Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-167832

CLINICAL PROTOCOL

A Phase 1/2, Active-controlled, Randomized, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Multiple Oral Doses of OPC-167832 Tablets in Subjects with Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis

Protocol No. 323-201-00003
IND No. 129303

CONFIDENTIAL - PROPRIETARY INFORMATION

Drug Development Phase:	1/2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. Rockville, Maryland 20850, United States
Immediately Reportable Event:	Clindev Pty Ltd Fax: [redacted] E-mail: [redacted]
Issue Date:	26 Feb 2018
Amendment 1:	29 Jan 2019
Amendment 2:	25 Oct 2019
Amendment 3:	20 Dec 2019
Amendment 4:	17 Aug 2020
Amendment 5:	10 May 2021
Protocol Version Number:	6.0

Protocol 323-201-00003

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: OPC-167832	Protocol No.: 323-201-00003 IND No.: 129303
Protocol Title:	A Phase 1/2, Active-controlled, Randomized, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Multiple Oral Doses of OPC-167832 Tablets in Subjects with Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis
Clinical Phase:	Phase 1/2
Treatment Indication:	Pulmonary tuberculosis (TB)
Objectives:	**Primary:** Stage 1 To evaluate the efficacy, pharmacokinetics (PK), safety, and tolerability of multiple ascending oral doses of OPC-167832 compared with the administration of rifampicin, isoniazid, ethambutol, and pyrazinamide (RHEZ) in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB. Stage 2 • To evaluate the safety and tolerability of multiple oral doses of OPC-167832 when administered with delamanid and/or bedaquiline (BDQ) compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB. • To evaluate the PK of OPC-167832 and delamanid and/or BDQ after coadministration. **Secondary:** Stage 1 • To evaluate the relationship between OPC-167832 exposure and efficacy determined by changes of sputum lipoarabinomannan (LAM) and Mycobacteria Growth Indicator Tube® (MGIT) time to detection, after multiple ascending oral doses of OPC-167832. • To evaluate the relationship between QT interval and plasma concentrations of OPC-167832.

	Stage 2 • To evaluate the efficacy of OPC-167832 when administered with delamanid and/or BDQ compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB. • To evaluate the relationship between OPC-167832 exposure and efficacy determined by changes of sputum LAM and MGIT time to detection, after OPC-167832 when administered with delamanid and/or BDQ. • To evaluate the relationship between QT interval and plasma concentrations of OPC-167832 when administered with delamanid and/or BDQ. • To evaluate the PK of DM-6705 after coadministration of OPC-167832 and delamanid and/or BDQ. Stage 1 and Stage 2 To evaluate the efficacy, safety, and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) compared with the administration of OPC-167832 alone (data derived from stage 1).
Trial Design:	This will be a multiple-dose trial of OPC-167832 with 2 stages. Stage 1 Stage 1 will be a randomized, open-label, active-controlled, multiple ascending dose stage in approximately 72 subjects. Dosing is planned to be conducted in 4 sequential cohorts of 18 subjects each: • Cohort 1: 10 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects) • Cohort 2: 30 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects) • Cohort 3: 90 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects) • Cohort 4: 3 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects) Subjects will provide signed informed consent and be admitted to the trial site at screening. Subjects will be screened for up to 4 days (Days −6 to −3) prior to the start of the Day −2 assessments; however, screening can be extended up to 7 days, if needed. Eligible subjects will be housed at the trial site until discharge or early termination.

In Cohort 1, subjects will be randomized to 10 mg OPC-167832 or RHEZ prior to first dosing on Day 1. Subjects randomized to OPC-167832 will receive once daily (QD) oral doses of investigational medicinal product (IMP; OPC-167832) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected. After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

Following review of the safety, tolerability, PK, and efficacy data from Cohort 1, a decision will be made to start Cohort 2. Cohort 2 will be completed as described above for Cohort 1 at the selected dose of OPC-167832. The same process will be followed for Cohort 3 after the completion of Cohort 2 and for Cohort 4 after the completion of Cohort 3.

The safety, tolerability, PK, and efficacy (results from Otsuka TB LAM enzyme-linked immunosorbent assay [ELISA] only) data from each cohort will be reviewed by the trial review team at the end of each cohort. Once all the data for dose selection for the next cohort are available, the data collected from each cohort will be provided to the trial review team. The data will be evaluated to determine if (i) the dose level for the next cohort will be escalated, (ii) the dose level from the previous cohort will be repeated, or (iii) the dose level will be decreased. The dose of OPC-167832 will not exceed the highest tolerated dose studied in the single ascending dose trial, ie, 480 mg.

For efficacy, the selection of the dose level for each cohort after Cohort 1 will be assisted by the results of the Otsuka TB

	LAM ELISA instead of solid media culture, since those results are available in near real time and will facilitate faster decisions.
	<u>Stage 2</u> Stage 2 will be a randomized, open-label, active-controlled, parallel group comparison stage comprising of 46 subjects (subjects who were randomized in stage 1 cannot enroll in stage 2). Subjects will provide signed informed consent and be admitted to the trial site at screening. Subjects will be screened for up to 4 days (Days −6 to −3) prior to the start of the Day −2 assessments; however, screening can be extended up to 7 days, if needed. Eligible subjects will be housed at the trial site until discharge or early termination. All subjects enrolled during this stage of the trial will be randomized prior to first dosing on Day 1 to one of the following 4 treatments in a ratio of 14:14:14:4: • 30 mg OPC-167832 and 300 mg delamanid QD (14 subjects) • 30 mg OPC-167832 and 400 mg BDQ QD (14 subjects) • 30 mg OPC-167832 and 300 mg delamanid and 400 mg BDQ QD (14 subjects) • RHEZ QD (4 subjects) • Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for Days 3 to 14 Based on the stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in $\log_{10}$CFU, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose. Subjects randomized to OPC-167832 and/or delamanid and/or BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward. Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

	Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected. After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.
Subject Population:	Approximately 118 male or female subjects with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary TB who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled and randomized into this trial. In stage 1, approximately 72 subjects will be enrolled and randomized to 1 of 4 cohorts (18 subjects per cohort). Approximately 46 subjects will be enrolled and randomized in stage 2. Subjects who were randomized to stage 1 cannot enroll in stage 2.
Inclusion/Exclusion Criteria:	Subjects are required to meet the following inclusion criteria (summary of main criteria): • Male or female subjects between 18 and 64 years of age (inclusive) with newly diagnosed (within the 3 months prior to screening), uncomplicated, drug-susceptible (rifampicin and isoniazid susceptible) pulmonary TB. • Microscopy performed on a sputum smear indicates presence of acid-fast bacilli (at least 1+). Subjects will be excluded if they meet the following exclusion criteria (summary of main criteria): • Subjects are known or suspected of having resistance to rifampicin, isoniazid, ethambutol, or pyrazinamide using any combination of Xpert MTB/RIF, line probe assay, culture, and/or epidemiologic history at screening. • Any prior treatment for *Mycobacterium tuberculosis* within the past 3 years. • Clinical evidence of severe extrapulmonary TB (eg, miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis). • Subjects with significant medical comorbidities that in the opinion of the investigator, should not participate in the trial.
Trial Site:	This trial will be conducted at 1 or more trial sites in South Africa.

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Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:	<u>Stage 1</u> Subjects randomized to OPC-167832 will receive QD oral doses of IMP (OPC-167832) from Day 1 through Day 14. The planned dose escalation steps of OPC-167832 for Cohorts 1 to 4 are 10, 30, 90, and 3 mg, respectively. The doses for Cohorts 2, 3, and 4 may be adjusted based on the safety, PK, and efficacy data from the previous cohorts. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature, within 5 minutes after the completion of a meal. <u>Stage 2</u> Subjects randomized to the 30 mg OPC-167832 and 300 mg delamanid or 30 mg OPC-167832 and 400 mg BDQ, or 30 mg OPC-167832 and 300 mg delamanid and 400 mg BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature.
Reference Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:	<u>Stage 1 and Stage 2</u> Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20. Subjects will receive Rifafour® single-dose combination tablets. Each RHEZ tablet contains 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol. Subjects will receive the following number of Rifafour tablets per day based on their pretreatment body weight: • Subjects weighing 30 to 37 kg will receive 2 tablets per day. • Subjects weighing 38 to 54 kg will receive 3 tablets per day. • Subjects weighing 55 to 70 kg will receive 4 tablets per day. • Subjects weighing > 70 kg will receive 5 tablets per day. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. Note: Subjects randomized to IMP will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ) after Day 14. In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Trial Assessments:	Pharmacokinetic: • Stage 1: blood sampling for OPC-167832, rifampin, and isoniazid plasma concentrations. • Stage 2: blood sampling for OPC-167832, delamanid, and its metabolite DM-6705, BDQ and its metabolite N-monodesmethyl metabolite (M2), rifampin, and isoniazid plasma concentrations. Safety: adverse event reporting, clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), physical examination, vital signs, electrocardiograms (ECGs), and concomitant medications. Efficacy: quantitative sputum testing (by Otsuka TB LAM ELISA, solid media, and MGIT) to assess the change in TB bacterial load in sputum as a measure of early bactericidal activity (EBA). Pharmacodynamics: Holter monitoring and sputum testing. Screening (excluding safety assessments mentioned above)/Other: demographics, medical history, and prior medications; height and weight; chest x-ray; spot sputum for confirmation of acid-fast bacilli (microscopy from smear ≥ 1+) and drug-susceptible TB; serum hepatitis (hepatitis B surface antigen and hepatitis C antibodies) and human immunodeficiency virus screening; urine pregnancy testing; follicle-stimulating hormone testing; and urine/blood alcohol and urine drug screen.
Criteria for Evaluation:	**Primary Endpoints:** <u>Efficacy - Stage 1</u> Efficacy will be assessed by the change in TB bacterial load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by colony-forming unit (CFU) counts on agar media culture. The EBA will be measured as the slope of the change in log-CFU on agar media from baseline (ie, the mean of the values from Day -2 and Day -1) to Day 14. <u>Pharmacokinetics - Stage 1</u> The following PK parameters will be determined for plasma OPC-167832: • Day 1: Maximum (peak) plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration-time curve (AUC) from time zero to time t (the last observable concentration) (AUC_t).

	• Day 14: C_{max} during the dosing interval at steady-state ($C_{max,ss}$), t_{max}, terminal-phase elimination half-life ($t_{1/2,z}$), apparent clearance of drug from plasma at steady-state (CL_{ss}/F), AUC_t, AUC calculated over the dosing interval at steady-state (AUC_τ), accumulation ratio of C_{max} (R_{Cmax}), accumulation ratio of AUC (R_{AUC}), C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose). <u>Pharmacokinetics - Stage 2</u> The following PK parameters will be determined for plasma OPC-167832, delamanid, and BDQ: • Day 1: C_{max}, t_{max}, and AUC_t.
	• Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, CL_{ss}/F, AUC_τ, R_{Cmax}, R_{AUC}, and C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose). <u>Pharmacokinetics/Pharmacodynamics – Stage 1</u> The maximum effect (E_{max}) and exposure producing 80% of E_{max} (EC_{80}) for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the decline of log-CFU counts on agar media. <u>Pharmacokinetics/Pharmacodynamics – Stage 2</u> The E_{max} and EC_{80} for OPC-167832 in combination with delamanid and/or BDQ will be determined from an exposure-response analysis of the decline of log-CFU counts on agar media. <u>Safety and tolerability - Stage 1 and Stage 2</u> Safety and tolerability will be assessed based on the incidence of adverse events and the incidence of abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), vital signs, ECGs, and physical examinations. **Secondary Endpoints:** <u>Efficacy - Stage 1</u> The slope of the change in log-LAM values and the change in time to detection in the MGIT system will be assessed from baseline to Day 14.

	Efficacy - Stage 2 Efficacy will be assessed by the change in TB bacterial load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by CFU counts on agar media. The EBA will be measured as the slope of the change in log-CFU from baseline (ie, the mean of the values from Day -2 and Day -1) to Day 14. Pharmacokinetics - Stage 1 Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance. Pharmacokinetics - Stage 2 The following PK parameters will be determined for plasma DM-6705 (metabolite of delamanid) and M2 (metabolite of BDQ): • Day 1: C_{max}, t_{max}, and AUC_t. • Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, and AUC_t. Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance.
	Pharmacokinetics/Pharmacodynamics - Stage 1 and Stage 2 The maximum effect and EC_{80} for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the results from the Otsuka TB ELISA LAM. The relationship between QT interval and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid (stage 2) will be evaluated. Safety and tolerability - Stage 1 and Stage 2 Safety and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) will be compared with the administration of OPC-167832 alone (data derived from stage 1). Safety and tolerability will be assessed based on the incidence of adverse events and the incidence of abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), vital signs, ECGs, and physical examinations.

Statistical Methods:	The trial is not powered for formal statistical hypothesis testing or comparisons. The sample size is based on sample sizes from several similar trials in the literature. Pharmacokinetics Pharmacokinetic concentrations and parameters will be summarized by treatment using descriptive statistics (number, median, mean, standard deviation (SD), percent coefficient of variation, minimum, and maximum). Pharmacokinetic concentrations and parameters will also be listed by subject. Population PK modeling will be performed on OPC-167832 PK data from both stages. Pharmacokinetics/Pharmacodynamics Exposure-response modeling will be performed in both stages for OPC-167832 PK measures versus bacterial load using LAM and CFU counts on agar media. The relationship between QT interval (Holter data) and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid and/or BDQ (stage 2) will be examined using an exposure-response analysis.
	Safety Safety data will be summarized by randomized treatment using descriptive statistics (number, median, mean, SD, minimum, and maximum) for numeric variables and frequency and count for discrete variables. Incidence of clinically notable values will be summarized where applicable. Safety assessments will also be listed by subject. Efficacy Efficacy data will be summarized by randomized treatment using descriptive statistics (number, median, mean, SD, percent coefficient of variation, minimum, and maximum) or presented in figures (where applicable). In addition, listings will be presented for efficacy assessments by subject.
Trial Duration:	In stage 1 or stage 2, the expected duration of trial participation for each individual subject, including screening, the treatment period, and follow-up is approximately 34 days. • Screening: Subjects will be admitted to the trial site at screening and will be screened for up to 4 days (Days −6

	to −3); however, screening can be extended up to 7 days, if needed. • Treatment Period: Subjects can proceed with the Day −2 assessments as soon as the screening assessments have been completed. Subjects randomized to OPC-167832 (stage 1) or OPC-167832 and/or delamanid and/or BDQ (stage 2) will receive QD oral doses of IMP from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward. Subject randomized to RHEZ will receive QD doses of RHEZ from Day 1 through Day 20. Subjects will be discharged on Day 20. • Follow-up: 14 (± 3) days after the last dose of trial treatment. Trial duration: approximately 24 months.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{24h}	Area under the concentration-time curve from zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_{τ}	Area under the concentration-time curve calculated over the dosing interval at steady-state
AUC_t	Area under the concentration-time curve from time zero to time t (the last observable concentration)
BDQ	Bedaquiline
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Science
CFU	Colony-forming unit
CL_{ss}/F	Apparent clearance of drug from plasma at steady-state
C_{max}	Maximum (peak) plasma concentration
$C_{max,ss}$	C_{max} during the dosing interval at steady-state
CYP	Cytochrome P450
DAIDS	Division of AIDS
DprE1	Decaprenylphosphoryl-β-D-ribose 2'-oxidase
EBA	Early bactericidal activity
EC_{80}	Exposure producing 80% of maximum effect
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum effect
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation	**Definition**
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IRE	Immediately reportable event
LAM	Lipoarabinomannan
M2	N-monodesmethyl metabolite
MAME	Maximum efficacy
MDR	Multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacteria Growth Indicator Tube®
MIC	Minimum inhibitory concentration
MITT	Modified intent to treat
NOAEL	No observed adverse effect level
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PQC	Product quality complaint
QD	Once daily
QTcF	Corrected QT interval using Fridericia's method
QTcB	Corrected QT interval using Bazett's method
R_{AUC}	Accumulation ratio of AUC
RBC	Red blood cell
R_{Cmax}	Accumulation ratio of C_{max}
RHEZ	Rifampicin, isoniazid, ethambutol, and pyrazinamide
SAD	Single ascending dose
SAE	Serious adverse event
SD	Standard deviation
$t_{1/2,z}$	Terminal-phase elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
TTD	Time to detection
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US	United States
WBC	White blood cell
XDR	Extensively drug-resistant

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1 Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). Tuberculosis remains a major global health problem ranking alongside human immunodeficiency virus (HIV) infection as a leading cause of death worldwide.

Standard treatment for TB requires the combination of 3 or 4 drugs in order to cure the disease and prevent the emergence of drug resistance. Active, drug-susceptible TB is typically treated with a 6-month regimen, including a 2-month initial phase of isoniazid, rifampicin, pyrazinamide, and ethambutol, and followed by a 4-month continuation phase of isoniazid and rifampicin. Given the long period of treatment, management of the side effects from treatment with these drugs is necessary. For multidrug-resistant (MDR) TB, conventional treatment is even less satisfactory, requiring up to 20 months of chemotherapy with generally less effective and more toxic second-line drugs, including injectable drugs, with only about 54% of diagnosed MDR TB patients being successfully treated.[1] Shortening the treatment period, reducing the side effects, and improving the treatment outcomes are major obstacles to be addressed in the treatment of TB.

Progress has been made in the research and development of new anti-TB drugs to help overcome the current TB treatment situation. In recent years, bedaquiline (Sirturo™) and the sponsor's delamanid (Deltyba™) were approved for use as part of a combination therapy in adults with pulmonary MDR TB. However, it is difficult to construct effective combination regimens due to the limited availability of safe and potent oral anti-TB drugs that can be used in combination with BDQ and/or delamanid. Thus, there is an urgent need for the both development of new potent anti-TB agents effective against drug-susceptible and drug-resistant strains of *M. tuberculosis* and with low toxicity, and for the development of new regimens that can shorten the treatment period for both drug-susceptible and MDR TB. Recognizing this serious situation, Otsuka Pharmaceutical Co., Ltd. initiated a program to screen for new anti-TB agents that can be used in combination with delamanid. As a result of research efforts, Otsuka Pharmaceutical Co., Ltd. discovered OPC-167832. OPC-167832 in combination with delamanid may provide the foundation for a pan-TB regimen for the treatment of pulmonary TB.[2]

This 2-stage trial will evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of multiple doses of OPC-167832 and evaluate the safety, PK, and efficacy when OPC-167832 is combined with delamanid or BDQ (a marketed MDR-TB drug), or

OPC-167832, delamanid, and BDQ administered together in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.

During stage 1, OPC-167832 in multiple ascending doses or standard treatment (rifampicin, isoniazid, ethambutol, and pyrazinamide [RHEZ]) will be administered to sequential cohorts of subjects. In stage 2, subjects will be randomized to receive multiple doses of a 30 mg of OPC-167832 in combination with delamanid (OPC-67683), BDQ, delamanid and BDQ, or RHEZ alone.

Efficacy will be determined by the decrease of sputum colony-forming units (CFUs) obtained on agar media and sputum lipoarabinomannan (LAM) concentrations, determined by the Otsuka TB LAM enzyme-linked immunosorbent assay (ELISA). Otsuka TB LAM ELISA is an immunoassay that quantifies the sputum LAM concentration in approximately 6 hours. Lipoarabinomannan is a key component of the *M. tuberculosis* cell wall and the decline of sputum LAM concentrations has been shown to correlate closely with CFU decreases in sputum counted on agar media during the first 14 days of TB treatment.[3,4] After reviewing a "Letter of Intent" submitted by the sponsor and the Critical Path to TB Drug Regimens, the United States (US) Food and Drug Administration (FDA) has accepted sputum LAM in to its biomarker qualification program. The qualification effort is ongoing to qualify sputum LAM as a pharmacodynamic (PD) biomarker and as a TB drug development tool. In stage 1, the selection of the dose level for each cohort after Cohort 1, as it relates to efficacy, will be based on the Otsuka TB LAM ELISA results instead of solid media culture, since LAM results are available in near real time and will facilitate faster decisions. The final assessment of the early bactericidal activity (EBA) for each treatment arm will be based on the CFU counts on solid media culture.

One dose of OPC-167832 will be chosen from stage 1, and evaluated in combinations with delamanid, or BDQ or the 3-drugs together in stage 2 to evaluate the safety and PK of the combinations and the efficacy when compared with OCP-167832 alone obtained in stage 1.

Please refer to the Investigator's Brochure (IB)[2] for more detailed information on nonclinical data and clinical data for OPC-167832. Brief summaries are included below.

[redacted]

[redacted]

1.2 Clinical Data

The first-in-human trial of OPC-167832 was a single ascending dose (SAD) trial (Trial 323-201-00001) of doses ranging from 30 to 480 mg in separate cohorts of healthy subjects to determine the safety, tolerability, and PK of OPC-167832.[5]

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1.3 Pharmacokinetics

1.3.1 OPC-167832

The results from Trial 323-201-00001 indicated that the median area under the concentration-time curve (AUC) from time zero to infinity (AUC_∞) at 30 mg was [redacted] h·ng/mL, which was greater than the maximal effective AUC in a nonclinical model, [redacted] h·ng/mL. The maximum (peak) plasma concentration (C_{max}) and AUC of OPC-167832 increased less than proportionately from [redacted] mg and then increased approximately proportionately. The terminal half-life ranged from about [redacted] hours and the peak (C_{max}) occurred at around [redacted] hours postdose. The median C_{max} at the highest dose (480 mg) was about [redacted] micromoles/L, which was well below the IC_{50} of inhibition of any of the isozymes.[5]

1.3.2 Delamanid

Systemic exposure is greater when delamanid is taken with food: about 2-fold greater with a standard meal and 4-fold greater with a high-fat meal. Peak plasma concentrations are reached in approximately 4 hours postdose, regardless of food intake. The elimination half-life of delamanid is about 30 to 38 hours, allowing steady-state to be reached after 10 to 14 days of dosing. The terminal-phase elimination half-life ($t_{1/2,z}$) of its major metabolite (DM-6705) is approximately 230 hours, and steady-state is reached by 8 weeks.

The single-dose ^{14}C-delamanid trial indicated that delamanid and its metabolites were predominantly excreted in the feces, while renal excretion is a negligible pathway for elimination. In vitro data suggest that delamanid is essentially metabolized by albumin, resulting in the formation of the primary metabolite DM-6705, which in turn is metabolized to DM-6704 and DM-6706. In vitro metabolism studies in human liver microsomes suggest limited contribution of CYP isoenzymes to the metabolism of delamanid, although CYP isoenzymes appear to be involved in consecutive metabolism. Eight metabolites have been identified in human plasma following multiple oral doses, though present at low concentrations after 10 to 14 days of dosing, representing all together about 1% to 10% of parent delamanid. Delamanid does not show clinically meaningful induction and/or inhibitory effects on CYP isoenzyme activity. Delamanid binds to all plasma proteins (> 99.5%) and most extensively (> 97%) to albumin and lipoproteins. The primary metabolites DM-6704, DM-6705, and DM-6706 extensively

(> 97%) bind to human serum proteins. Delamanid does not show affinity for red blood cells. Delamanid and metabolite PK parameters do not notably vary with gender or race.

Administration of delamanid has been shown to result in QT interval prolongation, an effect associated with delamanid and its metabolites but is most closely correlated with DM-6705 plasma concentrations. DM-6705 accumulates slowly over time to reach maximal concentrations after 6 to 10 weeks of treatment. The QT interval prolongation increased accordingly and reversed upon discontinuation of treatment.[6]

1.3.3 Bedaquiline

Bedaquiline is a diarylquinoline derivative that inhibits the proton pump of *M.tuberculosis* ATP synthase. After oral administration BDQ C_{max} are typically achieved at approximately 5 hours post-dose. The C_{max} and the AUC increased proportionally up to the highest doses studied in healthy volunteers (700 mg single-dose and once daily 400 multiple doses). Administration of BDQ with a standard meal containing increased the relative bioavailability by about 2-fold compared to administration under fasted conditions.

CYP3A4 was the major CYP isoenzyme involved in vitro in the metabolism of bedaquiline and the formation of the N-monodesmethyl metabolite (M2), which is 4 to 6-times less active in terms of antimycobacterial potency. Based on preclinical studies, bedaquiline is mainly eliminated in feces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged drug is insignificant. After reaching C_{max}, BDQ concentrations decline tri-exponentially. The mean terminal elimination half-life of BDQ and the M2 is approximately 5.5 months. This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.[7]

1.4 Risks and Benefits

1.4.1 OPC-167832

The results from safety pharmacology studies [redacted]

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[redacted]

Single oral doses up to 480 mg OPC-167832 were well tolerated during Trial 323-201-00001; there were no serious or severe adverse events (AEs) and no subjects were discontinued from the trial due to an AE.[5]

1.4.2 Delamanid

In healthy subjects, events that occurred with a frequency greater than placebo and in ≥ 3% of subjects who received delamanid were headache, nausea, diarrhea, vomiting, dizziness, abdominal pain, insomnia, generalized rash, back pain, and arthralgia. Additional information regarding the safety and the potential risks and benefits of delamanid is provided in the IB.[6]

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1.4.3 Bedaquiline

Both delamanid and BDQ have been studied together as part of a National Institutes of Health-sponsored combination drug-drug interaction/safety trial. Bedaquiline is indicated as part of combination therapy in adults (≥ 18 years) with pulmonary MDR-TB. For the known and potential risks of BDQ, please see the package insert for BDQ tablets.[7]

1.4.4 Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide

Rifafour® tablets are a combination of four first line agents used in the treatment of TB. Rifampicin is a semi-synthetic, broad-spectrum bactericidal antibiotic. Isoniazid is a synthetic, antitubercular agent which is bacteriostatic against semi-dormant bacilli and bactericidal against actively dividing mycobacteria. Pyrazinamide may be bactericidal or bacteriostatic, depending on its concentration and the susceptibility of the organism. Ethambutol is a synthetic, bacteriostatic antitubercular agent. All agents are readily absorbed following oral administration, with wide distribution to most tissues and fluids including cerebrospinal fluid. For the known and potential risks of RHEZ, please see the package insert for Rifafour single-dose combination tablets.[8]

2 Trial Rationale and Objectives

2.1 Trial Rationale

This trial will evaluate the safety, tolerability, PK, and efficacy of multiple oral doses of OPC-167832 in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.

The proposed dose levels to be studied in stage 1 are 3, 10, 30, and 90 mg (see Section 2.2.1 for the dosing rationale). The results from stage 1 will be used to determine the doses of OPC-167832 to be administered in stage 2. The stage 2 doses will not exceed the highest dose studied in stage 1. In stage 2 of the trial, the effect of the co-administration of OPC-167832 and delamanid on safety, tolerability, PK, and efficacy will be examined. Delamanid is approved in several countries (European Union, Japan, South Korea, India, South Africa, Peru, Mongolia, Ukraine, Turkmenistan, Turkey, Philippines, China, and Hong Kong) for the treatment of pulmonary MDR TB and is currently being investigated by the sponsor for the same indication in the US. Bedaquiline is indicated as part of combination therapy in adults (≥ 18 years) with pulmonary MDR-TB.

There is no need for an OPC-167832 alone treatment arm in stage 2, as the doses for OPC-167832 in stage 2 are defined from PK modeling of the data from all the cohorts in stage 1. Based on the stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in $\log_{10}$CFU, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose.

The standard treatment recommended by the World Health Organization for the treatment of drug-susceptible TB will be used as an active-control; the recommended treatment is a combination of RHEZ.[9]

Subjects randomized to OPC-167832 (stage 1) or OPC-167832 and/or delamanid and/or BDQ (stage 2) will receive once daily (QD) oral doses of investigational medicinal product (IMP; OPC-167832 [stage 1] or OPC-167832 and/or delamanid and/or BDQ [stage 2]) from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward. The reason for starting the local standard of care regimen on Day 18 is that PK samples will be drawn after the last dose on Day 14 to estimate the terminal elimination rate and the terminal half-life of OPC-167832 (stages 1 and 2) and delamanid (stage 2) following multiple dose administration. In order to obtain accurate estimates of these PK parameters, ideally, no additional medication should be administered for approximately 4 to 5 half-lives after the last dose of trial treatment (IMP or RHEZ).

Subjects with known or suspected resistance to OPC-167832, delamanid, or RHEZ will be excluded from this trial. After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB with the local standard of care regimen.

Overall, the results of this trial will be used for further development of OPC-167832.

2.2 Dosing Rationale

2.2.1 Stage 1

The planned dose escalation steps of OPC-167832 for Cohorts 1 to 4 are 10, 30, 90, and 3 mg, respectively.

Single doses up to and including 480 mg OPC-167832 were well tolerated in the SAD trial of OPC-167832 (Trial 323-201-00001). Based on modeling and simulation, following multiple doses of 60 mg, 95% of subjects are expected to have steady-state

AUC values greater than 2252 h·ng/mL, the minimum AUC to achieve maximum efficacy (MAME) based on a nonclinical model of infection in mice.[10] In order to completely characterize the entire exposure-response, doses lower than 30 mg need to be studied, as the median AUC_{∞} following a 30 mg dose exceeded the MAME (Section 1.3.1). Therefore, dose levels of 10, 30, 90, and 3 mg are proposed to be studied. The dose of OPC-167832 will not exceed the highest tolerated dose studied in the SAD trial, ie, 480 mg.

The RHEZ treatment group will receive Rifafour single-dose combination tablets based on the subject's pretreatment body weight.

2.2.2 Stage 2

The stage 2 dose of OPC-167832 will be 30 mg, based on preliminary data. Based on the stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in log_{10}CFU, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose.

Delamanid has been studied in an EBA trial (Trial 242-06-101) in South Africa in drug-susceptible pulmonary TB patients with monotherapy of 100 mg QD, 200 mg QD, 300 mg QD, or 400 mg QD doses for 14 days. In this trial, the EBA plateaued at 300 mg QD, hence, in order to maximize the chances of observing activity in combination with OPC-167832, the 300 mg dose of delamanid will be used.

Subjects will receive a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for Days 3 to 14. The BDQ dosing regimen, including the loading dose paradigm, are based on those utilized in two BDQ EBA trials.[11,12]

The RHEZ treatment group will receive Rifafour tablets based on the subject's pretreatment body weight.

