NCT02943577

Study ID: RAP-MD-03

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

Protocol Amendment 2 Date: 20 Nov 2018

1.0 TITLE PAGE

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

A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in Major Depressive Disorder

RAP-MD-03

IND # 107,974

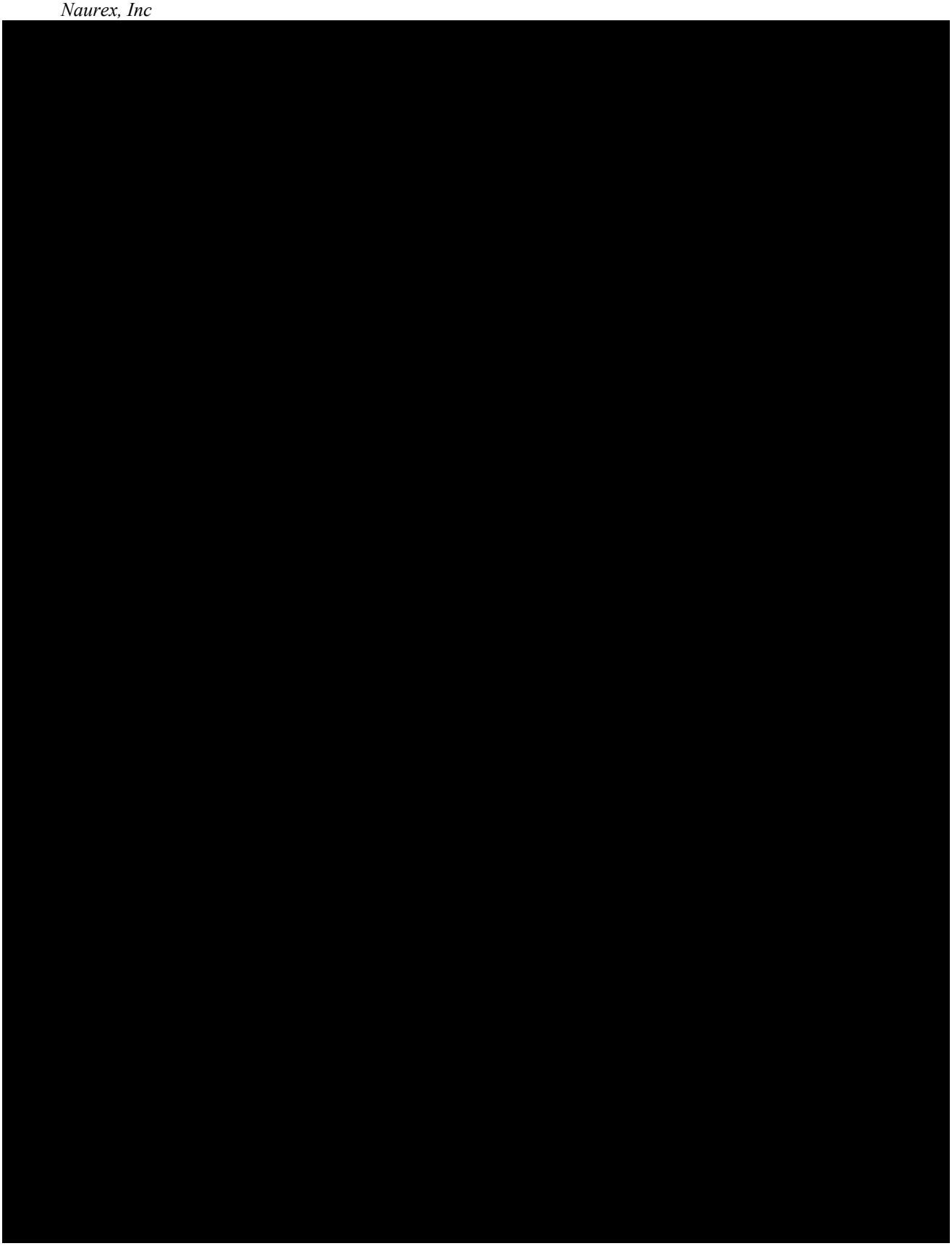
Original Protocol Date:	20 May 2016
Amendment 1:	10 Oct 2016
Amendment 2:	***20 Nov 2018***

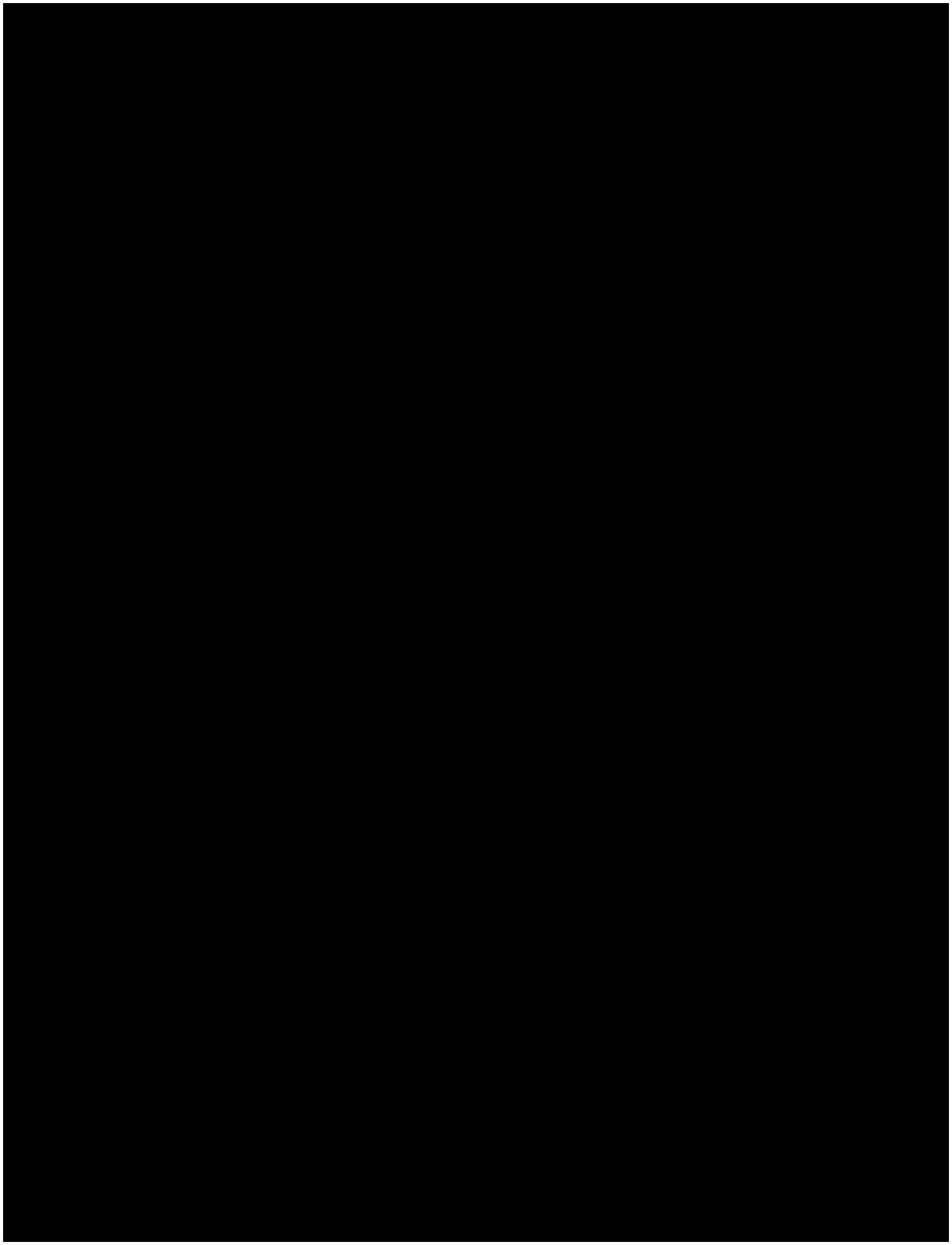
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study RAP-MD-03	
Study Number	RAP-MD-03
Title of Study	A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in Major Depressive Disorder
Study Centers (Country)	Approximately 35 study centers (United States)
Development Phase	3
Objective	To evaluate the efficacy, safety, and tolerability of rapastinel adjunctive to antidepressant therapy (ADT) in patients with major depressive disorder (MDD) who have a partial response to ADT
Methodology	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-week study in patients with MDD who have a partial response to ongoing ADT
Number of Patients	Approximately ***360*** planned to be enrolled
Diagnosis and Main Criteria for Inclusion	• Male and female outpatients who are 18 to 65 years of age • Meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1 [redacted] • Have no more than partial response (< 50% improvement) to ongoing treatment with a protocol-allowed ADT [redacted]
Test Product, Dosage, and Mode of Administration	Rapastinel (450 mg weekly intravenous [IV] administration) adjunctive to ongoing ADT, prefilled syringe

Duration of Treatment	Up to 14 days of screening and washout period, followed by a 3-week double-blind treatment period, followed by a 1-week safety follow-up period
Reference Therapy, Dosage, and Mode of Administration	Placebo adjunctive to ongoing ADT, weekly IV administration, prefilled syringe
Criteria for Evaluation	
Primary Endpoint	Change from baseline in MADRS total score at ***end of study***
Key Secondary Endpoint	Change from baseline in MADRS total score ***1 day after the first dose of randomized treatment***
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Pharmacokinetic Sampling	Optional: sparse pharmacokinetic (PK) samples will be taken from consented patients to determine plasma concentrations of rapastinel using a validated bioanalytical method.
Safety Measures	Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, electrocardiograms (ECGs), and physical examinations [redacted]

	[redacted]
Statistical Methods	The primary efficacy parameter will be the change from baseline in MADRS total score at ***end of study***. The primary analysis will be performed using ***a mixed-effects model for repeated measures (MMRM)*** with terms for treatment***, pooled*** study center, ***visit, and treatment-by-visit interaction as the fixed effects, and baseline MADRS total score, baseline MADRS total score-by-visit as covariates***. The key secondary efficacy parameter, change from baseline in MADRS total score ***1 day after randomized treatment*** will be analyzed using ***the same MMRM model as was used for the primary efficacy parameter***. An unstructured covariance matrix will be used to model the covariance of within-patient scores. Baseline will be defined as the last measurement prior to the first dose of ***double-blind*** treatment. ***To control the overall type I error rate for both the primary and key secondary endpoint, a sequential testing procedure will be implemented.*** 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 treatment. Efficacy analyses will be based on the ***modified*** Intent-to-Treat (***m***ITT) Population, defined as all patients ***who are randomized and receive at least 1 dose of treatment and have*** at least 1 postrandomization assessment of the MADRS total score.





3.0 TABLE OF CONTENTS

[redacted]

LIST OF FIGURES

4.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSST	Digit Symbol Substitution Test
DxV	Diagnostic Validation Questionnaire
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
[redacted]	[redacted]
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form

ICH	International Conference on Harmonisation of Technical Requirements
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-Asberg Depression Rating Scale
MDD	major depressive disorder
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
SCID	Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition
SD	standard deviation
[redacted]	[redacted]
SDMT	Symbol Digit Modalities Test
SNRI	selective serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD 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 35 study centers in the United States.

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

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

7.0 INTRODUCTION

Disease Burden of Major Depressive Disorder

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The purpose of this study is to prospectively confirm that rapastinel, when administered as an adjunctive treatment at a dose of 450 mg as a short IV infusion in patients with MDD, is significantly superior to placebo in rapidly reducing depressive symptoms. Furthermore, the safety and tolerability of rapastinel will be investigated. The study is intended to support an application for regulatory approval of rapastinel as adjunctive treatment for MDD.

8.0 STUDY OBJECTIVES

The objectives of this study are to evaluate ***the*** efficacy, safety, and tolerability of rapastinel adjunctive to ongoing ADT in patients with MDD who have a partial response to ADT.

Efficacy Objectives

- Primary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline ***to end of study*** in the Montgomery-Asberg Depression Rating Scale (MADRS) total score.

- Key secondary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline ***in the*** MADRS total score ***1 day after 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, 3-week study in patients with MDD who have a partial response to ADT. The study will include a total of 12 visits and will be approximately 4 to 6 weeks in duration (Figure 9.1-1):

- Up to 2-week screening period
- 3-week double-blind treatment period
- 1-week safety follow-up period (for patients who do not enter the RAP-MD-04 maintenance study)

9.1.1 Screening Period

After providing written consent, patients will enter a screening period of up to 14 days. The screening/washout period will be up to 2 weeks prior to Visit 2. Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate patient and study center schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period and the rater-administered MADRS and computer-administered MADRS must be collected on the same date. Patients will not receive any investigational product (IP) during the screening period but must continue their background ADT at the same dose. Patients meeting the eligibility criteria at the end of Visit 2 (Baseline) will be assigned a treatment by the interactive web response system (IWRS) and enter the double-blind treatment period.

9.1.2 Double-blind Treatment Period

Approximately 700 patients are planned for enrollment in the double-blind treatment period (350 patients each in the rapastinel 450 mg and placebo groups). Patients will be randomized in a ratio of 1:1 to 1 of 2 treatment groups: rapastinel 450 mg IV weekly or placebo IV weekly (both adjunctive to ongoing ADT).

During the double-blind treatment period, patients will have 3 study visits per week. The visits will occur in the following pattern: treatment day, 1 day following the treatment day, 4 days following the treatment day, and 7 days following the treatment day (which is the next treatment day). If necessary, study visits may be conducted up to 2 days before or after the scheduled visits with the exception of visits that are 24 hours apart (eg, Visits 2 and 3 must be conducted 1 day apart; similarly, Visits 5 and 6 as well as Visits 8 and 9 must be conducted 1 day apart). All patients who receive IP must complete Visit 11. Upon completion of the double-blind treatment period, patients are eligible to enter the RAP-MD-04 maintenance study. Patients who do not enter RAP-MD-04 will enter a 1-week safety follow-up period.

