NCT03352453

Study ID: RAP-MD-20

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy and Safety Study of Rapastinel for Rapid Treatment of Symptoms of Depression and Suicidality in Adult Patients with Major Depressive Disorder

Protocol Date: 26 Sept 2017

1.0 TITLE PAGE

Naurex, an indirect subsidiary of Allergan, plc.
Madison, NJ 07940

A Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy and Safety Study of Rapastinel for Rapid Treatment of Symptoms of Depression and Suicidality in Adult Patients with Major Depressive Disorder

Study #RAP-MD-20

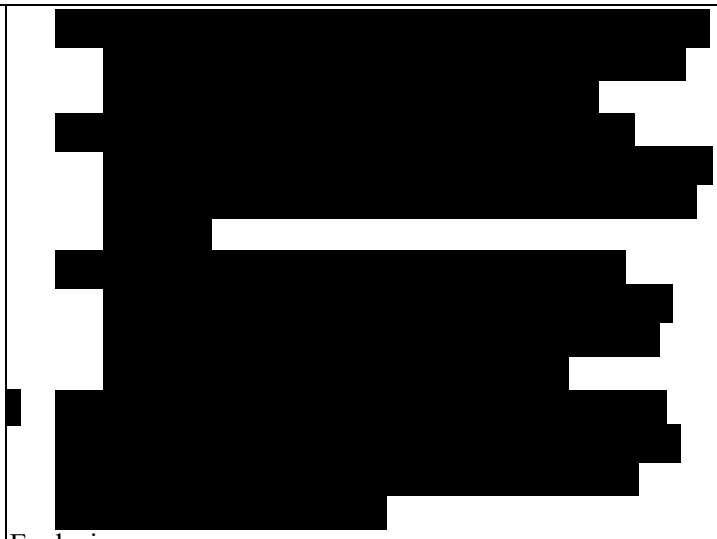
(3106-201-008)

IND #136,789

Original Protocol Date: 26 Sep 2017

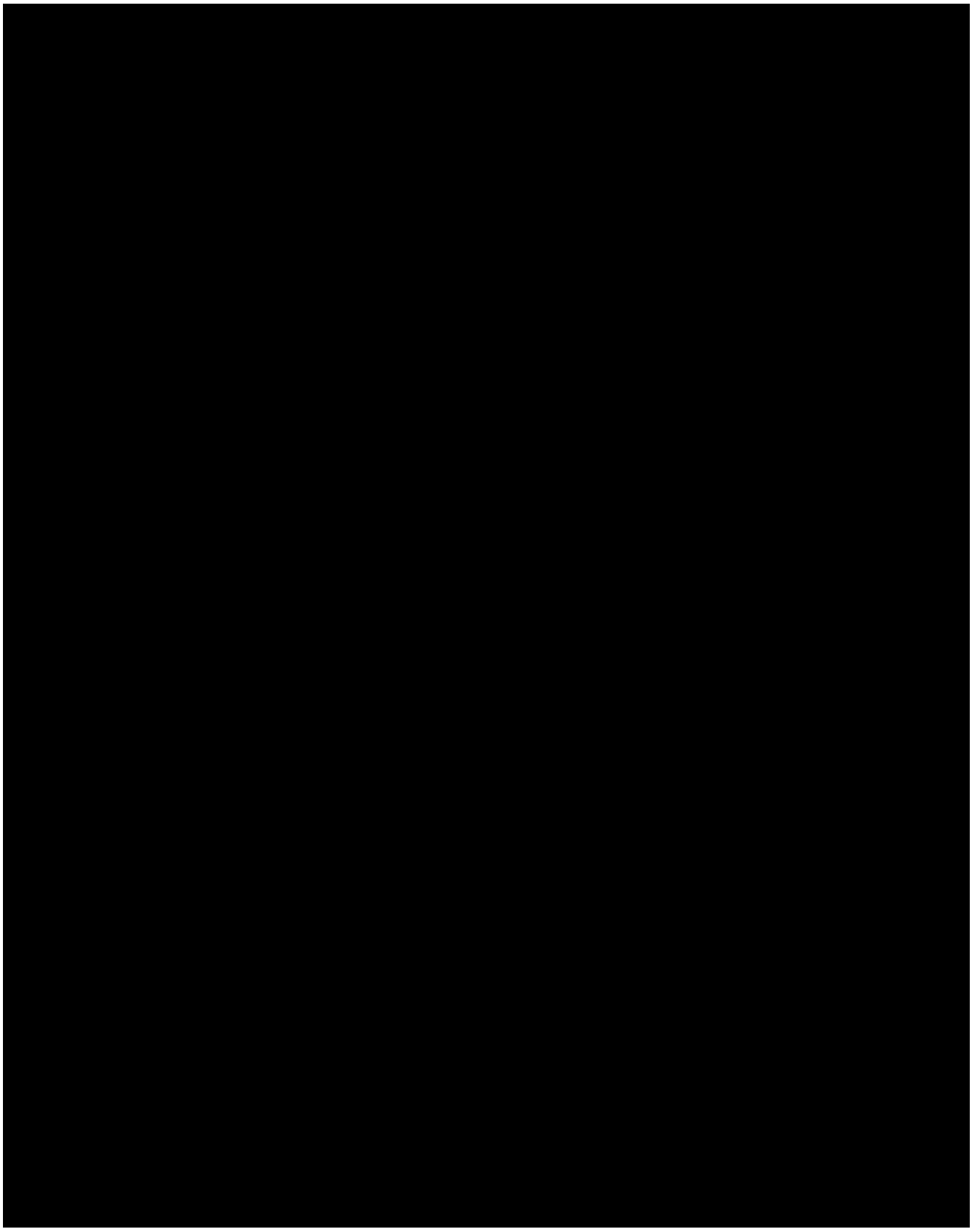
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

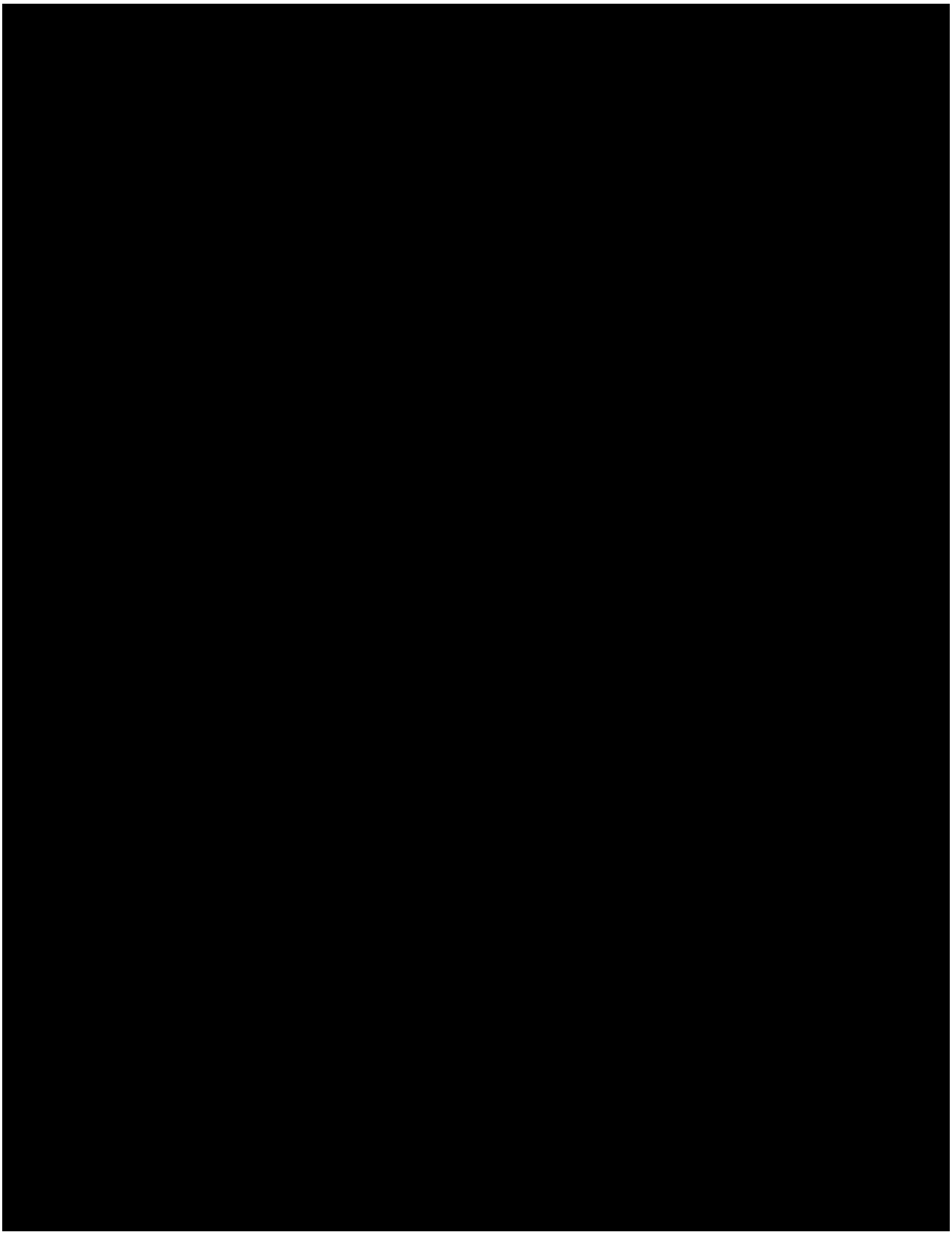
CLINICAL STUDY SYNOPSIS: Study RAP-MD-20	
Study Number	RAP-MD-20 (3106-201-008)
Title of Study	A Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy and Safety Study of Rapastinel for Rapid Treatment of Symptoms of Depression and Suicidality in Adult Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 20-30 study centers (United States)
Development Phase	2
Objective	To evaluate the efficacy, safety, and tolerability of rapastinel as a rapid treatment of symptoms of depression and suicidality in adult patients with major depressive disorder (MDD) who are at imminent risk of suicide
Study Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, 4-week, study in patients with MDD experiencing suicidality. Total study participation will be approximately 5 to 6 weeks in duration and will include the following periods: • Up to 5-day screening period • 4-week double-blind treatment period (DBTP) • 1-week safety follow-up period Patients are generally expected to remain in an inpatient setting through at least the completion of assessments conducted 4 days after the initial dose of investigational product (IP). During participation in the study, patients may be treated per local standard of care (SOC) with limited restrictions and IP will be administered in addition to SOC treatments.
Number of Patients	Approximately 300 planned to be enrolled
Diagnosis and Main Criteria for Inclusion	Inclusion: • Male or female outpatients, 18 to 65 years of age • Meet Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) criteria for MDD [redacted] • Have current, ongoing suicidality (ideation or behavior) of sufficient severity to warrant hospitalization based on the judgment of the investigator and at least one of the following:

	
	Exclusion:
	• DSM-5–based diagnosis of any disorder other than MDD that was the primary focus of treatment within 1 month before Visit 1
	• Have known lifetime history or currently meet 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
	• DSM-5–based diagnosis of borderline personality disorder or any other personality disorder of sufficient severity to interfere with participation in this study in the opinion of the investigator

Test Product, Dosage, and Mode of Administration	Rapastinel (450 mg weekly intravenous [IV] administration), prefilled syringe
Duration of Treatment	Up to 5-day screening period, followed by a 4-week DBTP, followed by a 1-week safety follow-up period
Reference Therapy, Dosage, and Mode of Administration	Placebo, weekly IV administration, prefilled syringe

Criteria for Evaluation	
Primary Endpoint	Change from baseline in MADRS total score at 1 day after first dose of IP
Key Secondary Endpoint	Change from baseline in S-STS total score at 1 day after first dose of IP
[redacted]	[redacted]
[redacted]	[redacted]
Statistical Methods	The primary and key secondary efficacy parameters will be analyzed using analysis of covariance (ANCOVA) models with terms for treatment, study center, and baseline. Baseline will be defined as the last measurement prior to the first dose of treatment. All safety parameters will be analyzed using descriptive statistics. Safety analyses will be based on the Safety Population, defined as all randomized patients who receive at least 1 dose of randomized IP. Efficacy analyses will be based on the Intent-to-Treat (ITT) Population, defined as all patients in the Safety Population with at least 1 post-randomization assessment of the MADRS total score.





3.0 TABLE OF CONTENTS

LIST OF FIGURES

4.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	serum β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
DBTP	double-blind treatment period
DSMB	Data Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register
GCP	good clinical practice
h	hours
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
[redacted]	[redacted]
MMRM	mixed-effects model for repeated measures
NMDAR	N-methyl-D-aspartate receptor
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]
SOC	standard of care
[redacted]	[redacted]
SIGMA	Structured Interview Guide for the MADRS
S-STS	Sheehan - Suicidality Tracking Scale
TEAE	treatment-emergent 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 give 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 20 to 30 study centers in the United States.

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

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

7.0 INTRODUCTION

Disease Burden of Major Depressive Disorder

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

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

MDD is a leading cause of disability in the United States (Murray et al, 2013). Moreover, MDD is known to be a significant risk factor for suicide and ischemic heart disease, as it accounted for 16 million of the disability adjusted life years associated with suicide and 4 million of the disability adjusted life years 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 that is a leading cause of disability in the world.

Disease Burden of Suicidality

Suicidality is a complex multifactorial public health problem with far-reaching consequences for individuals and families, as well as significant impacts on society at large. Suicide is the 10th leading cause of death in the United States, and each year over 40,000 die by suicide in the United States (Centers for Disease Control and Prevention. 2017). It is estimated that suicide costs the United States $51 billion annually (Centers for Disease Control and Prevention, 2010). Approximately 7% of the US population knew someone who died by suicide during the past 12 months (Berman, 2011) and these survivors are deeply impacted psychologically (Brent, 2010). Suicide rates have increased from 1999 through 2014 with greater increases since 2006, indicating that the impact of suicide is growing over time (Curtin et al, 2016). Suicidal ideation and behavior is a common comorbidity across the spectrum of mental health disorders although it is strikingly associated with mood disorders, particularly MDD. Depression is the psychiatric diagnosis most commonly associated with suicide and approximately 2% to 9% of patients with a lifetime diagnosis of depression die of suicide (Bostwick and Pankratz, 2000; Nock et al, 2010).