2.3 Trial Objectives

2.3.1 Primary Objective

2.3.1.1 Stage 1

To evaluate the efficacy, PK, safety, and tolerability of multiple ascending oral doses of OPC-167832 compared with the administration of RHEZ in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.

2.3.1.2 Stage 2

- To evaluate the safety, and tolerability of OPC-167832 when administered with delamanid and/or BDQ compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary TB.
- To evaluate the PK of OPC-167832 and delamanid, and/or BDQ after coadministration.

2.3.2 Secondary Objectives

2.3.2.1 Stage 1

- To evaluate the relationship between OPC-167832 exposure and efficacy, determined by changes of sputum LAM and MGIT time to detection (TTD) after multiple ascending oral doses of OPC-167832.
- To evaluate the relationship between QT interval and plasma concentrations of OPC-167832.

2.3.2.2 Stage 2

- To evaluate the efficacy of OPC-167832 when administered with delamanid and/or BDQ compared with the administration of RHEZ alone in subjects with uncomplicated, smear-positive, drug susceptible pulmonary TB.
- To evaluate the relationship between OPC-167832 exposure and efficacy, determined by changes of sputum LAM and MGIT TTD after OPC-167832 when administered with delamanid and/or BDQ.
- To evaluate the relationship between QT interval and plasma concentrations of OPC-167832 when administered with delamanid and/or BDQ.
- To evaluate the PK of DM-6705 after coadministration of OPC-167832 and delamanid and/or BDQ.

2.3.2.3 Stage 1 and Stage 2

To evaluate the efficacy, safety, and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) compared with the administration of OPC-167832 alone (data derived from stage 1).

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3 Trial Design

3.1 Type/Design of Trial

This will be a multiple-dose trial of OPC-167832 with 2 stages at 1 or more trial sites in South Africa.

3.1.1 Stage 1

Stage 1 will be a randomized, open-label, active-controlled, multiple ascending dose stage in approximately 72 subjects. Dosing is planned to be conducted in 4 sequential cohorts of 18 subjects each:

- Cohort 1: 10 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 2: 30 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 3: 90 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)
- Cohort 4: 3 mg OPC-167832 or RHEZ (14 OPC-167832 subjects and 4 RHEZ subjects)

Subjects will provide signed informed consent and be admitted to the trial site at screening. Subjects will be screened for up to 4 days (Days −6 to −3) prior to the start of the Day −2 assessments; however, screening can be extended up to 7 days, if needed. Eligible subjects will be housed at the trial site until discharge or early termination (ET).

In Cohort 1, subjects will be randomized to 10 mg OPC-167832 or RHEZ prior to first dosing on Day 1. Subjects will be centrally randomized through an interactive voice response technology system with no stratification.

Subjects randomized to OPC-167832 will receive QD oral doses of IMP (OPC-167832) from Day 1 through Day 14. The IMP will be administered as described in Section 3.2.1.1. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20. RHEZ will be administered as described in Section 3.2.2.1.

Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected. After completion of the inpatient stay, all

subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

Following review of the safety, tolerability, PK, and efficacy data from Cohort 1, a decision will be made to start Cohort 2. Cohort 2 will be completed as described above for Cohort 1 at the selected dose of OPC-167832. The same process will be followed for Cohort 3 after the completion of Cohort 2 and for Cohort 4 after the completion of Cohort 3.

The safety, tolerability, PK, and efficacy ([redacted]) data from each cohort will be reviewed by the trial review team at the end of each cohort. Once all the data for dose selection for the next cohort are available, the data collected from each cohort will be provided to the trial review team. The data will be evaluated to determine if (i) the dose level for the next cohort will be escalated, (ii) the dose level from the previous cohort will be repeated, or (iii) the dose level will be decreased. The dose of OPC-167832 will not exceed the highest tolerated dose studied in the SAD trial, ie, 480 mg.

The trial review team will consist of Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) staff, including the project leader, Clinical Management representative(s), Global Pharmacovigilance representative(s), Clinical Pharmacology representative(s), OPDC medical monitor; the principal investigator (or designee); Microbiology and Diagnostic Director; and other staff, as needed.

Decisions to proceed to the next dose level should be based on, but not limited to, the following safety aspects:

- No death assessed as related to OPC-167832
- No more than 2 subjects with Grade 4/5 AEs ("Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric AEs" [Appendix 3]) assessed as related to OPC-167832

For efficacy, the selection of the dose level for each cohort after Cohort 1 will be assisted by the results of the Otsuka TB LAM ELISA instead of solid media culture, since those results are available in near real time and will facilitate faster decisions.

The trial design schematic is presented in Figure 3.1.1-1.

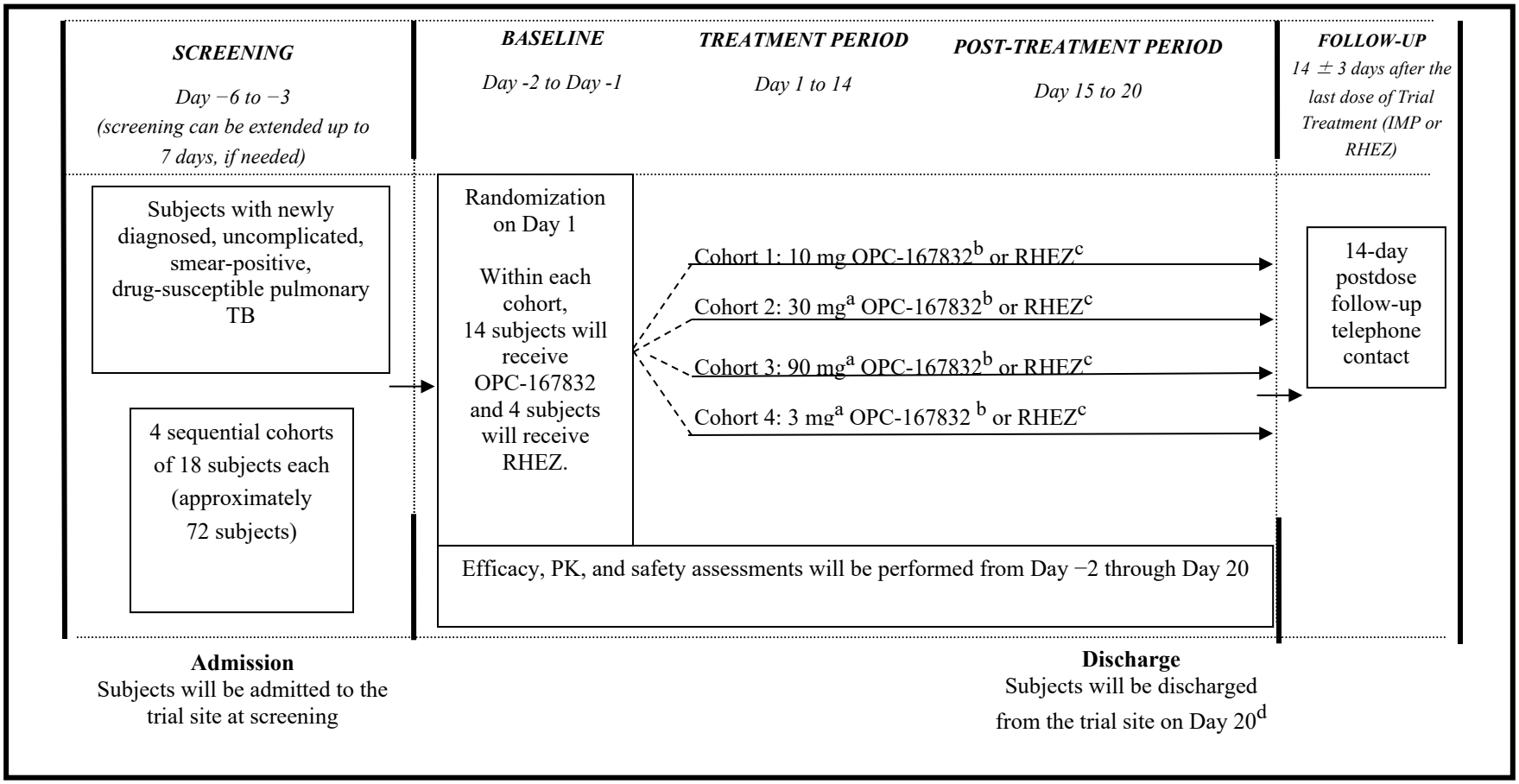

Figure 3.1.1-1 Trial Design Schematic - Stage 1

[a]The safety, tolerability, PK, and efficacy data ([redacted]) from the previous cohort(s) will be evaluated to determine the dose for the next cohort.

[b]Subjects randomized to OPC-167832 will receive QD oral doses of IMP from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB, according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

[c]Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

[d]After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

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3.1.2 Stage 2

Stage 2 will only start once stage 1 has been concluded and after data are available from the nonclinical toxicological study to evaluate the effect of co-administration of OPC-167832 and delamanid on QTc.

The dose of OPC-167832 for stage 2 has been determined based on the safety, tolerability, PK, and efficacy data from stage 1 of this trial. Based on the stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in $\log_{10}$CFU, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose.

Stage 2 will be a randomized, open-label, active-controlled, parallel group comparison stage comprising of 46 subjects (subjects who were randomized in stage 1 cannot enroll in stage 2).

Subjects will provide signed informed consent and be admitted to the trial site at screening. Subjects will be screened for up to 4 days (Days −6 to −3) prior to the start of the Day −2 assessments; however, screening can be extended up to 7 days, if needed. Eligible subjects will be housed at the trial site until discharge or ET. All subjects enrolled during this stage of the trial will be randomized prior to first dosing on Day 1 to one of the following 4 treatments in a ratio of 14:14:14:4:

- 30 mg OPC-167832 and 300 mg QD delamanid (14 subjects)
- 30 mg OPC-167832 and 400 mg BDQ (14 subjects)
- 30 mg OPC-167832 and 300 mg delamanid QD and 400 mg BDQ (14 subjects)
- RHEZ QD (4 subjects)
- Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for days 3 to 14

Subjects will be centrally randomized through an interactive voice response system with no stratification.

Subjects randomized to OPC-167832 and/or delamanid and/or BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. The IMP will be administered as described in Section 3.2.1.2. After Day 14, the subjects will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20. RHEZ will be administered as described in Section 3.2.2.1.

Subjects will be discharged on Day 20 once all safety assessments have been completed and all PK samples have been collected. After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

The trial design schematic is presented in Figure 3.1.2-1.

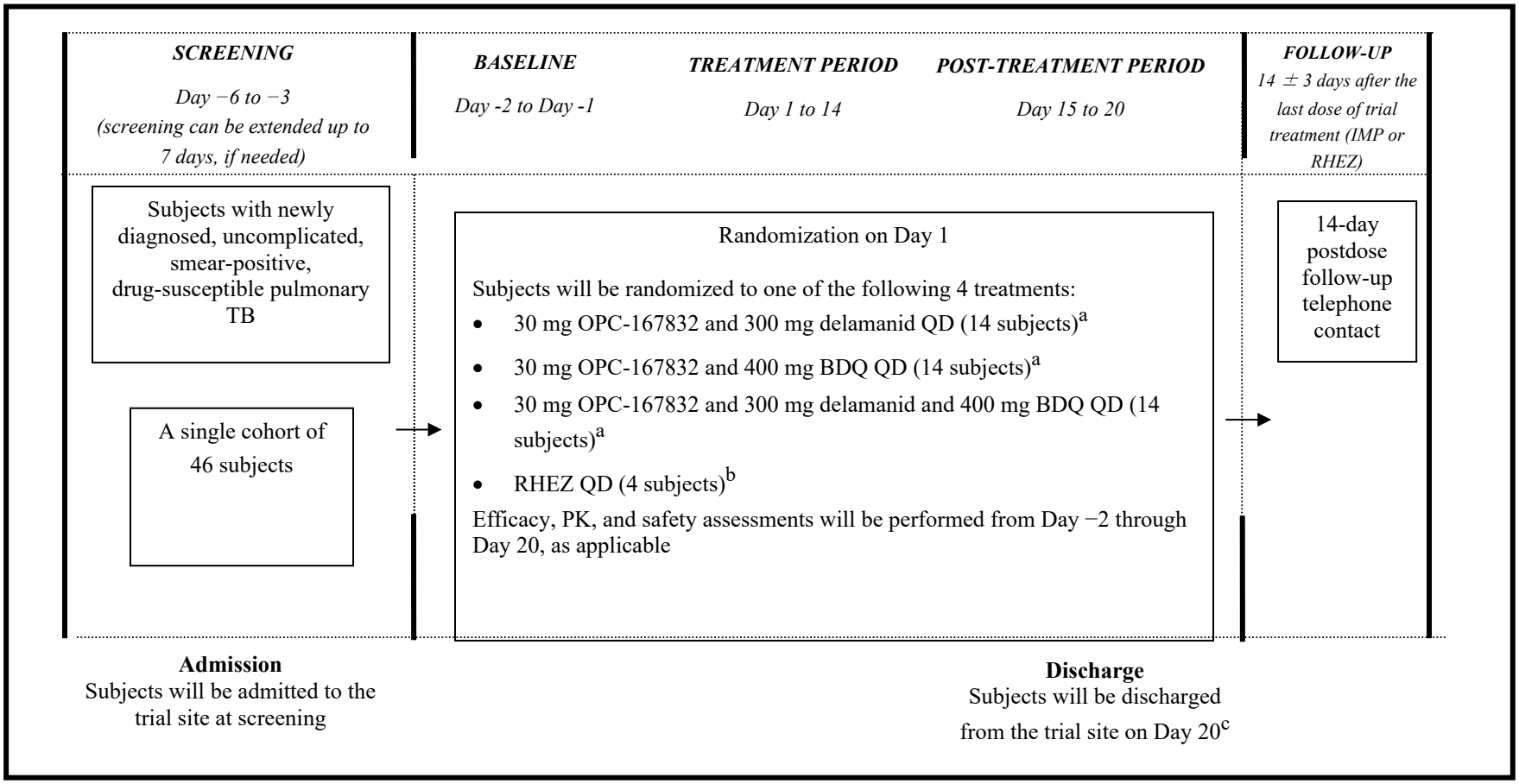

Figure 3.1.2-1 Trial Design Schematic - Stage 2

[a]Subjects randomized to OPC-167832 and/or delamanid and/or BDQ will receive QD oral doses of IMP from Day 1 through Day 14. After Day 14, the subjects will receive treatment for pulmonary TB, according to the local standard of care regimen (RHEZ). In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

Based on the stage 1 PK/PD analysis of OPC-167832 plasma concentrations and reduction in log_{10}CFU, a dose lower than the current 30 mg specified in the protocol may be considered, provided it can offer similar potential for efficacy as the 30 mg dose.

[b]Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

[c]After completion of the inpatient stay, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

Note: Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for days 3 to 14.

3.2 Trial Treatments

3.2.1 Investigational Medicinal Products

3.2.1.1 Stage 1

Subjects randomized to OPC-167832 will receive QD oral doses of IMP (OPC-167832) from Day 1 through Day 14.

The planned dose escalation steps of OPC-167832 for Cohorts 1 to 4 are 10, 30, 90, and 3 mg, respectively. The doses for Cohorts 2, 3, and 4 may be adjusted based on the safety, PK, and efficacy data from the previous cohorts as described in Section 3.1.1. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature, within 5 minutes after the completion of a meal.

3.2.1.2 Stage 2

Subjects randomized to 30 mg OPC-167832 and 300 mg delamanid or 30 mg OPC-167832 and 400 mg BDQ, or 30 mg OPC-167832 and 300 mg delamanid and 400 mg BDQ will receive QD oral doses of IMP (OPC-167832 and/or delamanid and/or BDQ) from Day 1 through Day 14. Subjects receiving BDQ will take a loading dose of 700 mg BDQ on Day 1 and 500 mg on Day 2. The dose of BDQ will be 400 mg QD for days 3 to 14.

Delamanid (300 mg) should be administered orally once daily (QD), within 5 to 10 minutes after the completion of a meal.

OPC-167832 (30 mg QD) and BDQ should be administered orally, approximately 30 minutes after administration of delamanid.

The dose of OPC-167832 for stage 2 was determined from stage 1 of this trial. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature.

3.2.2 Reference Product

3.2.2.1 Stage 1 and Stage 2

Subjects randomized to RHEZ will receive QD oral doses of RHEZ from Day 1 through Day 20.

Subjects will receive Rifafour single-dose combination tablets. Each RHEZ tablet contains 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide, and 275 mg ethambutol.[8] Subjects will receive the following number of Rifafour tablets per day based on their pretreatment body weight:

- Subjects weighing 30 to 37 kg will receive 2 tablets per day.

- Subjects weighing 38 to 54 kg will receive 3 tablets per day.
- Subjects weighing 55 to 70 kg will receive 4 tablets per day.
- Subjects weighing > 70 kg will receive 5 tablets per day.

RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal.

Note: Subjects randomized to IMP will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ) after Day 14. In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

Approximately 118 male or female subjects with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary TB who meet all of the inclusion criteria (Section 3.4.2) and none of the exclusion criteria (Section 3.4.3) will be enrolled and randomized into this trial.

In stage 1, approximately 72 subjects will be enrolled and randomized to 1 of 4 cohorts (18 subjects per cohort). Approximately 46 subjects will be enrolled and randomized in stage 2. Subjects who were randomized in stage 1 cannot enroll in stage 2.

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique identification number (subject identifier) upon signing the informed consent form (ICF). Subjects who meet the inclusion criteria and do not fulfill any of the exclusion criteria will be eligible for the trial and will be enrolled as needed. Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for treatment assignment. The trial site will maintain a list identifying all subjects by their identification numbers and initials.

Subjects may be replaced at the discretion of the sponsor if discontinuations or withdrawals occur, so that at least 18 subjects complete each cohort of stage 1 and approximately 46 subjects' complete stage 2.

3.4 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, either by the investigator or by the medical monitor.

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws) in their native or preferred language (English/Afrikaans/Xhosa) before any trial-related procedures (including any screening procedures) are performed. Consent will be documented on a written ICF. The ICF will be approved by the same independent ethics committee (IEC) that approves this protocol. Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[13] and local regulatory requirements. The investigator agrees to obtain the ICF to be provided by the sponsor in English and, if applicable, the primary language(s) of the patient, as applicable, prior to submission to the IEC.

The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial before submission to the IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator. Additional copies will be filed according to local requirements.

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria in Table 3.4.2-1.

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Table 3.4.2-1 Inclusion Criteria	
1.	Able to provide written, informed consent prior to initiation of any trial-related procedures, and able, in the opinion of the investigator, to comply with all the requirements of the trial.
2.	Male or female subjects between 18 and 64 years of age (inclusive) at the screening visit.
3.	Body mass index ≥ 16.0 and ≤ 32.0 kg/m^2 (inclusive) at the screening visit.
4.	Newly diagnosed,[a] uncomplicated, drug-susceptible[b] pulmonary TB.
5.	Microscopy performed on a sputum smear at screening indicates presence of acid-fast bacilli (at least 1+).
6.	Able to produce an adequate volume of sputum (approximately 10 mL or more estimated overnight production).
7.	Female subjects of childbearing potential must agree to use 2 different approved methods of birth control or remain abstinent throughout the participation in the trial and for 12 weeks after the last dose of trial treatment (IMP or RHEZ).
8.	Male subjects must agree to use 2 different approved methods of birth control or remain abstinent throughout the participation in the trial and for 12 weeks after the last dose of trial treatment (IMP or RHEZ).

[a]Within the 3 months prior to screening.

[b]Rifampicin and isoniazid susceptible.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria	
1.	Subjects are known or suspected of having resistance to rifampicin, isoniazid, ethambutol, or pyrazinamide using any combination of Xpert MTB/RIF, line probe assay, culture, and/or epidemiologic history at screening.
2.	Poor general condition where no delay in treatment can be tolerated or where immediate hospital admission is warranted.
3.	Evidence of clinically significant metabolic (including ongoing or current hypokalemia), gastrointestinal, neurological, psychiatric, endocrine or liver (e.g. hepatitis B and C) disease; malignancy; or other abnormalities (other than the indication being studied).
4.	History of or current clinically relevant cardiovascular disorder such as heart failure, coronary heart disease, hypertension, arrhythmia or symptom strongly suggestive of such a problem (for example, syncope or palpitations), tachyarrhythmia or status after myocardial infarction.
5.	Known bleeding disorders or family history of bleeding disorders.
6.	Any diseases or conditions in which the use of delamanid, rifampicin, isoniazid, pyrazinamide, ethambutol, or BDQ is contraindicated.
7.	Any prior treatment for *M. tuberculosis* within the past 3 years.
8.	Any treatment with a drug active against *M. tuberculosis* (eg, quinolones) within the 3 months prior to screening.
9.	Clinical evidence of severe extrapulmonary TB (eg, miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis).
10.	Evidence of pulmonary silicosis, lung fibrosis, or other lung condition considered as severe by the investigator (other than TB). In particular any underlying condition that could interfere with the assessment of x-ray images, sputum collection, or interpretation of sputum findings, or otherwise compromise the subject's participation in the trial.

Table 3.4.3-1 Exclusion Criteria	
11.	Any renal impairment characterized by serum creatinine clearance of < 60 mL/min, or hepatic impairment characterized by alanine transaminase, aspartate transaminase, or total bilirubin > 1.5 × upper limit of normal of the clinical laboratory reference range at screening.
12.	Stage 1: Subjects who are HIV positive are excluded from the trial. Stage 2: Subjects with HIV co-infection who are on antiretroviral drugs during screening or with CD4 cell count < 500/mm^3 are excluded from the trial.
13.	Changes in the ECG such as QTcF > 450 msec, atrioventricular block II or III, bi-fasicular block, at screening or current or history of clinically significant ventricular arrhythmias. Other ECG changes if considered clinically significant by the investigator.
14.	Subjects receiving any of the prohibited medications within the specified periods or who would be likely to require prohibited concomitant therapy during the trial.
15.	Female subjects who are breast-feeding or who have a positive pregnancy test result prior to receiving the first dose of IMP or RHEZ on Day 1.
16.	History of significant drug and/or alcohol abuse within 2 years prior to screening**.**
17.	History of or current hepatitis or carriers of HBsAg and/or anti-HCV.
18.	Positive urine or blood alcohol test and/or urine drug screen for substance abuse at screening (not including cannabinoids).
19.	History of having taken an investigational drug within 30 days preceding trial entry (ie, prior to screening).
20.	A history of difficulty in donating blood.
21.	Donation of blood or plasma within 30 days prior to dosing.
22.	Consumption of alcohol and/or grapefruit, grapefruit juice, Seville oranges, or Seville orange juice and related products within 72 hours prior to the first dose of IMP or RHEZ on Day 1.
23.	History of serious mental disorders that, in the opinion of the investigator, would exclude the subject from participating in this trial.
24.	Any known prior exposure to OPC-167832, delamanid, or BDQ.
25.	Subjects with significant medical comorbidities that in the opinion of the investigator, should not participate in the trial.

Anti-HCV = hepatitis C antibodies; HBsAg = hepatitis B surface antigen.

Subjects excluded for positive drug/alcohol screen are not eligible to be rescreened for participation in the trial. However, subjects excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that the subject is rescreened a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.5 Endpoints

3.5.1 Primary Endpoints

3.5.1.1 Efficacy - Stage 1

Efficacy will be assessed by the change in TB bacterial load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by CFU counts on agar media culture. The EBA will be measured as the slope of the change in log-CFU from baseline (ie, the mean of the values from Day -2 and Day -1) to Day 14.

3.5.1.2 Pharmacokinetics - Stage 1

The following PK parameters will be determined for plasma OPC-167832:

- Day 1: C_{max}, time to C_{max} (t_{max}), and AUC from time zero to time t (the last observable concentration) (AUC_t).
- Day 14: C_{max} during the dosing interval at steady-state ($C_{max,ss}$), t_{max}, $t_{1/2,z}$, apparent clearance of drug from plasma at steady-state (CL_{ss}/F), AUC_t, AUC calculated over the dosing interval at steady-state (AUC_τ), accumulation ratio of C_{max} (R_{Cmax}), and accumulation ratio of AUC (R_{AUC}), C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose).

3.5.1.3 Pharmacokinetics - Stage 2

The following PK parameters will be determined for plasma OPC-167832, delamanid, and BDQ:

- Day 1: C_{max}, t_{max}, and AUC_t.
- Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, CL_{ss}/F, AUC_τ, R_{Cmax}, R_{AUC}, and C_{max} normalized to dose (C_{max}/Dose), and AUC_τ normalized to dose (AUC_τ/Dose).

3.5.1.4 Pharmacokinetics/Pharmacodynamics - Stage 1

The maximum effect (E_{max}) and exposure producing 80% of E_{max} (EC_{80}) for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the decline of log-CFU count on agar media.

3.5.1.5 Pharmacokinetics/Pharmacodynamics - Stage 2

The E_{max} and EC_{80} for OPC-167832 in combination with delamanid and/or BDQ will be determined from an exposure-response analysis of the decline of log-CFU counts on agar media.

3.5.1.6 Safety and Tolerability - Stage 1 and Stage 2

Safety and tolerability will be assessed based on the incidence of AEs and the incidence of abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), physical examinations, vital signs, and electrocardiograms (ECGs).

3.5.2 Secondary Endpoints

3.5.2.1 Efficacy - Stage 1 and Stage 2

The slope of the change in log-LAM values and the change in TTD in the Mycobacteria Growth Indicator Tube® (MGIT) system will be assessed from baseline to Day 14.

Stage 2

Efficacy will be assessed by the change in TB bacterial load in sputum as a measure of EBA. Bacterial load in sputum at each collection time point will be measured by CFU counts on agar media culture. The EBA will be measured as the slope of the change in log CFU from baseline (ie, the mean of the values from Day -2 and Day -1) to Day 14 and compared with the administration of 30 mg OPC-167832 alone (data derived from Stage 1).

3.5.2.2 Pharmacokinetics - Stage 1

Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance.

3.5.2.3 Pharmacokinetics - Stage 2

The following PK parameters will be determined for plasma DM-6705 (metabolite of delamanid) and M2 (metabolite of BDQ):

- Day 1: C_{max}, t_{max}, and AUC_t.
- Day 14: $C_{max,ss}$, t_{max}, $t_{1/2,z}$, and AUC_t.

Plasma concentrations of rifampin and isoniazid at 2 and 6 hours postdose will be determined for compliance.

3.5.2.4 Pharmacokinetics/Pharmacodynamics - Stage 1 and Stage 2

The maximum effect and EC_{80} for OPC-167832, regardless of dose level, will be determined from an exposure-response analysis of the results from the Otsuka TB ELISA LAM.

The relationship between QT interval and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid and/or BDQ (stage 2) will be evaluated.

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3.5.2.5 Safety and Tolerability - Stage 1 and Stage 2

Safety and tolerability of OPC-167832 when administered with delamanid and/or BDQ (data derived from stage 2) will be compared with the administration of OPC-167832 alone (data derived from stage 1). Safety and tolerability will be assessed based on the incidence of AEs and the incidence of abnormal findings in clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation), physical examinations, vital signs, and ECGs.

3.6 Measures to Minimize/Avoid Bias

This trial is open-label due to the impracticality of blinding all dose levels of IMP and due to a weight-based standard of care of RHEZ. However, the microbiology laboratory will be blinded to the treatment assignment of each patient, in an effort to minimize bias.

3.7 Trial Procedures

The trial duration is expected to be approximately 24 months. In stage 1 or stage 2, the expected duration of trial participation for each individual subject, including screening, the treatment period, and follow-up is approximately 34 days.

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments - Stage 1 and Stage 2

	In-clinic														Follow-up
	Screening	Baseline		Treatment Period								Post-treatment Period			
	Day −6 to Day −3[a]	Day −2[b]	Day −1	Day 1	Day 2	Day 3	Day 4	Days 5 and 6	Day 7	Days 8 through 13	Day 14	Day 15	Days 16 through 19	Day 20/ET	14 (± 3) Days[c]
Informed consent	X														
Review inclusion/exclusion criteria	X		X												
Demographic information	X														
Medical history	X														
Height and weight[d]	X		X						X		X			X	
BMI	X														
Complete physical examination[e]	X		X												
Targeted physical examination[e]				X	X	X	X	X	X	X	X	X	X	X	
Chest x-ray[f]	X														
Spot sputum for confirmation of drug-susceptible TB[g]	X														
Serum hepatitis (HBsAg and anti-HCV) and HIV[h] screen	X														
Admission to trial site	X														

Table 3.7-1 Schedule of Assessments - Stage 1 and Stage 2

	In-clinic													Follow-up
	Screening	Baseline		Treatment Period								Post-treatment Period			
	Day −6 to Day −3[a]	Day −2[b]	Day −1	Day 1	Day 2	Day 3	Day 4	Days 5 and 6	Day 7	Days 8 through 13	Day 14	Day 15	Days 16 through 19	Day 20/ET	14 (± 3) Days[c]
Urine pregnancy test[i]	X														
FSH[j]	X														
Urine/blood alcohol and urine drug screen	X														
Serum chemistry, hematology, coagulation, and urinalysis[k]	X		X				X		X		X			X	
Vital signs[l]	X		X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[m]	X		X						X		X				
Holter[n]			X	X							X				
Randomization[o]				X											
Administration of IMP[p]				X	X	X	X	X	X	X	X				
Administration of RHEZ[q]				X	X	X	X	X	X	X	X	X	X	X[r]	
Treatment for pulmonary TB according to the local standard of care regimen												X[s]	X[s]	X[r]	

Table 3.7-1 Schedule of Assessments - Stage 1 and Stage 2

	In-clinic													Follow-up
	Screening	Baseline		Treatment Period								Post-treatment Period			
	Day −6 to Day −3[a]	Day −2[b]	Day −1	Day 1	Day 2	Day 3	Day 4	Days 5 and 6	Day 7	Days 8 through 13	Day 14	Day 15	Days 16 through 19	Day 20/ET	14 (± 3) Days[c]
PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid, DM-6705, and BDQ (stage 2)[t]				X	X					X (Days 12 and 13 only)	X	X	X	X	
PK blood samples rifampicin, and isoniazid (stages 1 and 2)[u]											X			(X)	
Overnight sputum collection[v]		X	X		X		X	X (Day 6 only)		X (Days 8, 10, and 12 only)	X				
Meals[w]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge from trial site														X	
Assess AEs[x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record prior/concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact															X

Note: This table presents the trial assessment time points and should be used in conjunction with the Trial Days and Activities table (Table 3.7.3-1), which summarizes the timing of assessments and activities by trial period/trial day.