9.1.3 Safety Follow-up Period

Patients who do not enter the RAP-MD-04 maintenance study upon completing the double-blind treatment period and patients who prematurely discontinue from the study before completing 3 weeks of double-blind treatment should enter the 1-week safety follow-up period.

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

A schematic of the study design is presented in Figure 9.1-1. The Schedule of Evaluations is provided in Section 2.0 and detailed descriptions of each study visit can be found in Section 9.5.6.

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

This multicenter, randomized, placebo-controlled, parallel-group study, with a 3-week double-blind treatment period, was designed based on prior studies that established rapastinel efficacy and safety in adult patients with MDD. 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 Modified Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition (SCID). The symptoms and severity of MDD will be assessed using the MADRS (Section 9.5.1.2.1).

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

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

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). The use of placebo in place of the 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).

In Study RAP-MD-03, 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 9.4.13). 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. Meet DSM-5 criteria for MDD (based on confirmation from the modified SCID), with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1

[redacted]

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

7. If female of childbearing potential, have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test

[redacted]

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 6 months before Visit 1. Comorbid generalized anxiety disorder, social anxiety disorder, or specific phobias are acceptable provided they play a secondary role in the balance of symptoms and are not the primary driver of treatment decisions.

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

   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 one of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Pregnancy
- Withdrawal of consent
- AE
    - Any patient may be withdrawn due to AE at the discretion of the Investigator
    - Any patient who meets any of the following criteria at any point during the study must be withdrawn from participation, due to AEs related to suicide:
        a) A suicide attempt

        [redacted]

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

- Lack of efficacy
- Protocol violation
- Noncompliance with IP
- Noncompliance with ADT
- 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 Early Termination (ET) Visit. A *final assessment* will be defined as completion of the evaluations scheduled for all patients at Visit 11. 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.

9.4.1 Background Antidepressant Therapy

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

Upon entry into the study at Screening (Visit 1), the dosage of the ADT must be held constant at a dose allowed in the respective label through Visit 11/ET. If a patient experiences an AE, intercurrent illness, or symptoms of intolerance, he or she will be permitted to stop taking the ADT for a maximum of 3 consecutive days at the discretion of the Investigator. No other alterations in the ADT dose regimen are allowed. If an ADT dose change is required during the study, the patient should be discontinued from the study.

Background ADT medication compliance will also be closely monitored. Patients should be questioned to determine if there were any missed doses or changes in dose at Visits 2, 5, 8, and 11. Every effort should be made to have patients bring their background ADT to Visits 5, 8, and 11 for verification of patient-reported compliance by pill count (to the extent possible).

9.4.2 Treatments Administered

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

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

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

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

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

9.4.3 Identity of Investigational Products

Rapastinel 450 mg IV Prefilled Syringes: [redacted]

Placebo rapastinel IV Prefilled Syringes: prefilled single-dose syringes for injection containing 3 mL of normal saline.

[redacted]

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

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.

9.4.4 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.

9.4.5 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] This PID number will be used to identify the patient throughout the study (ie, at all periods of the study).

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

9.4.6 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.

9.4.7 Selection and Timing of Dose for Each Patient

The IP will be administered IV using the assigned single-use prefilled syringes at Visits 2, 5, and 8.

9.4.7.1 *Screening Period*

At Screening (Visit 1) after written consent is obtained, patients enter a screening period of up to 14 days. No IP is administered during the screening period; however, patients must continue their background ADT at a stable dose.

9.4.7.2 *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 5 and 8).

Patients will receive either rapastinel 450 mg or placebo from a prefilled single-dose syringe at Visits 2, 5, and 8.

9.4.7.3 *Safety Follow-up Period*

Patients who complete 3 weeks of randomized treatment are eligible to enter the RAP-MD-04 maintenance study. If they do not enter RAP-MD-04, they should enter the safety follow-up period. Patients who discontinue the study prematurely should enter the safety follow-up period. No IP is administered during the safety follow-up period and patients' background ADT may be modified as deemed appropriate by the Investigator.

9.4.8 Blinding

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

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

9.4.9 Unblinding

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

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

For IWRS Unblinding

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

9.4.10 Prior and Concomitant Therapy

A list of example medications that are allowed and not allowed as concomitant medications for either episodic or chronic use is provided in Appendix III. Medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or any new medications added will be recorded in the eCRF.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

For Anxiety or Agitation

[redacted]

[redacted]

[redacted]

9.4.11 Other Restrictions

9.4.11.1 *Alcohol*

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

9.4.11.2 *Contraception*

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

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

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

See Section 9.5.2.3 for pregnancy reporting procedures.

9.4.12 Monitoring Treatment Compliance

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

Background ADT compliance will also be closely monitored. Patients should be questioned to determine if there were any missed doses or changes in dose at Visits 2, 5, 8, and 11. Every effort should be made to have patients bring their background ADT to Visits 5, 8, and 11 for verification of patient-reported compliance by pill count (to the extent possible). Missed doses or other changes in the dose of ADT and the reason should be captured in the eCRF.

9.4.13 Treatment After Discontinuation

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

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Diagnostic and Efficacy Assessments

9.5.1.1 Diagnostic Assessments

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

Patients will complete a computer-administered Diagnostic Validation (DxV) assessment at the Screening Visit prior to the rater-administered SCID, on a tablet computer provided to the study center. The DxV will collect data about the patients' history relative to lifelong history of MDD. The patient's diagnostic information, based on the responses to the computerized interview, will be reviewed by the independent clinical reviewers team appointed by the Sponsor, and any uncertainty raised by the patient's responses on the diagnostic interview will be discussed with the Investigator/study center clinician in order to establish confidence in the diagnosis. Patients for whom diagnostic agreement between the Investigator/study center clinician and the rater vendor clinician cannot be reached, may not be appropriate for study participation.

9.5.1.2 Efficacy Assessments

The efficacy assessments (MADRS [redacted] will be administered by a psychiatrist, doctoral level clinical psychologist, or other clinician who has extensive professional training and experience in the diagnosis of mental illness and who meets the training requirements and qualifications standards set by the Sponsor and rater training vendor.

9.5.1.2.1 The Montgomery-Åsberg Depression Rating Scale

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

9.5.1.2.1.1 MedAvante Central Ratings for MADRS

In order to control for possible bias in face-to-face ratings and to obtain a "blinded" rating of patient symptom severity and change, blinded expert raters will administer, through remote teleconference, the MADRS. The remote (or centralized) raters will be blind to the study design, entry criteria, and visit number (except for Screening [Visit 1] and Baseline [Visit 2]).

The MedAvante rater may be observed during the interview by another mental health evaluator for quality control purposes. At the study center, the evaluations must be conducted in a private room, with the door closed and a study center representative (eg, study coordinator) may be present during the rating session at the discretion of the Investigator. Every effort should be made to administer the MADRS prior to other assessments.

[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.

9.5.2.1.4 Reporting Adverse Events and Serious Adverse Events

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

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

For every AE, the Investigator must:

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

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

9.5.2.1.4.1 MedAvante Reporting of Safety/Adverse Events

MedAvante Raters will complete a safety reporting form (ie, Potential Clinical Events Notification Form), including an additional risk assessment form if certain triggers are met during their interviews with the patients at the study centers (ie, risk assessment forms for suicide, homicide, suspected child abuse, and suspected elder/dependent adult abuse). MedAvante Raters feel morally and ethically obligated to report this information to the study center, and the principal Investigator is responsible for follow-up, including management of the patient and further reporting as necessary.

Patients may spontaneously report possible clinical events to the centralized rater during an assessment. Possible clinical events as determined by the centralized rater will be recorded on a central rater source document and will be forwarded to the study center for further evaluation at the conclusion of the assessment. It is the study center's responsibility to determine, with further patient questioning, whether this event qualifies as an AE or SAE and to adhere to the methods described in Section 9.5.2.1.4 for reporting such events to the Sponsor.

If, while conducting the assessment, the centralized rater feels that there is an emergent risk to the safety of the patient, or to a third party, the study center will be contacted immediately by the centralized rater to intervene in the patient assessment room. The central rater shall stay on the teleconference call with the patient until appropriate personnel from the study center arrive. Information regarding the assessment shall be documented by the central rater and forwarded to the study center where the patient is physically present. The principal Investigator at the study center shall be responsible for compliance with any state law reporting requirements such as, for example, those governing the reporting of child abuse, or any duty to warn third parties of potential harmful conduct by the patient.

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 Global Drug Safety on the SAE Form for Clinical Trials. The Study Physician may also be notified by telephone.

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

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

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

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

Fax the SAE Form for Clinical Trials to the Sponsor.

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]

Whenever possible, the patient's weight will be measured at the same time of day;

[redacted]

9.5.6 Schedule of Assessments

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

Upon providing written informed consent, patients enter a screening period of up to 14 days. Following the screening period, patients enter the 3-week, double-blind treatment period. During the double-blind treatment period, patients have 3 study visits per week. The visits occur in the following pattern: treatment day, 1 day following the treatment day, 4 days following the treatment day, and 7 days following the treatment day (which is the next treatment day). If necessary, study visits may be conducted up to 2 days before or after the scheduled visits with the exception of visits that are 24 hours apart (ie, Visits 2 and 3 must be conducted 1 day apart; similarly, Visits 5 and 6 as well as Visits 8 and 9 must be conducted 1 day apart). Upon completion of the double-blind treatment period, patients are eligible to enter the RAP-MD-04 maintenance study or enter a 1-week safety follow-up period.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.5.6.13 Unscheduled Visits

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

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

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

9.6.2 Data Recording and Documentation

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

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

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

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

[redacted] Source documents will be used at the study centers and may include a patient's medical record, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood samples. Additional information on the collection and handling of samples is detailed in the Lab Procedure Manual.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Analysis Populations

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

9.7.1.1 *Enrolled* Population

The ***Enrolled*** Population will consist of all patients who sign informed consent, receive a patient identification (PID) number, ***and enter into screening***.

9.7.1.2 Safety Population

The Safety Population will consist of all patients who ***receive*** at least 1 dose of randomized IP.

9.7.1.3 *Modified* Intent-to-Treat Population

The ***modified*** Intent-to-Treat (***m***ITT) Population will consist of all patients ***who are randomized, receive at least 1 dose of IP and have*** at least 1 postbaseline assessment of the MADRS total score.

9.7.2 Patient Disposition

The number and percentage of patients in the ***Enrolled***, Safety, and ***m***ITT populations will be summarized by treatment group and study center.

Screen-failure ***patients*** (ie, patients screened but not ***included in the Enrolled Population***) and the associated reasons for failure to randomize will be tabulated overall for ***all screened patients***.

The number and percentage of patients ***in the mITT Population*** who complete the double-blind treatment period ***and of*** patients who prematurely discontinue during the same period ***will be presented for each treatment group and pooled across treatment groups***. The reasons for premature discontinuation ***during*** the double-blind treatment period as recorded on the ***disposition*** pages of the eCRFs will be summarized by treatment group for the ***mITT*** Population.

9.7.3 Demographics and Other Baseline Characteristics

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

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Patients in the Safety Population will be categorized by the number of IP doses received. The number and percentage of patients in each category will be summarized by treatment group.

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 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.

IV administration notes including site reaction at placement of IV, reaction to adhesive, infusion interruption, failure of administration device, increase in suicidality based on clinical evaluation, and perceptual disturbance based on mental status assessment are collected. For each item, the number and percentage of patients who had a 'yes' response will be summarized by treatment group and visit for the Safety Population. The number and percentage of patients taking each qualifying ADT will be summarized by treatment group for the ***mITT*** Population. Mean daily dose for each qualifying ADT will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], median, ***Q1, Q3,*** minimum, and maximum) by treatment group for the ***mITT*** Population.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for the background ADT during a specified period is defined as the ***total daily dose administered to a patient during that period divided by the total daily dose prescribed during the same period multiplied by 100, as captured in the eCRF***.. Descriptive statistics for ADT compliance will be presented for each ADT ***and overall*** by treatment group for the ***mITT*** Population.

9.7.5 Efficacy Analyses

All efficacy analyses will be based on the ***m***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 ***m***ITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes ≥ 2 ***m***ITT patients within the center. ***Details of the pooling algorithm will be provided in the Statistical Analysis Plan (SAP)***.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter will be the change from baseline in MADRS total score at ***end of study***. The primary analysis will be performed using ***a mixed-effects model for repeated measures (MMRM***) with treatment ***group, pooled*** study center***, visit and randomized treatment-by-visit interaction as the fixed effects, and baseline MADRS total score and baseline MADRS total score-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom (Kenward et al, 1997; Kenward et al, 2003).*** The treatment difference for rapastinel versus placebo will be estimated and reported along with the corresponding 95% CI and ***nominal*** p-value.

In the case that the MMRM model with unstructured covariance fails to converge with the default algorithm, then the Fisher scoring algorithm will be used to provide better initial values of the covariance parameters; if the model still does not converge, a simplified model without term for study center will be used to find the initial values of the covariance parameters. In the rare event that the model still does not converge after using those initial values, simplified covariance structures will be used to fit the model in the following order: (1) ante-dependence, (2) heterogeneous autoregressive, (3) Toeplitz, and (4) compound symmetry.

To assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption, a sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions (Kenward et al, 2003) will be performed. The pattern for the pattern-mixture model will be defined by the patient's last visit with observed value. The observed MADRS total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The missing values will be imputed under the assumption that the distribution of the missing observations differs from the observed only by a shift parameter value Δ. The dataset with missing values will be analyzed using the same model as the primary analysis for between-treatment group comparisons at the end of the treatment. The imputation of missing values and the analysis will be performed multiple times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values of Δ will be selected as 0 to 8.

9.7.5.2 *Key Secondary Efficacy Parameter*

The key secondary efficacy parameter will be the change from baseline ***to 1 day after the first dose of treatment*** in MADRS total score. ***This*** parameter will be analyzed using ***the same MMRM as will be used for the primary efficacy parameter***. The treatment difference for rapastinel versus placebo will be estimated and reported along with the corresponding 95% CI and ***nominal*** p-value.

A sequential testing procedure will be used to control the overall type I error rate at 5% for the primary and secondary efficacy parameters.

[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. ***An AE that becomes serious after the date of first dose of IP will also be considered as a TEAE.*** 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 double-blind treatment period 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.

A ***serious adverse event (***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 ***a treatment-emergent*** SAE ***(TESAE)***. The number and percentage of patients who have ***TE***SAEs will be summarized by preferred term and treatment group. In addition, the incidence of ***TE***SAEs that ***lead*** to death will be summarized separately by preferred term for each treatment group.

Overall summaries of AEs will be provided on a per-patient basis for categories of all TEAEs, treatment-related TEAEs, TESAEs, and TEAEs leading to study discontinuation.

[redacted]

[redacted]

[redacted]

[redacted]

9.7.8 Interim Analysis

At the time of preparation for Protocol Amendment 2, a blinded interim analysis was performed as part of data quality review as the study was progressing. In this review, it was observed that the SD for the primary and secondary endpoints were substantially lower than the originally assumed values for sample size calculations. The observed SDs in the blinded reviews of this study and other ongoing acute studies at the same time (RAP-MD-01 and RAP-MD-02) were taken into consideration for revising the estimate of the sample size as proposed in the next section (Section 9.7.9 Determination of Sample Size).

9.7.9 Determination of Sample Size

The originally proposed primary efficacy variable is the change from baseline in the MADRS total score at 1 day after the first dose of treatment. The study was planned to randomize 700 patients assuming SD of 10 points, which provides 99% power to detect a difference of 3.25 points in MADRS total score between rapastinel 450 mg and placebo at a 2-sided significance level of 0.05.

While the study was ongoing, various feedbacks were received from the regulatory agencies including the FDA, EMA, and the Japanese regulatory agency. Following the feedbacks, the primary efficacy variable was revised to be the change from baseline in MADRS score at the last visit, Day 21, and included in Amendment 2 of the protocol. At the same time of Amendment 2, a blinded data review was conducted for Studies RAP-MD-01, RAP-MD-02, and RAP-MD-03. The pooled SD for the 3 studies were 7.4, 8.0, and 8.7, respectively, all smaller than the originally assumed 10 points. Sample size was re-calculated using 8.7 as the common SD. The calculation used MMRM model with simulations; it also assumed correlation of 0.5 between the repeated measures and an overall drop-out rate of 15%. To have 90% power, the total sample size required is 360 patients. However, the study had already enrolled more than 390 patients with less than 5% of overall drop-out rate, surpassing the re-estimated sample size of 360 patients. The study enrollment was halted as soon as operationally feasible. The final sample size is approximately 420 patients (210 patients per treatment group).

9.7.10 Computer Methods

Statistical analyses will be performed using version 9.3 (or newer) of SAS.

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 wellbeing, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified timepoints, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the Sponsor.

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

10.0 STUDY SPONSORSHIP

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

10.1 STUDY TERMINATION

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

10.2 REPORTING AND PUBLICATION

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

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

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

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

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1.
- A copy of the IRB-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB members or the 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-03 ***Amendment 2, dated 20 Nov 2018***) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Investigator's Name

13.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

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

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, the Sponsor, the IRB, or an authorized contract research organization may inspect the records

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

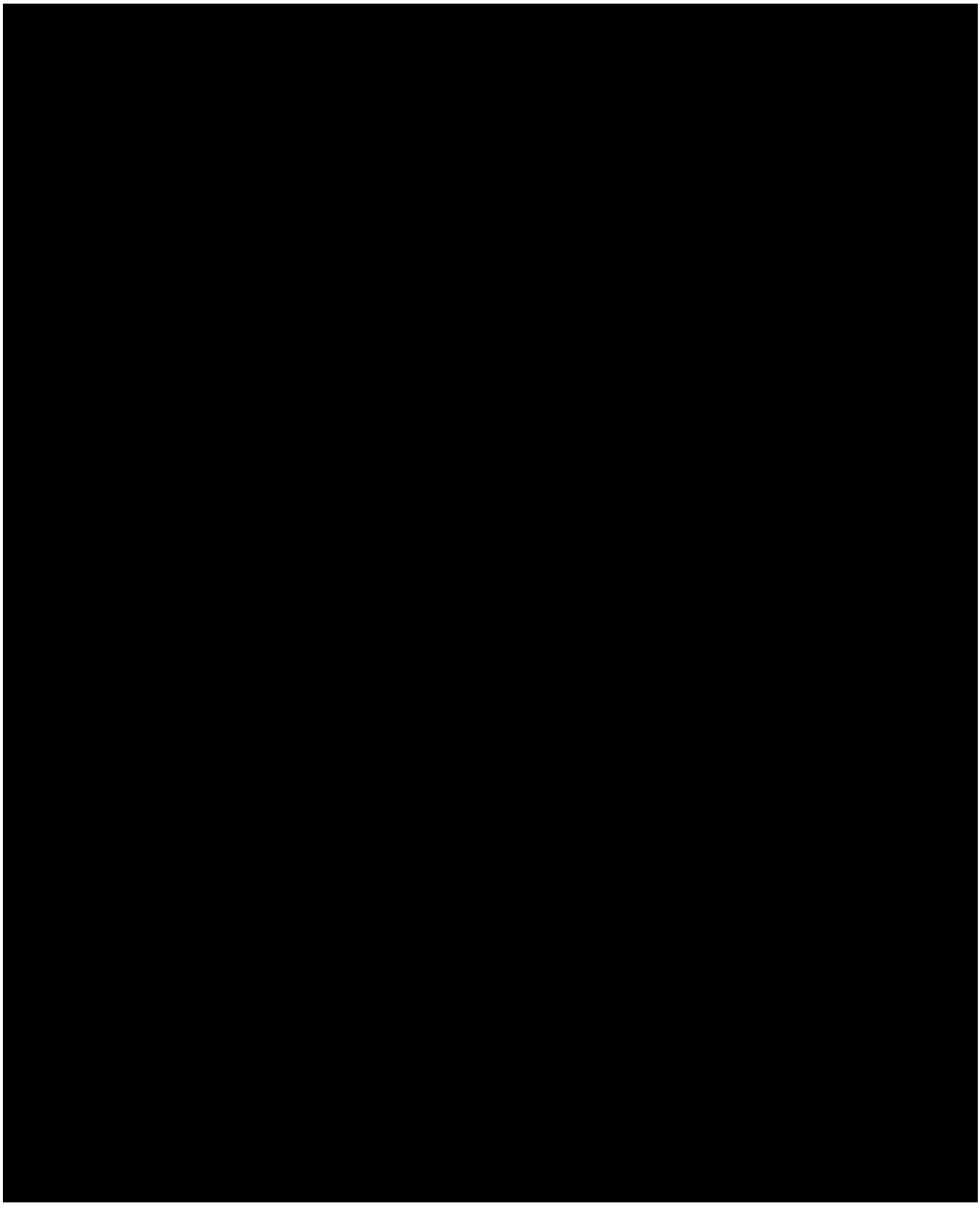
- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

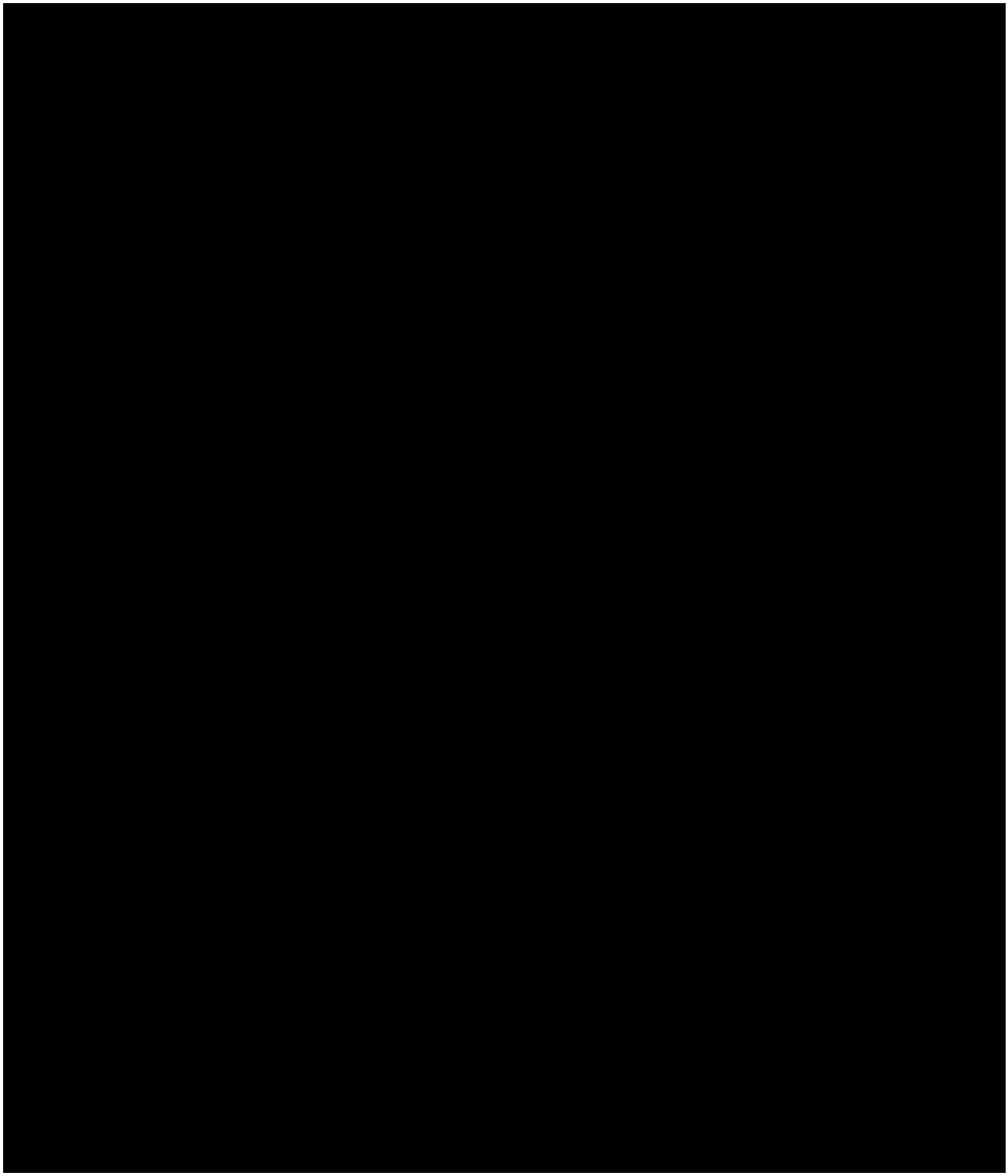
- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of permission, providing consent for the patient to participate (eg, "I agree to participate . . .")
- A place for the patient's signature and date of signing 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.

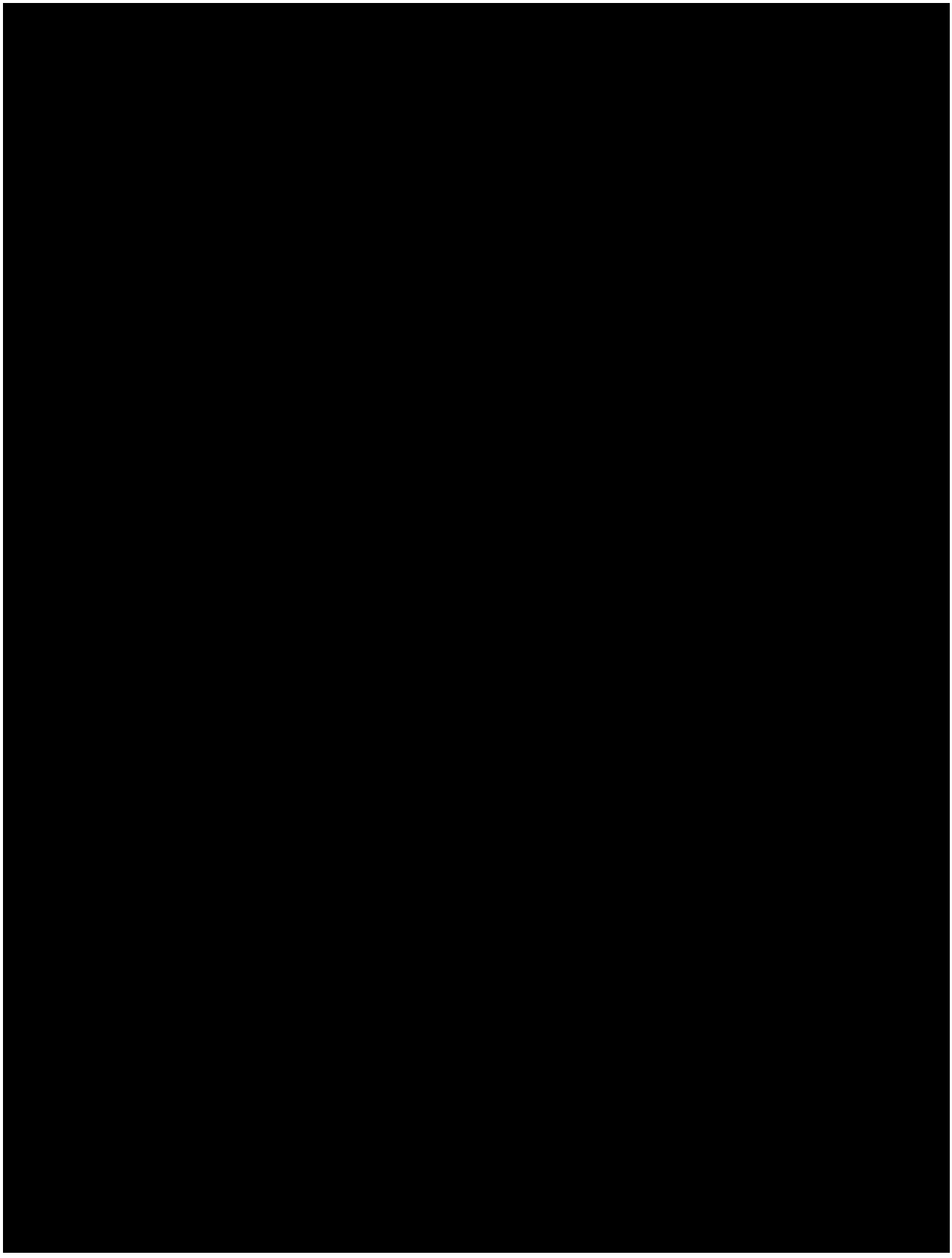
A copy of the signed consent form must be given to the patient.

