NCT03002077

Study ID: RAP-MD-06

Title: An Open-label, Long-term Safety Study of Rapastinel as Adjunctive Therapy in Patients With Major Depressive Disorder

Protocol Date: 07 Jun 2016

1.0 TITLE PAGE

Naurex, Inc, an affiliate of Allergan, plc.
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

An Open-label, Long-term Safety Study of Rapastinel as Adjunctive Therapy in Patients with Major Depressive Disorder

RAP-MD-06

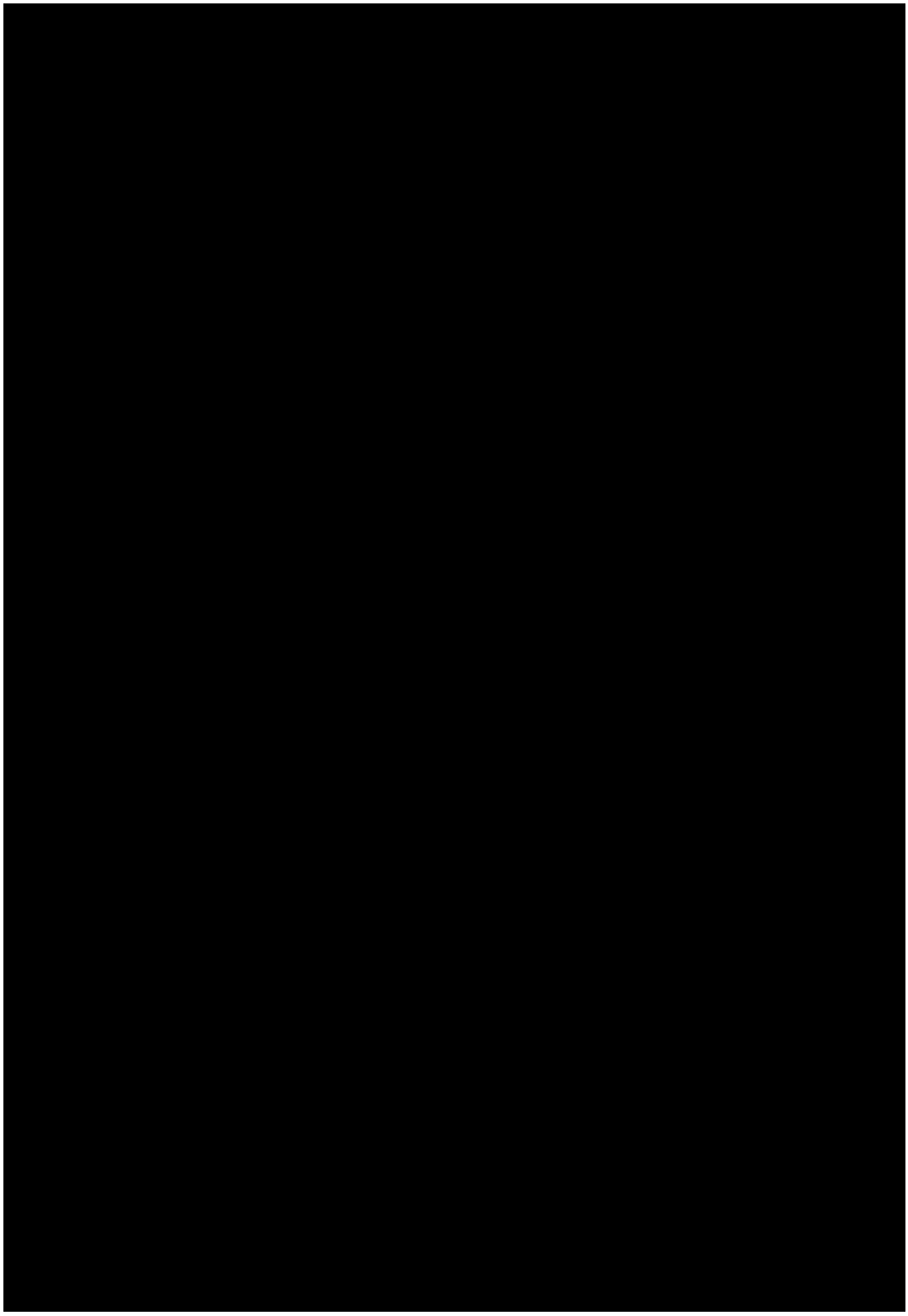
IND # 107,974

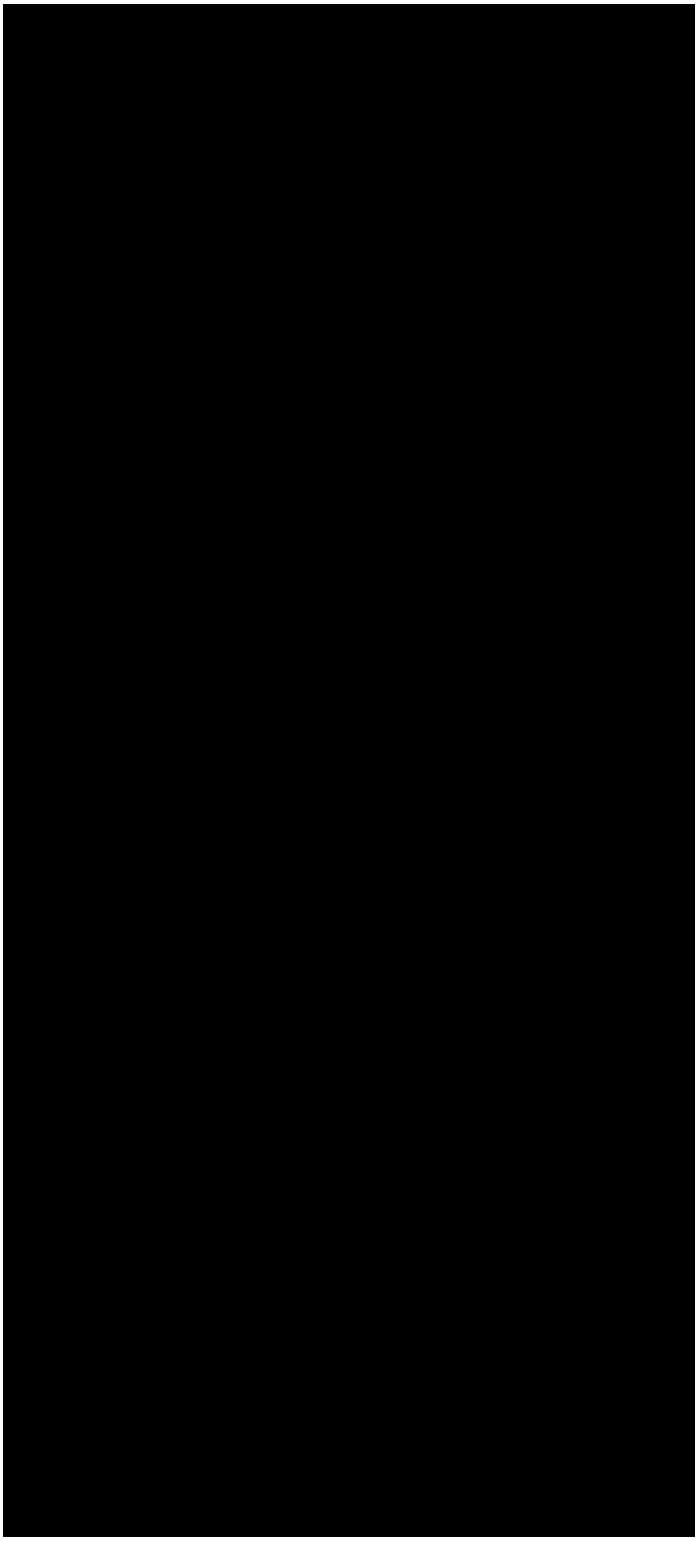
Original Protocol Date: 07 Jun 2016

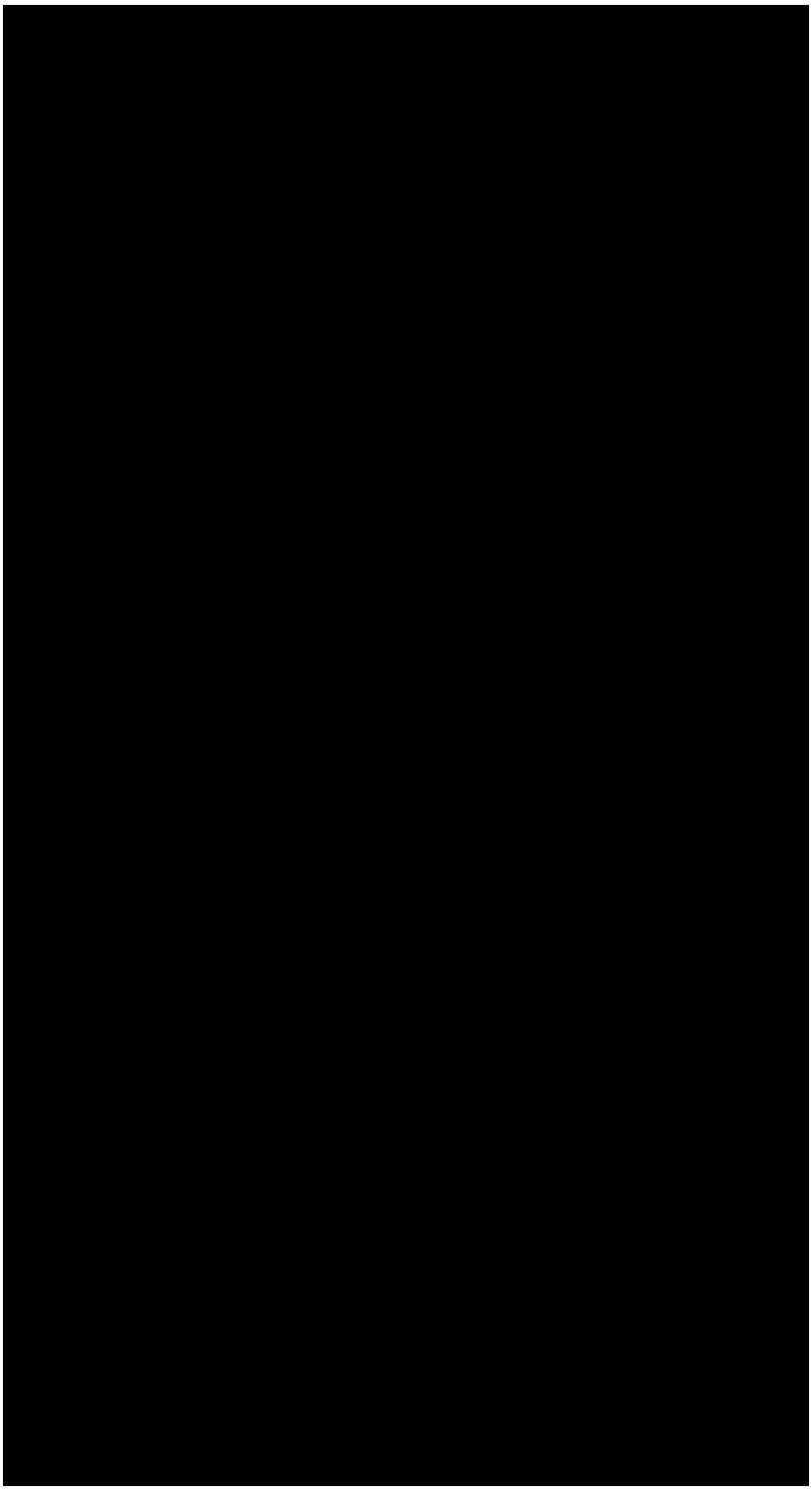
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study RAP-MD-06	
Title of Study	An Open-label, Long-term Safety Study of Rapastinel as Adjunctive Therapy in Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 105 to 110 study centers (United States)
Development Phase	3
Objective	To evaluate the long-term safety and tolerability of rapastinel as an adjunctive to antidepressant therapy (ADT) in patients with major depressive disorder (MDD)
Methodology	Multicenter, open-label, long-term study in adult patients with a primary diagnosis of MDD. For patients enrolling from RAP-MD-04, the final visit from that study (ie, Visit 122) will serve as Visit 1 in RAP-MD-06 and, after obtaining informed consent, open-label rapastinel will be administered at Visit 1 to ensure continuity of treatment. The enrollment of patients who did not participate in RAP-MD-04 (identified as *de novo* enrollment patients) may be allowed at select study centers at the discretion of the Sponsor in the event that overall program enrollment indicates such *de novo* enrollment is necessary. Should *de novo* patients be enrolled with Sponsor approval, such patients will include adult patients with MDD who have no more than a partial response (defined as < 50% improvement) to ongoing ADT treatment in the current episode. Upon written informed consent, *de novo* enrollment patients will enter a screening period of up to 14 days. Following the screening period, all patients will enter the 52-week Open-label Treatment Period (OLTP). The OLTP consists of weekly or biweekly (once every 2 weeks, based on Investigator discretion) visits for up to 52 weeks. Upon completion of the OLTP, patients will enter a 2-week safety follow-up period.
Number of Patients	Approximately 500 patients are expected to enter the OLTP. The study will be terminated when 100 patients have completed the 52-week OLTP.
Diagnosis and Main Criteria for Inclusion	The following are requirements for entry into the study (patients entering from RAP-MD-04 are considered to have met inclusion criteria for diagnosis, severity, and prior ADT response, and are not required to meet these criteria upon entry into RAP-MD-06): • Male or female outpatients, ages 18 to 65 years who meet *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for MDD based on Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition (SCID), with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1 • Have no more than partial response (< 50% improvement) to ongoing treatment with a protocol-allowed ADT ([redacted]

Test Product, Dosage, and Mode of Administration	Rapastinel 450 mg given intravenously (IV) either weekly or biweekly, per Investigator discretion, as adjunctive to ongoing ADT during the OLTP.
Duration of Treatment	For patients enrolling into RAP-MD-06 from RAP-MD-04 there will be a 1-week screening period, up to 52 weeks of open-label rapastinel as adjunctive treatment to ongoing ADT, and a 2-week safety follow-up period. Should *de novo* patients be enrolled at a later date, there will be a screening period of up to 2 weeks, up to 52 weeks of open-label rapastinel as adjunctive treatment to ongoing ADT, and a 2-week safety follow-up period.
Reference Therapy, Dosage, and Mode of Administration	None
Criteria for Evaluation	
[redacted]	[redacted]
[redacted]	[redacted]
Safety Measures	• Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, electrocardiograms (ECGs), and physical examinations • Measure of psychotomimetic effects: Brief Psychiatric Rating Scale Positive Symptoms subscale (BPRS+) • Measure of dissociative effects: Clinician Administered Dissociative States Scale (CADSS) [redacted]
Pharmacokinetic Analysis	None
Pharmacogenetic Analysis	None
Statistical Methods	Descriptive statistics will be presented for all efficacy and safety parameters. No inferential statistical analyses will be performed. All safety parameters will be summarized for the Safety Population, defined as all patients who receive at least 1 dose of investigational product (IP) in this study. [redacted]







3.0 OVERALL TABLE OF CONTENTS

3.1 LIST OF IN-TEXT FIGURES

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4.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BPRS+	Brief Psychiatric Rating Scale – Positive Symptoms Subscale
CADSS	Clinician Administered Dissociative States Scale
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
DALY	disability-adjusted life-year
DBTP	double-blind treatment period
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
[redacted]	[redacted]
ICF	informed consent form

ICH	International Conference on Harmonisation
IND	Investigational New Drug (application)
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
NEAE	newly emergent adverse event
NMDAR	N-methyl-D-aspartate receptor
OLTP	open-label treatment period
PCS	potentially clinically significant
PID	patient identification
PRN	as needed
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{½}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{⅓}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID	Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition
SD	standard deviation
SDC	Symbol Digit Coding
SDMT	Symbol Digit Modalities Test
SNRI	selective serotonin and norepinephrine reuptake inhibitor
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to the Sponsor along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with the US CFR, Title 21, Part 56.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997), as well as the US CFR, Part 312.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study and before participating in any study procedures, each patient must provide written informed consent (in compliance with 21 CFR, Parts 50 and 312) and HIPAA authorization.

Each patient will read and sign an ICF and/or other authorization form as per local regulations; each patient will be made aware that he or she may withdraw from the study at any time.

The ICF contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF and the HIPAA or other locally applicable form will be given to the patient, and both documents will be placed in the Investigator's study files.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 105 to 110 study centers in the United States.

The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An investigator shall obtain the informed consent for each patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at each study center must meet his or her obligations to the patients, ethics committee, Sponsor, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of staff capabilities and performance is consistent with the study investigational plan. The Investigator at each study center will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

Disease Burden of Major Depressive Disorder

Major depressive disorder (MDD) is a highly disabling, serious condition which is associated with significant morbidity and mortality. MDD manifests as a major depressive episode (which may be singular or recurrent) in which the affected individual experiences 1) depressed mood, or 2) loss of interest or pleasure (as well as other symptoms) for most of the day, nearly every day, for at least 2 weeks. MDD affects approximately 14.8 million American adults, or about 6.7% of the US population 18 years of age and older, in a given year (Kessler et al, 2005). Worldwide, about 15% of the adult population is at lifetime risk of developing MDD (Kessler et al, 1994).

Depression may cause serious, long-lasting symptoms and often disrupts a person's ability to perform routine tasks. In 2000, unipolar depressive disorders were by far the leading cause (11.9%) of worldwide years of life lived with disability (World Health Organization, 2001), and the total economic burden of treating depression in the United States was $83.1 billion, with workplace costs, including missed days and lack of productivity due to illness, accounting for most of the total economic burden (62%). Other economic burdens in 2000 included $26.1 billion (31%) for treatment costs and $5.4 billion (7%) for suicide-related costs (Greenberg et al, 2003).