BMI = body mass index; FSH = follicle-stimulating hormone.

[a]Screening can be extended up to 7 days (Day −9 to Day −3), if needed.

[b]Subjects can begin with the Day −2 assessments as soon as all their screening assessments have been completed.

[c]Follow-up: 14 (± 3) days after the last dose of trial treatment. Trial treatment is defined as IMP or RHEZ, received on Days 1 to 14.

[d]Height will only be measured at screening.

[e]Complete physical examinations will be performed at screening and on Day −1. Targeted physical examinations will be performed on Days 1 through 14 (predose and 4 hours postdose) and Days 15 through 20 or at ET. A targeted physical examination should include at a minimum a general assessment and examination of the cardiac and respiratory systems (additional systems may be assessed as clinically indicated). The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint.

[f]If a chest x-ray is available that has been taken within 2 weeks prior to screening, which in the opinion of the investigator is a reflection of the subject's TB status, is of adequate quality, and which can be kept with the trial documentation for the required duration, this x-ray can be used as the screening x-ray.

[g]Confirmation of acid-fast bacilli (microscopy from smear ≥ 1+) and drug-susceptible TB using any combination of Xpert MTB/RIF, line probe assay, culture, and/or epidemiologic history.

[h]For HIV positive subjects who are included in stage 2, HIV testing does not need to be repeated at screening if the HIV positive status has been documented prior to screening (within the last month) and the documentation can be kept with the trial documentation for the required duration. For subjects who are HIV positive, blood samples are to be drawn for CD4 assessment at the local laboratory.

[i]Female subjects only.

[j]Postmenopausal female subjects only.

[k]Serum chemistry, hematology, urinalysis, and coagulation testing will be performed at screening, Day −1, Day 4 (predose), Day 7 (predose), Day 14 (predose), and Day 20 or at ET.

[l]Vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be assessed at screening and on Day −1, Day 1 (predose and at 1, 2, 4, 8, and 12 hours postdose), Days 2 through 6 (predose and 2 and 4 hours postdose), Day 7 (predose and 1, 2, 4, 8, and 12 hours postdose), Days 8 through 13 (predose and 2 and 4 hours postdose), Day 14 (predose and 1, 2, 4, 8, and 12 hours postdose), and Days 15 through 20 or at ET. **At screening**, blood pressure and heart rate will be taken with the subject in the **supine (performed first) and sitting position** after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the subject in the supine position. At all other time points, vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. Vital signs will be obtained prior to the ECG and PK blood draw at the nominal time points, where applicable. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints.

[m]Standard 12-lead ECGs will be collected in triplicate (5 minutes apart) at screening and on Day −1, Day 7 (predose), and Day 14 (predose). The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. Electrocardiograms will be obtained prior to the PK blood draw and after vital signs at the nominal time points, where applicable.

[n]Holter monitoring will be performed on Days −1, 1, and 14.

[o]Subjects will be randomized prior to first dosing on Day −1 or Day 1.

[p]Subjects randomized to IMP (OPC-16782 [stage 1] or OPC-167832 and/or delamanid and/or BDQ [stage 2]) will receive QD oral doses of IMP on Days 1 through 14. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature.

[q]Subjects randomized to RHEZ will receive QD oral doses of RHEZ on Days 1 through 20. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal.

[r]After completion of Day 20 or at ET, all subjects will be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen.

[s]Subjects randomized to IMP (OPC-16782 [stage 1] or OPC-167832 and/or delamanid and/or BDQ [stage 2]) will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ) after Day 14. In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

[t]For subjects randomized to OPC-167832 (stage 1); OPC-167832 and/or delamanid and/or BDQ (stage 2), PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid, its metabolite DM-6705, or BDQ (stage 2) will be collected on Day 1 (predose [within 2 hours prior to dosing] and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose), Day 2 (24 hours after the Day 1 dose), Day 12 (predose [within 2 hours prior to dosing]), Day 13 (predose [within 2 hours prior to dosing]), Day 14 (predose [within 2 hours prior to dosing] and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose), Day 15 (24 and 36 hours after the Day 14 dose), Day 16 (48 hours after the Day 14 dose), Day 17 (72 hours after the Day 14 dose), Day 18 (96 hours after the Day 14 dose), Day 19 (120 hours after the Day 14 dose), and Day 20 (144 hours after the Day 14 dose). For the delamanid / OPC-167832 / BDQ arms, the PK samples will be drawn based on the delamanid dosing. If a PK blood sample cannot be drawn at the designated time, a window of ± 15 minutes for each blood draw is acceptable, with the exception of the 0.5 hour draw. The acceptable window for the 0.5 hour draw is + 5 minutes. For all blood draws, the exact time should be recorded. A PK sample should be collected for the ET visit, if applicable.

[u]For subjects randomized to RHEZ, PK blood samples for rifampicin, and isoniazid (stages 1 and 2) will be collected on Day 14 (2 and 6 hours postdose). If a PK blood sample cannot be drawn at the designated time, a window of ± 15 minutes for each blood draw is acceptable, with the exact time recorded. A PK sample should be collected for the ET visit, if applicable.

[v]Sputum samples (approximately 10 mL or more) will be collected from between approximately 3:00 PM (first day of collection) and 7:00 AM (second day of collection) for 16 hours overnight. The overnight sputum specimen collection will begin on Days −2, −1, 2, 4, 6, 8, 10, 12, and 14. The 16-hour sputum sampling must be finished prior to the administration of the next day's IMP or RHEZ, if applicable. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination and assessed in the LAM assay. In addition, MIC testing for OPC-167832 will be performed on Day -2 and Day 14 specimens in stages 1 and 2. MIC testing for delamanid and BDQ will be performed on Day -2 and Day 14 specimens in stage 2 only.

[w]Meals are breakfast, lunch, dinner, and an evening snack. On days when subjects are admitted and discharged, not all meals may be provided depending on the time of admission or discharge.

[x]Adverse events will be assessed and recorded starting at the time the ICF is signed.

[y]Recording of prior/concomitant medication taken within 30 days prior to signing of the ICF through completion of trial.

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3.7.1 General Inpatient Procedures

Subjects will remain either in a seated or semi-recumbent position for the first 4 hours following dosing except during brief periods where protocol-related procedures will be performed. During the 4 hours postdose, restroom visits should be brief (< 10 minutes). Following the 4-hour postdose period, the subjects will be allowed to ambulate, but should not exercise strenuously.

3.7.2 Dietary Requirements

During the in-clinic period, meals will include breakfast, lunch, dinner, and an evening snack. On days when subjects are admitted and discharged, not all meals may be provided depending on the time of admission or discharge.

RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. OPC-167832, delamanid, and BDQ (stage 2 only) will be administered with 240 mL of still (noncarbonated) water at room temperature.

3.7.3 Schedule of Assessments

Vital signs will be obtained prior to the ECG and PK blood draw at the nominal time points, where applicable. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. Electrocardiograms will be obtained prior to the PK blood draw and after vital signs at the nominal time points, where applicable.

If a PK blood sample cannot be drawn at the designated time, a window of ± 15 minutes for each blood draw is acceptable, with the exception of the 0.5 hour draw. The acceptable window for the 0.5 hour draw is + 5 minutes. For all blood draws, the exact time should be recorded. For the delamanid / OPC-167832 and the delamanid / OPC-167832 / BDQ arms, the PK sample will be drawn based on the delamanid dosing.

The 16-hour sputum sampling must be finished prior to the administration of the next day's IMP or RHEZ, if applicable.

Trial days and activities are summarized in Table 3.7.3-1 (Note: activities to be performed throughout the trial are provided in the last row of the table).

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Table 3.7.3-1 Trial Days and Activities
Screening (Days −6 to −3) (Screening can be extended up to 7 days [Day −9 to Day −3], if needed)
Subjects will be screened for up to 4 days prior to the Day −2 assessments. At the screening, the following will be performed: • Review trial procedures and information regarding the nature of the trial and obtain informed consent prior to any trial-related procedures. • Admission of subjects to trial site. • Review inclusion and exclusion criteria. • Collect demographic information. • Document medical history. • Measure height and weight and calculate BMI. • Perform a complete physical examination. • Perform a chest x-ray (if a chest x-ray is available that has been taken within 2 weeks prior to screening, which in the opinion of the investigator is a reflection of the subject's TB status, is of adequate quality, and which can be kept with the trial documentation for the required duration, this x-ray can be used as the screening x-ray). • Perform spot sputum for confirmation of acid-fast bacilli (microscopy from smear ≥ 1+) and drug-susceptible TB using any combination of Xpert MTB/RIF, line probe assay, culture, and/or epidemiologic history. • Perform serum hepatitis (HBsAg and anti-HCV) and HIV screen. For HIV positive subjects who are included in stage 2, HIV testing does not need to be repeated at screening for HIV positive subjects if the HIV positive status has been documented within a month prior to screening and the documentation can be kept with the trial documentation for the required duration. For subjects who are HIV positive, blood samples are to be drawn for CD4 assessment at the local laboratory. • Perform urine pregnancy test (female subjects only). • Perform FSH testing (postmenopausal female subjects only). • Perform urine/blood alcohol and urine drug screen. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate). Blood pressure and heart rate will be taken with the subject in the supine (performed first) and sitting position after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the subject in the supine position. • Collect a standard 12-lead ECG in triplicate (5 minutes apart). The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG.
Day −2
Subjects can proceed with the Day −2 assessments as soon as the screening assessments have been completed. On Day −2, the following will be performed: • Start overnight sputum collection for Day −2 sample (approximately 10 mL or more) at approximately 3:00 PM. • Provide meals as necessary.

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Table 3.7.3-1 Trial Days and Activities

Day −1
On Day −1, the following will be performed: • End overnight sputum collection (for Day −2 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. Positive MTB isolates will be tested for MIC to OPC-167832 in stages 1 and 2, and for MIC to delamanid in stage 2 only. • Review inclusion and exclusion criteria. • Measure weight. • Perform a complete physical examination. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate). Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. • Collect a standard 12-lead ECG in triplicate (5 minutes apart). The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. • Perform Holter monitoring. • Start overnight sputum collection for Day −1 sample (approximately 10 mL or more) at approximately 3:00 PM. • Provide breakfast, lunch, dinner, and an evening snack.
Day 1
On Day 1, the following will be performed: • End overnight sputum collection (for Day −1 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and at 1, 2, 4, 8, and 12 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Perform Holter monitoring. • Randomize subjects to a treatment prior to first dosing. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705 or BDQ and its metabolite M2 (stage 2) at predose (within 2 hours prior to dosing) and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.

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Table 3.7.3-1 Trial Days and Activities
Day 2
On Day 2, the following will be performed: • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood sample for OPC-167832 only (stage 1) or OPC-167832, delamanid, and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 24 hours after the Day 1 dose. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Start overnight sputum collection for Day 2 sample (approximately 10 mL or more) at approximately 3:00 PM. • Provide breakfast, lunch, dinner, and an evening snack.
Day 3
On Day 3, the following will be performed: • End overnight sputum collection (for Day 2 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.
Day 4
On Day 4, the following will be performed: • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples at predose. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Start overnight sputum collection for Day 4 sample (approximately 10 mL or more) at approximately 3:00 PM. • Provide breakfast, lunch, dinner, and an evening snack.

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Table 3.7.3-1 Trial Days and Activities

Days 5 and 6
On Days 5 and 6, the following will be performed: • End overnight sputum collection (for Day 4 sample) at approximately 7:00 AM (Day 5 only). Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Start overnight sputum collection for Day 6 sample (approximately 10 mL or more) at approximately 3:00 PM (Day 6 only). • Provide breakfast, lunch, dinner, and an evening snack.
Day 7
On Day 7, the following will be performed: • End overnight sputum collection (for Day 6 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Measure weight. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples at predose. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 1, 2, 4, 8, and 12 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Collect a standard 12-lead ECG in triplicate (5 minutes apart) at predose. The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.
Day 8
On Day 8, the following will be performed: • Start overnight sputum collection for Day 8 sample (approximately 10 mL or more) at approximately 3:00 PM. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints.

Table 3.7.3-1 Trial Days and Activities
• Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.
Day 9
On Day 9, the following will be performed: • End overnight sputum collection (for Day 8 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.
Day 10
On Day 10, the following will be performed: • Start overnight sputum collection for Day 10 sample (approximately 10 mL or more) at approximately 3:00 PM. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.
Day 11
On Day 11, the following will be performed: • End overnight sputum collection (for Day 10 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • Provide breakfast, lunch, dinner, and an evening snack.

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Table 3.7.3-1 Trial Days and Activities
Day 12
On Day 12, the following will be performed: • Start overnight sputum collection for Day 12 sample (approximately 10 mL or more) at approximately 3:00 PM. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • For subjects randomized to OPC-167832 (stage 1) and /or delamanid and/or BDQ (stage 2), collect a PK blood sample for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ (stage 2) at predose. • Provide breakfast, lunch, dinner, and an evening snack.
Day 13
On Day 13, the following will be performed: • End overnight sputum collection (for Day 12 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. • Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) at predose and 2 and 4 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ(stage 2), collect a PK blood sample for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at predose. • Provide breakfast, lunch, dinner, and an evening snack.
Day 14
On Day 14, the following will be performed: • Measure weight. Perform a targeted physical examination at predose and 4 hours postdose. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples at predose. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate) predose and 1, 2, 4, 8, and 12 hours postdose. Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints. • Collect a standard 12-lead ECG in triplicate (5 minutes apart) at predose. The ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG.

Table 3.7.3-1 Trial Days and Activities

- Perform Holter monitoring.
- For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705 or BDQ and its metabolite M2 (stage 2) at predose (within 2 hours prior to dosing) and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose.
- For subjects randomized to RHEZ only, collect PK blood samples for rifampin and isoniazid at 2 and 6 hours postdose.
- Administer oral dose of RHEZ or IMP. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. The IMP will be administered with 240 mL of still (noncarbonated) water at room temperature.
- Start overnight sputum collection for Day 14 sample (approximately 10 mL or more) at approximately 3:00 PM.
- Provide breakfast, lunch, dinner, and an evening snack.

Day 15

On Day 15, the following will be performed:

- End overnight sputum collection (for Day 14 sample) at approximately 7:00 AM. Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay. Positive MTB isolates will be tested for MIC to OPC-167832 in stages 1 and 2, and for MIC to delamanid in stage 2 only.
- Perform a targeted physical examination.
- Assess vital signs.
- For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 24 and 36 hours after the Day 14 dose.
- Administer RHEZ to subjects randomized to RHEZ. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. Administer treatment for pulmonary TB to subjects randomized to IMP according to the local standard of care regimen (RHEZ) if clinically necessary.[a]
- Provide breakfast, lunch, dinner, and an evening snack.

Day 16

On Day 16, the following will be performed:

- Perform a targeted physical examination.
- Assess vital signs.
- For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 48 hours postdose.
- Administer RHEZ to subjects randomized to RHEZ. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. Administer treatment for pulmonary TB to subjects randomized to IMP according to the local standard of care regimen (RHEZ) if clinically necessary.[a]
- Provide breakfast, lunch, dinner, and an evening snack.

Day 17

On Day 17, the following will be performed:

- Perform a targeted physical examination.
- Assess vital signs.
- For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705 or BDQ and its metabolite M2 (stage 2) at 72 hours postdose.
- Administer RHEZ to subjects randomized to RHEZ. RHEZ will be administered with 240 mL of still (noncarbonated) water 1 hour prior to a meal or 2 hours after a meal. Administer treatment for

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Table 3.7.3-1 Trial Days and Activities
pulmonary TB to subjects randomized to IMP according to the local standard of care regimen (RHEZ) if clinically necessary.[a] • Provide breakfast, lunch, dinner, and an evening snack.
Day 18
On Day 18, the following will be performed: • Perform a targeted physical examination. • Assess vital signs. • Provide treatment for pulmonary TB according to the local standard of care regimen. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 96 hours postdose. • Administer RHEZ (treatment for pulmonary TB to all subjects according to the local standard of care regimen) to all subjects. • Provide breakfast, lunch, dinner, and an evening snack.
Day 19
On Day 19, the following will be performed: • Perform a targeted physical examination. • Assess vital signs. • Provide treatment for pulmonary TB according to the local standard of care regimen. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect PK blood samples for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 120 hours postdose. • Administer treatment for pulmonary TB to all subjects according to the local standard of care regimen (RHEZ). • Provide breakfast, lunch, dinner, and an evening snack.
Day 20/ET
On Day 20 (or at ET), the following will be performed: • Perform a targeted physical examination. • Measure weight. • Assess vital signs (blood pressure, heart rate, temperature, and respiratory rate). Vital signs will be obtained after the subject has been at rest in the supine position for at least 1 minute. • Collect serum chemistry, hematology, urinalysis, and coagulation clinical laboratory samples. • For subjects randomized to OPC-167832 (stage 1) and/or delamanid and/or BDQ (stage 2), collect a PK blood sample for OPC-167832 only (stage 1) or OPC-167832, delamanid and its metabolite DM-6705, or BDQ and its metabolite M2 (stage 2) at 144 hours after the Day 14 dose.[b] • Administer treatment for pulmonary TB to all subjects according to the local standard of care regimen (RHEZ). • After completion of the inpatient stay, all subjects must be referred to local community clinics to receive continued treatment for pulmonary TB per the local standard of care regimen. • Provide meals as needed. • Discharge subjects from the trial site.
Follow-up (14 ± 3 Days After the Last Dose of Trial Treatment [IMP or RHEZ])
Contact the subjects via telephone for follow-up of AEs and concomitant medication.
Throughout the Trial
The following will be performed from the screening visit through and during the follow-up telephone call: • Assess and record AEs • Record prior/concomitant medications (including current oral antipsychotic medication), as applicable.

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[a]In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, or 17) under close supervision in the trial site hospital ward

[b]The Day 20 PK sample will be collected during the ET visit.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the case report form. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the case report form.

3.7.5 Efficacy Assessments

3.7.5.1 Spot Sputum Samples

Spot sputum samples will be collected at the time point presented in the Schedule of Assessments, Table 3.7-1. Microscopy results from a smear will be used to confirm the presence of acid-fast bacilli (≥ 1+). Confirmation of drug-susceptible TB will be performed using any combination of Xpert MTB/RIF, line probe assay, culture, and/or epidemiologic history.

3.7.5.2 Overnight Sputum Samples

Sputum samples (approximately 10 mL or more) will be collected from between approximately 3:00 PM (first day of collection) and 7:00 AM (second day of collection) for 16 hours overnight at the time points presented in the Schedule of Assessments, Table 3.7-1. The 16-hour sputum sampling must be finished prior to the administration of each day's IMP or RHEZ. The appropriately labeled sputum container must be placed in a biohazard bag, in the fridge until collection by the courier. The fridge temperature should be between 2 and 8°C.

Sputum will be cultured on solid media for quantification of bacterial load and in the MGIT system for TTD determination, and assessed in the LAM assay.

Minimum inhibitory concentration testing for delamanid, BDQ (stage 2 only), and OPC-167832 (stage 1 and stage 2) will be batch tested at the end of each stage of the trial on baseline (Day −2) and Day 14 positive isolates.

M. tuberculosis isolates will be retained at the local laboratory for potential additional analysis of the TB bacilli.

3.7.6 Safety Assessments

3.7.6.1 Adverse Events

Refer to Section 5 for the methods and timing for assessing, recording, and analyzing AEs.

3.7.6.2 Clinical Laboratory Tests

The clinical laboratory tests listed in Table 3.7.6.2-1 will be collected at the times presented in the Schedule of Assessments, Table 3.7-1, and processed in accordance with directions from the clinical laboratory.

Table 3.7.6.2-1 Clinical Laboratory Tests

Hematology:	Serum Chemistry:
Hematocrit	Albumin
Hemoglobin	ALP
Platelet count	ALT
Mean corpuscular hemoglobin concentration	AST
Mean corpuscular volume	Bilirubin, total
RBC count	Blood urea nitrogen
WBC count with differential	Calcium
	Carbon dioxide
Urinalysis:	Creatinine
Appearance	Creatine kinase
Bilirubin	GGT
Color	Glucose
Glucose	Lactic dehydrogenase
Ketones	Magnesium
Leukocytes	Potassium
Microscopic analysis of RBC/WBC (per high powered field)	Protein, total
	Sodium
Nitrites	Uric acid
Occult blood	Triglycerides
Protein	
Urobilinogen	Drug Screen (all items in urine except where noted)
	Alcohol (urine or blood test)
Coagulation:	Amphetamines
International normalized ratio	Barbiturates
Partial thromboplastin time	Benzodiazepines
Prothrombin time	Cannabinoids
	Cocaine
Additional Tests:	Methadone
anti-HCV	Opiates
CD4 count	Phencyclidine
HBsAg	
HIV	
Urine pregnancy test (female subjects)	
FSH (postmenopausal female subjects)	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; RBC = red blood cell; WBC = white blood cell.

A urine pregnancy test will be conducted prior to trial intervention (at screening) in female subjects; results will be available prior to the first administration of IMP or RHEZ on Day 1.

3.7.6.3 Physical Examination and Vital Sign Assessments

Complete and targeted physical examinations will be performed at the time points presented in the Schedule of Assessments, Table 3.7-1.

The physical examination will include an evaluation of the following: head, ears, eyes, nose, and throat; neck and chest; abdomen; extremities; nervous system; and skin and mucosae. A targeted physical examination is a review that focuses on subject driven issues eg, the investigator enquires if the subject has any complaints, pains or disturbances and this would lead to further evaluation of the problematic area. At a minimum, there should be an assessment of general appearance and a chest examination should be performed. The 4-hour post-dose targeted physical examination could be performed ± 30 minutes after the expected post-dose timepoint. The principal investigator or appointed medical doctor is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for each subject. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Any clinically significant condition present at physical examinations performed after the first dose of IMP or RHEZ on Day 1 that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

Body height and weight will also be measured at the time points presented in the Schedule of Assessments, Table 3.7-1. For the measurement of height, the measurement will be made without shoes. For the measurement of weight, all efforts will be made to use the same scale for all measurements throughout the trial.

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be assessed at the time points presented in the Schedule of Assessments, Table 3.7-1. Vital signs will be obtained prior to PK blood draws and ECGs at the nominal time points, where applicable. At screening, blood pressure and heart rate will be taken with the subject in the supine (performed first) and sitting position after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the subject in the supine position. At all other time points, vital signs will be obtained after the subject has been at

rest in the supine position for at least 1 minute. The post-dose vital signs could be performed within 15 minutes earlier than the expected post-dose timepoints.

3.7.6.4 Standard 12-lead Electrocardiograms

Standard 12-lead ECGs will be collected in triplicate (5 minutes apart) at the time points presented in the Schedule of Assessments, Table 3.7-1. The mean ECGs of the 3 time points will be utilized to determine subject's eligibility during screening. The ECGs will be collected prior to PK blood draws and after vital signs at the nominal time points, where applicable.

Standard 12-lead ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. Heart rate, ventricular rate, RR interval, PR interval, QRS duration, and QT intervals will be recorded. The QTcF and corrected QT interval using Bazett's method (QTcB) will be calculated. The 12-lead ECGs will be evaluated at the trial sites to determine the subject's eligibility and to monitor safety during the trial. The principal investigators or designees (licensed physician) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. The reviewers must be listed on FDA Form 1572 and the trial site delegation of responsibility form. Electrocardiogram data will be recorded electronically by the central ECG laboratory(ies) and by the trial site(s). Eligibility for the trial will be based on the central ECG report at the screening visit.

3.7.7 Pharmacokinetic and Pharmacodynamic Assessments

3.7.7.1 Pharmacokinetic Assessments

Blood samples for PK analysis will be collected at the time points presented in the Schedule of Assessments, Table 3.7-1. If a sample cannot be drawn at the designated time, a window of ± 15 minutes for each blood draw is acceptable; the exact time of the draw must be recorded in the electronic case report form (eCRF).

Stage 1: Concentrations of OPC-167832, rifampicin, and isoniazid will be analyzed.

Stage 2: Concentrations of OPC-167832, delamanid, and its metabolite DM-6705, BDQ, rifampicin, and isoniazid will be analyzed.

Additional metabolites that are not identified in the protocol may also be analyzed if new information becomes available.

Plasma samples will be shipped to the bioanalytical laboratory identified in Appendix 2 and stored in a freezer at the trial site(s). Detailed handling and shipping instructions are provided in the Operations Manual.

3.7.7.2 Pharmacodynamic Assessments

Holter monitoring will be performed on Days −1, 1, and 14 as per the Schedule of Assessments, Table 3.7-1.

Overnight sputum specimens will be provided to the microbiological laboratory for sputum culture and Otsuka TB LAM ELISA measurements.

3.7.8 Genetic Assessments

No assessments of human genetic material are planned for this protocol.

3.7.9 Future Biospecimen Research Samples

No future biospecimen research assessments are planned for this protocol.

3.7.10 End of Trial

The end of trial date is defined as the last date of contact or the date of the final contact attempt from the post-treatment follow-up eCRF page for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

In the event of sponsor termination or suspension of the trial for any reason, prompt notification will be given to investigators, IEC, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

The sponsor, investigator, or the IEC has the right to terminate the participation of a particular trial site, if necessary, due to lack of subject enrollment, noncompliance with the protocol, or if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The sponsor is to be notified promptly if the trial was terminated by the investigator or the IEC at the trial site.

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3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After the first dose of IMP or RHEZ on Day 1, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the investigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.8.3.2 Documenting Reasons for Discontinuation

All subjects have the right to withdraw and the investigator can discontinue a subject's participation in the trial at any time if medically necessary.

In addition, subjects meeting the following criteria must be withdrawn from the trial (only one reason for discontinuation [the main reason] can be recorded in the eCRF):

- Death
- TB disease relapse or TB disease progression
- Failure to meet inclusion and exclusion criteria
- Lost to follow-up
- Occurrence of QTcF > 500 msec
- Noncompliance with IMP or RHEZ (if confirmed not related to an AE)
- Physician decision (other than AE)
- Pregnancy (see Section 5.5)
- Major protocol deviation (other than noncompliance with IMP or RHEZ)
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal of consent by parent/guardian (if confirmed not related to an AE)
- Withdrawal of consent by subject (if confirmed not related to an AE)

If the subject discontinues IMP or RHEZ due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 3.8.3.1 must be followed. Subjects may be replaced, if discontinuations/withdrawals occur, as described in Section 3.3.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation.

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be understood, documented, and managed to protect the rights of the subject and the integrity of the trial.

Subjects who withdraw, should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.9 Screen Failures

Subjects who sign an ICF but who do not receive IMP or RHEZ are permitted to be rescreened. In the event that the subject is rescreened for trial participation, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject signs an ICF), but who is not randomized or assigned trial treatment.

3.10 Definition of Completed Subjects

The evaluation period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether the subject actually consumes all doses of IMP or RHEZ. Subjects who are evaluated at the last scheduled visit during the evaluation period will be defined as trial completers. For purposes of this trial, subjects who complete Day 20 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before 14 (± 3) days after the last dose of trial treatment (IMP or RHEZ) and who do not have a known reason for discontinuation (eg, withdrew consent or AE, etc.), except those who have completed the trial as defined in Section 3.10, will be classified as "lost to follow-up" as the reason for discontinuation.

The trial site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to

contact the subject via certified mail or an alternative similar method where appropriate, before assigning a “lost to follow-up” status.

3.12 Subject Compliance

The time and dose of IMP and RHEZ administration during the trial will be recorded on the eCRF. Information regarding any inappropriately administered doses will also be documented on the eCRF.

All doses of IMP and RHEZ will be administered at the trial site while subjects are inpatient. Compliance will be ensured by a hand and mouth check during the oral dosing administration.

3.13 Protocol Deviations

In the event of a major deviation from the protocol due to an emergency, accident, or mistake (eg, IMP or RHEZ dispensing or subject dosing error or concomitant medication), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator, medical monitor, and sponsor will come to a joint decision as quickly as possible regarding the subject’s continuation in the trial. If the decision reached is to allow the subject to continue in the trial, this must be documented by the investigator and the sponsor, and approved or disapproved by the medical monitor.

4 Restrictions

4.1 Prohibited Medications

Quinolones and prednisolone should not be used within 3 months prior to the screening visit and during the screening period until Day 20. Subjects should not be taking or start antiretroviral therapy within 2 weeks of the completion of the trial.

The selected CYP3A4 inhibitors and inducers presented in Table 4.1-1 and Table 4.1-2, respectively should be not used from Day −2 until Day 20.[14]

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Table 4.1-1	**List of Selected Cytochrome P450 3A4 Inhibitors Prohibited During the Trial**
Potent CYP3A4 Inhibitors:	
Viekira PAK2	Danoprevir
Indinavir	Elvitegravir
Tipranavir	Saquinavir
Ritonavir	Lopinavir
Cobicistat	Itraconazole
Ketoconazole	Voriconazole
Troleandomycin	Mibefradil
Telaprevir	Clarithromycin
Posaconazole	Nelfinavir
Telithromycin	Nefazodone
Grapefruit juice	Idelalisib
Conivaptan	Boceprevir
Moderate CYP3A Inhibitors:	
Erythromycin	Faldaprevir
Fluconazole	Imatinib
Atazanavir	Verapamil
Diltiazem	Netupitant
Darunavir	Nilotinib
Dronedarone	Tofisopam
Crizotinib	Cyclosporine
Atazanavir	Ciprofloxacin
Aprepitant	Isavuconazole
Casopitant	Cimetidine
Amprenavir	

Note: Please communicate with the sponsor's medical monitor if the subject needs to receive any medication (other than IMP or RHEZ) that is not on this list.

Table 4.1-2	**List of Selected Cytochrome P450 3A4 Inducers Prohibited During the Trial**
Potent CYP3A4 Inducers:	
Carbamazepine	Enzalutamide
Mitotane	Phenytoin
Rifampin	St. John's wort
Moderate CYP3A Inducers:	
Bosentan	Efavirenz
Etravirine	Modafinil

Note: Please communicate with the sponsor's medical monitor if the subject needs to receive any medication (other than IMP or RHEZ) that is not on this list.

