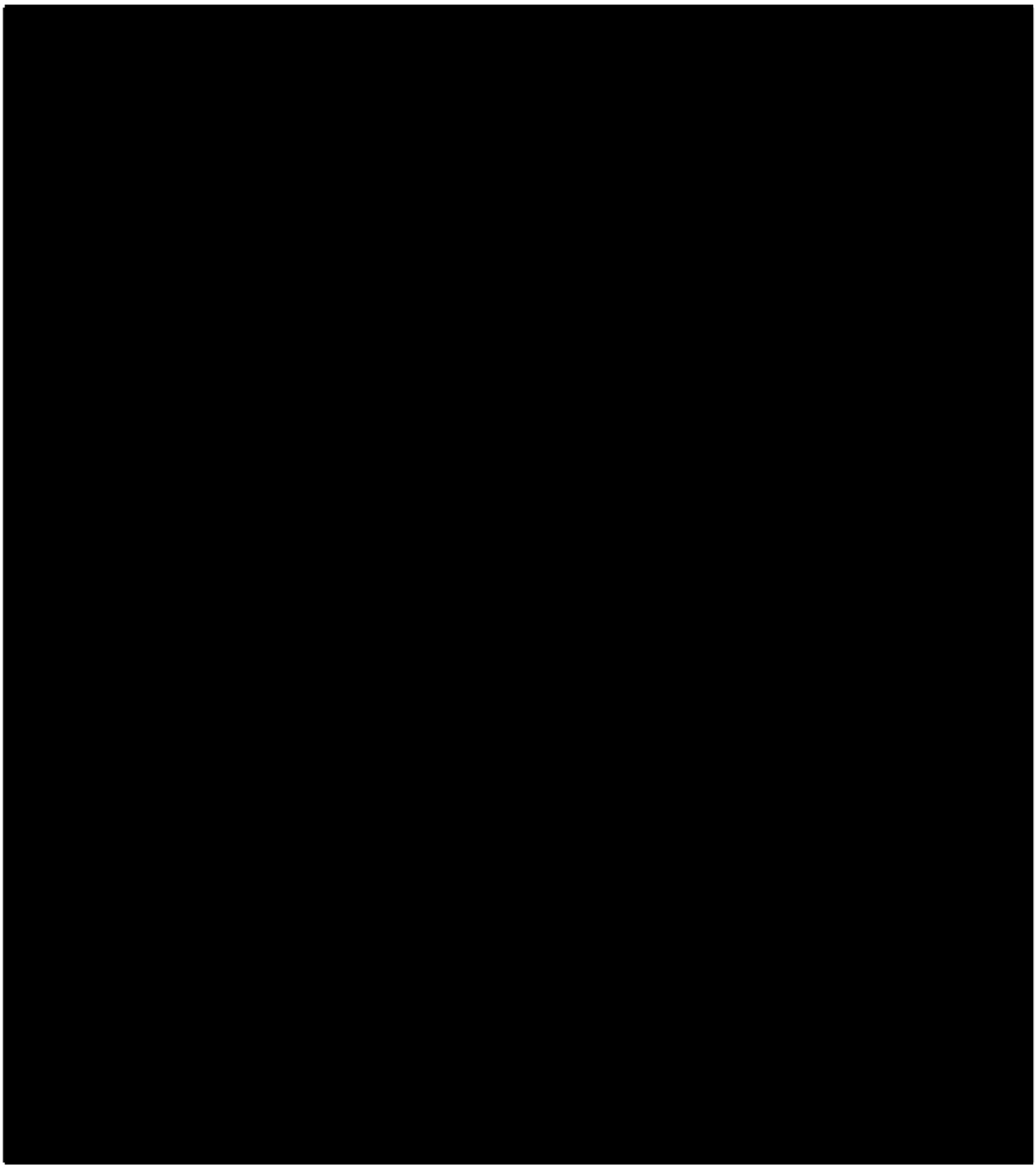

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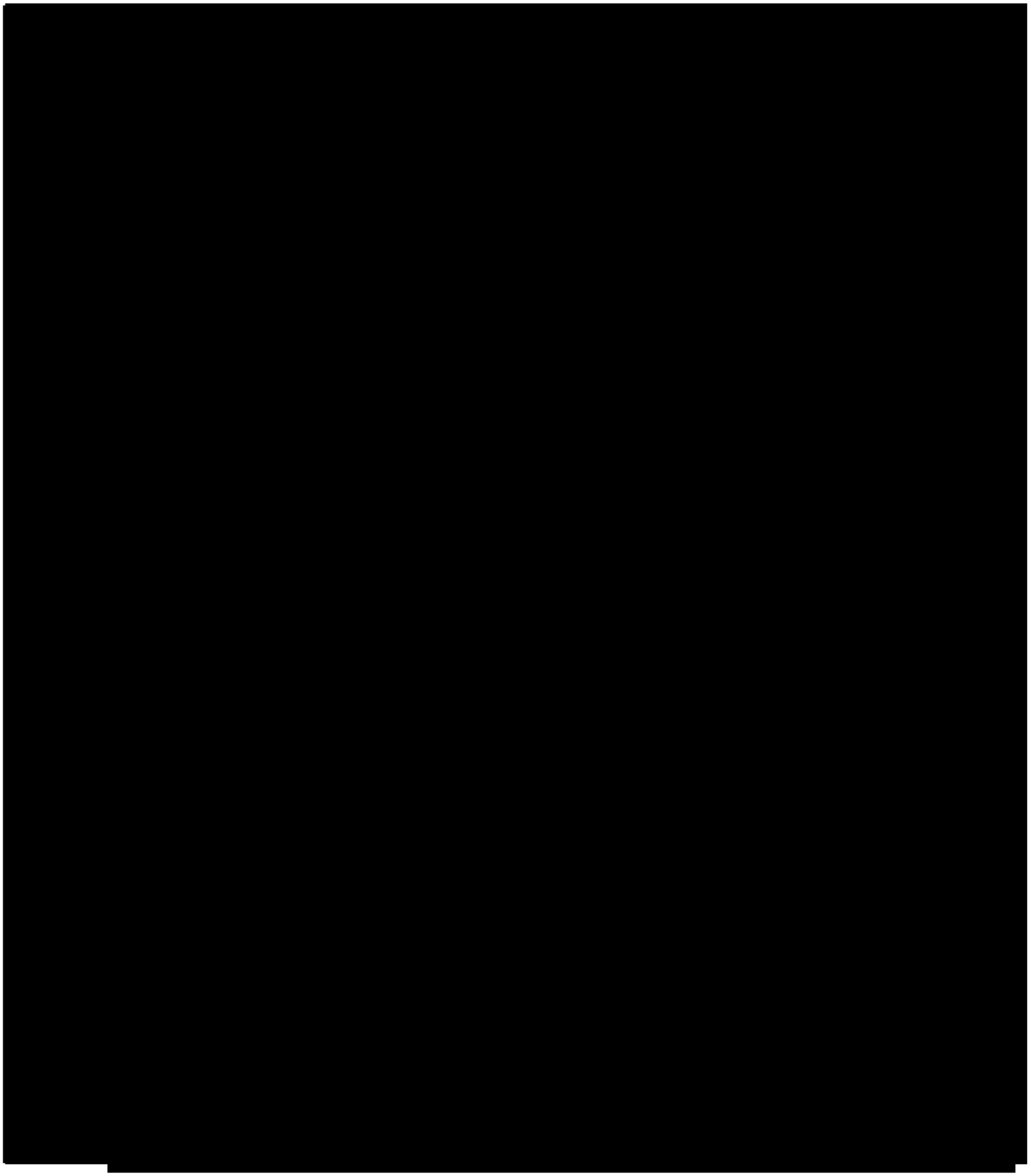

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