MDD is a leading cause of disability in the United States (Murray et al, 2013). Moreover, MDD is known to be a significant risk factor for suicide and ischemic heart disease, as it accounted for 16 million of the disability-adjusted life-years (DALYs) associated with suicide and 4 million of the DALYs associated with ischemic heart disease. Research has shown that untreated depression has both a functional (social and work role) as well as a neuroanatomical (hippocampal shrinkage) effect on the patient (Videbech and Ravnkilde, 2004). Given the disease burden and link to suicidality as well as increased mortality with other comorbid conditions, MDD is a serious and life-threatening condition which is a leading cause of disability in the world.

Selective Serotonin Reuptake Inhibitors and Selective Serotonin and Norepinephrine Reuptake Inhibitors in Major Depressive Disorder

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) currently represent the first line of treatment of depression in the United States. Unfortunately, a large number of patients do not experience therapeutic benefit from these first-line agents (Rosenzweig-Lipson et al, 2007). Lack of sufficient response to adequate treatment remains a critical problem in the management of patients with MDD. Up to two thirds of patients treated with first-line antidepressant monotherapy do not reach full remission, and as many as a third become treatment resistant (Fava and Davidson, 1996; Trivedi et al, 2006). Not achieving remission has been shown to be predictive of poorer psychosocial functioning, higher rates of relapse, and higher rates of rehospitalization (McIntyre and O'Donovan, 2004).

The results of the STAR*D study suggest that with successive failures of treatment, patients are less and less likely to respond to subsequent treatment, and those who do respond are more likely to relapse (Rush et al, 2006). Present strategies available to treat patients who do not respond to first-line antidepressant monotherapy include switching of antidepressant (either within or between classes); combination therapy in which multiple antidepressants are used simultaneously; augmentation of ongoing antidepressant monotherapy with adjunctive use of drugs such as mood stabilizers or atypical antipsychotics (Boland and Keller, 2006); and the use of nonpharmacologic treatments including psychotherapy and phototherapy, vagus nerve stimulation, transcranial magnetic stimulation, and electroconvulsive therapy (ECT).

Existing antidepressants have a number of limitations, leading to considerable unmet medical need in the effective treatment of MDD, with up to 50% of patients with MDD having an inadequate response or failing current antidepressant therapy (ADT). Currently available first-line antidepressants (SSRIs, SNRIs) typically take 3 to 4 weeks or more of continuous daily dosing to relieve symptoms of MDD and are associated with side effects related to their pharmacological mechanisms of action (sexual dysfunction, weight gain, jitteriness, sleep disturbances), which are further associated with poor patient compliance (Masand 2003, Ashton et al, 2005). Patients often experience undesirable side effects before they experience an improvement in depressive symptoms, which could lead to premature discontinuation of therapy. Taken together, these factors define significant areas for improvement of ADT.

Patients vary greatly in their response to antidepressants and it is not possible to reliably predict whether an individual patient will respond to a given antidepressant. This leads to clinicians often using a trial-and-error approach to identify an effective antidepressant. Due to the gradual development of the full therapeutic effect of currently available antidepressants, each antidepressant needs to be administered for 4 weeks or longer in order to determine the individual therapeutic benefit, making the process of finding an effective antidepressant a lengthy process for patients who are often severely depressed and at a high risk for suicide. Clearly a drug that could induce a rapid antidepressant effect would represent a major advancement for these patients.

Atypical Antipsychotics as Adjunctive Therapy in Major Depressive Disorder

The available treatments for adjunctive therapy in MDD also have substantial safety and efficacy limitations. The drugs currently approved for use as adjunctive therapy to antidepressants for the treatment of MDD—namely, the atypical antipsychotics Abilify® (aripiprazole), Seroquel XR® (quetiapine fumarate), and Rexulti® (brexpiprazole)—are associated with significant adverse reactions, as well as a number of serious warnings and precautions. Originally developed for the treatment of psychotic disorders, these drugs share a number of clinically relevant adverse effects based on their mechanisms of action.

As all current antipsychotic agents modulate central dopaminergic systems, they all carry a risk of extrapyramidal symptoms such as muscular rigidity, acute dystonia, as well as akathisia, which is a particularly relevant adverse event (AE) that complicates clinical management in a significant number of treated individuals, as high as 45% (Sachdev, 1995). In addition, these compounds are associated with a risk of neuroleptic malignant syndrome and tardive dyskinesia. Depending on their individual pharmacological profile, antipsychotics also carry a risk for metabolic changes including hyperglycemia/diabetes mellitus, dyslipidemia and body weight gain; blood dyskrasias such as leucopenia, neutropenia, and agranulocytosis; orthostatic hypotension; cognitive and motor impairment; cataracts; and insomnia (Abilify, 2014; Seroquel, 2013; Rexulti, 2015). The range of clinically relevant side effects with antipsychotics has to be balanced carefully against the potential for therapeutic benefits in patients with major depression. In this context, it is important to highlight that for the approved atypical antipsychotics the full therapeutic benefit required several weeks of daily adjunctive dosing to become apparent, and in many patients, adverse effects occurred substantially earlier than the mood-alleviating effects of these drugs.

Furthermore, the drugs currently approved for adjunctive treatment of MDD also have limited efficacy. The pivotal studies for Abilify, the atypical antipsychotic most commonly used for adjunctive treatment of MDD, showed a delayed onset of effect (1-2 weeks), a modest magnitude of effect (effect sizes were 0.35-0.39 after 6 weeks of repeat dosing) and modest rates of response and remission after 6 weeks of repeat dosing (response rates were 32-34% and remission rates were 25-26%) (Berman et al, 2007; Marcus et al, 2008).

Clearly, there is a substantial need for the development of novel treatments with a better safety/tolerability profile and a faster onset of full therapeutic benefit. Rapastinel has initially shown substantially improved safety/tolerability as well as promising efficacy, in both speed of onset and overall magnitude, for adjunctive therapy in MDD.

Rapastinel as a Novel Approach to Treatment of Major Depressive Disorder

The mechanism of action of rapastinel is entirely different from that of atypical antipsychotics. Rapastinel is an N-methyl-D-aspartate receptor (NMDAR) modulator with a novel and complex pharmacological mechanism of action, acting as a nonselective agent at NR2 subunits and displaying properties as a functional partial agonist in a number of pharmacological assays.

Rapastinel has demonstrated antidepressant properties in relevant animal models, displays cognitive enhancing properties in treated animals, and facilitates hippocampal long-term potentiation of synaptic transmission in preclinical models. In contrast to ketamine, no signal of abuse liability was detected in informative animal models.

Rapastinel is available as an intravenous (IV) formulation only. In two Phase 2 clinical studies in patients with MDD, single IV doses of rapastinel 5 mg/kg and 10 mg/kg have been shown to produce marked antidepressant effects within 1 day that lasted for approximately 1 week or longer in responding patients. These antidepressant effects are very similar to ketamine's effects when administered at a low dose as an infusion. In a systematic review and meta-analysis of ketamine and other NMDAR antagonists in the treatment of major depression, a single infusion of ketamine produced a rapid, yet transient antidepressant effect, accompanied by brief psychotomimetic and dissociative effects (Newport et al, 2015).

The available Phase 1 and 2 data demonstrated a favorable safety and tolerability profile of rapastinel. In contrast to ketamine, rapastinel has not shown a high likelihood to induce psychotomimetic or dissociative effects in humans so far.

The purpose of this study is to assess the safety and tolerability of rapastinel when administered open-label as an adjunctive treatment at a dose of 450 mg as a short IV infusion in patients with MDD. The study is intended to support an application for regulatory approval of rapastinel as adjunctive treatment for MDD.

8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the long-term safety and tolerability of rapastinel as adjunctive to ADT in patients with MDD.

Safety Objectives

- To evaluate the safety and tolerability of rapastinel (450 mg IV weekly or once every 2 weeks [biweekly]) as an adjunct to ongoing ADT, as evaluated by AEs, clinical laboratory measures, ECGs, vital signs, [redacted]

- To evaluate the psychotomimetic effects of rapastinel (450 mg IV weekly or once every 2 weeks) as an adjunct to ongoing ADT, as measured by the change from baseline in BPRS+ at all postdose evaluations

- To evaluate the dissociative effects of rapastinel (450 mg IV weekly or once every 2 weeks) as an adjunct to ongoing ADT, as measured by the change from baseline in CADSS at all postdose evaluations

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

Study RAP-MD-06 is a multicenter, open-label study to evaluate the long-term safety and tolerability of rapastinel as adjunctive therapy to ADT in adult patients with MDD who either completed the RAP-MD-04 Double-blind Treatment Period (DBTP) at Visit 122 (Week 104, ET) or who do not meet criteria to be randomized into the DBTP of RAP-MD-04 and are therefore discontinued from that study. The enrollment of patients who did not participate in RAP-MD-04 (identified as *de novo* enrollment patients) may be considered at some study centers if enrollment of rollover patients does not meet targeted projections and will not be allowed unless specified in an official communication from the Sponsor.

The study will be conducted in the following periods:

- Up to 2-week screening period
- Up to 52-week OLTP
- 2-week safety follow-up period

The study is planned to be terminated when 100 patients have completed the 52-week OLTP. The actual sample size is expected to be larger than 100 patients and some patients will have less than 52 weeks of open-label treatment (as many as 500 patients are expected to enter the OLTP of Study RAP-MD-06).

Figure 9.1-1 provides the study design schematic. The schedule of evaluations is presented in Section 2.0, and detailed descriptions of the procedures conducted at each study visit can be found in Section 9.5.

9.1.1 Screening

The screening period will occur up to 2 weeks prior to Visit 2:

- For patients enrolling from Study RAP-MD-04, the final visit from that study (Visit 122 [Week 104, ET]) will serve as Visit 1 in RAP-MD-06. These rollover patients will receive the first dose of open-label investigational product (IP) (ie, rapastinel 450 mg IV) at Visit 1 to ensure continuity of treatment.

- Upon providing written informed consent, *de novo* patients will enter a screening period of up to 14 days. *De novo* patients will not receive any IP during the screening period but must continue their background ADT at the same dose and wash out of prohibited medications (Appendix III). *De novo* patients meeting the eligibility criteria at the end of Visit 2 (Baseline) will be assigned a treatment by IWRS and enter the OLTP.

All patients will maintain usage of their ADT throughout participation in the study (see Section 9.4.10.1).

9.1.2 Open-label Treatment Period

Approximately 500 patients are planned for enrollment in the OLTP; all patients will receive open-label rapastinel at 450 mg IV (adjunctive to ADT), either weekly or once every 2 weeks, based upon the Investigator's discretion. Patients will skip odd-numbered visits if being treated on a biweekly basis). The once-every-2-weeks schedule can only be initiated on even-numbered visits in order to maintain the appropriate visit schedule. Patients who are on a once-every-2-weeks schedule can be transitioned back to weekly visits at any visit.

Upon completion of the OLTP at Visit 54 (Week 52, ET), patients will enter a 2-week safety follow-up period and will return to the clinic at Visit 55 (Week 54). The maximum duration of the study will be 56 weeks.

The study will be terminated when 100 patients have completed the 52-week OLTP.

9.1.3 Safety Follow-up Period

All patients who complete or discontinue from the OLTP should enter the 2-week safety follow-up period.

Additional follow-up visits may be scheduled within 30 days, if necessary, for safety reasons.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The 52-week, open-label study was designed to assess long-term safety following continued adjunctive rapastinel treatment in adult patients with MDD. In this study, investigators will enroll patients who completed Study RAP-MD-04 or, as needed, enroll patients 18 through 65 years of age who meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD (American Psychiatric Association, 2013). The MDD diagnosis will be confirmed using the Modified Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition (SCID). The symptoms and severity of MDD will be assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Section 9.5.1.2.1).

Study centers will have experience with the study population and will be encouraged to apply available guidelines to minimize patient risk or distress.

Dose selection information is presented in Section 9.4.6. The planned dosing regimen is based on experience from previous rapastinel studies.

The 2-week safety follow-up period allows continued patient monitoring after IP has been discontinued.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Note: For rollover patients who completed the lead-in study (RAP-MD-04), medical, psychiatric, and medication histories from Visit 1 of RAP-MD-04 will be used. For such patients, Inclusion Criteria 2, 4, 5, and 6 are not applicable based on participation in RAP-MD-04.

To be eligible to participate in the study, patients must meet the following criteria:

1. Written informed consent, obtained from the patient before the initiation of any study-specific procedures (Section 5.3)

2. Male or female outpatients who are 18 to 65 years of age

3. For rollover patients from RAP-MD-04, completion of Study RAP-MD-04 (either OLTP or DBTP) with continued ADT treatment

4. Meet DSM-5 criteria for MDD based on confirmation from the modified SCID, with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1

[redacted]

6. Have no more than partial response (< 50% improvement) to ongoing treatment with a protocol-allowed ADT [redacted]

[redacted]

8. If female of childbearing potential, have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at Screening (Visit 1). Because Visit 1 pregnancy test results will not be available on the day of Visit 1, rollover patients can be discontinued at Visit 2 if Visit 1 pregnancy test is positive.

[redacted]

9.3.2 Exclusion Criteria

Note: For rollover patients who completed the lead-in study (RAP-MD-04), medical, psychiatric, and medication histories from Visit 1 of the lead-in study will be used (Exclusion Criteria Nos. 1-8, 12-14, 17, 21-25, and 27). Because Visit 1 clinical laboratory or ECG results will not be available on the day of Visit 1, if there are any safety concerns related to Visit 1 clinical laboratory or ECG results, patients can be discontinued at Visit 2.

Patients who meet any of the following criteria will not be eligible to participate in the study**:**

Exclusion criteria to be assessed at Screening (Visit 1)

Psychiatric and Treatment-Related Criteria:

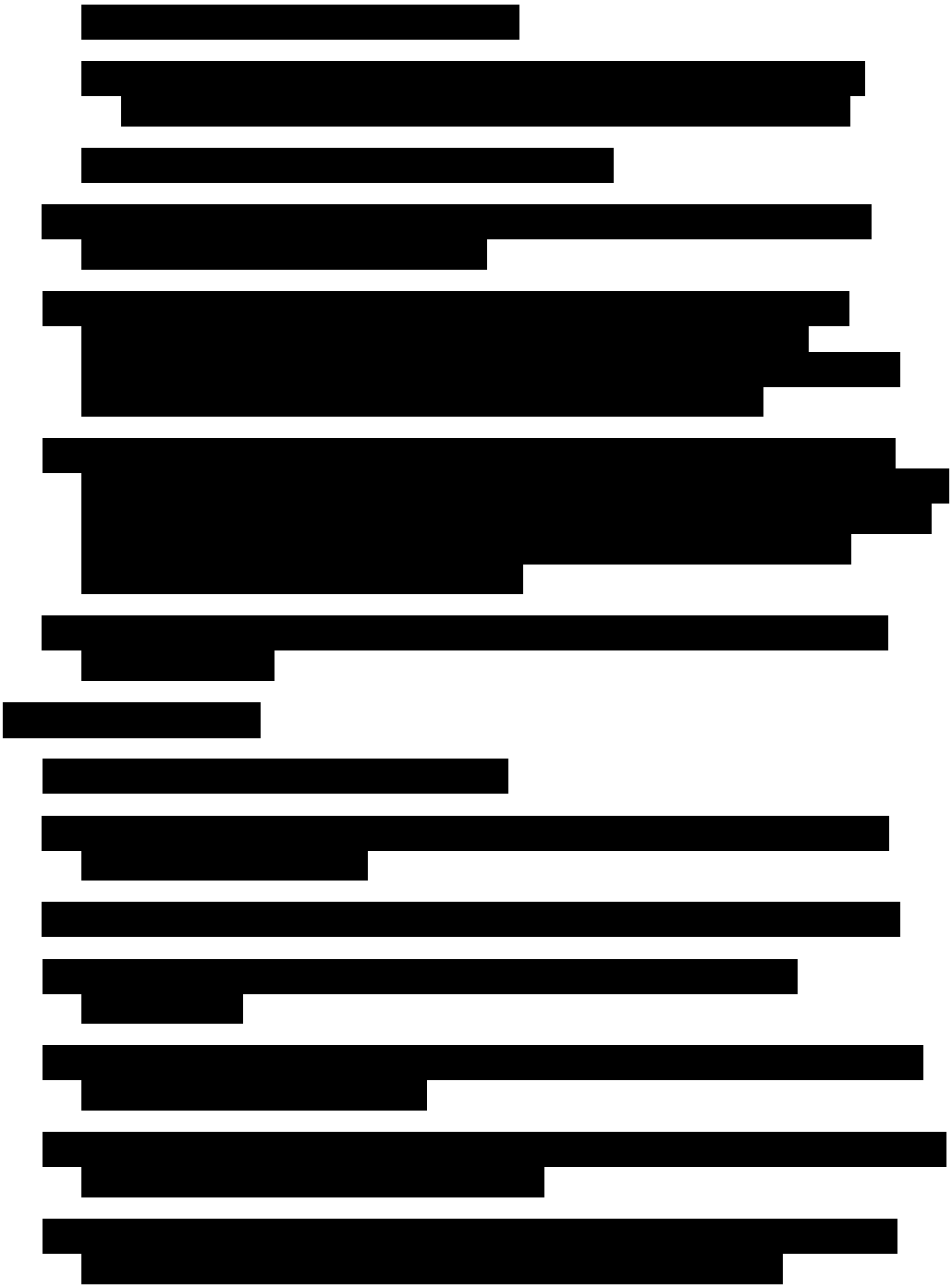
1. DSM-5-based diagnosis of any disorder other than MDD that was the primary focus of treatment within 6 months before Visit 1. Comorbid generalized anxiety disorder, social anxiety disorder, or specific phobias are acceptable provided they play a secondary role in the balance of symptoms and are not the primary driver of treatment decisions.