4.2 Other Restrictions

Consumption of alcohol and/or grapefruit, grapefruit juice, Seville oranges, or Seville orange juice and related products within 72 hours prior to the first dose of IMP or RHEZ on Day 1 until Day 20 is prohibited. Restrictions on activity following dosing are described in Section 3.7.1.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred.

An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction”.

A serious AE (SAE) includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization
  - Hospitalization itself should not be reported as a serious treatment-emergent AE (TEAE); whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered serious TEAEs.
- Congenital anomaly/birth defect.

- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event:

- Any SAE
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as immediately reportable events (IREs). Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is a complication or abnormality in the newborn.

Clinical Laboratory Assessment Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically relevant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically relevant by the investigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, treatment interruption, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

In addition, all AEs will be graded on a 5-point scale according to the "DAIDS Table for Grading the Severity of Adult and Pediatric AEs" (Appendix 3).

Causality: Assessment of causal relationship of an AE to the use of trial treatment (IMP or RHEZ):

Related: There is a reasonable possibility of a temporal and causal relationship between the trial treatment (IMP or RHEZ) and the AE.

Not Related: There is no temporal or reasonable relationship between the trial treatment (IMP or RHEZ) and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will assess subjects for the occurrence of AEs from the time the ICF is signed until the end of the trial. For this trial, information on AEs will be followed for up to 14 (± 3) days after the last dose of trial treatment (IMP or RHEZ) has been administered. To avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How are you feeling?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as AEs only if there are unusual or severe clinical features that were not present, not experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor and Clindev Pty Ltd must be notified immediately by fax or e-mail of any IREs according to the procedure outlined below in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must report any SAE, potential serious hepatotoxicity, or confirmed pregnancy, immediately after either the investigator or trial site personnel become aware of the event. An IRE form should be completed and sent by fax or e-mail using the contact information on the title page of this protocol, and as follows:

[redacted]

Fax: [redacted]

E-mail: [redacted]

(Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE eCRF.)

Subjects experiencing SAEs should be followed clinically as described in Section 5.7.2. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

5.5 Pregnancy

Women of childbearing potential are women whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For men and women of childbearing potential, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 12 weeks after the last dose of trial treatment (IMP or RHEZ). Unless the subject is sterile (ie, women who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent during the trial and for 12 weeks after the last dose of trial treatment (IMP or RHEZ), 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control implant, birth control depot injection, condom, sponge, or occlusive cap (vaginal diaphragm or cervical/vault cap). Due to safety considerations, spermicides are no longer recommended to be used by subjects who will be participating in this trial. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF. Male subjects must also agree not to donate sperm from trial screening through 12 weeks after the last dose of trial treatment (IMP or RHEZ).

Before enrolling men and women in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, men and women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine pregnancy test for human chorionic gonadotropin will be performed at screening on all female subjects. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects should also be instructed to contact the investigator immediately, during the trial, if their partners suspect that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the sponsor or medical monitor.

The investigator(s) must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for at least 12 weeks after the last dose of trial

treatment (IMP or RHEZ), and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth. Local regulatory requirements must be followed for follow-up and reporting on pregnancy cases or infants.

5.6 Procedure for Breaking the Blind

Not applicable, this is an open-label trial.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during data analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for ongoing SAEs and IREs up to 14 (± 3) days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are identified or ongoing at the last scheduled contact must be recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page or the safety database if the eCRF data is locked, according to the appropriate reporting procedures. The investigator(s) will follow SAEs until the events are resolved or stabilized, or the subject is lost to follow-up or has

died. Resolution means the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator(s) will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring After Last Scheduled Contact

Any new SAEs or IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator(s) to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator(s) should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic Analysis

6.1 Pharmacokinetic Methods

Pharmacokinetic parameters will be determined using noncompartmental analysis methods. If data are not adequate, certain parameters may not be calculated. Pharmacokinetic concentrations and parameters will be summarized by treatment using descriptive statistics (number, median, mean, standard deviation [SD], percent coefficient of variation, minimum, and maximum). Pharmacokinetic concentrations and parameters will also be listed by subject.

In addition to the noncompartmental analysis, population PK modeling will be performed on OPC-167832 PK data from both stages.

No PK analysis will be performed on rifampin and isoniazid concentrations.

6.2 Pharmacodynamic Methods

Holter monitoring will be summarized descriptively by treatment. Data will also be presented in listings.

Colony-forming units from solid culture, LAM concentrations from the Otsuka TB LAM ELISA, and MGIT TTD will be utilized for PK/PD correlations.

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6.3 Pharmacokinetics/Pharmacodynamics Methods

Exposure-response modeling will be performed in both stages for OPC-167832 PK measures versus bacterial load using LAM and CFU counts on agar media, with the intent of identifying E_{max}, the maximum estimated decline in LAM and CFU counts and EC_{80}, the exposure that corresponds to 80% of the E_{max}.

For stage 2, the E_{max} and EC_{80} for subjects receiving OPC-167832 and 300 mg delamanid will be compared with the E_{max} and EC_{80} of OPC-167832 given alone in stage 1.

Published studies have established that EC_{80} can be used for strong bactericidal drugs as the "optimal" target from the PK/PD analysis.[15,16,17,18,19] In the data submitted to the European Medicines Agency to qualify the hollow-fiber system as a drug development tool for TB[20] EC_{80} was used as the optimal target for bactericidal drugs (personal communication: T. Gumbo, University of Baylor, Dallas, Texas, US, and D. Hanna, Critical Path to TB Drug Regimens, Tempe, Arizona, US).

The relationship between QT interval (Holter data) and plasma concentrations of OPC-167832 (stage 1) and OPC-167832 when administered with delamanid and/or BDQ (stage 2) will be examined using an exposure-response analysis.

6.4 Pharmacogenomic Methods

No pharmacogenomics analysis is planned.

7 Statistical Analysis

7.1 Determination of Sample Size

The trial is not powered for formal statistical hypothesis testing or comparisons. The sample size is based on sample sizes from several similar trials in the literature.[21]

7.2 Datasets for Analysis

The PK population will include all subjects with adequate data for deriving the PK parameters.

Safety analysis will be conducted based upon the safety population. All subjects who received any dose of IMP or RHEZ will be included in the safety population.

Efficacy analyses will be conducted based upon the modified intent-to-treat (MITT) population. The MITT population will include all subjects who were quantitative culture-positive at baseline and met all of the inclusion criteria.

7.3 Handling of Missing Data

No data imputation will be performed for missing plasma or sputum concentrations in this trial.

7.4 Primary and Secondary Endpoint Analyses

Pharmacokinetic methods are described in Section 6.1 and safety analysis is described in Section 7.6.

Primary and secondary efficacy endpoint analyses are described in Section 7.4.1 and Section 7.4.2, respectively. Other efficacy analyses are described in Section 7.8. Efficacy data will be summarized by randomized treatment using descriptive statistics (number, median, mean, SD, percent coefficient of variation, minimum, and maximum) or presented in figures (where applicable). Change from baseline in log-CFU, log-LAM, and MGIT TTD will be presented by randomized treatment group in each stage. In addition, listings will be presented for efficacy assessments by subject.

7.4.1 Primary Efficacy Endpoint Analyses

7.4.1.1 Stage 1

The EBA of OPC-167832 will be determined by the decline in bacterial load.

Individual subject EBA estimates will be obtained using both a two-point EBA calculation as well as a linear-regression based approach. Early bactericidal activity estimates will be derived over the first 14 days (see equation 1 in Section 7.4.1.1.1).

The EBA for the RHEZ comparator arm will be based on the results for all of the subjects receiving RHEZ treatment in each of the treatment cohorts in stage 1. After the completion of stage 2, the EBA for the RHEZ comparator arm will be recalculated including subjects assigned to the RHEZ regimen in both stage 1 and stage 2.

7.4.1.1.1 Two-time Point Early Bactericidal Activity Calculation

Early bactericidal activity (EBA) between day x and day y will be defined by the following equation:

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$$EBA_{x-y,i} = \frac{Log_{10}\ value_{x,i} - Log_{10}\ value_{y,i}}{y - x} \quad (1)$$

where y and x are trial days in integer values (with baseline defined as the average of measurements at Day-2 and Day -1), $EBA_{x\text{-}y,i}$ is the EBA estimate for the i^{th} subject across days x to y, and Log_{10} $value_{x,i}$ and Log_{10} $value_{y,i}$ are the log_{10}-transformed assay values on days x and y, respectively, for the specified assay on samples from the i^{th} subject.

The EBA effect size will be expressed as a ratio of the estimated EBA for OPC-167832 and the estimated EBA for RHEZ. For example, the 14-day EBA for delamanid 200 mg QD was 0.84 log-CFU and the 14-day EBA for RHEZ was 1.44 log-CFU; the 14-day EBA of delamanid was estimated to be 58% of the EBA of the 4-drug RHEZ regimen.[22]

7.4.1.1.2 Early Bactericidal Activity Estimation via Linear Mixed Effects Modeling

When each stage assay data are available, linear mixed effects modeling will also be used to determine the EBA estimates across all available time points from baseline through Day 14 of treatment. Details will be documented in the statistical analysis plan prior to database lock.

7.4.2 Secondary Efficacy Endpoint Analyses

The secondary analyses of EBA will estimate the slope of the change in log-LAM values and the change in TTD in the automated MGIT system.

The analyses of the secondary endpoints of change in log-LAM values and change in TTD in stage 2 will be conducted in a way similar to comparisons of change in log-CFU specified above for stage 2. The endpoint is change in EBA from baseline to Day 14.

Treatment group comparisons in stage 2 are:

1) OPC-167832 30 mg + delamanid 300 mg + BDQ 400 mg vs OPC-167832 30 mg + delamanid 300 mg;
2) OPC-167832 30 mg + delamanid 300 mg + BDQ 400 mg vs OPC-167832 30 mg + BDQ 400 mg;
3) OPC-167832 30 mg + delamanid 300 mg vs OPC-167832 30 mg in Stage 1 using connectivity of RHEZ in Stages 1 and 2;
4) OPC-167832 30 mg + BDQ 400 mg vs OPC-167832 30 mg in Stage 1 using connectivity of RHEZ in Stages 1 and 2.

7.4.3 Interim Analysis

An interim analysis of safety, tolerability, PK, and efficacy of OPC-167832 is planned after the end of stage 1.

7.5 Analysis of Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized by treatment using descriptive statistics (number, median, mean, SD, minimum, and maximum for continuous variables and number and percentage of subjects for discrete variables, eg, race and gender).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 (or a later version if updated during the trial). All medical history will be listed, and the number and percentage of subjects will be summarized by treatment.

7.6 Safety Analysis

Safety data will be summarized by randomized treatment using descriptive statistics (number, median, mean, SD, minimum, and maximum) for numeric variables and frequency and count for discrete variables. Incidence of clinically notable values will be summarized where applicable. Safety assessments will also be listed by subject.

7.6.1 Adverse Events

All AEs will be coded by MedDRA system organ class and preferred term. The incidence of the following events will be summarized by treatment:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP or RHEZ
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP or RHEZ
- TEAEs by DAIDS grading

Treatment-emergent AEs are defined as AEs that occur after the initiation of trial treatment; or an event or pre-existing medical problem that has changed adversely in nature or severity from baseline in a subject while receiving trial treatment.

Adverse event data will be presented in listings.

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7.6.2 Clinical Laboratory Tests Data

For clinical laboratory tests data, baseline is defined as the last nonmissing value obtained at a scheduled visit on or before Day −1. If the Day −1 measurement is missing, the baseline value will be the last nonmissing measurement from the screening visit (the previous scheduled visit). Clinical laboratory test parameters and mean changes from baseline will be summarized by treatment. The incidence of clinical laboratory test abnormalities, as defined in the "DAIDS Table for Grading the Severity of Adult and Pediatric AEs" (Appendix 3) will be summarized by treatment. Clinical laboratory test data will be presented in listings.

7.6.3 Physical Examination and Vital Signs Data

Physical examination data will be presented in listings.

Vital sign parameters and mean changes from baseline will be summarized by treatment. The incidence of vital signs abnormalities, as defined in the "DAIDS Table for Grading the Severity of Adult and Pediatric AEs" (Appendix 3) will be summarized by treatment. Vital sign data will be presented in listings.

7.6.4 Electrocardiogram Data

Electrocardiogram measurements and mean changes from baseline will be summarized by treatment. Baseline of ECG is defined as Day -1. If the measurement from Day -1 is missing, the screening ECG is taken as baseline. The incidence of potentially clinically significant changes and abnormalities in ECG evaluations will be summarized. Electrocardiogram data will be presented in listings.

7.7 Pharmacodynamic Analysis

Pharmacodynamic methods and PK/PD methods are described in Section 6.2 and Section 6.3, respectively.

7.8 Other Efficacy Analysis

7.8.1 Bacterial Load Changes as Measured by the Change of Sputum Lipoarabinomannan Concentration

The decline in log-CFU on agar media at the end of 14 days as measured by the Otsuka TB LAM ELISA will be utilized with a two-time point EBA estimates (see equation 1 in Section 7.4.1.1.1) for the selection of the dose level for each cohort after Cohort 1, since those results are available in near real time and will facilitate faster decisions.

[redacted]

8 Management of Investigational Medicinal Product

The IMPs to be administered during this trial include OPC-167832 (stage 1 and stage 2) and delamanid and/or BDQ (stage 2 only). The reference product to be administered includes RHEZ (stage 1 and stage 2).

Note: Subjects randomized to IMP will receive treatment for pulmonary TB according to the local standard of care regimen (RHEZ) after Day 14. In subjects with no clinical indication to start RHEZ immediately, commencement of RHEZ can be delayed for up to 3 days (Days 15, 16, and 17) under close supervision in the trial site hospital ward.

8.1 Packaging and Labeling

OPC-167832 and delamanid will be provided to the investigator(s) and the persons designated by the investigator(s) or institutions by the sponsor or designated agent.

OPC-167832 and delamanid will be supplied as follows:

- OPC-167832 will be supplied as 3-, 10-, and 30-mg immediate-release tablets
- Delamanid will be supplied as 50-mg tablets

Each bottle of IMP provided by the sponsor will be labeled to clearly disclose the compound identity, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

The RHEZ will be sourced and supplied as Rifafour single-dose combination tablets by the trial site(s). The BDQ will be sourced in country.

8.2 Storage

The IMP and RHEZ will be stored in a securely locked cabinet or enclosure. Access will be limited to the investigator(s) and designees. Neither the investigator(s) nor any designees may provide IMP or RHEZ to any subject not participating in this protocol.

The IMP and RHEZ will be stored according to the storage conditions indicated on the clinical labels.

The clinical trial site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator(s), or designee(s), must maintain an inventory record of IMP (including OPC-167832, delamanid, and BDQ) and RHEZ received, dispensed, administered, destroyed, or returned (as applicable).

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMPs, and partially-used IMPs must be returned to the sponsor or a designated agent, or destroyed at the trial site(s). The IMPs may be destroyed by the trial site(s), only if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMPs returned to the sponsor must be accompanied by appropriate documentation and be clearly identified by the protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return or destruction of used IMP containers, unused IMPs, and partially-used IMPs.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate, or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

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8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator(s) or designees must record all PQCs identified through any means from the receipt of the IMP (OPC-167832 and delamanid) from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator(s) or designees must notify the sponsor (or sponsor's designee) by e-mail or telephone immediately after of becoming aware of the PQC according to the procedure outlined below.

Identification of a PQC by the subject should be reported to the trial site investigator, who should then follow one of the reporting mechanisms below.

- E-mail - Send information required for reporting purposes (listed in Section 8.5.2) to [redacted]
- Phone - [redacted]

8.5.2 Information Required for Reporting Product Quality Complaints

The following information is required for reporting purposes:

- Description of complaint
- Reporter identification (eg, subject, investigator, site information, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, kit number, or bottle number)
- Clinical protocol reference (number and trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process for Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide instructions for complaint sample return, when applicable.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigator(s) and made available for direct inspection by authorized persons.

The investigator(s)/institution(s) will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the trial site, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject in the trial, the review of all inclusion/exclusion criteria prior to IMP or RHEZ administration on Day 1, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding visit or day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP or RHEZ must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of all clinicians (or designees) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from the trial progress notes and other source documents will be entered by trial site personnel directly onto eCRFs in the sponsor's electronic data capture system.

Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Electronic data not entered on the eCRFs, such as data received from central laboratories and central ECG readers, will be reconciled by the sponsor or the contract research organization with the eCRF data to ensure consistency.

9.3 File Management at the Trial Site

The investigator(s) will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The trial site file will include all source documentation for all subjects screened or enrolled at the trial site. The investigator(s)/institution(s) will take measures to ensure confidentiality and prevent accidental or premature destruction of these documents.

9.4 Record Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that the participating investigator(s) maintains detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region (or at least 2 years after the formal discontinuation of clinical development of the investigational product); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable. If regional requirements are longer, the specific information for the region should be stated in the investigator's contract.

The investigator(s) must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator(s) will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated

during this trial, including the eCRF data on the CD-ROM and any data clarification forms received from the sponsor (or sponsor's designee). Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial or withdraws during the record retention period (eg, due to relocation or retirement or trial site closure), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's (or sponsor designee's) monitors will visit the trial site(s) during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site clinical personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's (or designee's) Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator(s) agrees to participate with audits.

Regulatory authorities may inspect the trial site(s) during or after the trial. The investigator(s) will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.3 Protocol Deviations

Due to the complexity of clinical trial protocols and despite training and preventive efforts, deviations from the written protocol may occur and potentially result in harm to subjects, biased or inaccurate results, and possible rejection of all or part of the trial data. Per the ICH E3 guidance on the structure and content of clinical study reports, Section 10.2, protocol deviations should be summarized by site and grouped into different categories such as:

- Major IMP or RHEZ dosing errors that may compromise subject safety or efficacy assessments.
- Administration of an excluded concomitant medication during the course of the trial.

The FDA defines a protocol deviation/violation as an unplanned excursion from the protocol that is not implemented or intended as a systematic change.

Otsuka categorizes clinical protocol deviations as major versus minor. A major deviation is an intentional or accidental action or omission in a trial conduct that could potentially have a negative impact on the integrity of the trial's primary scientific objectives or has a significant potential to have a negative impact on the safety or efficacy assessments of any trial subject. Major deviations are those that might significantly affect the completeness, accuracy, or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

A minor deviation is an intentional or accidental action or omission during trial conduct in which the protocol is not strictly followed, but which has inconsequential impact on the integrity of the trial as a whole or the safety or efficacy analyses of an individual subject.

All protocol deviations will be categorized as major or minor according to the above definitions and only major deviations will be summarized in the clinical study report.

If the same protocol deviation occurs for multiple subjects, it must be recorded separately for each subject.

Investigators are expected to document potential protocol deviations as well as their medical assessment regarding continuation of the subject(s) due to the protocol deviation.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. The trial site(s) will seek approval/favorable opinion by an IEC according to regional requirements, and the investigator(s) will provide that documentation to the sponsor. The IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator(s), sub-investigator(s), and their staff will take measures to ensure adequate

care in protecting subject privacy. To this end, a subject number or subject identifier will be used to identify each subject.

Financial aspects, subject insurance, and publication policy for the trial will be documented in the agreement between the sponsor and the investigator(s).

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor. Subjects will be identified only by unique subject identifiers in eCRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator(s) will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IEC. Any permanent change to the protocol, whether an overall change or a change for a specific trial site, must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IEC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMPs used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agency within local applicable timelines.

When the IEC, investigators, or the sponsor conclude that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the

currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations).

According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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Appendix 1 Names of OPDC Personnel

Report IREs (SAEs, potential serious hepatotoxicity, pregnancies, and AEs requiring discontinuation of IMP) to:

[redacted]
Fax: [redacted]
E-mail: [redacted]

For Medical Emergencies (use only if OPDC personnel listed below are unavailable):
[redacted]

Medical Monitor and Director, Clinical Development
[redacted] Otsuka Novel Products TB, Global Clinical Development, TB
Phone: [redacted]
Fax: [redacted]

Head, Clinical Pharmacology
[redacted] Clinical Pharmacology
Phone: [redacted]
Fax: [redacted]

Manager, Clinical Development
[redacted] Clinical Management, Global Clinical Development, TB
Phone: [redacted]
Fax: [redacted]

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Appendix 2 Institutions Concerned with the Trial

Independent Ethics Committee
Pharma-Ethics Independent Research Ethics Committee
123 Amcor Road
Lyttelton Manor
Centurion 0157, South Africa
Phone: +27 (0) 12 664-8690/0219
Fax: + 27 (0) 12 664-7860

University of Cape Town Faculty of Health Sciences Human Research Ethics Committee
E 53 Room 46
Old Main Building
Groote Schuur Hospital
Observatory 7925, Cape Town, South Africa
Phone: +27 (0) 21 406-6626

Contract Research Organizations
PRA Health Sciences

Clindev Pty Ltd, A Micron Group Company

Trial Sites
TASK Clinical Research Centre
1 Smal Street
Bellville 7530, Cape Town, South Africa
Phone: +27 (0) 21 917-1044
Fax: +27 (0) 21 918-1378
E-mail: tcrc@task.org.za

University of Cape Town Lung Institute (Pty) Ltd.
George Street
Mowbray 7700, Cape Town, South Africa
Phone: +27 (0) 21 406-6850
Fax: +27 (0) 917-1046

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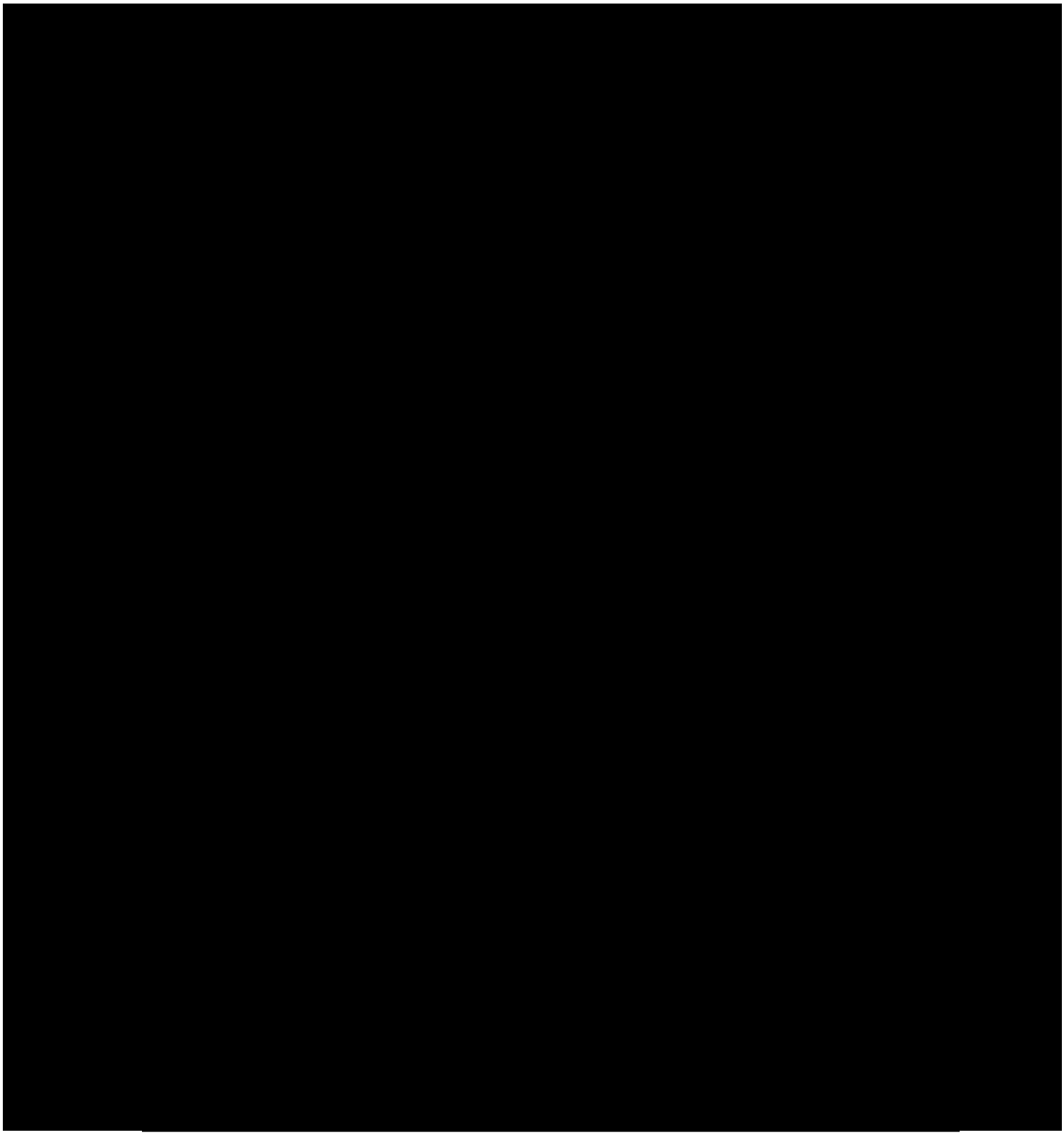

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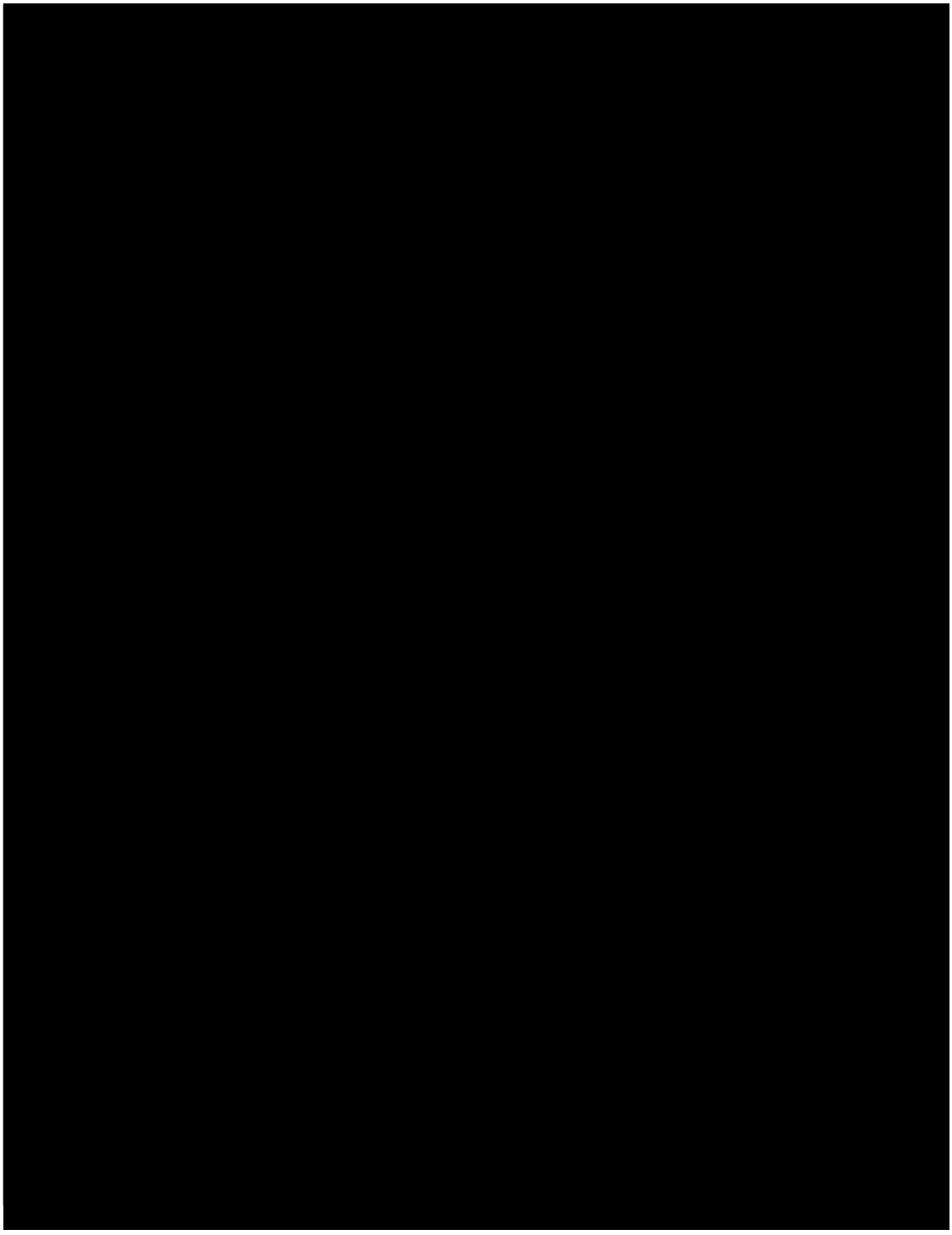