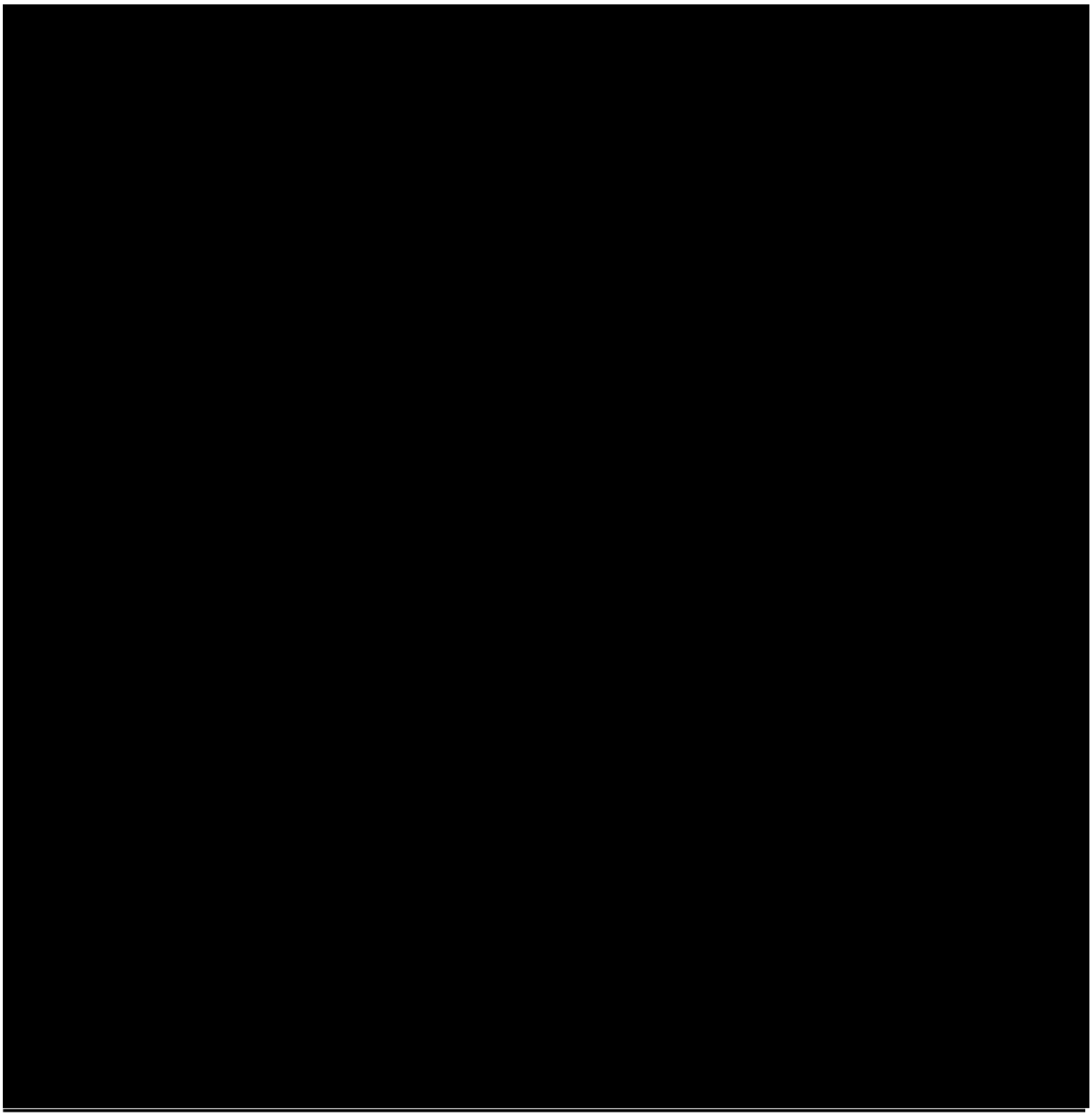

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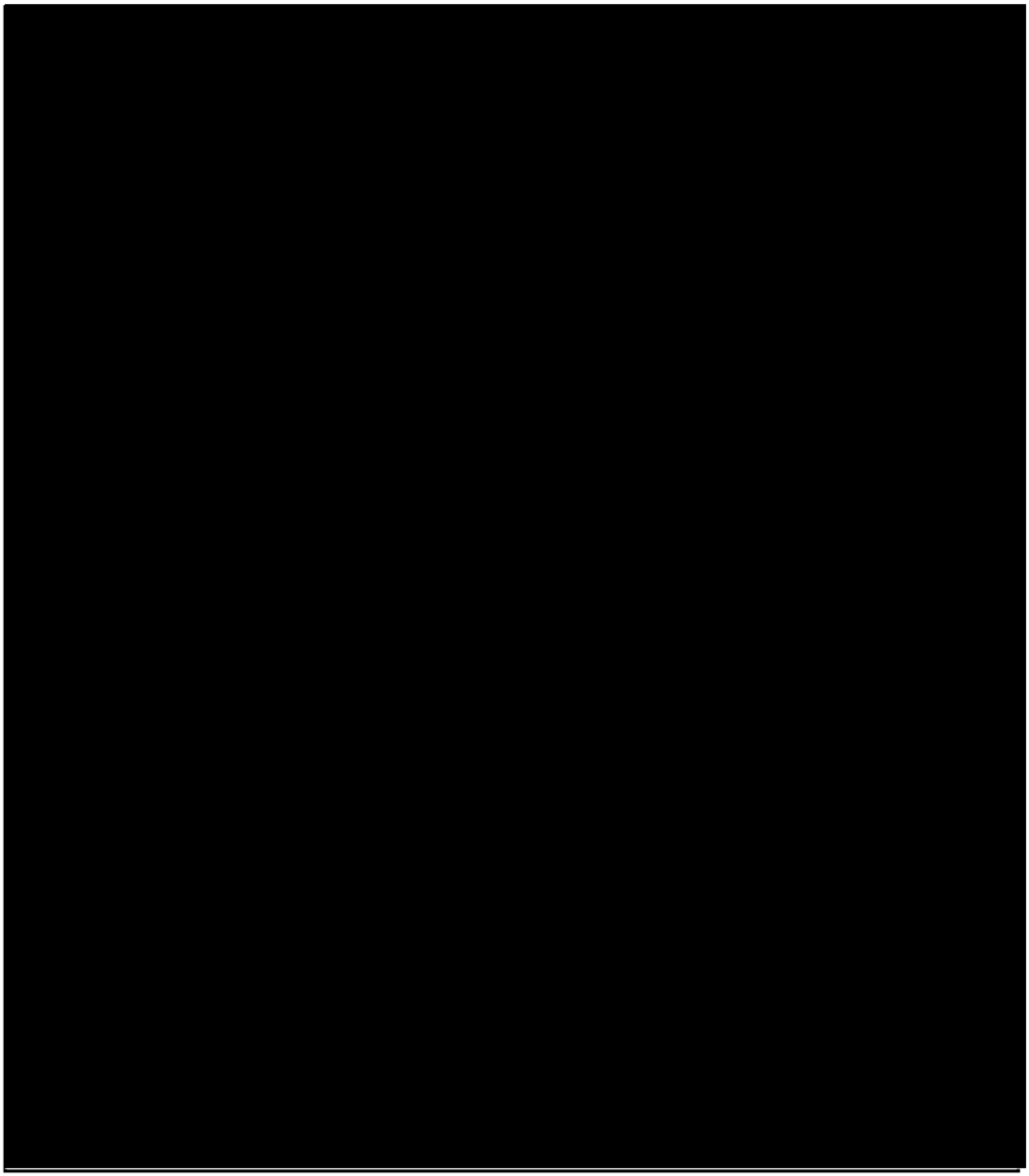