2. Lifetime history of meeting DSM-5 criteria for:

    - Schizophrenia spectrum or other psychotic disorder
    - Bipolar or related disorder
    - Major neurocognitive disorder
    - Neurodevelopmental disorder of greater than mild severity or of a severity that impacts the patient's ability to consent, follow study directions, or otherwise safely participate in the study
    - Dissociative disorder

[redacted]

9. Suicide risk, as determined by meeting any of the following criteria:



[redacted]

9.3.3 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study visits and procedures. Patients can be prematurely discontinued from the study after careful consideration for one of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Pregnancy
- Withdrawal of consent
- AE
- Lack of efficacy
- Protocol violation
- Noncompliance with IP
- Noncompliance with ADT
- Lost to follow-up
- Study terminated by Sponsor
- Study center terminated by Sponsor
- Other

All patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at an ET Visit. A f*inal assessment* will be defined as completion of the evaluations scheduled for all patients at Visit 54 (Week 52). All patients discontinuing the study prematurely should enter the 2-week safety follow-up period.

Patients who discontinue from the study and do not return to the study center for final assessments must be requested in writing to return to the study center for a final assessment. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study center staff will be contacted by the Sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

9.3.4 Patient Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

9.4 TREATMENTS

During the OLTP, all eligible patients will receive open-label, once-weekly or once every 2 weeks (biweekly, at Investigator's discretion) IV rapastinel 450 mg. Patients receiving biweekly treatment will skip all odd-numbered visits on the Schedule of Evaluations (Section 2.0).

9.4.1 Background Antidepressant Therapy

De novo patients must enter the study while having no more than partial response (< 50% improvement) to ongoing treatment with a protocol-allowed ADT [redacted]

Patients entering from Study RAP-MD-04 will have already fulfilled this requirement but must continue their background ADT as described below.

Upon entry into the study at Screening/Visit 1, the dosage of the ADT must be held constant at a dose in accordance with the respective label throughout participation in RAP-MD-06. If a patient experiences an AE, intercurrent illness, or symptoms of intolerance, he or she will be permitted to stop taking the ADT for a maximum of 5 consecutive days at the discretion of the Investigator. No other alterations in the ADT dose regimen are allowed. If an ADT dose change is required during the study, the patient should be discontinued from the study.

Background ADT medication compliance will also be closely monitored. Compliance will be based on patient report. Every effort should be made to have patients bring their background ADT to each study visit for verification of patient-reported compliance by pill count (to the extent possible).

9.4.2 Treatments Administered

The IP will only be administered to eligible patients under the supervision of the Investigator or identified subinvestigators or other assigned personnel authorized to administer IV drugs. IP will be administered in a "slow bolus" injection to an upper extremity vein within approximately 1 to 2 minutes to each study patient. The patient should not be discharged from the study center until the Investigator or medically qualified subinvestigator determines that the patient is medically able to leave the study center (recommended not less than 15 minutes following administration).

9.4.3 Identity of Investigational Product

Rapastinel 450 mg IV Prefilled Syringes: [redacted].

[redacted]

The study center personnel will complete the kit label and attach the tear-off portion from the kit label to the source documents.

The prefilled syringe will be labeled with the protocol number and kit number. The study center personnel will write the PID number on the prefilled syringe associated with the kit mentioned above. The prefilled syringe will not have a tear-off and the label will remain on the prefilled syringe.

9.4.4 Handling of Investigational Product

The IP must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

[redacted]

At the end of the study, all IP must be accounted for. In addition, at the end of the study, all unused IP and empty IP packages should be returned to the Sponsor or the local distributor at the address provided in the Study Reference Manual.

9.4.5 Method of Assigning Patients to Treatment Groups

Patients enrolling from RAP-MD-04 will keep the same PID number that was assigned in that study.

For *de novo* patients (new patients who did not participate in RAP-MD-04), after a patient signs the ICF at Screening (Visit 1), study personnel will register the patient in the IWRS, and the system will assign the patient a sequential PID number. [redacted]

The IP will be labeled with medication kit numbers. The IWRS will provide the study center with the specific medication kit number(s) for each patient. Study centers will dispense IP according to the IWRS instructions. Study centers will also log onto the IWRS at subsequent visits to obtain a study medication kit number for dispensing IP. Study centers will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

9.4.6 Selection of Dosages in the Study

A rapastinel dose of 450 mg was chosen for this study based on results from 2 Phase 2 clinical studies of patients with MDD in which single IV doses of rapastinel 5 mg/kg and 10 mg/kg were shown to produce marked antidepressant effects within 1 day that lasted approximately 1 week or longer in responding patients. The 450-mg IV dose is expected to provide an appropriate dose for most patients based upon the Phase 2 study results. The use of a single-unit dose is intended to aid in the simplicity of administration and avoid dosing errors.

RAP-MD-04 also assessed both weekly and biweekly dosing regimens. While the GLYX13-C-202 study also assessed the effect of weekly and biweekly administration after initial stabilization, and found no differences, the comparison was only carried out for 6 weeks in that study. Assessing a less frequent dosing regimen over the more substantial time period of 26 weeks to 2 years in RAP-MD-04 followed by an additional 52 weeks of treatment in RAP-MD-06 is expected to yield a better understanding of the long-term safety characteristics of rapastinel treatment and allow proper guidance to physicians regarding treatment beyond initial stabilization.

9.4.7 Selection and Timing of Dose for Each Patient

The IP will be administered IV using the assigned single-use prefilled syringes either weekly or biweekly based on the discretion of the Investigator, per the Schedule of Evaluations (Section 2.0). A patient may be switched between weekly and biweekly treatment at any time during the OLTP. For patients on a biweekly schedule, only odd-numbered visits during the OLTP may be skipped.

9.4.7.1 Screening Period

For patients enrolling from RAP-MD-04, the final visit from that study (Visit 122 [Week 104, ET]) will serve as Visit 1 in this study, after written consent is obtained. Rollover patients will receive open-label IP at Visit 1 to ensure continuity of treatment.

For *de novo* patients, at Visit 1, after written consent is obtained, patients will enter a screening period of up to 14 days. No IP is administered to *de novo* patients during the screening period; however, patients must continue their background ADT at a stable dose. During this time *de novo* patients will wash out of prohibited medications, per Appendix III.

9.4.7.2 Open-label Treatment Period

Patients enrolling from RAP-MD-04 who meet all eligibility criteria at Screening (Visit 1) will receive IP at Visit 1, and patients who continue to meet all the eligibility criteria for participation in the study at Baseline (Visit 2) will continue to receive IP during the OLTP.

De novo patients who meet all eligibility criteria at Screening (Visit 1) and who continue to meet all the eligibility criteria for participation in the study at Baseline (Visit 2) will be assigned an IP kit number via IWRS at Visit 2.

All eligible patients will receive rapastinel 450 mg IV from a prefilled single-dose syringe at Visits 2 through Visit 53 (Week 51).

9.4.7.3 Safety Follow-up Period

Patients who complete the OLTP or patients who prematurely discontinue from the study should enter the 2-week safety follow-up period, returning to the clinic for Visit 55 (Week 54). No IP is administered during the safety follow-up period. Patients' background ADT may be modified as deemed appropriate by the Investigator.

9.4.8 Blinding

Not applicable

9.4.9 Unblinding

Not applicable

9.4.10 Prior and Concomitant Therapy

A list of example medications that are allowed and not allowed as concomitant medications for either episodic or chronic use is provided in Appendix III.

For *de novo* patients, medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or any new medications added will be recorded in the eCRF.

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

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

[redacted].

9.4.11 Other Restrictions

9.4.11.1 Alcohol

It is recommended that patients abstain from alcohol consumption during the study.

9.4.11.2 Contraception

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause.

For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or sexual abstinence.

The Investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

See Section 9.5.2.3 for pregnancy reporting procedures.

9.4.12 Monitoring Treatment Compliance

IP compliance during any period will be closely monitored by capturing the date and time of each injection of IP. If a scheduled injection does not occur, the Sponsor must be notified and the reason captured in the eCRF.

Background ADT compliance will also be closely monitored. Background ADT medication compliance will be based on patient report. Every effort should be made to have patients bring their background ADT to each study visit for verification of patient-reported compliance by pill count (to the extent possible). Missed doses or other changes in the dose of ADT and the reason should be captured in the eCRF.

9.4.13 Treatment After Discontinuation

Patients whose MDD symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the OLTP will be allowed to discontinue the study and start appropriate treatment at the Investigator's discretion. This new treatment will not be provided by the Sponsor. Patients who initiate a new treatment must be discontinued from the study.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Diagnostic and Efficacy Assessments

9.5.1.1 Diagnostic Assessments

The SCID will be administered during the screening interviews by a psychiatrist, doctoral level clinical psychologist, or other clinician who has extensive professional training and experience in the diagnosis of mental illness and who meets the training requirements and qualifications standards set by the Sponsor and rater training vendor.

[redacted]

[redacted]

[redacted]

9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately-trained healthcare professional at every visit and the evaluation must be documented. The procedures discussed in the following sections will be completed at the designated visits.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of the study center's data collection responsibilities, any untoward event that was reported from the time the patient signed the ICF until 30 days after the final protocol-defined study visit or the last known dose of IP (if the final visit does not occur) is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study center personnel
- All diseases that occur after signing informed consent, including any change in severity or frequency of pre-existing disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note that medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

9.5.2.1.1 Causality Assessment

For each AE, the Investigator must provide an assessment of causal relationship to the IP. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the IP caused the event?

Yes: There is evidence to suggest a causal relationship between the IP and AE, ie:

- There is a reasonable temporal relationship between the IP and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the IP and AE, ie:

- There is no reasonable temporal relationship between the IP and the event, or

- The patient did not take the IP, or
- The event is likely to be attributed to underlying/concurrent disease or other factors, or
- The event is commonly occurring in the (study) population independent of IP exposure

9.5.2.1.2 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.1.3). Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.5.2.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of IP dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for pre-existing conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.1.4 Reporting Adverse Events and Serious Adverse Events

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, “How do you feel since your last visit?” Study center personnel will record all pertinent information in the patient’s eCRF.

All AEs must be recorded on the appropriate AE reporting page of the patient’s eCRF whether or not they are considered causally related to the IP.

For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and casual relationship
- Document all actions taken with regard to the IP
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, patients are to be reminded, as described in the ICF and in accordance with Section 9.5.2.1, to notify study center personnel of any AEs occurring during the 30-day poststudy period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least one of the following conditions is met: 1) the event meets the criteria for an SAE (see Section 9.5.2.1.3 and Section 9.5.2.1.4), and/or 2) the event is judged by the Investigator to be potentially causally related to IP.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the IP. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

9.5.2.2 Immediate Reporting of Serious Adverse Events and Events of Special Interest

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to Global Drug Safety on the SAE Form for Clinical Trials. The Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE Form for Clinical Trials to the SAE fax number provided at the end of this section. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. ***The Sponsor may contact the study center to solicit additional information or follow up on the event.***

Fax the SAE Form for Clinical Trials to the Sponsor.

[redacted]

9.5.2.3 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the patient signs the ICF until 30 days after the last dose of IP. Within 24 hours of learning of the pregnancy, the study center personnel must report the event to Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE/pregnancy fax number provided in Section 9.5.2.2, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the timeframe described above must also be reported.

Any pregnancy of a patient treated with IP must be followed to term and the outcome reported by completing a follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 9.5.2.2 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the pregnancy form.

9.5.2.4 Potential Hy's Law Cases

The criteria for potential Hy's Law cases are as follows:

- ALT or AST ≥ 3 × ULN and
- Total bilirubin ≥ 2 × ULN and
- Alkaline phosphatase < 2 × ULN

Study center personnel must report every patient who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the ICF is signed for the study until 30 days after the final protocol-defined study visit or the last known dose of IP (if the final visit does not occur).

A laboratory alert for potential Hy's Law cases will be in place, and the laboratory must notify investigators and the Sponsor immediately when the above criteria have been met. A potential Hy's Law case must be faxed to the Sponsor on an AE of Interest Form as soon as possible (within 24 hours of learning of the potential Hy's Law) to the SAE/pregnancy fax number stated in Section 9.5.2.2, even if no AE has occurred. The eCRF for potential Hy's Law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Study Physician and in accordance with the FDA Guidance for Industry: Drug Induced Liver Injury - Pre-Marketing Clinical Evaluation, July 2009.

9.5.2.5 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as detailed in the Schedule of Evaluations (Section 2.0). During screening, the Investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory; patients with abnormalities judged to be clinically significant will be excluded from the study.

Patients will be asked to fast overnight or for at least 8 hours before arriving at the study center for appointments involving the collection of clinical laboratory blood tests.

The following clinical laboratory levels will be measured:

Hematology: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Sodium, potassium, calcium, chloride, bicarbonate, magnesium, gamma glutamyl transferase, phosphate, glucose, blood urea nitrogen, creatinine, creatine phosphokinase, total protein, alkaline phosphatase, albumin, bilirubin (total; direct; indirect), ALT, AST, total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides

HbA1c and fasting insulin: As specified in the Schedule of Evaluations (Section 2.0)

Urinalysis: Specific gravity, pH, protein, glucose, ketones, and blood

Thyroid function: Thyroid function test at Screening (Visit 1) and periodically as specified in the Schedule of Evaluations (Section 2.0)

UDS: Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine, performed at Screening (Visit 1), and periodically as specified in the Schedule of Evaluations (Section 2.0) (and at Investigator's discretion)

Serum β-hCG: Serum β-hCG will be performed at Screening (Visit 1) and periodically as specified in the Schedule of Evaluations (Section 2.0) (and at Investigator's discretion)

Hepatitis screening: Hepatitis–C virus antibody, hepatitis–B surface antigen, and hepatitis-B core antibody total will be tested. Reflex hepatitis-B core antibody IgM will be performed for all hepatitis–B core antibody total positive or reactive results. Positive test results will be sent for confirmation testing. Hepatitis screening is to be conducted at Screening (Visit 1) on *de novo* patients only (new patients who did not participate in RAP-MD-04).

Clinical laboratory tests may be performed under special circumstances (and at Investigator's discretion).

A negative UDS (except for benzodiazepines if prescribed by the Investigator as per the protocol) is required before Baseline (Visit 2) for the patient to continue in the study. A UDS may be performed at any time during the study at the discretion of the Investigator. A patient with a positive UDS for benzodiazepines or opiates at any visit may be allowed to continue in the study provided the patient has been prescribed the medication and it is being used for legitimate medical purpose in the Investigator's judgment.

Serum pregnancy test will be performed as specified in the Schedule of Evaluations (Section 2.0). Positive results on the pregnancy test at Screening (Visit 1) will exclude patients from participating in the study. Positive pregnancy test results during the study will result in patient termination from the study.

Other laboratory assessments may be repeated at any visit if there was an abnormal finding at the most recent previous evaluation or if additional information is clinically necessary to appropriately evaluate the patient's current condition, follow up, and/or manage an adverse experience.

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

9.5.2.6 Vital Signs

Vital signs (pulse rate, systolic and diastolic BP, oral or tympanic temperature, and body weight) will be assessed at every visit during the OLTP. Height will be assessed at Visit 1 for *de novo* patients only (Section 2.0).

BP and radial pulse rate will be measured in the supine position followed by the standing position. The standing measurements should be assessed after a sufficient amount of time has been elapsed to allow the BP to equilibrate in the standing state.

Radial pulse rate should be measured after BP measurements. BP may be measured manually or by machine, but radial pulse rate should only be measured manually and for a sufficient time to acquire an accurate measurement.

Patients should be instructed not to wear clothing with tight sleeves when they come for clinic visits. Additionally, patients should be kept as calm and undisturbed as possible while BP and pulse rate measurements are taken (eg, there should be no talking while the BP is being measured). The same arm and BP cuff (appropriate to the arm circumference) should be used for all BP measurements.

Whenever possible, the patient's weight will be measured at the same time of day; patients should wear their usual indoor clothing, but take off their jacket and shoes. For each patient, body weight should be determined using the same equipment during the study after ensuring its proper calibration.

9.5.2.7 Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in the Schedule of Evaluations (Section 2.0). The ECGs will be performed and electronically transmitted to a central ECG laboratory for analysis according to the instructions provided by the central ECG laboratory. Measurements (in msec) will be recorded for the following parameters: PR interval, QRS duration, and uncorrected QT interval. QTcB (Bazett corrected QT interval) and QTcF (Fridericia corrected QT interval) will be calculated.

The overall interpretation and determination of the clinical relevance of ECG findings using the central ECG interpretation laboratory report will be the responsibility of the Investigator and will be recorded in the patient's eCRF. For eligibility criteria, the values reported on the central ECG interpretation report will be used (not the values printed on the tracing itself).

[redacted]

9.5.2.8.3 Brief Psychiatric Rating Scale - Positive Symptoms Subscale

The BPRS is an 18-item evaluation that assesses psychiatric symptoms and unusual behavior (Overall and Gorham, 1962). The BPRS+ is a subset of the BPRS that assesses 4 components of the BPRS+ related to the degree of psychosis: Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Unusual Thought Content. Only the 4 items of the BPRS+ subscale will be collected and analyzed. The BPRS+ will be administered by the Investigator or designee with extensive professional training and experience in assessing mental illness.

9.5.2.8.4 Clinician Administered Dissociative States Scale

The Clinician Administered Dissociative States Scale (CADSS) is a 28-item clinician-administered measure of perceptual, behavioral, and attentional alterations occurring during active dissociative experiences composed of 23 subjective self-reported and 5 objective observer-reported ratings, each scored from 0 (not at all) to 4 (extremely). Only the 23 subjective items will be collected and analyzed. The CADSS provides a validated assessment of dissociative states sensitive to change over time and amenable to repeated measures (Bremner et al, 1998). The CADSS will be administered by the Investigator or designee with extensive professional training and experience in assessing mental illness.