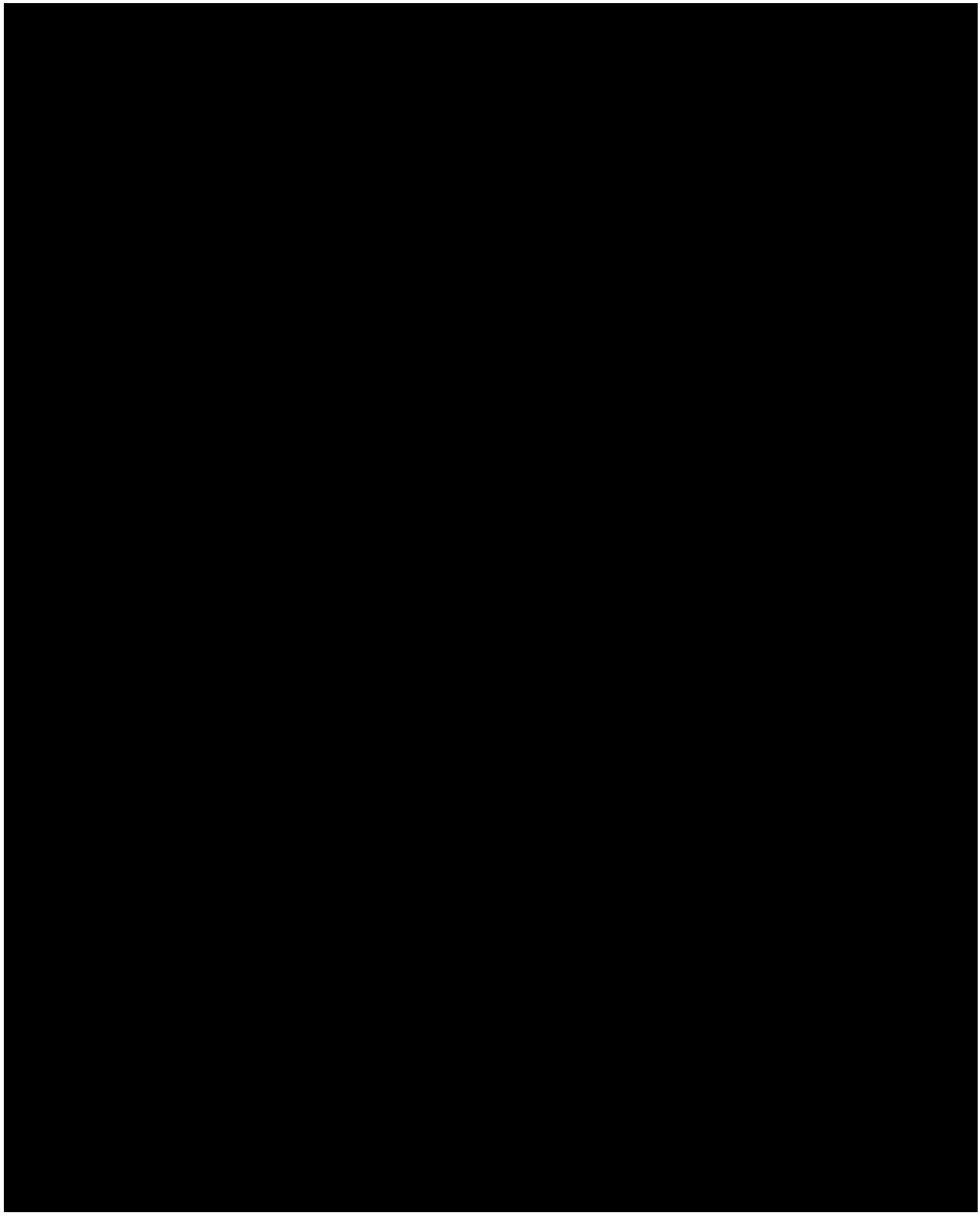
APPENDIX II. CONTACT INFORMATION

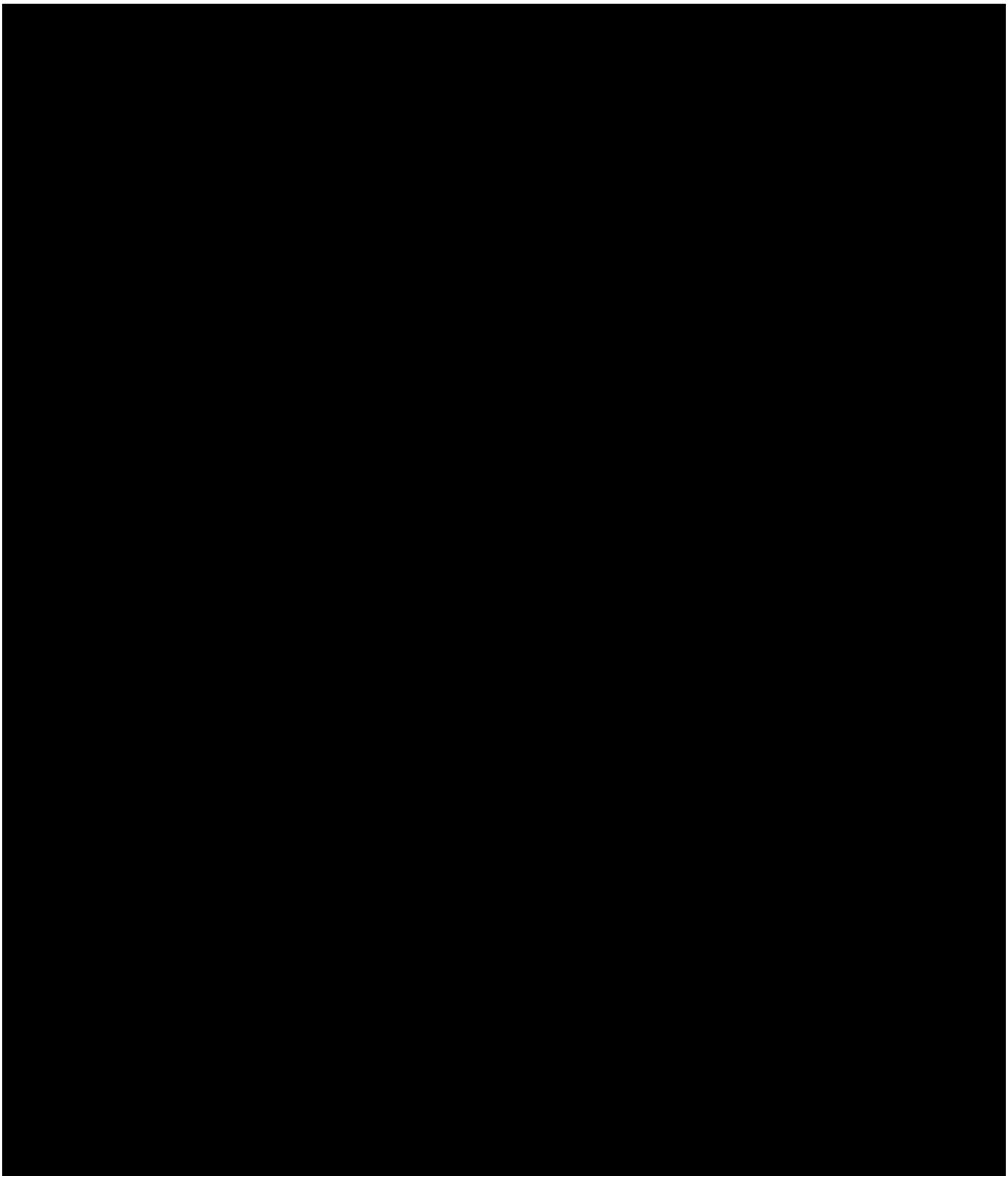
Contact information for the Sponsor personnel is maintained in the Study Reference Manual.

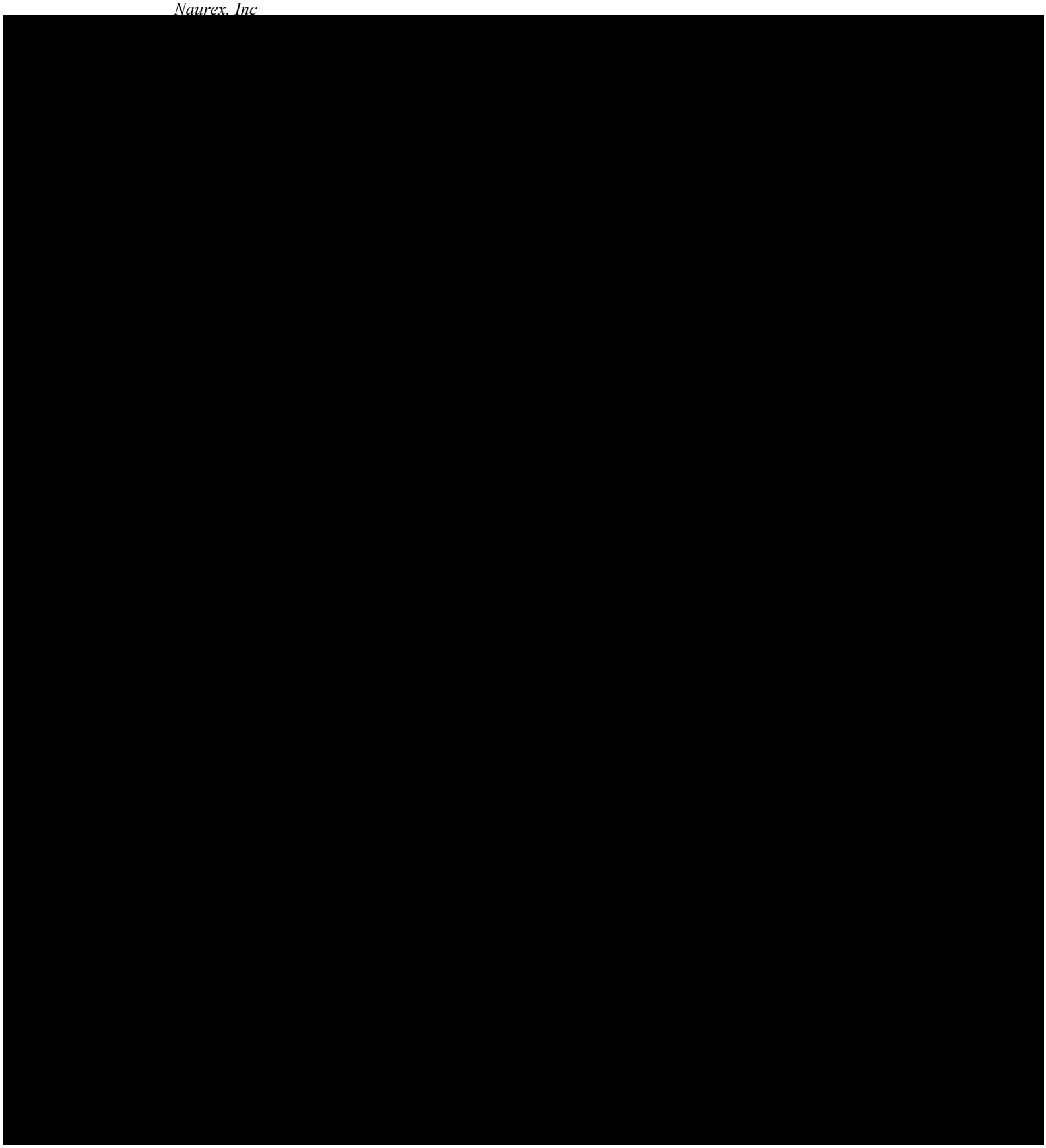












APPENDIX V. MONTGOMERY-ASBERG DEPRESSION RATING SCALE

1. **APPARENT SADNESS**—Representing despondency, gloom and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

   0 No sadness.
   1
   2 Looks dispirited but does brighten up without difficulty.
   3
   4 Appears sad and unhappy most of the time.
   5
   6 Looks miserable all the time. Extremely despondent.

