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Study ID: RAP-MD-30

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Monotherapy in Patients with Major Depressive Disorder

Protocol Date: 17 Apr 2018

1.0

TITLE PAGE

A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Monotherapy in Patients with Major Depressive Disorder

RAP-MD-30

(3106-330-008)

IND # 136,870

Original Protocol Date: 17 Apr 2018

Sponsor:	Naurex Inc., an indirect subsidiary of Allergan, plc 5 Giralda Farms Madison, NJ 07940	Allergan, Ltd. Marlow International The Parkway Marlow Buckinghamshire SL7 1YL, UK
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Confidentiality Statement

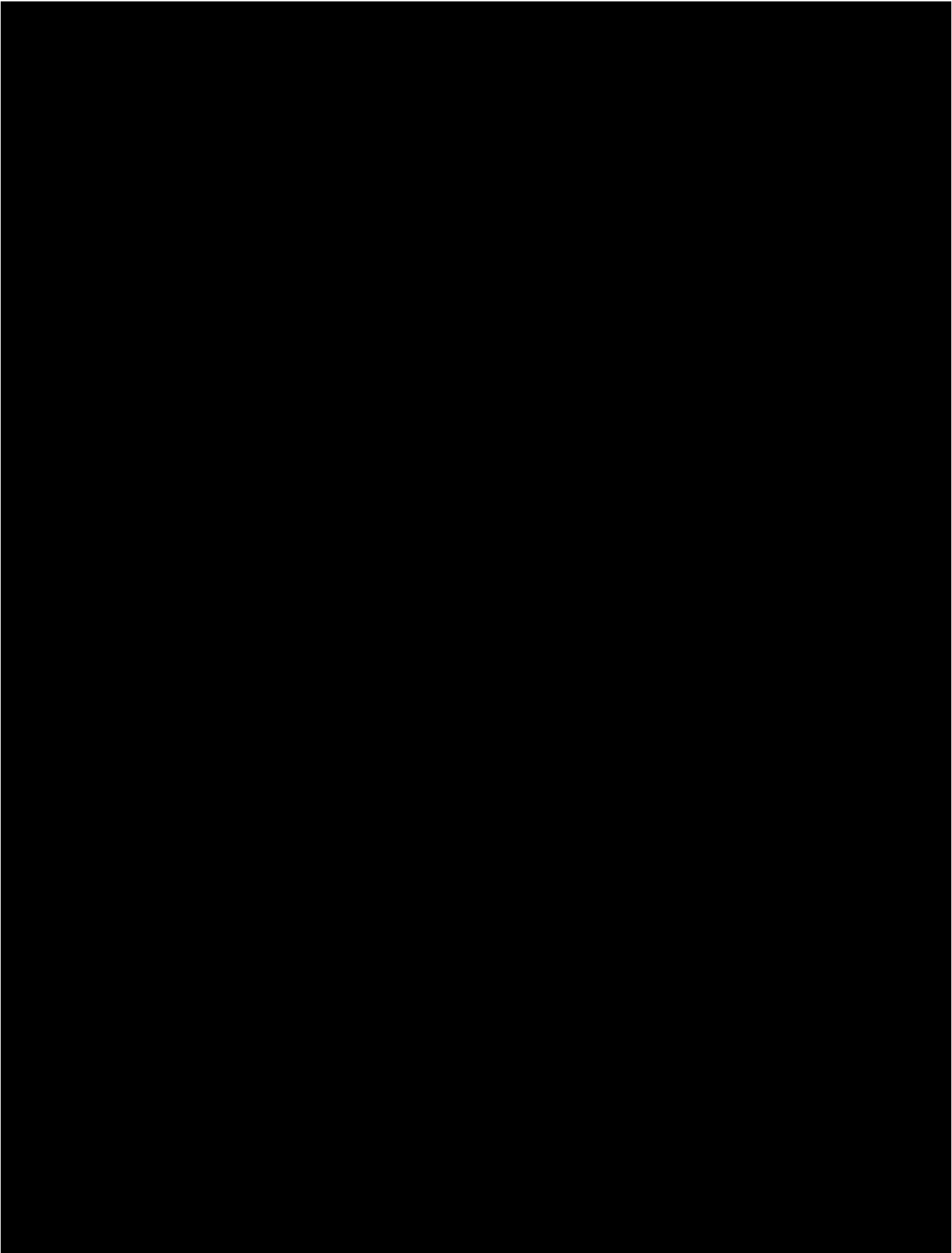
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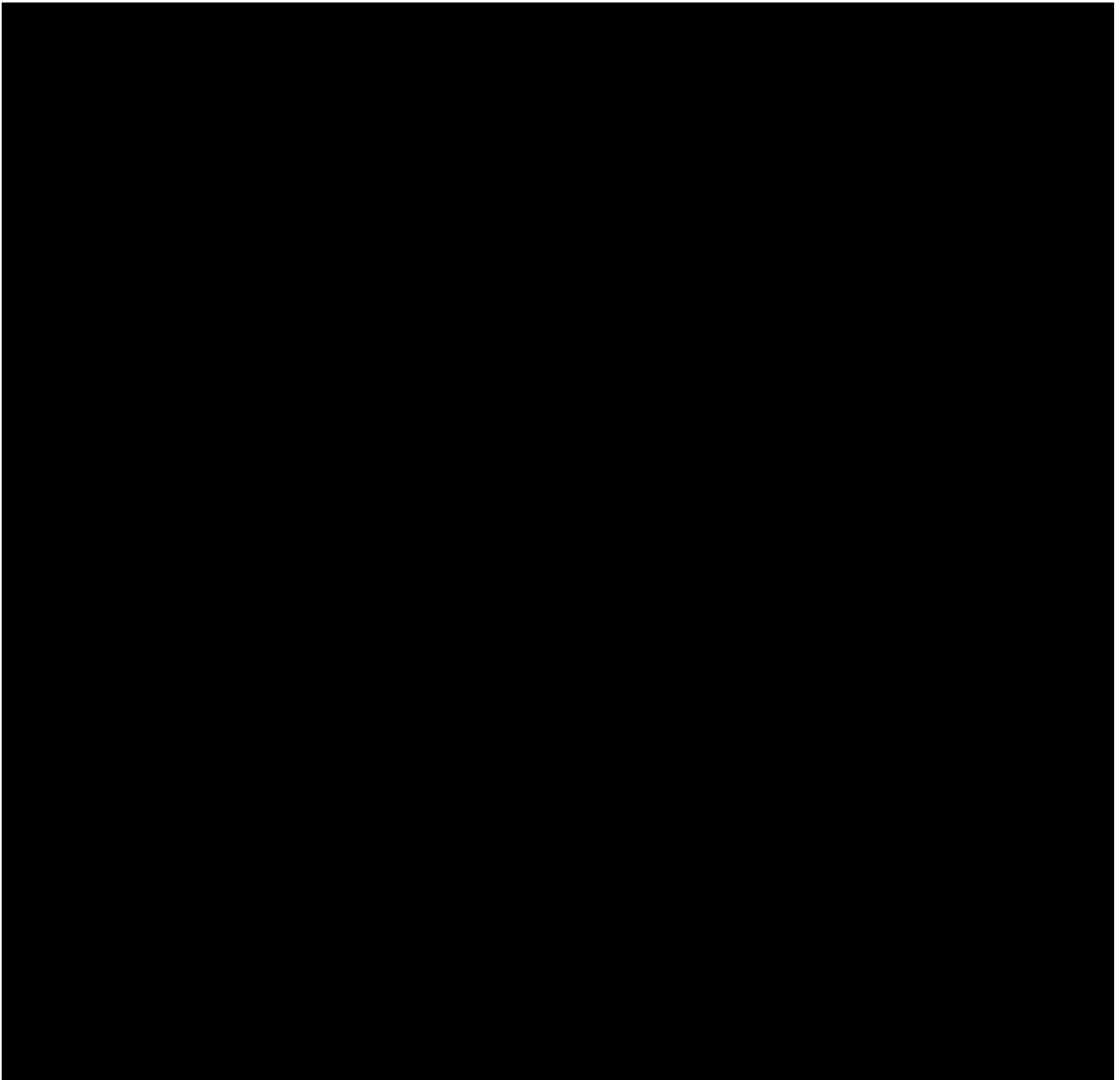
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study RAP-MD-30	
Study Number	RAP-MD-30 (3106-330-008)
Title of Study	A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Monotherapy in Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 54 study centers (primarily in Japan and Eastern Europe)
Development Phase	3
Objective	To evaluate the efficacy, safety, and tolerability of rapastinel as a monotherapy treatment in patients with major depressive disorder (MDD)
Methodology	Multicenter, randomized, 6-week double-blind, placebo-controlled, parallel-group study of two doses of intravenous (IV) rapastinel (450 mg and 225 mg) vs IV placebo (randomized 1:1:1) as monotherapy treatment in patients with MDD
Duration of Participation	<ul style="list-style-type: none"> Up to 2-week screening period Followed by a 6-week double-blind treatment period Followed by a 2-week safety follow-up period (for patients who do not roll over into the extension study)
Number of Patients	Approximately 690 planned to be enrolled
Diagnosis and Main Criteria for Inclusion	<ul style="list-style-type: none"> Male and female outpatients who are 18 to 75 years of age Meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD [REDACTED] [REDACTED] with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1 [REDACTED] [REDACTED] Treatment naive (defined as those who have not received antidepressant or those who have received antidepressant but not meeting adequate dose or duration criteria per the Antidepressant Treatment Response Questionnaire [ATRQ]) in the present episode or inadequate response (< 50% reduction in depressive symptoms) to 1 to 3 antidepressant therapies [ADTs] given at adequate doses (as defined by the ADT package insert) and duration of ≥ 4 weeks during the present episode as documented using the ATRQ