Rationale for Rapastinel as a Rapid Treatment of Symptoms of Depression and Suicidality in MDD

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 demonstrated antidepressant properties in relevant animal models, displayed cognitive enhancing properties in treated animals, and facilitated 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 hypothesized to produce its long-lasting antidepressant effects via triggering NMDAR-dependent processes that lead to increased sensitivity to LTP that persist for up to 2 weeks (Burgdorf et al, 2015).

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

Naurex, Inc initially developed rapastinel as a treatment for patients with MDD who manifest a serious and common aspect of the disease: inadequate response to existing antidepressant therapy. In Phase 2 studies, single doses of 5 or 10 mg/kg showed rapid antidepressant effects, with a large effect detected after 1 day. Repeated doses demonstrated a rapid, sustained antidepressant effect and were well tolerated with adjunctive treatment in patients with partial responses to their antidepressants. To date, rapastinel has been shown to be safe and well tolerated and the observed safety of rapastinel is significantly better than that of NMDAR antagonists, which induce psychotomimetic side effects and have abuse/diversion potential. Rapastinel showed a low propensity to induce psychotomimetic side effects or effects that might predict abuse potential. The available clinical data also suggest that rapastinel is not associated with the serious metabolic and extrapyramidal side effects seen with the atypical antipsychotics currently approved for adjunctive treatment of MDD.

The efficacy of rapastinel is consistent with that observed in several other studies utilizing NMDAR modulators (such as ketamine). Such NMDAR modulating drugs are increasingly being recognized as having potential as treatments for suicidality (Griffiths et al, 2014; Reinstatler and Youssef, 2015; Price and Matthew, 2015). Multiple small studies have been undertaken with ketamine (Burger et al, 2016; De Gioannis et al, 2014; Lee et al, 2015) and esketamine has entered late stage clinical trials (NCT03039192; NCT03097133) targeting suicidality after promising proof-of-concept results (Canuso et al, 2016a; Canuso et al, 2016b). Of interest are recent indicators that the anti-suicidality effects of ketamine may be due at least in part to procognitive effects (Price et al, 2009; Price et al, 2014). Preclinical data indicate that rapastinel has strong procognitive effects which has led to suggestions from experts that the study of rapastinel for suicidality is warranted (Lee et al, 2016). The rapid onset of efficacy and favorable safety profile seen with rapastinel provide a compelling rationale for evaluating its potential for rapid treatment of symptoms of depression and suicidality in MDD.

The purpose of this study is to prospectively confirm that rapastinel, when administered along with standard of care (SOC) at a dose of 450 mg as a short IV infusion in adult patients with MDD who are at imminent risk of suicide, is significantly superior to placebo in rapidly reducing symptoms of depression and suicidality. Furthermore, the safety and tolerability of rapastinel will be investigated. The study is intended to support an application for regulatory approval of rapastinel as a rapid treatment for symptoms of depression and suicidality in adult patients with MDD at imminent risk of suicide.

8.0 STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy, safety, and tolerability of rapastinel as a rapid treatment of symptoms of depression and suicidality in adult patients with MDD who are at imminent risk of suicide.

Efficacy Objectives

- Primary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo as a rapid treatment of MDD symptoms in adult patients with MDD who are at imminent risk of suicide, as measured by the change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) total score at 1 day post-first dose of treatment

- Key secondary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo as a rapid treatment of suicidality symptoms in adult patients with MDD who are at imminent risk of suicide, as measured by the change from baseline on the Sheehan-Suicidality Tracking Scale (S-STS) total score at 1 day post-first dose of treatment

[redacted]

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 4-week, fixed-dose study comparing rapastinel with placebo in patients with a diagnosis of in patients with MDD defined by DSM-5 criteria. The study will be approximately 5 to 6 weeks in duration and will include the following periods (Figure 9.1.3-1):

- Approximately 5-day screening period
- 4-week double-blind treatment period (DBTP)
- 1-week safety follow-up period

Approximately 300 patients are planned to be randomized in the DBTP (150 patients per treatment group).

A schematic of the study design is presented in Figure 9.1.3-1. The Schedule of Evaluations is provided in Section 2.0 and detailed descriptions of each study visit can be found in Section 9.5.5.

9.1.1 Screening Period

Consent and screening procedures are to be conducted in an inpatient setting for suicidality (see Inclusion Criterion #3). After providing written consent, patients will enter a screening period of no more than 5 days. Every effort should be made to conduct all procedures as early as possible in the Screening. Patients will not receive any investigational product (IP) during the screening period. Treatment for suicidality should proceed per local SOC with limited restrictions (Section 9.4.9.1).

Efforts should be made to minimize the length of the Screening Period and proceed to randomization or screen failure as rapidly as clinically reasonable. Patients meeting the eligibility criteria at Assessment/Visit 2 (Baseline) will be assigned a treatment by the interactive web response system (IWRS) and enter the DBTP.

9.1.2 Double-blind Treatment Period

Patients will be randomized in a ratio of 1:1 to 1 of 2 treatment groups: rapastinel 450 mg IV weekly injection or placebo IV weekly injection. During participation in the study, patients may be treated per local SOC with limited restrictions (see Section 9.4.9.1) and IP will be administered in addition to SOC treatments.

There will be 4 study visits during the first week of the DBTP:

- Visit 2: Baseline IP dosing

Note: If Baseline is ≤ 1 day since Screening assessments were conducted, specified Baseline assessments do not need to be repeated and Screening assessments will count as Baseline (see Section 9.5.5.2 for details).

- Visit 3: 4 hours following the baseline IP dosing
- Visit 4: 1 day following the baseline IP dosing
- Visit 5: 4 days following the baseline IP dosing

There will be 2 study visits during the second week of the DBTP:

- Visit 6: 7 days following Visit 2
- Visit 7: 1 day following Visit 6

There will be 3 weekly study visits during the remainder of the DBTP:

- Visit 8: 14 days following Visit 2
- Visit 9: 21 days following Visit 2
- Visit 10: 28 days following Visit 2

If necessary, study visits may be conducted up to 2 days before or after the scheduled visits except for Assessment/Visit 3 (which must be conducted approximately 4 hours after Visit 2), Visit 4 (which must be conducted 1 day after Visit 2), and Visit 7 (which must be conducted 1 day after Visit 6). All patients who receive IP must complete Visit 10 or Early Termination (ET) Visit.

Generally, it is expected that patients will remain in an inpatient setting until approximately 4 days after IP is administered (Visit 5), although this may be adjusted at the investigator's discretion to be shorter or longer to accommodate local SOC based upon the patient's clinical condition. Patients who require hospitalization for greater than 14 days (Visit 8) after initial dose of IP should be evaluated regarding other potential treatment options and appropriateness of continuing in the study.

Upon completion of the DBTP, patients will enter a 1-week safety follow-up period.

9.1.3 Safety Follow-up Period

Patients completing the DBTP and patients who prematurely discontinue from the study before completing 4 weeks of double-blind treatment should enter the 1-week safety follow-up period.

Additional follow-up visits may be scheduled within 30 days of last dose of IP or last study visit, if necessary for safety reasons.

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

This multicenter, randomized, placebo-controlled, parallel-group study with a 4-week DBTP, was designed based on prior studies that established rapastinel efficacy and safety in adult patients with MDD as well as consideration of the sponsor's participation in and recommendations from a recent International Society for CNS Clinical Trials and Methodology Consensus Meeting (Chappell et al, 2017). The design was further developed with the aid of an advisory board conducted on 24 Apr 2017 with participation from several recognized experts in the study of suicidality. In this study, investigators will enroll patients 18 through 65 years of age who meet the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria for MDD (American Psychiatric Association, 2013). The MDD diagnosis will be confirmed using the Mini International Neuropsychiatric Inventory (MINI). The symptoms and severity of MDD will be assessed using the MADRS (Section 9.5.1.2.1). The symptoms and severity of suicidality will be assessed using the S-STS (Section 9.5.1.2.2).

Allergan has carefully considered the overall study design and setting in light of the unique requirements of conducting a clinical trial in this at-risk population. Study centers will have experience with the study population and will be encouraged to apply available guidelines to minimize patient risk or distress. Because patients will enter the study with symptoms of acute suicidality, the study is a partially inpatient design with a required initial period of hospitalization of flexible duration intended to accommodate the variability of SOC across study centers while ensuring that patients receive appropriate monitoring. Patients may enter the study once being admitted to an inpatient setting after initially presenting at an emergency room setting or via referral from an outpatient healthcare provider, such as a psychiatric private practice or clinic. Generally, it is expected that patients will remain in an inpatient setting until approximately 4 days after IP is administered, although this may be adjusted at the investigator's discretion to be shorter or longer to accommodate local SOC based upon the patient's clinical condition. Patients who require hospitalization for greater than 14 days after initial dose of IP should be evaluated regarding other potential treatment options and appropriateness of continuing in the study.

Dose selection information is presented in Section 9.4.5. The planned dosing regimen is based on experience from previous rapastinel studies.

A placebo treatment group is included in the study to comply with worldwide regulatory preferences (Laughren, 2001; Gispen-de Wied et al, 2012), since placebo-controlled superiority trials have been shown to be conducive to higher-quality studies and to provide more reliable outcomes (Feifel, 2008; Laughren, 2001; Gispen-de Wied et al, 2012). Additionally, from a scientific point of view, randomized double-blind comparisons versus placebo are needed to permit adequate evaluation of efficacy. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions to the IP (EMA guidance, 2013). At present, there is no approved pharmacologic therapy as an acute intervention for treatment of symptoms of suicidality and depression. However, patients who present with imminent risk of suicide require careful assessment, monitoring, and are typically treated with pharmacologic agents based upon their primary diagnosis and comorbidities (Jacobs et al, 2010). For this reason, the IP will be given in addition to standard therapy. The use of placebo given in addition to standard therapy should not cause irreversible health problems or extreme suffering (depression is recognized by the FDA as a condition in which there is substantial improvement and variability in placebo groups) (FDA Guidance for Industry: E10, May 2001).

Safety and efficacy assessments are included at every visit to determine adequacy of response, safety, and tolerability. In the event of insufficient therapeutic response or worsening of the patient's initial condition, the IP should be discontinued and an alternative treatment will then be allowed (Section 9.4.12). An independent Data and Safety Monitoring Board (DSMB) will evaluate safety data during the study (Section 9.8).

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

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

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

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

3. Have current, ongoing suicidal ideation or behavior of sufficient severity to warrant hospitalization based on the judgment of the investigator and at least one of the following:

[redacted]

5. Meet DSM-5 criteria for MDD[redacted] with a current major depressive episode of at least 4 weeks and not exceeding 24 months in duration at Visit 1)

[redacted]

8. If female of childbearing potential, have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test (local laboratory results may be used for purposes of inclusion)

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

9.3.2 Exclusion Criteria

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 1 month before Visit 1. Some comorbid conditions (eg, generalized anxiety disorder, social anxiety disorder, or specific phobias) are acceptable provided they play a secondary role in the balance of symptoms, are not the primary driver of treatment decisions, and are not excluded in other criteria

2. Have known lifetime history or currently meet DSM-5 criteria for:

    a. Schizophrenia spectrum or other psychotic disorder

    b. Bipolar or related disorder

    c. Major neurocognitive disorder

    d. 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

    e. Dissociative disorder

    f. Posttraumatic stress disorder

    g. MDD with psychotic features

[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 1 of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Pregnancy
- Withdrawal of consent
- AE
    - Any patient who meets any of the following criteria at any point during the study must be withdrawn from participation due to suicidality-related AE:
        a) A treatment-emergent suicide attempt, interrupted attempt, or aborted attempt
        b) Significant increase in suicide risk, requiring removal from study as judged by the investigator, based on all available information such as the psychiatric interview or information collected in the study assessments

Note: In the event that a patient is withdrawn for a suicidality-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
- Protocol deviation
- Lost to follow-up
- Study terminated by sponsor
- Study center terminated by sponsor
- Other

All randomized patients who prematurely discontinue from the study, 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 10. All patients discontinuing the study prematurely should enter the 1-week safety follow-up period.

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

9.3.4 Patient Replacement Procedures

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

9.4 TREATMENTS

Patients meeting the eligibility criteria at the end of Visit 2 (Baseline) will be randomized in double-blind fashion to 1 of 2 treatment groups: placebo or rapastinel 450 mg weekly. The treatments will be given in a double-blind fashion. The study treatments are to be given in addition to local SOC treatment with limited restrictions as described in Section 9.4.9.1.

9.4.1 Treatments Administered

The 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 post-administration 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 state and local regulations/SOC, to resuscitate a patient in the event of a medical emergency.

At IP administration visits conducted on an outpatient basis after hospital discharge, the patient should not be released 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 release 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)

9.4.2 Identity of Investigational Products

Rapastinel 450 mg IV Prefilled Syringes: [redacted]

Placebo rapastinel IV Prefilled Syringes: [redacted]

[redacted]

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

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

9.4.3 Handling of Investigational Products

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.

9.4.4 Method of Assigning Patients to Treatment Groups

After a patient signs the ICF at Screening (Visit 1), study personnel will register the patient in the IWRS, and the system will assign the patient a sequential PID. [redacted]

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

9.4.5 Selection of Dosages in the Study

The dose of rapastinel in this study was selected based on 2 Phase 2 clinical studies in patients with MDD, in which single IV doses of rapastinel 5 mg/kg and 10 mg/kg were shown to produce marked antidepressant effects within 1 day that lasted approximately 1 week or longer in responding patients.

A 450-mg unit dose is expected to be appropriate for most patients as this represents a dose of 4.5 mg/kg in a 100-kg patient and a dose of 9 mg/kg in a 50-kg patient.

9.4.6 Selection and Timing of Dose for Each Patient

The IP will be administered IV using the assigned single-use prefilled syringes at Visits 2, 6, 8, and 9.