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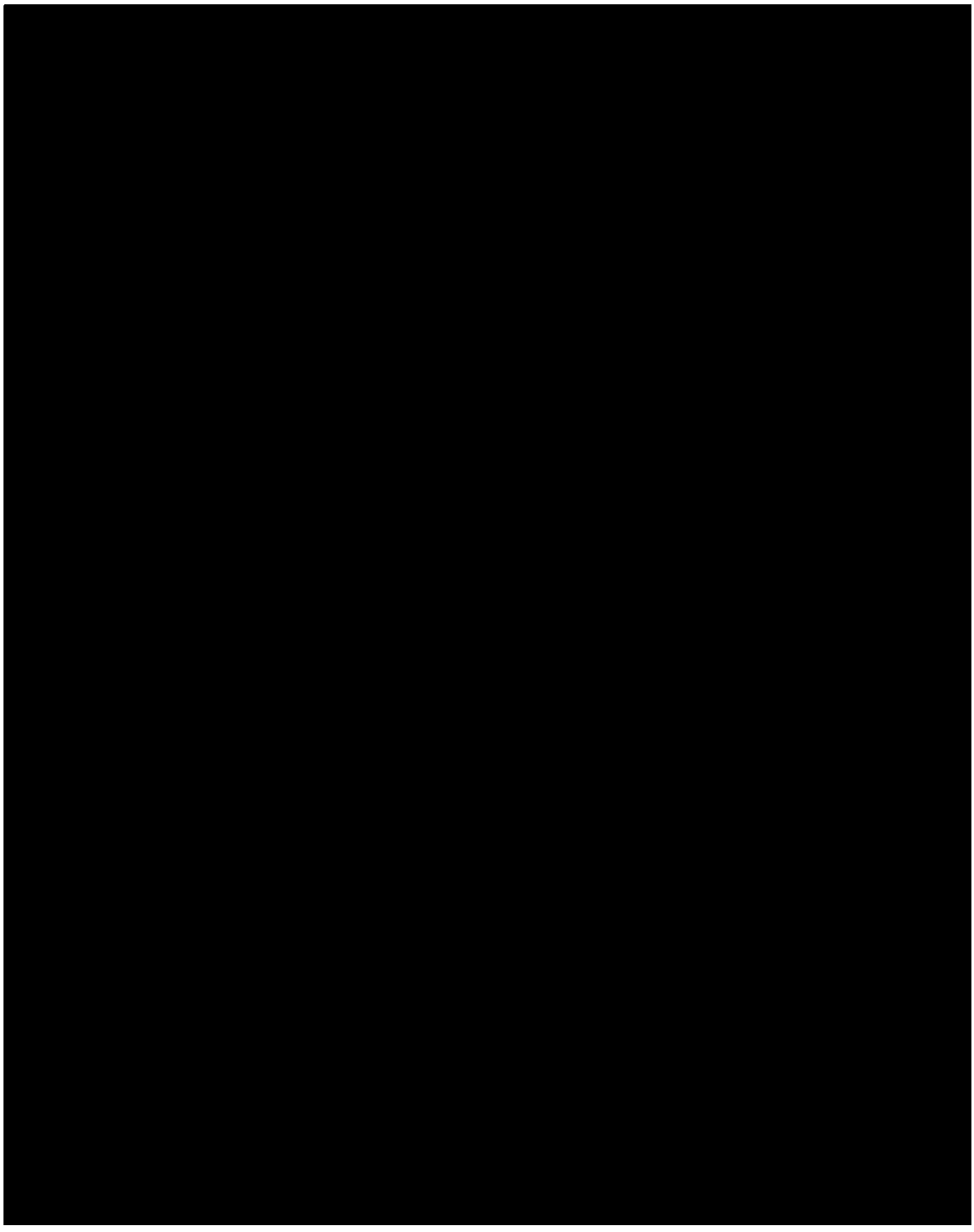

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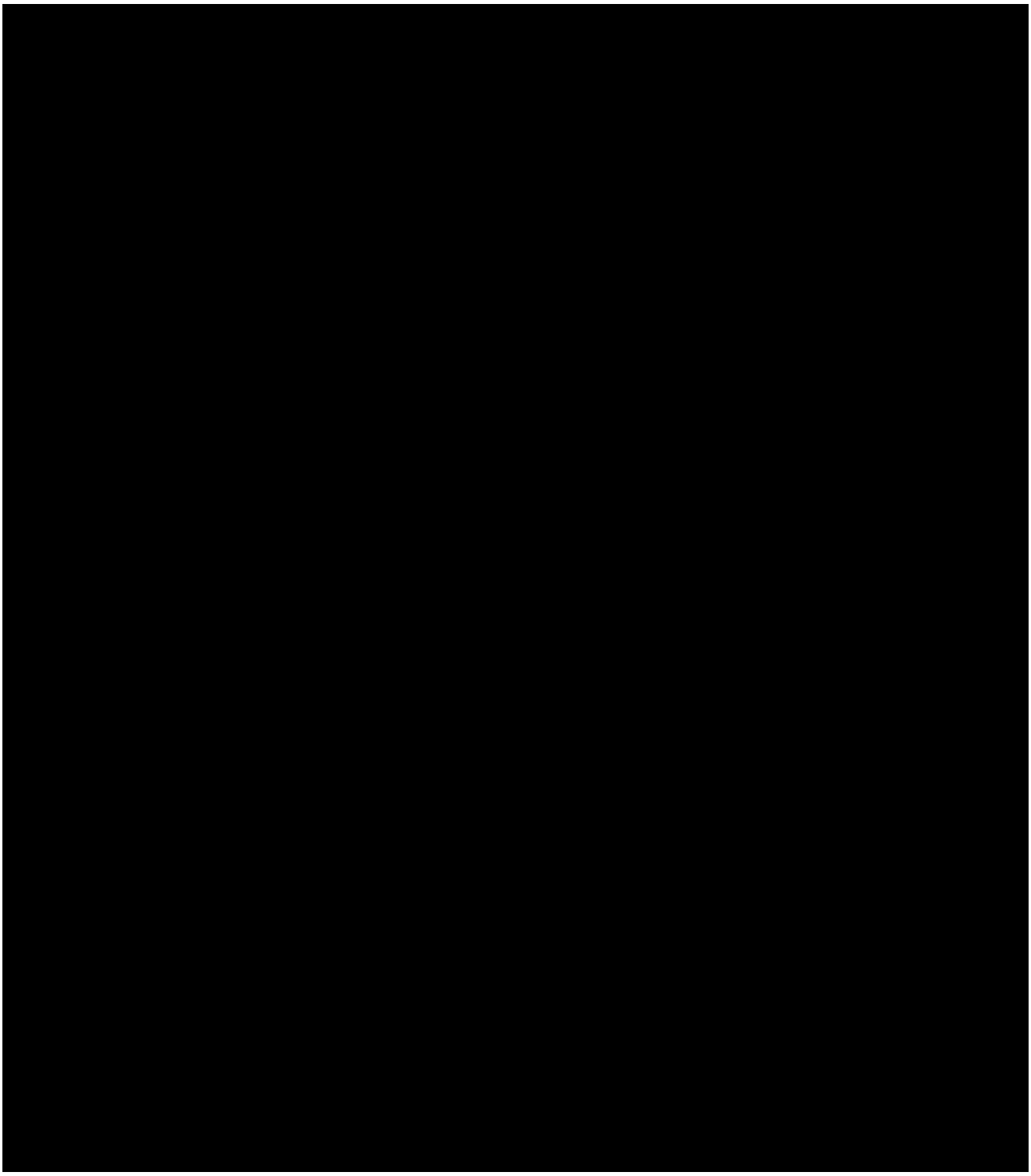

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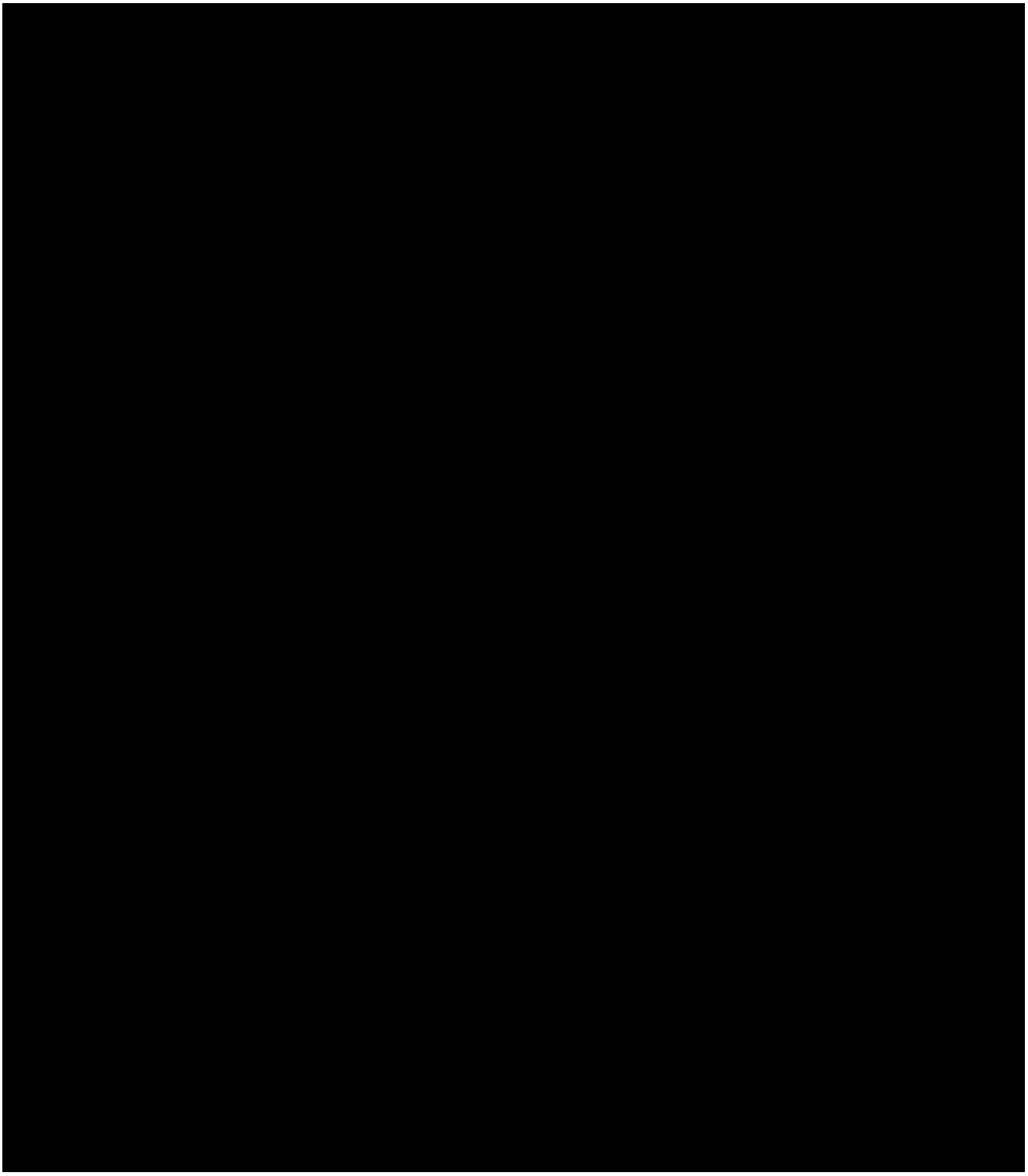

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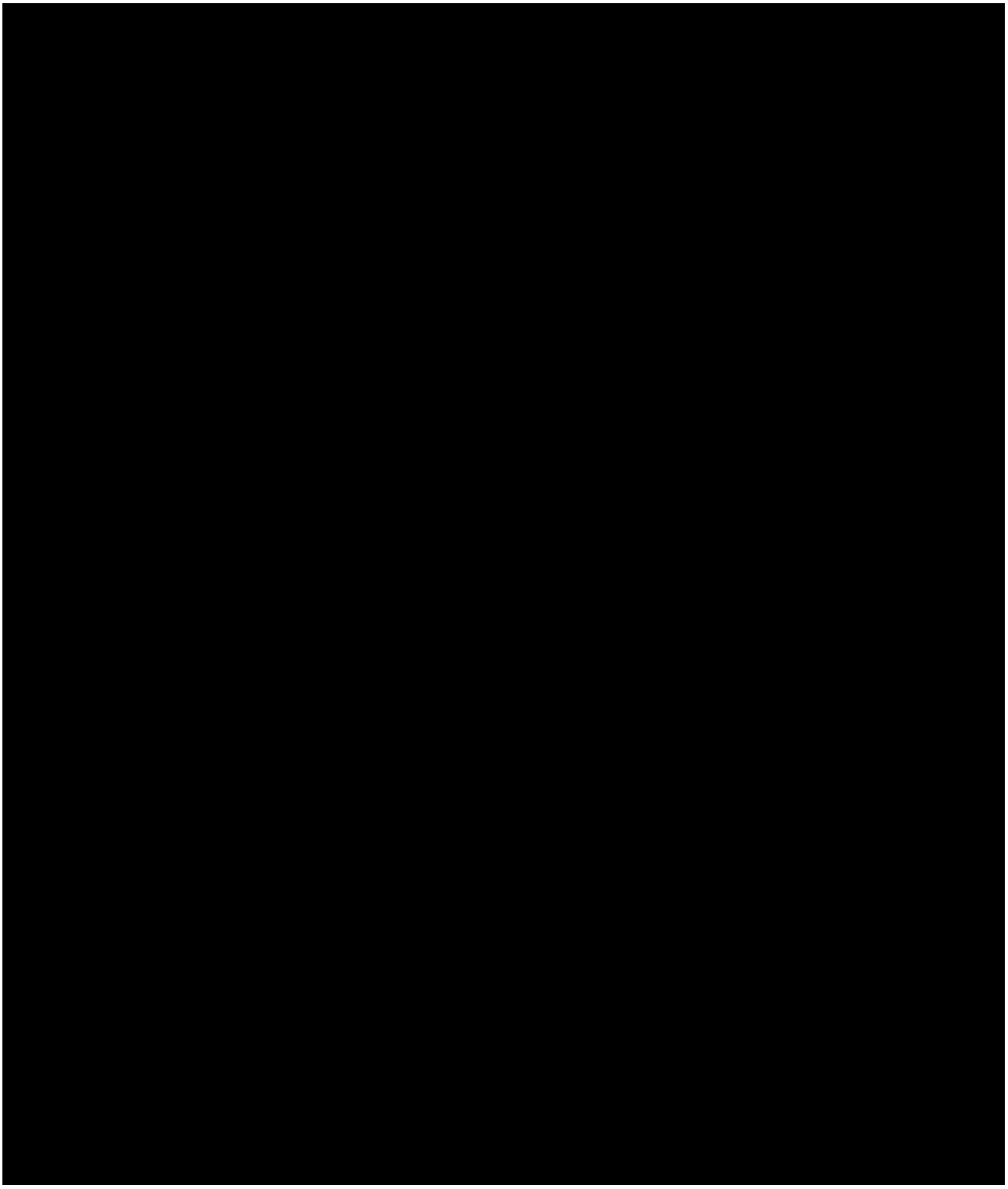

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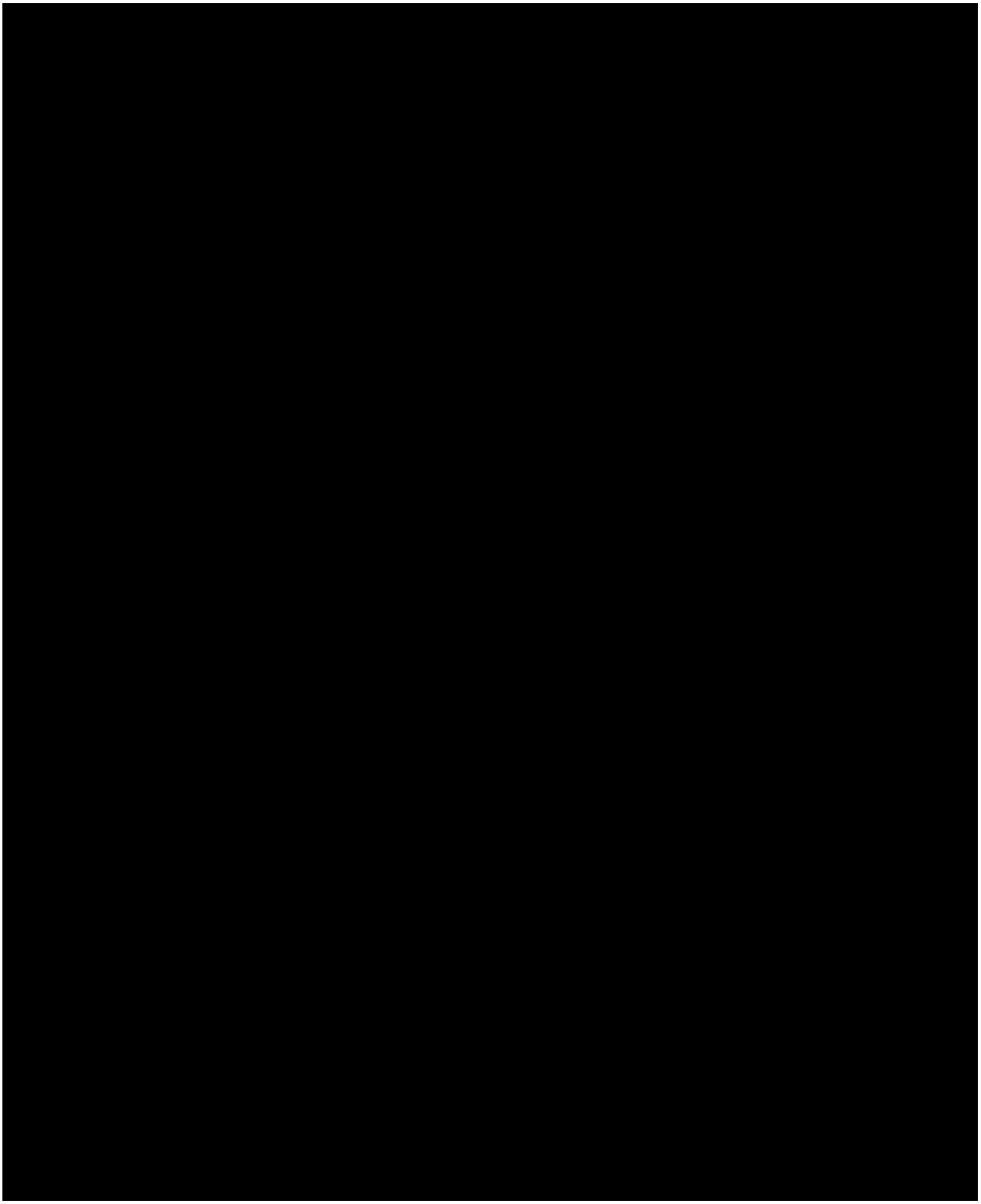

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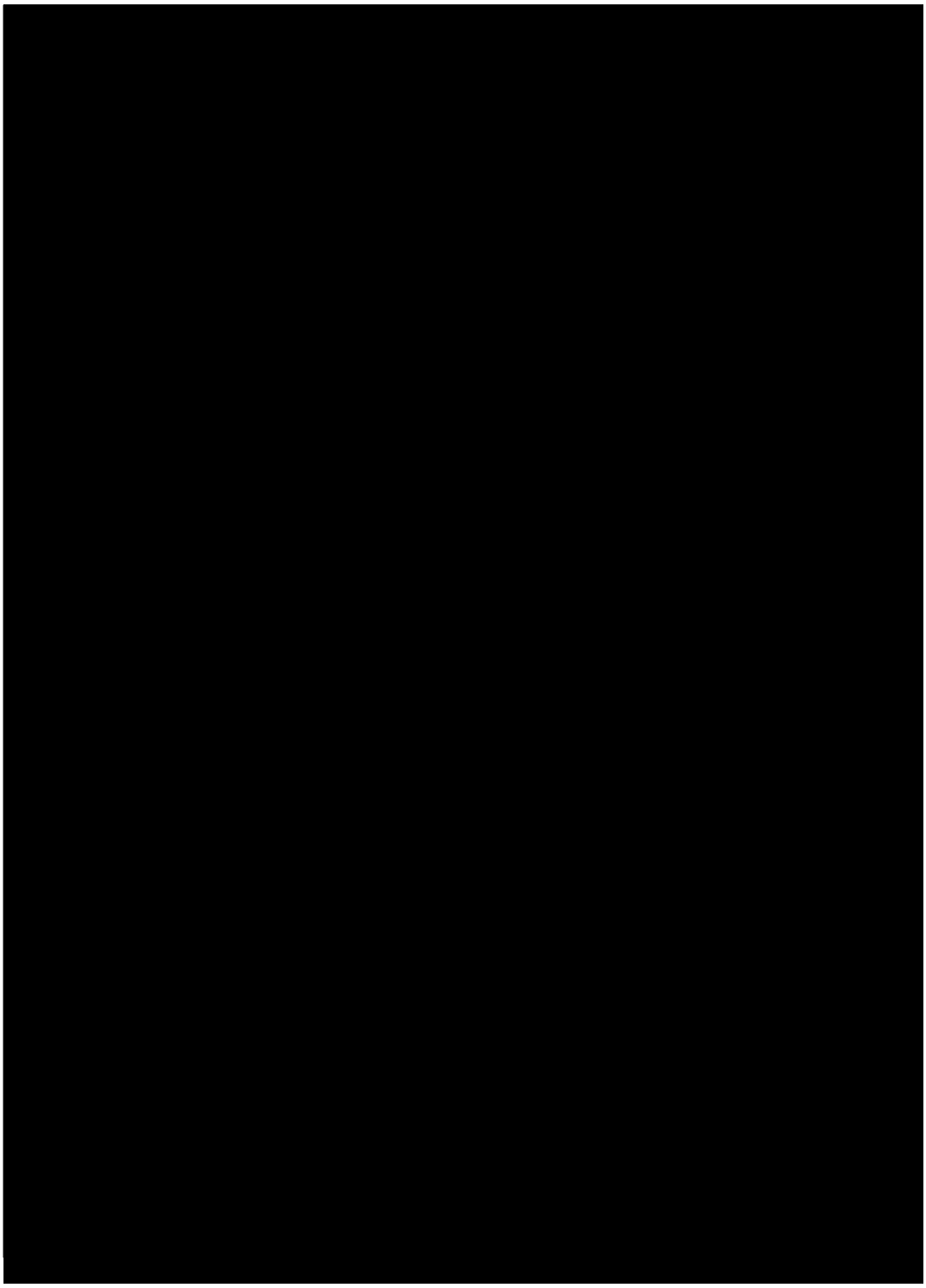

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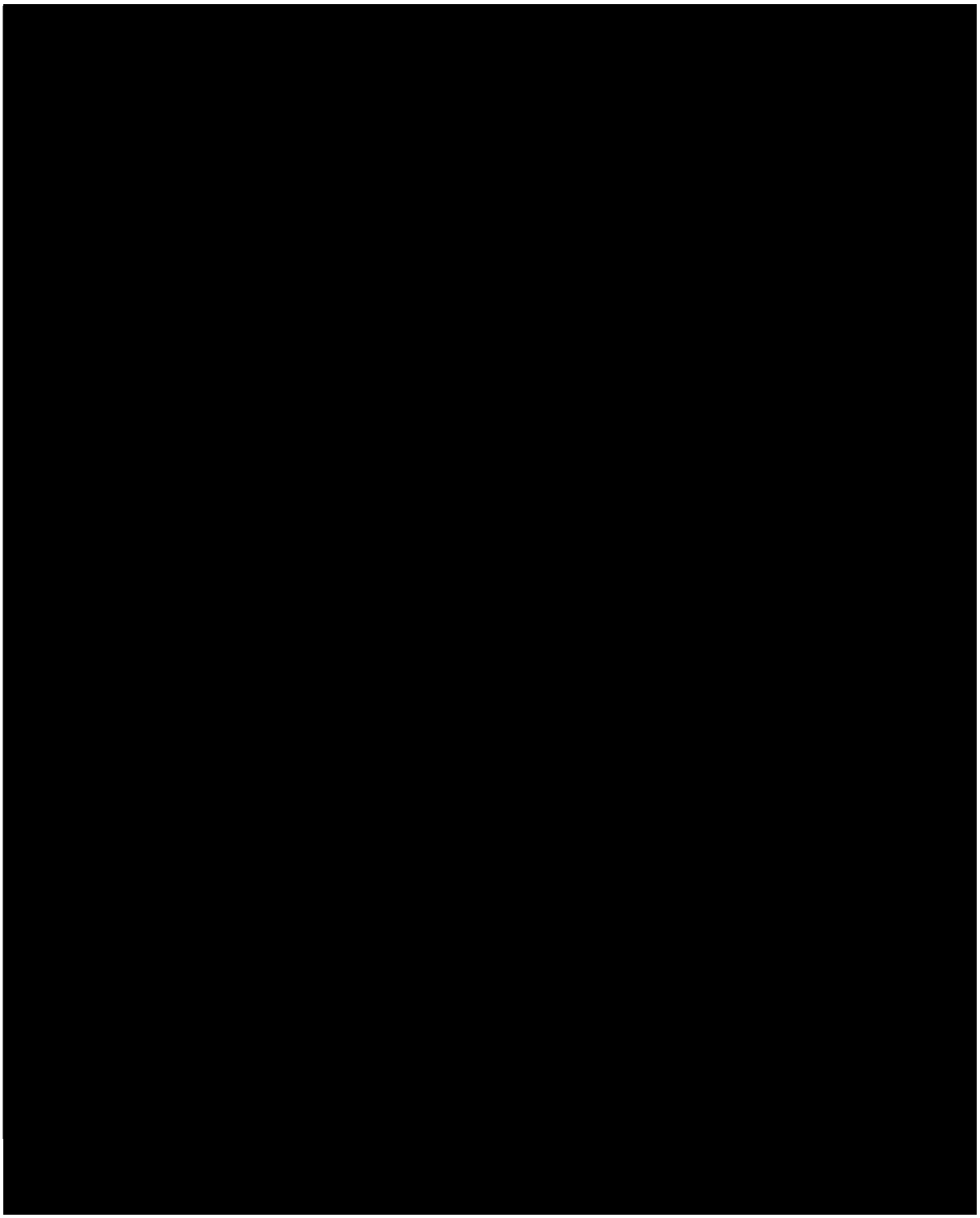

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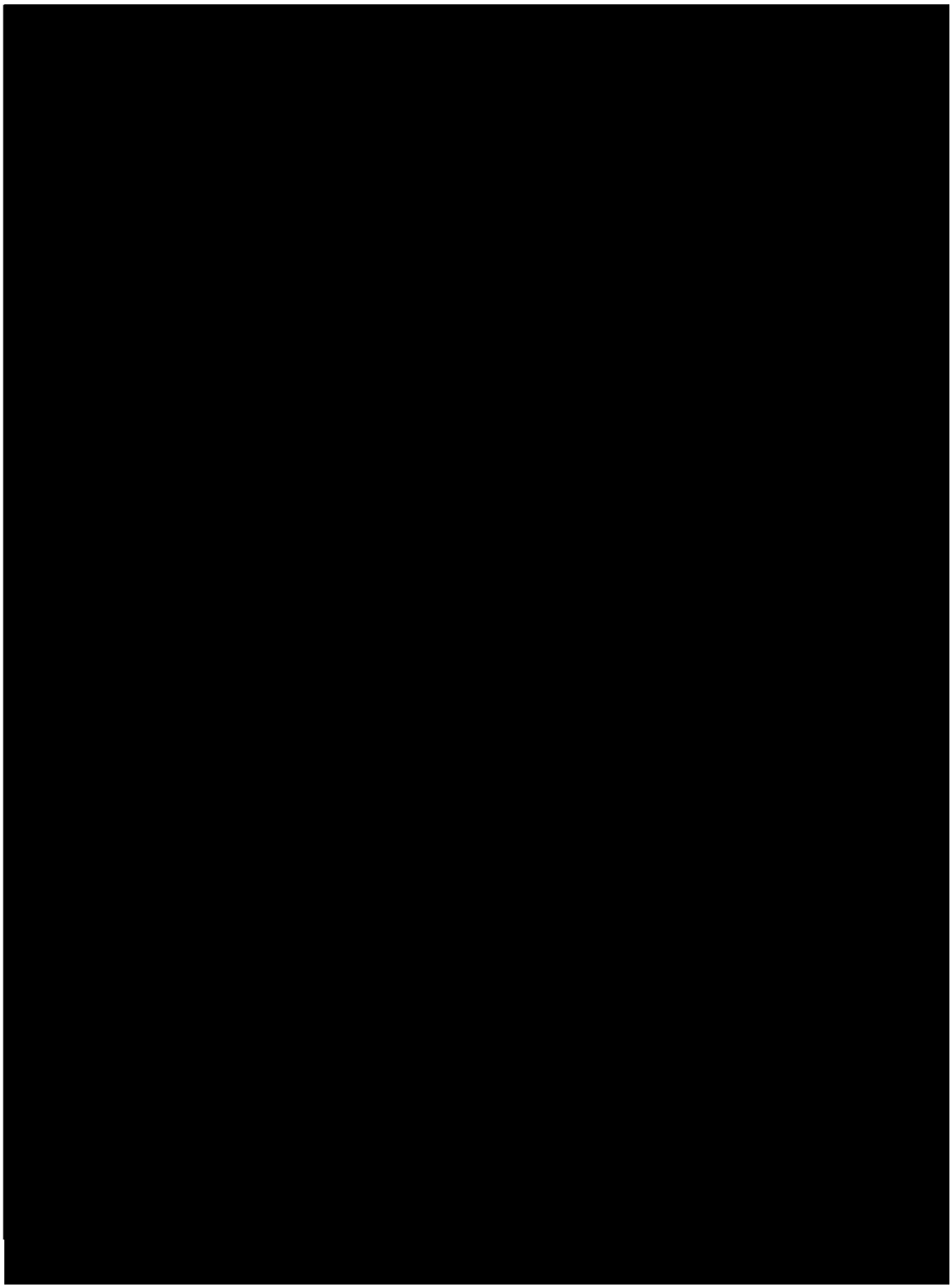