2. **REPORTED SADNESS—**Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

   0 Occasional sadness in keeping with the circumstances.
   1
   2 Sad or low but brightens up without difficulty.
   3
   4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
   5
   6 Continuous or unvarying sadness, misery or despondency.

3 **INNER TENSION**—Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

   0 Placid. Only fleeting inner tension.
   1
   2 Occasional feelings of edginess and ill-defined discomfort.
   3
   4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   5
   6 Unrelenting dread or anguish. Overwhelming panic.

4. **REDUCED SLEEP**—Representing the experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well.

   0 Sleeps as usual.
   1
   2 Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep.
   3
   4 Sleep reduced or broken by at least 2 hours.
   5
   6 Less than 2or 3 hours sleep.

5. **REDUCED APPETITE**—Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

   0 Normal or increased appetite.
   1
   2 Slightly reduced appetite.
   3
   4 No appetite. Food is tasteless.
   5
   6 Needs persuasion to eat at all.

6. **CONCENTRATION DIFFICULTIES**—Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

   0 No difficulties in concentrating.
   1
   2 Occasional difficulties in collecting one's thoughts.
   3
   4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
   5
   6 Unable to read or converse without great difficulty.

7. **LASSITUDE**—Representing a difficulty getting started or slowness initiating and performing everyday activities.

   0 Hardly any difficulty getting started. No sluggishness.
   1
   2 Difficulties in starting activities.
   3
   4 Difficulties in starting simple routine activities which are carried out with effort.
   5
   6 Complete lassitude. Unable to do anything without help.

8. **INABILITY TO FEEL**—Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

   0 Normal interest in the surroundings and in other people.
   1
   2 Reduced ability to enjoy usual interests.
   3
   4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
   5
   6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives or friends.

9. **PESSIMISTIC THOUGHTS**—Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

   0 No pessimistic thoughts.
   1
   2 Fluctuating ideas of failure, self-reproach or self-deprecation.
   3
   4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
   5
   6 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

10. SUICIDAL THOUGHTS—Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.

1

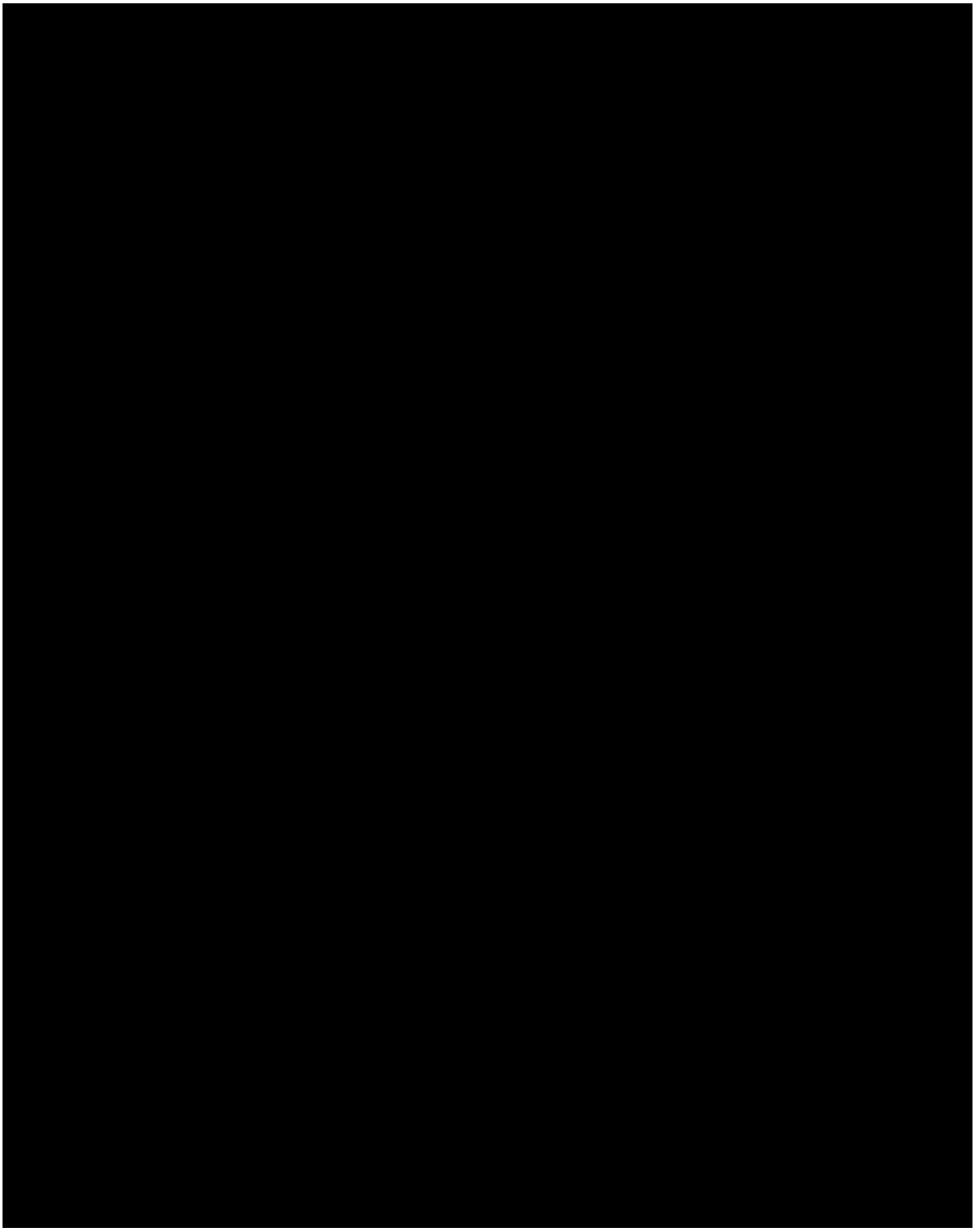
2 Weary of life. Only fleeting suicidal thoughts.

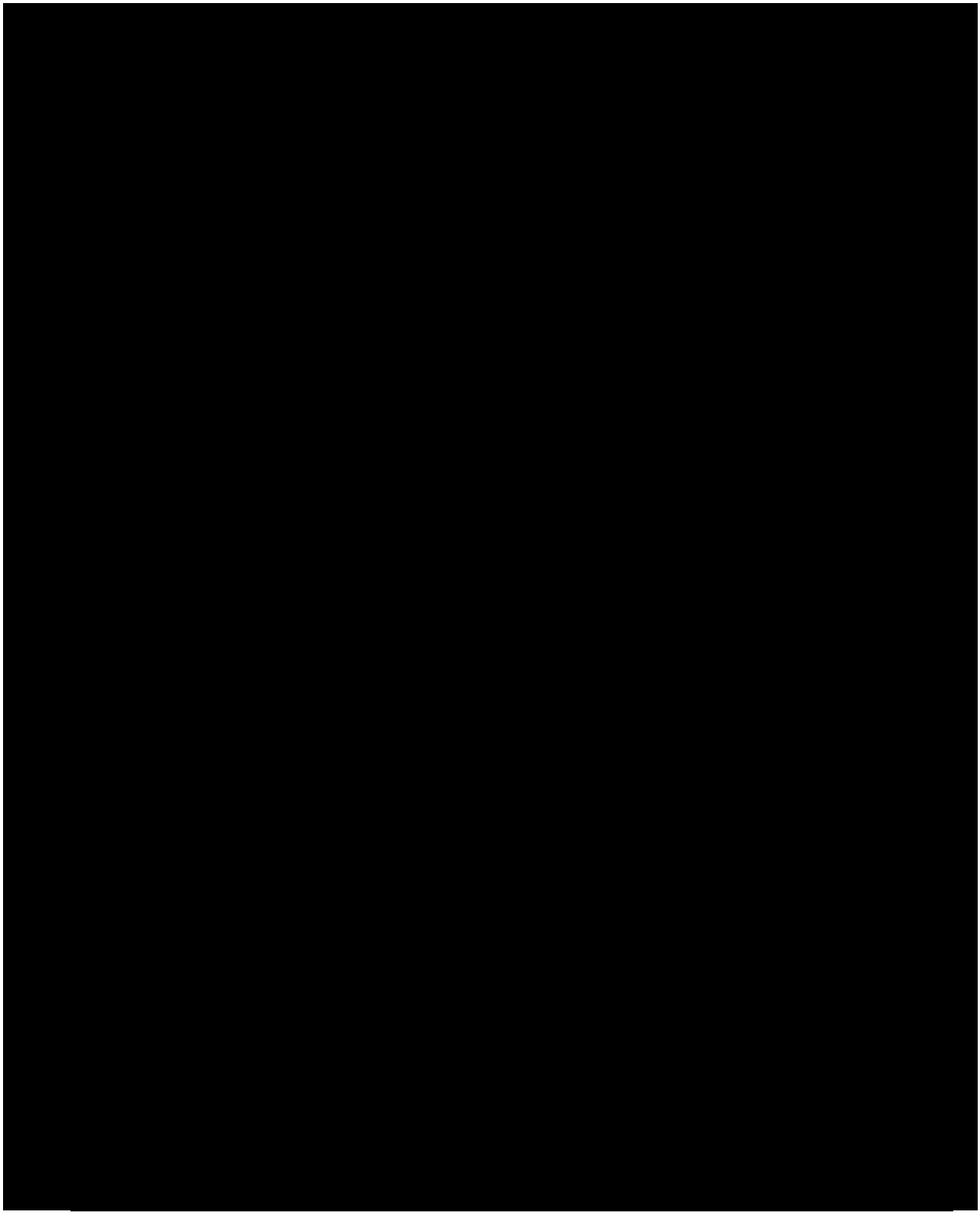
3

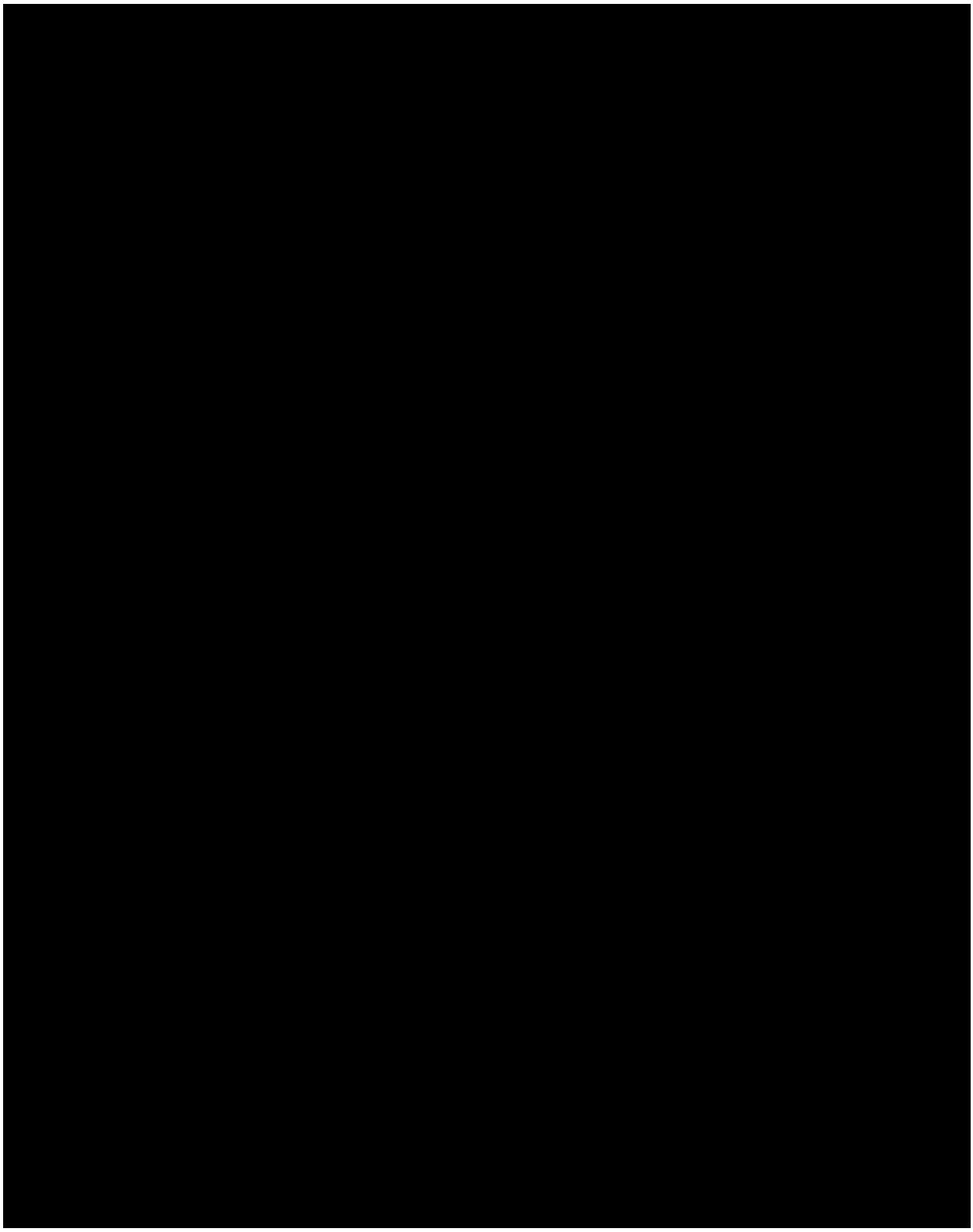
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

