NCT02951988

Study ID: RAP-MD-04

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in the Prevention of Relapse in Patients With Major Depressive Disorder

Protocol Amendment 2: 06 Nov 2018

1.0 TITLE PAGE

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A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in the Prevention of Relapse in Patients with Major Depressive Disorder

RAP-MD-04

IND # 107, 974

Original Protocol Date:	04 May 2016
Amendment 1:	29 Sep 2016
Amendment 2:	***06 Nov 2018***

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

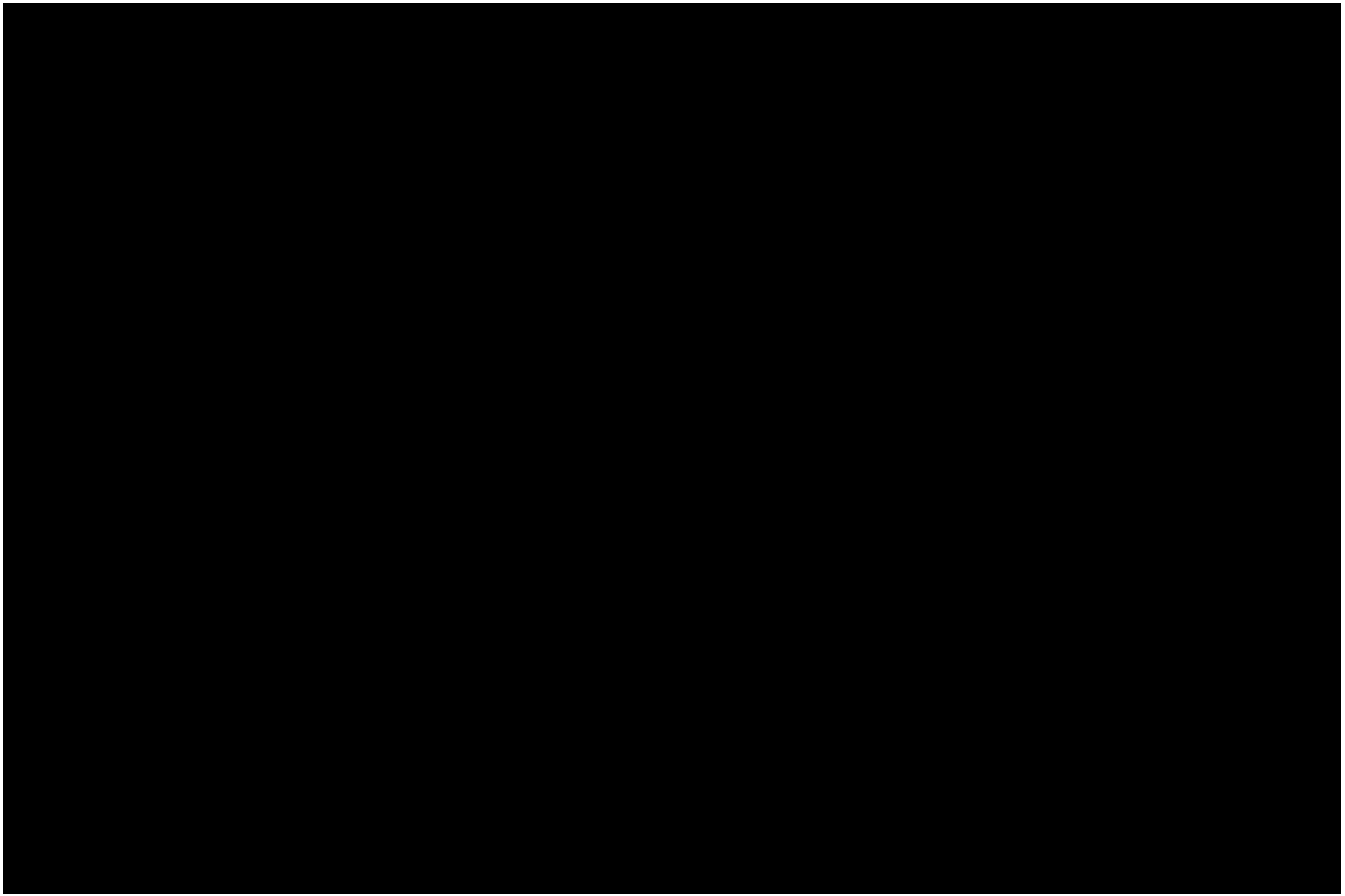
CLINICAL STUDY SYNOPSIS: Study RAP-MD-04	
Title of Study	A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in the Prevention of Relapse in Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 105 to 110 study centers (United States)
Development Phase	3
Objective	To evaluate the efficacy, safety, and tolerability of rapastinel relative to placebo in the prevention of relapse in patients with major depressive disorder (MDD)
Methodology	This study comprises the following periods: • An 8- to 16-week, open-label treatment period (OLTP) during which patients will receive 450 mg intravenous (IV) rapastinel once weekly adjunctive to ongoing antidepressant therapy (ADT) to identify stable responders. Individual treatment duration in the period will be at least 8 weeks and up to 16 weeks to accommodate variability among patients and adequately identify stable responders (patients treated for a minimum of 8 weeks and meet response criteria for at least 6 weeks) • A 26- to 104-week, double-blind randomized-withdrawal period during which stable responders from the open-label period will be randomized (1:1:1) to 1 of 3 double-blind treatment arms: o Weekly adjunctive IV administration of 450 mg rapastinel o Adjunctive IV administration of 450 mg rapastinel once every 2 weeks o Weekly adjunctive IV administration of placebo Individual double-blind treatment period (DBTP) durations will vary with a minimum duration of 26 weeks and a maximum duration of 104 weeks (the study ends when all randomized patients have either met relapse criteria, early terminated for other reasons, or completed 26 weeks of the double-blind treatment period [DBTP]). Upon completion of the DBTP, patients will be eligible to enroll in the open-label safety extension study, RAP-MD-06. The last visit in the DBTP will become the first visit of Study RAP-MD-06 for such patients. Patients who do not enroll in RAP-MD-06 will enter a 2-week safety follow-up period.

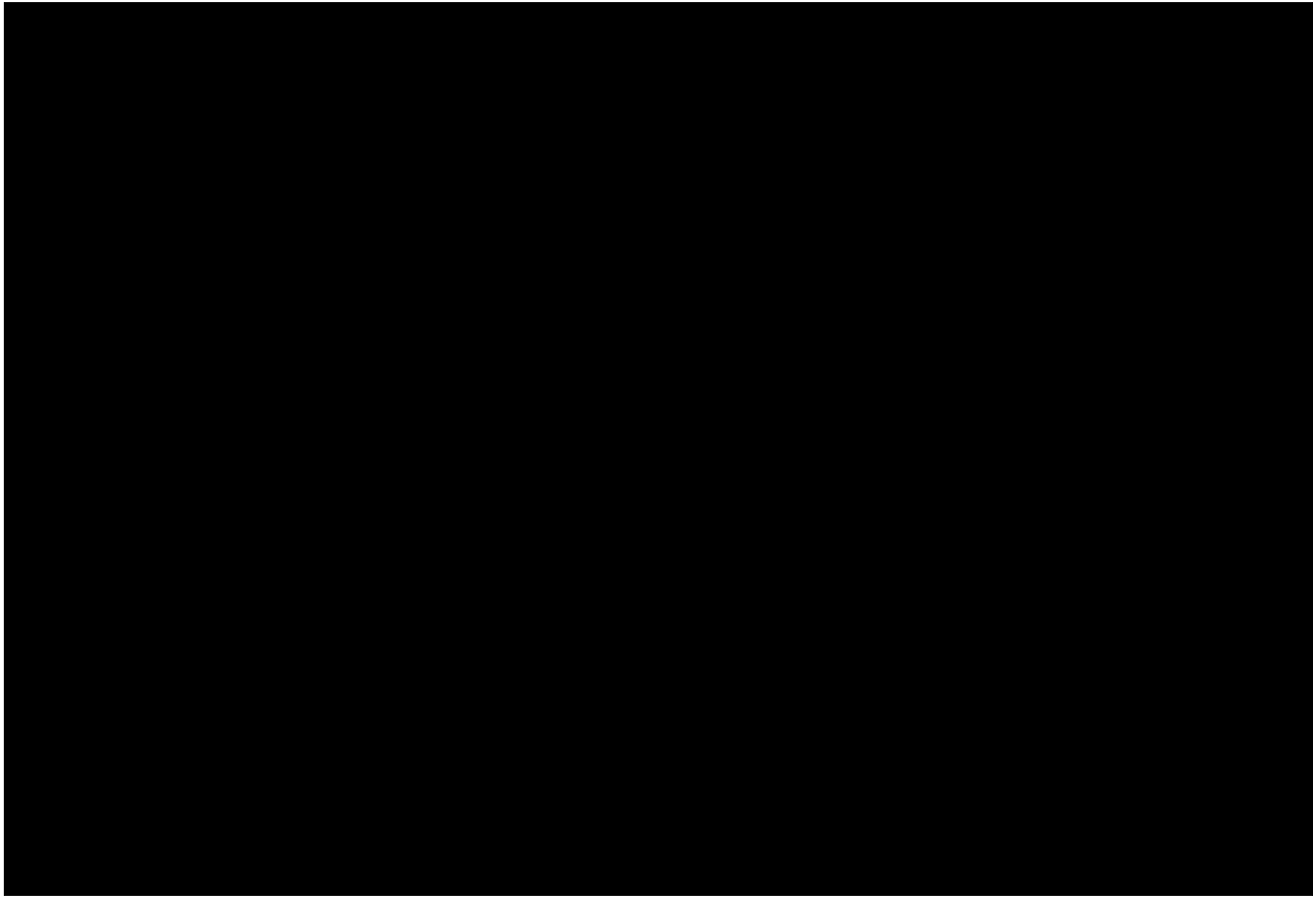
Number of Patients	Approximately 1500 planned to be enrolled in the OLTP; approximately 600 planned to be randomized during the DBTP
Diagnosis and Main Criteria for Inclusion	*Patients who completed lead-in studies* RAP-MD-01, RAP-MD-02, and RAP-MD-03 (*rollover patients*) are considered to have met inclusion criteria for diagnosis, severity, and prior ADT response and are not required to meet these criteria upon entry into RAP-MD-04. *De novo* patients may be considered for enrollment if enrollment of rollover patients does not meet targeted projections. Entry criteria for *de novo* patients are as follows: • Male and female outpatients, ages 18 to 65 years, who meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria for MDD with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1 [redacted] • Have no more than partial response (< 50% improvement) to ongoing treatment with a protocol-allowed ADT ([redacted]
Test Product, Dosage, and Mode of Administration	During the OLTP: Rapastinel 450 mg IV administered weekly as adjunctive to ongoing ADT. During the DBTP: Rapastinel 450 mg IV administered weekly or administered once every 2 weeks (IV placebo will be given on alternating weeks to patients randomized to this once-every-2-weeks rapastinel group)

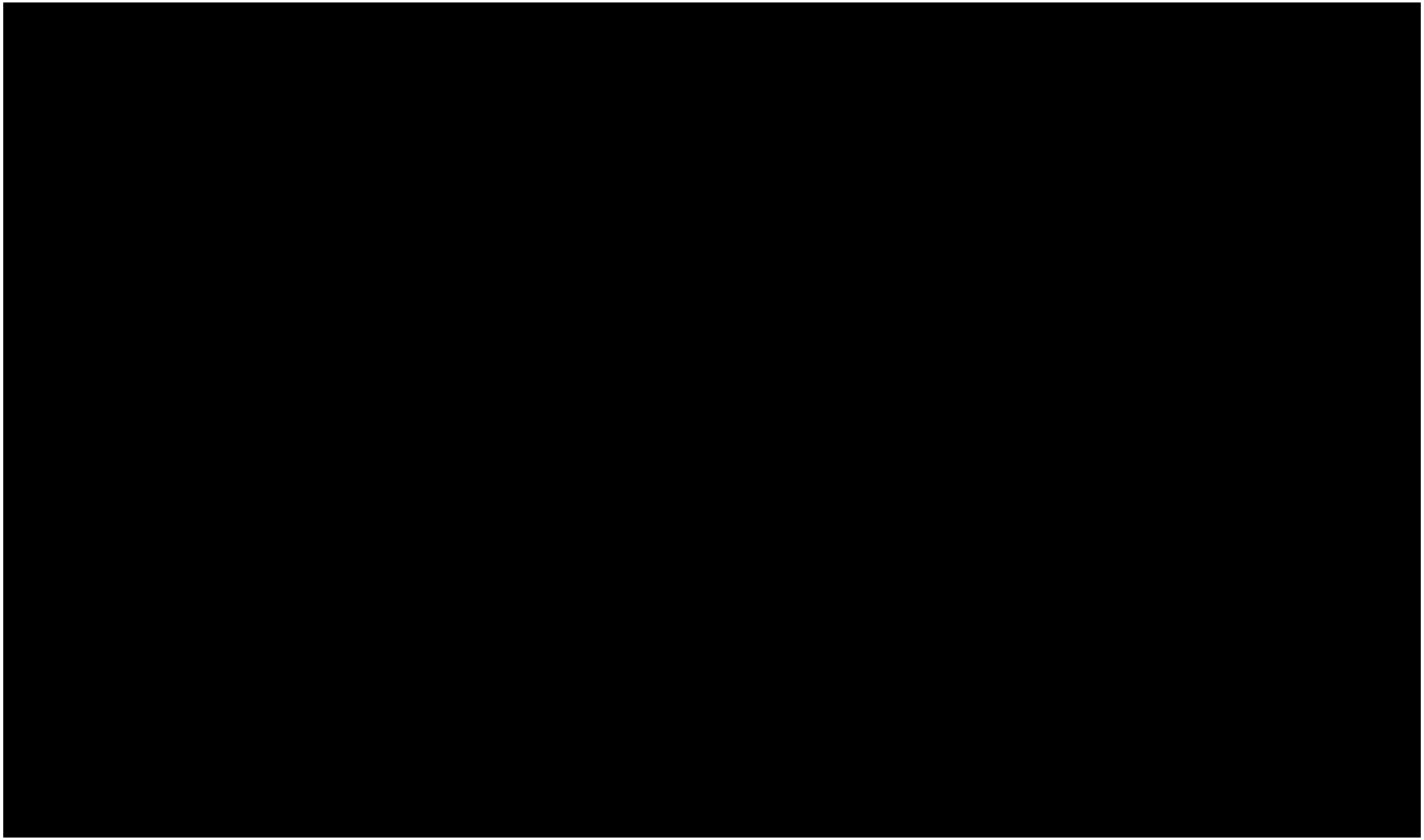
Duration of Treatment	An 8- to 16-week open-label period; a variable double-blind period with a minimum duration of 26 weeks and a maximum duration of 104 weeks (the study ends when all randomized patients have either met relapse criteria, early terminated for other reasons, or completed 26 weeks of the DBTP); and a 2-week safety follow-up period
Reference Therapy, Dosage, and Mode of Administration	IV administration of placebo as adjunctive to ongoing ADT, weekly
Criteria for Evaluation	
Primary Efficacy Endpoint	Time to first relapse during the first 52 weeks of the DBTP, defined as the number of days from the randomization date to the relapse date. Relapse during the DBTP is defined as meeting 1 or more of the following criteria within 52 weeks of randomization: o MADRS total score ≥ 18 at 2 consecutive visits, or o A ≥ 2 increase in Clinical Global Impressions-Severity (CGI-S) score compared with that obtained at randomization, or o Risk of suicide as determined by the Investigator, or o Need for hospitalization due to worsening of depression as determined by the Investigator, or o Need for alternative treatment of depressive symptoms as determined by the Investigator
Secondary Efficacy Endpoint	Time to first relapse during the entire DBTP, defined as the number of days from the randomization date to the relapse date. Relapse during the DBTP is defined as meeting 1 or more of the following criteria: o MADRS total score ≥ 18 at 2 consecutive visits, or o A ≥ 2 increase in CGI-S score compared with that obtained at randomization, or o Risk of suicide as determined by the Investigator, or o Need for hospitalization due to worsening of depression as determined by the Investigator, or o Need for alternative treatment of depressive symptoms as determined by the Investigator
[redacted]	[redacted]

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

[redacted]	[redacted]
Statistical Methods	The primary and secondary efficacy analyses will compare the time to relapse between placebo and rapastinel groups in the respective time-frame (within the first 52 weeks of the DBTP for the primary endpoint and during the entire DBTP for the secondary endpoint) using the log-rank test using the Double-blind ***modified*** Intent-To-Treat (***m***ITT) Population. Estimates of the hazard ratio and 95% confidence intervals will be based on the Cox proportional hazards model with treatment group as an explanatory variable. The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves. All safety parameters will be analyzed descriptively for the Open-label Safety Population and the Double-blind Safety Population. The Open-label Safety Population will consist of all patients ***who signed the informed consent form (ICF) if they participated in the lead-in studies, and all de novo patients who signed the ICF and underwent OLTP Screening Visit procedures and receive*** at least 1 dose of ***open-label rapastinel*** during the OLTP ***of the study***. The Double-blind Safety Population will consist of all patients ***in the Open-label Safety Population who are randomized to a treatment group during the DBTP of the study and receive*** at least 1 dose of IP ***during the DBTP.*** ***The Open-label ITT population will consist of all patients in the Open-label Safety Population who have at least 1 postbaseline assessment of the MADRS during the OLTP of the study.*** The Double-blind ***m***ITT Population will consist of all patients in the Double-blind Safety Population.







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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	human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
DALY	disability-adjusted life-year
DBTP	double-blind treatment period
DSMB	Data Safety Monitoring Board
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 of 1996
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
IWRS	interactive web response system
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
mITT	modified Intent-to-Treat
NEAE	newly emergent adverse event
NMDAR	N-methyl-D-aspartate receptor
OLTP	open-label treatment period
PCS	potentially clinically significant
PID	patient identification
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{1/3}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	standard deviation
[redacted]	[redacted]
SDMT	Symbol Digit Modalities Test
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

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 Part 312 of the US CFR.

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

7.1 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 a 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 and a leading cause of disability in the world.

7.2 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). Clearly, there remains a critically important unmet medical need for this patient population.

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 to 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.

7.3 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.

7.4 RAPASTINEL AS A NOVEL APPROACH TO THE 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 2 Phase 2 clinical studies in patients with MDD, single IV doses of rapastinel at 5 mg/kg and10 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 those of ketamine 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.

As rapastinel constitutes a fundamentally novel approach to the treatment of depression, the best practice for the long-term use of rapastinel, particularly as an adjunctive treatment, is not comprehensively characterized at this time. The purpose of this study is to evaluate the safety, tolerability, and efficacy of rapastinel, administered as an IV injection at a dose of 450 mg weekly or 450 mg once every 2 weeks, as an adjunctive treatment to ongoing ADT in patients with MDD. Specifically, this study is designed to assess whether rapastinel is superior to placebo in maintaining clinical response in stabilized patients. The data gathered in this study are expected to provide substantial empirical evidence to address several questions with regard to the durability of treatment effect following acute and long-term treatment, the safety and tolerability of long-term treatment, and the effect of varying the treatment frequency after initial stabilization. This study is intended to support an application for regulatory approval of rapastinel as an adjunctive treatment for MDD.