9.4.6.1 Screening Period

At Screening (Visit 1) after written consent is obtained, patients enter a screening period of up to 5 days. No IP is administered during the screening period.

9.4.6.2 Double-blind Treatment Period

Patients who meet all eligibility criteria at Screening (Visit 1) and who continue to meet all the eligibility criteria for participation in the study at the Baseline Visit (Visit 2) will be assigned an IP kit number via IWRS at Baseline (Visit 2). Patients will receive the first dose of IP that day. The IP kit numbers will also be assigned by IWRS at subsequent treatment visits (ie, Visits 6, 8, and 9).

Patients will receive either rapastinel 450 mg or placebo from a prefilled single-dose syringe at Visits 2, 6, 8, and 9.

9.4.6.3 Safety Follow-up Period

Patients who complete 4 weeks of randomized treatment and those who discontinue the study prematurely should enter the safety follow-up period. No IP is administered during the safety follow-up period and patients may be treated as deemed appropriate by the investigator.

9.4.7 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.

9.4.8 Unblinding

Any unblinding at the study center level should be done only in an emergency that requires identification of the IP for the medical management of the patient. The investigator must notify the Medical Safety Physician immediately (refer to Appendix II) and a full written explanation must be provided if the blind is broken. Before IP is unblinded, every attempt should be made to discuss the case with the study physician or Medical Safety 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.

9.4.9 Prior and Concomitant Therapy

Medication history (psychotropic medication history during the previous 2 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.

9.4.9.1 Permitted Medications/Treatments

[redacted]

[redacted]

9.4.10 Other Restrictions

9.4.10.1 Alcohol

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

9.4.10.2 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.

9.4.11 Monitoring Treatment Compliance

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

9.4.12 Treatment After Discontinuation

Patients whose MDD or suicidality 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.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Diagnostic and Efficacy Assessments

9.5.1.1 Diagnostic Assessments

[redacted]

[redacted]

9.5.1.2 Efficacy Assessments

The efficacy assessments (MADRS and S-STS) 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. 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.

The MADRS will be evaluated at the timepoints indicated in Schedule of Evaluations (Section 2.0) using the Structured Interview Guide for the MADRS (SIGMA) methodology (Williams and Koback 2008). At Screening (Visit 1) and Baseline (Visit 2) the MADRS will be administered with a look-back timeframe of 1 week. At all other administrations, the MADRS will be administered with a look-back timeframe of "since last evaluation".

9.5.1.2.2 Sheehan - Suicidality Tracking Scale

The Sheehan - Suicidality Tracking Scale (S-STS) (Sheehan et al, 2014a; Sheehan et al, 2014b) is a patient-report informed, clinician-rated scale used to rate the severity of both suicidal ideation and behavior. The scale is compatible with the FDA categories for prospective assessment of suicidal ideation and behavior (FDA, 2012). Developed for use as both a safety and efficacy outcome measure in research and in clinical settings, the scale is sensitive enough to detect an efficacy signal in conventional sample sizes used in clinical trials. Each administration of the S-STS will include the patient- and clinician-rated "Global Severity of Suicide Impulses, Thoughts, and Behaviors" items extracted from the Sheehan - Suicidality Tracking Scale: Clinically Meaningful Change Measures (S-STS CMCM) (Sheehan et al, 2014b).

The S-STS will be evaluated at the timepoints indicated in the Schedule of Evaluations (Section 2.0). At Screening (Visit 1) and Baseline (Visit 2) the S-STS will be administered with a look-back timeframe of 1 week. At all other administrations, the S-STS will be administered with a look-back timeframe of "since last evaluation".

9.5.1.2.3 Clinician's Assessment of Readiness for Hospital Discharge

The clinician's assessment of readiness for hospital discharge will capture the date of readiness for discharge based solely on clinical factors associated with the patient's initial hospitalization for acute suicidality, regardless of whether actual discharge occurred on that date. The assessment should reflect the date upon which the patient has clinically improved to the extent that they would be eligible for discharge without consideration of protocol requirements, social factors, or other reasons that may prevent the actual discharge from occurring on that date. This assessment will be administered by a psychiatrist or other clinician who has extensive professional training and experience in the diagnosis of mental illness and is authorized to make decisions regarding hospitalization and discharge of patients.

[redacted]

9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

9.5.2.1 Adverse Events

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

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

Examples of AEs are as follows:

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

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

9.5.2.1.1 Causality Assessment

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

Is there a reasonable possibility the IP caused the event?

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

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

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

- There is no reasonable temporal relationship between the IP and the event, or
- The patient did not take the IP, or
- The event is likely to be attributed to underlying/concurrent disease or other factors, or
- The event is commonly occurring in the (study) population independent of IP exposure

9.5.2.1.2 Severity Assessment

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

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

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

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

9.5.2.1.3 Serious Adverse Events

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

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

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

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

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

Any postbaseline *worsening* (as opposed to lack of improvement) of symptoms of suicidal ideation or behavior that is clinically significant based on the judgment of the investigator should be captured as an SAE.

Any extension of hospitalization beyond 14 days postbaseline for symptoms of suicidal ideation, behavior, or depression (eg, lack of improvement over 14 days), excluding other reasons such as placement issues, should be captured as an SAE.

9.5.2.1.4 Reporting Adverse Events and Serious Adverse Events

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

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

For every AE, the investigator must:

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

- Document the outcome of the AE

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

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

9.5.2.2 Immediate Reporting of Serious Adverse Events and Events of 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 the sponsor 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 provided 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]

9.5.4 Health Economic and Outcomes Research Assessments

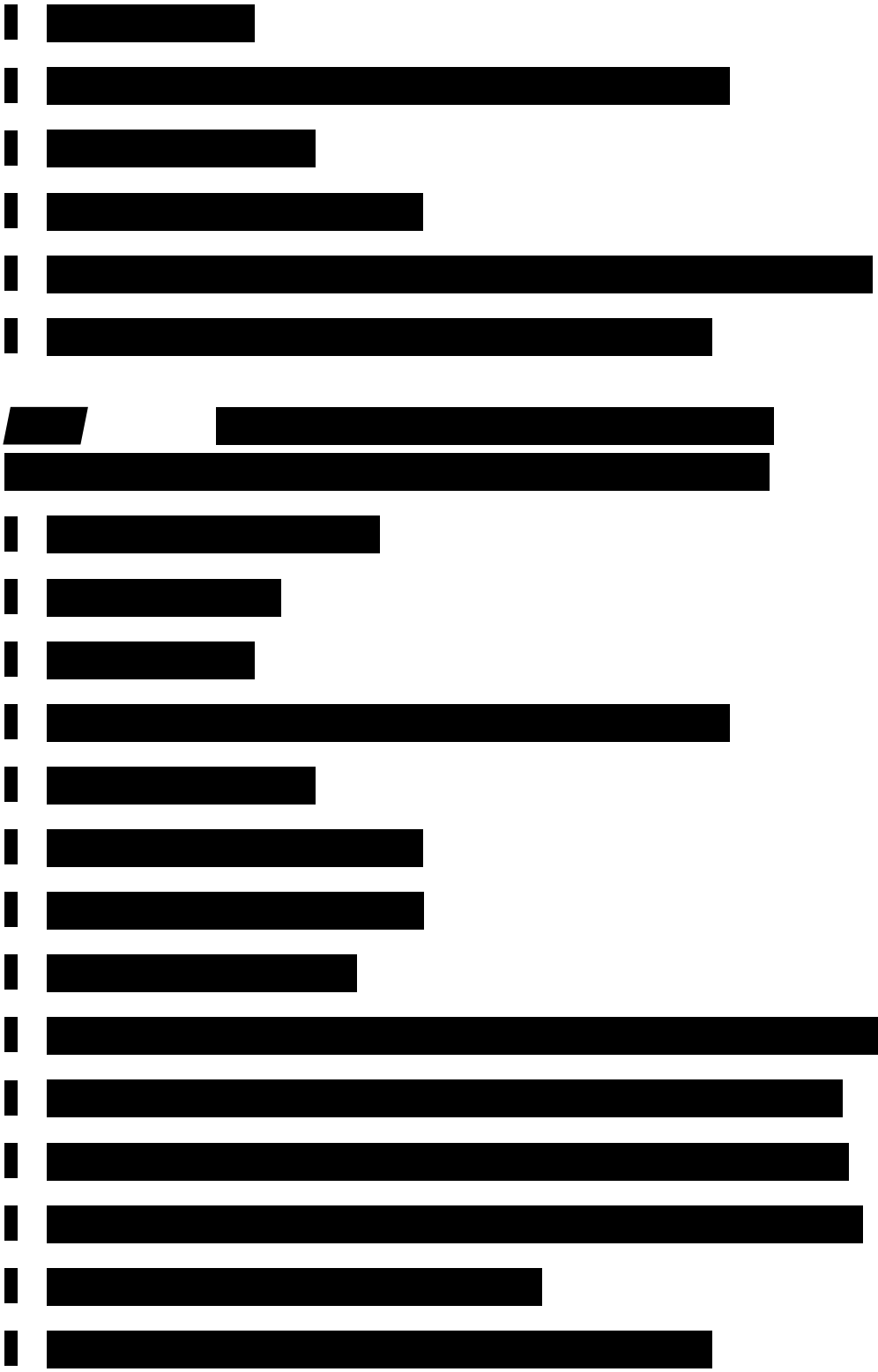
Health outcomes will not be assessed in this study.

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

9.5.5.12 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, 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.

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. [redacted] will be captured using an electronic source tablet-based system, with paper source to be used only as a backup if it is not possible to use the tablet-based system. 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

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

9.7.1.1 Screened Population

The Screened Population will consist of all patients who sign informed consent and receive a PID number.

9.7.1.2 Randomized Population

The Randomized Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

9.7.1.3 Safety Population

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of randomized IP.

9.7.1.4 Intent-to-Treat Population

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

9.7.2 Patient Disposition

The number and percentage of patients in the Randomized, Safety, and ITT populations will be summarized by treatment group and study center; the Screened Population will only be summarized overall and by study center.

Screen failures (ie, patients screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population. The number and percentage of patients who complete the DBTP, patients who prematurely discontinue during the same period and who enter the safety follow-up period will be presented for each treatment group and pooled across treatment groups for the Randomized Population. The reasons for premature discontinuation from the DBTP as recorded on the termination pages of the eCRFs will be summarized (number and percentage) by treatment group for the Randomized Population.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, body mass index [BMI]) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

The number and percent of patients who received 1, 2, 3, and 4 randomized IV doses will be summarized by treatment group for the Safety Population.

Prior medication is defined as any medication taken before the date of the first dose of randomized IP. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of randomized IP.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a patient will only be counted once.

9.7.4.2 Measurement of Treatment Compliance

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

9.7.5 Efficacy Analyses

All efficacy analyses will be based on the ITT Population, unless stated otherwise. The baseline for each specific efficacy endpoint is defined as the last measurement prior to the first dose of randomized treatment. All statistical hypothesis tests will be performed at the 2-sided 5% significance level for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with < 2 patients in ≥ 1 treatment group in the ITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes ≥ 2 ITT patients within the center. Pooling will be done using the following algorithm:

Based on the number of ITT patients, small centers will be ordered from the largest to the smallest, and centers of the same size will be ordered from the largest center code to the smallest center code. The pooling process starts with the largest small center from the top, which will be pooled with the smallest from the bottom until a non-small center is formed. The process will be repeated using the small centers left out after the first pass. If any centers are left out at the end of the process, they will be pooled with the smallest pseudo-center. If there is > 1 smallest pseudo-center, the pseudo-center with the smallest center code will be selected. In case the pseudo-center formed by pooling all small centers is still a small center, it will be pooled with the smallest non-small center. If there is > 1 smallest non-small center, the one with the smallest center code will be selected.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter will be the change from baseline in MADRS total score at 1 day after first dose of treatment. The primary analysis will be performed using an analysis of covariance (ANCOVA) model with terms for treatment, study center, and baseline MADRS total score. The analysis will be performed based on postbaseline scores using only the observed cases without imputation of missing values. The treatment difference for rapastinel versus placebo will be estimated and reported along with the corresponding 95% CI and the p-value for superiority testing.

9.7.5.2 Key Secondary Efficacy Parameter

The key secondary efficacy parameter will be the change from baseline in S-STS total score at 1 day after first dose of treatment. The same statistical method for the primary efficacy parameter will be used for the key secondary efficacy parameter with baseline S-STS total score as the covariant in the ANCOVA model.

To control the overall type I error rate for multiple comparisons of rapastinel with placebo for primary and key secondary endpoints, Hochberg testing procedure will be implemented.

[redacted]

[redacted]

[redacted]

[redacted]

9.7.6.1 Adverse Events

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

An AE (classified by preferred term) will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of IP or was present before the date of the first dose of IP and increased in severity after the first dose of IP. If more than 1 AE is reported before the first dose of IP and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the DBTP that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of IP will not be considered as a TEAE.

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

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

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

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

An SAE that occurred between the date of the first dose of IP and 30 days after the date of the last dose of IP, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs will be summarized by preferred term and treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.

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

[redacted]

[redacted]

[redacted]

9.7.7 Health Economics and Outcomes Research Analyses

Not applicable.

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

This study will randomize approximately 300 patients to the rapastinel 450 mg and placebo groups in a 1:1 ratio. The primary efficacy endpoint is the change from baseline in the MADRS total score at 1 day after the first dose of treatment. Assuming the SD is 10 points, a sample size of 150 patients per treatment group will provide 90% power to detect a difference of 3.76 points for a rapastinel dose versus placebo at a 2-sided significance level of 5%.

9.7.10 Computer Methods

Statistical analyses will be performed using version [redacted].

9.8 DATA AND SAFETY MONITORING BOARD

The study will be conducted under the supervision of an independent 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 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.

9.10 PROTOCOL DEVIATIONS

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

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

10.0 STUDY SPONSORSHIP

This study is sponsored by Naurex, an indirect subsidiary of Allergan, plc.