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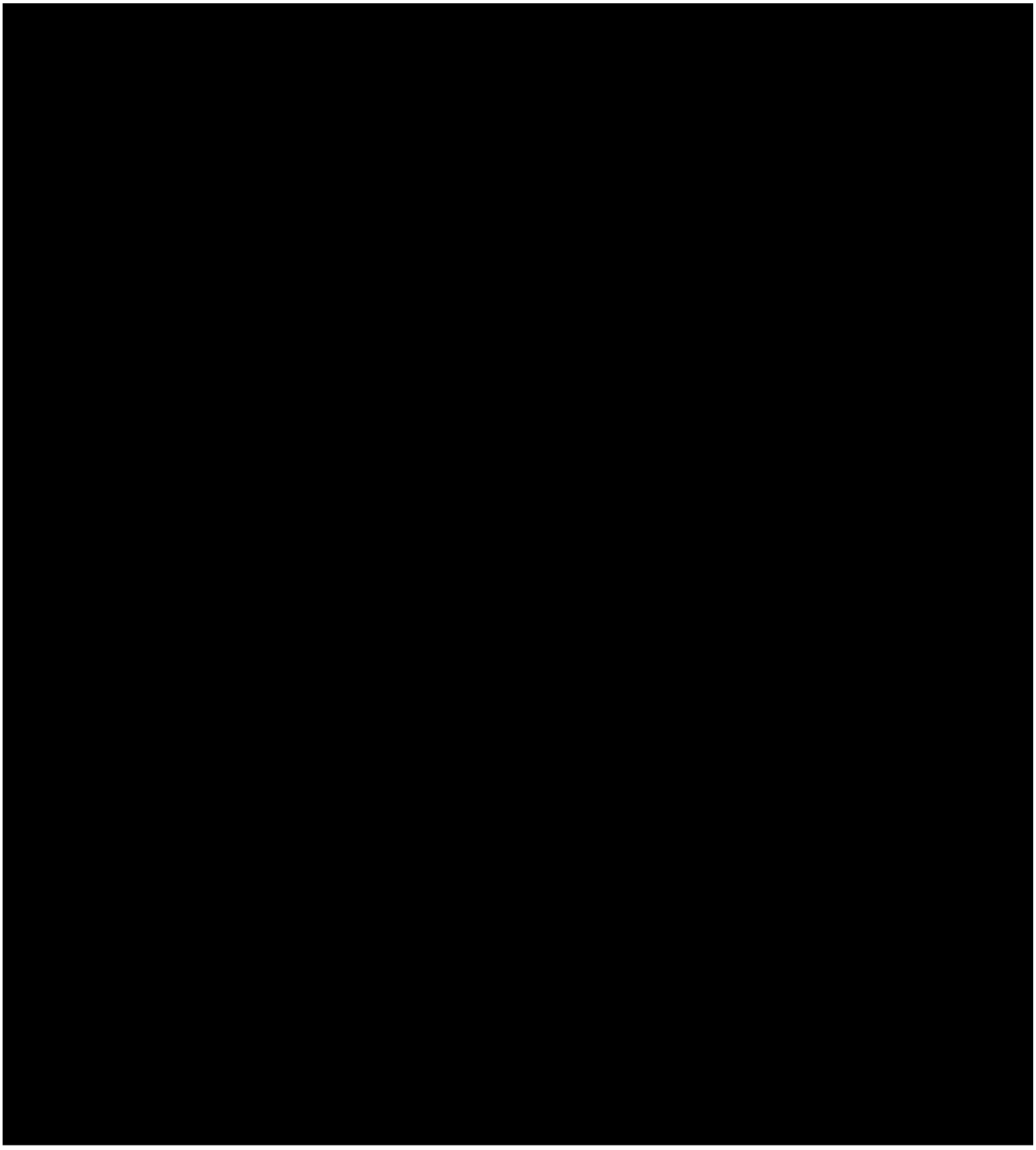

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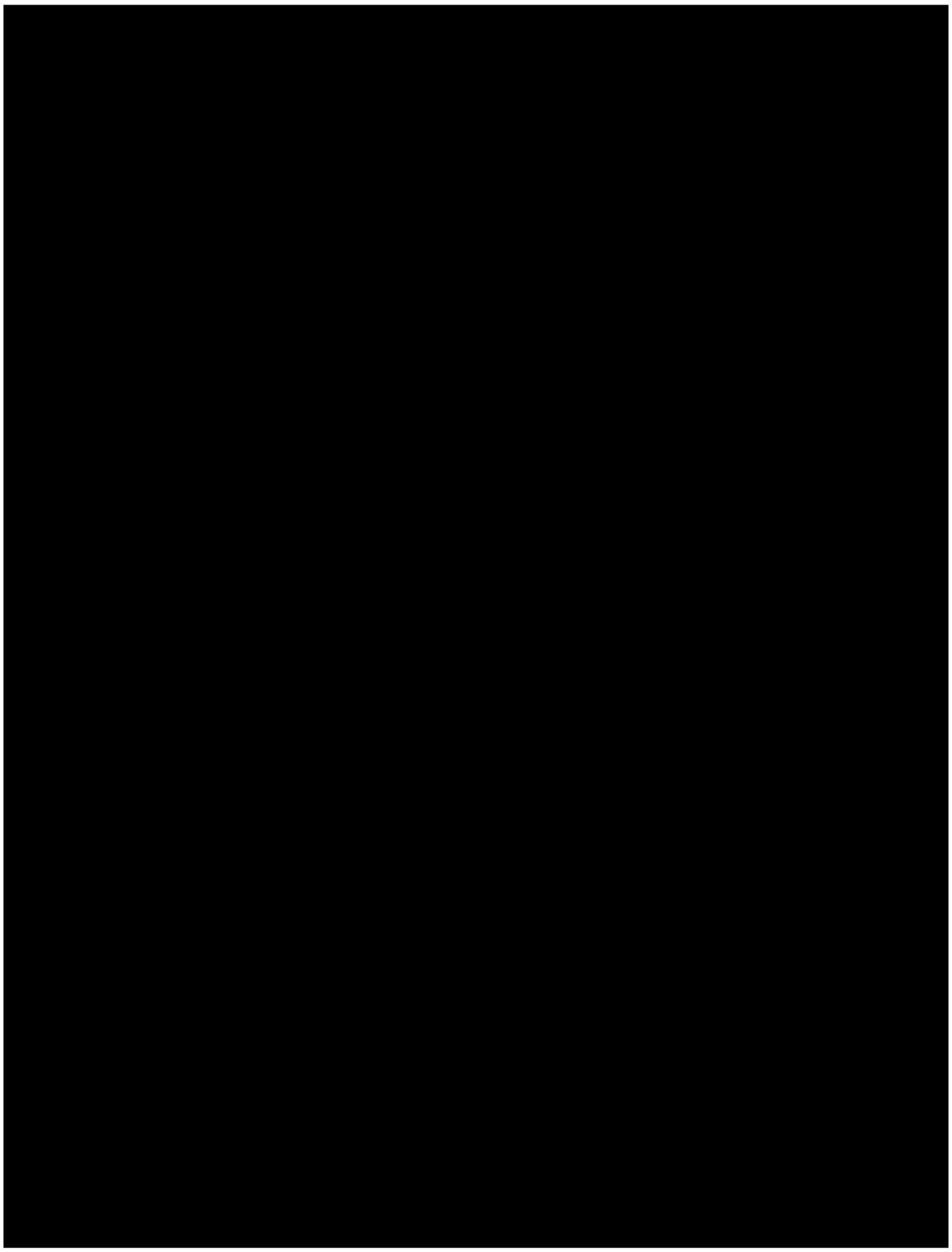