8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and tolerability of rapastinel relative to placebo in the prevention of relapse in patients with MDD.

Efficacy Objectives

- Primary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV weekly or once every 2 weeks) versus placebo in the maintenance treatment of MDD as an adjunctive treatment to ongoing ADT, as measured by time to relapse during the first 52 weeks of the double-blind treatment period (DBTP)

- Secondary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV weekly or once every 2 weeks) versus placebo in the maintenance treatment of MDD as an adjunctive treatment to ongoing ADT, as measured by time to relapse during the DBTP

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

Study RAP-MD-04 is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of rapastinel as long-term maintenance treatment for patients with MDD who either completed 1 of the rapastinel lead-in studies (RAP-MD-01, RAP-MD-02, or RAP-MD-03) or who are *de novo* patients (patients who did not participate in one of the lead-in studies). Enrollment of *de novo* 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:

- A screening period of up to 14 days (for *de novo* patients only)
- An 8- to 16-week open-label treatment period (OLTP)
- A randomized DBTP of at least 26 weeks (and up to 104 weeks)
- A 2-week safety follow-up period (for patients who do not enter the RAP-MD-06 extension study only)

Individual treatment durations will vary, as patients enrolled early in the study will be allowed to continue double-blind treatment until a relapse occurs or the study is terminated. The maximum duration of the study will be 104 weeks (the study ends when all randomized patients have either met relapse criteria, early terminated for other reasons, or completed 26 weeks of the DBTP).

Figure 9.1–1 and Figure 9.1–2 provide study design schematics for rollover and *de novo* patients, respectively. The schedules of evaluations for the OLTP and DBTP are presented in Section 2.0. Detailed descriptions of the procedures conducted at each study visit can be found in Section 9.5.5.

9.1.1 Screening *Period*

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

- For completers of 1 of the lead-in studies RAP-MD-01, RAP-MD-02, or RAP-MD-03 (rollover patients), the final/Early Termination (ET) visit of the lead-in study will serve as the Screening Visit/Visit 1 for RAP-MD-04. Rollover patients will receive the first dose of open-label investigational product (IP) (ie, rapastinel 450 mg IV) at Visit 1 of the OLTP to ensure continuity of treatment.

- Upon providing written informed consent, *de novo* patients will enter a screening period of up to 14 days. Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate patient and study center schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period and the rater-administered MADRS and computer-administered MADRS must be collected on the same date. Following the screening period, patients enter the 8- to 16-week OLTP.

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

9.1.2 Open-Label Treatment Period

Approximately 1500 patients are planned for enrollment in the OLTP to achieve 600 randomized patients in the DBTP. When 600 patients are randomized into the DBTP, enrollment in the OLTP will be closed.

The OLTP consists of weekly visits for at least 8 weeks (and up to 16 weeks). During this period, patients will be treated with weekly IV injections of 450 mg rapastinel in addition to the continued unchanged ADT. The purpose of this period is to identify stable responders who will be eligible for the randomized-withdrawal period.

A patient will be considered a stable responder upon achieving both:

- MADRS total score ≤ 12 with no more than 1 modest MADRS excursion (MADRS > 12 but ≤ 16) during 6 consecutive weeks, and
- MADRS total score ≤ 12 for 2 consecutive visits prior to randomization

Stability criteria may be met at any point from Study Week 7 to Study Week 15 for rollover patients and at any point from Study Week 8 to Study Week 16 for *de novo* patients.

Patients who do not meet stability criteria within these timeframes will undergo the End-of-Treatment/Early Termination assessments (Visit 122/Week 104/ET) at their last OLTP visit and will exit the study. Such patients are eligible to enroll in the Open-label Safety Extension study RAP-MD-06. The last visit in End-of-Treatment/Early Termination (Visit 122/Week 104/ET) will be the first visit of the Study RAP-MD-06 for such patients.

Patients who discontinue from RAP-MD-04 and do not enroll in RAP-MD-06 will enter a 2-week safety follow-up period.

9.1.3 Double-blind Treatment Period

Approximately 600 patients are planned for randomization in the DBTP.

Upon meeting stability criteria, patients will enter the DBTP. Each patient entering the DBTP will be randomized 1:1:1 to either adjunctive weekly IV administration of 450 mg rapastinel, adjunctive IV administration of 450 mg rapastinel once every 2 weeks (with weekly IV administration of placebo to maintain blinding of the overall treatment regimen), or weekly IV administration of placebo.

Patients will be monitored for relapse events defined as meeting any of the following criteria:

- MADRS total score ≥ 18 at 2 consecutive MADRS assessments
- ≥ 2 increase in CGI-S score compared with that obtained at randomization
- Risk of suicide as determined by the Investigator
- Need for hospitalization due to worsening of depression as determined by the Investigator
- Need for alternative treatment (including dose increase of background ADT) of depressive symptoms as determined by the Investigator

Upon meeting any of the relapse criteria at any visit in the DBTP, the patient will be considered a completer and the Visit 122/ET Visit procedures should be conducted.

Each randomized patient will be treated until relapse criteria are met or until he/she has completed a minimum of 26 weeks of double-blind treatment. Individual treatment durations will vary, as patients enrolled early in the study will be allowed to continue double-blind treatment until a relapse occurs or up to a maximum of 104 weeks of double-blind treatment. The study will be terminated when all randomized patients have either met relapse criteria, early terminated for other reasons, or completed 26 weeks of the DBTP.

Upon completion of the DBTP, patients will be eligible to enroll in the open-label safety extension study, RAP-MD-06. The last visit in the DBTP will become the first visit of Study RAP-MD-06 for such patients. Patients who do not enroll in Study RAP-MD-06 will enter a 2-week safety follow-up period.

9.1.4 Safety Follow-up Period

All patients who complete or discontinue from the OLTP or the DBTP and who do not enroll in Study RAP-MD-06 will enter a 2-week safety follow-up period.

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

The placebo-controlled withdrawal design is considered standard to demonstrate effectiveness of long-term maintenance treatment.

The 8- to 16-week OLTP was designed to ensure sustained response following continued adjunctive rapastinel treatment. The double-blind design is included to minimize systematic bias resulting from the scale raters, patient, or Investigator knowing the treatment being administered. Randomization at the beginning of the DBTP is expected to minimize patient selection bias and increase baseline comparability of the 3 treatment groups.

The use of placebo control is critical to the study design both to understand the safety findings of the drug and to ensure that efficacy results can be interpreted. In this study, the placebo control is used during the DBTP to demonstrate the reemergence of MDD symptoms upon withdrawal of rapastinel compared with patients who continue adjunctive rapastinel treatment. Patients who continue adjunctive rapastinel treatment should maintain improvement in their MDD symptoms, whereas those who switch to placebo should have a return of MDD symptoms.

The variable duration of the DBTP with a maximum of 104 weeks and a minimum of 26 weeks was selected to provide sufficient time to demonstrate MDD relapse upon withdrawal of rapastinel.

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

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Note: For rollover patients who completed one of the lead-in studies (RAP-MD-01, RAP-MD-02, or RAP-MD-03), medical, psychiatric, and medication histories from Visit 1 of the lead-in study will be used. In addition, Inclusion Criteria Nos. 2 to 5 are not applicable to rollover patients.

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

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

3. Meet DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) 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

[redacted]

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

[redacted]

7. 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.

8. Ability to follow study instructions and likely to complete all required visits

9.3.2 Exclusion Criteria

Note: For rollover patients who completed one of the lead-in studies (RAP-MD-01, RAP-MD-02, or RAP-MD-03), 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
    - Posttraumatic stress disorder
    - MDD with psychotic features

[redacted]

[redacted]

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

[redacted]

[redacted]

[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

- Any patient may be withdrawn due to AE at the discretion of the Investigator
- Any patient who meets any of the following criteria at any point during the study must be withdrawn from participation, due to AEs related to suicide:
  - A suicide attempt
  - [redacted]
  - [redacted]

  In the event that a patient is withdrawn for a suicide-related AE, the patient should be referred for additional treatment or hospitalization, as clinically indicated, in addition to withdrawing the patient from the study.

- Lack of efficacy (applicable only to patients in the OLTP)
- 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 OLTP or DBTP, regardless of cause, should be seen for a final assessment at an ET Visit. A *final assessment* will be defined as completion of the evaluations scheduled for all patients at Visit 122. 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 who prematurely discontinue treatment during the OLTP or DBTP will not be replaced.

9.4 TREATMENTS

During the OLTP, all eligible patients will receive open-label, once-weekly IV rapastinel 450 mg. Patients who meet eligibility criteria at the end of the OLTP will be randomized in a double-blind fashion to 1 of 3 treatment groups: once-weekly IV placebo, once-weekly IV rapastinel 450 mg, or IV rapastinel 450 mg once every 2 weeks.

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 lead-in studies RAP-MD-01, RAP-MD-02, or RAP-MD-03 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-04. 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

During the OLTP and DBTP, IP will only be administered to eligible patients by a medically qualified person as per the local state regulations. The range of persons who can administer an IV can be a physician, a physician assistant, nurse, or nurse practitioner, etc, depending on the local and/or state law.

IP should be administered after all efficacy and safety assessments with the exception of the post-dose assessments described below. IP will be administered in a "slow bolus" injection to each study patient in an upper extremity vein within approximately 1 to 2 minutes.

During IP administration and until completion of postadministration assessments, a licensed physician must be immediately available and in close proximity to the patient(s) to attend to medical emergencies ***The facility must have the capabilities, in accordance with the applicable country, local, and/or state regulations and standard of care, to resuscitate a patient in the event of a medical emergency.***

The patient should not be discharged from the study center until the following are completed:

- Postadministration vital sign measures (approximately 15 minutes after administration)
- Patient is clinically assessed and determined to not be at increased risk of suicidality in the opinion of the Investigator (or medically qualified subinvestigator)
- Patient is assessed for mental status and is determined to be free of perceptual disturbances or other conditions that would deem them not ready for discharge from the study center, in the opinion of the Investigator (or medically qualified subinvestigator)
- A physician licensed in the state (Investigator or subinvestigator) determines that they are medically able to leave the study center and provides written sign off not less than 15 minutes following administration (see IV Administration and Discharge Notes document in Program Reference Manual)

9.4.3 Identity of Investigational Product

The following IP will be administered intravenously during this study:

- Rapastinel 450 mg IV Prefilled Syringes: [redacted]
- Placebo rapastinel IV Prefilled Syringes: [redacted]

[redacted]

In addition to contents identified for double-blind IP described above, open-label IP will also present the lot number.

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 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 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] Study centers must report any temperature excursions as described in the Study Reference Manual or contact the Sponsor or its designee for further instructions.

At the end of the study, all IP must be accounted for. In addition, at the end of the study, all unused IP 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

After a patient signs the consent at Screening (Visit 1), study personnel will register the patient in the interactive web response system (IWRS) which will assign the patient a sequential PID number.

All rollover patients will be identified using the same PID that was assigned by the IWRS in the lead-in study.

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 randomized patient at the time of randomization. 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 was based on results from 2 Phase 2 studies of patients with MDD in which single IV doses of rapastinel 5 mg/kg and 10 mg/kg demonstrated marked antidepressant effects within 1 day that lasted for 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.

This study assesses both weekly and once-every-2-weeks dosing regimens. While the GLYX13-C-202 study also assessed the effect of weekly and once-every-2-weeks 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 this more substantial time period of 26 weeks to 2 years is expected to yield a better understanding of the long-term efficacy and 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 at each weekly visit. Patients in the 450 mg once-every-2-weeks treatment arm will receive placebo on intervening weeks to maintain the blinding of the overall treatment regimen.

9.4.7.1 Screening Period

For rollover patients enrolling from one of the lead-in studies, the final visit from the lead-in study will serve as Visit 1 in this study. Rollover patients will receive open-label treatment at Visit 1 to ensure continuity of treatment.

At Visit 1, after written consent is obtained, *de novo* patients will enter a screening period of up to 14 days before entering the OLTP. No IP will be administered to *de novo patients* during the screening period. However, *de novo* patients must continue their background ADT at a stable dose.

9.4.7.2 Open-label Treatment Period

All rollover patients will have received open-label rapastinel at Visit 1 of the OLTP. At Baseline/Visit 2 of the OLTP, additional eligibility criteria will be reviewed for all patients. Rollover and *de novo* patients who meet the Baseline/Visit 2 eligibility criteria will receive open-label IP from Baseline/Visit 2 through open-label Visit 18/Week 16.

Open-label dosing will continue for patients who do not meet stability criteria at open-label Visits 10-18 (Weeks 8-16).

9.4.7.3 Double-blind Treatment Period

Patients will be randomized in a 1:1:1 ratio to receive either weekly IV rapastinel 450 mg, IV rapastinel 450 mg once every 2 weeks, or IV placebo at DBTP Visits 18-121 (Weeks 1-103 for *de novo* patients and Weeks 0-103 for rollover patients).

After all DBTP Baseline/Visit 18 assessments are completed for patients who meet stability criteria, eligible patients will be randomized into the DBTP. The IWRS will assign an IP kit number during the DBTP Baseline visit and at all subsequent DBTP visits. Patients will receive the first dose of double-blind IP at the DBTP Baseline Visit.

9.4.7.4 Safety Follow-up Period

Patients who complete the DBTP or patients who prematurely discontinue from the study should enter the 2-week safety follow-up period. 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

A list of patient randomization codes will be generated by Statistical Programming and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

All study treatments will be provided in identical syringes and cartons to maintain masking of the study.

9.4.9 Unblinding

Any unblinding at the study center level should be done only in an emergency that requires the IP to be identified for the medical management of the patient. The Investigator must notify the Study Physician immediately (refer to Appendix II) and a full written explanation must be provided if the blind is broken. Before the IP is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study center will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Global Drug Safety for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the patient will not need to be disqualified from the study.

For IWRS Unblinding

In an emergency, the Investigator can obtain the treatment assignment of any patient at his or her study center through the IWRS. The Investigator will access the IWRS to break the blind and record the unblinding in the eCRF.

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.

9.4.10.1 Permitted Medications/Treatments

[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 and male partners 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 must be 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 DBTP 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.

9.5.1.2 Efficacy Assessments

All efficacy assessments (MADRS and CGI-S) will be administered 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.

9.5.1.2.1 The Montgomery-Åsberg Depression Rating Scale

The MADRS (Montgomery and Åsberg, 1979) is a clinician-rated scale. The MADRS will be used to assess depressive symptomatology during the past week. Patients are rated on 10 items to assess feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating and lack of interest. Each item will be scored on a 7-point scale. A score of 0 indicates the absence of symptoms, and a score of 6 indicates symptoms of maximum severity. This instrument will be administered by an experienced rater meeting the training requirements and qualifications set by the rater-training vendor.

At each visit with a MADRS assessment, the rater-administered MADRS interview will be audio recorded; a computer-administered MADRS interview will also be completed by patients. The computer-administered interview will involve a series of probe and follow-up questions with multiple-choice response options. At the screening visit of the OLTP, for *de novo* patients only, the computer administered MADRS will be conducted prior to the rater-administered MADRS. At all other visits, the rater-administered MADRS will be conducted first.

9.5.1.2.2 The Clinical Global Impressions-Severity

The CGI-S (Guy, 1976) is a clinician-rated scale used to rate the severity of the patient's current state of mental illness compared with a patient population with MDD. The patient will be rated on a scale from 1 to 7 with 1 indicating a "normal, not at all ill" and 7 indicating "among the most extremely ill patients." The CGI-S will be administered by the Investigator or by a subinvestigator with extensive professional training and experience in assessing mental illness and qualifications standards established by the Sponsor and rater training vendor.

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 below will be completed at 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 ICF was signed 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 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 post-study period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. They are also to be recorded in the eCRF if at least one of the following conditions are met: 1) those that meet the criteria for an SAE (see Sections 9.5.2.1.3 and 9.5.2.1.4), and/or 2) those 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 shown below. 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.

[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 stated in Section 9.5.2.2, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

Any pregnancy of a patient treated with IP (or in female partners of male patients occurring during the time frame described above) 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.

[redacted]

[redacted]

[redacted]

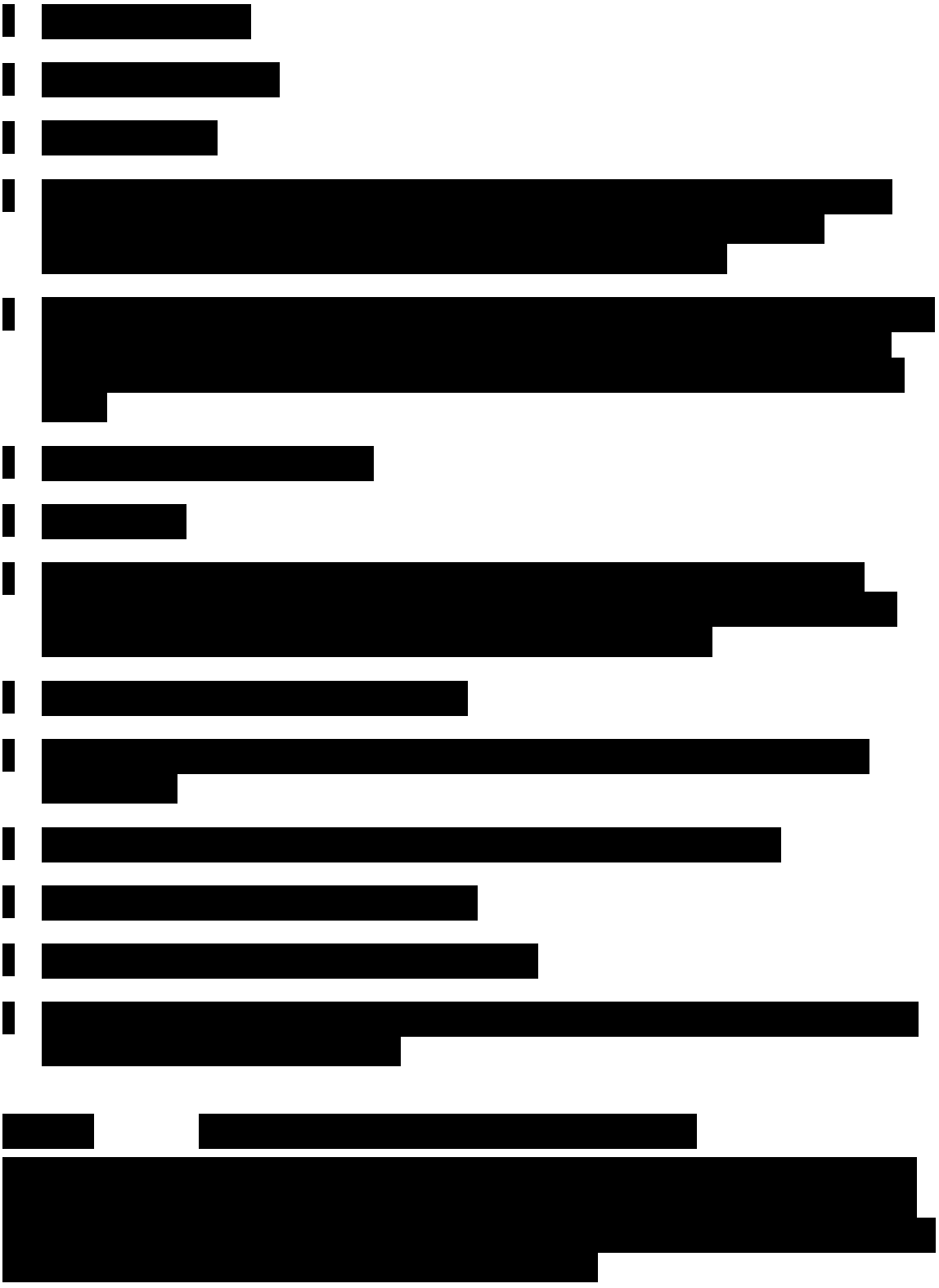
[redacted]

[redacted]

[redacted]

9.5.5 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.