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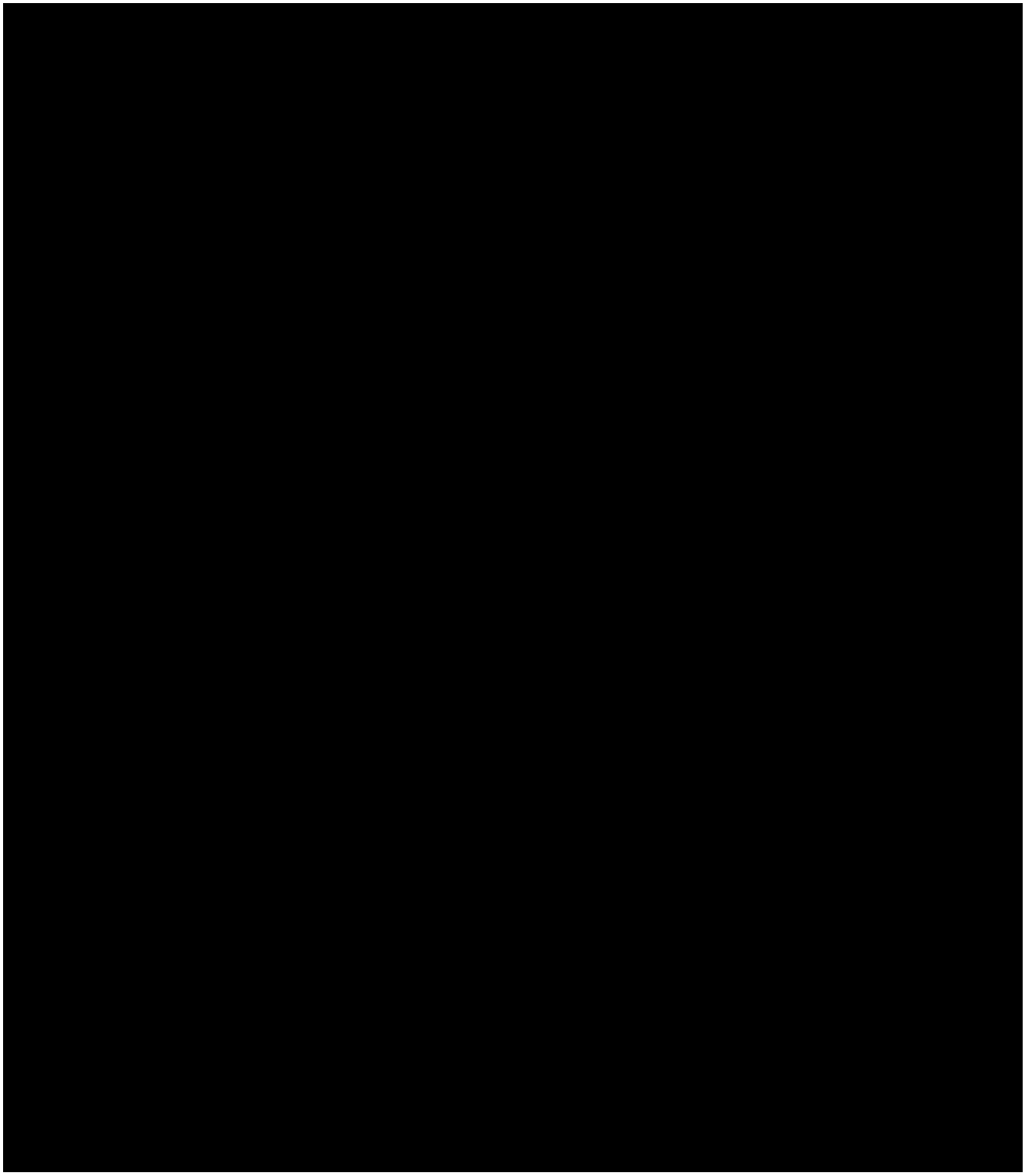

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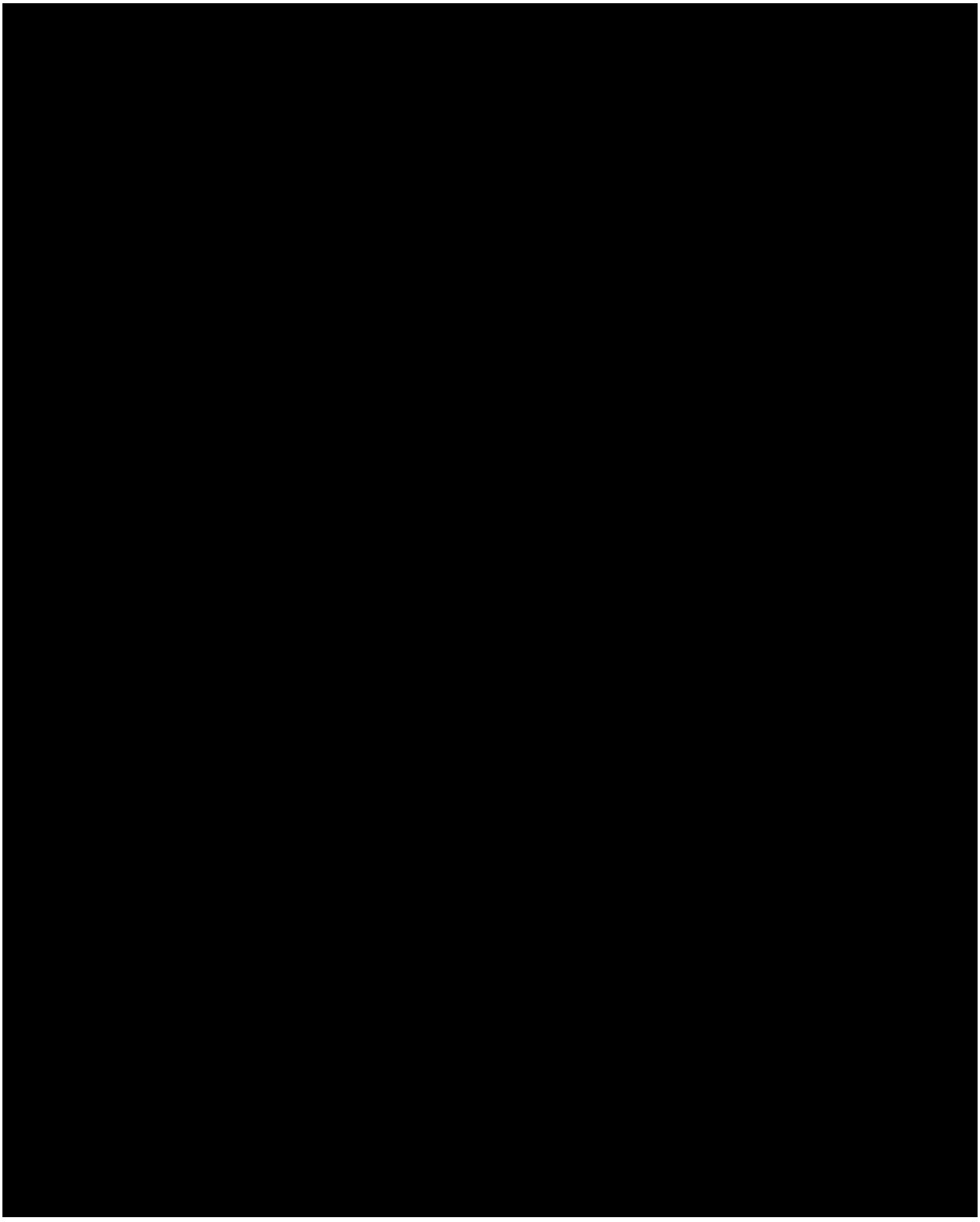

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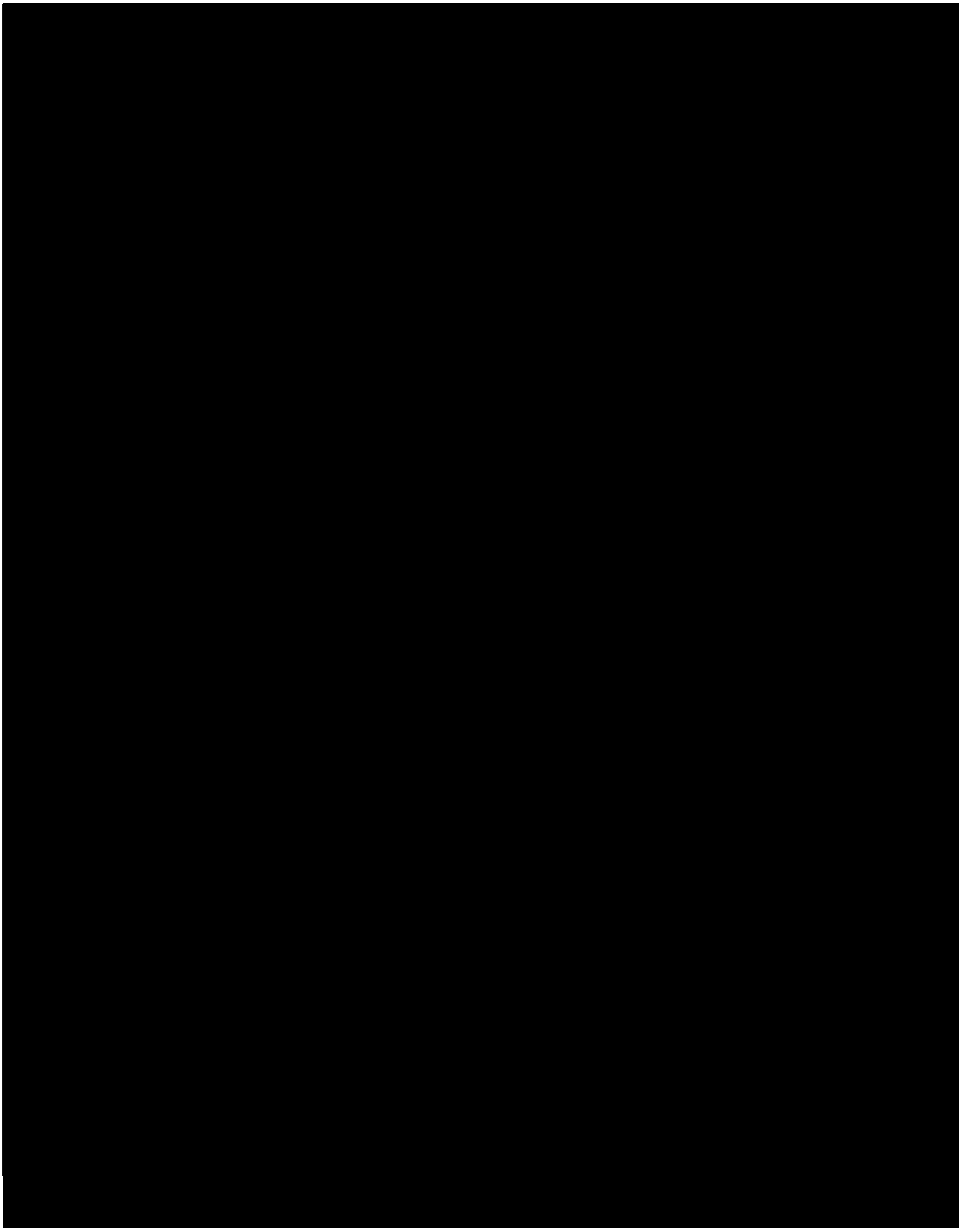

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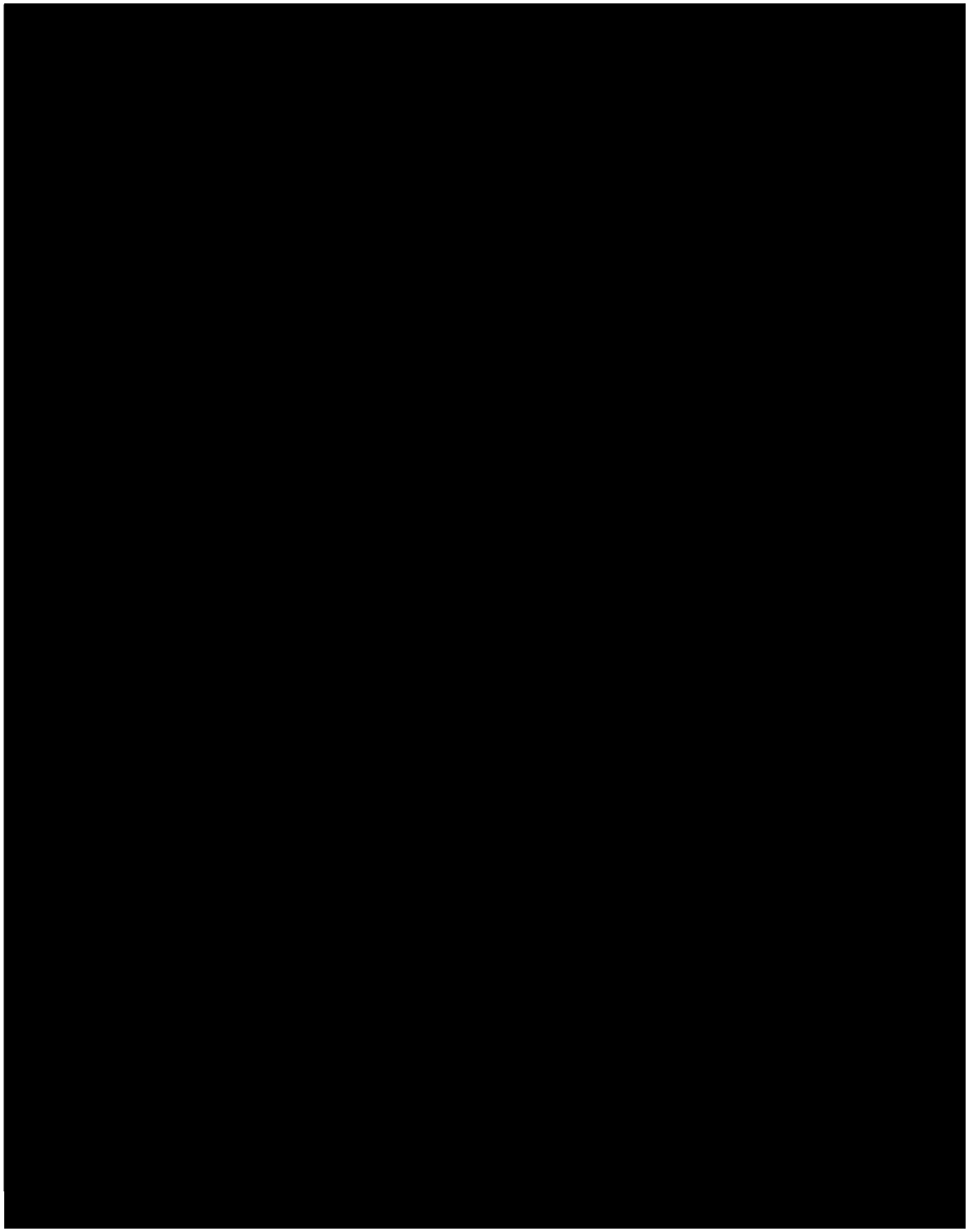

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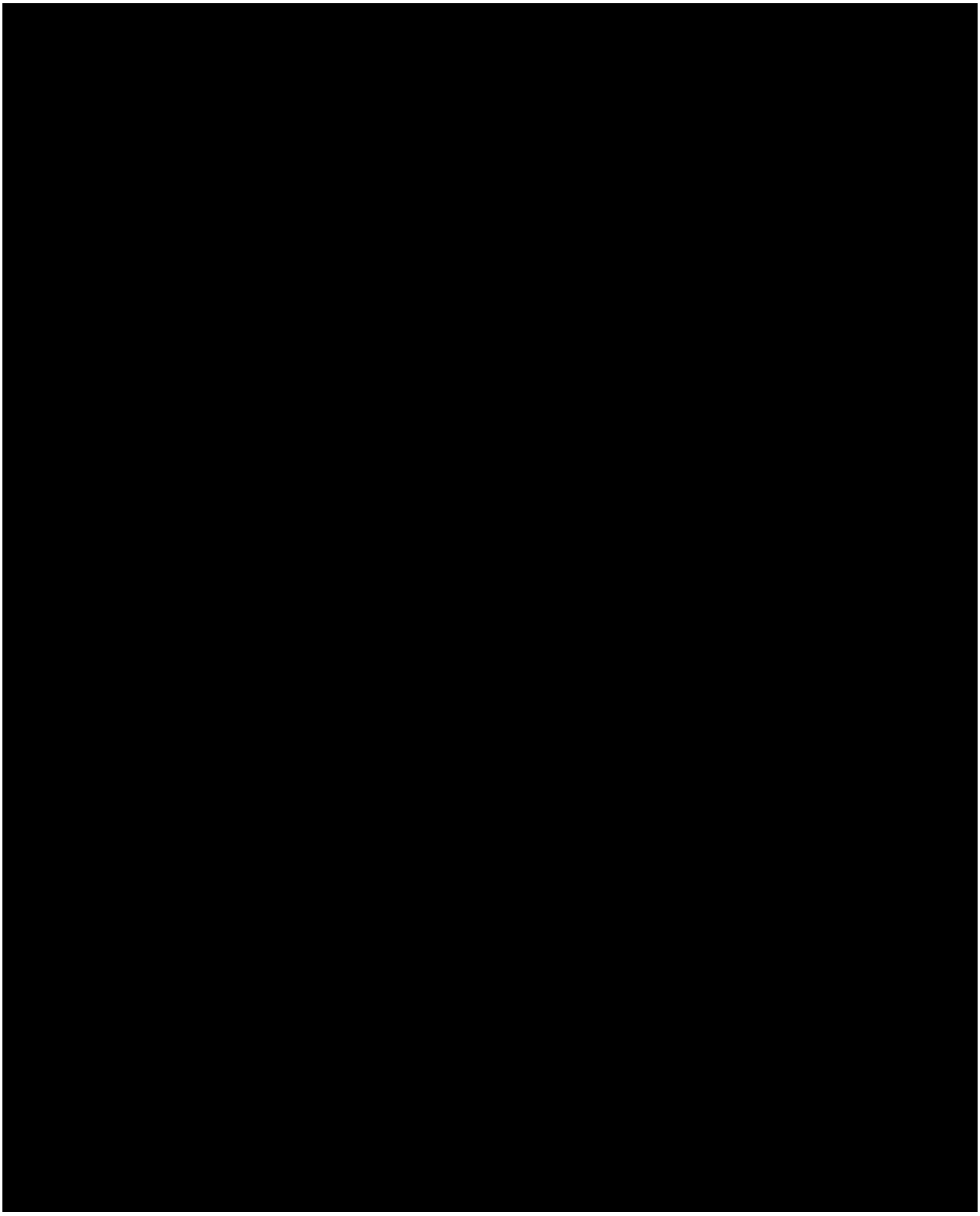

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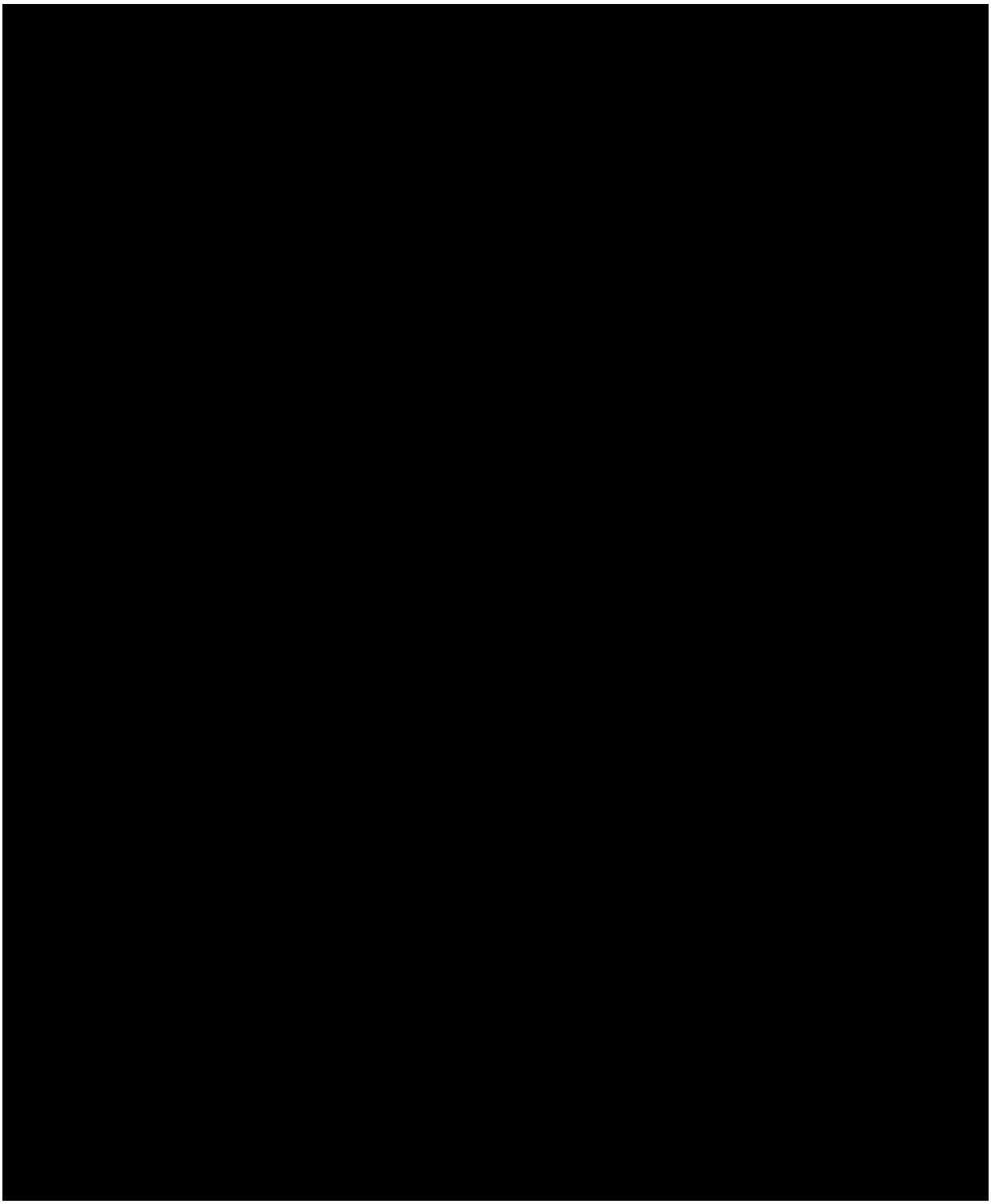

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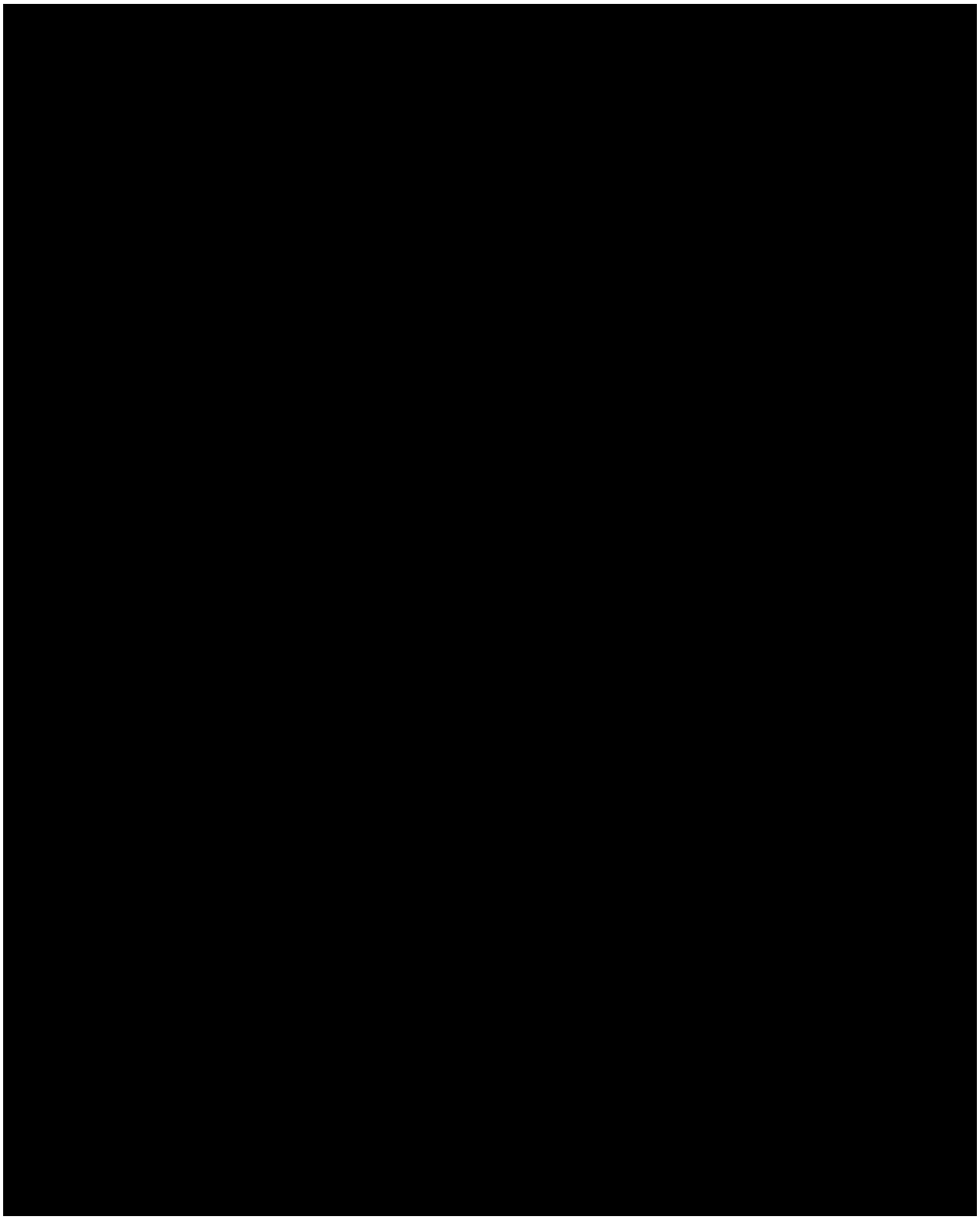

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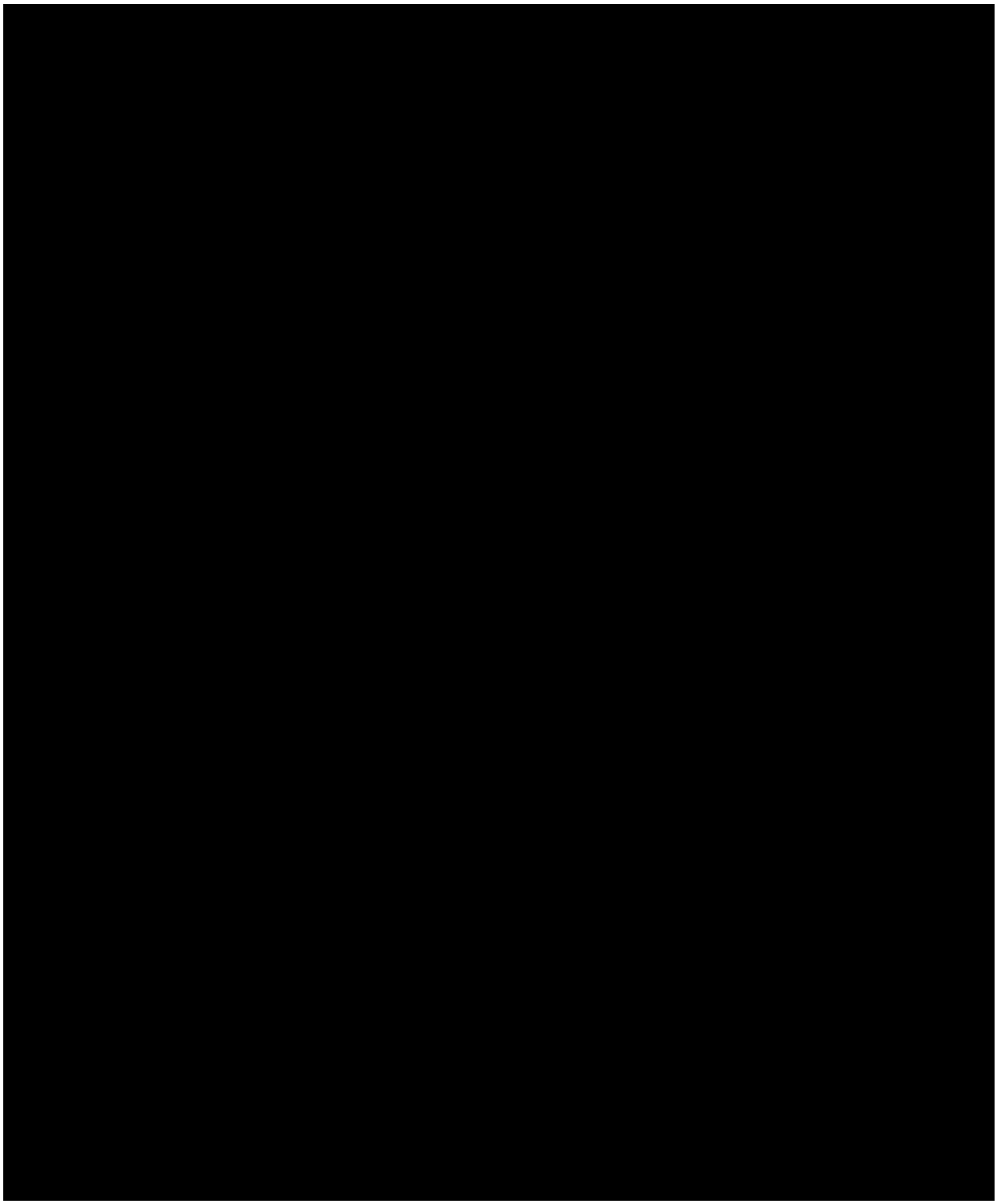