[redacted]

[redacted]

[redacted]

[redacted]

9.5.6 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0. The descriptions of the procedures to be performed at each visit are provided in the following sections.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.5.6.9 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the Investigator. Additional examinations may be performed as necessary to ensure the safety and well-being of the patients during the study.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study center staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first patient is enrolled, the Sponsor representative, a Regional Site Manager or designee, will periodically monitor the progress of the study by conducting on-site visits. This Regional Site Manager or designee will review query statuses remotely, possibly warranting more frequent communication and/or study center visits with the Investigator and the study center staff. The Investigator will make available to the Regional Site Manager or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study center staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the EDC system, to which only authorized personnel will have access. Patient's data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edit checks, data monitoring, and reviews, queries may be electronically issued to the study center and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date, and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, and regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, the FDA, or other health authorities.

Data for the [redacted] C-SSRS, BPRS+, CADSS, and [redacted] will be captured using an electronic source tablet-based system. [redacted] Source documents will be used at the study centers and may include a patient's medical record, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood samples. Additional information on the collection and handling of samples is detailed in the Lab Procedure Manual.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Analysis Populations

Three populations will be considered in the statistical analysis of the study, as specified in the following subsections.

9.7.1.1 Screened Population

The Screened Population will consist of all patients who signed the RAP-MD-06 ICF if they participated in Study RAP-MD-04, and all patients who underwent the Screening Visit, received a PID number, and signed the ICF if they didn't participate in Study RAP-MD-04.

9.7.1.2 Safety Population

The Safety Population will consist of all patients in the Screened Population who took at least 1 dose of rapastinel during the OLTP of the study.

9.7.1.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had at least 1 postbaseline assessment of the MADRS total score during the OLTP of the study.

9.7.2 Patient Disposition

The number and percentage of patients in the 3 analysis populations will be summarized overall by study center.

For *de novo* enrolled patients, screen failures (ie, patients who were screened but not included in the Safety Population) and the associated reasons for failure to enroll will be tabulated overall for the Screened Population.

The number and percentage of patients who complete the OLTP, who prematurely discontinue from the OLTP, and who complete the safety follow-up period will be summarized overall and by reasons for premature discontinuation for the Safety Population.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized overall for the Safety Population and the ITT Population.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to rapastinel for the Safety Population during the OLTP will be summarized for treatment duration, calculated as the number of days from the date of the first dose of open-label rapastinel taken to the date of the last dose taken during the OLTP, inclusive. Descriptive statistics (number of patients, mean, SD, minimum, median, and maximum) will be presented.

Prior medication will be defined as any medication started before the date of first dose of IP in the first lead-in study for rollover patients or any medication started before the date of the first dose of open-label IP in this study for *de novo* patients. *Concomitant medication* during the OLTP will be defined as any medication taken on or after the date of the first dose of open-label IP during the OLTP.

The use of prior medication will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Safety Population. The use of concomitant medications during the OLTP will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Safety Population. Multiple use of the same medication by a patient will only be counted once.

The number and percentage of patients taking each qualifying ADT in the OLTP will be summarized for the Safety Population. Mean daily dose and duration of treatment with each qualifying ADT will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) for the Safety Population.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of IV doses actually taken by a patient during that period divided by the number of IV doses that were expected to be taken during the same period multiplied by 100. Descriptive statistics for IP compliance will be presented for each week, as well as for the whole OLTP for the Safety Population.

Dosing compliance for the background ADT during a specified period is defined as the doses actually taken by a patient during that period divided by the dose expected to be taken during the same period multiplied by 100. Descriptive statistics for ADT compliance during the OLTP will be presented for each ADT for the Safety Population.

[redacted]

9.7.6 Safety Analyses

The safety analysis will be performed using the Safety Population, defined as all patients who receive at least 1 dose of IP during the OLTP.

The safety parameters will include AEs; clinical laboratory, vital signs, and ECG parameters; and the BPRS+, CADSS, [redacted].

For each safety parameter, the last assessment made before the first dose of open-label IP will be used as the baseline for *de novo* patients, and the baseline of the first lead-in study will be used as the baseline for rollover patients for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

9.7.6.1 Adverse Events

AEs will be coded by system organ class (SOC) and preferred term using the *Medical Dictionary for Regulatory Activities*.

For rollover patients, an AE (classified by preferred term) that occurs during the OLTP will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of IP in the first lead-in study or was present before the first dose of IP in the first lead-in study and increased in severity during the OLTP. If more than 1 AE is reported before the first dose of IP in the first lead-in study and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the OLTP that were also coded to that preferred term.

For *de novo* patients, an AE (classified by preferred term) that occurs during the OLTP will be considered a TEAE if it was not present before the first dose of open-label IP or was present before the date of the first dose of open-label IP and increased in severity after the first dose of open-label IP. If more than 1 AE is reported before the first dose of open-label IP and is coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the OLTP that were also coded to that preferred term.

An AE that occurs more than 30 days after the date of the last dose of IP will not be considered a TEAE.

A TEAE occurring during the OLTP will be considered a newly emergent AE (NEAE) if the AE was not present before the first dose of open-label IP or was present before the first dose of open-label IP but increased in severity during the OLTP. The number and percentage of patients reporting NEAEs during the OLTP will be summarized by SOC and preferred term.

The number and percentage of patients reporting TEAEs will be tabulated by SOC and preferred term and further categorized by severity and causal relationship to the IP. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The distribution of TEAEs by severity and relationship to the IP will be summarized.

An AE that occurs more than 30 days after the date of the last dose of IP will not be summarized.

The incidence of common (≥ 2% of patients) TEAEs and AEs leading to premature discontinuation of IP will be summarized by preferred term and will be sorted by decreasing frequency.

An SAE that occurred between the date of the first dose of the open-label IP and 30 days after the date of the last dose of IP, inclusive, will be considered an on-therapy SAE.

The number and percentage of patients who have on-therapy SAEs will be summarized by preferred term. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term.

The incidence of AEs leading to premature discontinuation of IP during the OLTP will be summarized by preferred term and will be sorted by decreasing frequency.

Listings will be presented for all patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any). All patients with SAEs, including SAEs reported during the screening period and the safety follow-up period, and patients discontinuing because of AEs occurring before the start of IP will be included in these listings.

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline values at each assessment timepoint will be presented for each clinical laboratory parameter.

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment timepoint will be presented for selected clinical laboratory parameters listed in the Statistical Analysis Plan (SAP).

The number and percentage of patients who have potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the OLTP. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline, and all postbaseline (including non-PCS) values. In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of study for clinical laboratory parameters will be presented for the following categories: low, normal, and high, which are provided by the laboratory vendor.

Patients who meet the potential Hy's Law criteria from the first dose of IP to within 30 days after the last dose of IP will be summarized. Supportive tabular displays will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP, body weight, oral or tympanic temperature, and body weight) and changes from baseline values at each visit and at the end of study will be presented.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline value criteria. The criteria for PCS vital sign values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the OLTP or the safety follow-up period. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with postbaseline PCS values will be provided, including the PID number, baseline values, and postbaseline values. A listing of all AEs occurring in patients who have PCS vital sign values will also be provided.

9.7.6.4 Electrocardiogram

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB interval, and QTcF interval) and changes from baseline values at each assessment timepoint will be presented.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated for the OLTP. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the OLTP. The numerator is the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline values, all postbaseline (including non-PCS) values, and change from baseline. In addition, a tabular display showing all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of study in the Investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not clinically significant; and abnormal, clinically significant. A tabular display showing patients with postbaseline clinically significant ECG abnormalities according to the Investigator's overall interpretation will be provided.

The number and percentage of patients with change from baseline QTc > 30 msec but not exceeding 60 msec and of patients with an increase > 60 msec will be tabulated. A supportive listing that includes the PID number, all QTc values (including change from baseline values), and all AEs will be provided for all patients who have postbaseline QTc changes > 30 msec.

9.7.6.5 Other Safety Parameters

Other safety parameters comprise the BPRS+, CADSS, [redacted]

Descriptive statistics of actual values and change from baseline for BPRS+ total score will be presented at each assessment timepoint during the OLTP.

Descriptive statistics of actual values and change from baseline for CADSS total score will be presented at each assessment timepoint during the OLTP. CADSS total score is defined as the sum of scores for 23 subjective items.

[redacted]

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

Approximately 500 patients are expected to enter the OLTP. The study will be terminated when 100 patients have completed the 52-week OLTP.

9.7.10 Computer Methods

Statistical analyses will be performed using [redacted].

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified timepoints, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the Sponsor.

Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.

An *important protocol deviation* is a form of protocol deviation that has a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Important protocol deviations must be reported to the Sponsor within 24 hours, if possible. The IRB must be notified within the time period dictated by the IRB associated with this study.

10.0 STUDY SPONSORSHIP

This study is sponsored by Naurex, Inc, an affiliate of Allergan, plc.

10.1 STUDY TERMINATION

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 REPORTING AND PUBLICATION

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and the Sponsor and will follow the Sponsor's Standard Operating Procedure on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must provide the following to the Sponsor before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA.
- A fully executed contract
- The curricula vitae for the Investigator and all subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1.
- A copy of the IRB-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB members or the DHHS general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol, signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all subinvestigators listed on Form FDA 1572. The Investigator and all subinvestigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.

11.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the IP supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Subinvestigators listed on Form FDA 1572. The IP must be stored in a secured place and must be locked. At study initiation, a representative from the Sponsor will inventory the IP at the study center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor will supply forms on which to record the date the IP was received and a dispensing record in which to record each patient's use. All unused IP must be returned to the Sponsor.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by the Sponsor through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to the Sponsor. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and ECGs) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and PID number. Patients' names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol (RAP-MD-06, dated 07 Jun 2016) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

13.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained for each patient participating in a clinical research study. This consent must include the following items:

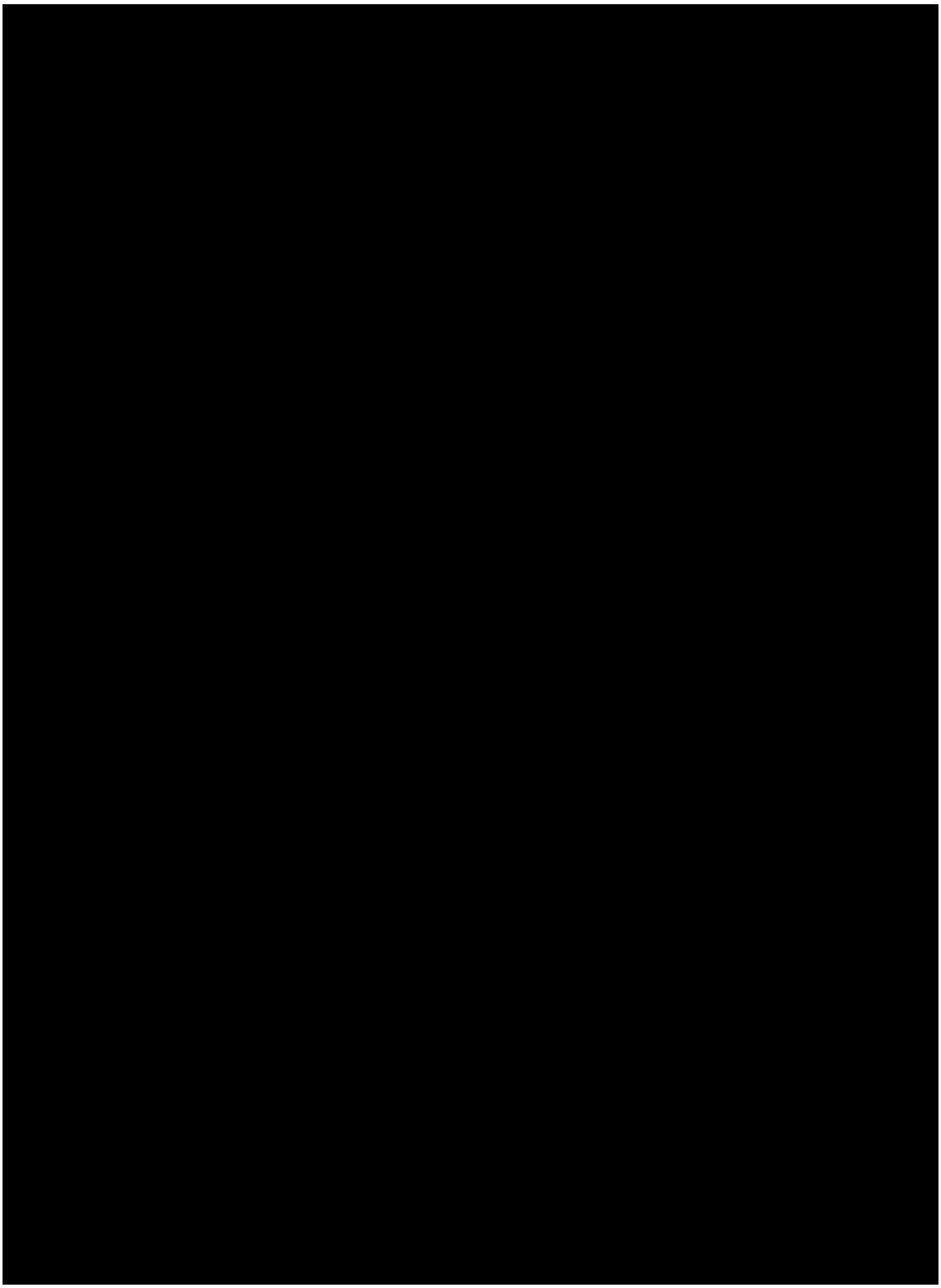
- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, the Sponsor, the IRB, or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required.)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

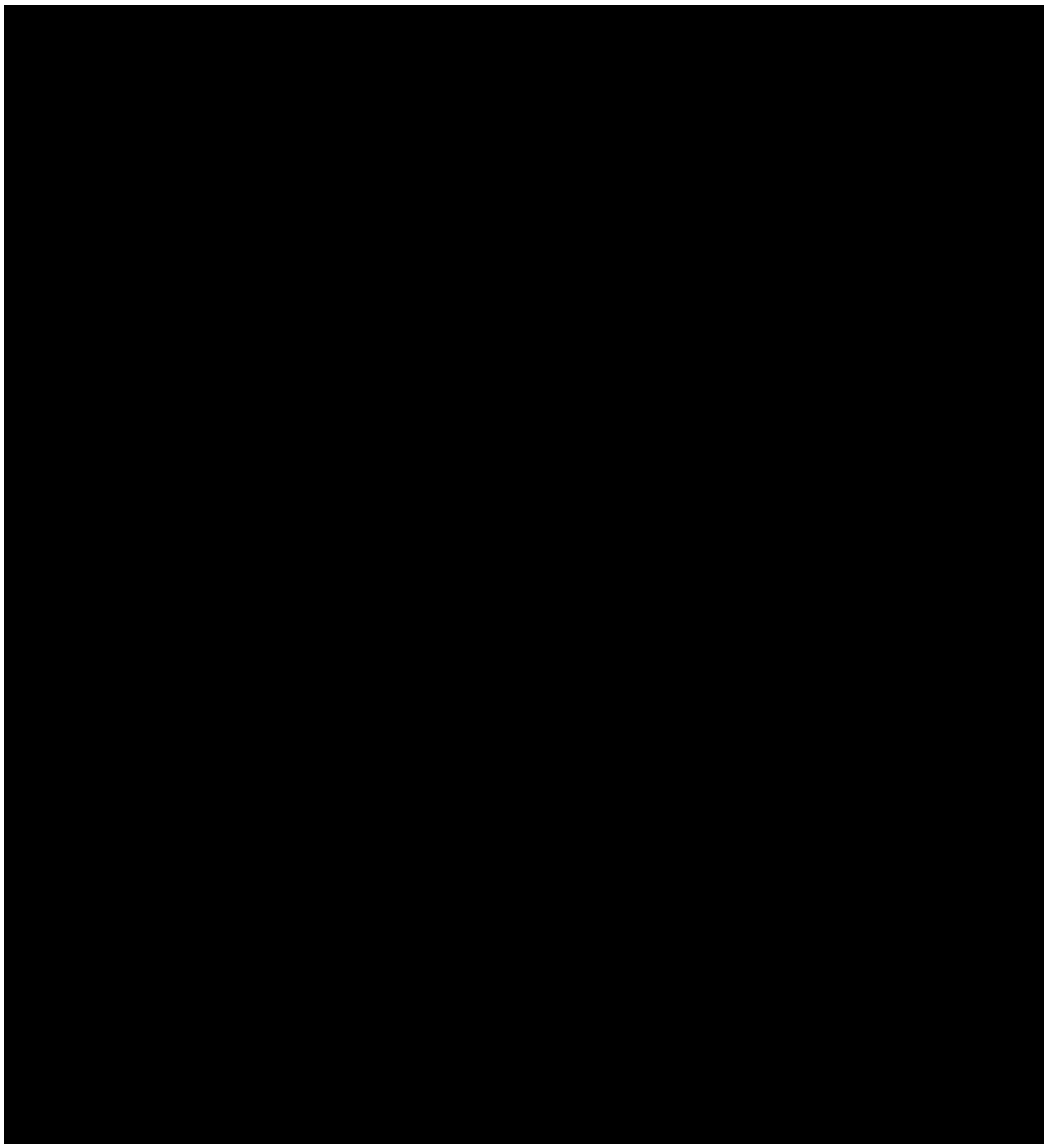
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of permission, providing consent for the patient to participate (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing of the ICF
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