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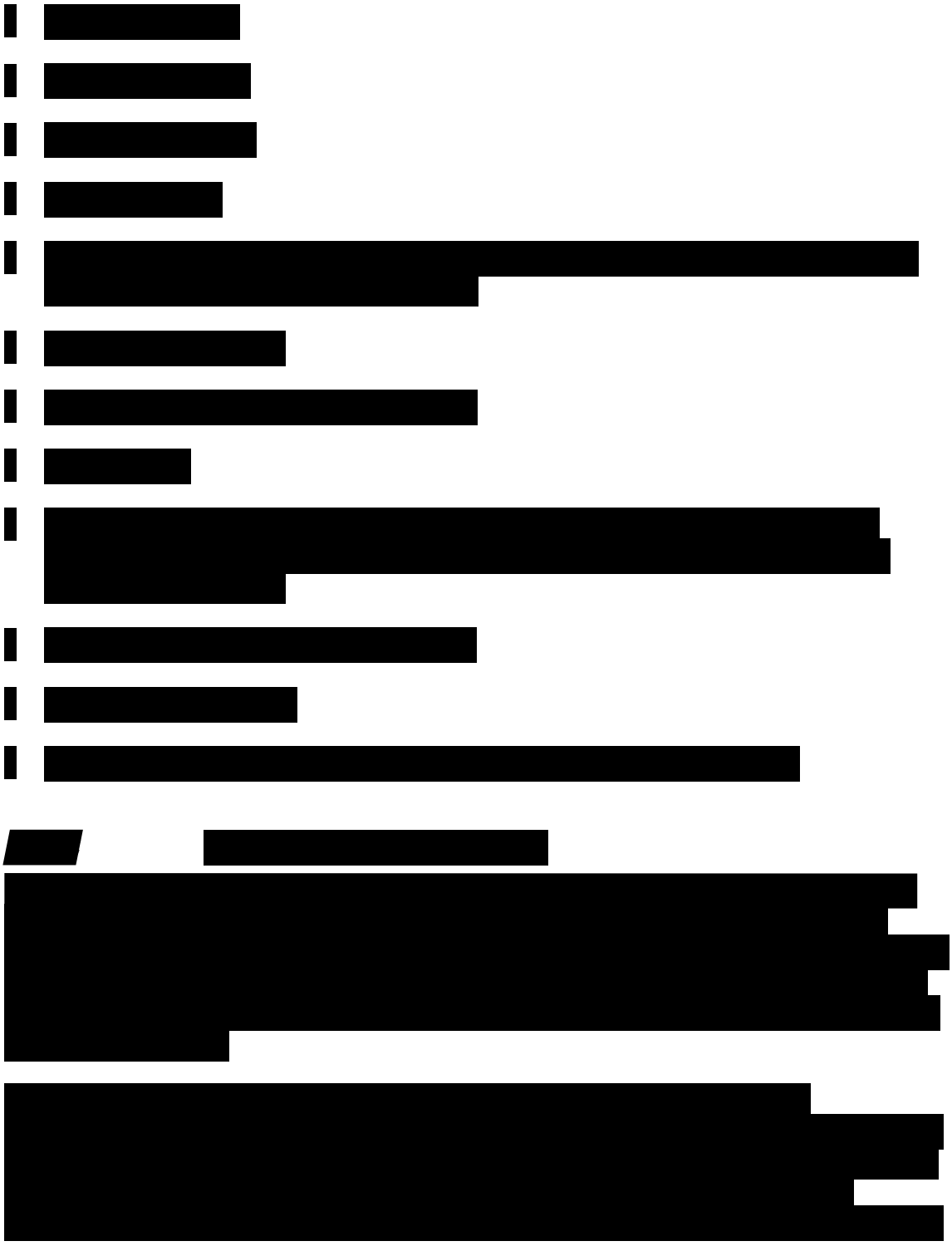

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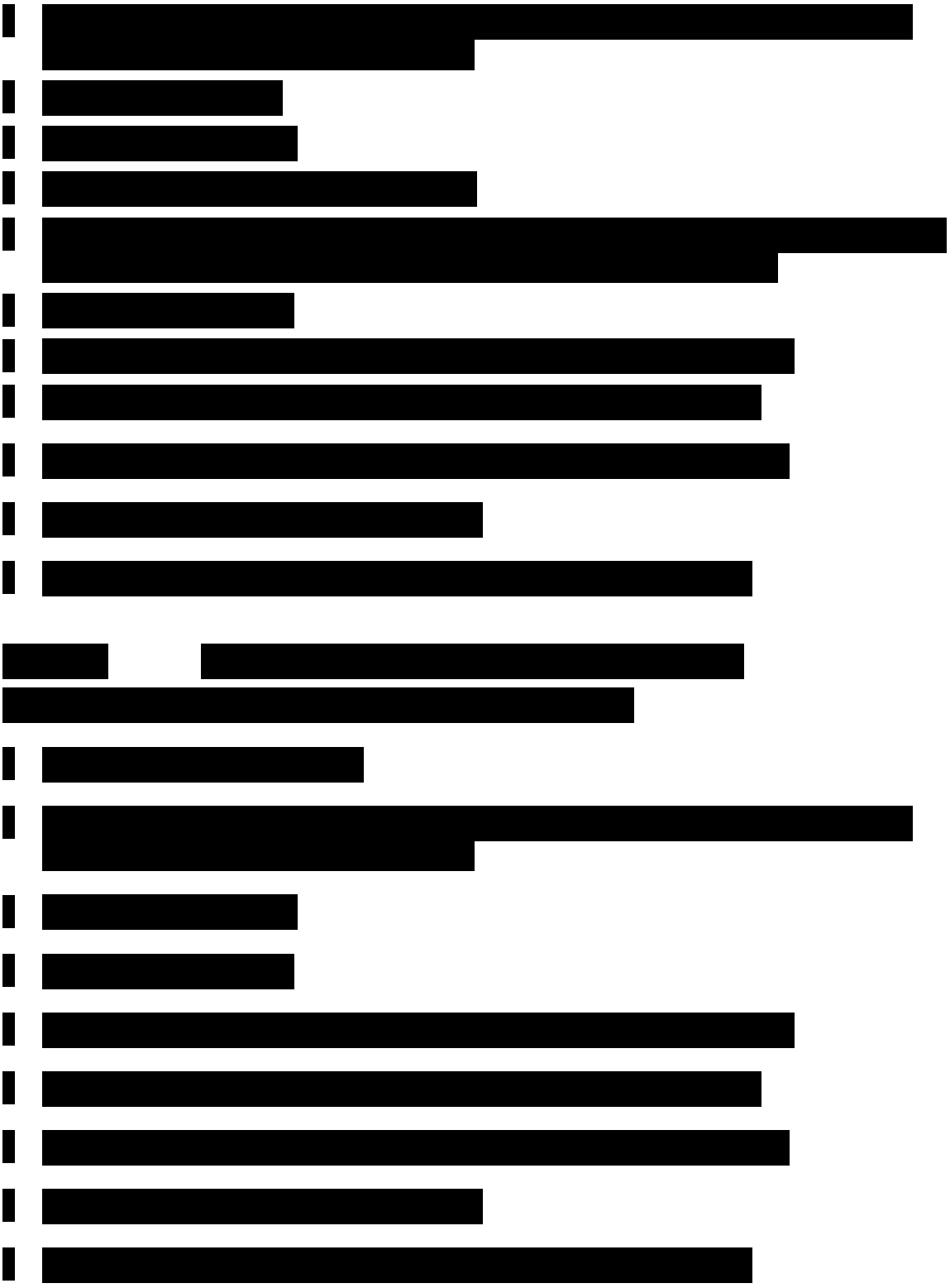

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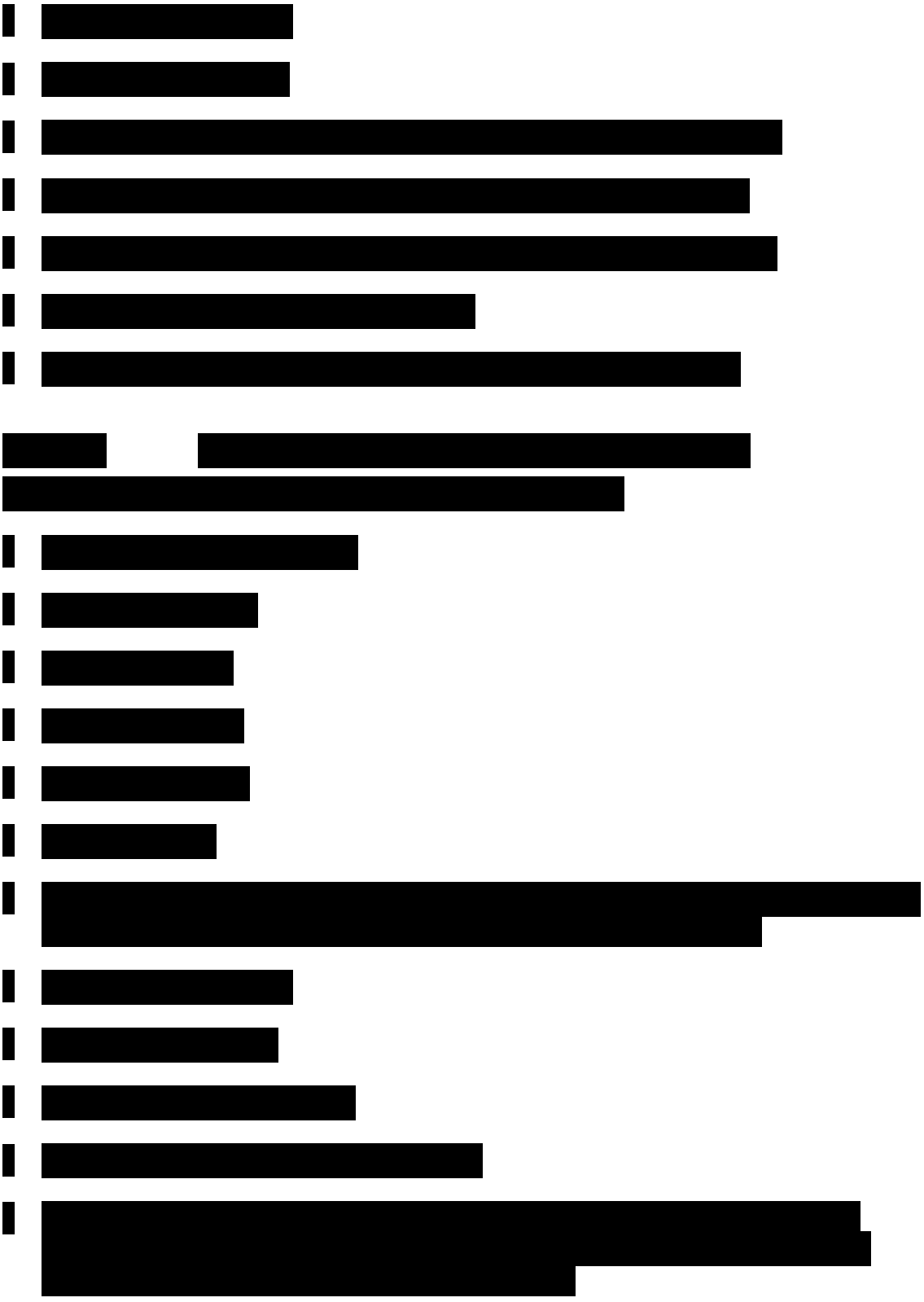

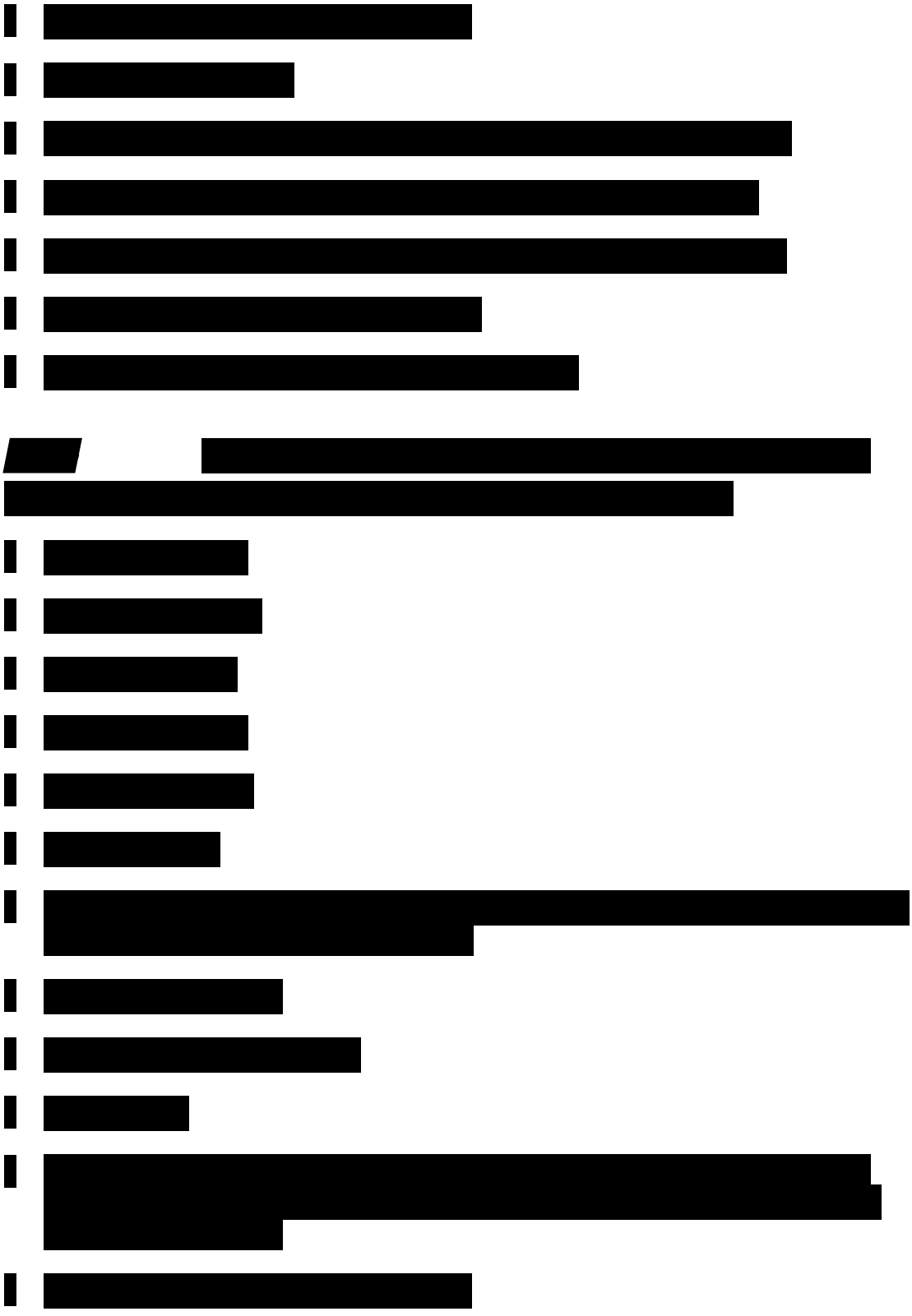

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9.5.5.5 Unscheduled Visits

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.

[redacted] may be captured using an electronic source tablet-based system. 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

The following analysis populations will be considered in the statistical analysis of the study.

9.7.1.1 Open-label Safety Population

The Open-label Safety Population will consist of all patients ***who signed the ICF if they participated in the lead-in studies, and all de novo patients who signed the ICF and underwent OLTP Screening Visit procedures and*** receive at least 1 dose of open-label rapastinel during the OLTP of the study.

9.7.1.2 Open-label Intent-to-Treat Population

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

9.7.1.3 Double-Blind Safety Population

The Double-blind Safety Population will consist of all patients ***in the Open-label Safety Population who are randomized to a treatment group during the DBTP of the study and receive at least 1 dose of IP during the DBTP.***

9.7.1.4 Double-Blind Modified Intent-to-Treat Population

The Double-blind ***modified*** Intent-to-Treat (Double-blind ***m***ITT) Population will consist of all patients in the Double-blind Safety Population.

9.7.2 Patient Disposition

The number of patients in the Open-label Safety, and Open-label ITT Populations will be summarized overall by study center. The number of patients in the Double-blind Safety and Double-blind ***m***ITT Populations will be summarized overall, by treatment group and study center.

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

The number and percentage of patients who entered the OLTP, who prematurely discontinued from the OLTP, who completed the OLTP, who met or did not meet the criteria to enter the DBTP at the end of the OLTP, and who entered the DBTP will be summarized overall and by reasons for premature discontinuation for the Open-label Safety Population. Similarly, the number and percentage of patients who completed the DBTP and who prematurely discontinued from the DBTP will be summarized overall, by double-blind treatment group, and by reasons for premature discontinuation for the Double-blind 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 Open-label Safety Population and by treatment group for the Double-blind mITT population.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to open-label rapastinel for the Open-label 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.

Exposure to double-blind IP for the Double-blind Safety Population during the DBTP will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind IP taken to the date of the last dose taken during the DBTP, inclusive. Descriptive statistics (number of patients, mean, SD, minimum, median, and maximum) will be presented by treatment group.

Prior medication is defined as any medication started before the date of first dose of open-label IP. *Concomitant medication* during the OLTP is defined as any medication taken on or after the date of the first dose of open-label IP during the OLTP. Concomitant medication during the DBTP will be defined as any medication taken on or after the date of the first dose of double-blind IP.