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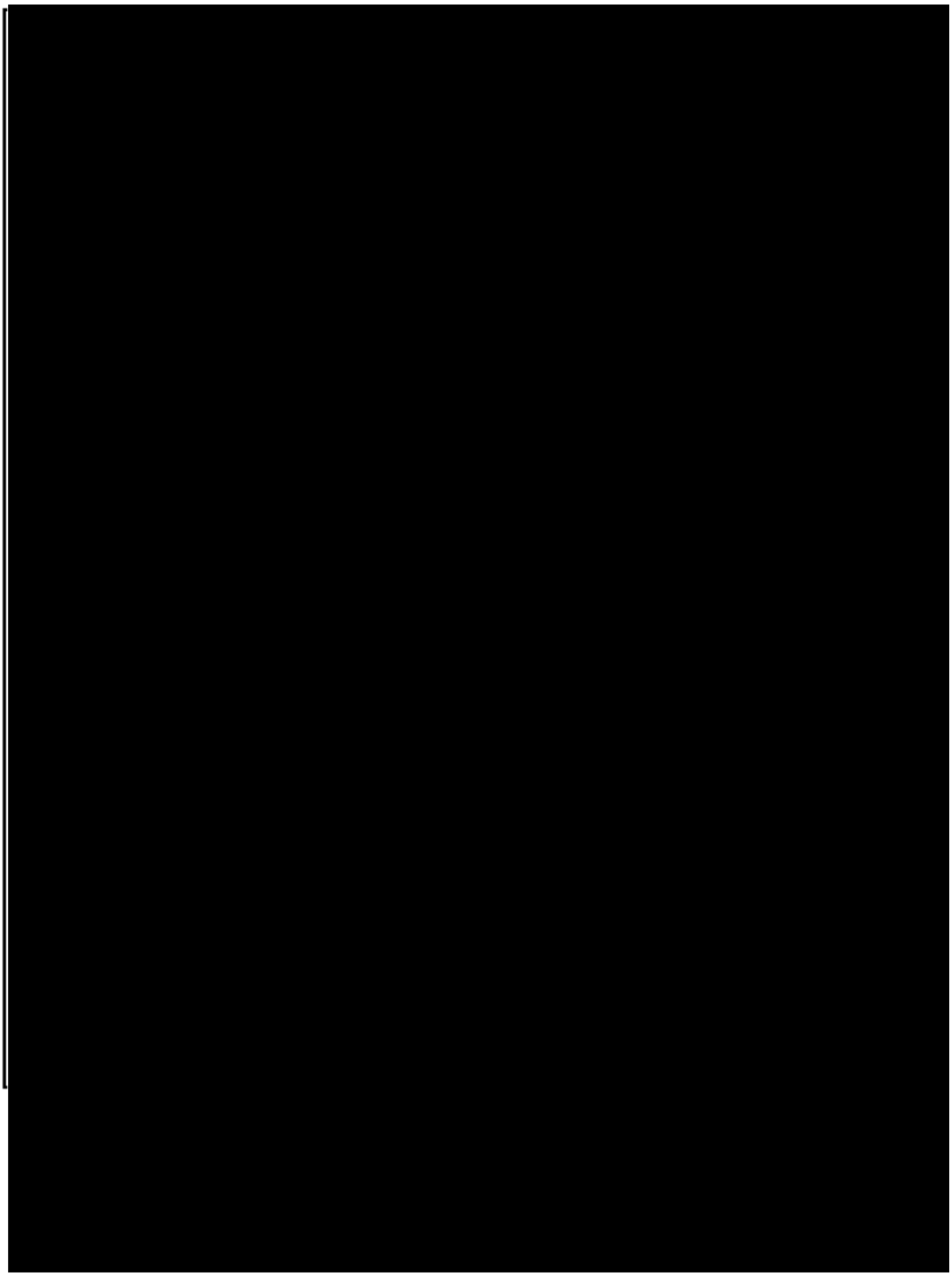

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