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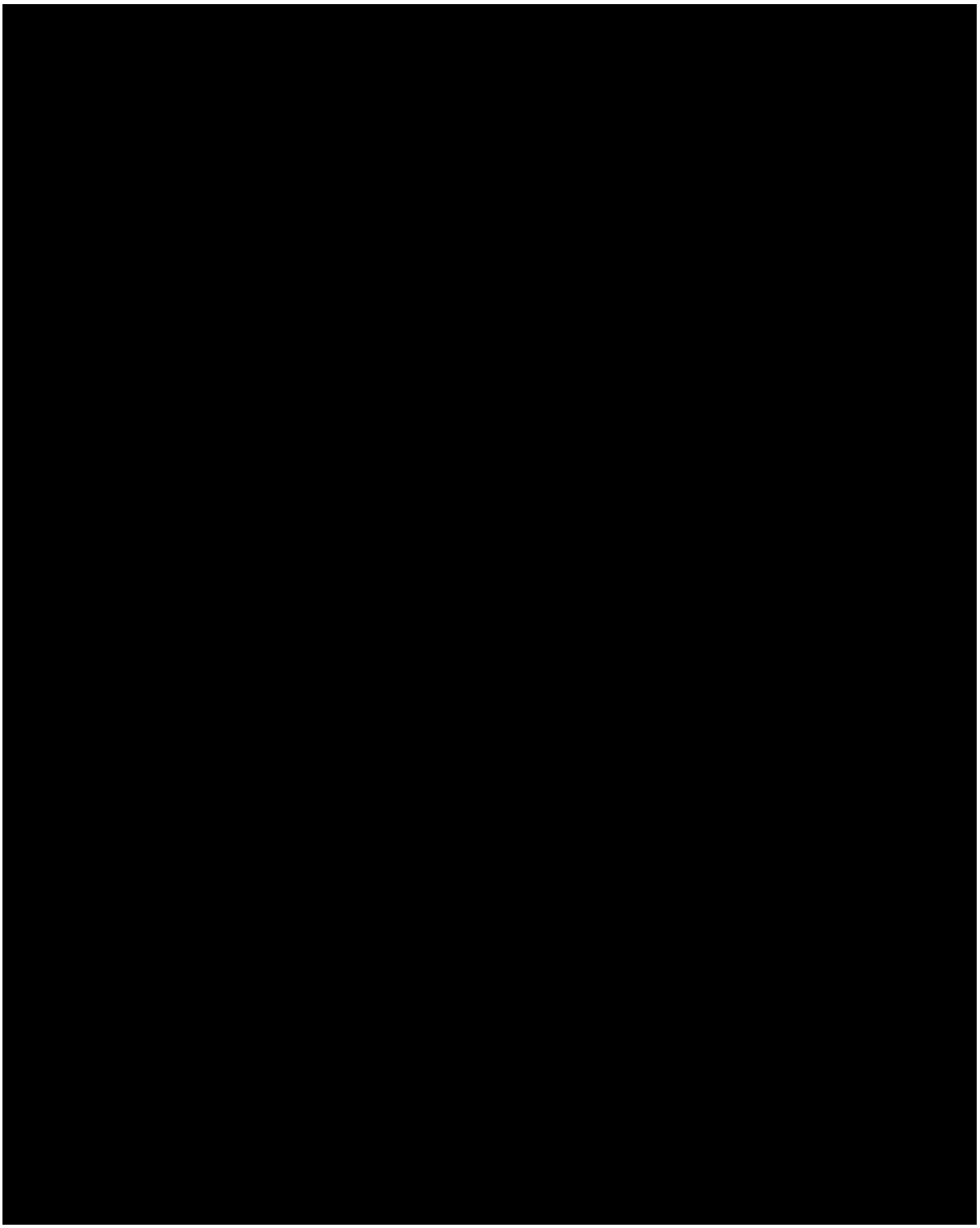

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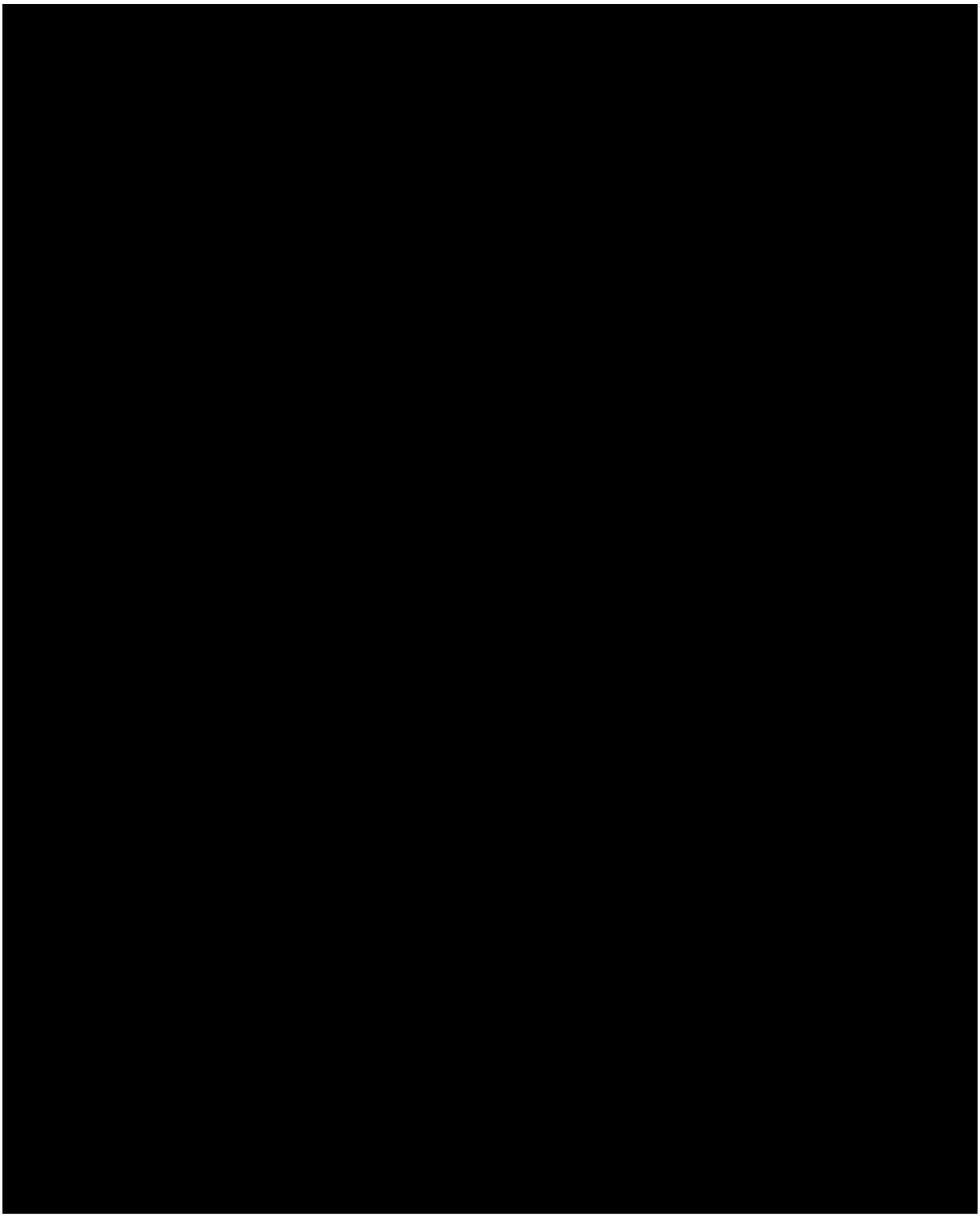

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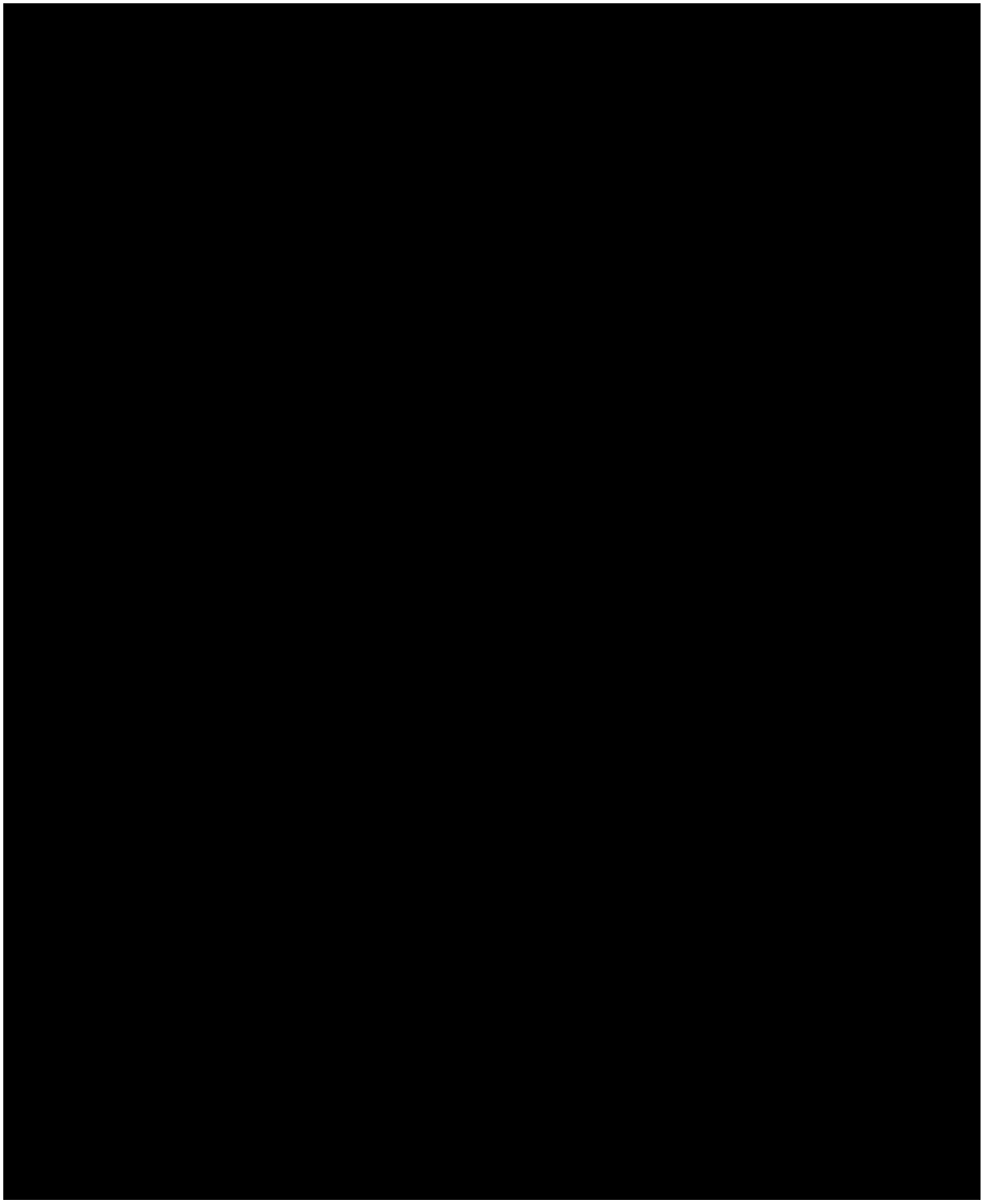

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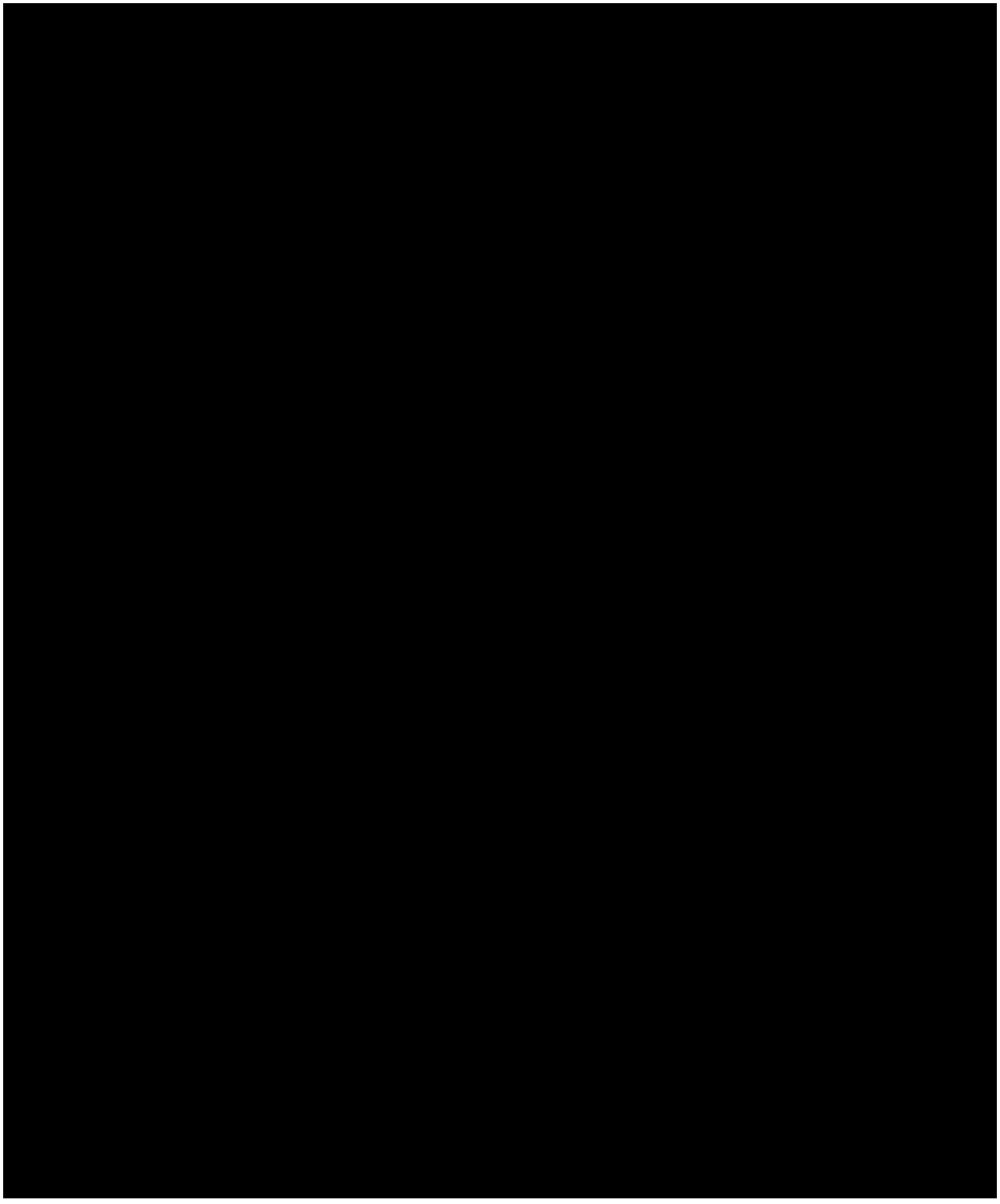

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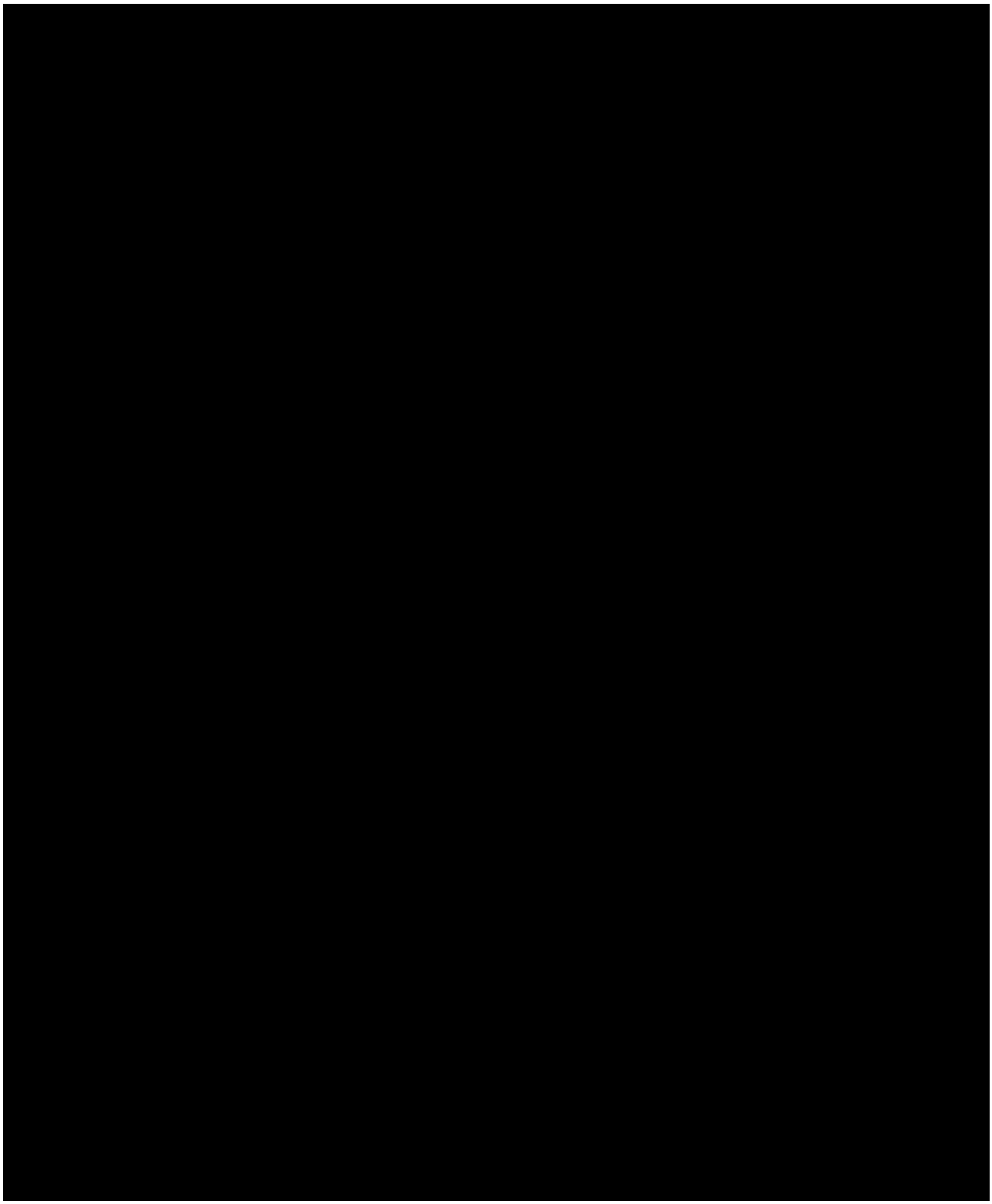

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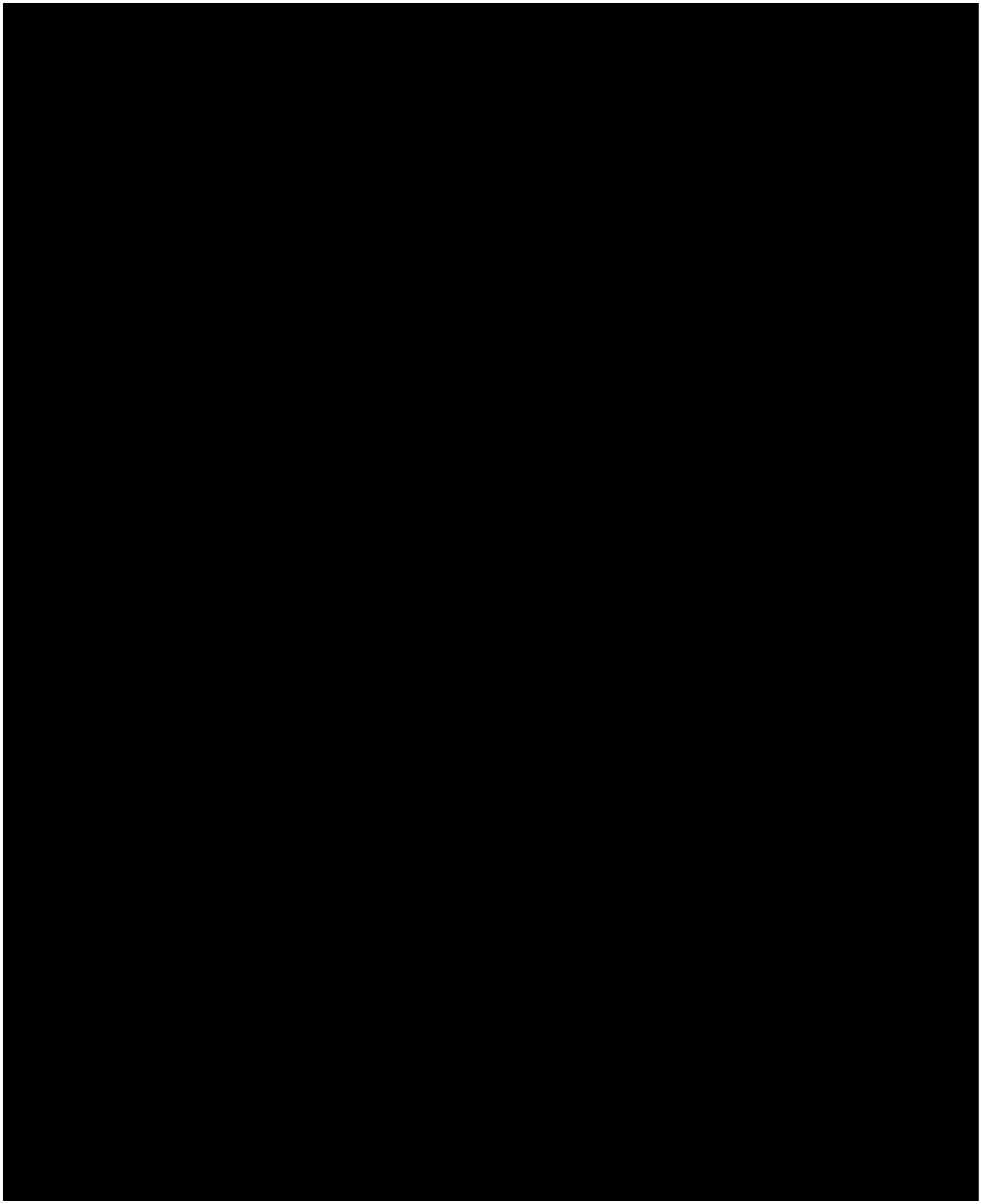

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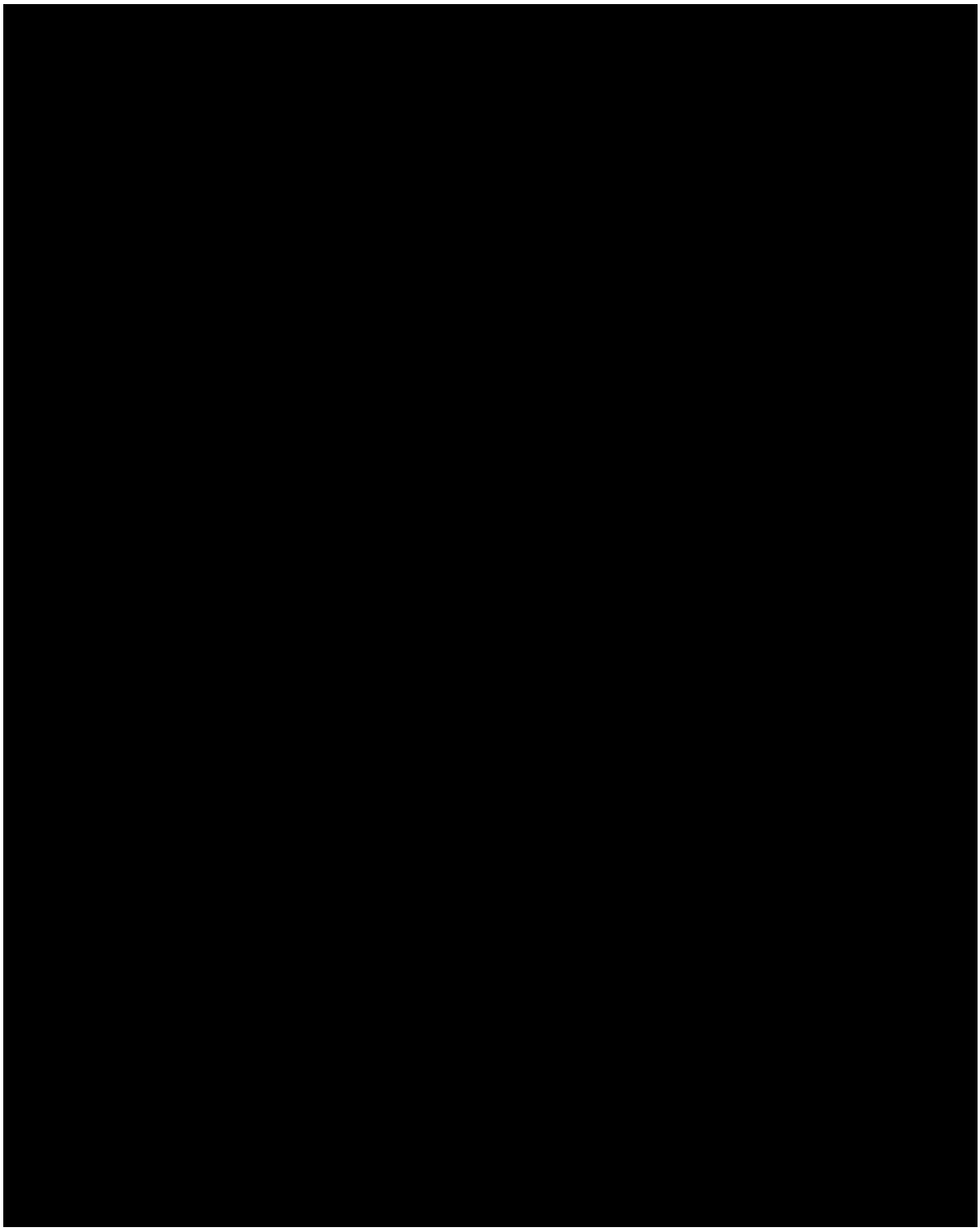

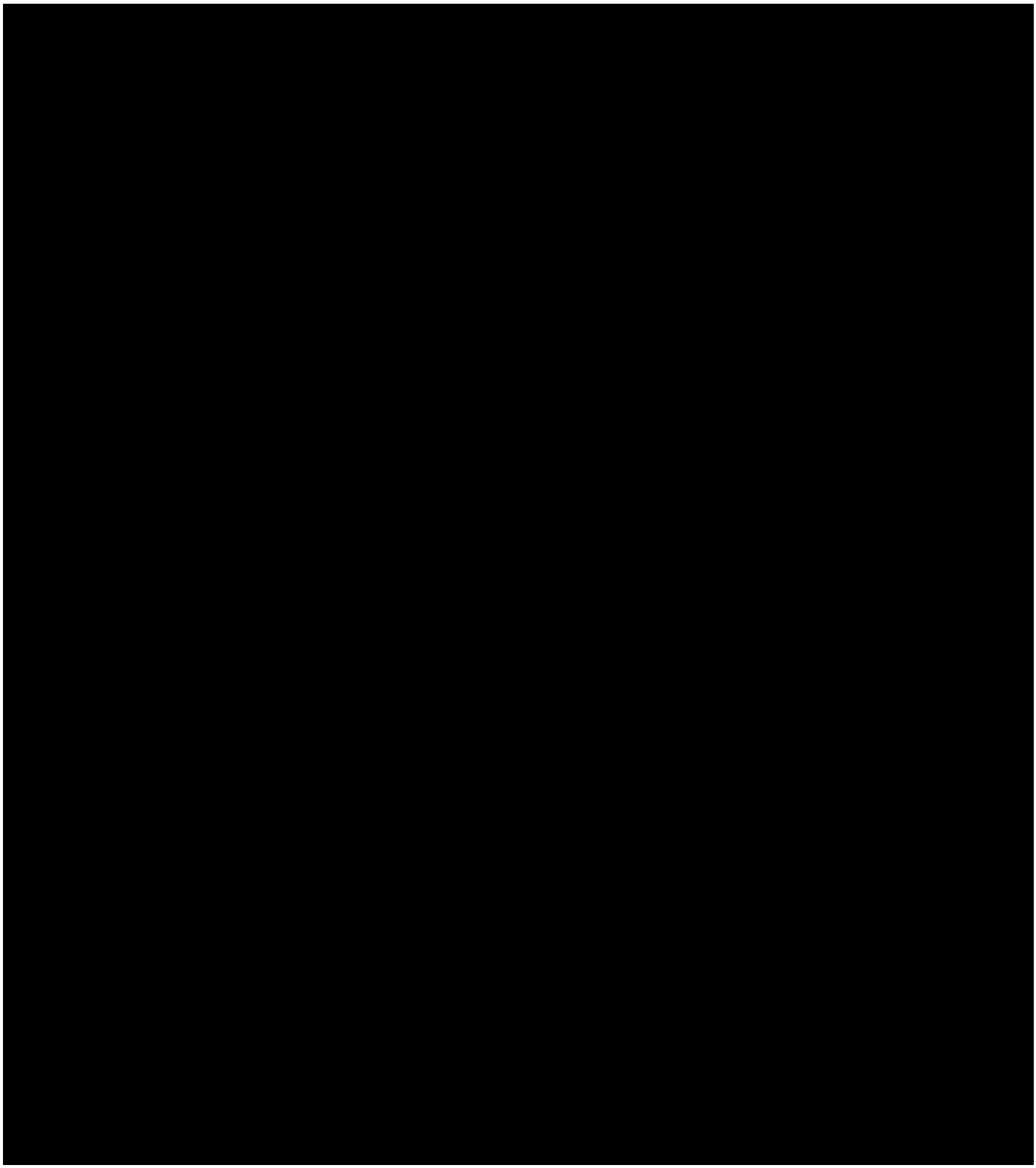

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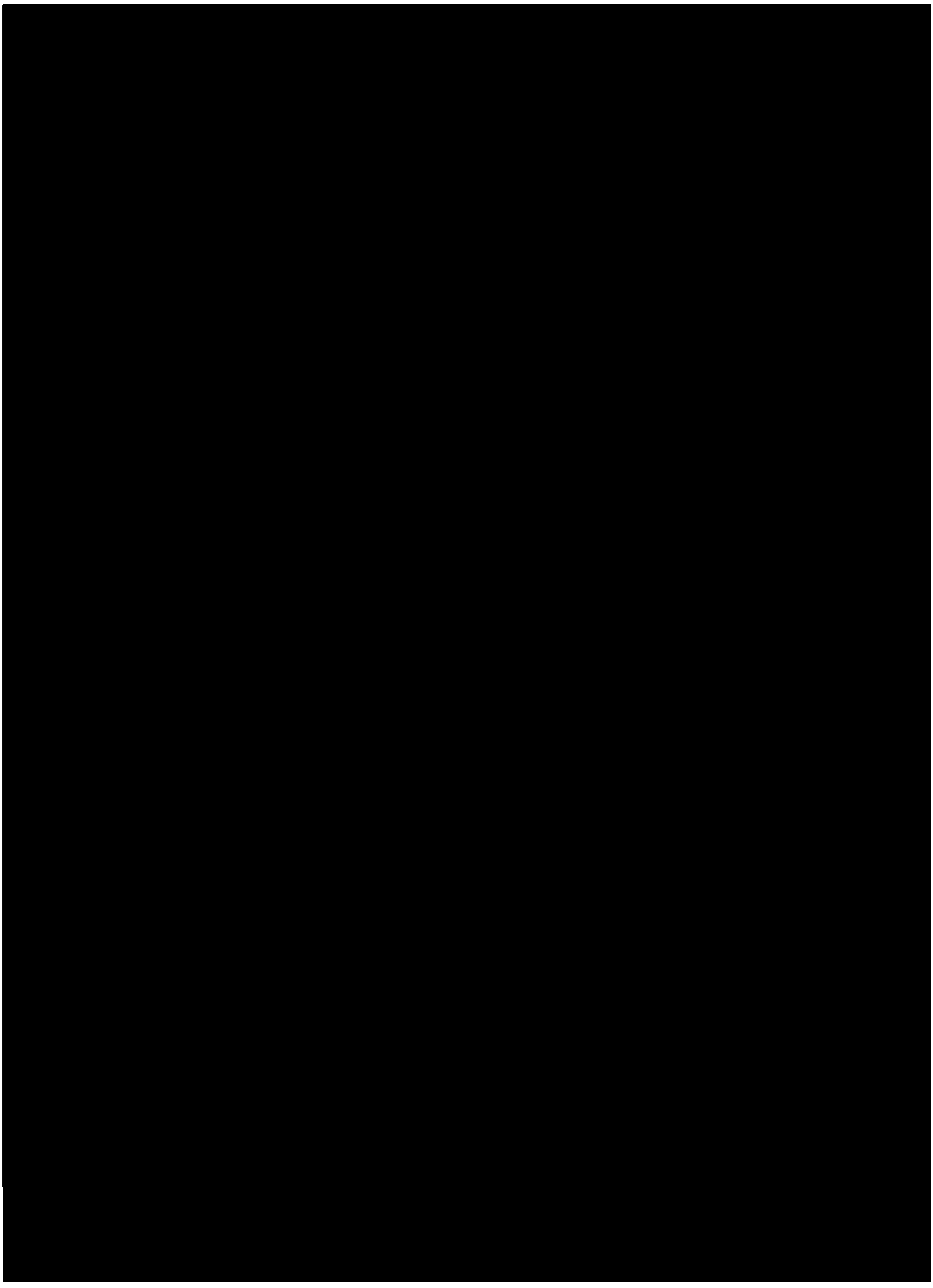