The use of prior medication will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Open-label 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 Open-label Safety Population. The use of concomitant medications during the DBTP will be summarized by treatment group by the number and percentage of patients receiving each medication within each therapeutic class for the Double-blind 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 Open-label ITT Population; the number and percentage of patients taking each qualifying ADT in the DBTP will be summarized by double-blind treatment group for the Double-Blind mITT Population. Mean daily dose and duration of previous treatment with each qualifying ADT will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) for the OLTP and by double-blind treatment group for the DBTP for the respective ITT or mITT populations.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period will be 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. The total number of IV doses actually taken during a specific time period is calculated as the sum of IV doses taken during that period as obtained from the study medication record. The number of IV doses expected to be taken for a specific treatment period will be the number of weeks in that period.

Descriptive statistics for open-label IP compliance will be presented for the OLTP for the Open-label Safety Population. Descriptive statistics for double-blind IP compliance will be presented by treatment group for the DBTP for the Double-blind 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 doses 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 Open-label ITT Population. Descriptive statistics for ADT compliance during the DBTP will be presented for each ADT by the double-blind treatment group for the Double-blind mITT Population.

9.7.5 Efficacy Analyses

All efficacy analyses for the OLTP will be performed using the Open-label ITT Population. All efficacy analyses for the DBTP will be performed using the Double-blind ***m***ITT Population. For rollover patients, the baseline of the lead-in study will be used as the baseline for the OLTP. ***The last nonmissing assessment before the first dose of Double-blind IP will be used as the baseline for*** the DBTP. For *de novo* patients, the last measurement before the first dose of open-label IP will be used as baseline. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the time to first relapse during the first 52 weeks of the DBTP, defined as the number of days from the randomization date to the relapse date during the first 52 weeks of the DBTP. Relapse during the DBTP is defined as meeting any of the following criteria:

- MADRS total score ≥ 18 at 2 consecutive visits
- ≥ 2 increase in CGI-S score compared with that obtained at randomization
- Risk of suicide as determined by the Investigator

- Need for hospitalization due to worsening of depression as determined by the Investigator

- Need for alternative treatment of depressive symptoms as determined by the Investigator

For patients who did not meet the above relapse criteria during the first 52 weeks of the DBTP, the time to relapse will be censored at the time of completion or discontinuation from the study, or 52 weeks, whichever is earlier.

The primary efficacy analysis will compare the time to relapse between placebo and rapastinel treatment groups using the log-rank test. Estimates of the hazard ratio and 95% CI will be based on the Cox proportional hazards model with treatment group as an explanatory variable. The cumulative distribution function of time to relapse will be characterized by the Kaplan-Meier curves.

Three sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis assumes that patients who discontinued without meeting any of the relapse criteria during the DBTP relapsed instead of being censored. The second sensitivity analysis will be based on the delta-adjusted method examined by Zhao et al. (2014). The third sensitivity analysis is an extension of the placebo-based pattern mixture model proposed by Lu (2014, 2015). The placebo-based pattern mixture model assumes that patients who discontinued from the rapastinel treatment groups would have disease progression after discontinuation similar to that of placebo. The extended placebo-based pattern mixture model uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring underlying the placebo-based pattern mixture model.

9.7.5.2 Secondary Efficacy Parameter

The secondary efficacy parameter is the time to first relapse during the entire DBTP, defined as the number of days from the randomization date to the relapse date during the entire DBTP. For patients who did not meet the relapse criteria during the DBTP, their time to relapse will be censored at the time of completion or discontinuation from the study.

The same analysis methods for the primary endpoint will be applied to the secondary endpoint.

In order to control the overall Type I error rate for the primary and secondary hypotheses, the following sequential testing procedure will be implemented in the following order:

1) ***The comparison of time to relapse during the first 52 weeks between rapastinel 450 mg weekly and placebo***

2) ***The comparison of time to relapse during the entire DBTP between rapastinel 450 mg weekly and placebo,***

3) ***The comparison of time to relapse during the first 52 weeks between rapastinel 450 mg biweekly and placebo***

4) ***The comparison of time to relapse during the entire DBTP between rapastinel 450 mg biweekly and placebo***

Each of the 4 hypothesis tests above will be implemented at the 2-sided 0.05 significance level. A given hypothesis test will be carried out only when each of the preceding hypothesis tests have concluded rejection of the null hypothesis at the 0.05 significance level. In the event a given hypothesis test fails to reject its null hypothesis at the 0.05 significance level, the conclusion for the subsequent hypotheses not tested is to not reject their respective null hypotheses. This testing strategy will control the overall Type I error rate at 0.05 significance level.

9.7.6.1 Adverse Events

AEs will be coded using the *Medical Dictionary for Regulatory Activities*.

For rollover patients, an AE (classified by preferred term) that occurs during the OLTP or thereafter will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of IP in the lead-in study or was present before the first dose of IP in the lead-in study and increased in severity during the OLTP or thereafter. If more than 1 AE is reported before the date of the first dose of IP in the 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 or thereafter that were also coded to that preferred term. ***An AE that becomes serious during the OLTP or thereafter will also be considered as a TEAE.***

For *de novo* patients, an AE (classified by preferred term) that occurs during the OLTP or thereafter will be considered a TEAE if it was not present before the date of 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 during the OLTP or thereafter. If more than 1 AE is reported before the date of the first dose of open-label IP 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 or thereafter that were also coded to that preferred term. ***An AE that becomes serious during the OLTP or thereafter will also be considered as a TEAE.***

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

An AE (classified by preferred term) that occurs during the DBTP of the study will be considered a newly emergent adverse event (NEAE) if the AE was not present before the first dose of the double-blind IP or it was present before the first dose of the double-blind IP and increased in severity during the DBTP. If more than 1 AE is reported before the first dose of the double-blind IP 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 DBTP that were also coded to that preferred term. ***An AE that becomes serious during the DBTP will also be considered as an NEAE for the DBTP.*** An AE that occurs more than 30 days after the date of the last dose of IP will not be counted as a NEAE.

The number and percentage of patients reporting TEAEs during the OLTP will be tabulated by SOC and preferred term.. The number and percentage of patients in each treatment group reporting TEAEs and NEAEs during the DBTP will be tabulated by SOC and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and causal relationship to the IP. If more than 1 AE is coded to the same preferred term for the same patient during the same treatment period, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the IP.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs and NEAEs during the DBTP will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the weekly rapastinel group.

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 a ***treatment-emergent*** SAE ***(TESAE***). The number and percentage of patients who had ***TE***SAEs during the OLTP will be summarized by preferred term and sorted by decreasing frequency. The number and percentage of patients who had ***TE***SAEs during the DBTP will be summarized by treatment group and preferred term and will be sorted by decreasing frequency for the weekly rapastinel group.

The number and percentage of patients who had fatal ***TE***SAEs during the OLTP will be summarized by preferred term and sorted by decreasing frequency. The number and percentage of patients who had fatal ***TE***SAEs during the DBTP will be summarized by treatment group and preferred term and sorted by decreasing frequency for the weekly rapastinel group.

The incidence of ***TE***AEs leading to premature discontinuation of IP during the OLTP will be summarized by preferred term and will be sorted by decreasing frequency. The incidence of ***TE***AEs leading to premature discontinuation of IP during the DBTP will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the weekly rapastinel group.

Listings will be presented for all patients with SAEs, patients with AEs leading to discontinuation, and patients who died (if any).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.7.9 Interim Analysis

No interim analysis is planned for this study.

9.7.10 Determination of Sample Size

The sample size and power calculations are based on the analysis of time to relapse during the first 52 weeks of the DBTP. Assuming a relapse rate of 19% per 26 weeks in the placebo group and a dropout rate of 20% per 26 weeks in all treatment groups, the sample size of 200 per group will have 90% power to detect a hazard ratio of 0.475 for a rapastinel treatment versus placebo at a 0.05 significance level. To achieve this number of randomized patients, approximately 1500 patients need to be enrolled in this study if 40% of patients are qualified for randomization.

9.7.11 Computer Methods

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

9.8 DATA AND SAFETY MONITORING BOARD

The study will be conducted under the supervision of an independent Data and Safety Monitoring Board (DSMB) to be chartered to review safety data at predetermined points during the study. The DSMB may also decide to meet and review safety data at other timepoints should it be deemed necessary. The DSMB is responsible for the ongoing review of the safety data in the clinical study and for making recommendations concerning the continuation, modification, and termination of the study (FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006).

All analyses that are required to support the DSMB will be performed by an independent unblinded statistician not otherwise involved in the study. Details of the DSMB membership, meeting schedule, and data review and analysis will be documented in the DSMB Charter.

9.9 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.

If unclarities arise with regard to interpretation or conduct of the approved protocol during the conduct of the study, the sponsor will provide guidance in the form of a protocol clarification letter. Such guidance will be used to clarify only within the bounds of the approved protocol.

9.10 PROTOCOL DEVIATIONS AND VIOLATIONS

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.

A ***significant*** *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. 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 Procedures 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 US Department of Health and Human Services 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-04, ***Amendment 2, dated 06 Nov 2018***) 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 . . .")

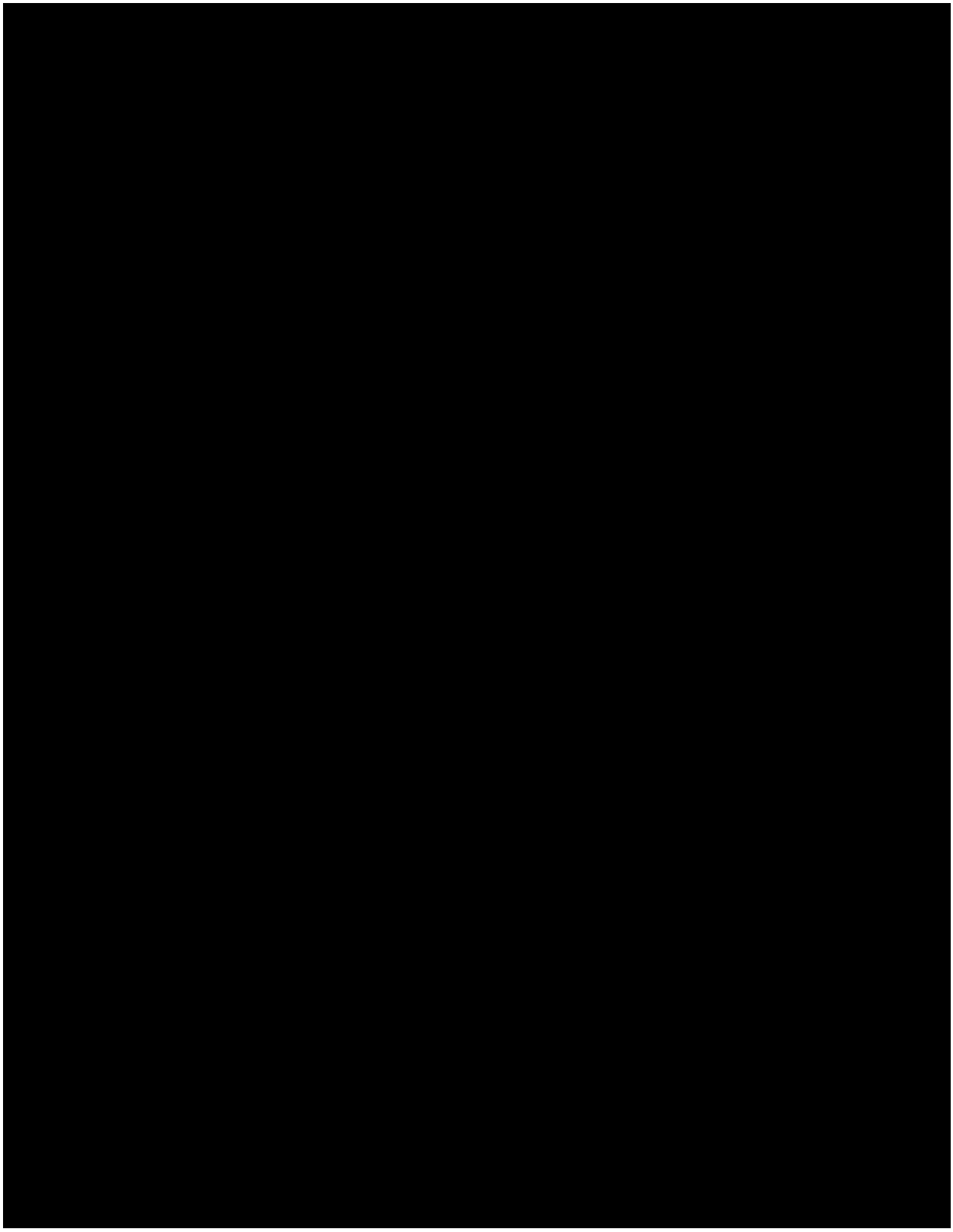
- A place for the patient's signature and date of signing of the ICF

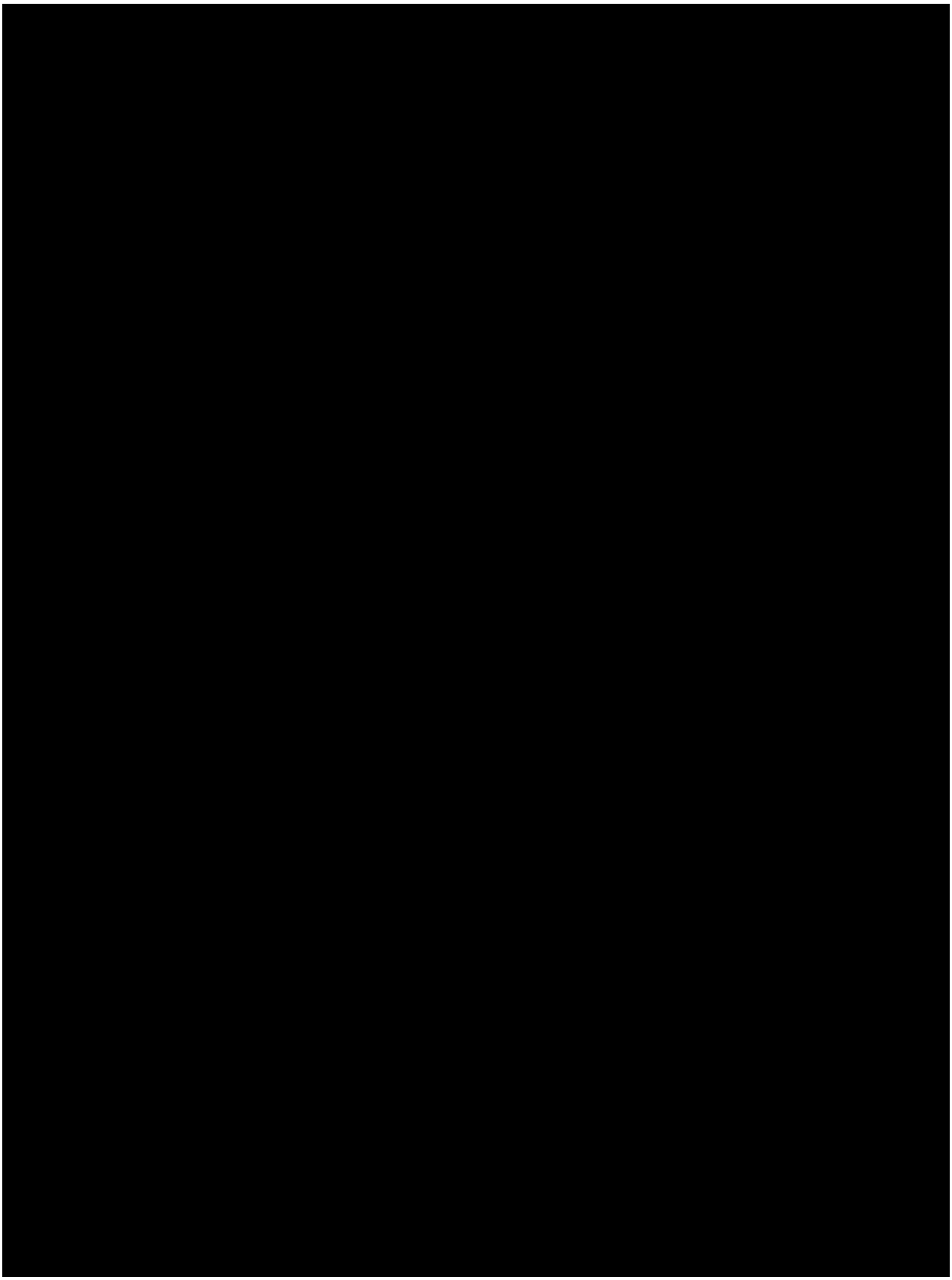
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

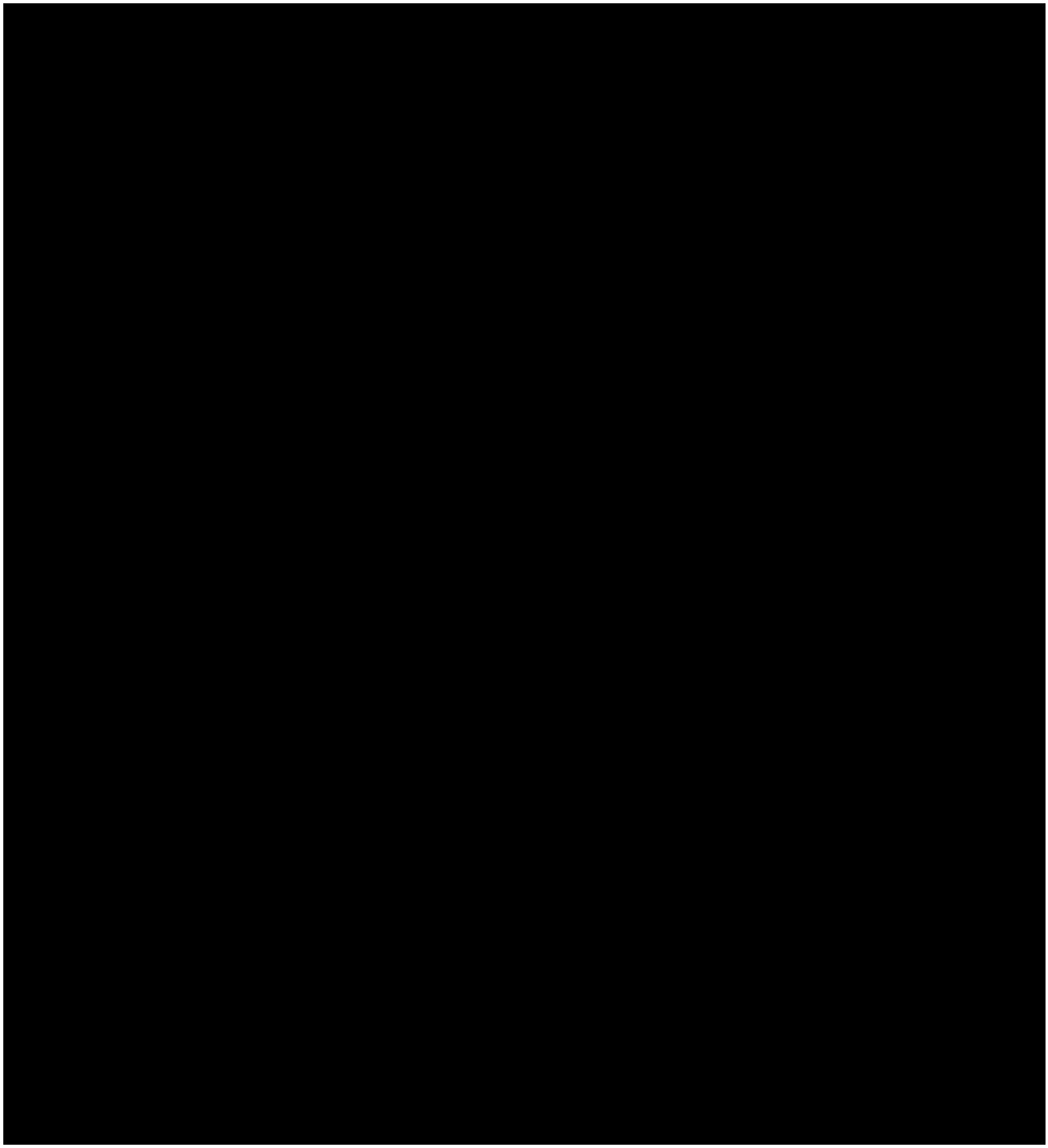
A copy of the signed consent form must be given to the patient.