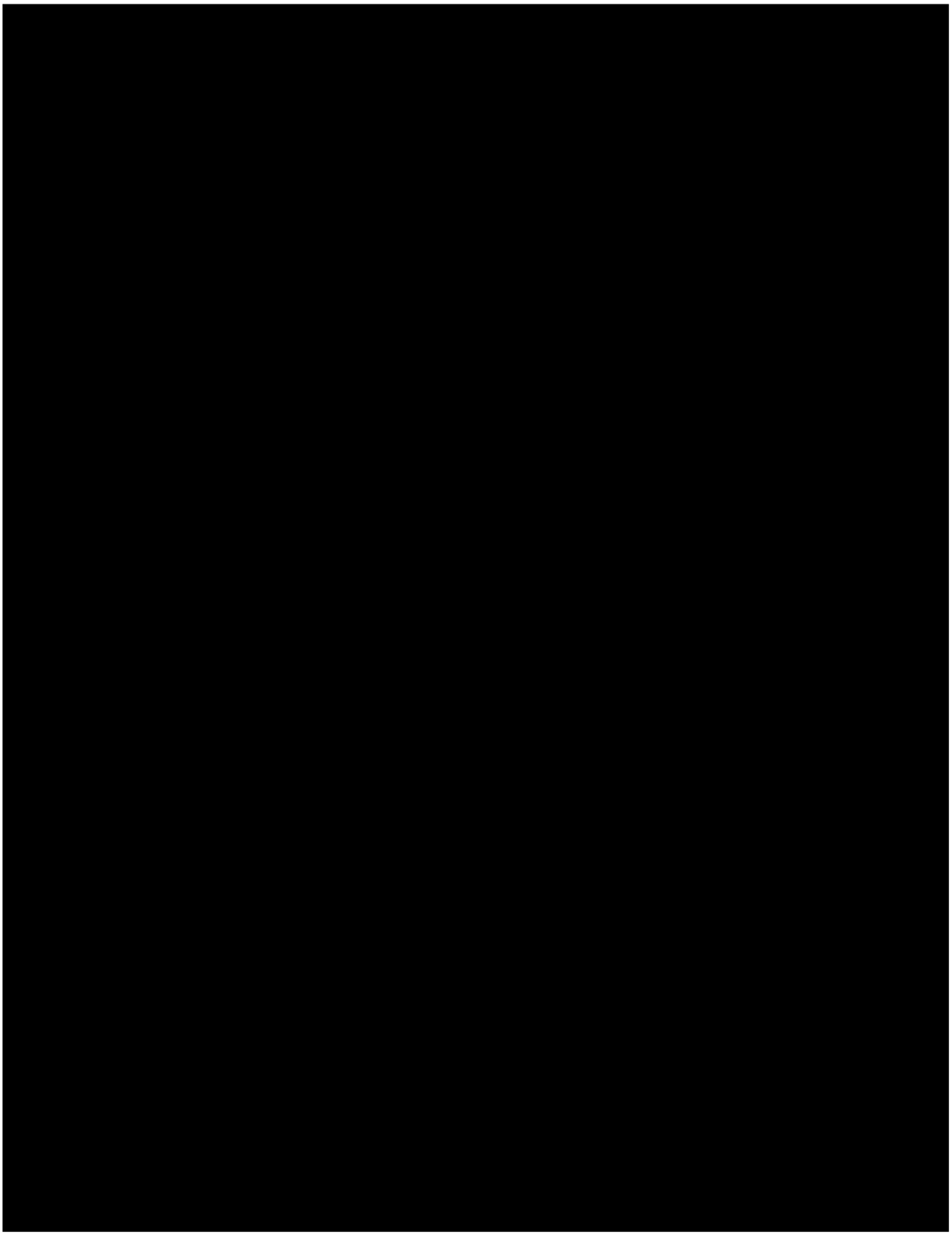

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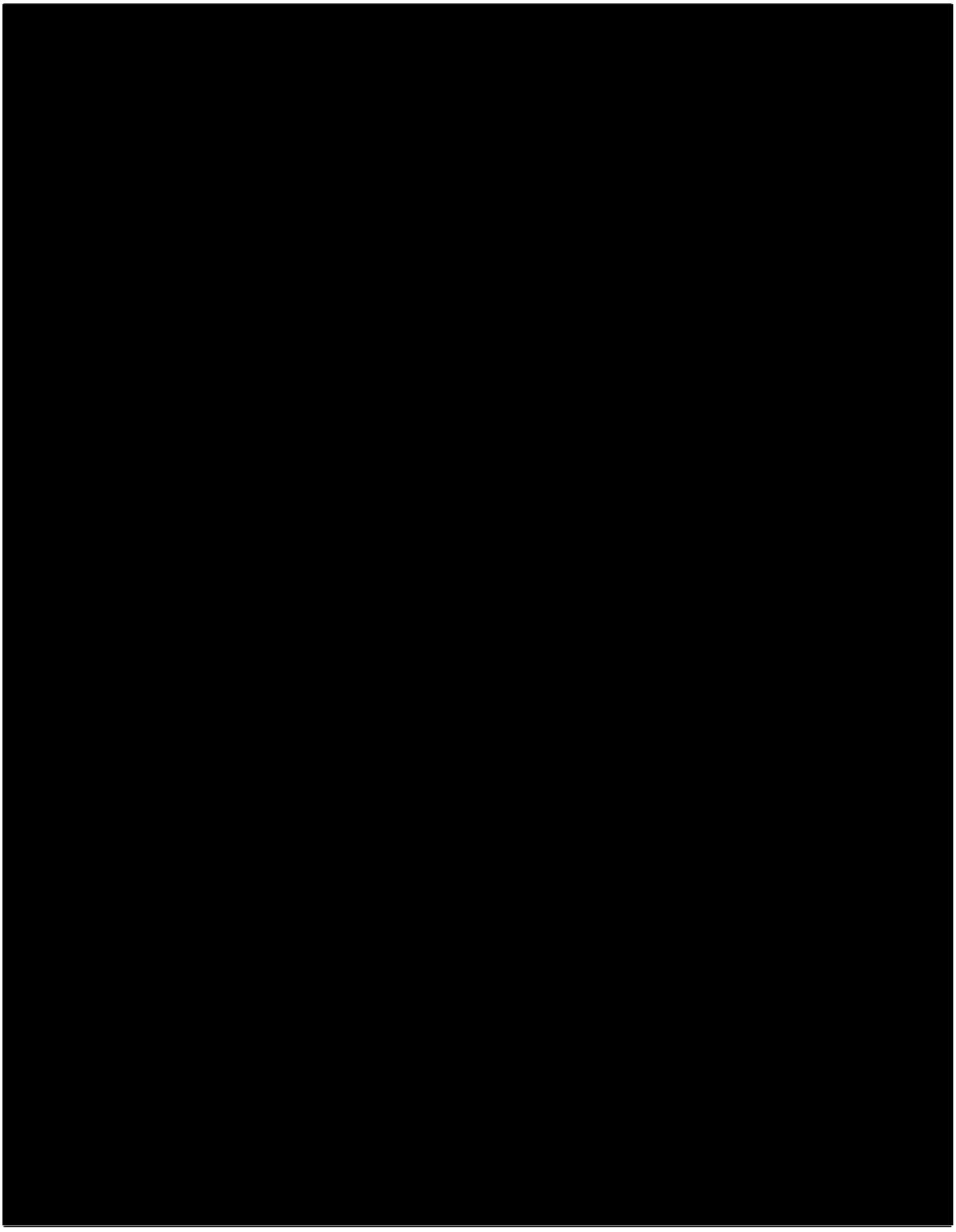

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