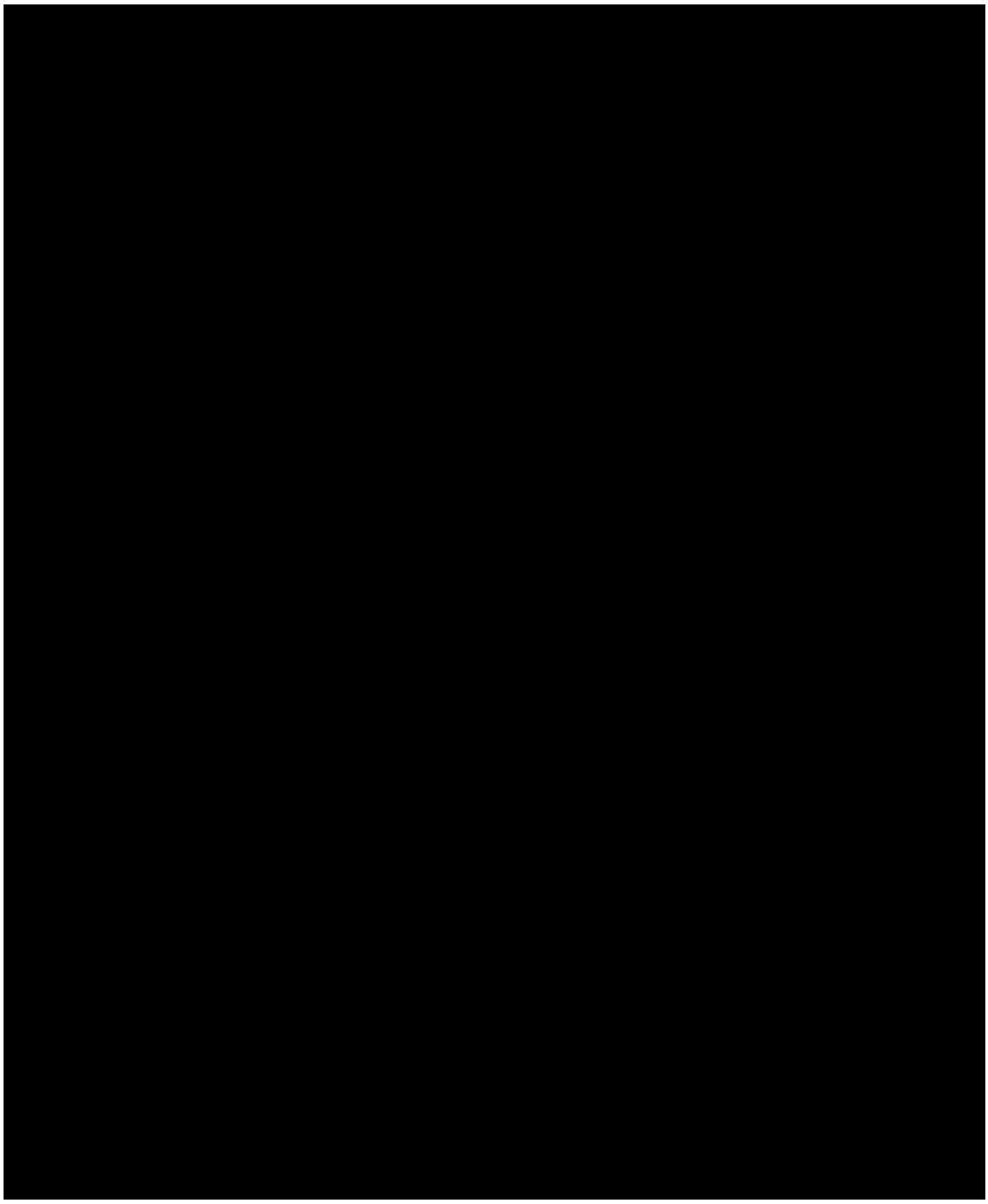
A copy of the signed consent form must be given to the patient.

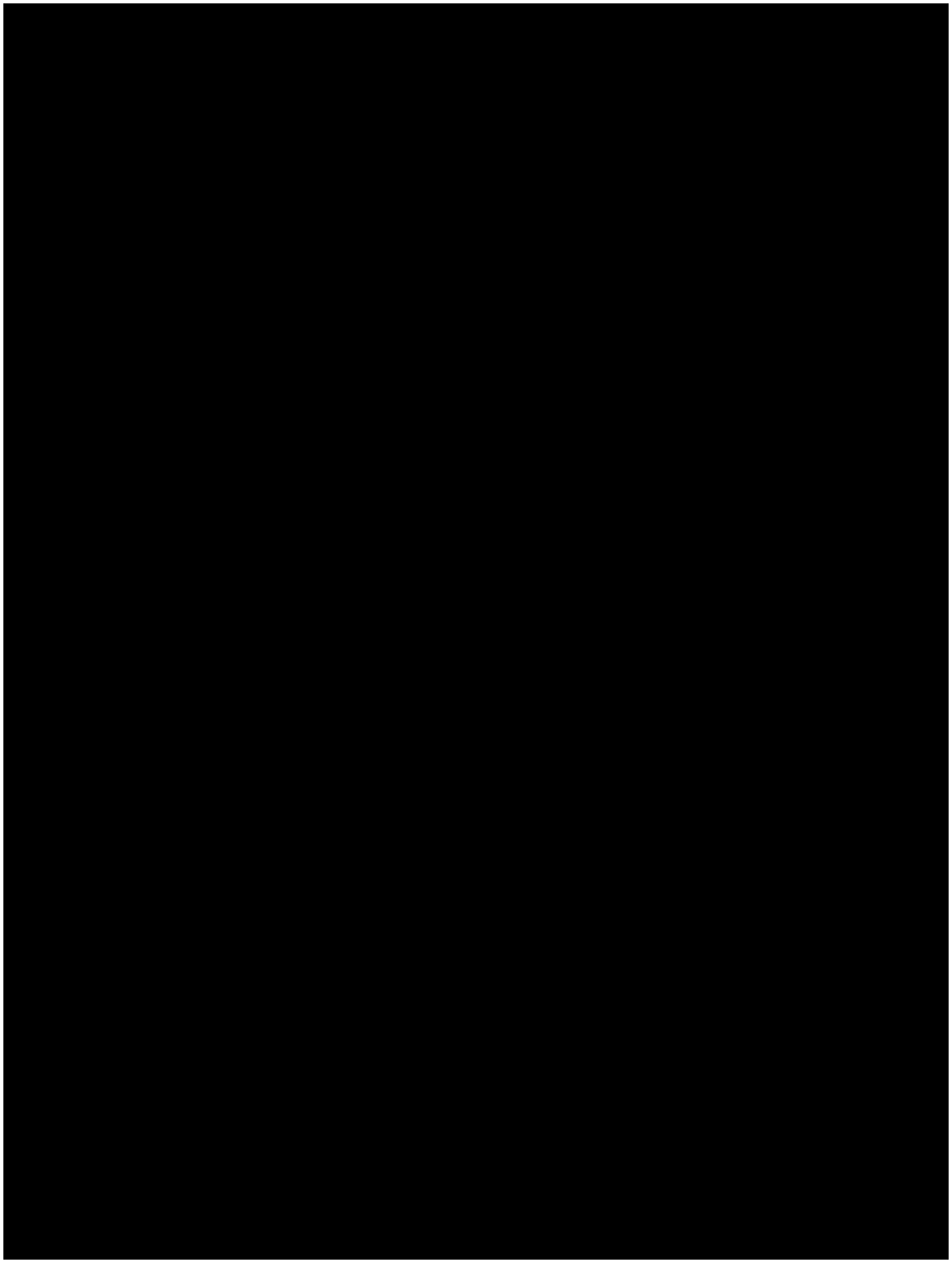
APPENDIX II. CONTACT INFORMATION

Contact information for the Sponsor personnel is maintained in the Study Reference Manual.









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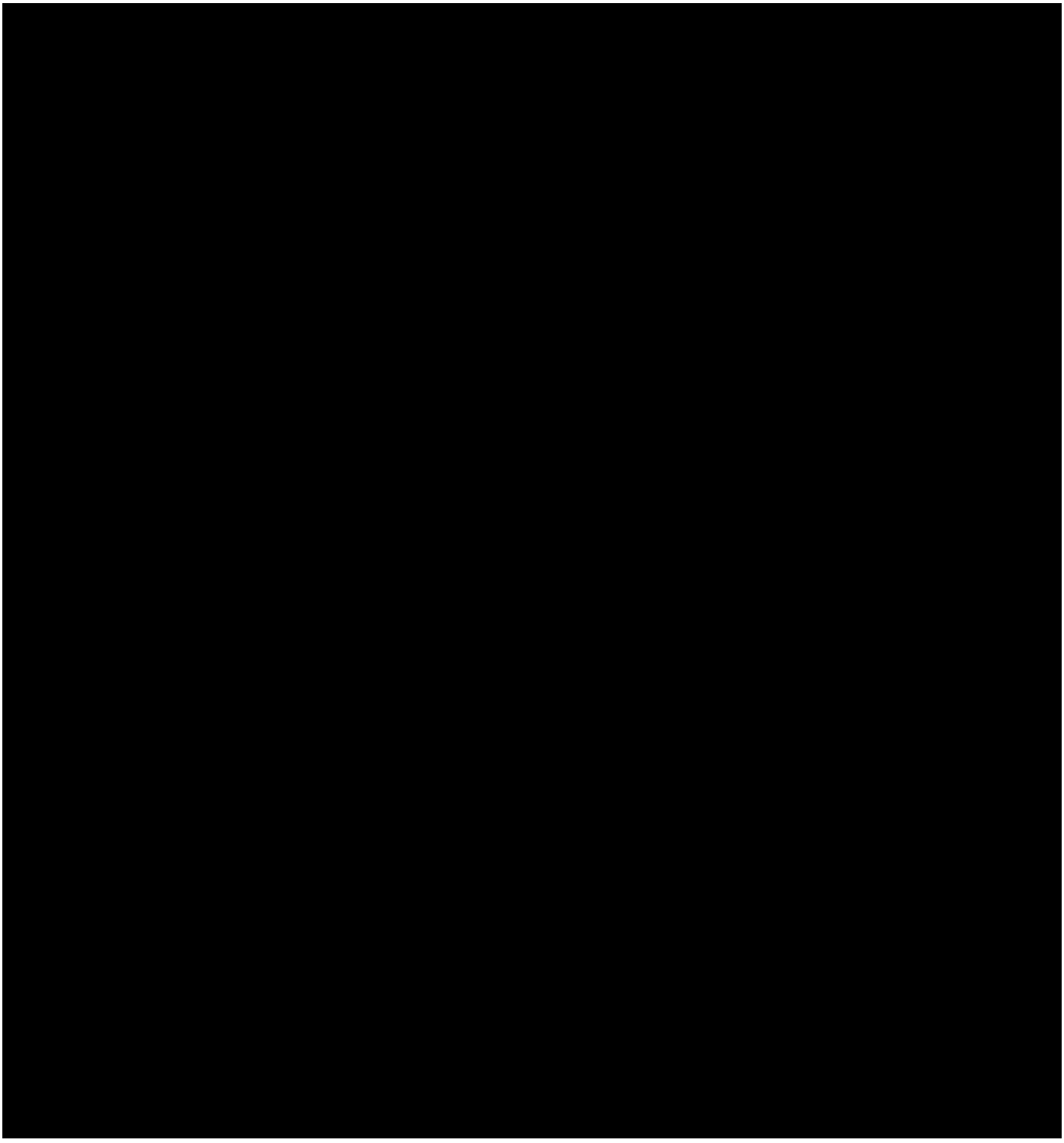