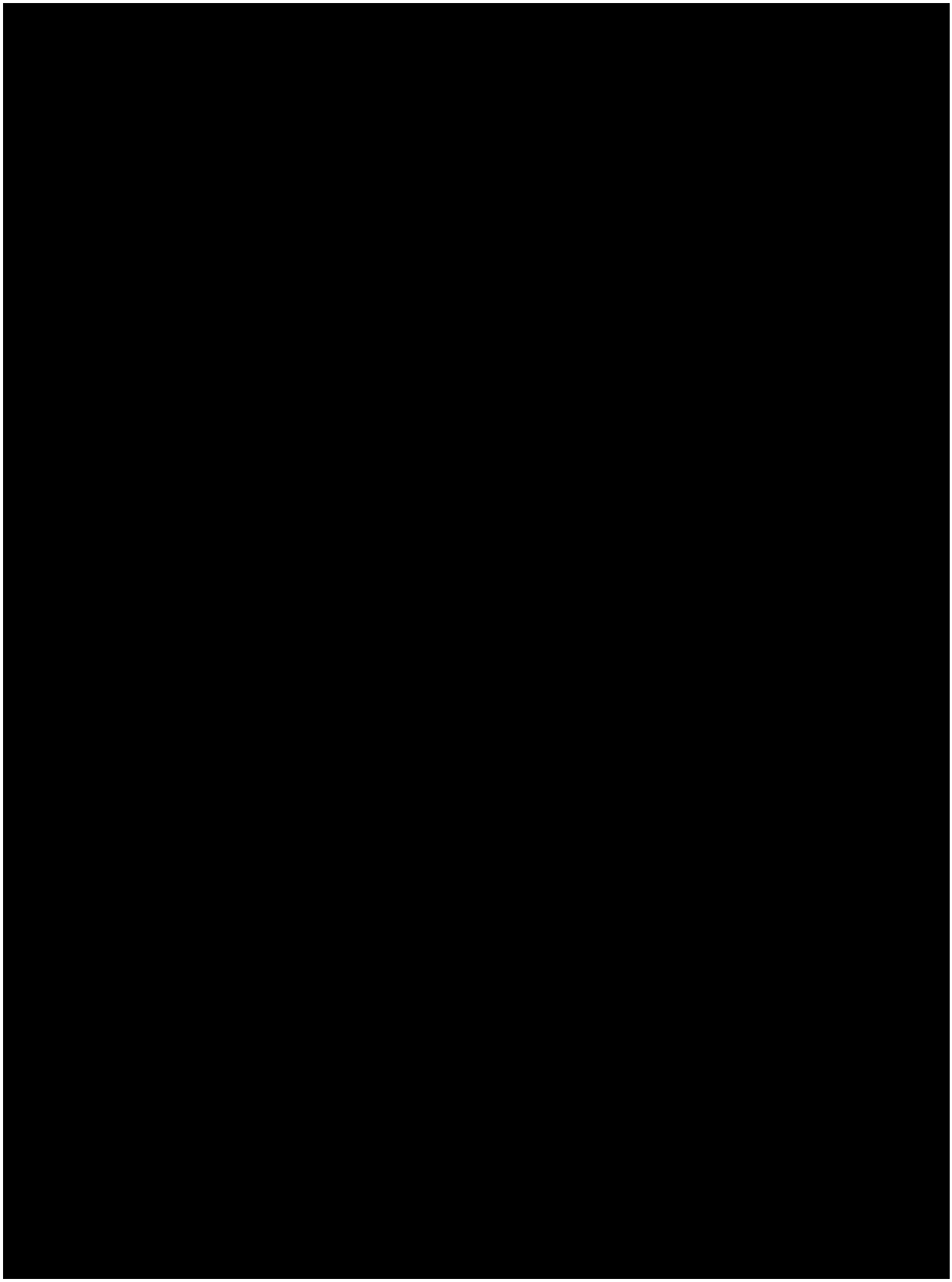
APPENDIX II. CONTACT INFORMATION

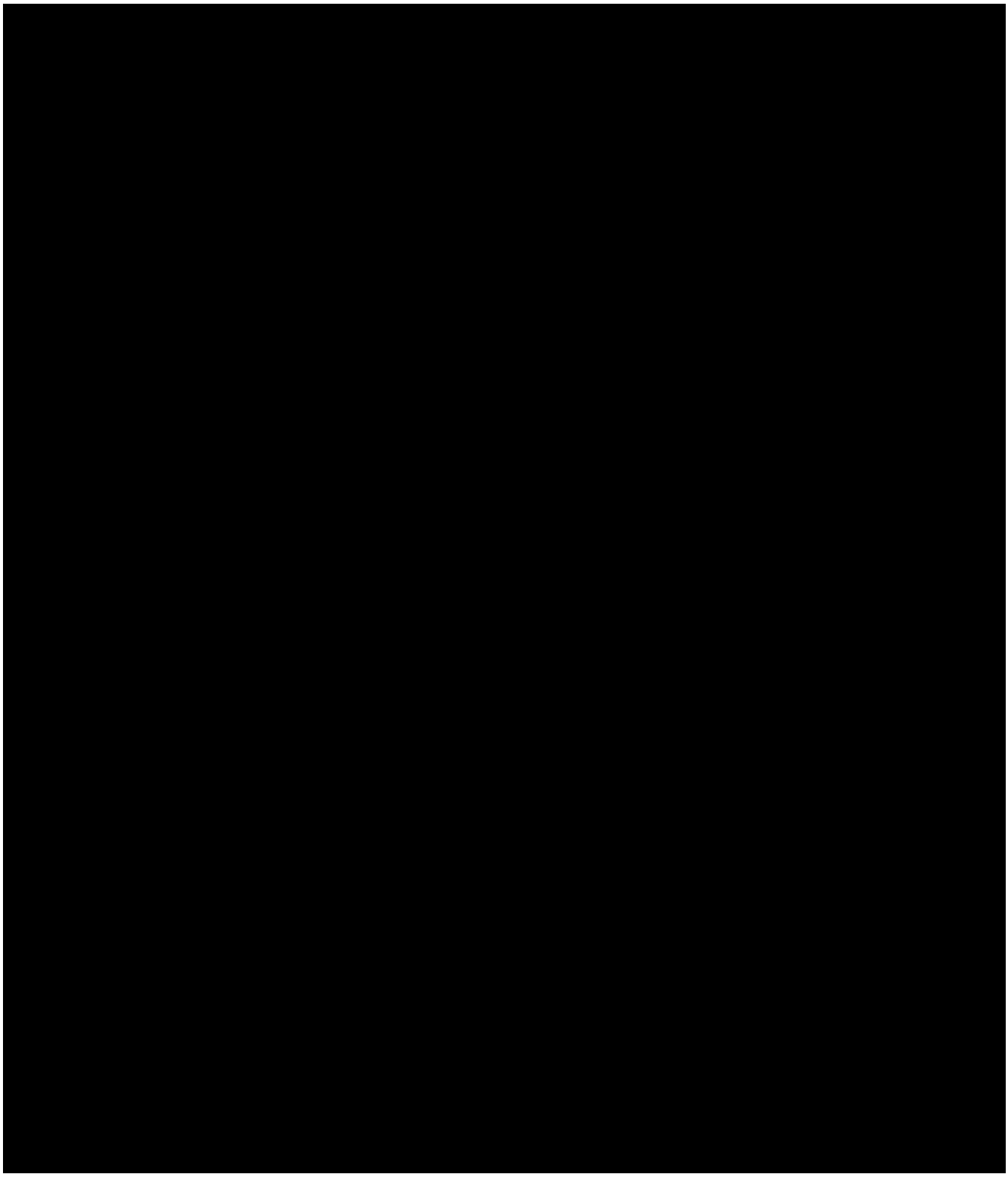
Contact information for the Sponsor personnel is maintained in the Study Reference Manual.