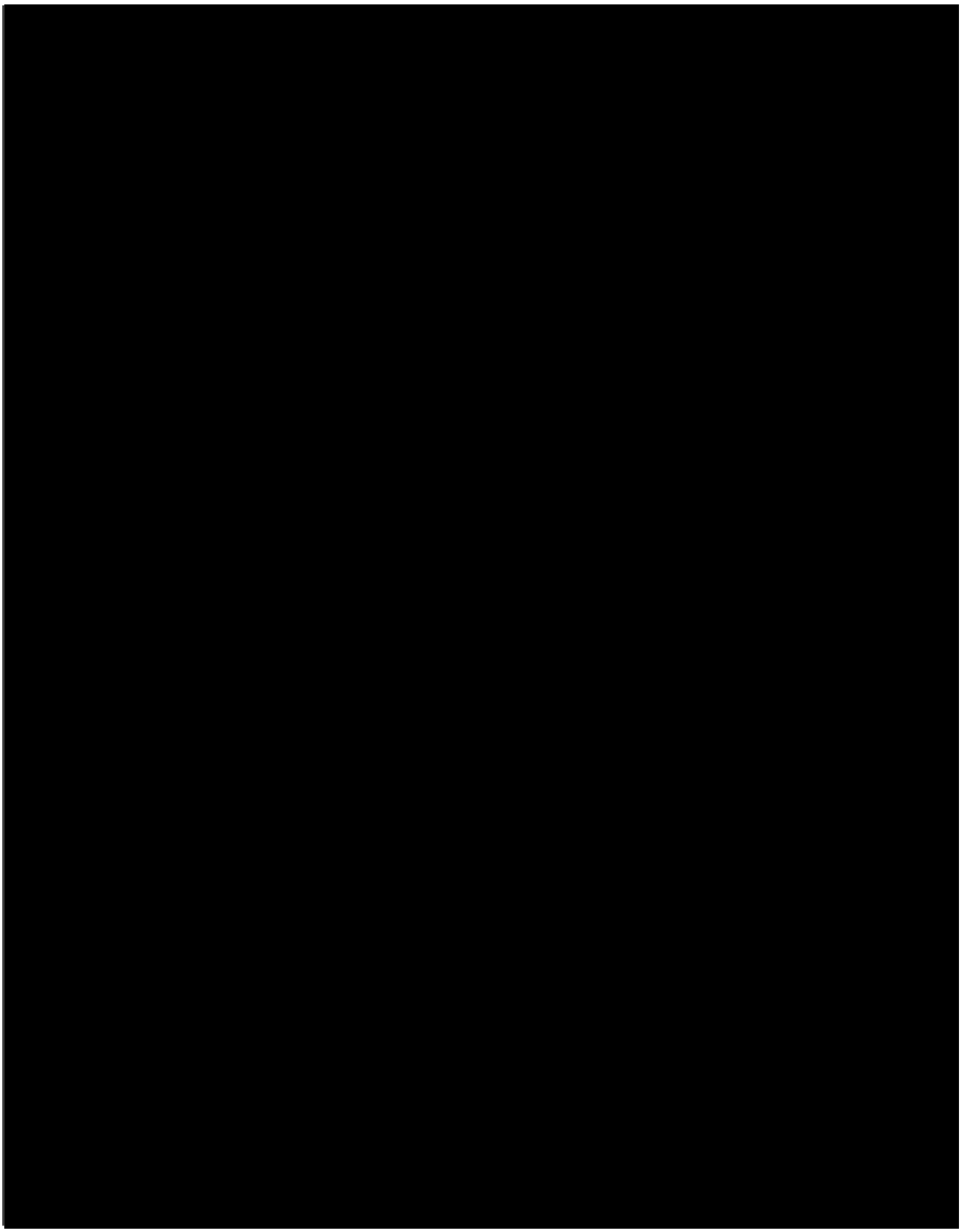

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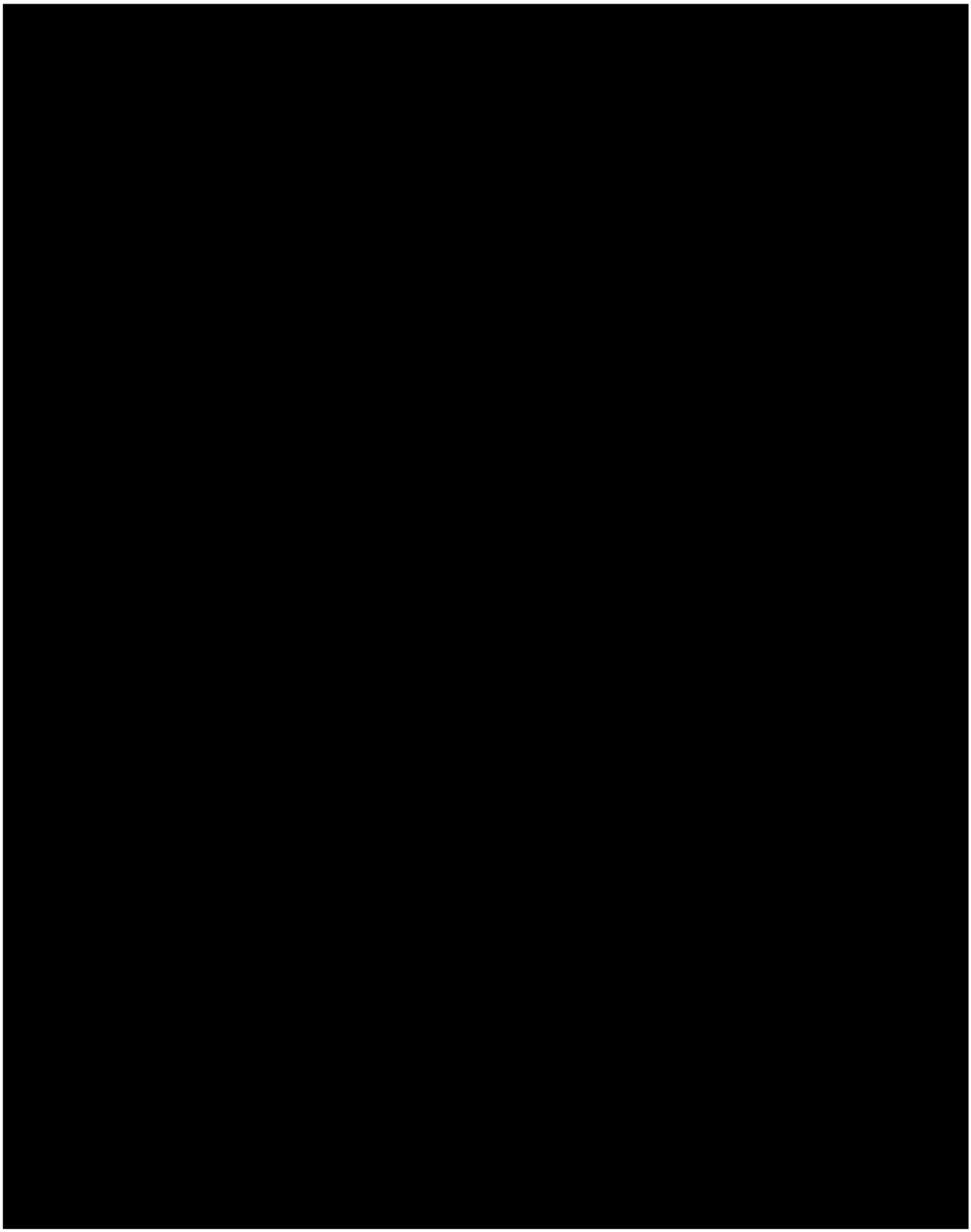