Test Product, Dosage, and Mode of Administration	<ul style="list-style-type: none">• 450 mg rapastinel (prefilled syringe, weekly intravenous [IV] administration)• 225 mg rapastinel (prefilled syringe, weekly IV administration)
Reference Therapy, Dosage, and Mode of Administration	Placebo (prefilled syringe, weekly IV administration)
Criteria for Evaluation	
Primary Endpoint	Change from baseline in MADRS total score at the end of the double-blind treatment period (end of Week 6)
Key Secondary Endpoint	Change from baseline in MADRS total score at 1 day after first dose of treatment
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

	
Statistical Methods	<p>Efficacy analyses will be based on the modified Intent-to-Treat (mITT) Population, defined as all randomized patients who have received randomized investigational product (IP) and have at least 1 postrandomization assessment of the MADRS total score. Safety analyses will be based on the Safety Population, defined as all randomized patients who received at least 1 dose of randomized IP.</p> <p>The primary efficacy parameter, change from baseline in MADRS total score at the end of treatment (end of Week 6), will be analyzed using a mixed-effects model for repeated measures (MMRM) with treatment group, (pooled) study center, visit, and treatment group-by-visit interaction as fixed effects and baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The key secondary efficacy parameter, change from baseline in MADRS total score at 1 day after the first dose of treatment, will be analyzed using the same MMRM model for the primary efficacy parameter. Baseline will be defined as the last measurement prior to the first dose of treatment.</p> <p>All safety parameters will be analyzed using descriptive statistics.</p>