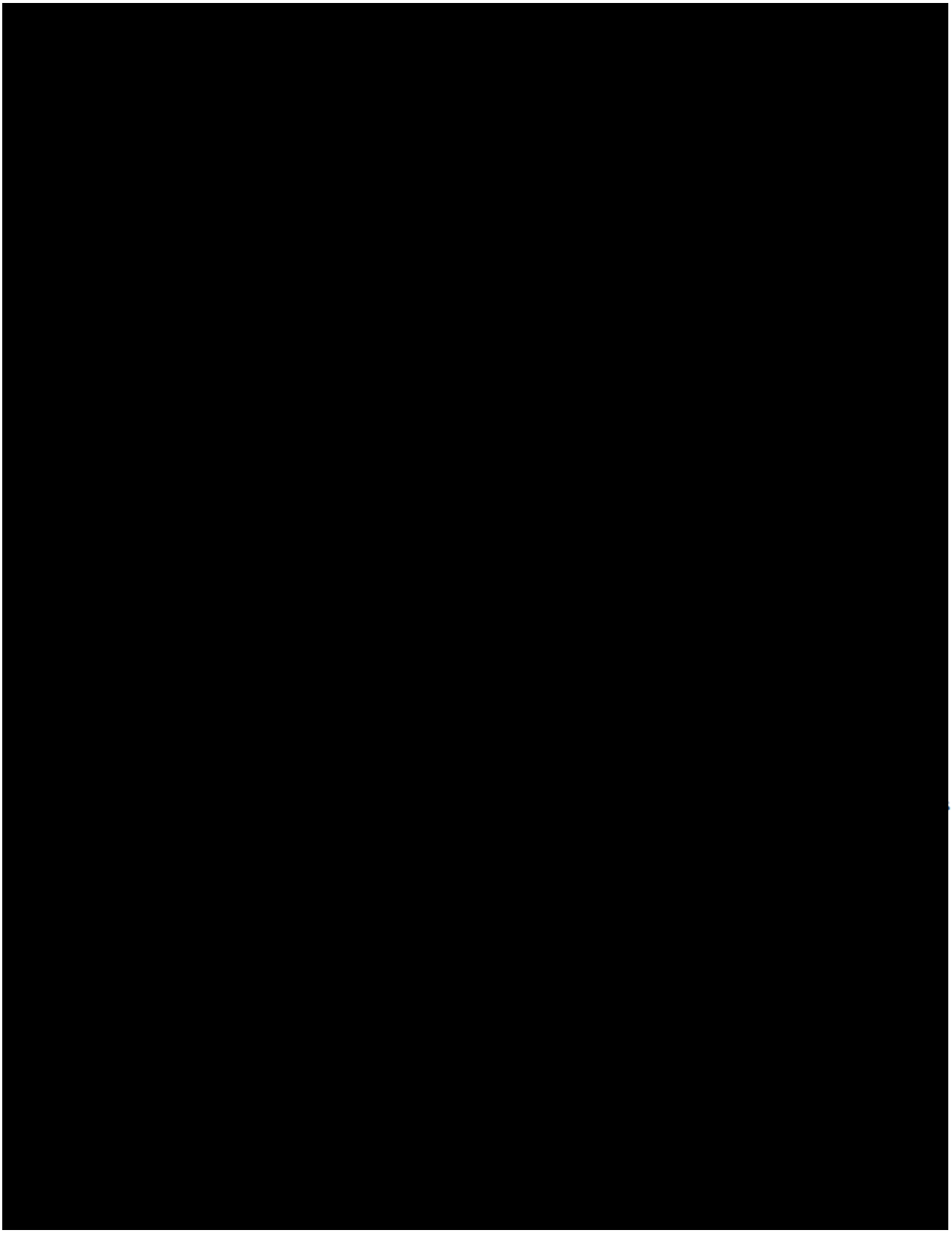
5

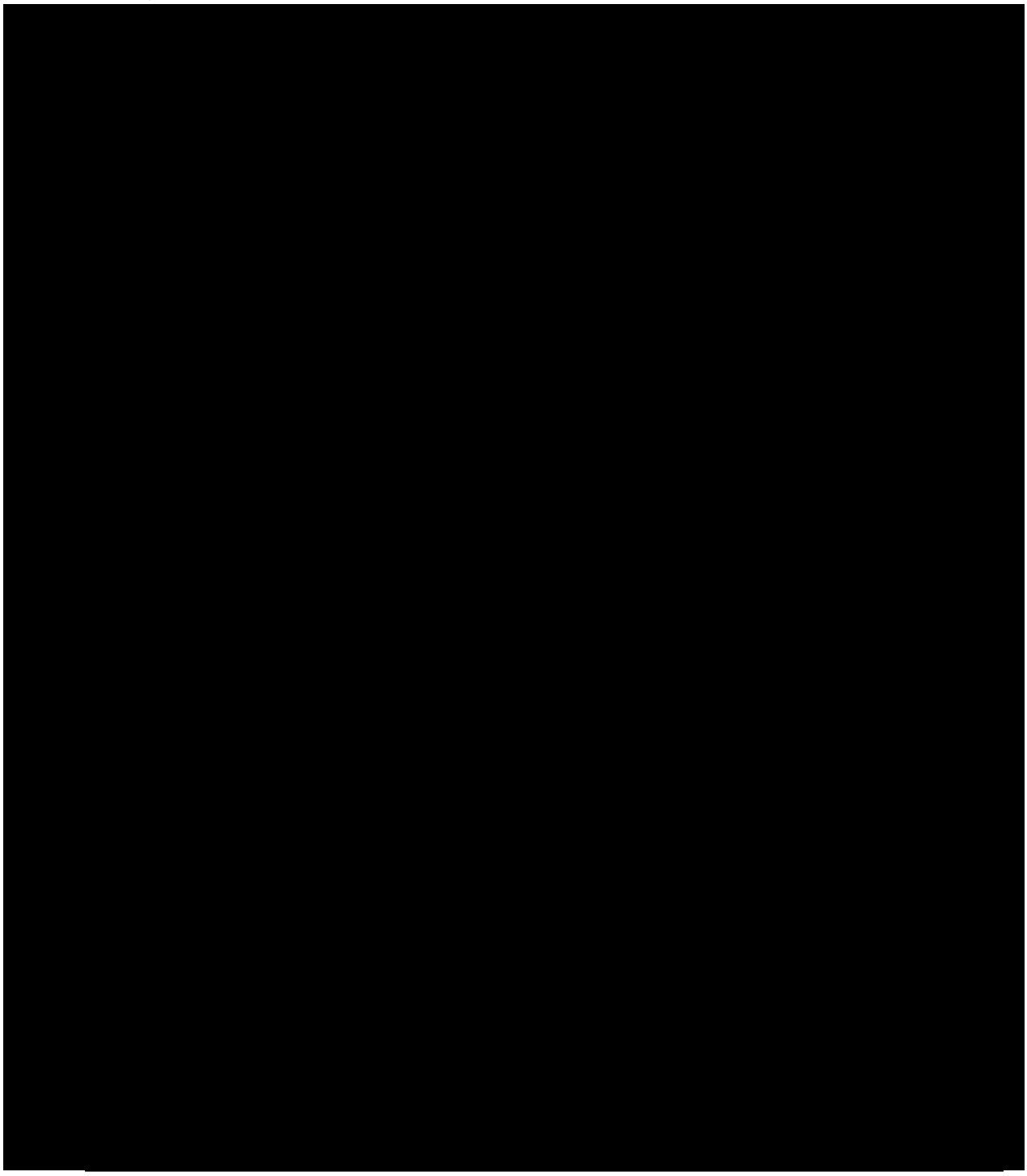
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