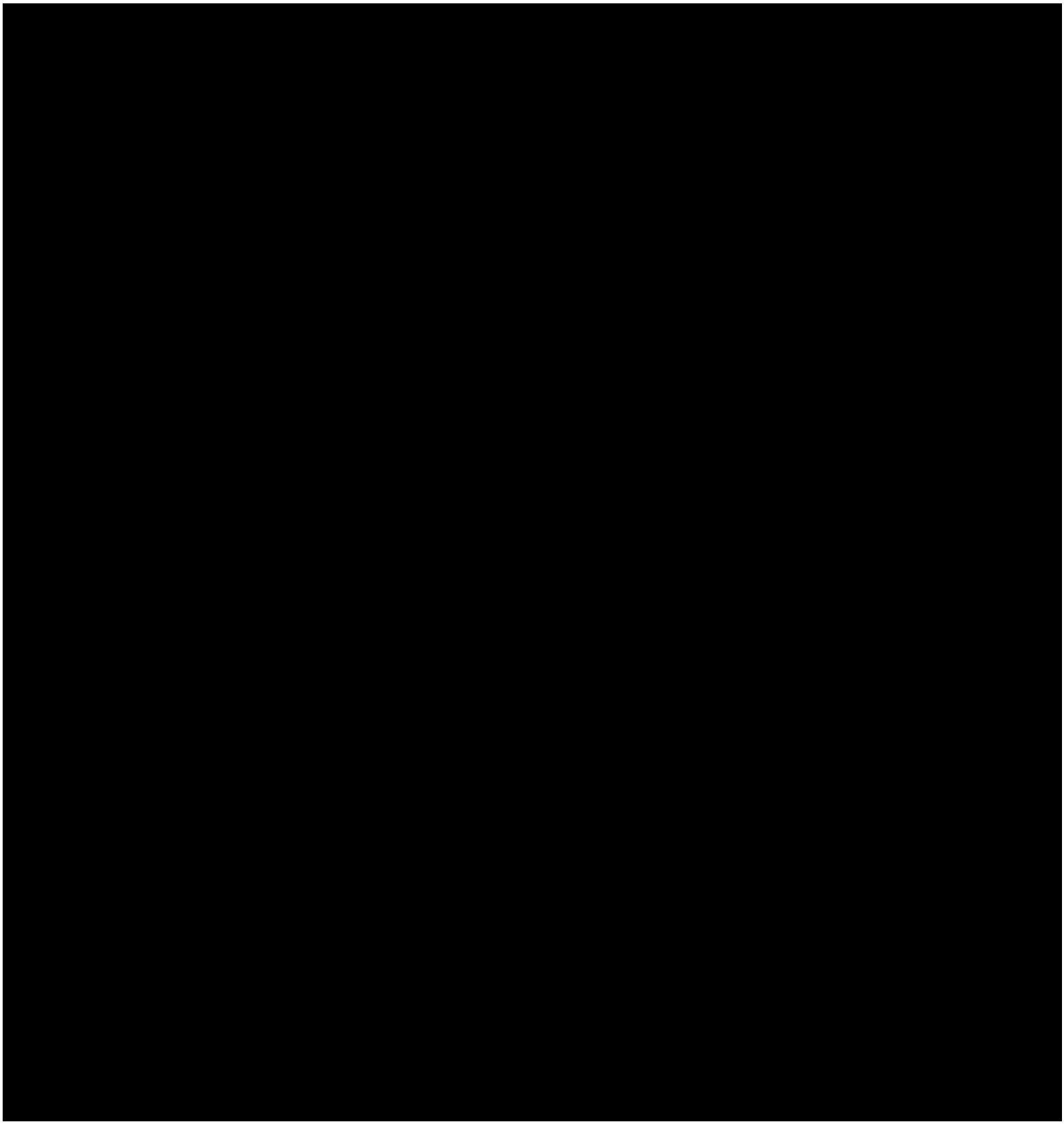


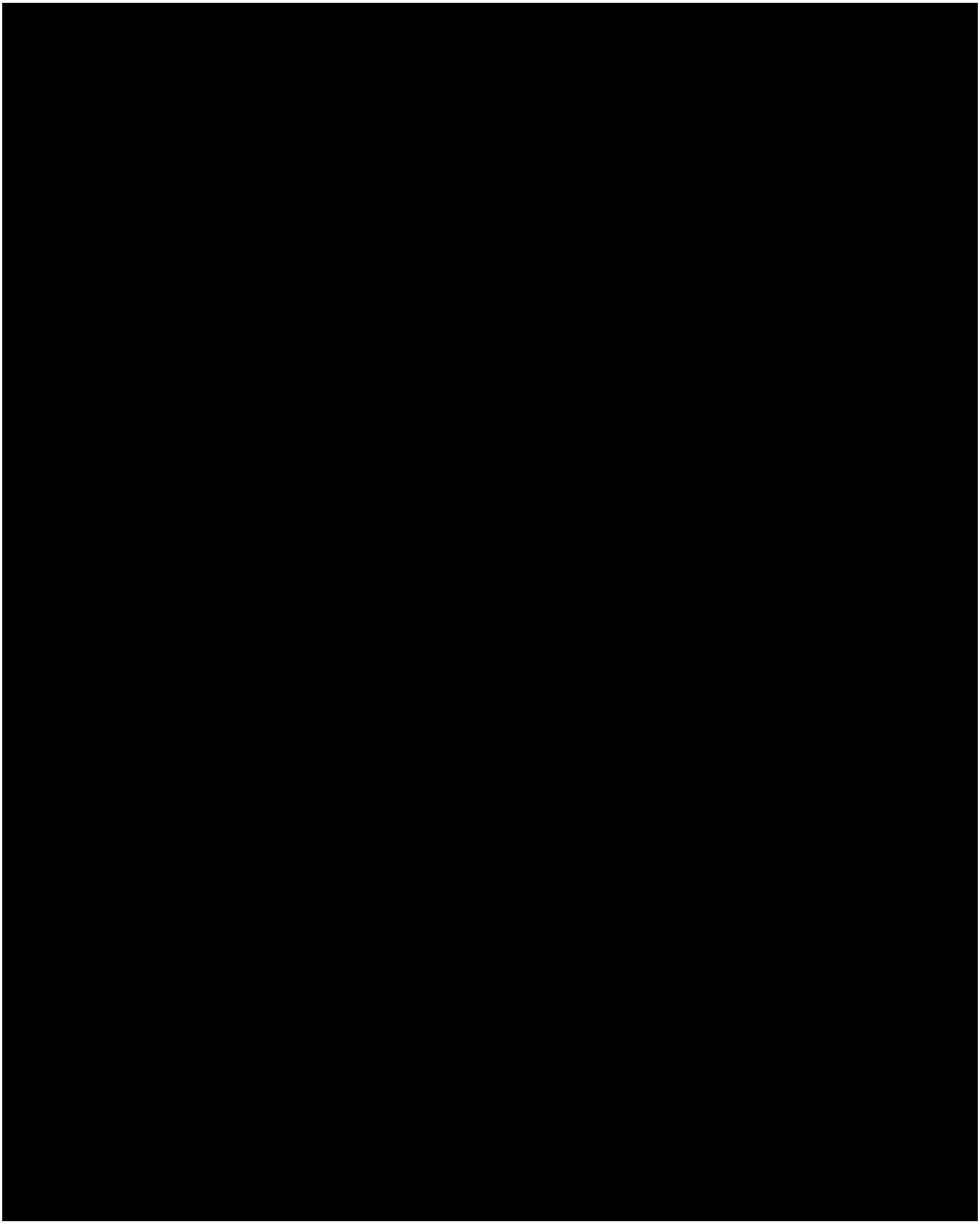


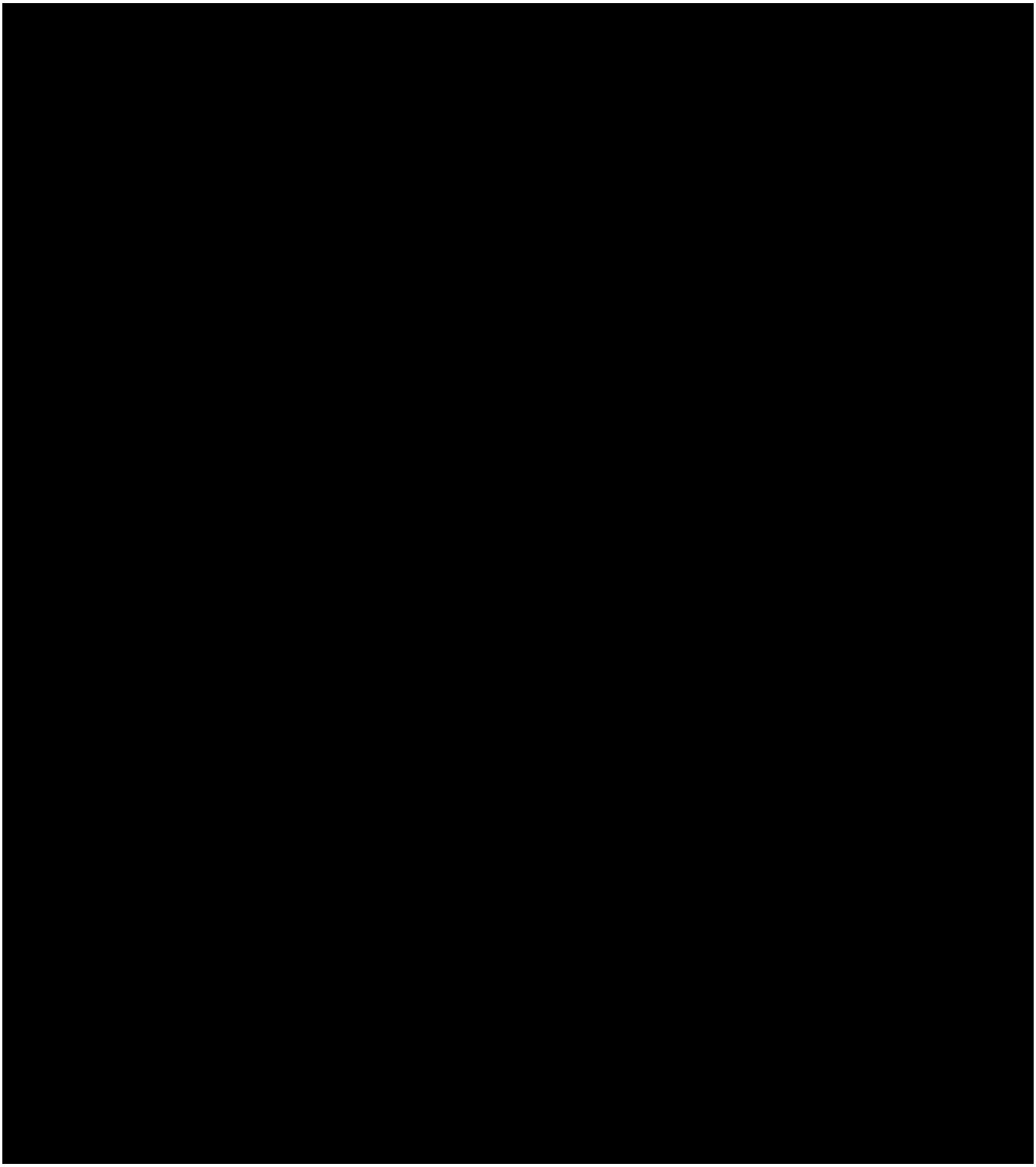


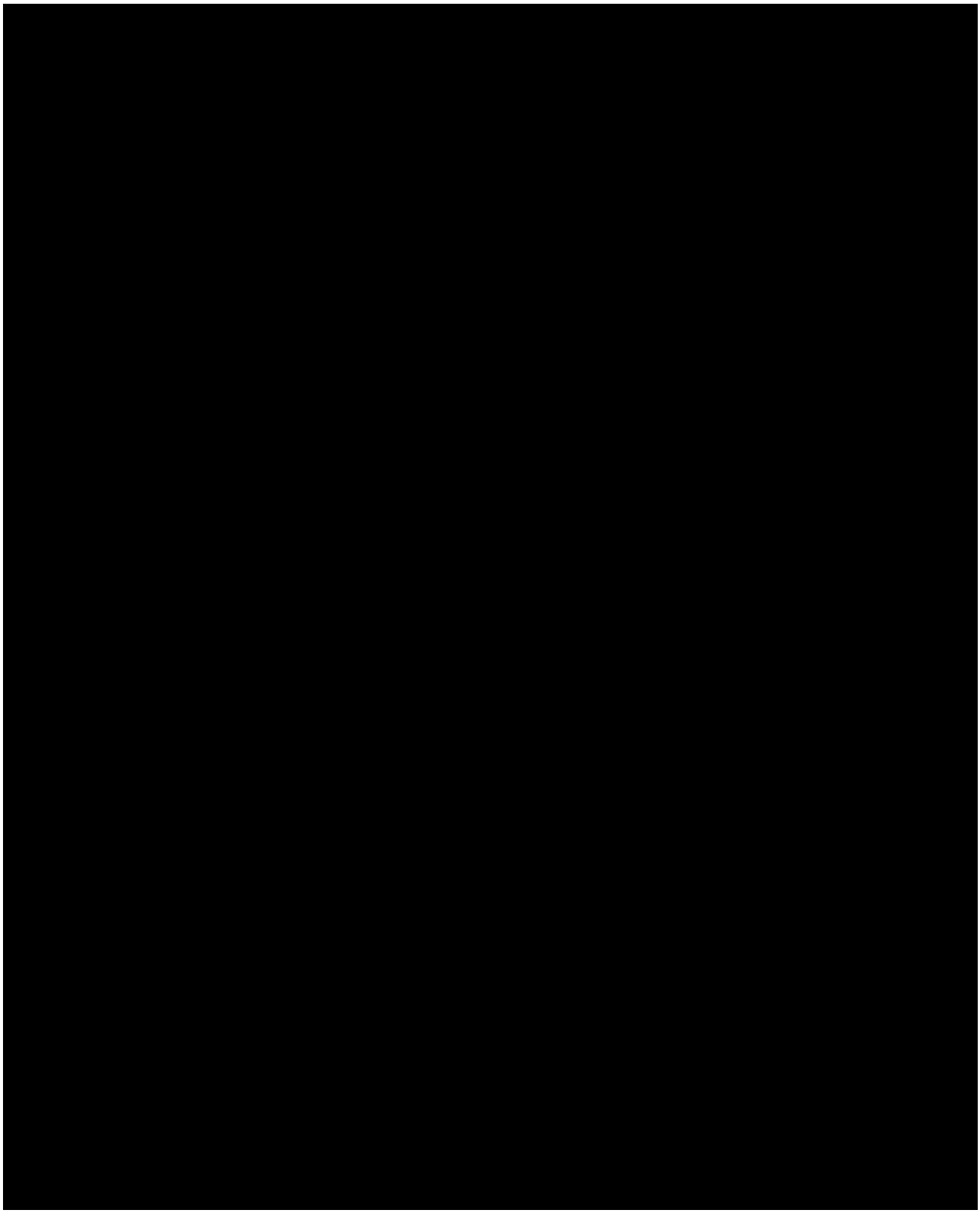


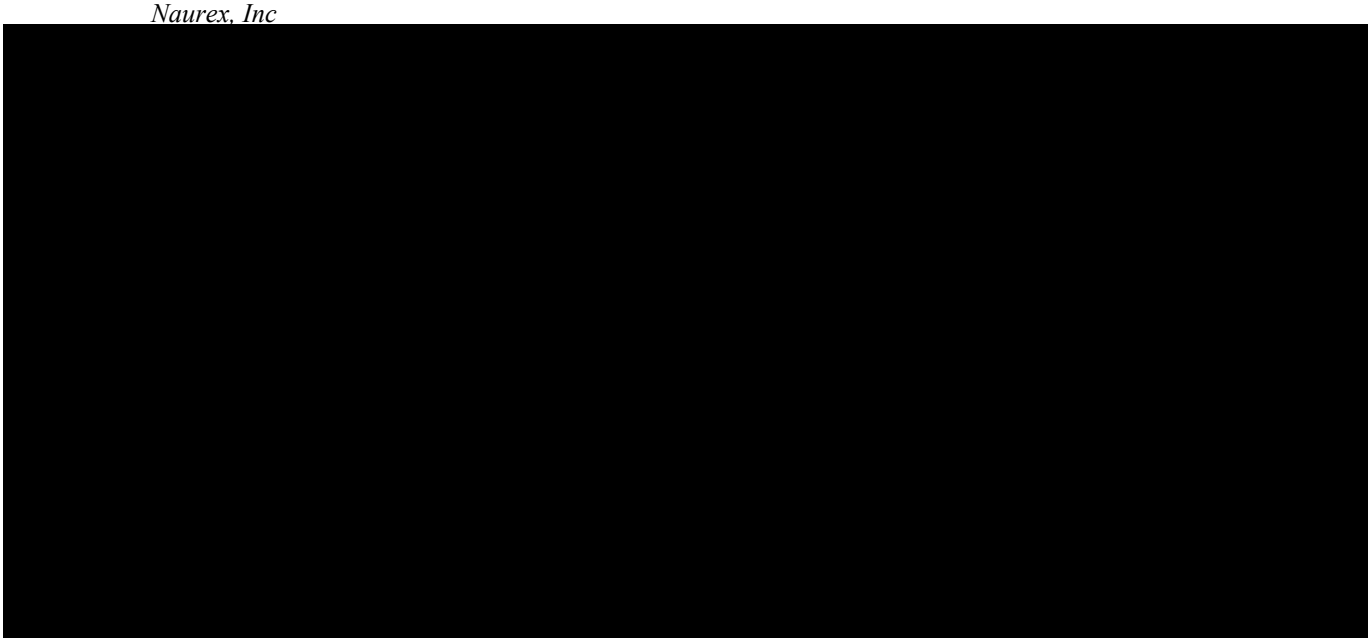


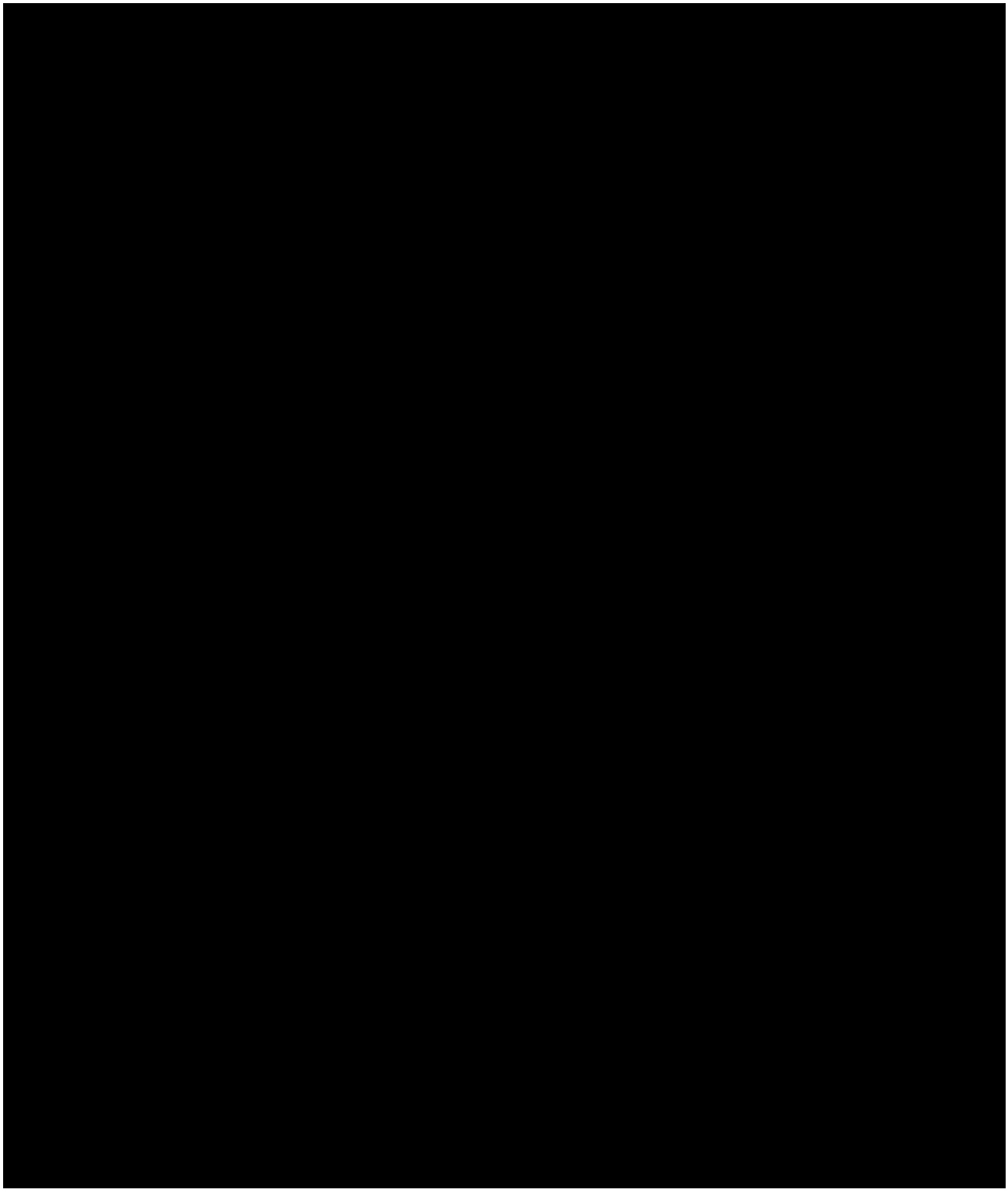


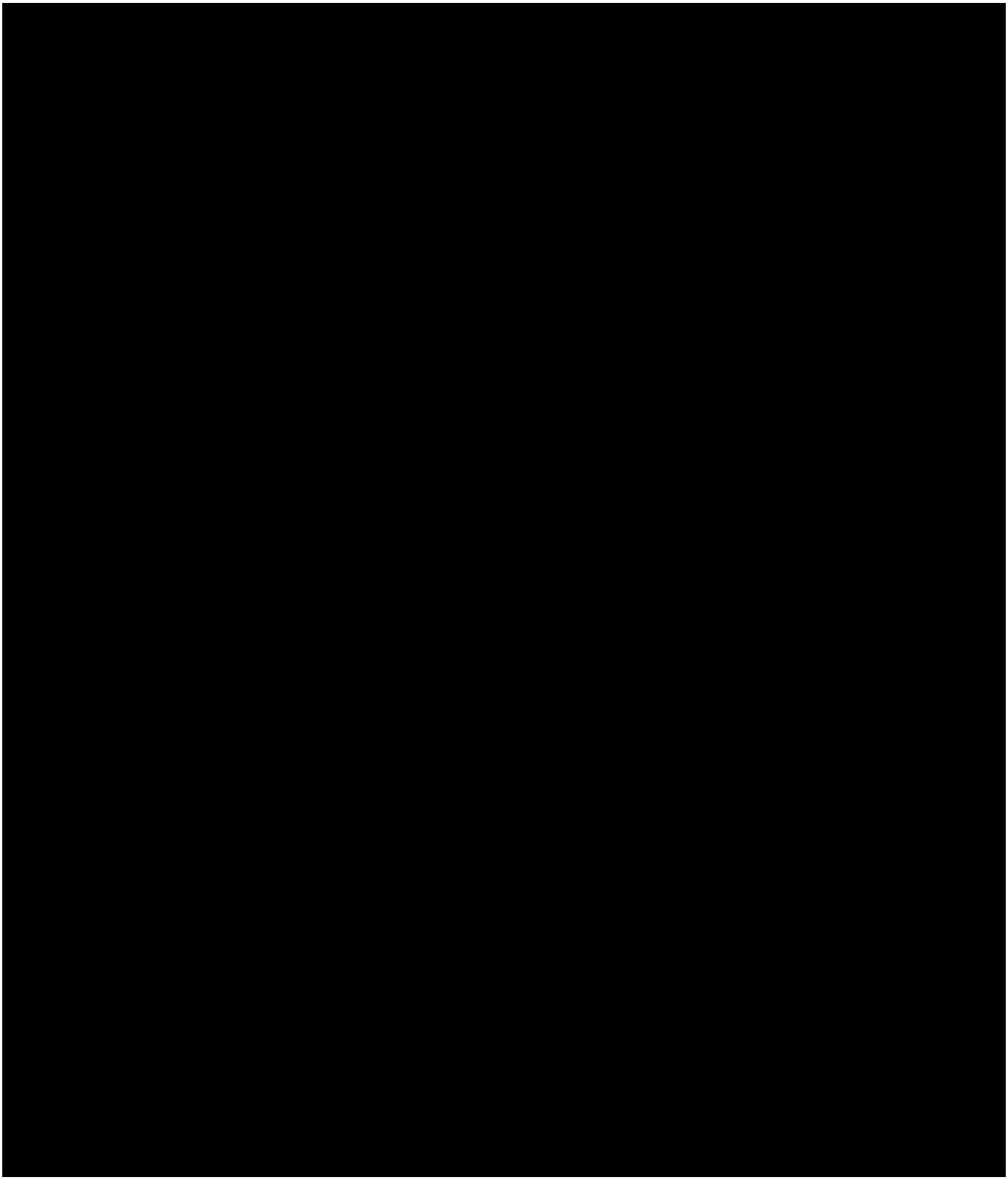