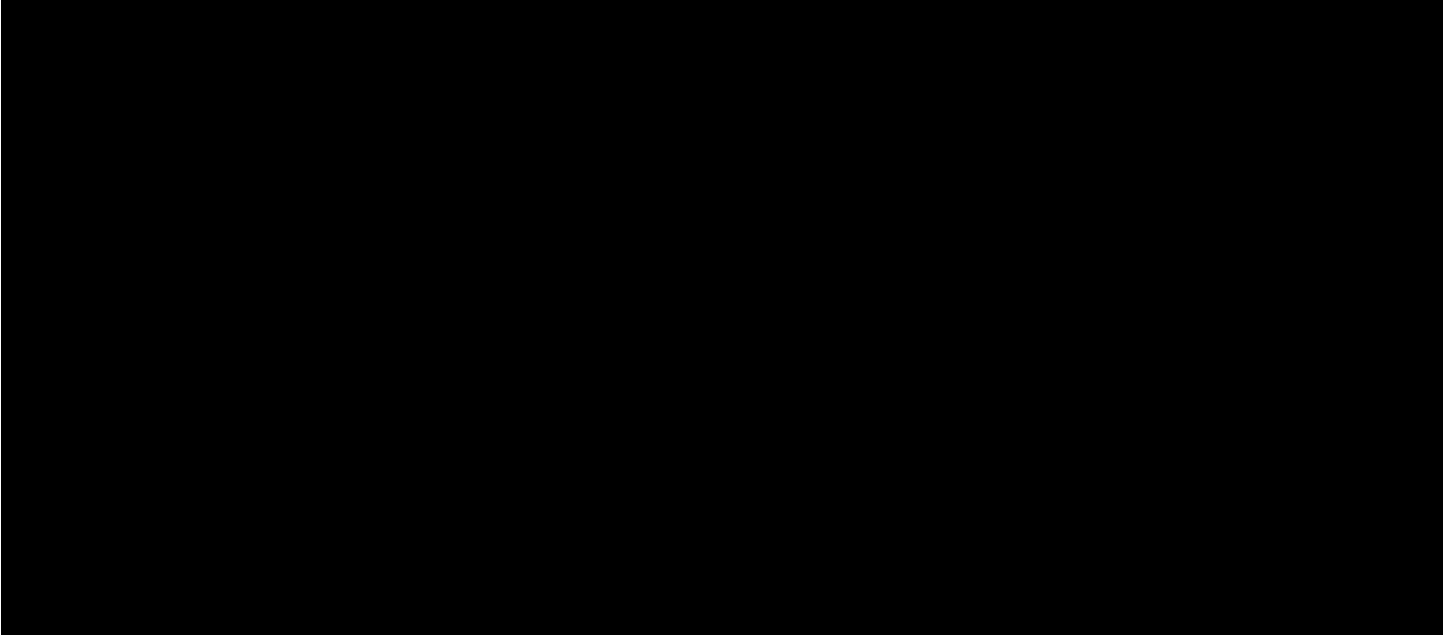




Approval Page

Name of Investigational Product: Rapastinel

Document: RAP-MD-30 Protocol



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ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
mITT	modified Intent-to-Treat
MMRM	mixed-effect 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
█	█
SD	standard deviation
█	█
█	█
█	█
SNRI	selective serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States

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 (if applicable), and amendments (if any) will be approved by the IRBs at the study centers in conformance with the US CFR, Title 21, Part 56.

Outside the United States

This study will be carried out in full compliance with the guidelines of the independent ethics committee (EC) or IRB (as applicable) and/or government agencies as applicable for each respective country as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the study centers will require approval from an EC/IRB and government agency. During the course of the study, the sponsor or authorized representative will provide timely and accurate reports to the EC/IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the EC/IRB of SAEs or other significant safety findings. The study protocol, ICF, information sheet, advertisements (if applicable), and amendments (if any) will be approved by the EC/IRB at the study centers in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

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 that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

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 54 study centers in Japan and Eastern Europe.

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/EC (where applicable), 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 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 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. 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 lengthy for patients who are often severely depressed and at a high risk for suicide. A drug that could induce a rapid antidepressant effect would represent a major advancement for these patients.

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 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 first-line antidepressants (SSRIs, SNRIs) or adjuvant drugs currently approved for treatment of MDD such as 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 at a dose of 450 or 225 mg as a slow bolus IV injection 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 monotherapy treatment for MDD.

8.0 STUDY OBJECTIVES

The objectives of this study are to evaluate efficacy, safety, and tolerability of rapastinel as a monotherapy treatment in patients with MDD.

Efficacy Objectives

- **Primary efficacy objective:** To evaluate the efficacy of rapastinel (450 mg IV) versus placebo and rapastinel (225 mg IV) versus placebo in the treatment of MDD, as measured by the change from baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score at end of treatment (end of week 6)
- **Key secondary efficacy objective:** To evaluate the efficacy of rapastinel (450 mg IV) versus placebo and rapastinel (225 mg IV) versus placebo in the treatment of MDD, as measured by the change from baseline MADRS total score at 1 day post-first dose of treatment

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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-arm fixed-dose study of weekly IV rapastinel 450 mg, rapastinel 225 mg, and placebo in outpatients with a diagnosis of MDD as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

The study will include a total of 10 visits and will be approximately 8 weeks in duration (Figure 9.1.3–1):

- Up to 2-week screening period
- 6-week double-blind treatment period
- 2-week safety follow-up period (no treatment) for patients who do not roll over into the extension study

Approximately 690 patients are planned to be randomized in the double-blind treatment period (230 patients per treatment group). Note that the sponsor may restrict enrollment based on patient treatment history to ensure an appropriate balance of patients with an inadequate response to 1 to 3 ADTs if deemed necessary during study conduct.

9.1.1 **Screening Period**

After providing written consent, patients will enter a screening period of up to 2 weeks, prior to Visit 2. Patients will not receive any investigational product (IP) during the screening period. Patients will wash out of any ADT and prohibited medications under the supervision of the study investigator staff during the screening period. 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**

Patients will be randomized in a ratio of 1:1:1 to 1 of 3 treatment groups: rapastinel 225 mg IV weekly, rapastinel 450 mg IV weekly, or placebo IV weekly.

During the double-blind treatment period:

- Patients will have 2 study visits during the first week (treatment day [Visit 2] and 1 day following the treatment day [Visit 3]). Visits 2 and 3 should be conducted 1 day apart. Visit 4 will occur approximately 7 days following Visit 2 with subsequent visits occurring at weekly intervals.