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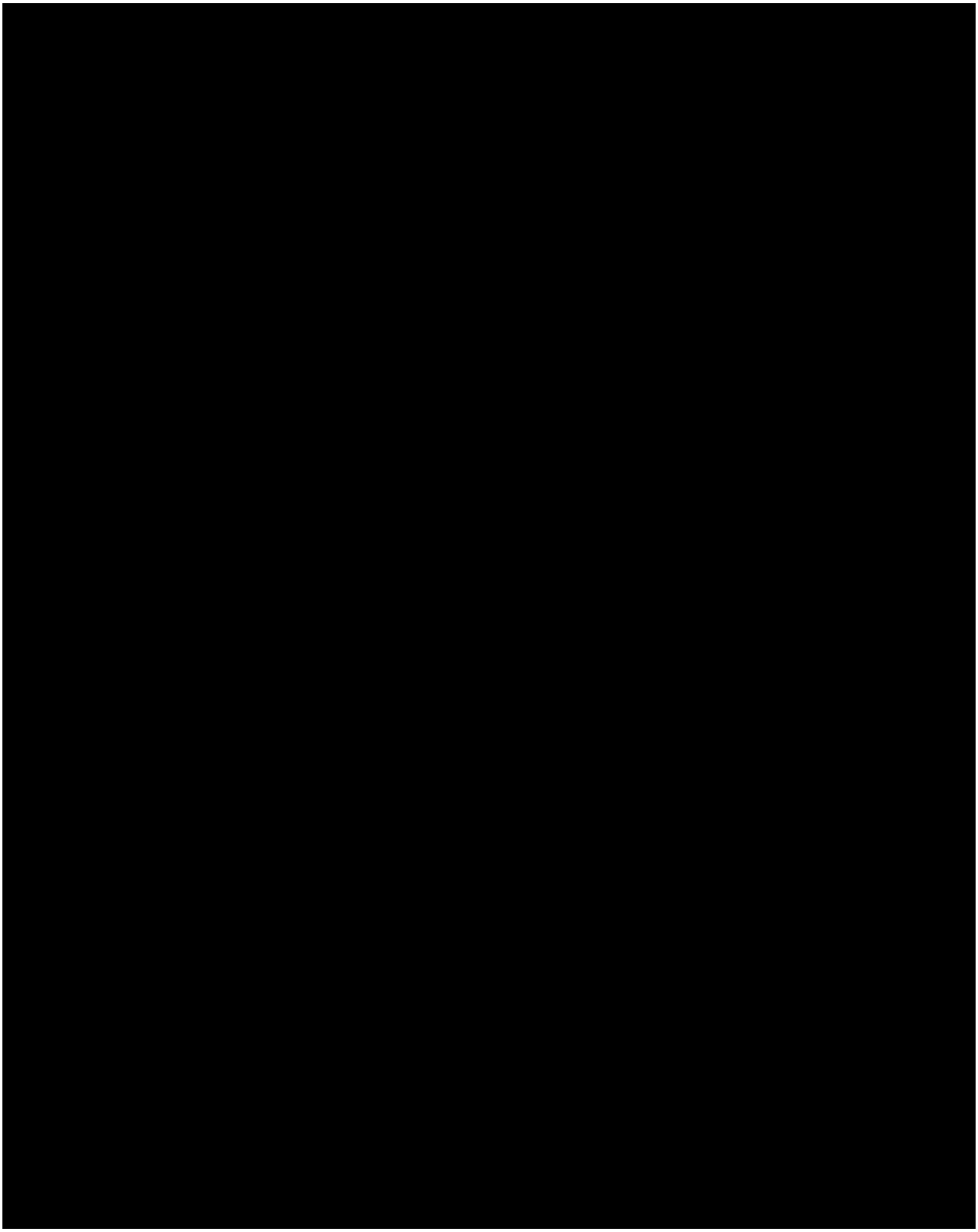

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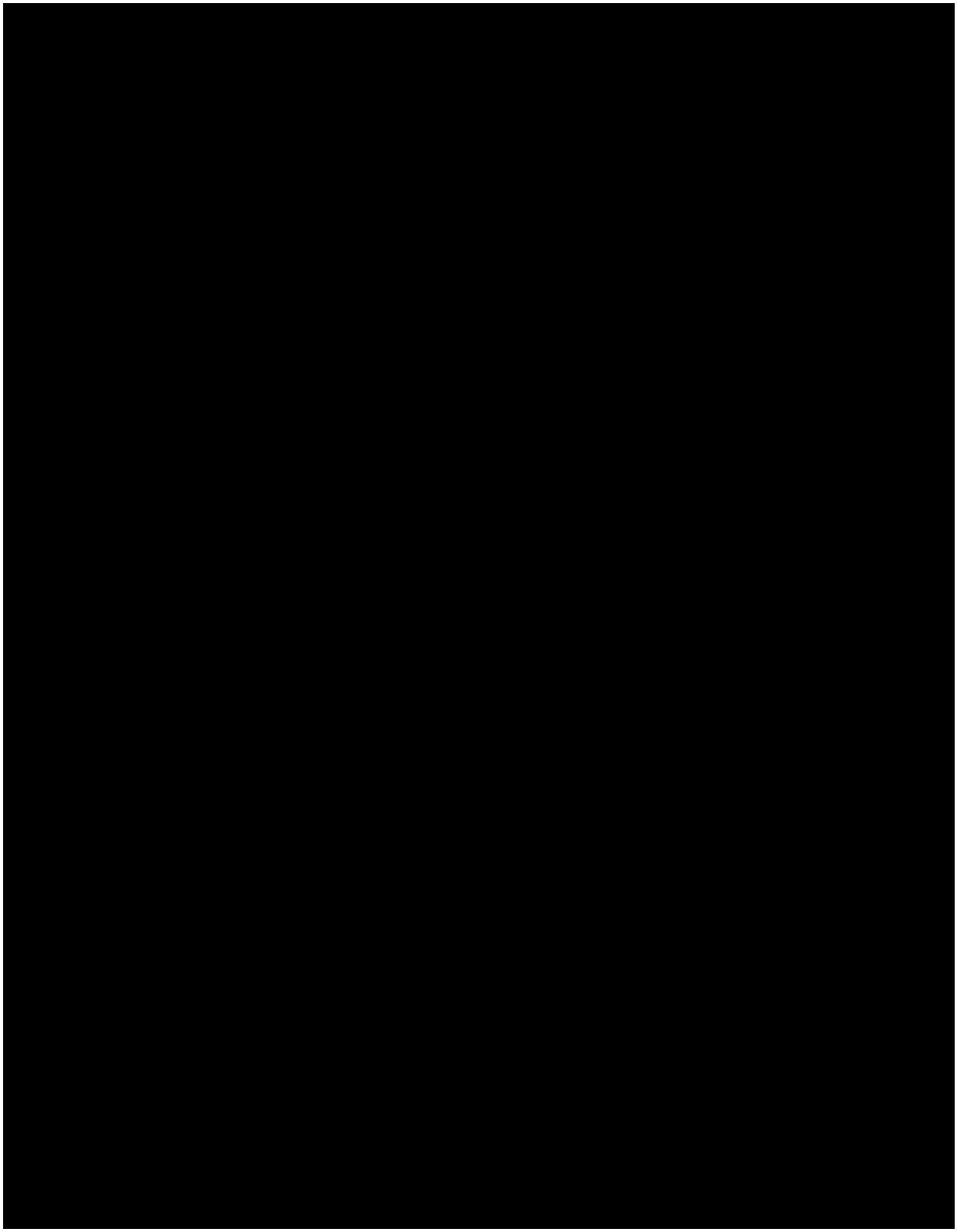

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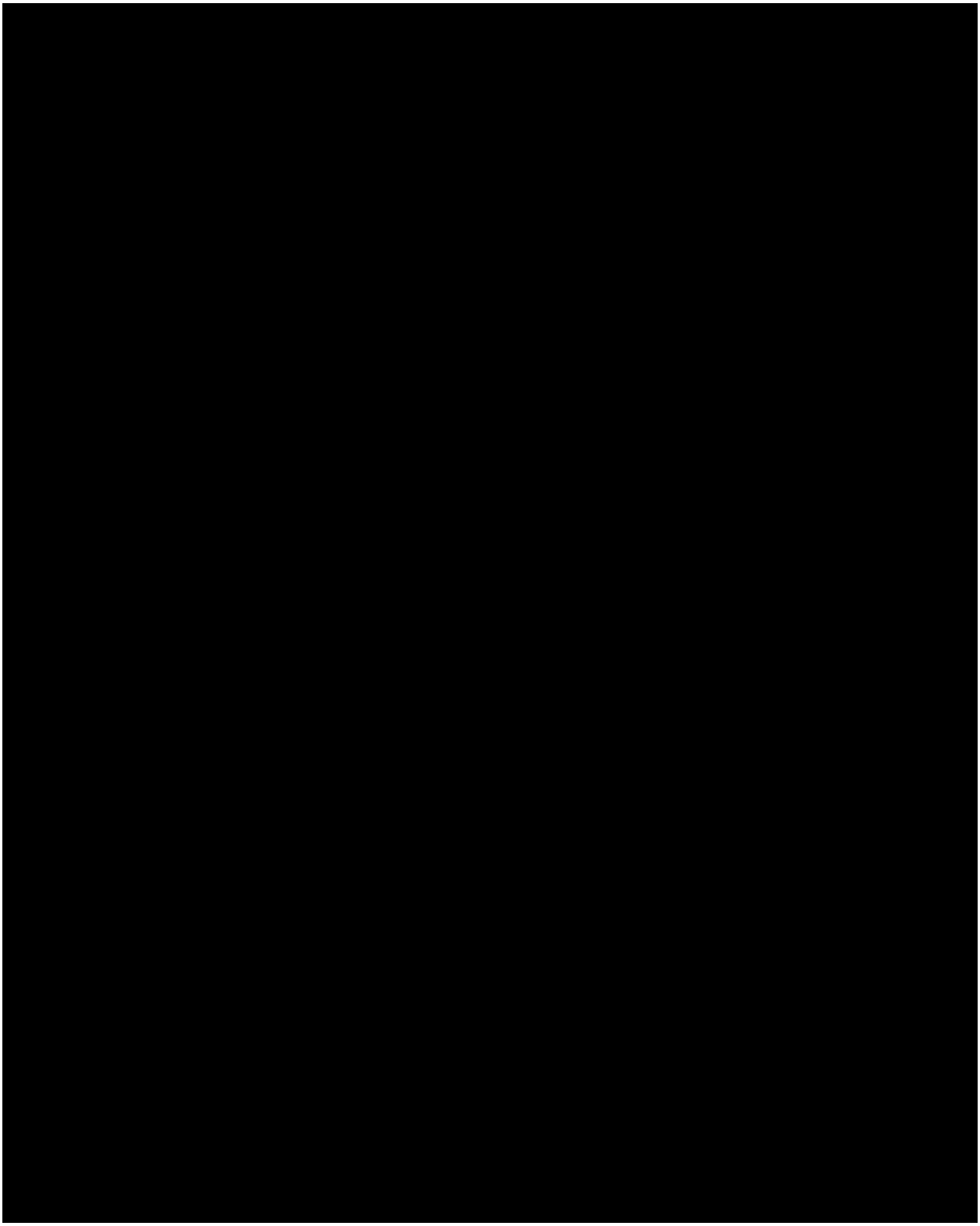

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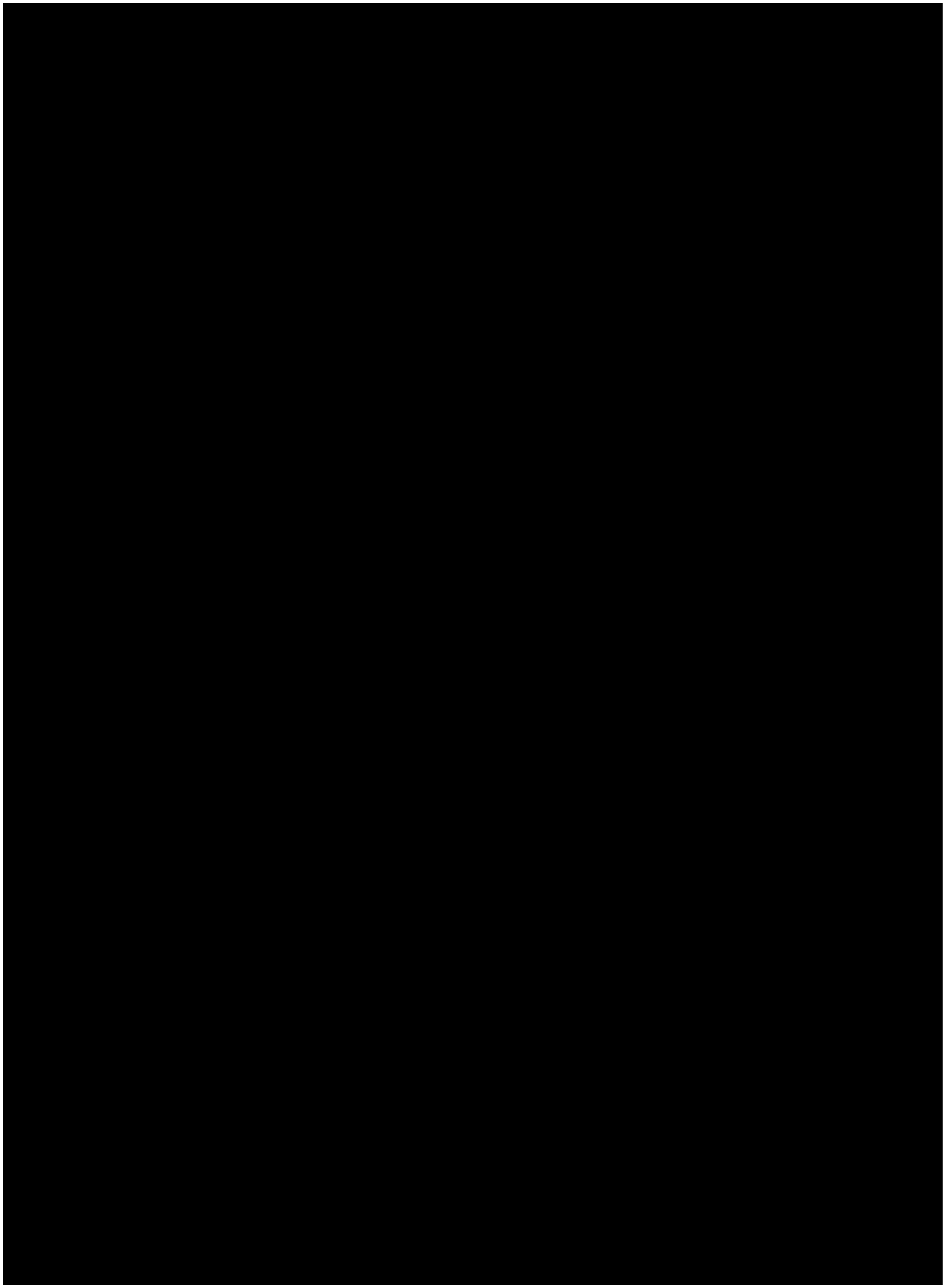

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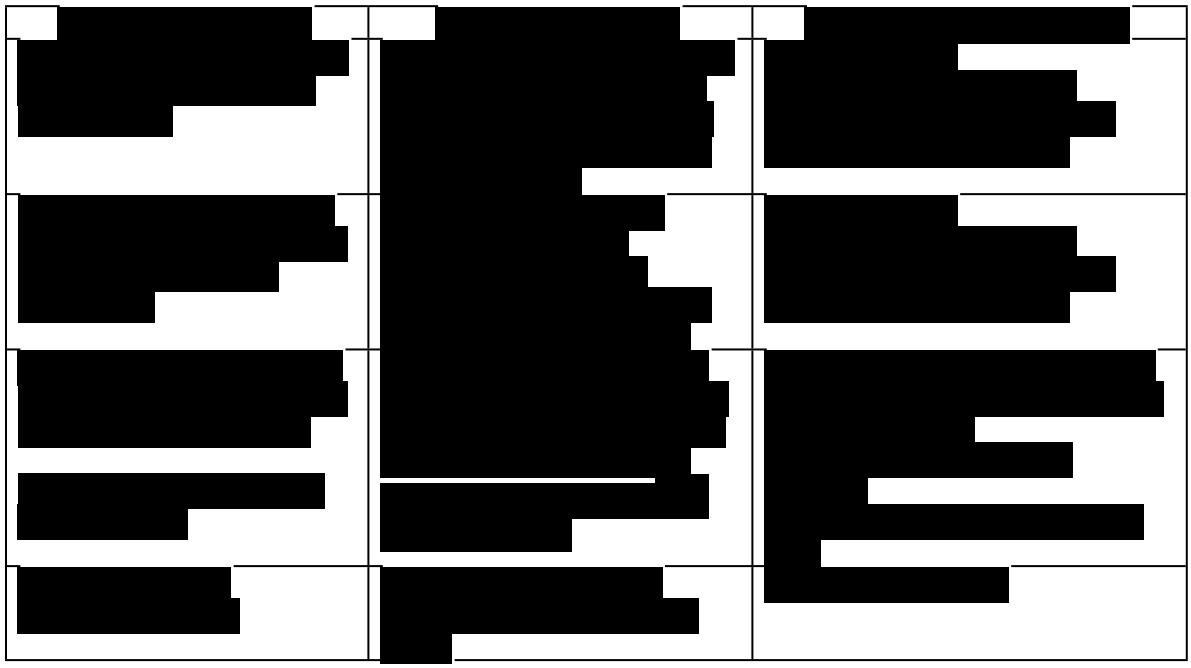

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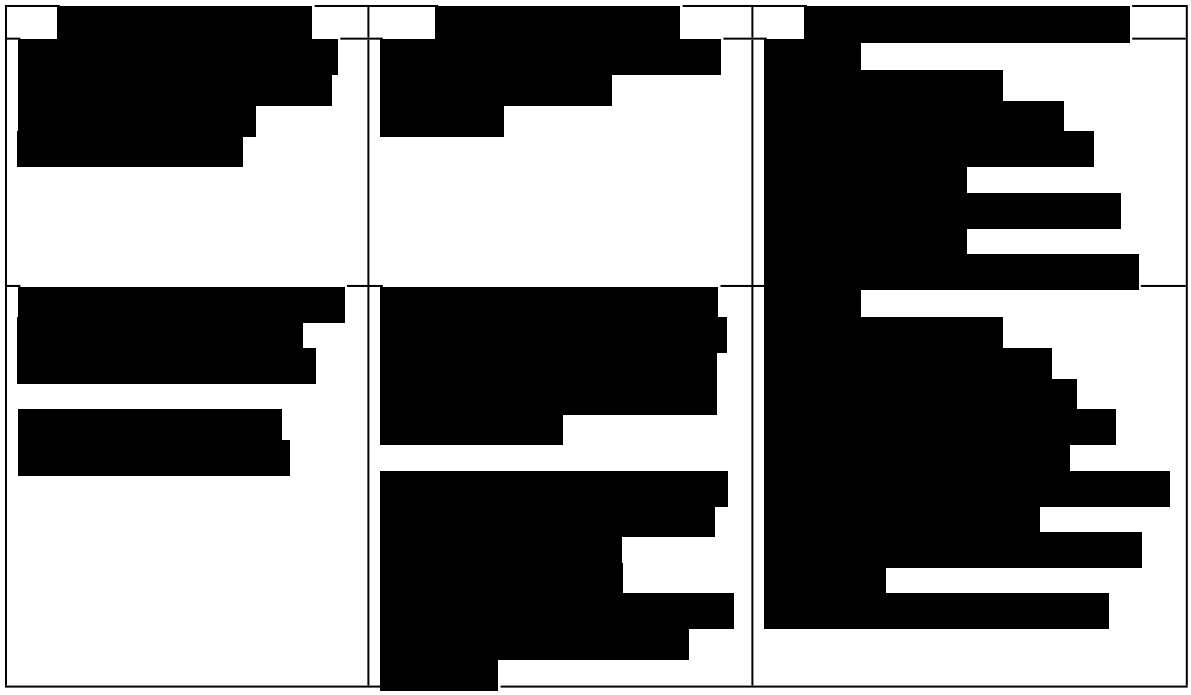

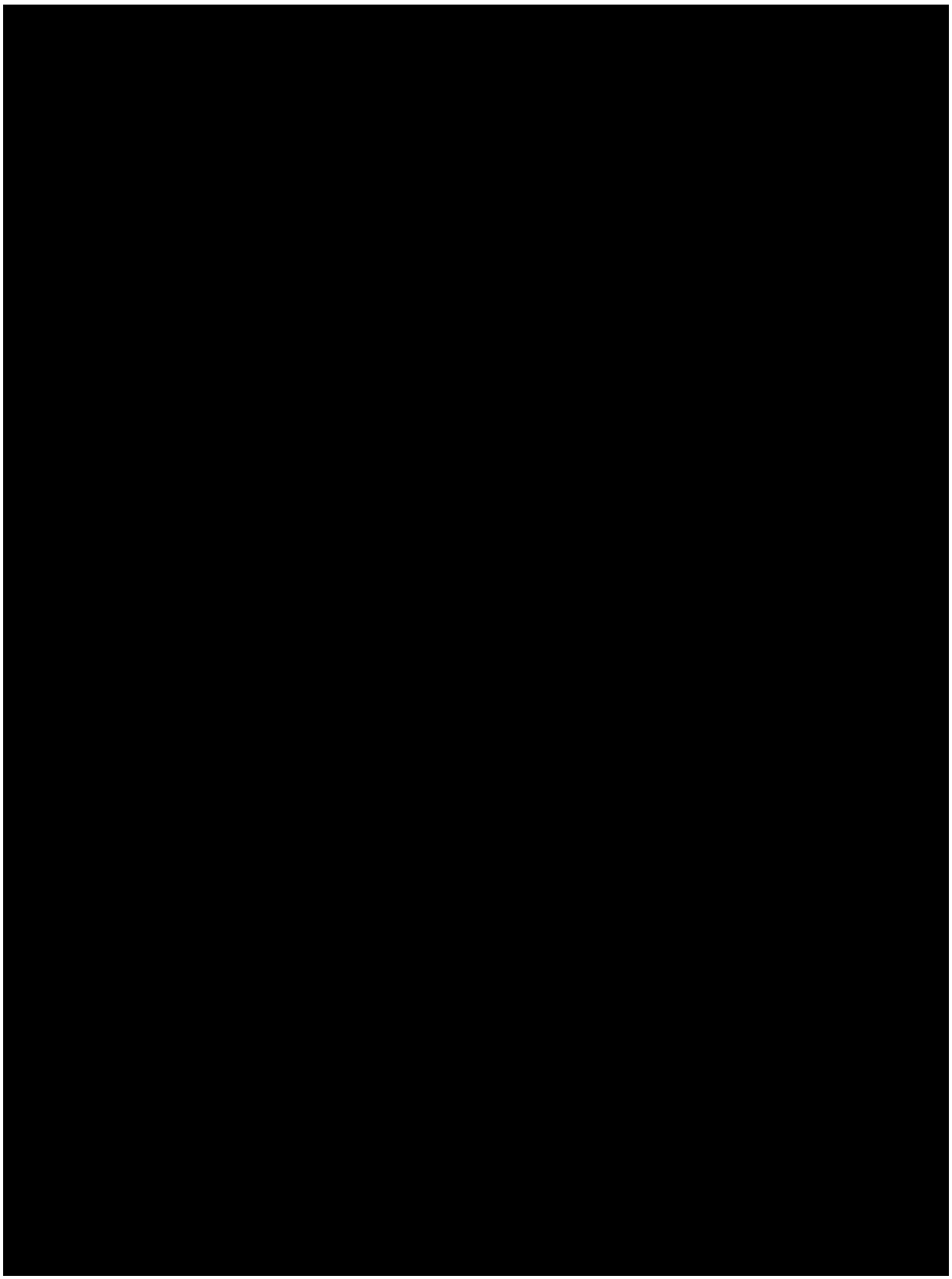

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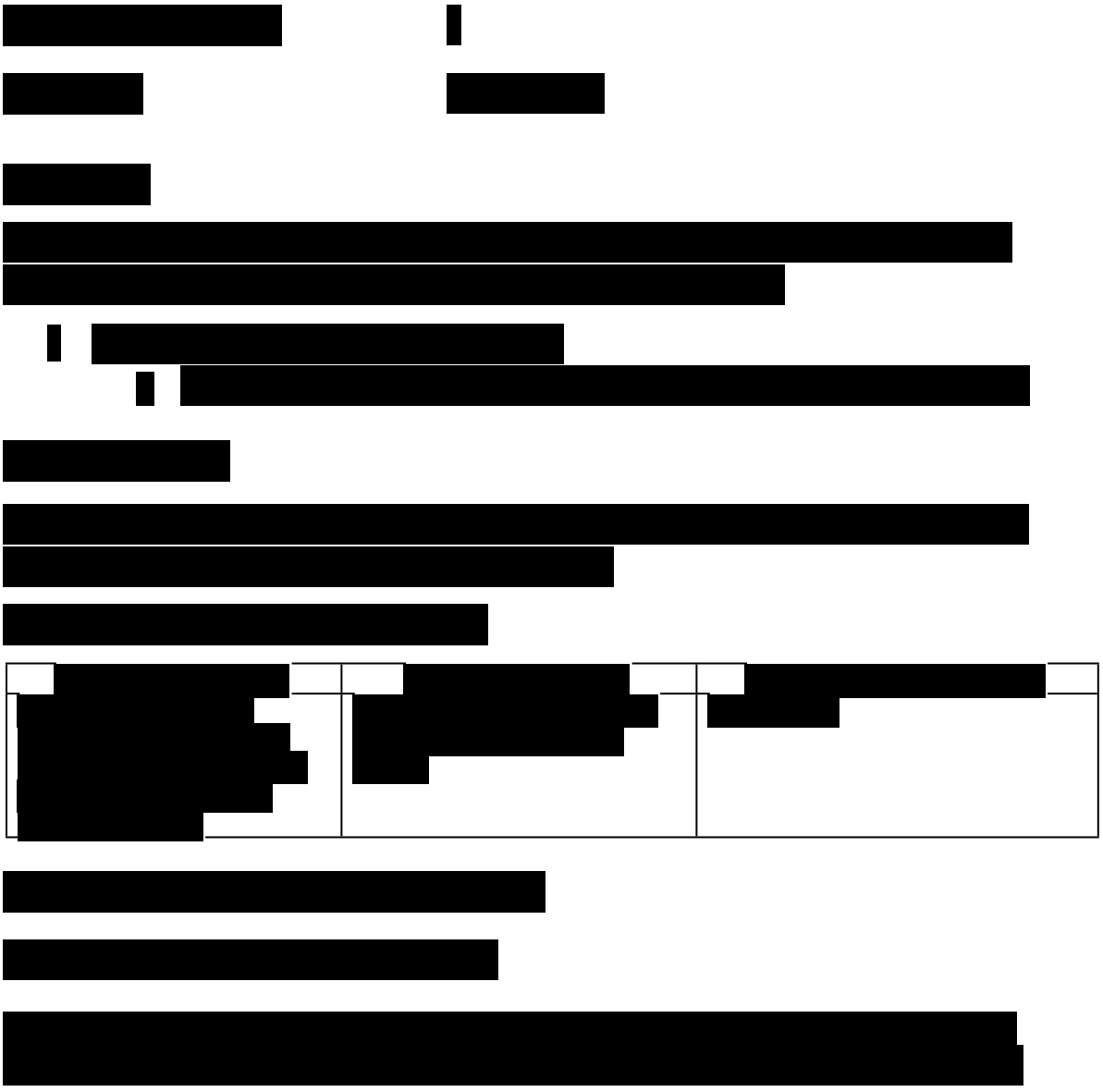

Protocol 323-201-00003

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the Investigational New Drug, OPC-167832, the concurrent medications, the efficacy and safety parameters, and the conduct of the trial in general. I am aware that this protocol must receive a favorable opinion by the independent ethics committee (IEC) responsible for such matters in the clinical trial facility where OPC-167832 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways such as for submission to governmental regulatory authorities or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await for IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol may involve a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: Protocol 323-201-00003 Amendment 5

Document Number: [redacted]

Document Version: 8.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Approval	12-May-2021 19:31:32
[redacted]	Clinical Pharmacology Approval	12-May-2021 19:33:12
[redacted]	Biostatistics Approval	12-May-2021 18:16:27