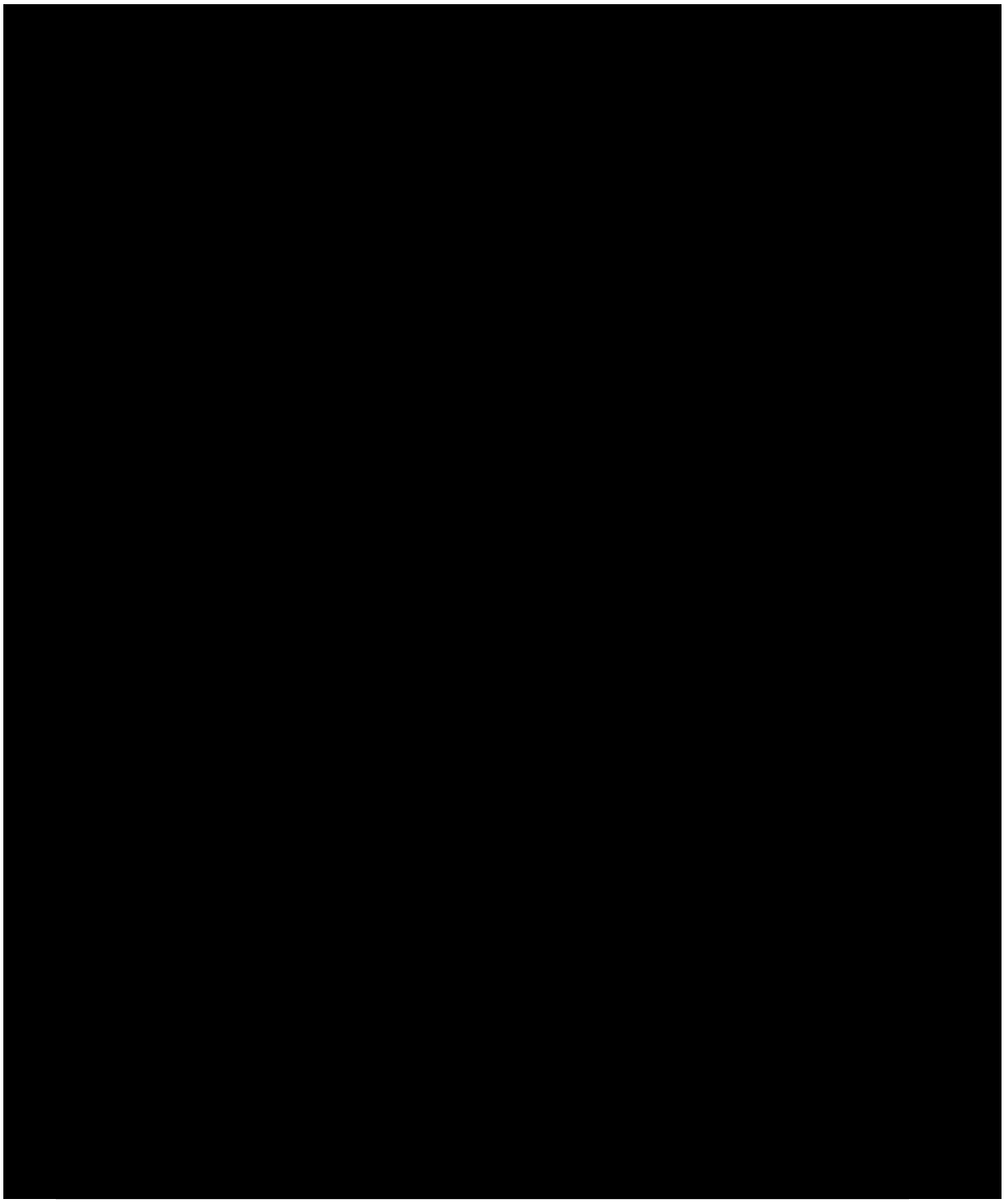


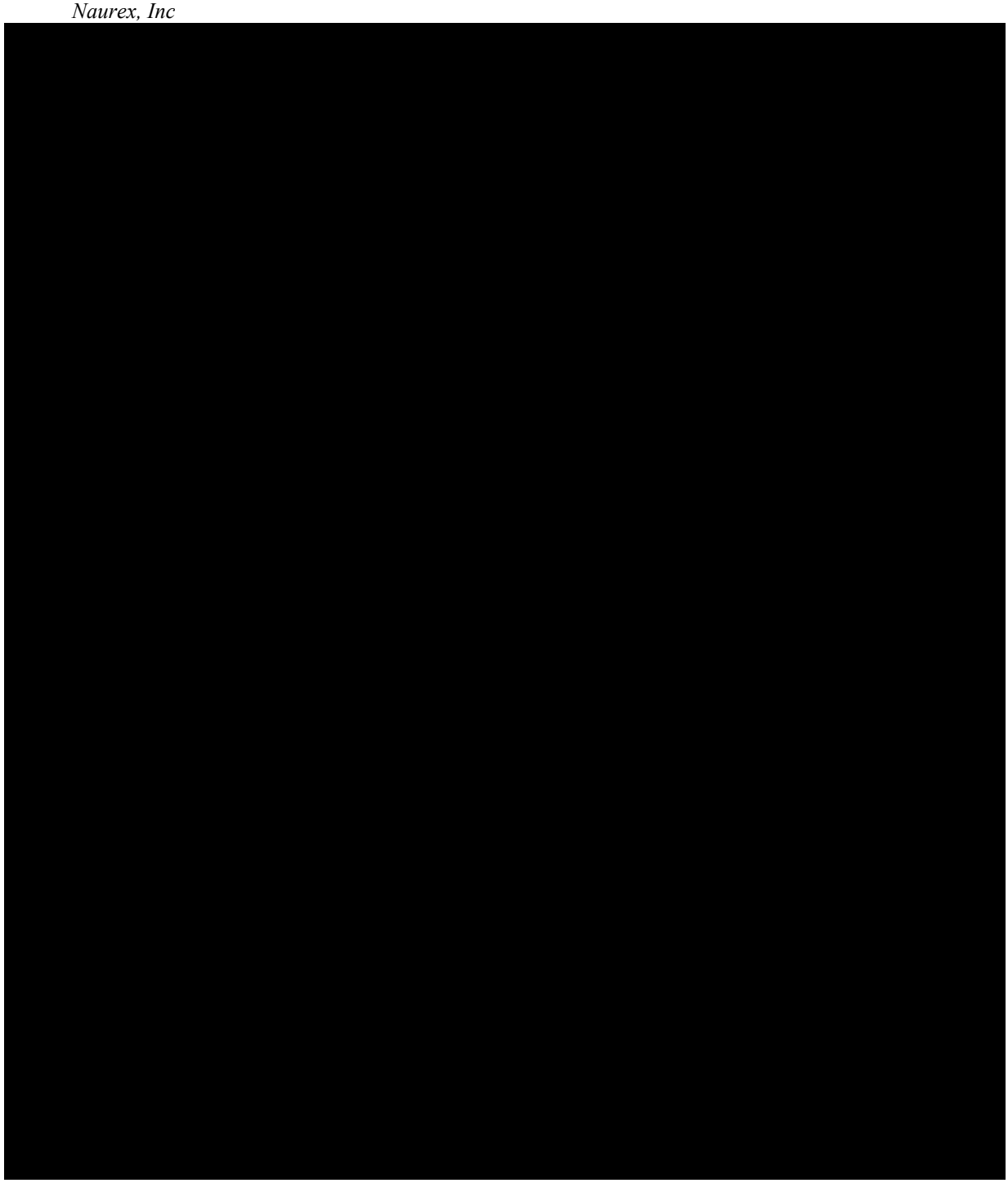


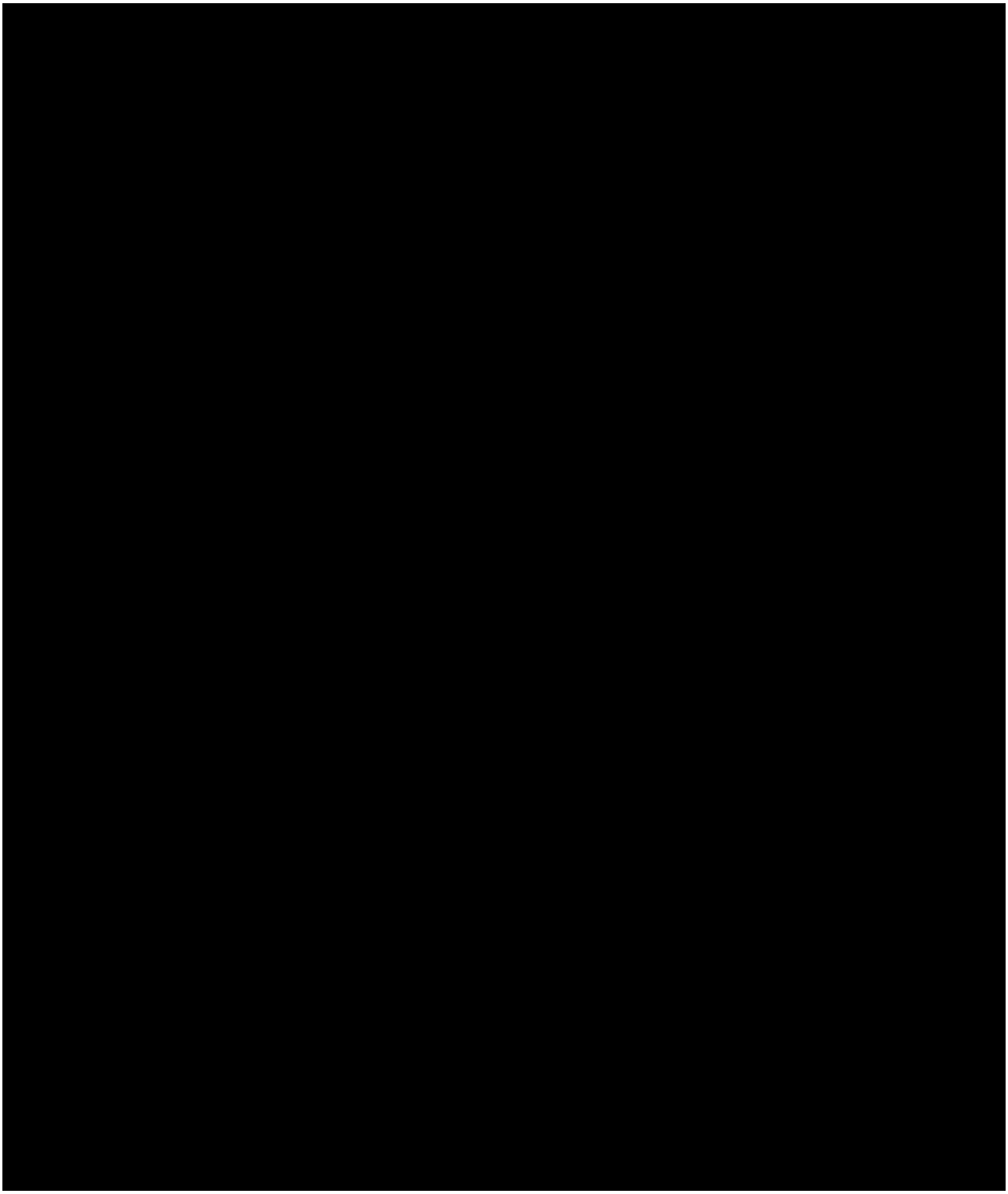


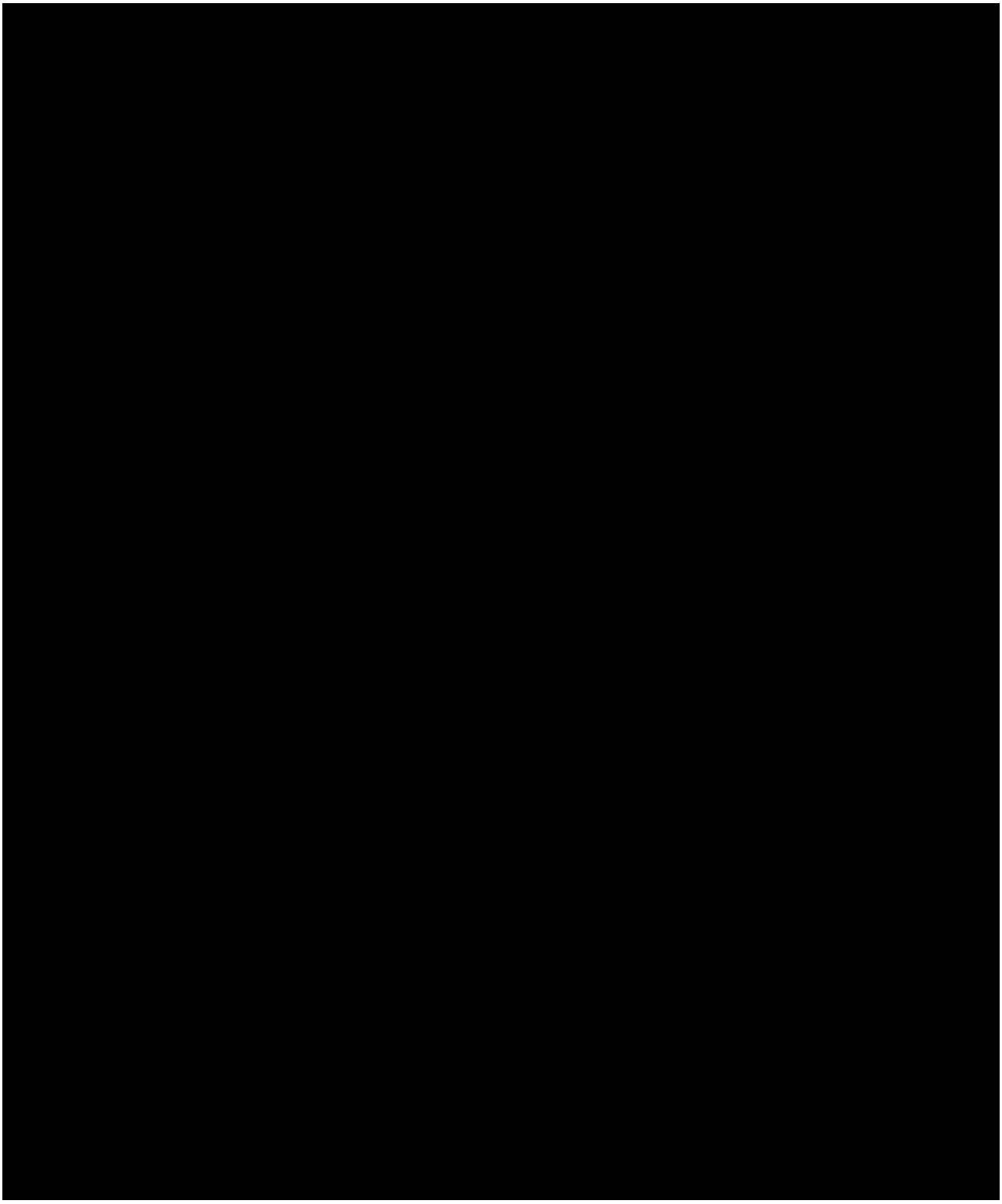


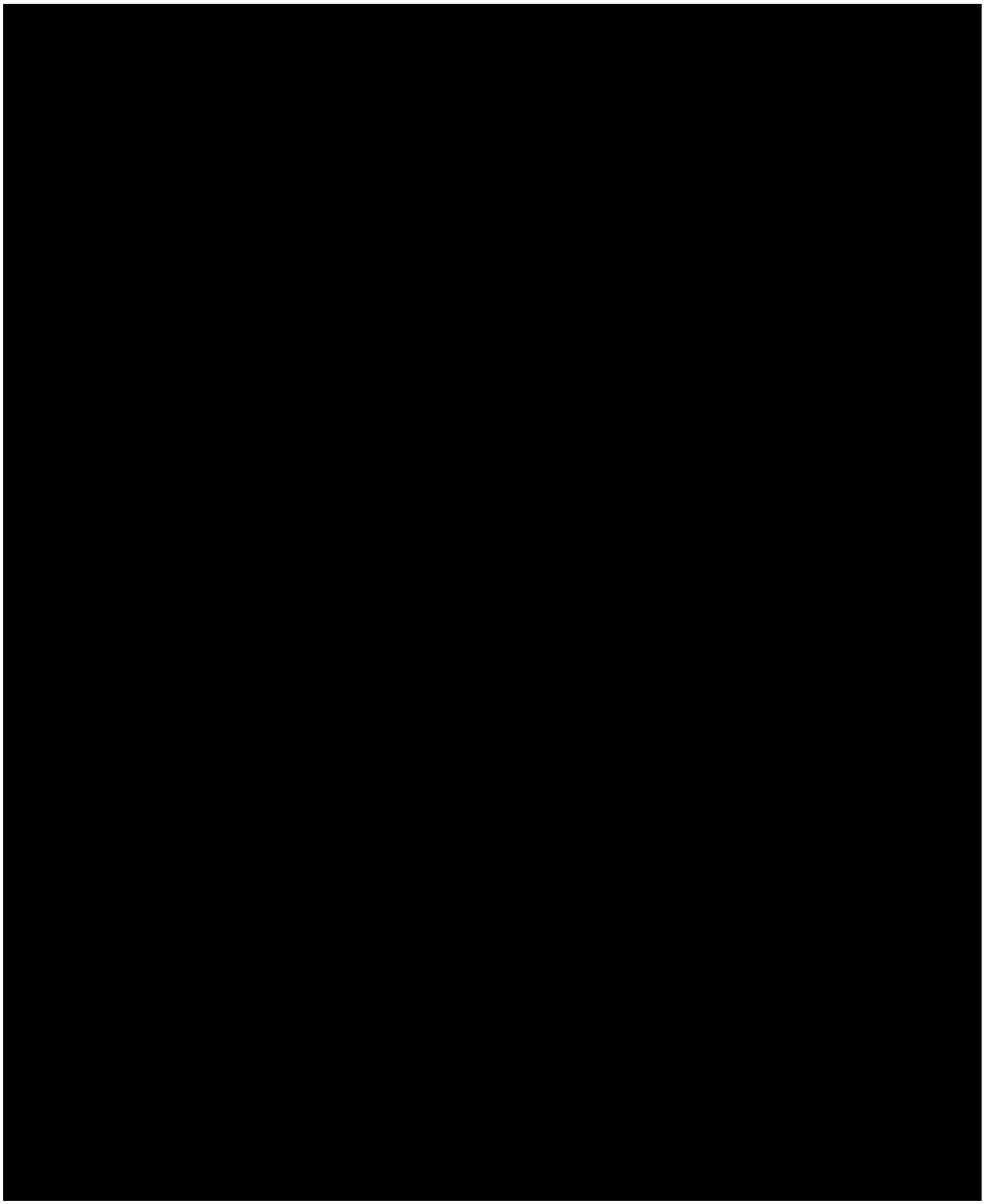


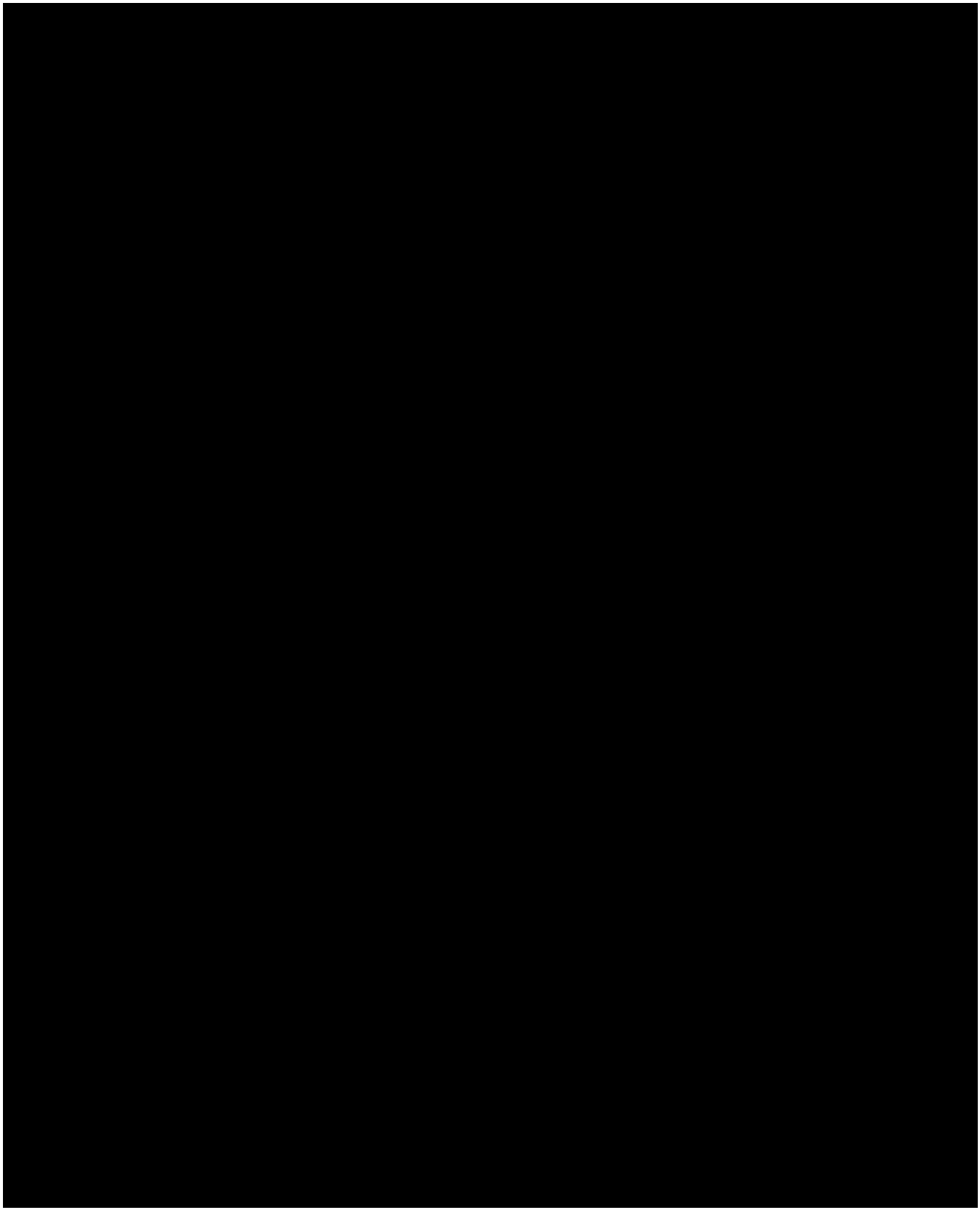


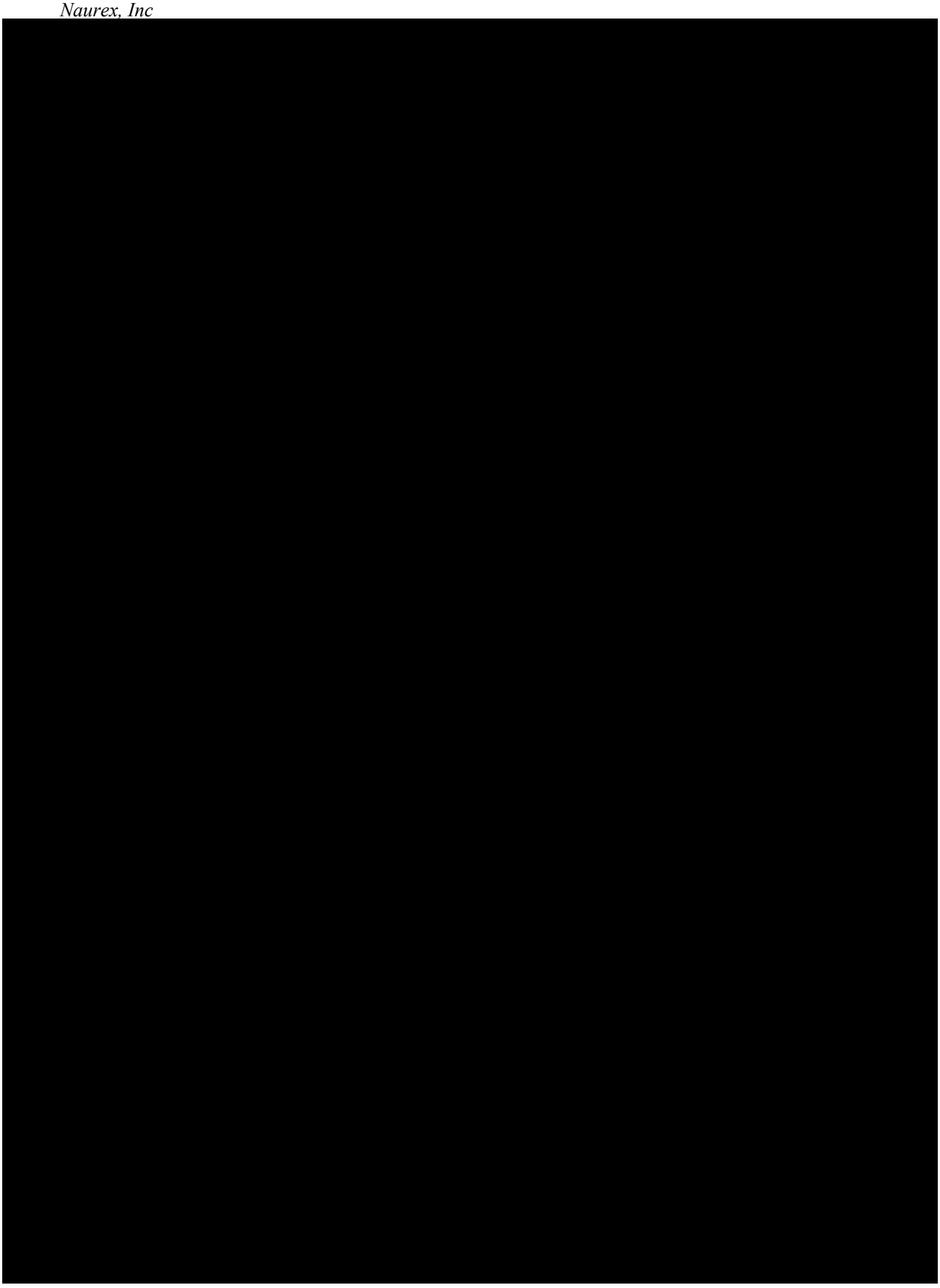


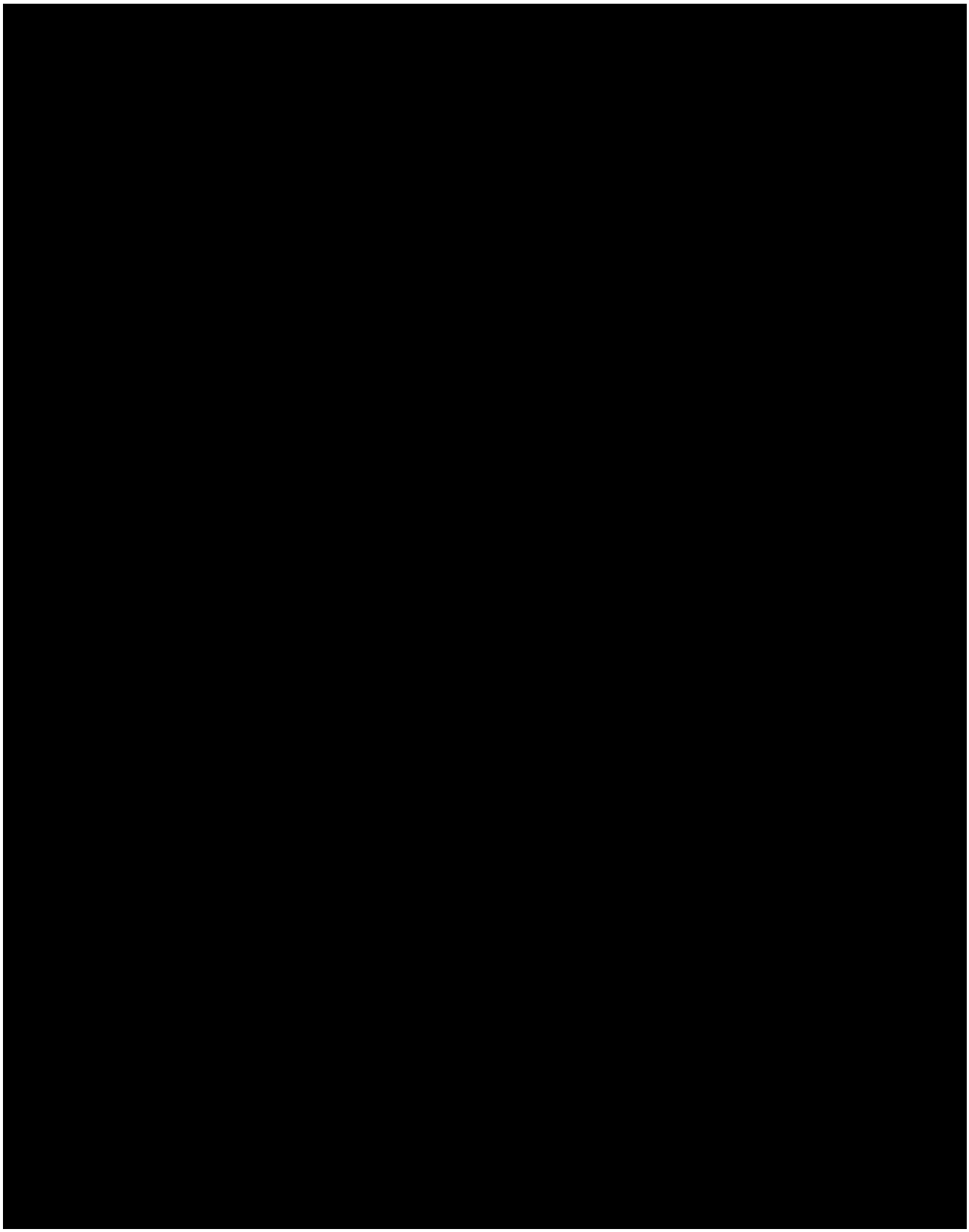












14.0 LITERATURE CITED

Abilify [package insert]. Tokyo, Japan; Otsuka Pharmaceutical Co., Ltd. December 2014.

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

Ashton AK, Jamerson BD, Weinstein W, et al. Antidepressant-related adverse effects impacting treatment compliance: Results of a patient survey. Current Therapeutic Research, Clinical and Experimental 2005;66(2):96-106.doi:10.1016/j.curtheres.2005.04.006.

Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68(6):843-53.

Boland RJ, Keller MB. Treatment of depression. In: Schatzberg AF, Nemeroff CB, editors. Essentials of clinical psychopharmacology. 2nd ed. Arlington, VA: American Psychiatric Publishing, Inc.; 2006. p 465-78.

Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;11:125–36.

EMA/CHMP/185423/2010 Rev. 2 previously (CPMP/EWP/518/97, Rev. 1) Committee for Medicinal Products for Human Use (CHMP) 30 May 2013 Guideline on clinical investigation of medicinal products in the treatment of depression

Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 1996 Jun;19(2):179-200.

FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

FDA Guidance for Industry: Drug Induced Liver Injury- Pre-Marketing Clinical Evaluation, July 2009

FDA Guidance for Industry: E10, Choice of Control Group and Related Issues in Clinical Trials, May 2001

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(3)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(12):1465-75.

Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol. 2006 Oct;21(7):623-43.

Guy W: ECDEU Assessment Manual for Psychopharmacology - Revised, in (ed DHEW Publ No ADM 76-338). Rockville, MD, U.S., U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976, pp 218-222