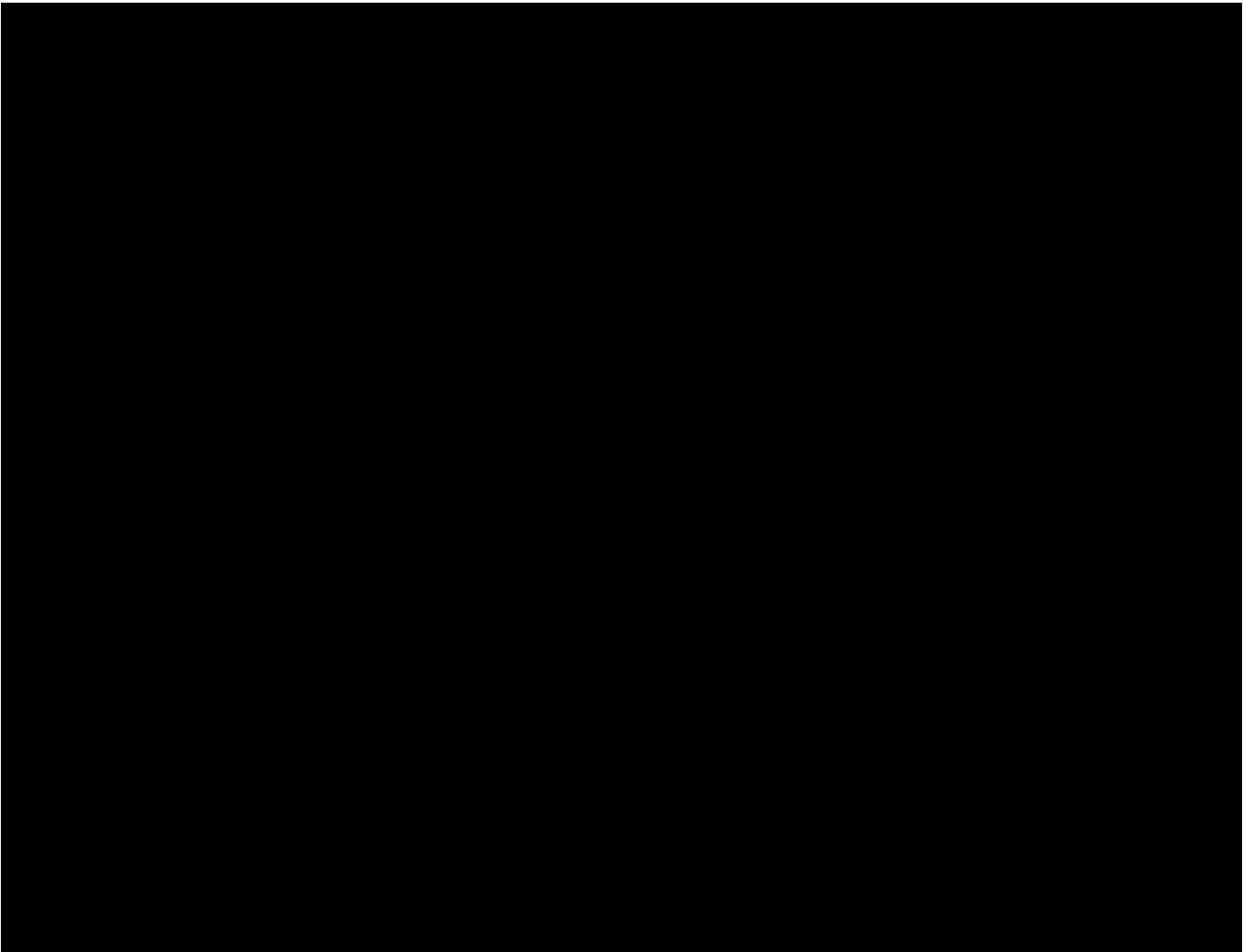
- If necessary, study visits, except for those visits specified above as being conducted 1 day apart, may be conducted up to 2 days before or after the scheduled visits.
- All patients who receive IP must complete Visit 9/Early Termination (ET).
- Upon completion of the double-blind treatment period, patients may be eligible to enter the extension study (RAP-MD-33). Patients who do not enter the extension study will enter a 2-week safety follow-up period.

9.1.3 Safety Follow-up Period

Patients who do not roll over into the extension study after completing the double-blind treatment period and patients who prematurely discontinue from the study before completing 6 weeks of double-blind treatment should enter the 2-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 9.1.3–1](#). The Schedule of Evaluations is provided in [Section 2.0](#) and detailed descriptions of each study visit can be found in [Section 9.5.6](#).



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

This multicenter, randomized, placebo-controlled, parallel-group study, with a 6-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 75 years of age who meet the DSM-5 criteria for MDD ([American Psychiatric Association, 2013](#)).

he 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 applicable local guidelines to minimize patient risk or distress.