10.1 STUDY TERMINATION

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

10.2 REPORTING AND PUBLICATION

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

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

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The investigator must provide the following to the sponsor before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the sponsor for submission to the FDA.
- A fully executed contract
- The curricula vitae for the investigator and all subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1.
- A copy of the IRB-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB members or the 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-20 [3106-201-008]) 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 from 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 . . .")

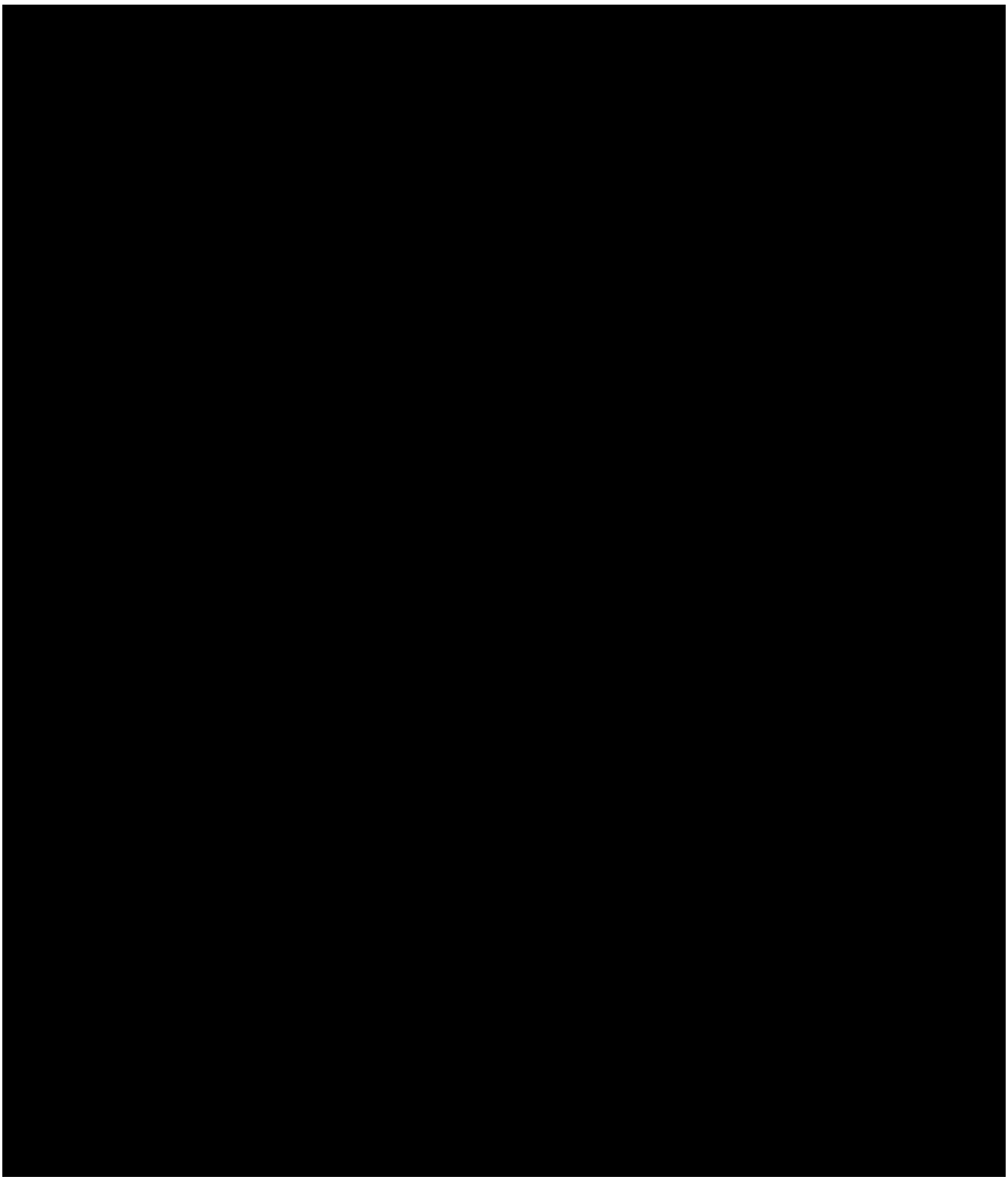
- A place for the patient's signature and date of signing the ICF

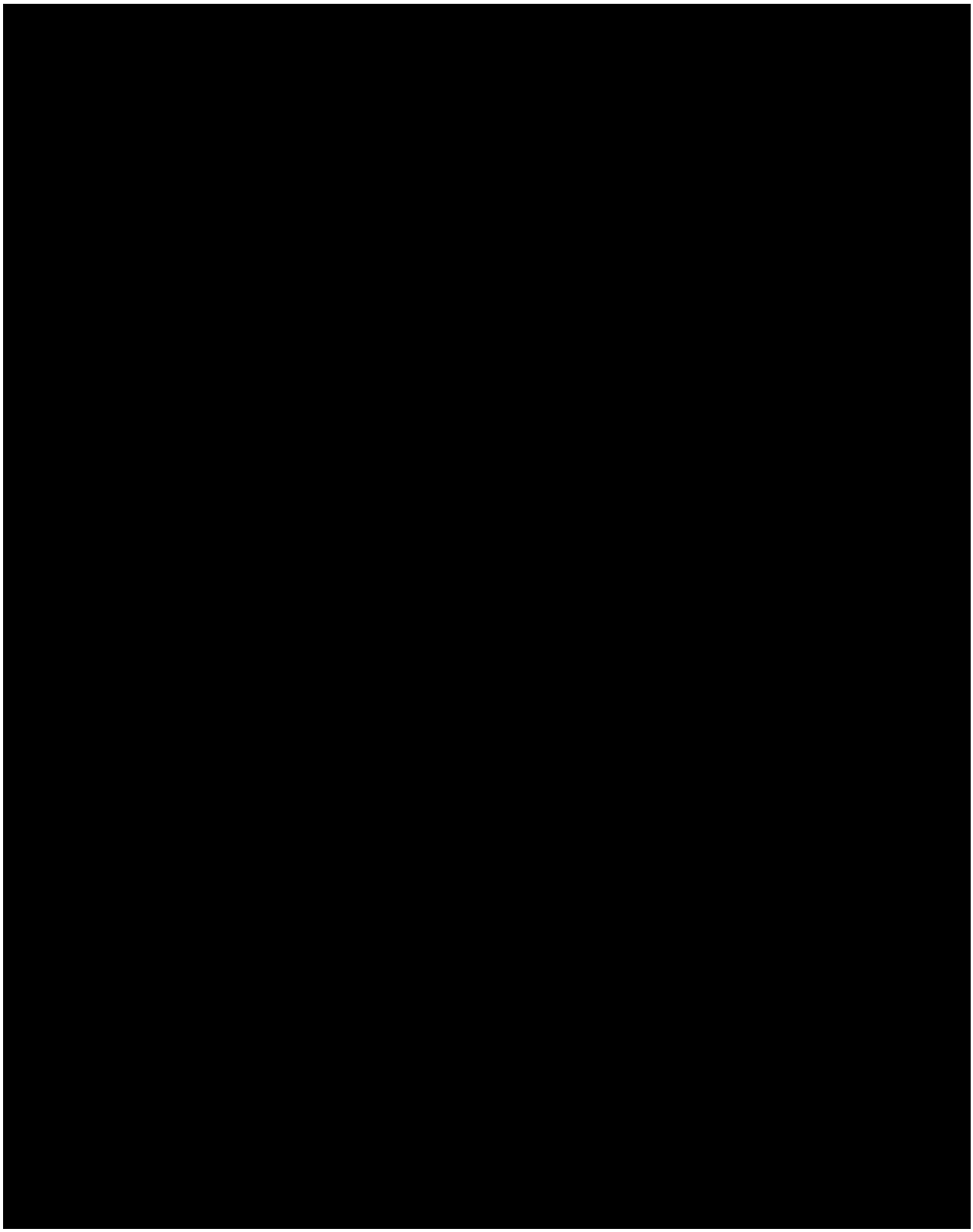
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

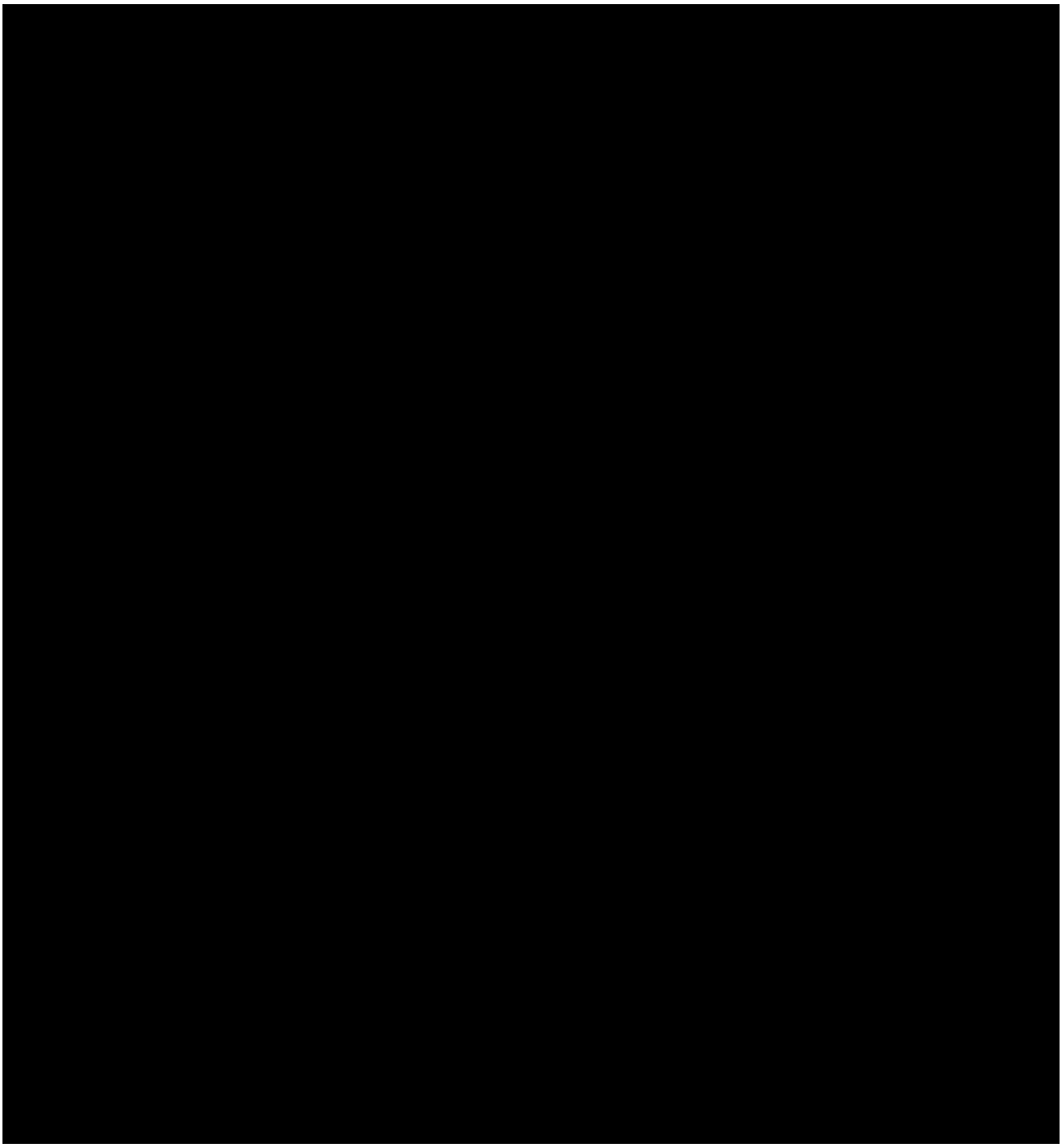
A copy of the signed consent form must be given to the patient.