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20 (10):1727-36.

Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. Biometrika 2003; 90(1): 53-71

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97

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.

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(6): 617-27.

Laughren TP. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. Eur Psychiatry. 2001; 16(7):418-23

Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008;28(2):156-65.

Masand PS. Tolerability and adherence issues in antidepressant therapy. Clin Ther 2003;25(8):2289-304.

McIntyre RS and O'Donovan C. The human cost of not achieving full remission in depression. Can J Psychiatry 2004;49(suppl 1):10S-16S.

Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382-9

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(6):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(10):950-66.

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

Rapastinel: Investigator's Brochure. Edition 7. Evanston, IL: Naurex, Inc; 01 Jul 2014.

Rexulti [package insert]. Tokyo, Japan; Otsuka Pharmaceutical Co., Ltd. August 2015.

Rosenzweig-Lipson S, Beyer CG, Hughes ZA, et al. Differentiating antidepressants of the future: efficacy and safety. Pharmacol Ther 2007;113(1):134-53.

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.

Sachdev P. The epidemiology of drug-induced akathisia part II. Chronic, tardive, and withdrawal akathisias. Schizophren Bull 1995;21(3):451-61.

Seroquel [package insert]. Wilmington, DE; AstraZeneca Pharmaceuticals LP. October 2013.

Smith DW and Jones KL (1982). Recognizable Patterns of Human Malformation. (3 ed.) Philadelphia: Saunders.

Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentations after the failure of SSRIs for depression. N Engl J Med 2006;354(12):1243-52.

Videbech P and Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 2004;161:1957-66.

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