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

A placebo treatment group is included in the study to comply with worldwide regulatory preferences (Laughren, 2001; Gispen-de Wied et al, 2012), since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes (Feifel, 2008; Laughren, 2001; Gispen-de Wied et al, 2012). Additionally, from a scientific point of view, randomized double-blind comparisons versus placebo are needed to permit adequate evaluation of efficacy. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions of 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-30, safety and efficacy assessments are included at every visit to determine adequacy of response, safety, and tolerability. In the event of insufficient therapeutic response or worsening of the patient’s initial condition, the IP should be discontinued and an alternative treatment will then be allowed (Section 9.4.12). An independent Data and Safety Monitoring Board (DSMB) will evaluate safety data during the study (Section 9.8).

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

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

Criteria to be assessed at Visit 1 (Screening)

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 75 (inclusive) years of age at Visit 1
3. Meet DSM-5 criteria for MDD (based on confirmation from the SCID), with a current major depressive episode of at least 8 weeks and not exceeding 18 months in duration at Visit 1 (Patients in their first depressive episode may only be enrolled after documented discussion with the sponsor representative)

[REDACTED]

[REDACTED]

[REDACTED]

7. Treatment naive (defined as those who have not received antidepressant or those who have received antidepressant but not meeting adequate dose or duration criteria per the [REDACTED]) in the present episode or have inadequate response (< 50% reduction in depressive symptoms) to 1 to 3 ADTs given at adequate doses (as defined by the ADT package insert) and duration of \geq 4 weeks during the present episode as documented using the ATRQ

9. If female of childbearing potential, have a negative serum β -human chorionic gonadotropin (β -hCG) pregnancy test at Visit 1

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

9.3.2 Exclusion Criteria

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

Exclusion criteria to be assessed at Screening (Visit 1)

Psychiatric and Treatment-Related Criteria

1. DSM-5–based diagnosis of any disorder other than MDD that was the primary focus of treatment within 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]

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[Redacted]

[Redacted]

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[Redacted]

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[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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9.3.3 Removal of Patients from Therapy or Assessment

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

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

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at an ET Visit. A *final assessment* will be defined as completion of the evaluations scheduled for all patients at Visit 9. All patients discontinuing the study prematurely should enter the 2-week safety follow-up period.

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

9.3.3.1 Criteria for Required Removal of Patients from Therapy or Assessment

Any patient who meets any of the following criteria at any point during the study must be withdrawn from participation, due to AEs related to suicide:

- A suicide attempt

- Significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the C-SSRS
- Rater-administered or computer-administered MADRS Item 10 score ≥ 5

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.

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 3 treatment groups: placebo, rapastinel 450 mg, or rapastinel 225 mg.

9.4.1 Treatments Administered

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

IP should be administered after all efficacy and safety assessments with the exception of the postdose assessments described below.

The IP will be administered using the provided prefilled syringe in a “slow bolus” single injection to an upper extremity vein within approximately 1 to 2 minutes to each study patient. The patient should not be discharged from the study center until the investigator or medically qualified subinvestigator determines that they are medically able to leave the study center (recommended not less than 15 minutes following administration).

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

At IP administration visits, the patient should not be released from the study center until the following are completed:

- Postadministration pulse rate and BP measures (approximately 15 minutes after administration)

- Patient is clinically assessed and determined to not be at increased risk of suicidality in the opinion of the investigator (or medically qualified subinvestigator)
- Patient is assessed for mental status and is determined to be free of perceptual disturbances or other conditions that would deem them not ready for release from the study center, in the opinion of the investigator (or medically qualified subinvestigator)
- A physician licensed in the country, state, or other local regulatory authority (investigator or subinvestigator) determines that they are medically able to leave the study center and provides written signoff not less than 15 minutes following administration (see IV Administration and Evaluation Notes document in Study Reference Manual)

9.4.2 Identity of Investigational Products

Rapastinel 450 mg IV Prefilled Syringes: [REDACTED]

Placebo rapastinel IV Prefilled Syringes: [REDACTED]

[REDACTED]

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

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

9.4.3 Handling of Investigational Products

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

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

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

9.4.4 Method of Assigning Patients to Treatment Groups

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

The IP will be labeled with medication kit numbers. The IWRS will provide the study center with the specific medication kit number(s) for each randomized patient during Visit 2. Study centers will dispense IP according to the IWRS instructions. For randomized patients, study centers will also log onto the IWRS at subsequent dosing visits to obtain a study medication kit number for dispensing the IP. Study centers will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

9.4.5 Selection of Dosages in the Study

The doses of rapastinel in this study were 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 IV 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.

A 225-mg IV unit dose arm has been included to allow for further evaluation of the dose-response profile after multiple dosing.