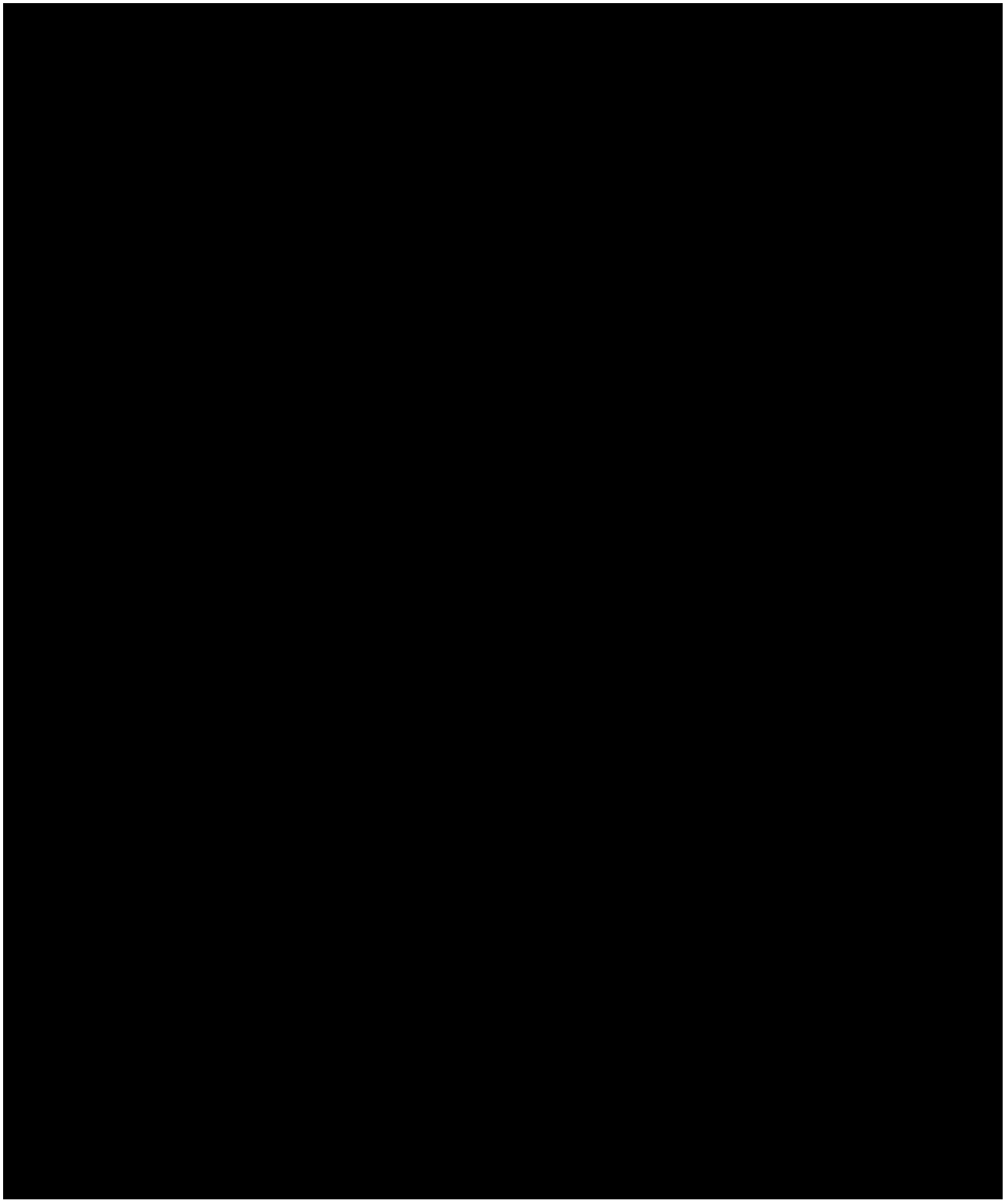
APPENDIX II. CONTACT INFORMATION

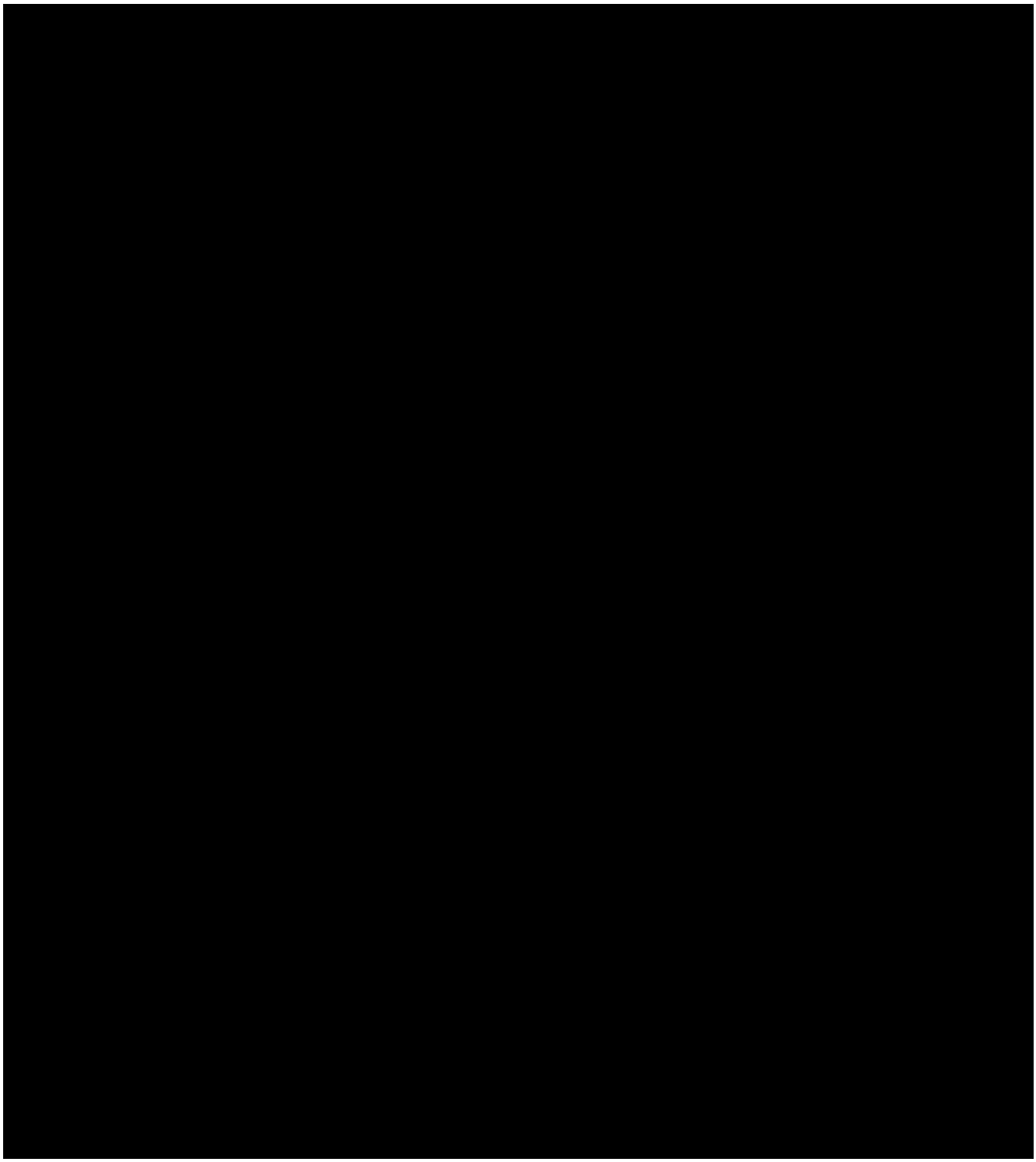
Contact information for the sponsor personnel is maintained in the Study Reference Manual.