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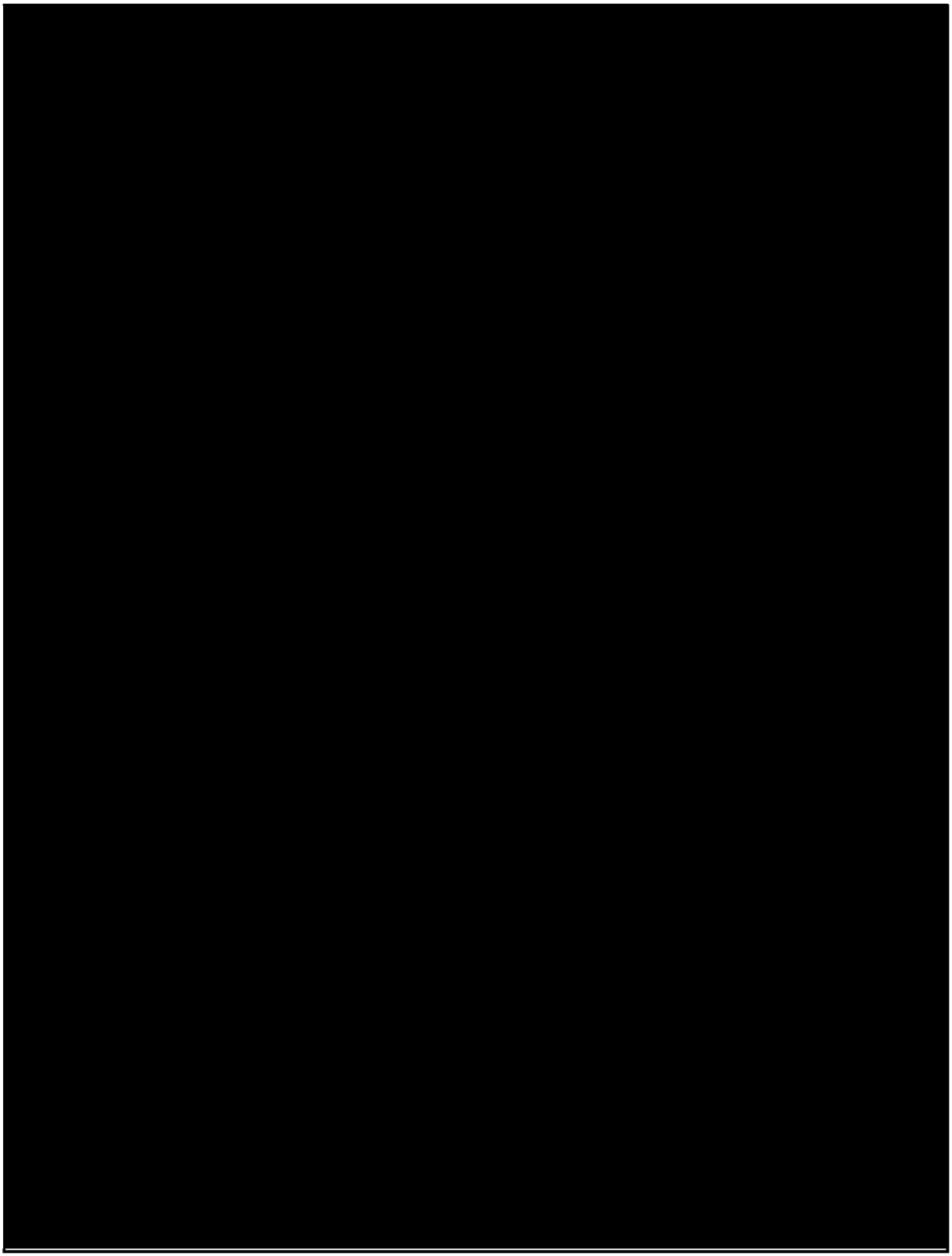

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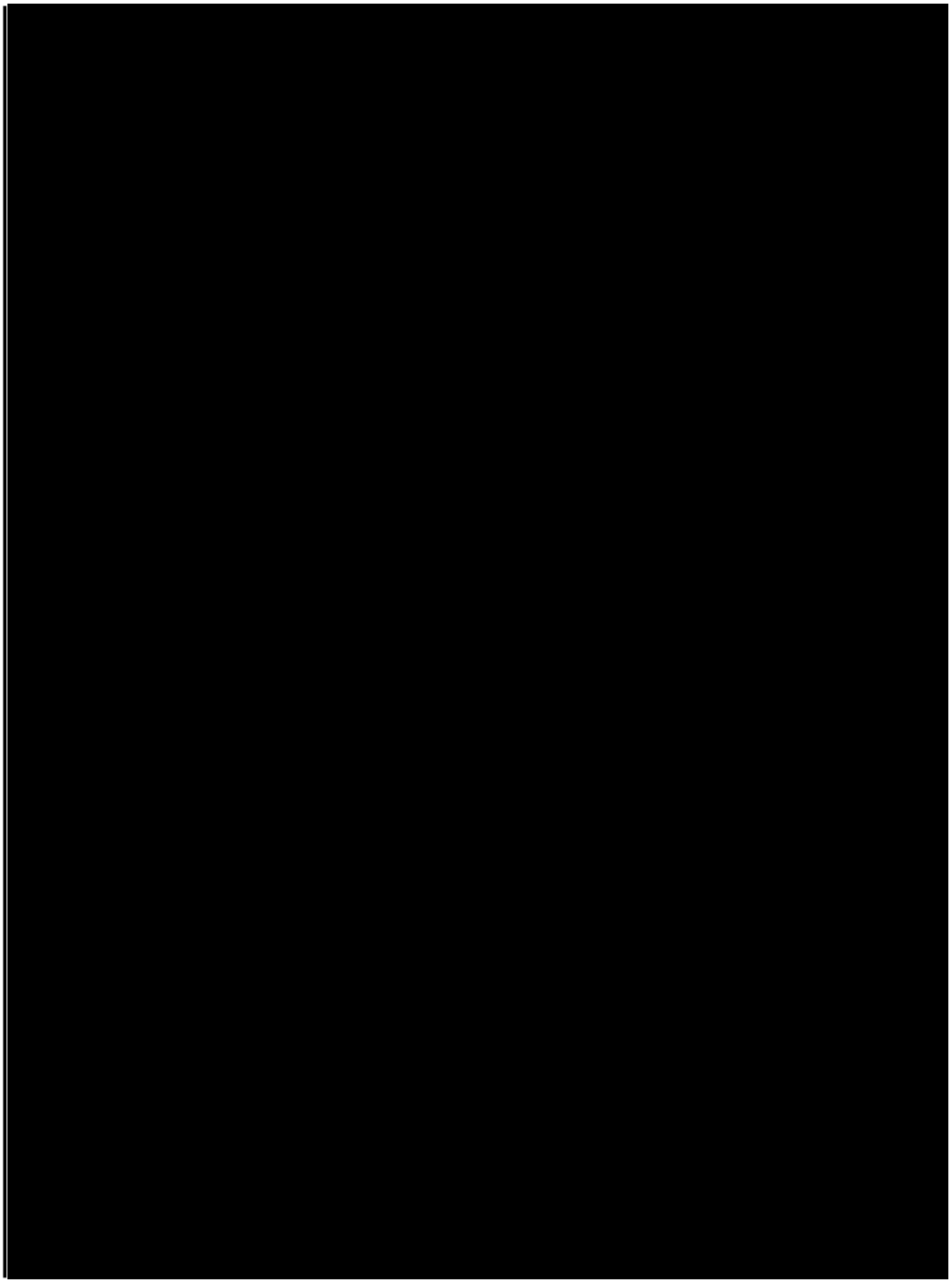