9.4.6 Selection and Timing of Dose for Each Patient

The IP will be administered IV using the assigned single-use prefilled syringes at Visits 2, 4, 5, 6, 7, and 8.

9.4.6.1 Screening Period

At Screening (Visit 1) after written consent is obtained, patients enter a screening period of up to 2 weeks. No IP is administered during the screening period.

9.4.6.2 Double-blind Treatment Period

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

Patients will receive rapastinel 450 mg, rapastinel 225 mg, or placebo from a prefilled single-dose syringe at Visits 2, 4, 5, 6, 7, and 8.

9.4.6.3 Safety Follow-up Period

Patients who complete 6 weeks of randomized treatment are eligible to enter the RAP-MD-33 extension study. If they do not enter RAP-MD-33, 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.

9.4.7 Blinding

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

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

9.4.8 Unblinding

Any unblinding at the study-center level should be done only in an emergency that requires identification of the IP for the medical management of the patient. The investigator must notify the 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.

In an emergency, the investigator can obtain the treatment assignment of any patient at his or her study center through the IWRS. The investigator will access the IWRS to break the blind.

9.4.9 Prior and Concomitant Therapy

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 [to the extent possible] 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.

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9.4.10 Other Restrictions

9.4.10.1 Alcohol

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

9.4.10.2 Contraception

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

For women of childbearing potential and male partners of women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), implantable permanent birth control device (eg, Essure; note: device must be in place at least 3 months and completed confirmation test), vasectomized partner, or complete abstinence for the duration of the study (periodic abstinence [such as calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Note: In Germany, the Czech Republic and other local regions as applicable, acceptable methods of contraception include complete abstinence; single barrier (diaphragm or condom) combined with the use of IUD or contraceptive (oral, implantable or injectable); or double barrier (diaphragm with condom).

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study with consideration for local regulatory or IRB/EC requirements.

See Section 9.5.2.3 for pregnancy reporting procedures.

9.4.11 Monitoring Treatment Compliance

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

9.4.12 Treatment After Discontinuation

Patients whose MDD 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.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Diagnostic and Efficacy Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.5.1.2 Efficacy Assessments

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

9.5.1.2.1 The Montgomery-Åsberg Depression Rating Scale

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

The MADRS will be evaluated at the timepoints indicated in Schedule of Evaluations (Section 2.0) using the Structured Interview Guide for the MADRS (SIGMA) methodology (Williams and Kobak, 2008). At Visit 3 (visit occurring 1 day following IP administration), the MADRS will be administered with a look-back timeframe of “since last evaluation”. At all other administrations, the MADRS will be administered with a look-back timeframe of 1 week.

A qualified rater (ie, who meets the training requirements and qualifications set by the rater training vendor) at each investigational center will conduct the MADRS assessment. The rater-administered MADRS will be used for analyses. In addition to MADRS administration by a qualified rater, each patient will complete an interactive, computer-administered MADRS interview on the dedicated study device. Data from the computer-administered interview will be compared with data derived from the rater-administered interview on an ongoing basis as part of a remote quality assurance program conducted by an independent vendor appointed by the sponsor.

At each visit with a MADRS assessment, the rater-administered MADRS interview will be audio recorded. The computer-administered interview will involve a series of probe and follow-up questions with multiple-choice response options. At the Screening Visit, the computer administered MADRS will be conducted prior to the rater-administered MADRS. At all other visits, the rater-administered MADRS will be conducted first.

[REDACTED]

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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 Sections 9.5.2.1.3 and 9.5.2.1.4), and/or 2) the event is judged by the investigator to be potentially causally related to IP (Section 9.5.2.1.1).

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

9.5.2.2 *Immediate Reporting of Serious Adverse Events*

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 email address or 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 emailed or 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.***

Email or 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 email or fax it to the SAE/Pregnancy email address or 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.



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9.5.6.11 *Unscheduled Visits*

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

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

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

9.6.2 Data Recording and Documentation

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

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

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

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

[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

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

9.7.1.1 Safety Population

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

9.7.1.2 Modified Intent-to-Treat Population

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

9.7.1.3 Pharmacokinetic Population

The PK Population will consist of all patients in the Safety Population with at least 1 evaluable PK sample.

9.7.2 Patient Disposition

The number and percentage of patients in the mITT Population will be summarized by treatment group.

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

9.7.3 Demographics and Other Baseline Characteristics

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

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to randomized IP for the Safety Population during the double-blind treatment period will be summarized in terms of treatment duration, calculated as the number of days from the date of first dose of randomized IP received to the date of the last dose received, inclusive. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment group for IP exposure.