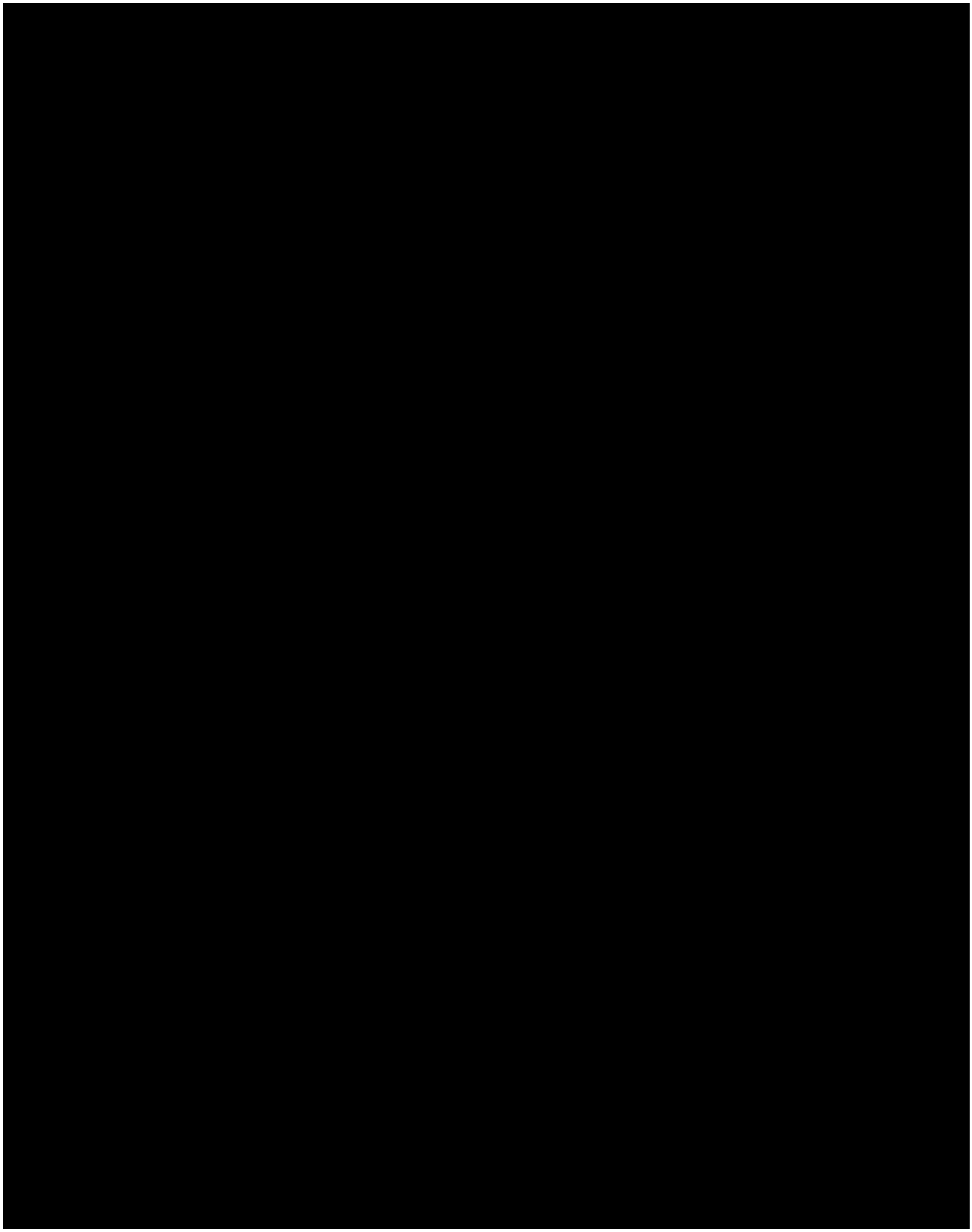


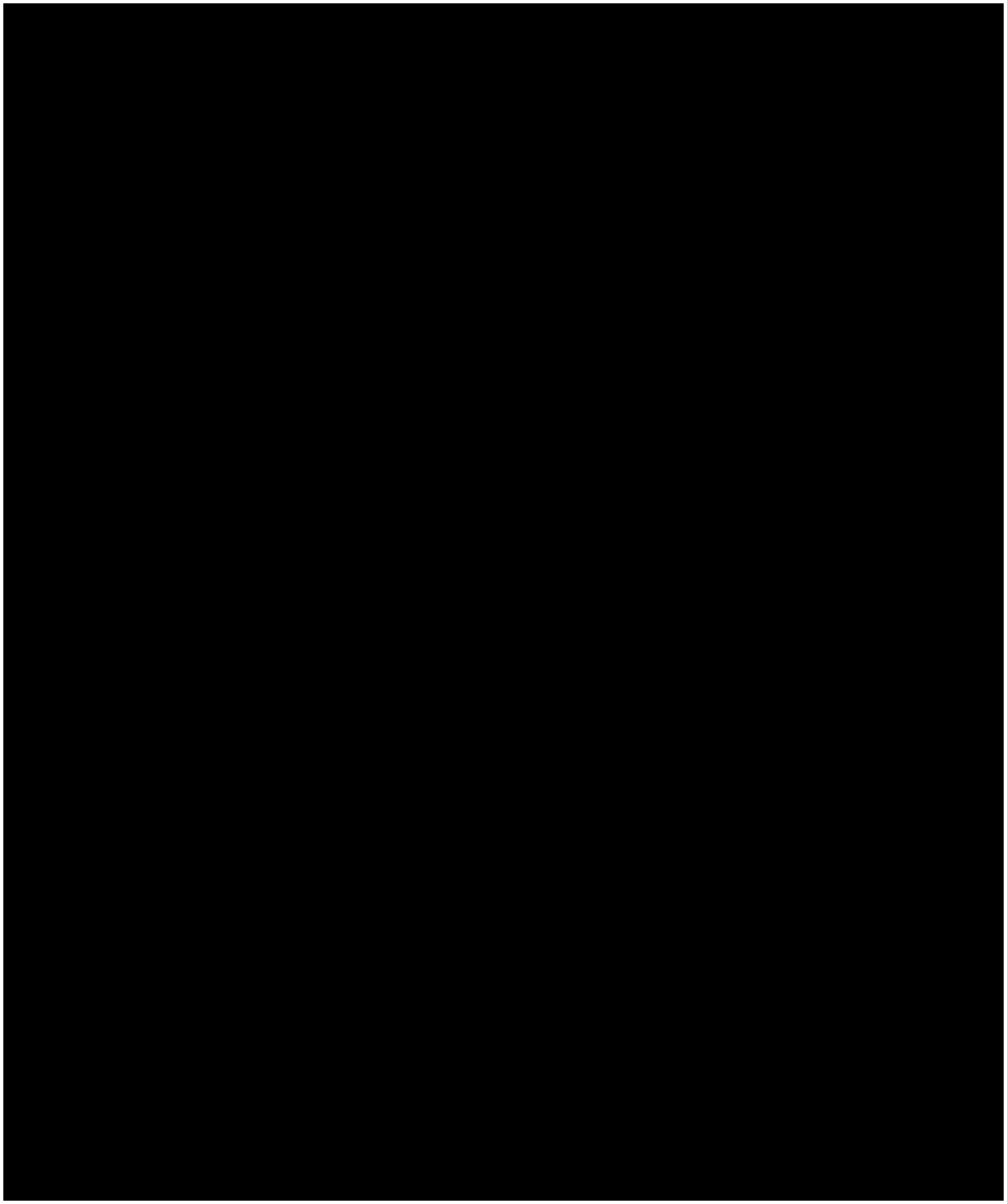


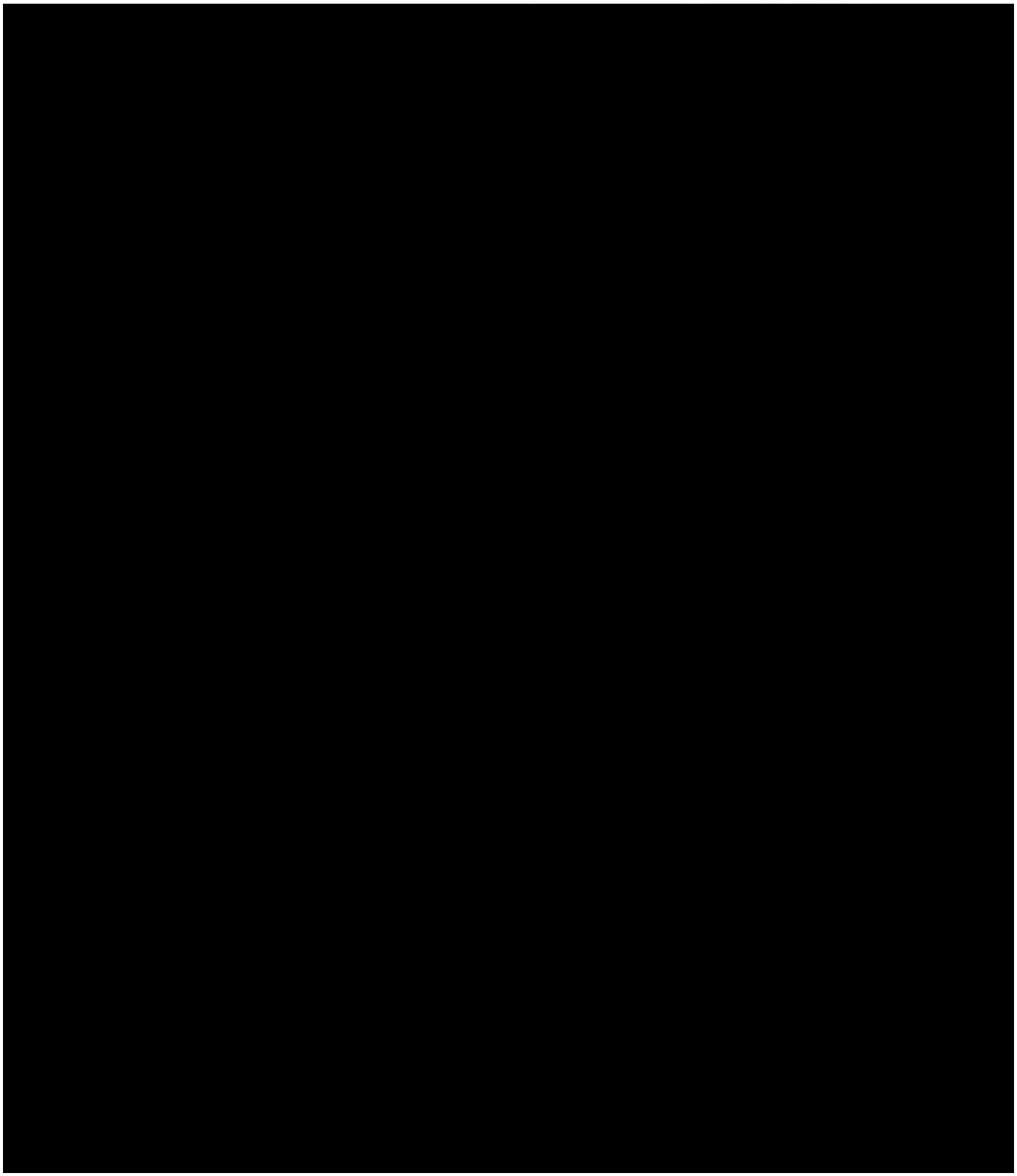


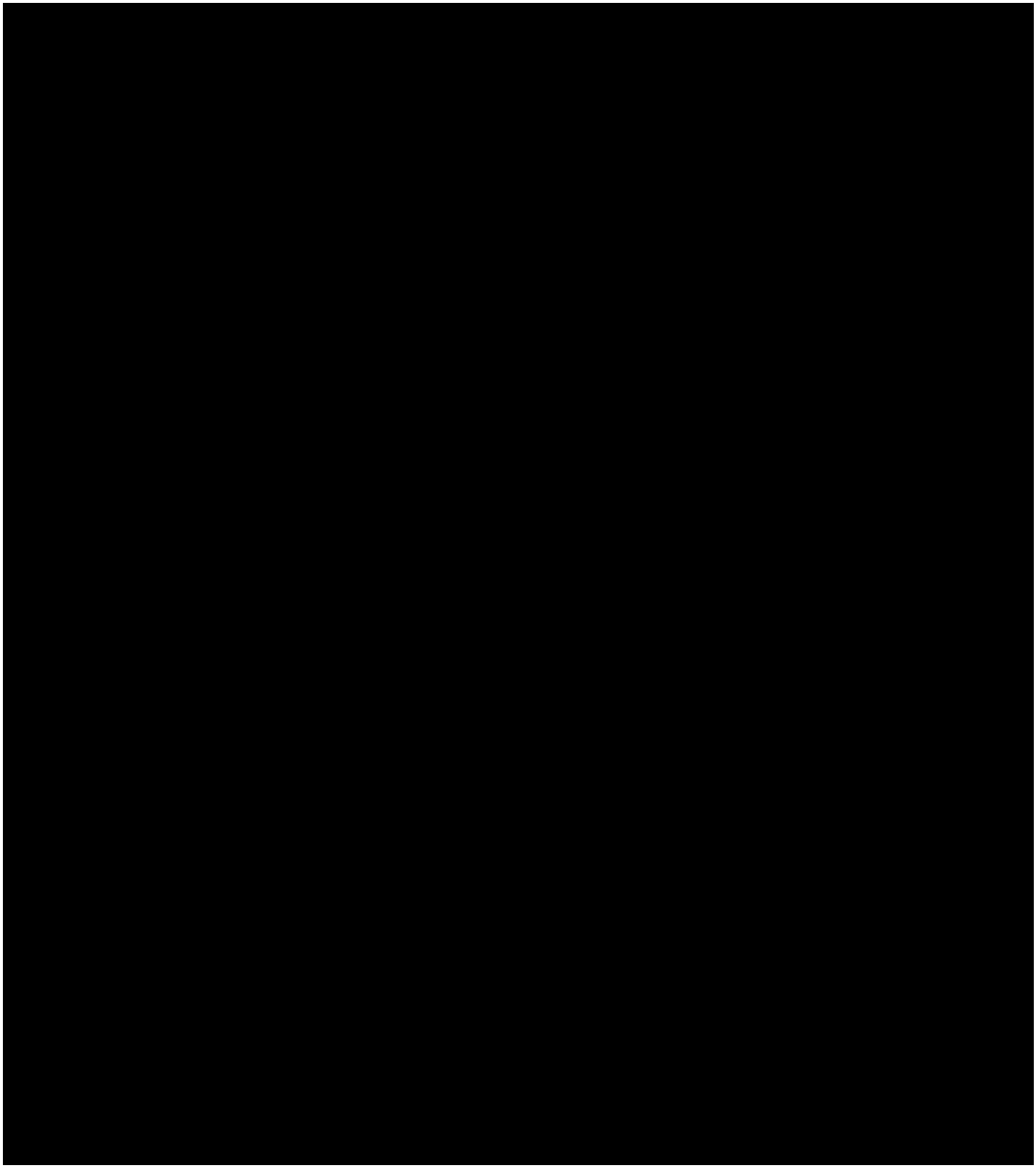


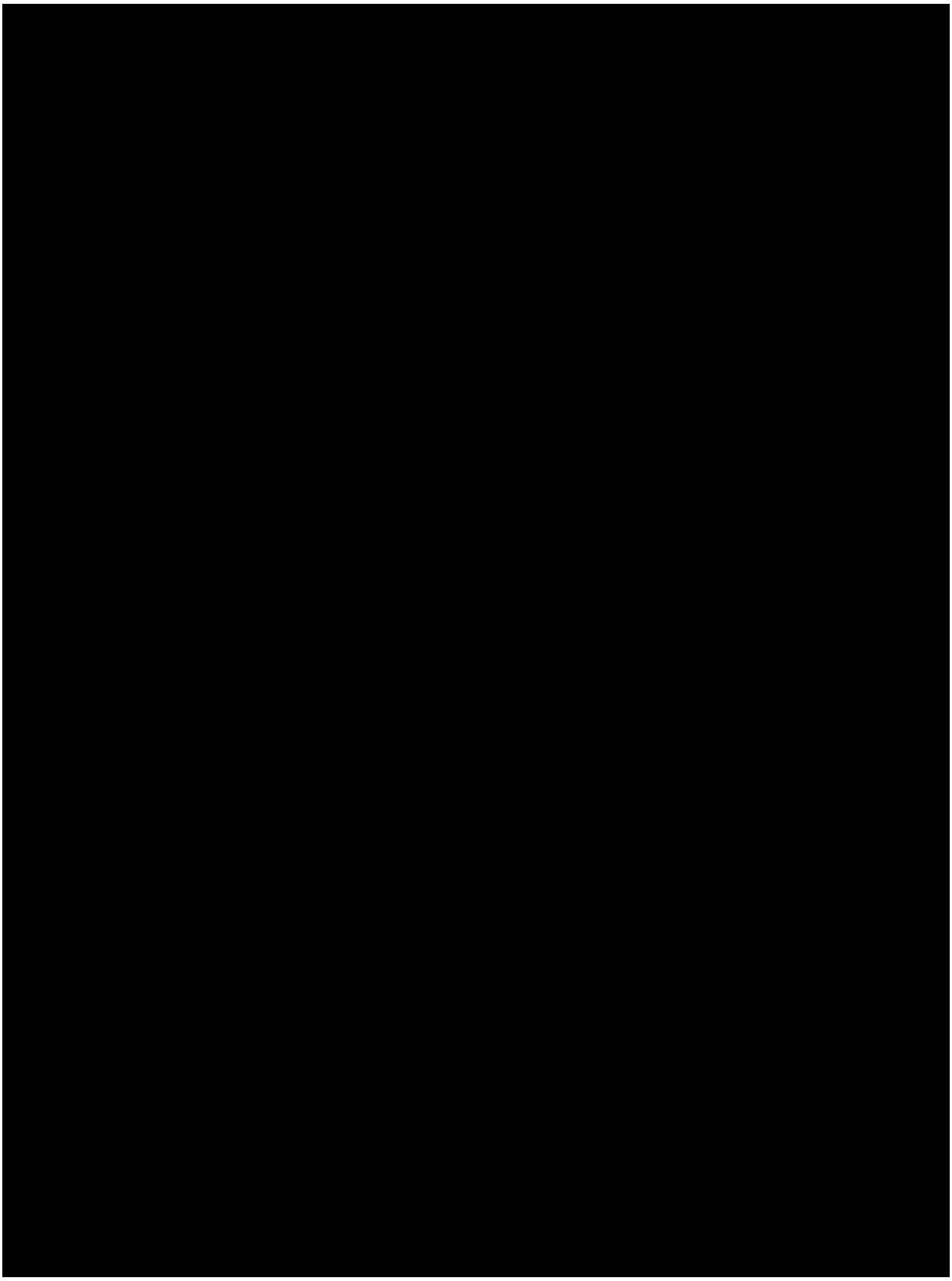


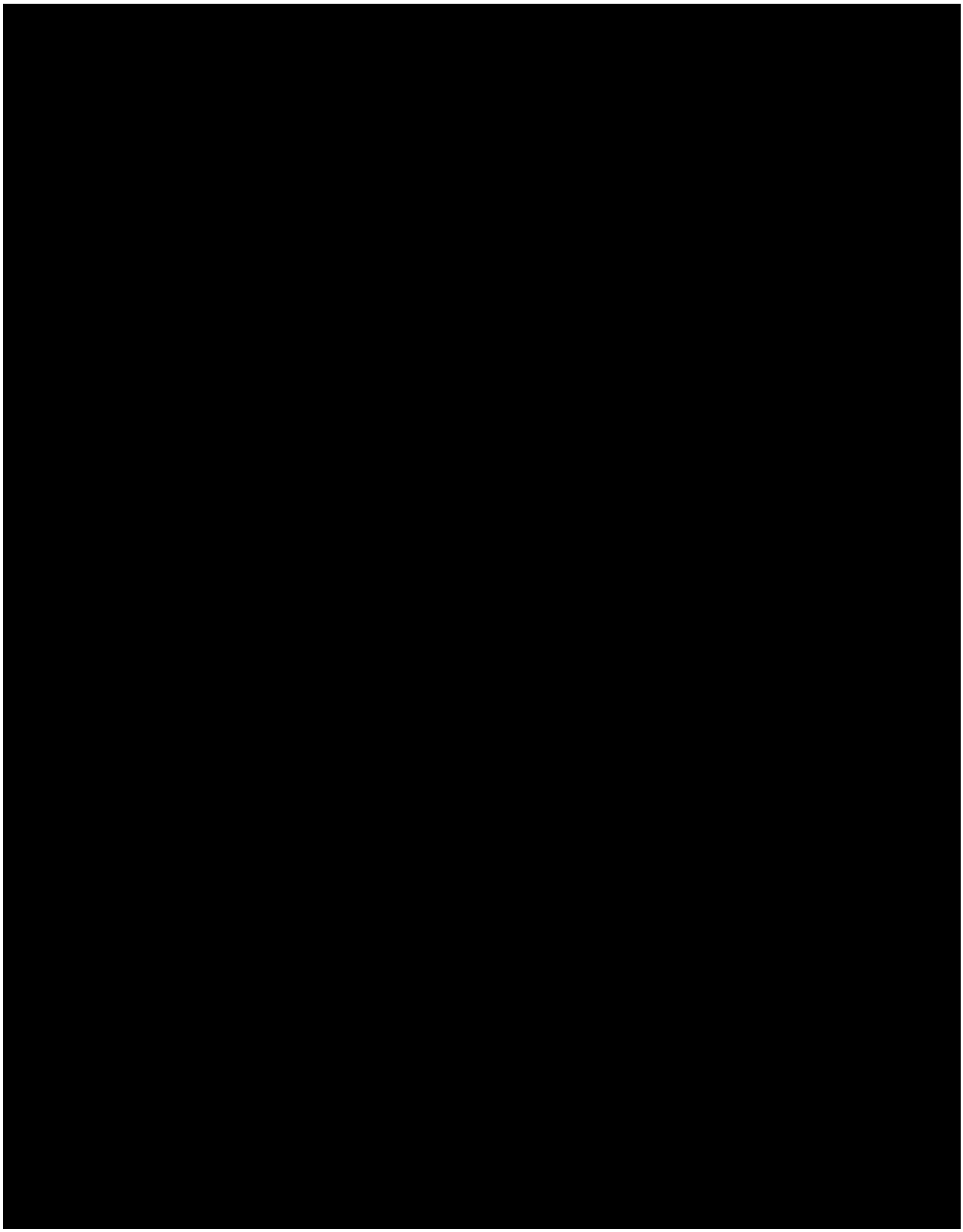


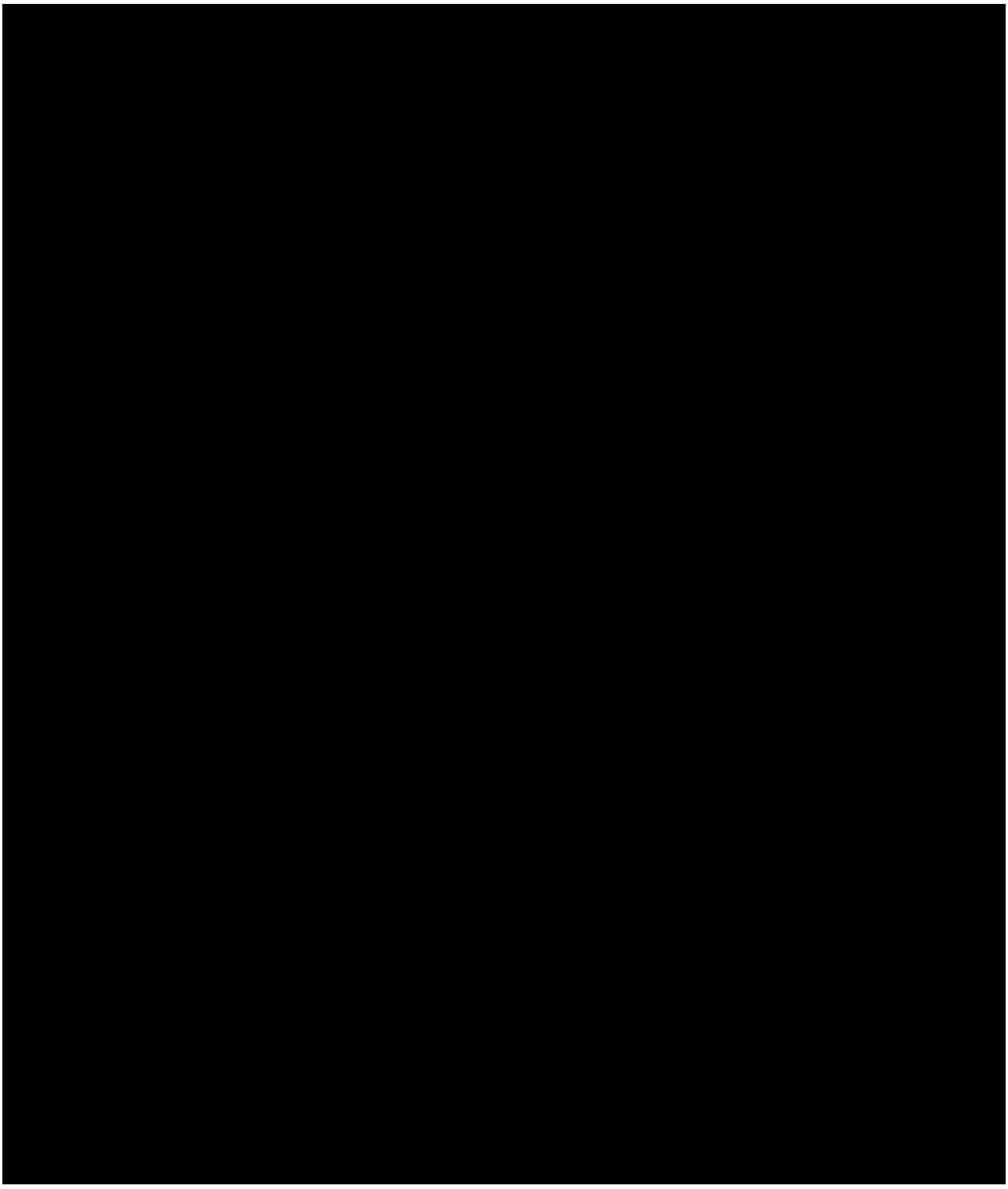


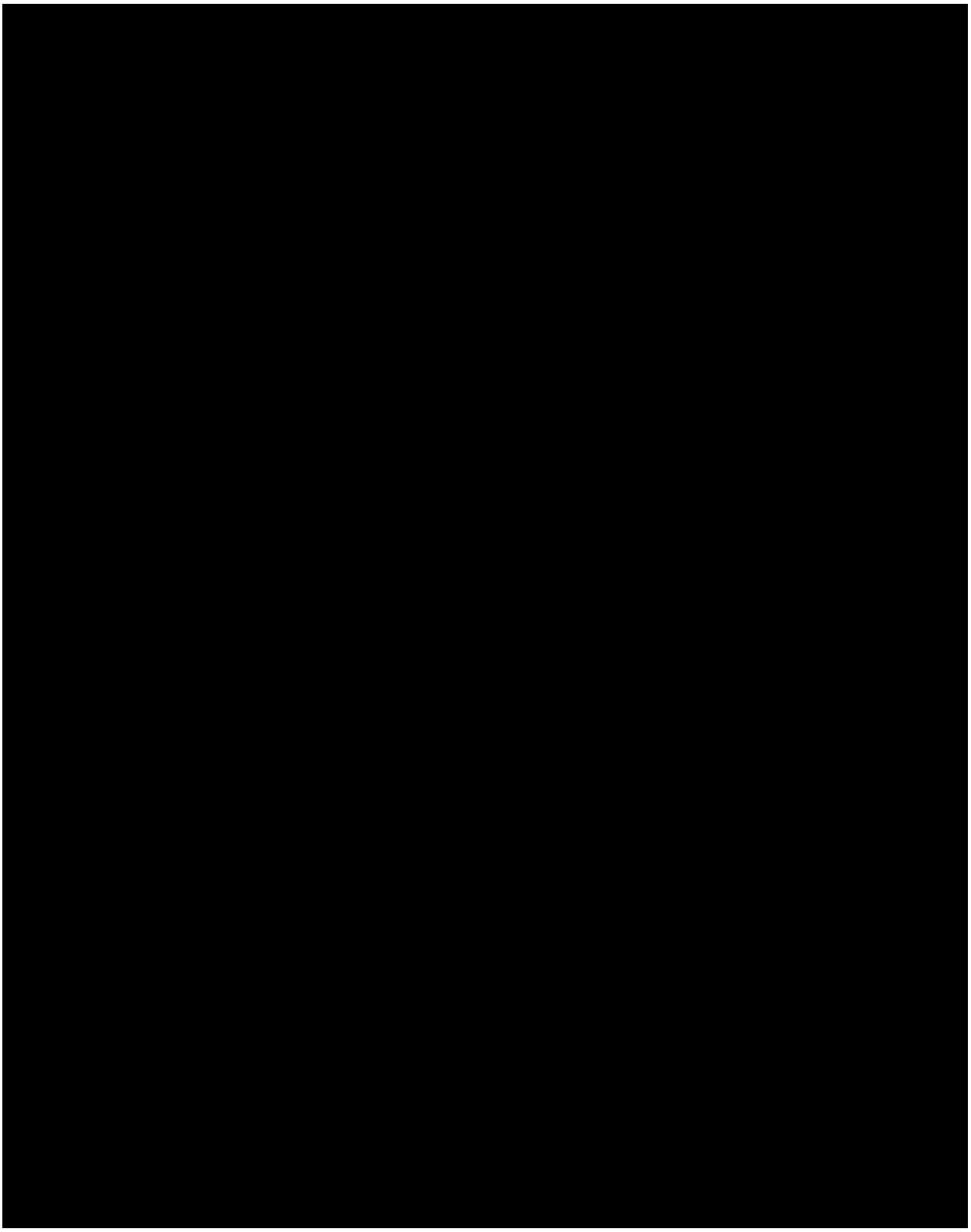


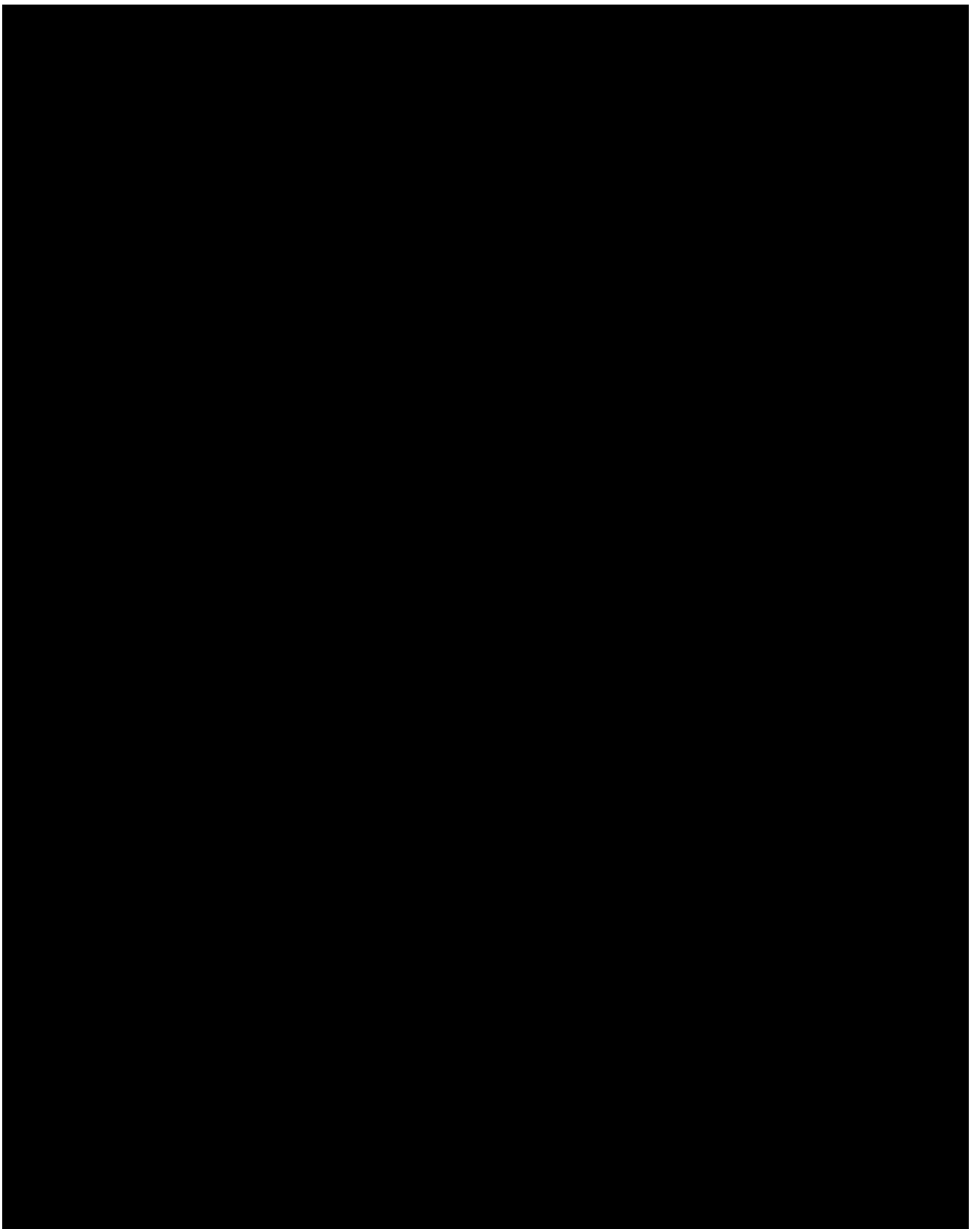


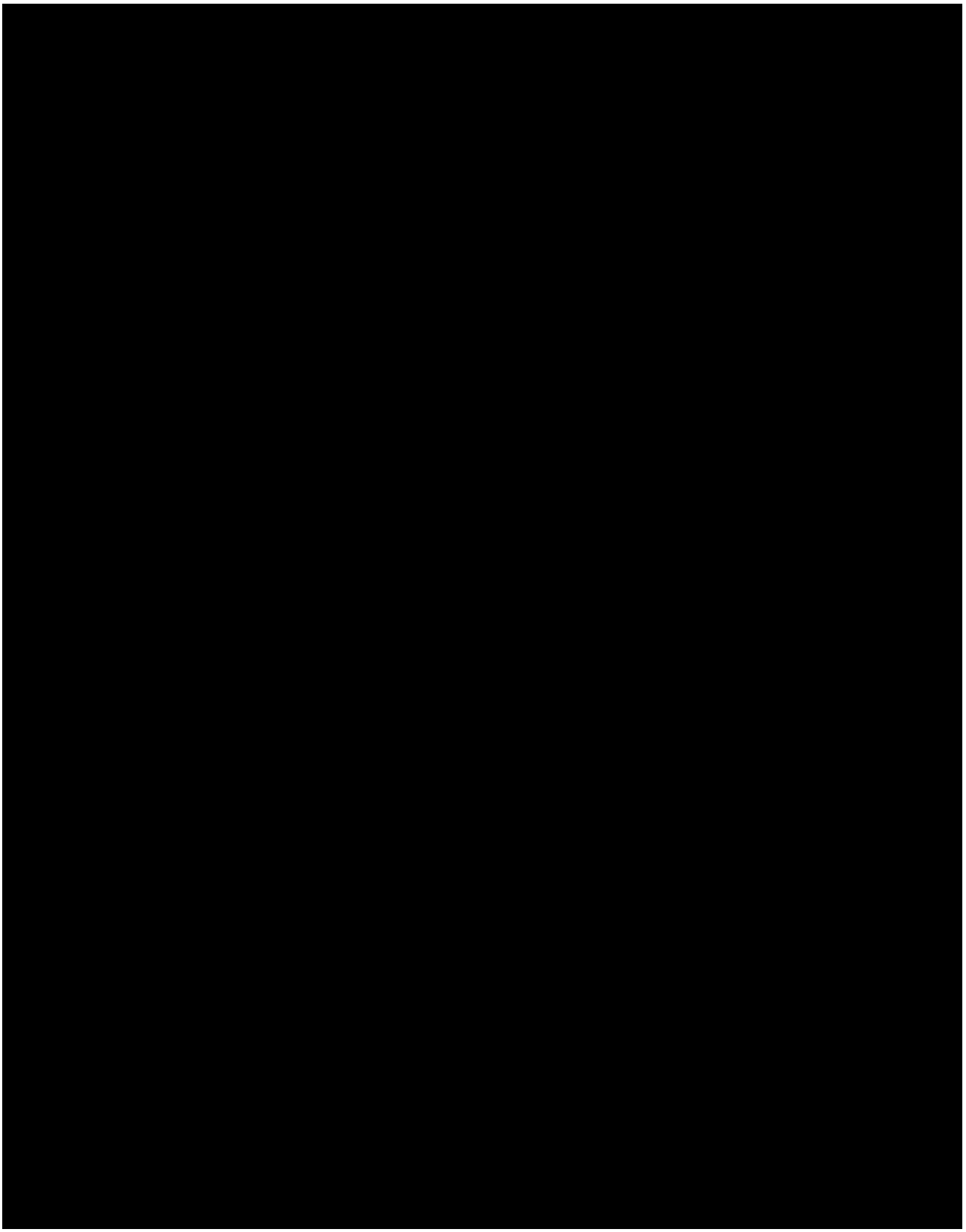


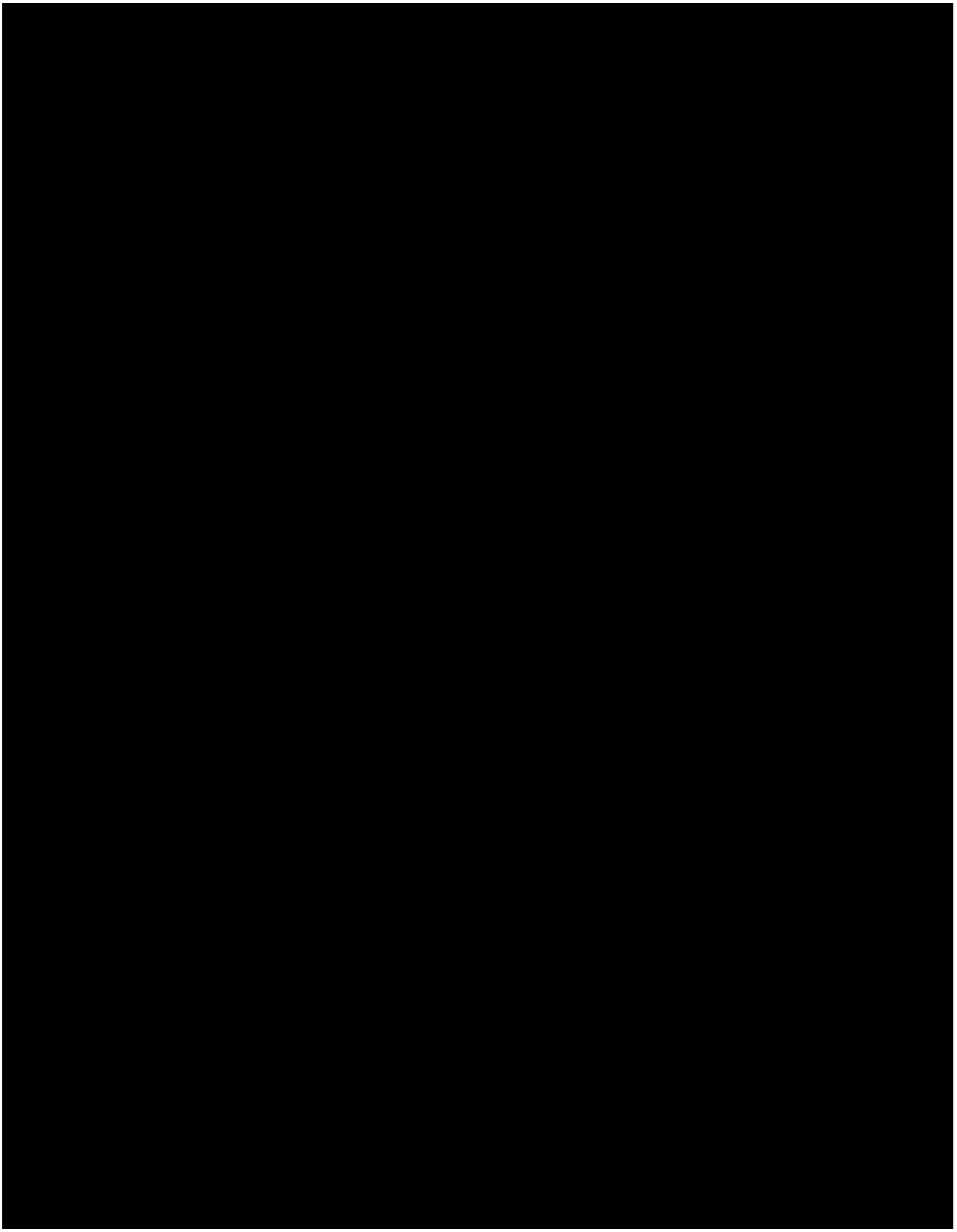


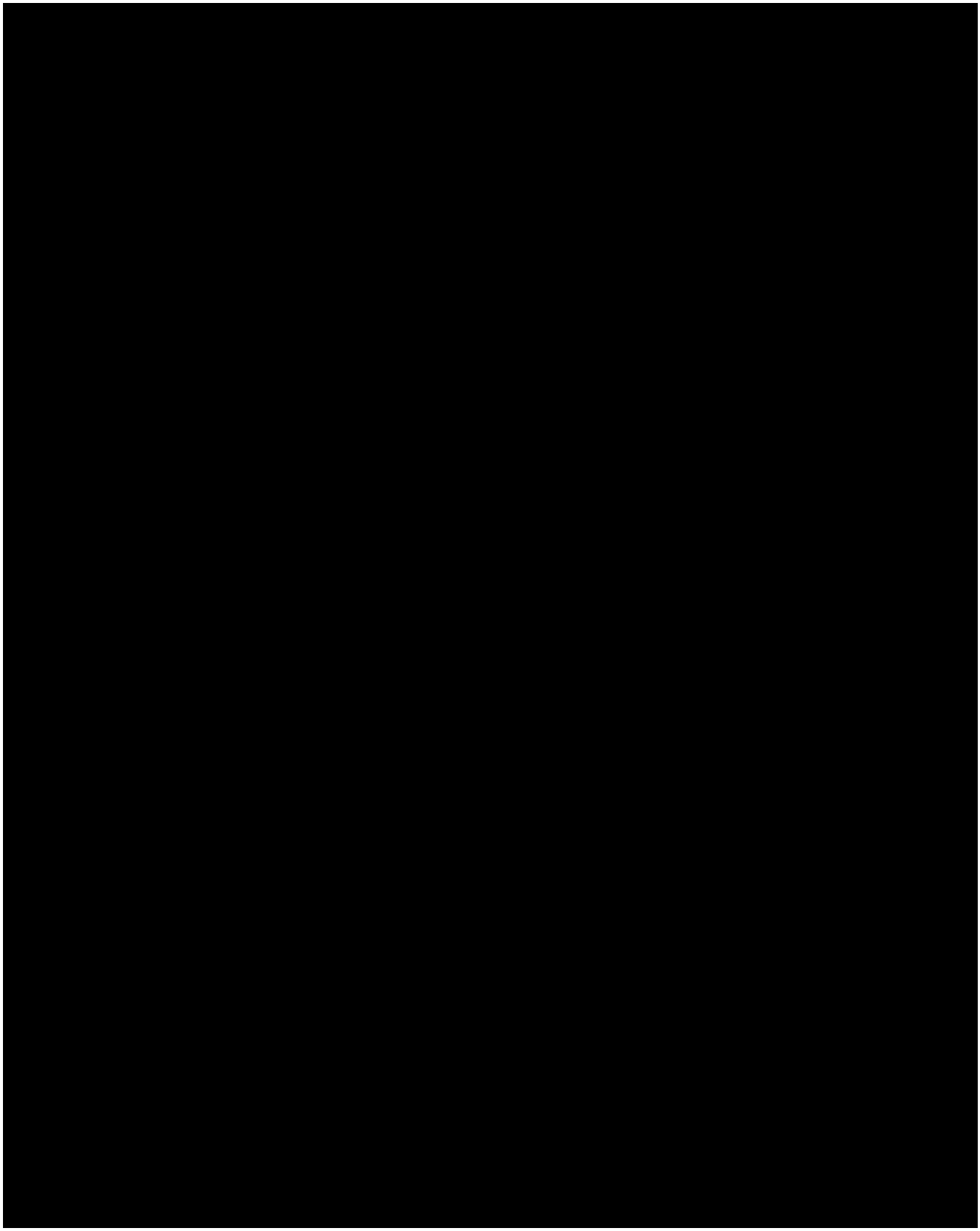












14.0 LITERATURE CITED

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association.

Berman, AL. Estimating the population of survivors of suicide: Seeking an evidence base. Suicide and Life-Threatening Behavior 2011;41:110-116.

Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000;157:1925-1932.

Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;11:125–136.

Brent D. What family studies teach us about suicidal behavior: implications for research, treatment, and prevention. Eur Psychiatry 2010;25:260–263.

Burgdorf J, Zhang XL, Weiss C, et al. The long-lasting antidepressant effects of rapastinel (GLYX-13) are associated with a metaplasticity process in the medial prefrontal cortex and hippocampus. Neuroscience 2015;308:2-2-11. Doi:10.1016/j.neuroscience 2015.09.004 Epub 2015 Sep 4.

Burger J, Capobianco M, Lovern R, et al. A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. Mil Med 2016;181:1195-1199.

Canuso CM, Singh JB, Fedgchin M, et al. PeSEVERe: a study of esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in patients assessed to be at imminent risk for suicide. Biol Psych 2016;81:S31.

Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of major depressive disorder, including suicidal ideation, in patients assessed to be at imminent risk for suicide: a proof-of-concept study. 55th annual meeting of American College of Neuropsychopharmacology. December 4-8, 2016. Hollywood, FL.

Centers for Disease Control and Prevention. Cost of Injury Reports 2010. Available online at https://wisqars.cdc.gov:8080/costT/

Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS). Atlanta, GA: National Center for Injury Prevention and Control. Available at https://www.cdc.gov/injury/wisqars/leading_causes_death.html Page last updated: February 19, 2017.