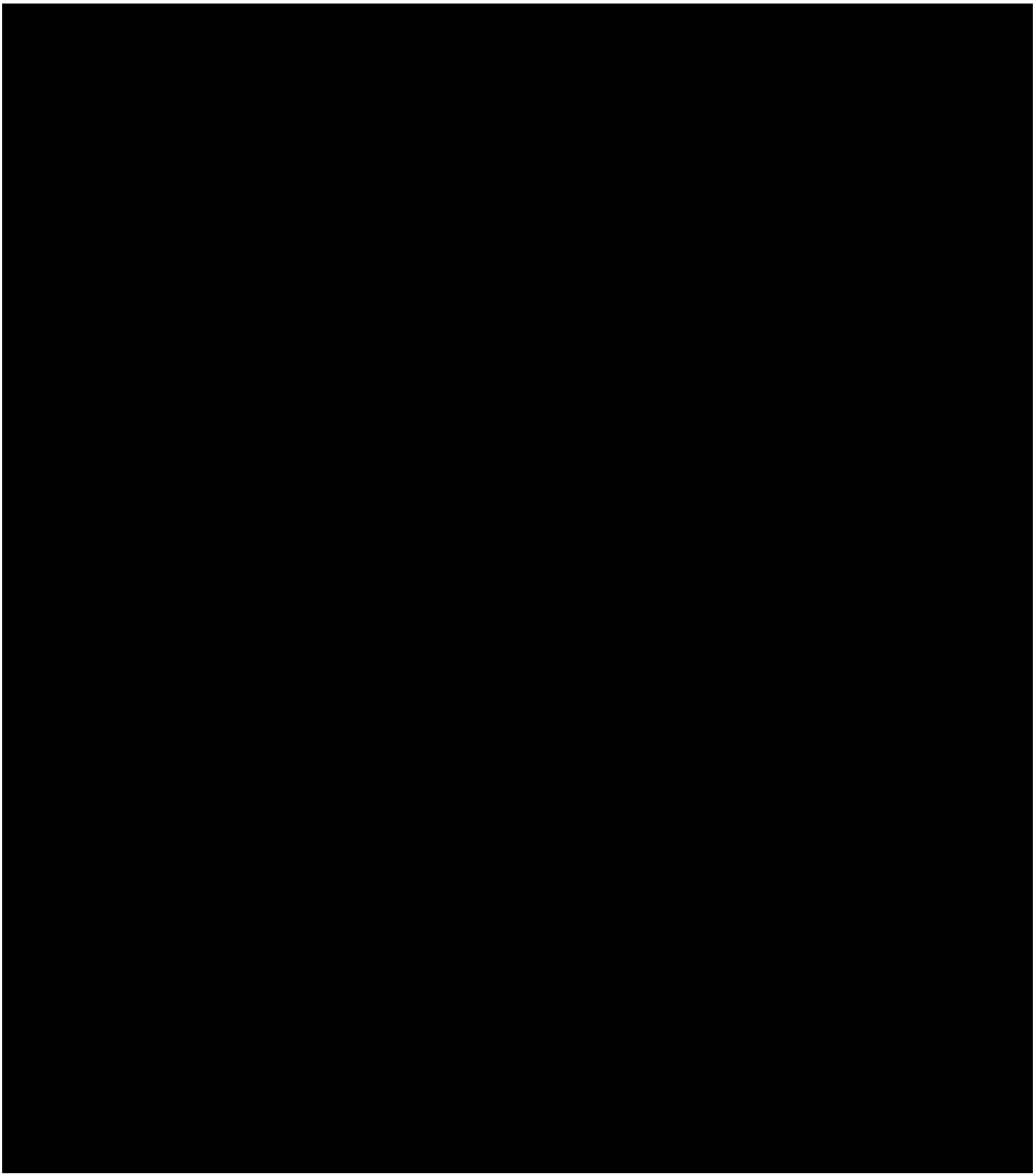

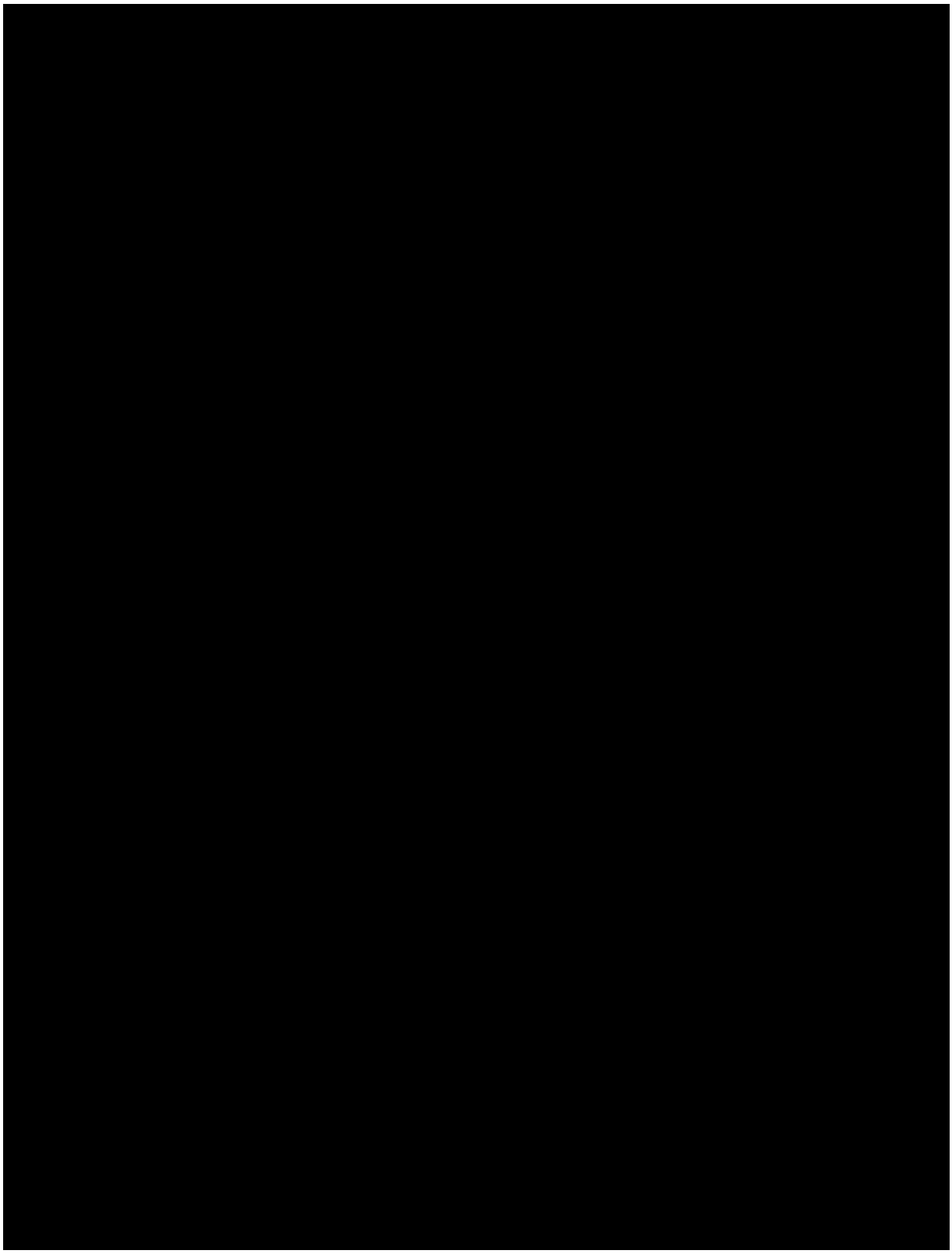

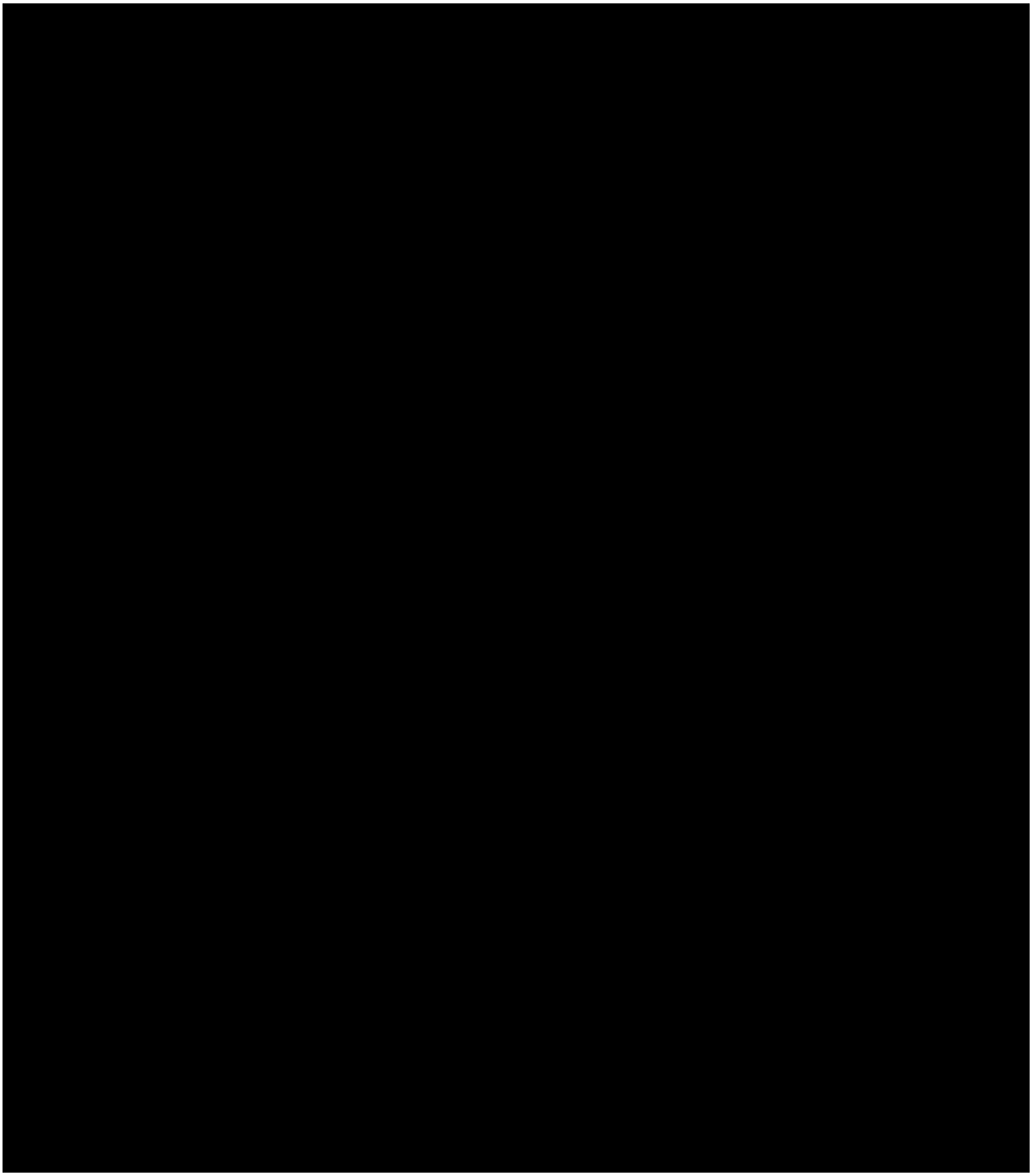

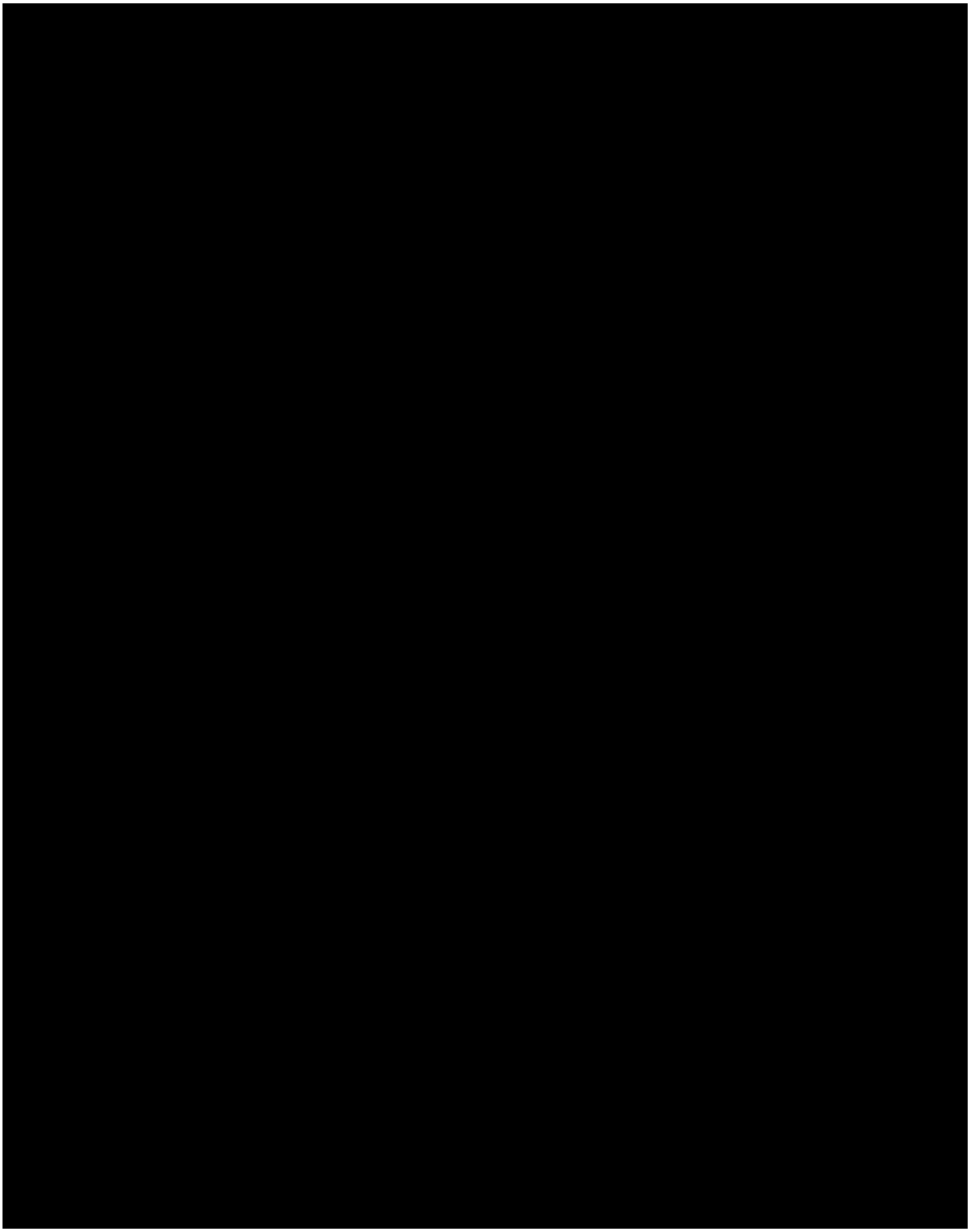

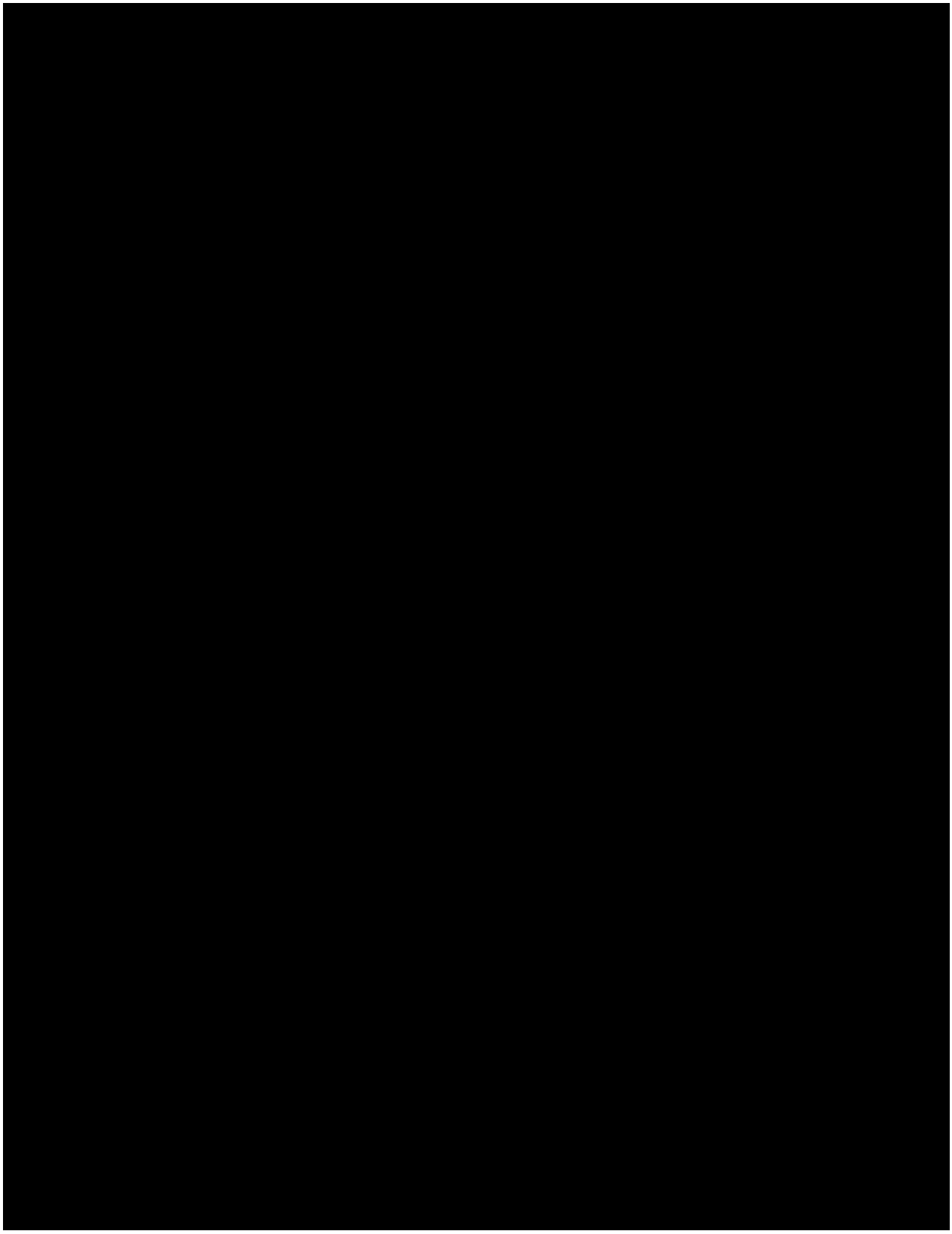

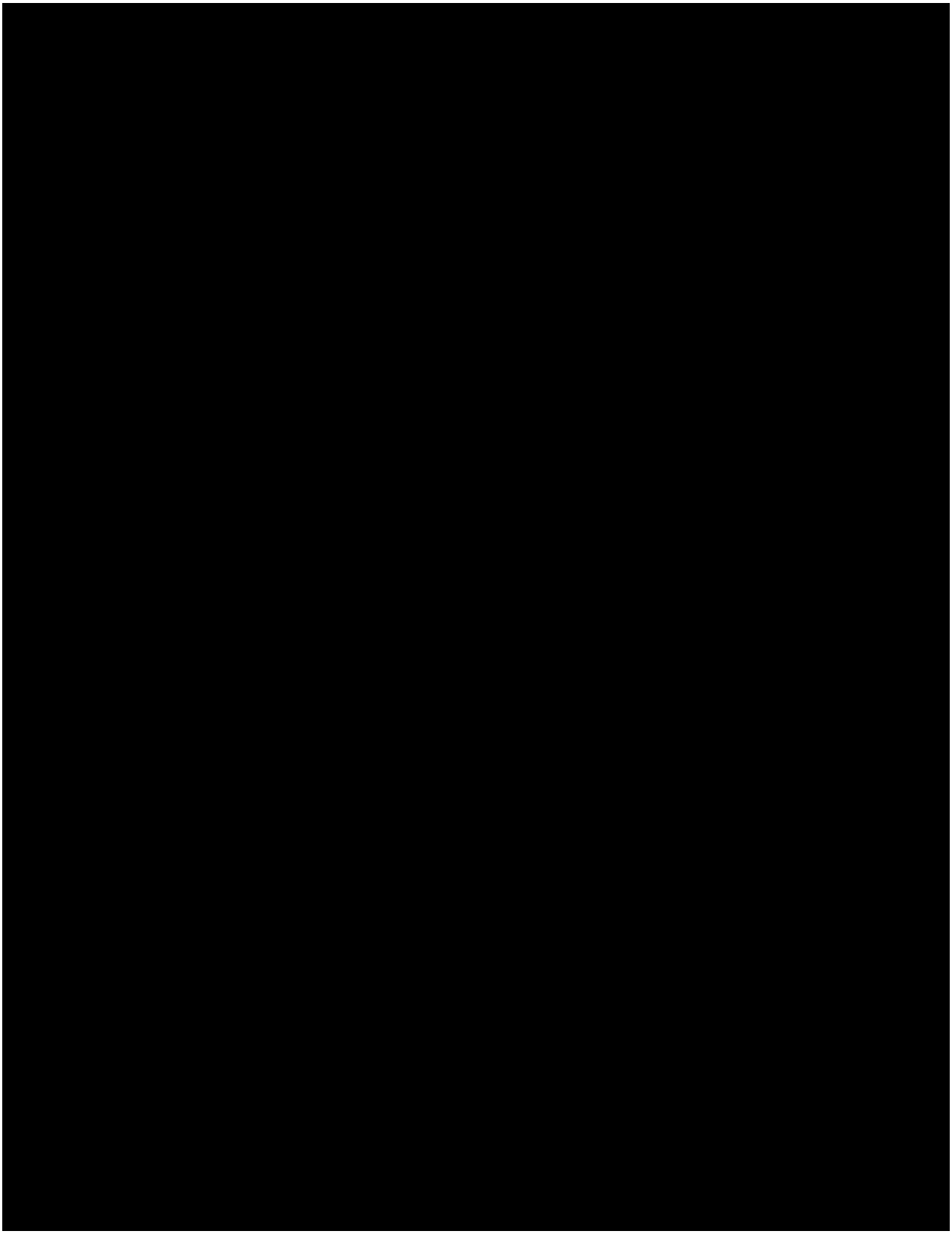

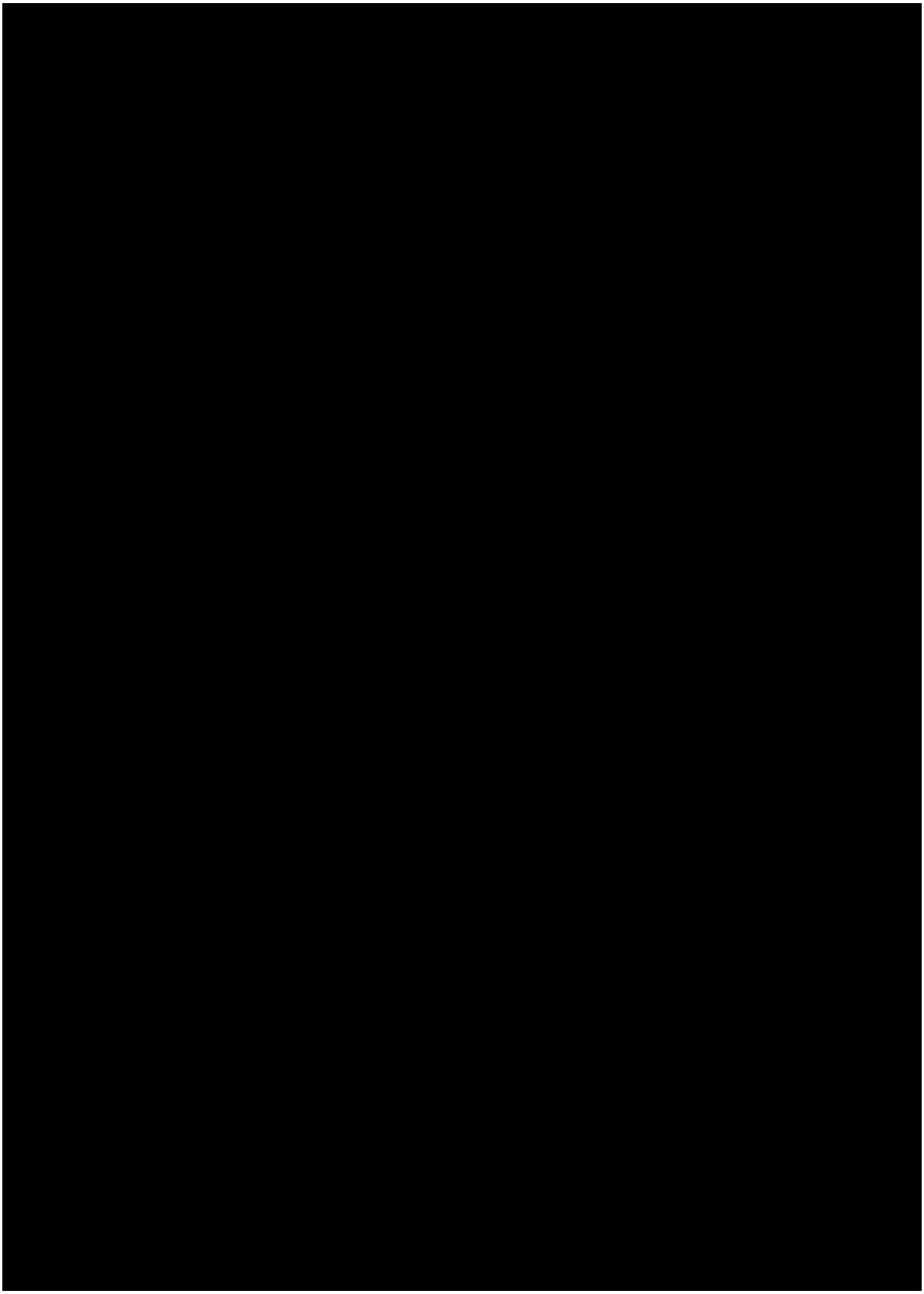