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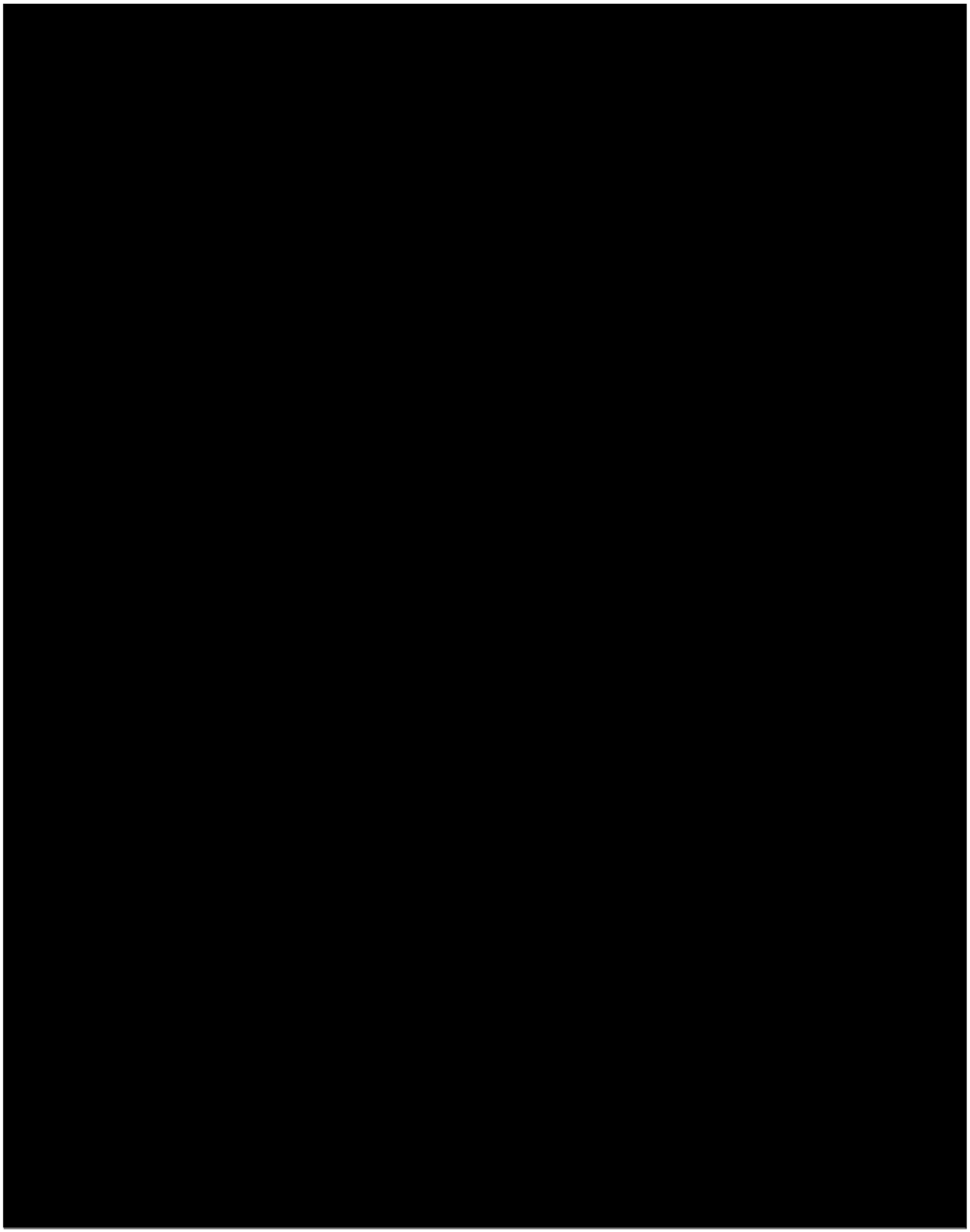

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