Chappell P, Stewart M, Alphs L, et al. Assessment of suicidal ideation and behavior: report of the International Society for CNS Clinical Trials and Methodology Consensus Meeting. J Clin Psychiatry 2017;78:e638–e647.

Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999-2014. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. NCHS Data Brief No. 241, April 2016.

De Gioannis A, De Leo D. Oral ketamine augmentation for chronic suicidality intreatment-resistant depression. Aust N Z J Psychiatry. 2014 Jul;48:686.

Feifel D. The use of placebo-controlled clinical trials for the approval of psychiatric drugs: Part I—Statistics and the Case for the "Greater Good". Psychiatry (Edgemont) 2008;6:41-43.

Gispen-de Wied C, Stoyanova V, Yu Y, et al. The placebo arm in clinical studies for treatment of Psychiatric Disorders: A Regulatory Dilemma. Eur Neuropsychopharmacol, 2012; 14 June (published ahead of print).

Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003;64:1465-1475.

Griffiths JJ, Zarate CA Jr, Rasimas JJ. Existing and novel biological therapeutics in suicide prevention. Am J Prev Med. 2014 Sep;47(3 Suppl 2):S195-203.

Jacobs DG, Baldessarini RJ, Conwell Y, et al. Practice guideline for the assessment and treatment of patients with suicidal behaviors. APA 2010.

Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. Biometrika 2003;90:53-71.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-997.

Kessler RC, Chiu WJ, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey. Arch Gen Psychiatry 2005;62:617-627.

Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Study. Arch Gen Psychiatry 1994;51:8-19.

Laughren TP. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. Eur Psychiatry. 2001;16:418-423.

Lee J, Narang P, Enja M, Lippmann S. Use of ketamine in acute cases of suicidality. Innov Clin Neurosci. 2015 Jan-Feb;12(1-2):29-31.

Lee Y, Syeda K, Maruschak NA, et al. A new perspective on the anti-suicide effects with ketamine treatment: a procognitive effect. J Clin Psychopharmacol. 2016;36:50-56.

Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-389.