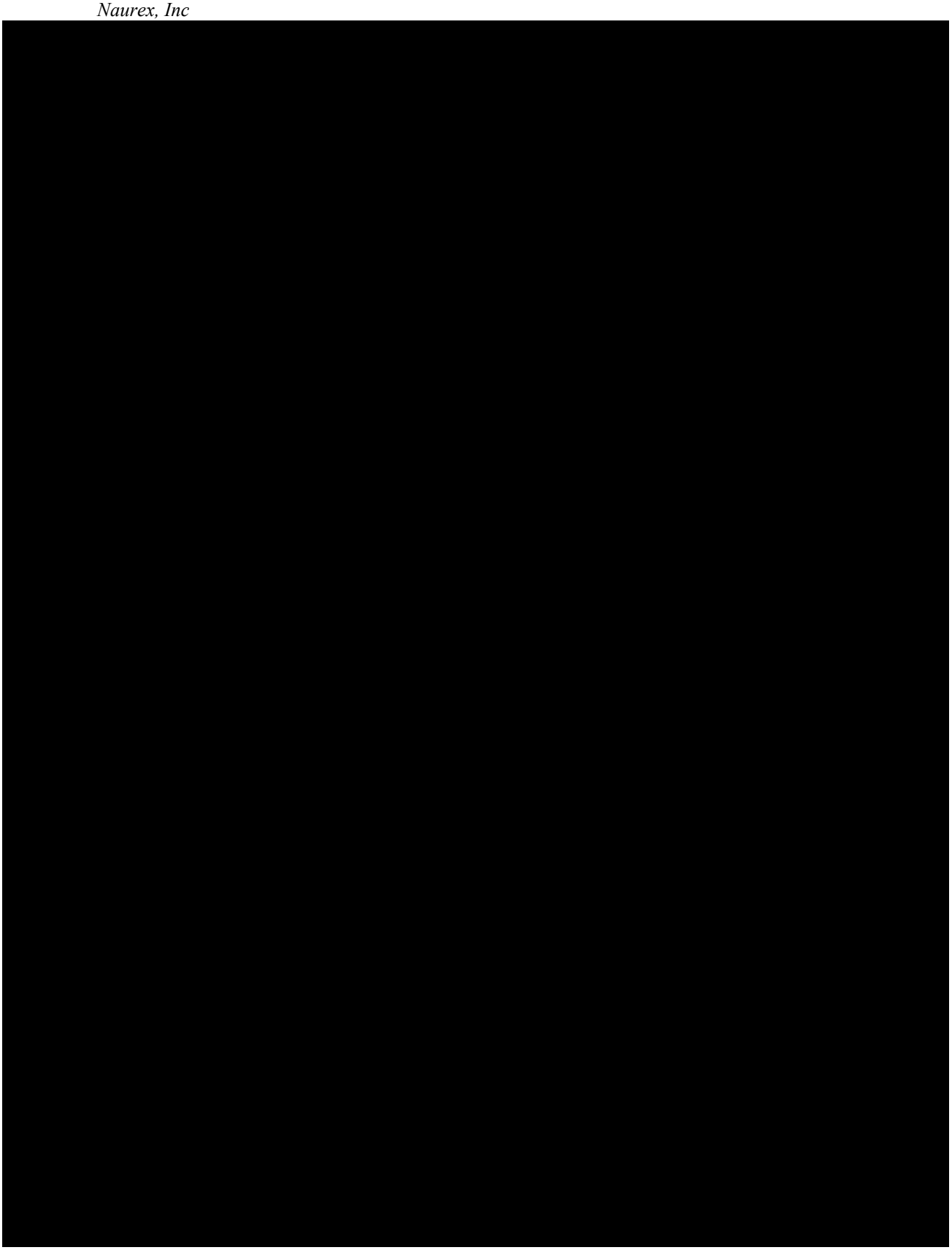


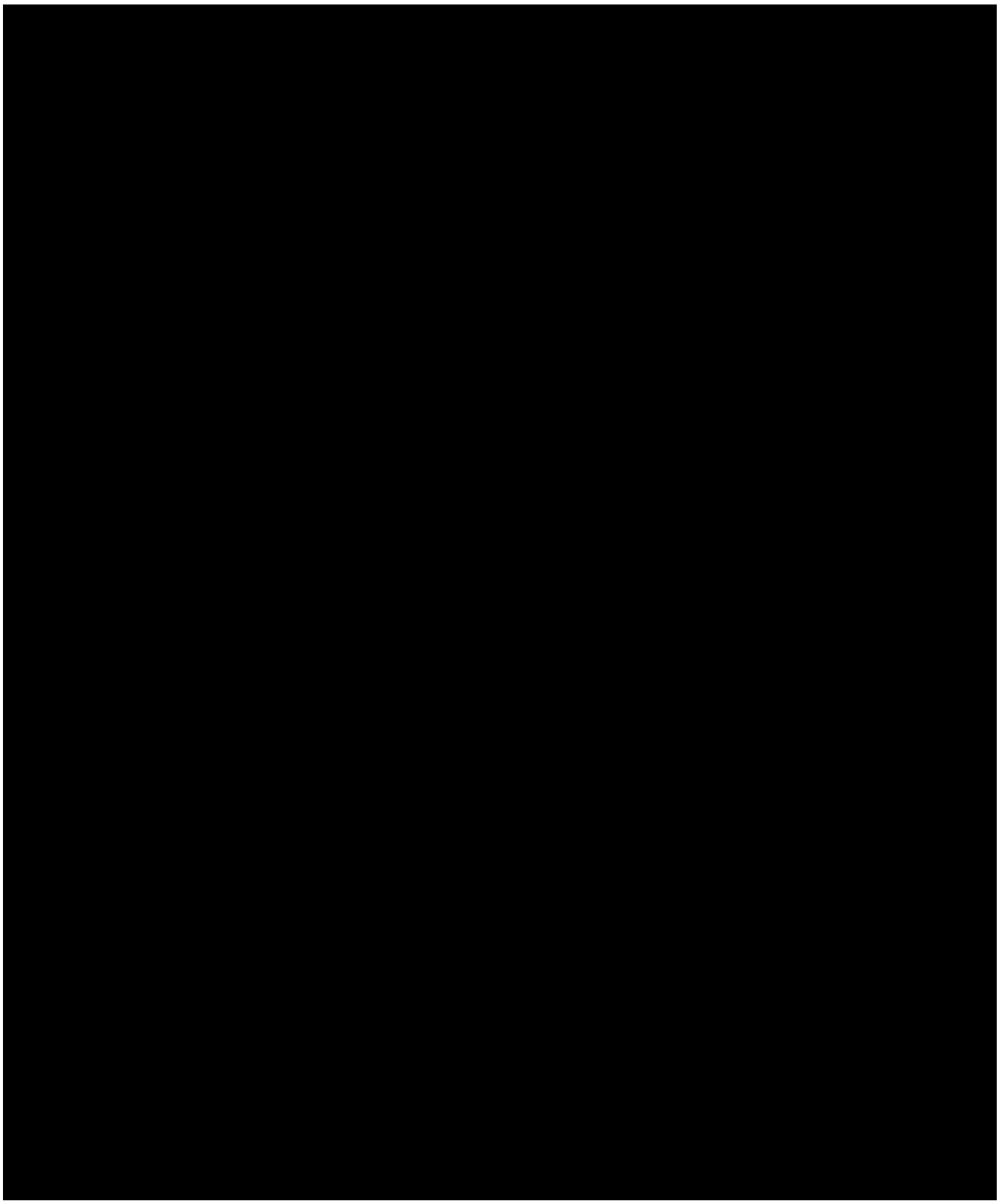


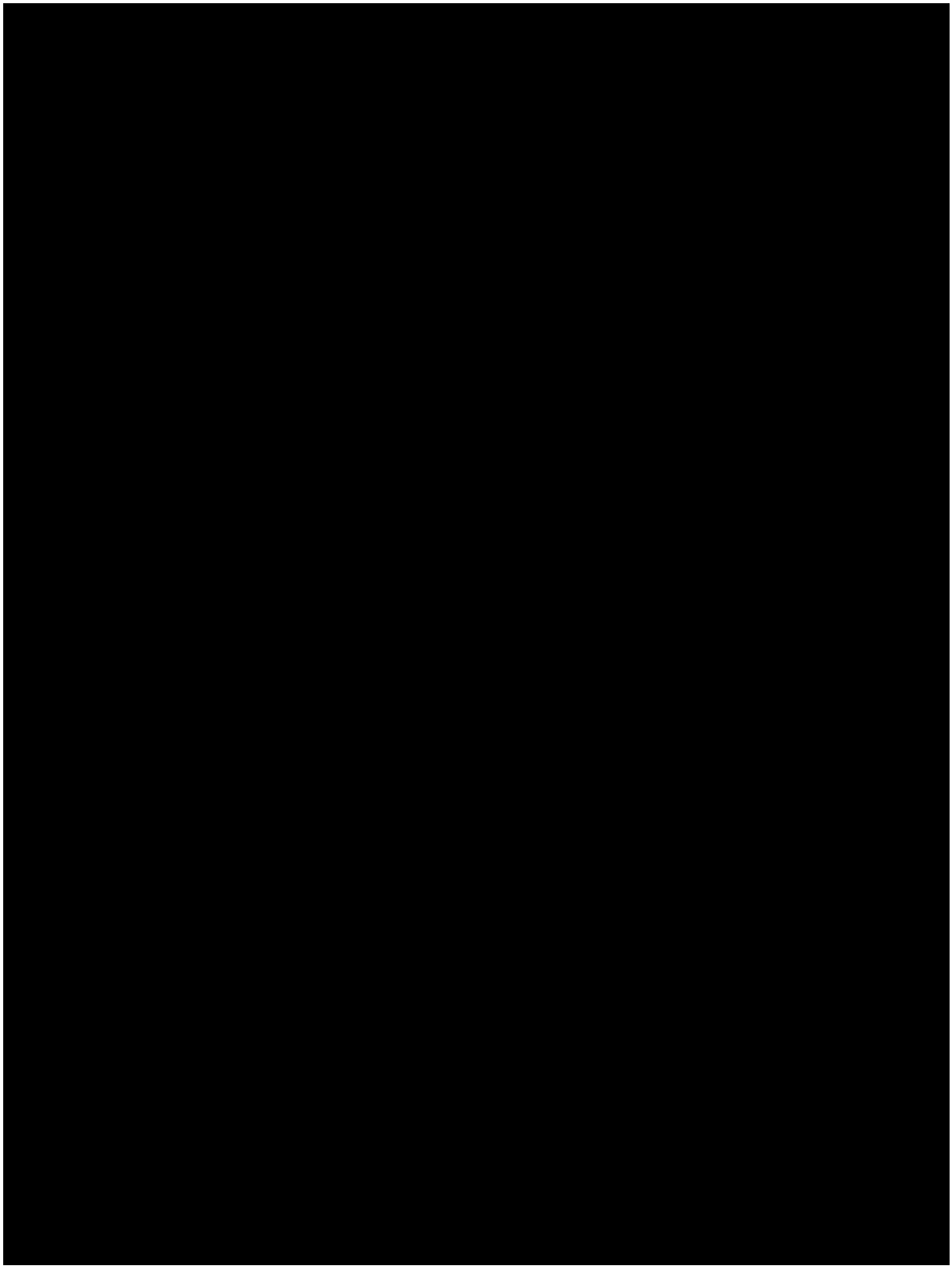


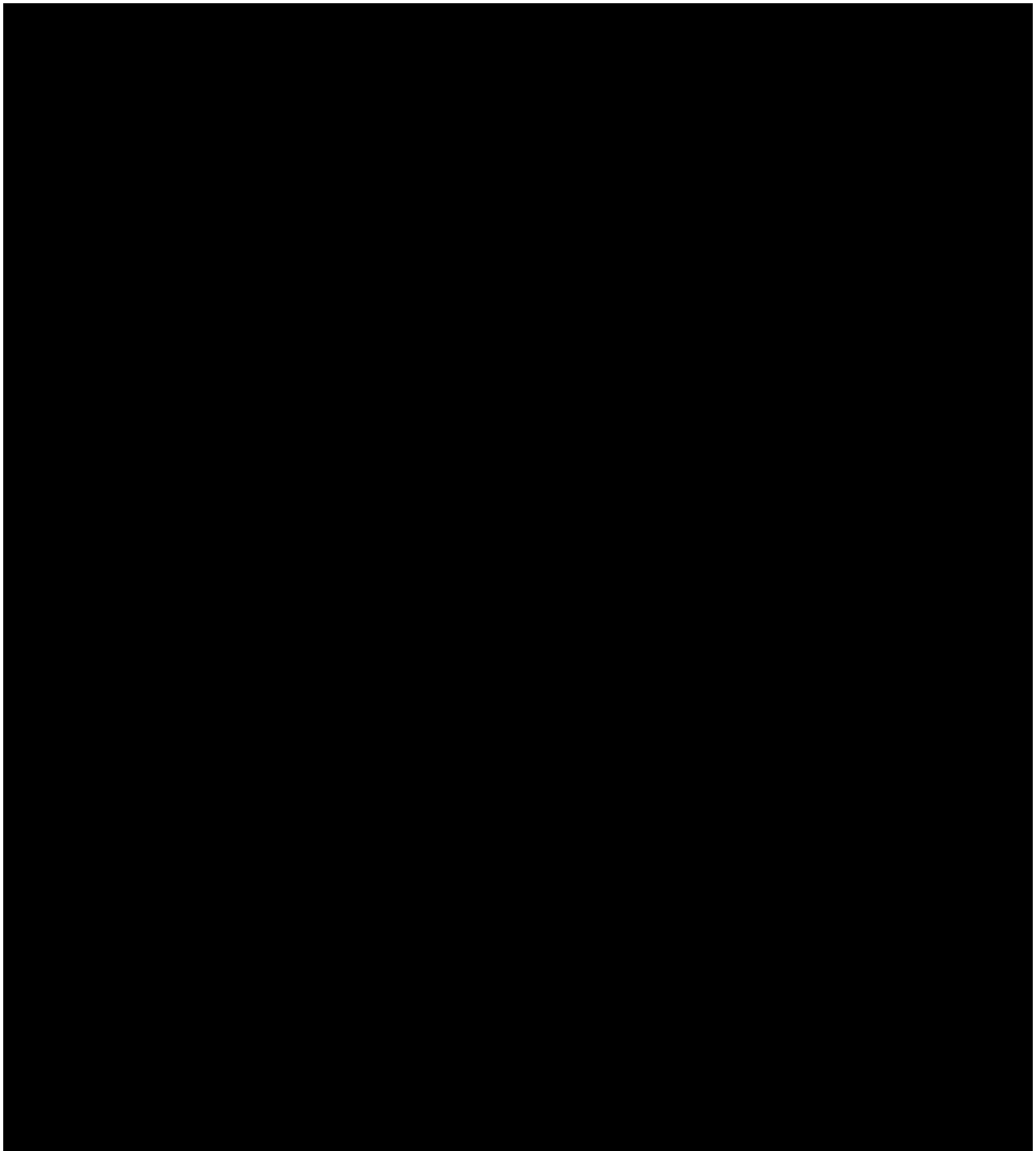












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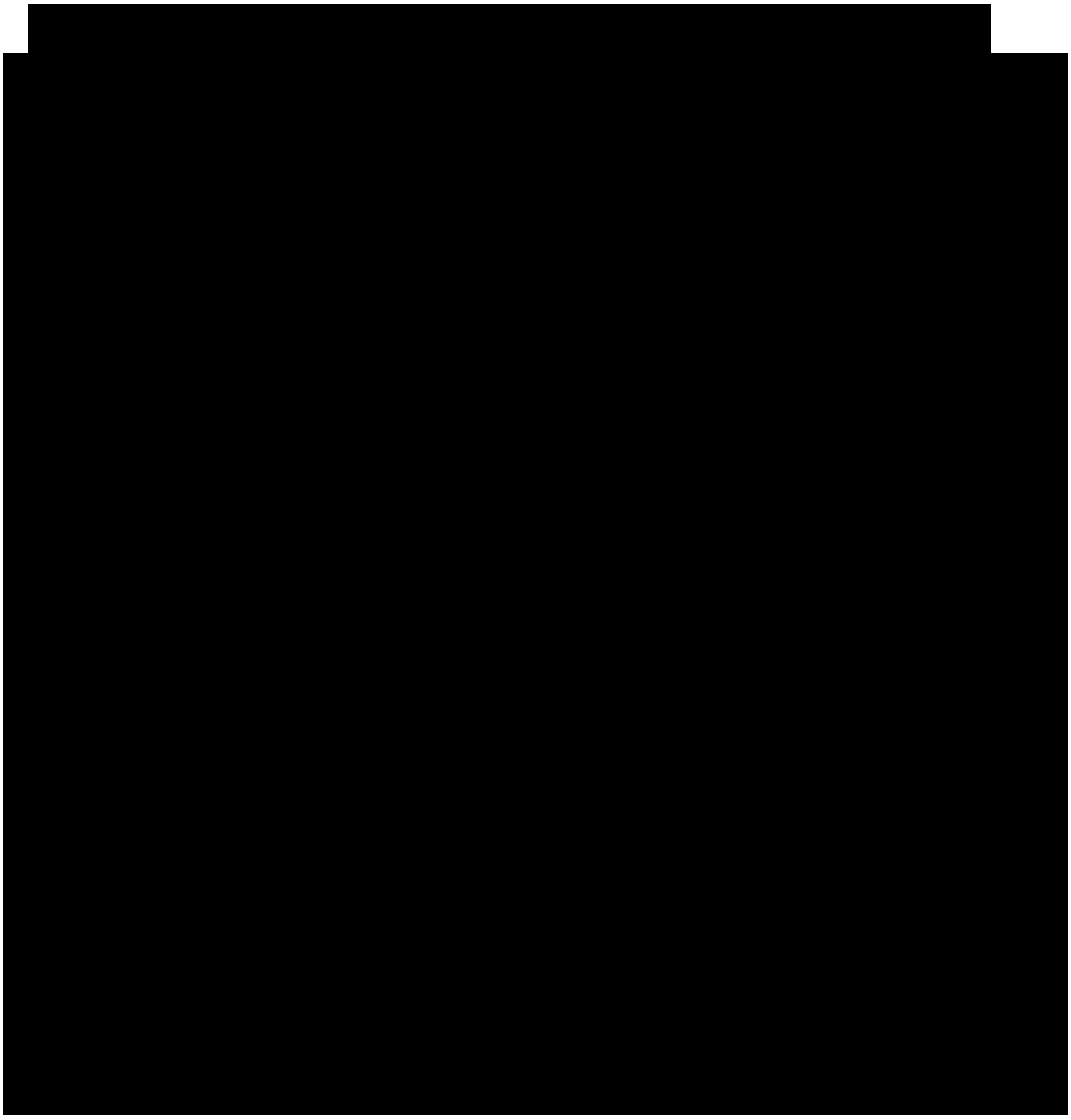