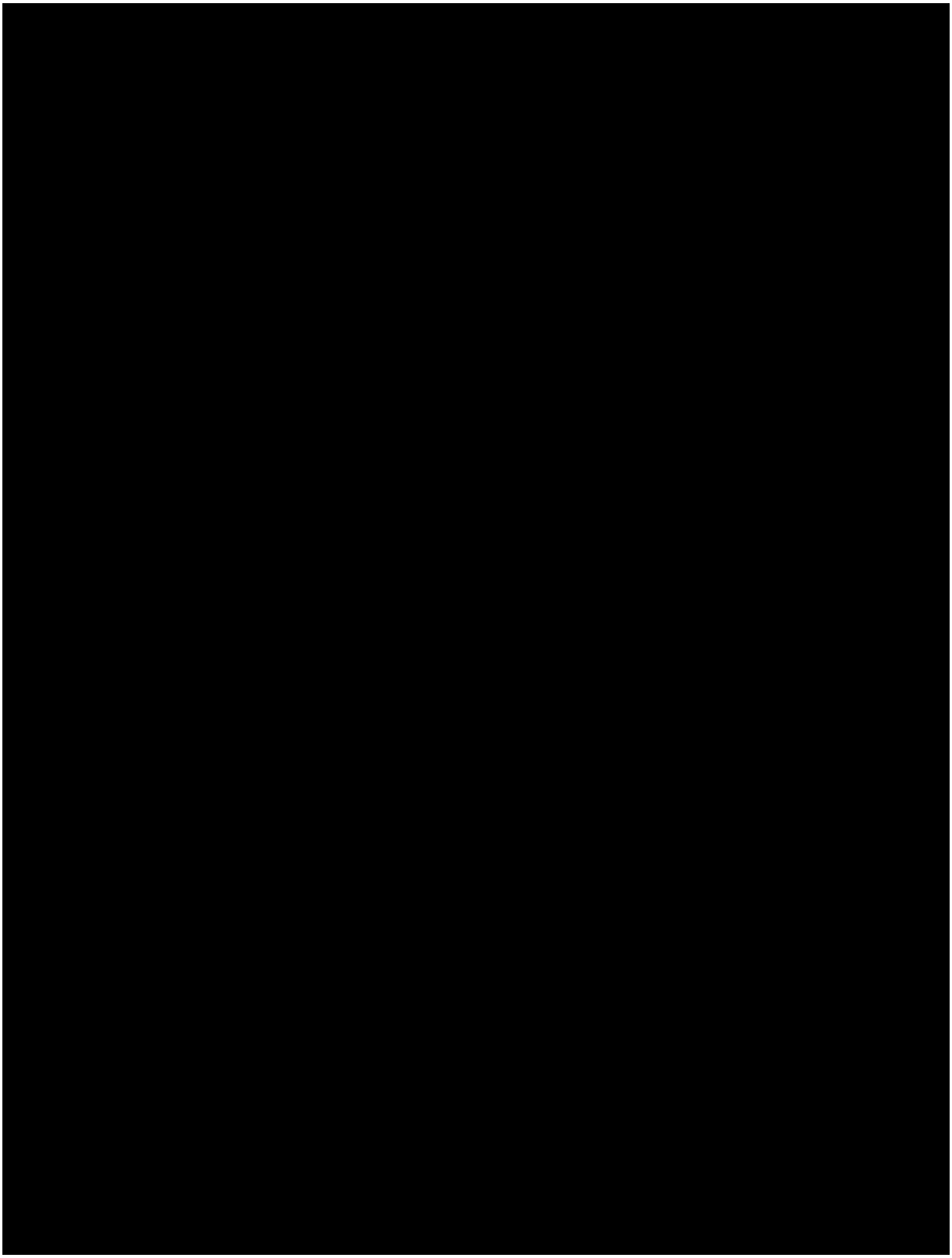

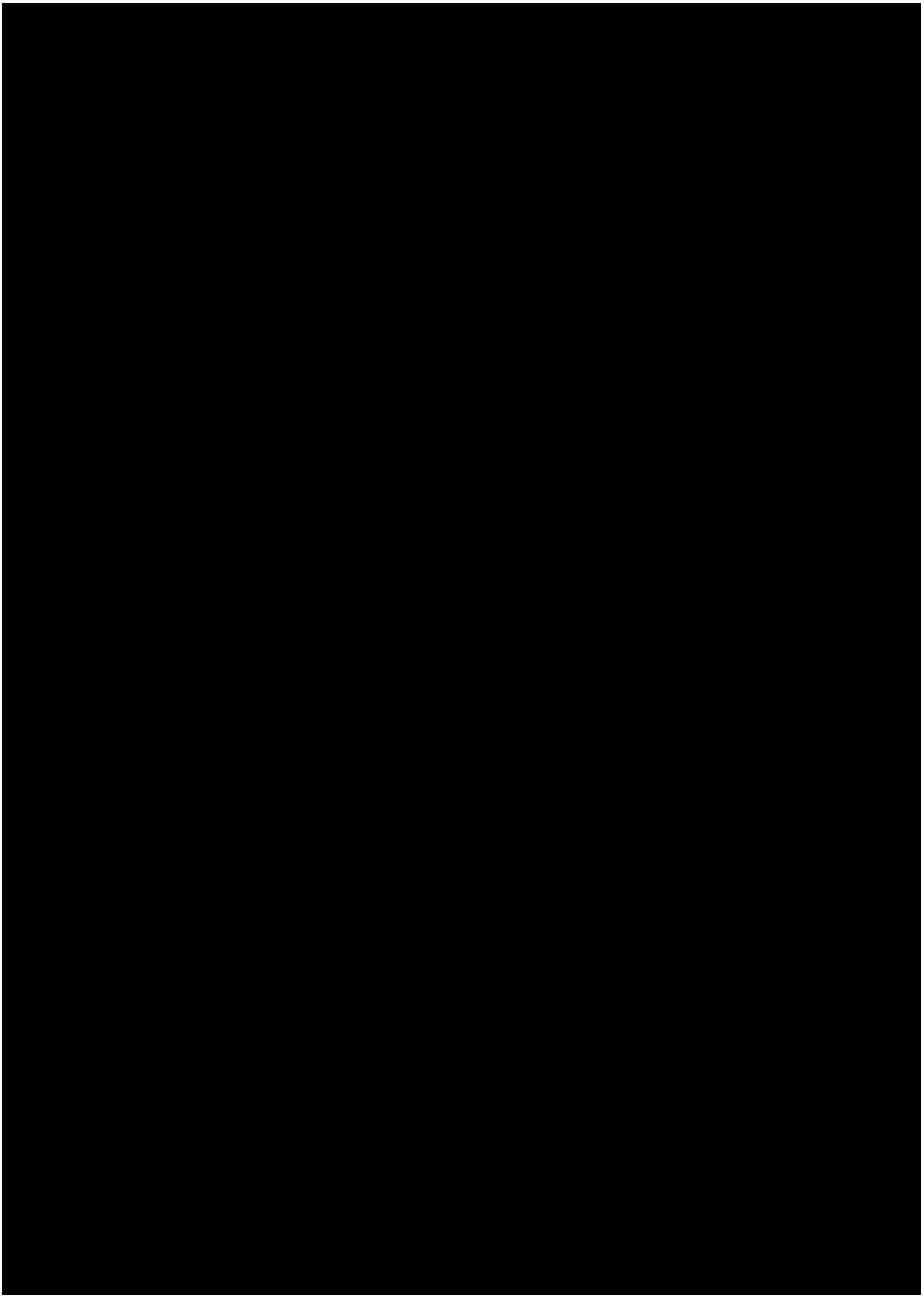

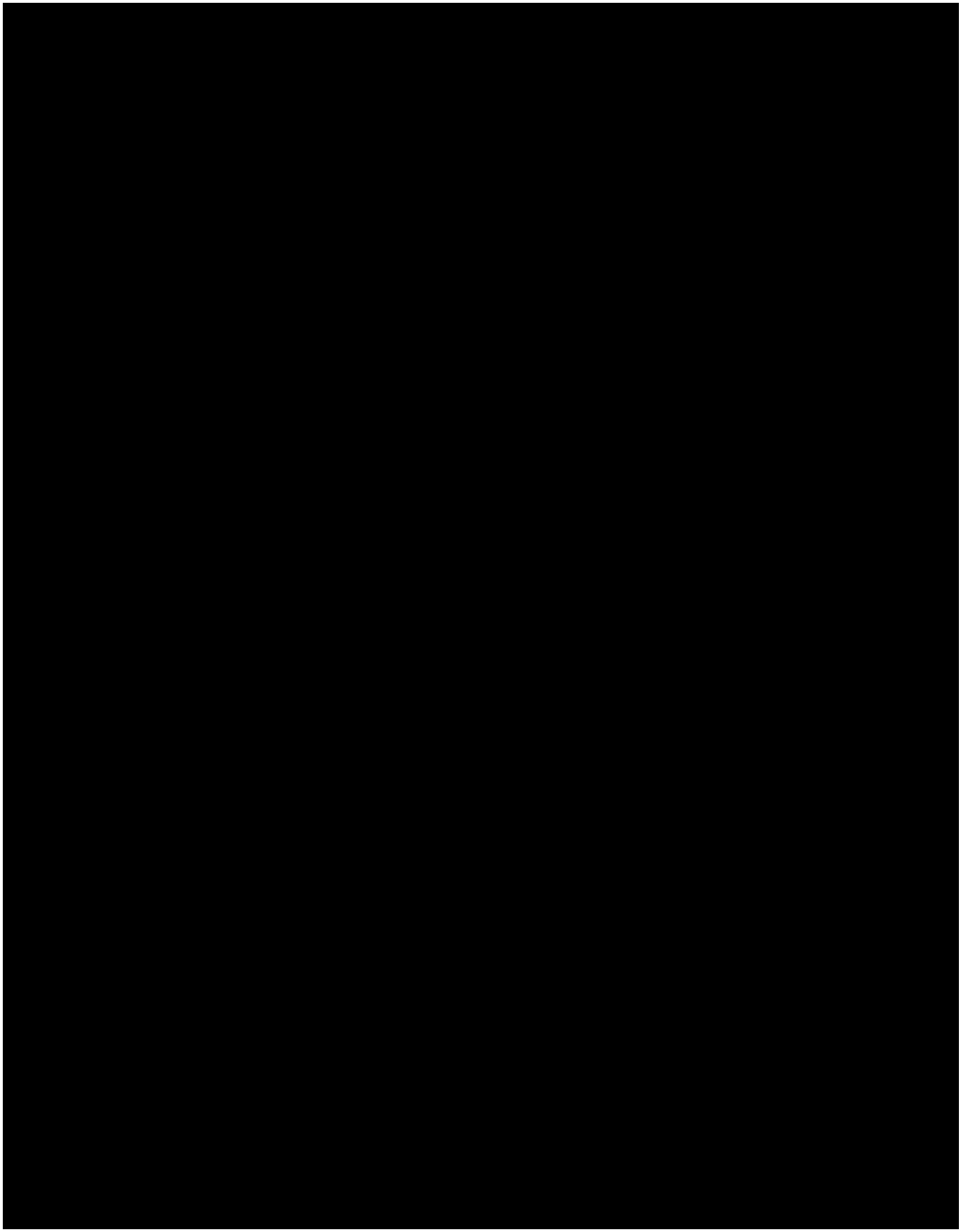

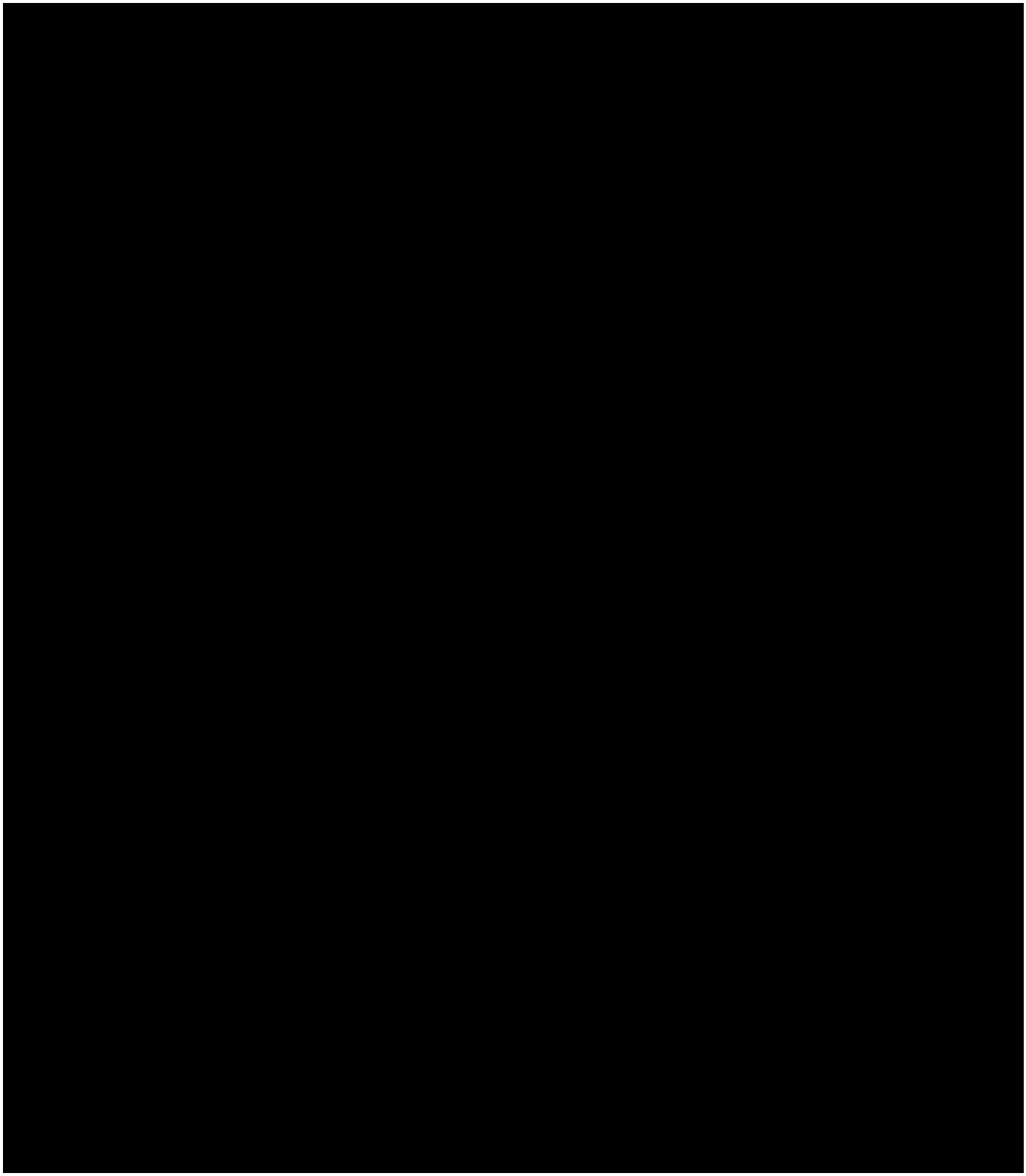

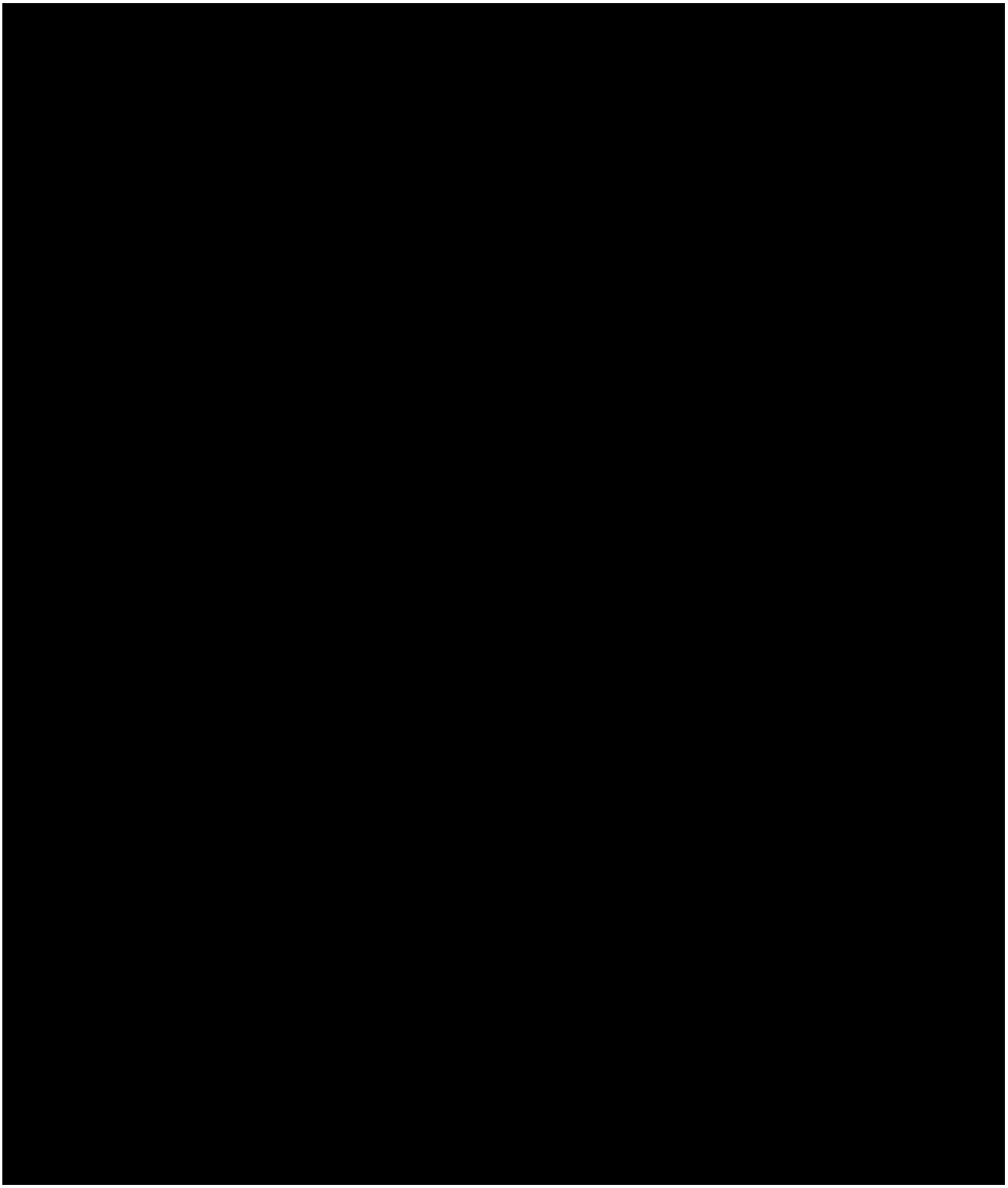

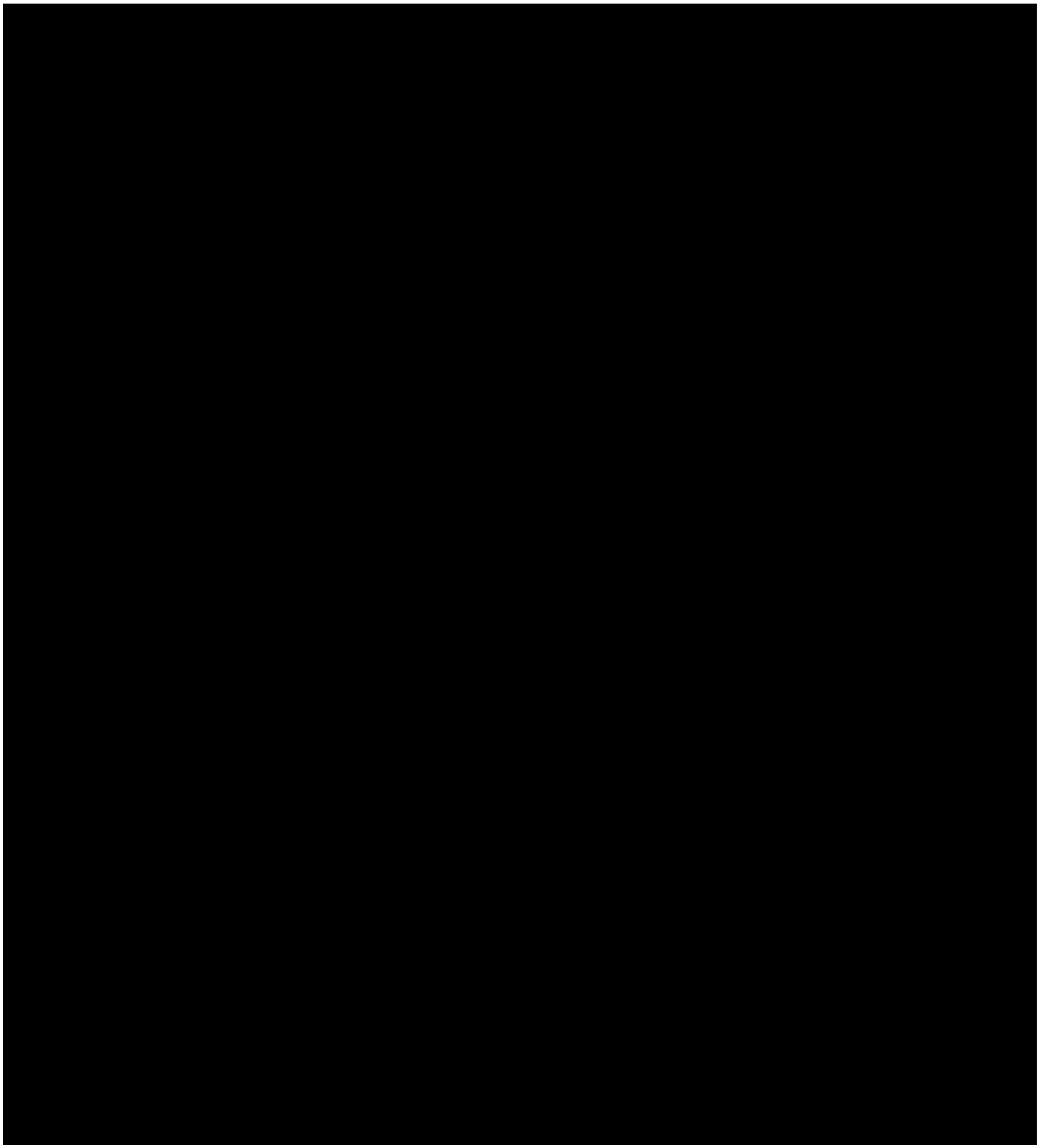