Moran P, Leese M, Lee T, et al. Standardised Assessment of Personality – Abbreviated Scale (SAPAS): preliminary validation of a brief screen for personality disorder. British J Psychiatry 2003;183:228-232.

Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 2013;310:591-608.

Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015;172:950-966.

Nock M, Hwang I, Sampson N, et al. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. Molecular Psychiatry 2010;15:868-876.

Overall JE, Gorham DR. The brief psychiatric rating scale. Psychological Reports 1962;10:799-812.

Price RB, Iosifescu DV, Murrough JW, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depression and Anxiety 2014;31:335-343.

Price RB, Mathew SJ. Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs 2015;29:181-188.

Price RB, Nock MK, Charney DS, et al. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biological Psychiatry. 2009;66:522-526.

Reinstatler L, Youssef NA. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drugs R D. 2015;15:37-43.

Sheehan DV, Alphs LD, Mao L, et al. Comparative validation of the S-STS, the ISST-Plus, and the C–SSRS for assessing the suicidal thinking and behavior. FDA 2012 Suicidality Categories. Innovations in Clinical Neuroscience 2014a;11(9-10):32-46.

Sheehan DV, Giddens JM, Sheehan IS. Status update on the Sheehan Suicidality Tracking Scale (S-STS) 2014. Innov Clin Neurosci. 2014b;11(9–10):93–140.

Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11 Suppl 3:89-95.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, et al. The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J Clin Psychiatry 1998;59(suppl 20):22-33.

United States Food and Drug Administration, United States Department of Health and Human Services. Guidance for Industry: Suicidality: Prospective Assessment of Occurrence in Clinical Trials, Draft Guidance. http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf August 2012. Revision 1.

Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 2004;161:1957-1966.

Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA). The British Journal of Psychiatry 2008;192:52-58.

World Health Organization. Mental health: new understanding, new hope. World Health Report 2001.