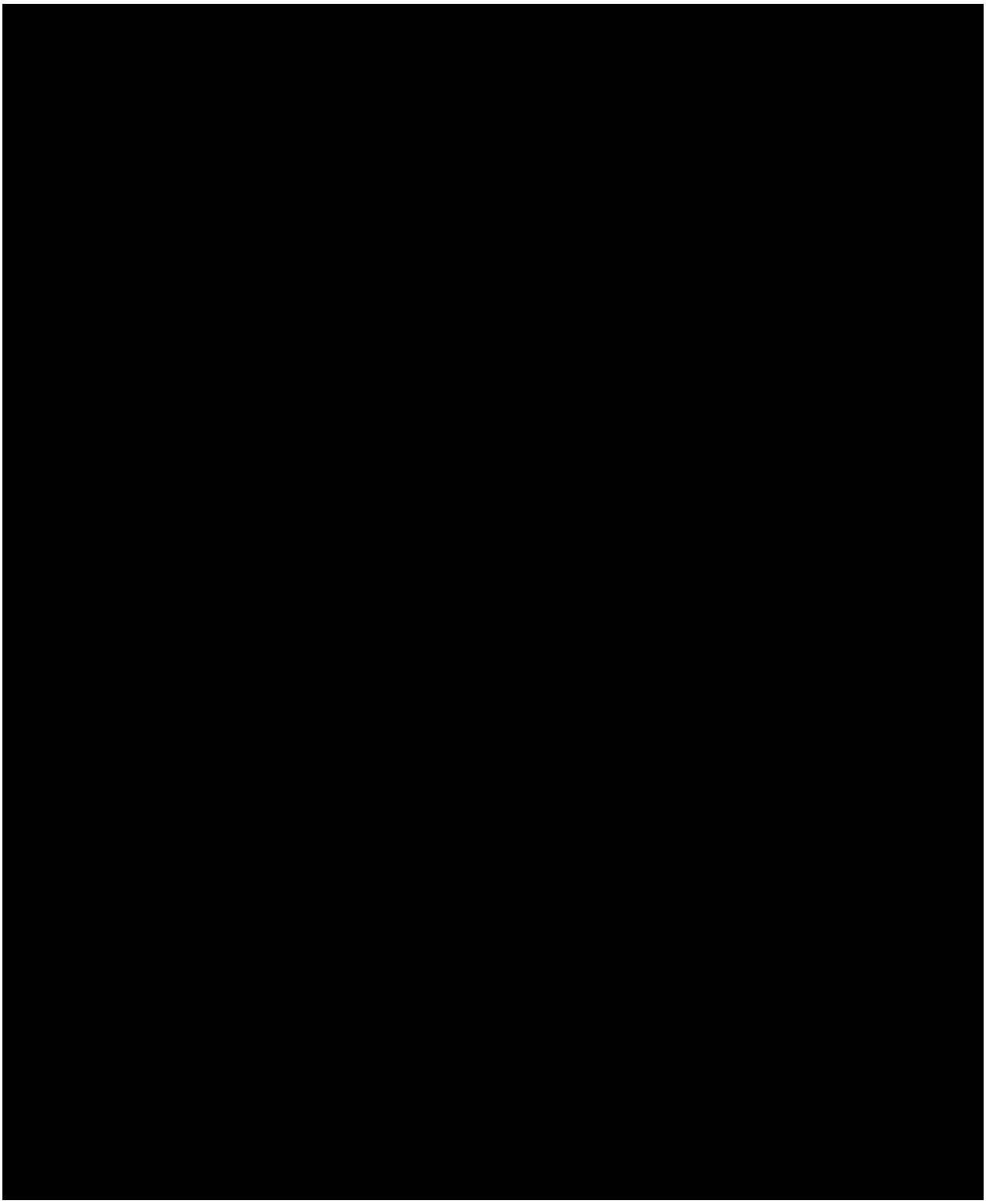

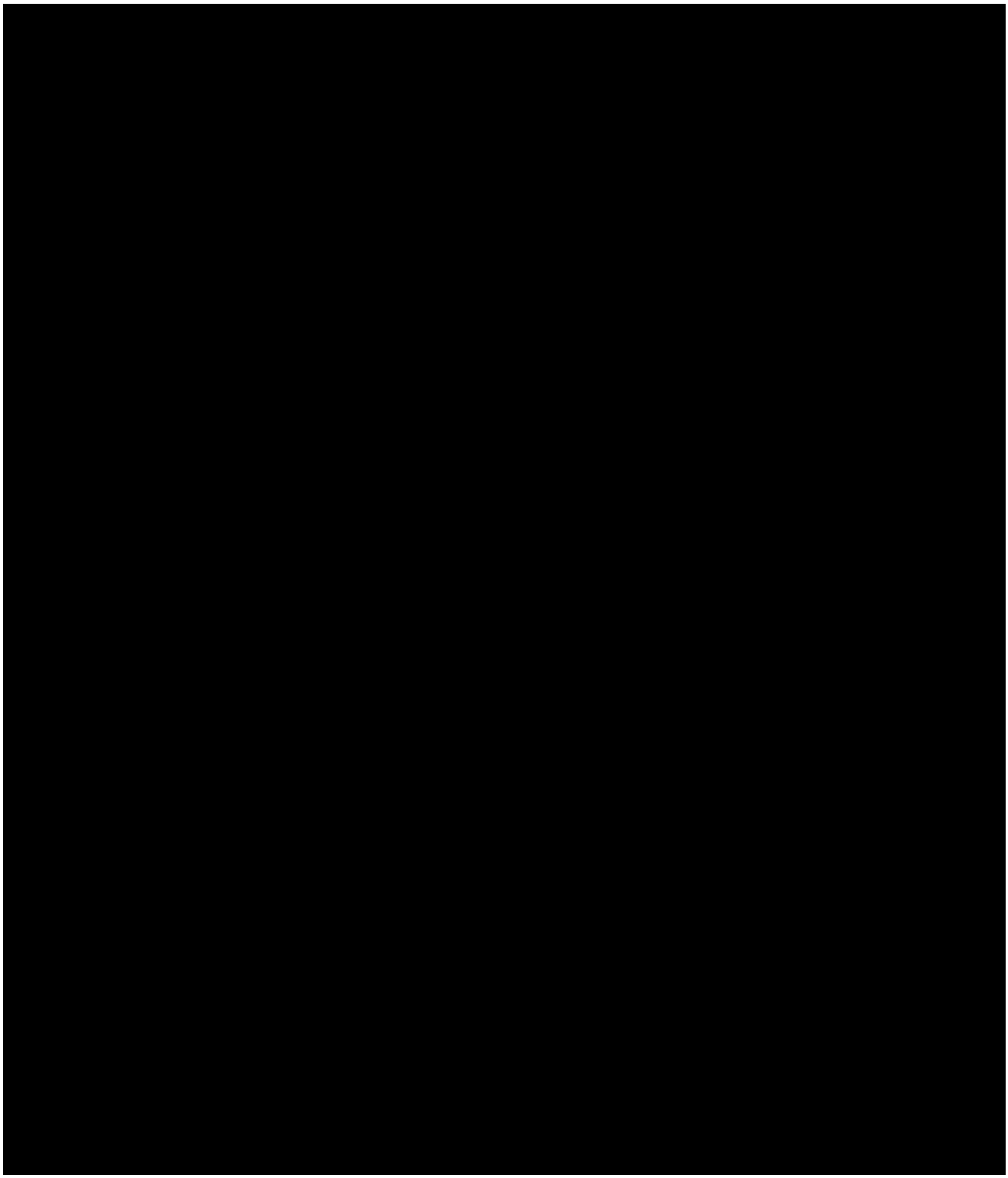

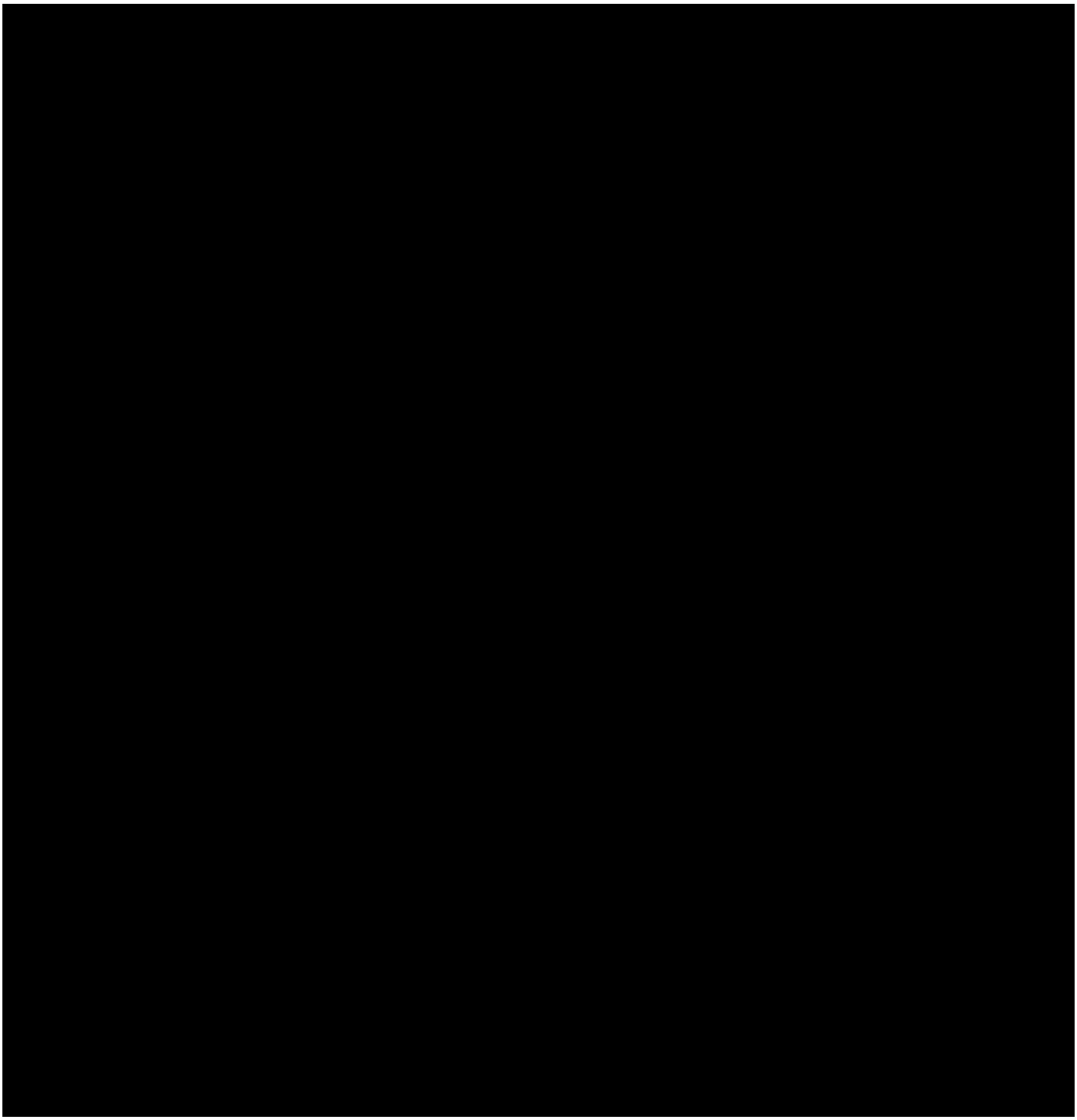

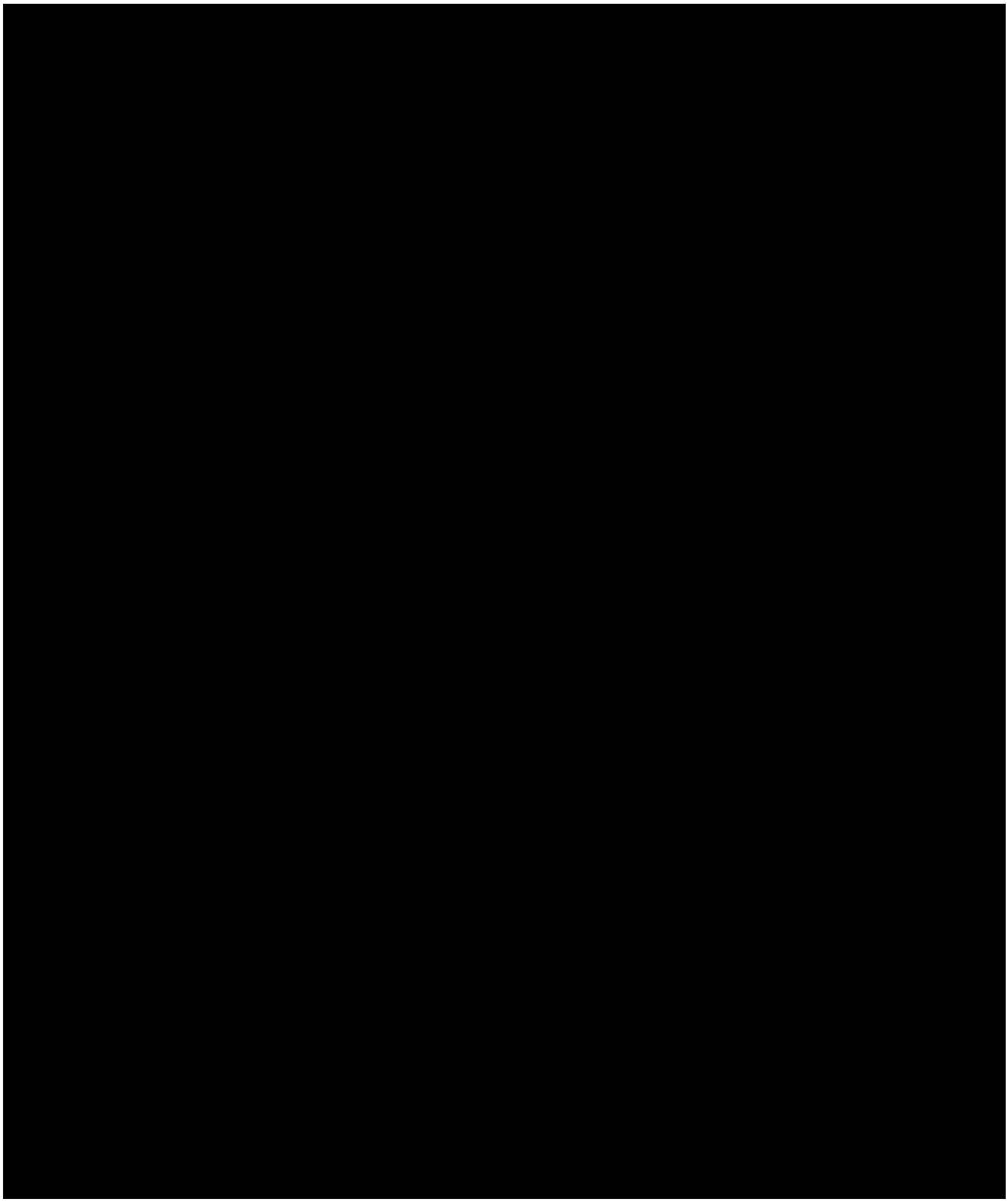

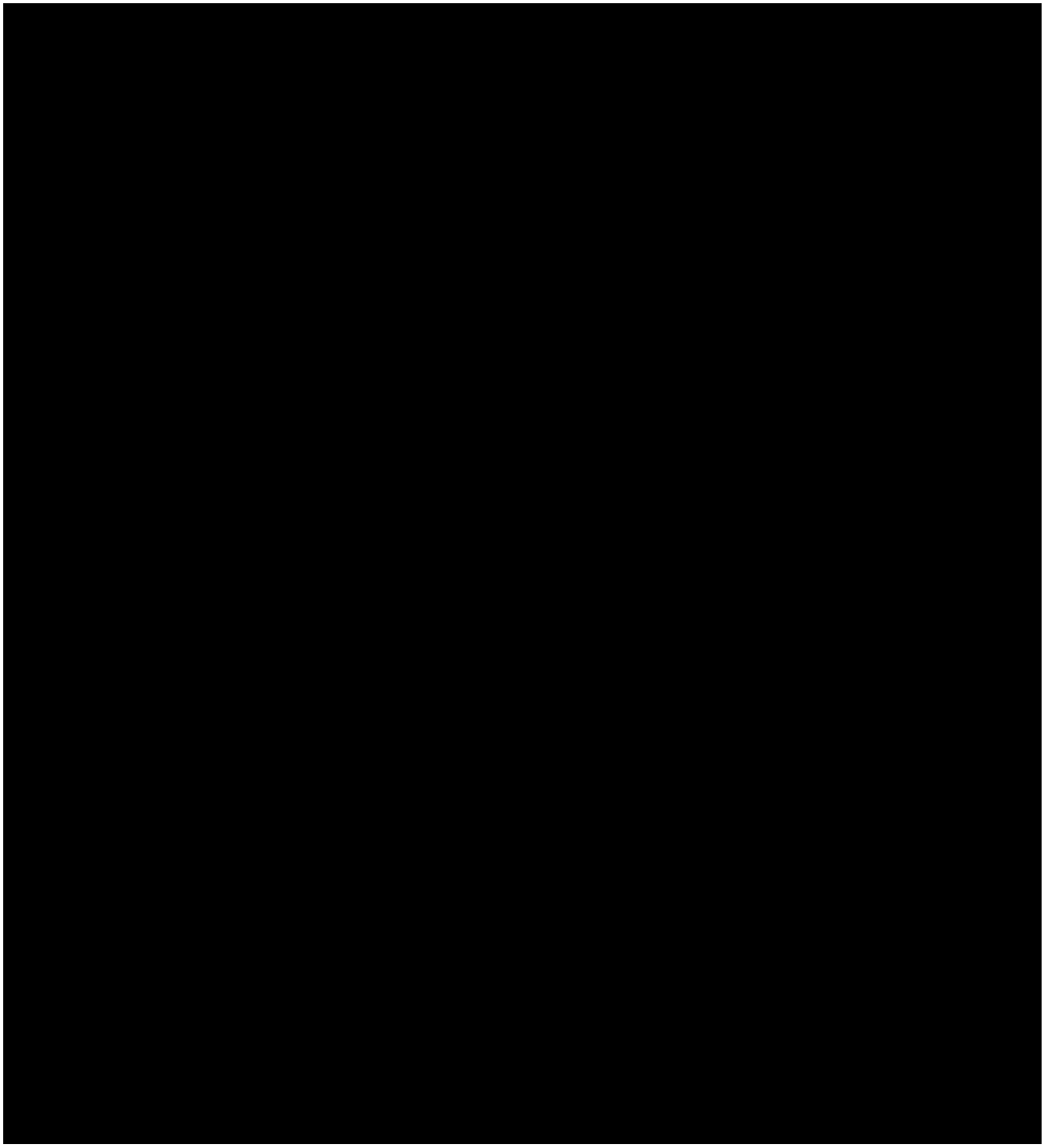

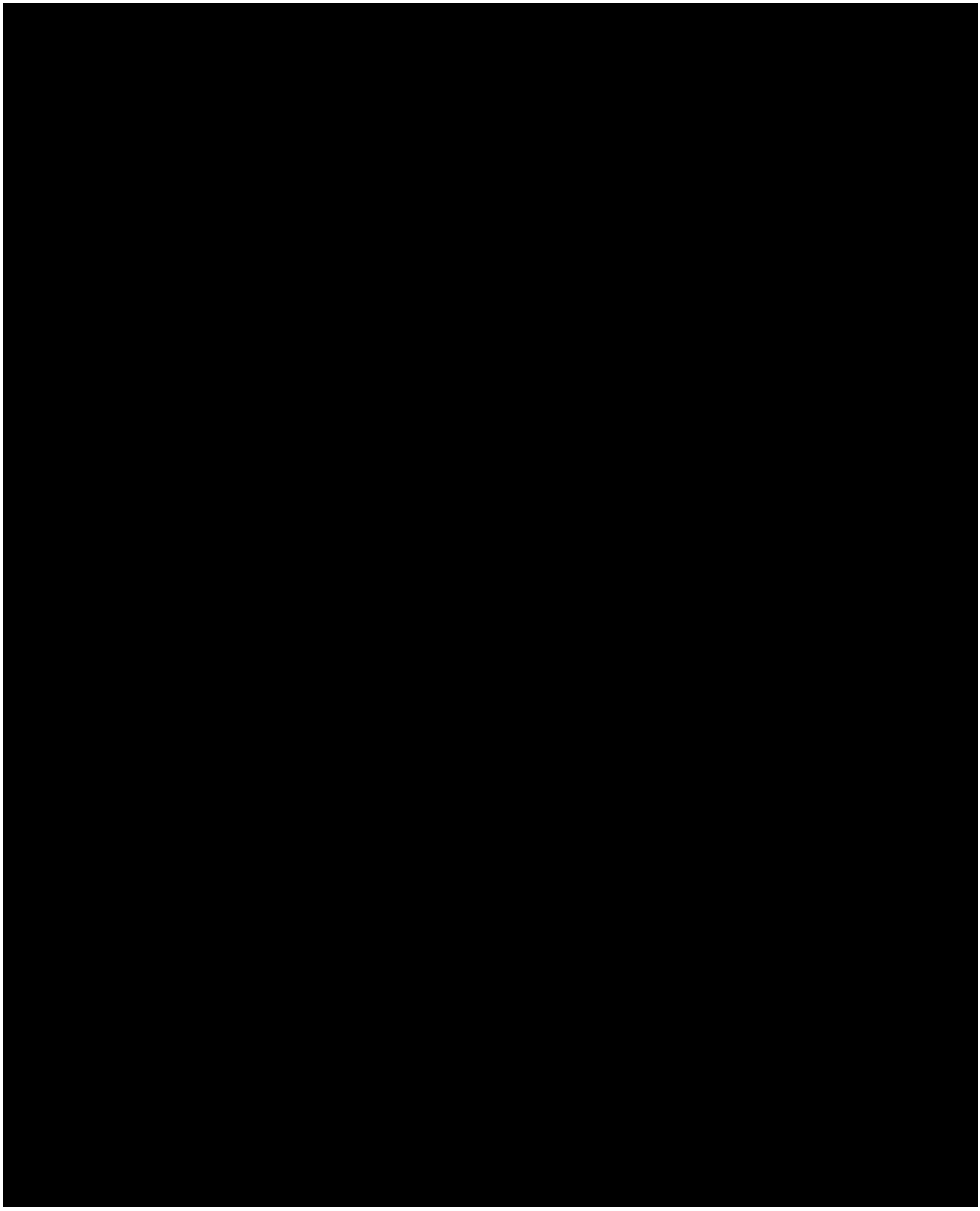

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