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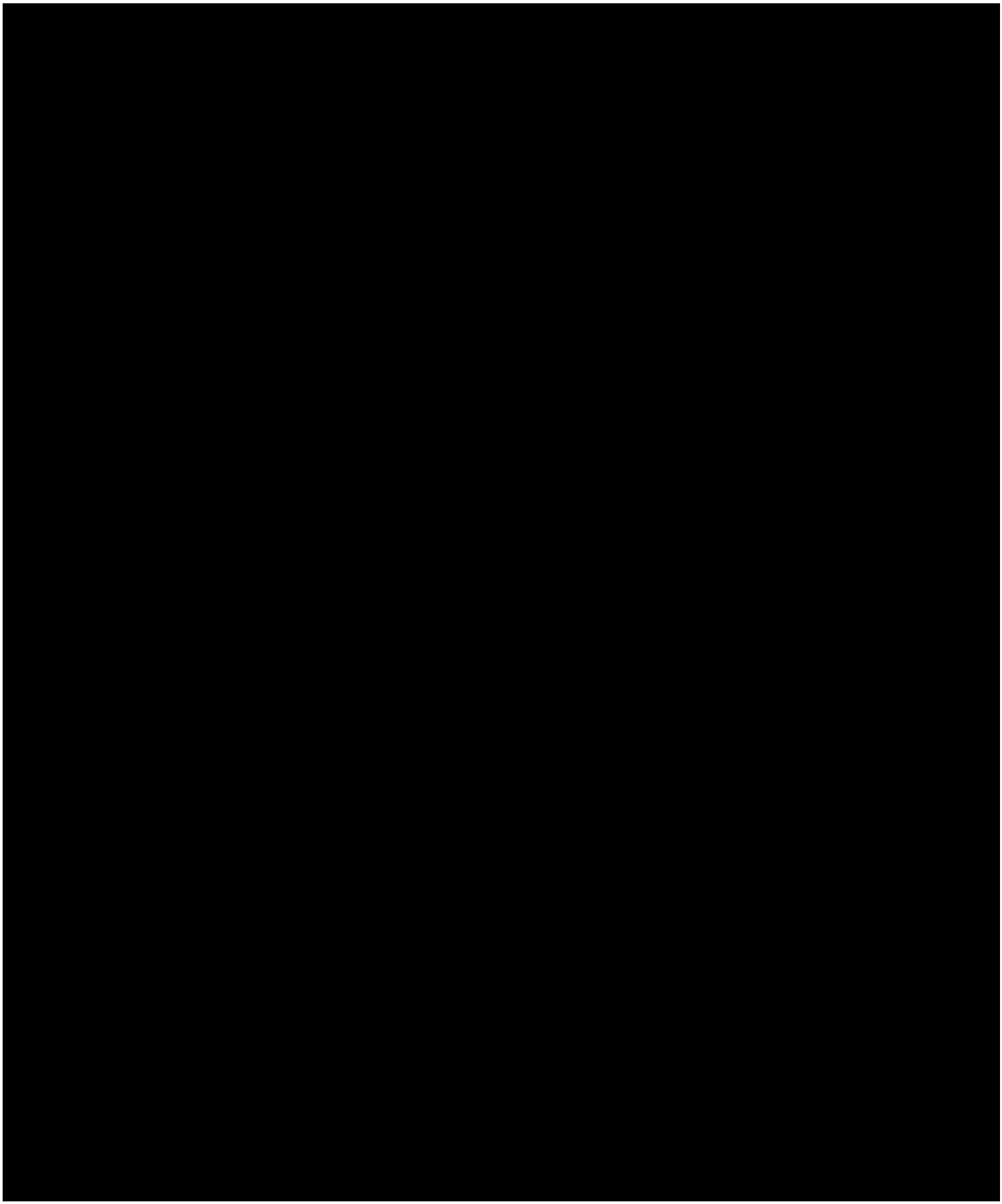

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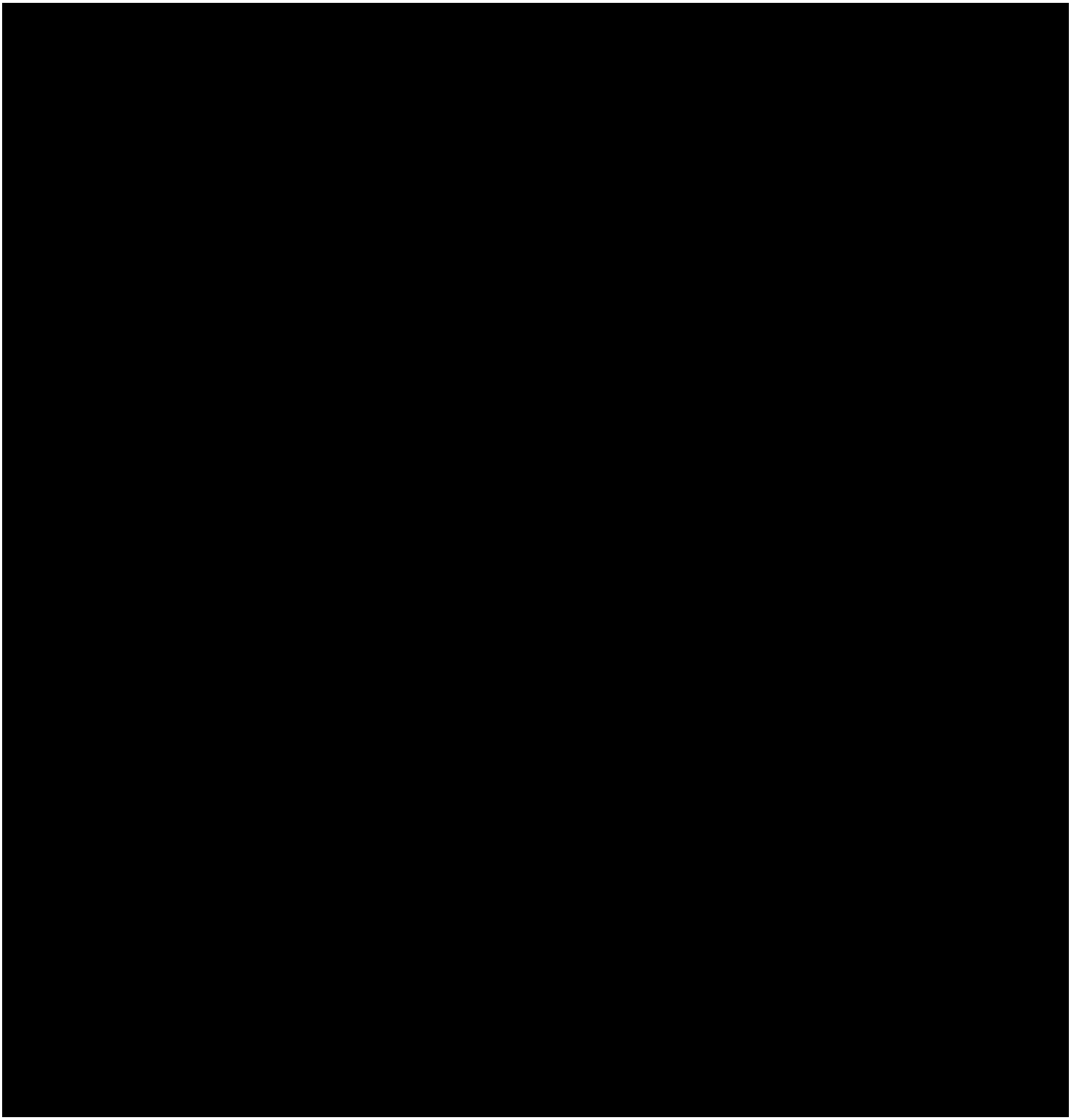

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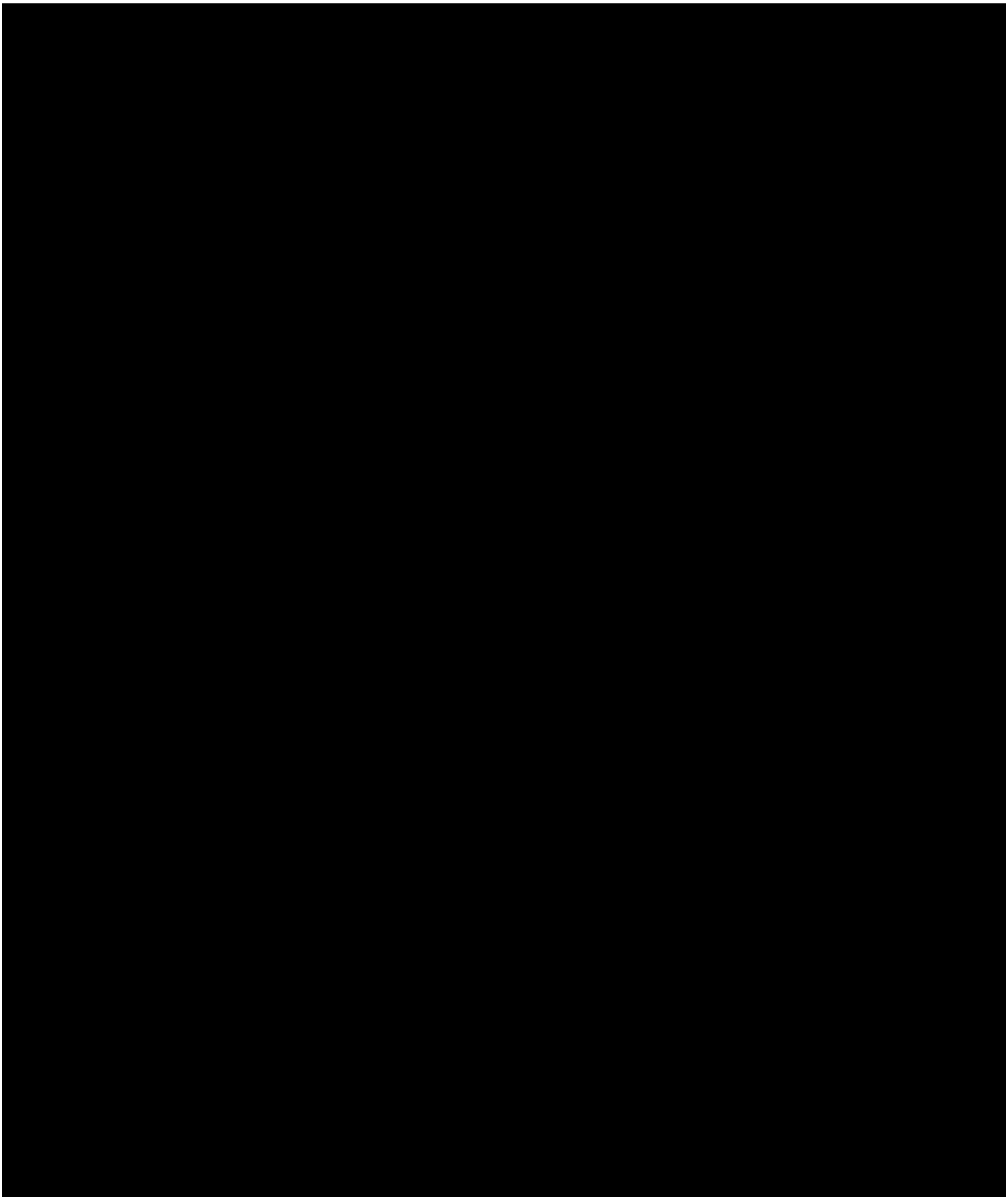

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