The total number of IV doses actually received by a patient during the double-blind treatment period will be summarized by treatment group for the Safety Population.

9.7.4.2 Prior and Concomitant Medication

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

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

9.7.4.3 Measurement of Treatment Compliance

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

9.7.5 Efficacy Analyses

All efficacy analyses will be based on the mITT 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 mITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes ≥ 2 mITT patients within the center. Pooling will be done using the following algorithm:

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

An additional analysis plan specific to European Medicines Agency will be presented in a stand-alone document.

9.7.5.1 Primary Efficacy Analyses

The primary efficacy parameter will be the change from baseline in MADRS total score at the end of treatment (end of Week 6). The primary parameter will be analyzed using a mixed model for repeated measures (MMRM) with terms for treatment, study center, visit, baseline, and treatment-by-visit and baseline-by-visit interactions. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward et al, 1997). This analysis will only use the observed postbaseline scores without imputation of missing values. The treatment differences for rapastinel 450 mg versus placebo and rapastinel 225 mg versus placebo will be estimated and reported along with the corresponding 95% CIs and the p-values for superiority testing.

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 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 will be conducted.

The sensitivity analysis will use a pattern-mixture model based on non-future- dependent missing-value restrictions (Kenward et al, 2003). 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 observed and imputed 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 20 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 Analysis

The key secondary efficacy parameter will be the change from baseline in MADRS total score at 1 day after first dose of treatment. The key secondary analysis will be analyzed using the same MMRM model for the primary efficacy parameter. The treatment differences for rapastinel 450 mg versus placebo and rapastinel 225 mg versus placebo will be estimated and reported along with the corresponding 95% CIs and the p-values for superiority testing.

The following serial gatekeeping procedure will be applied to control the overall type I error rate at the 0.05 level for the primary and secondary hypotheses.

Step 1: Rapastinel 450 mg is superior to placebo in MADRS at Week 6.

Step 2: Rapastinel 450 mg is superior to placebo in MADRS at Day 1.

Step 3: Rapastinel 225 mg is superior to placebo in MADRS at Week 6.

Step 4: Rapastinel 225 mg is superior to placebo in MADRS at Day 1.

The above hypotheses will be tested in the specified order. If at any step a test fails, the test procedure will stop and no further hypotheses will be tested.

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.7.6 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include AEs; clinical laboratory, vital sign, and ECG parameters; [REDACTED]. For each safety parameter, the last nonmissing safety assessment before the first dose of IP will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

9.7.6.1 Adverse Events

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

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

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

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.7.9 Interim Analysis

A blinded sample size reestimation will be conducted after approximately 60% of patients have completed the double-blind treatment period. This reestimation will be conducted in a blinded manner and will be based upon the observed variability of the overall treatment effect during the double-blind treatment period. The detailed procedure for blinded sample size reestimation will be described in the SAP.

9.7.10 Determination of Sample Size

This study will randomize approximately 690 patients to the rapastinel 450 mg, rapastinel 225 mg, and placebo groups in a 1:1:1 ratio. The primary efficacy endpoint is the change from baseline in the MADRS total score at the end of Week 6. Assuming the SD is 10 points, within-patient correlation is 0.6, and dropout rate over 6 weeks is 20%, adjusting for multiple comparisons of 2 rapastinel groups with placebo across the primary and secondary endpoints by using the serial gatekeeping procedure (Section 9.7.5.2) a sample size of 230 patients per treatment group will provide 90% power to detect a difference of 3.5 points for a rapastinel dose versus placebo at a 2-sided significance level of 5%.

9.7.11 Statistical Software

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 time points 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; European Medicines Agency Guideline on Data Monitoring Committees, EMEA/CHMP/EWP/5872/03, July 2005).

All analyses that are required to support the DSMB will be performed by independent statistician(s) 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/EC and the signature page, signed by the investigator, and 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/EC review and approval in jurisdictions where regulatory authorities allow such implementation. However, the IRB/EC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

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

9.10 PROTOCOL DEVIATIONS

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/EC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, dosing, duration of treatment, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the sponsor.

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

10.0 STUDY SPONSORSHIP

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

10.1 STUDY TERMINATION

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

10.2 REPORTING AND PUBLICATION

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

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

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The following must be in place and filed with the sponsor before the start of the study at each study center:

- A completed and signed Form FDA 1572 (for investigators in the US) or Investigator’s Information & Agreement in lieu of FDA 1572 (for investigators outside the US). If, during the course of the study, any changes are made that are not reflected on Form FDA 1572 or Investigator’s Information & Agreement in lieu of FDA 1572, a new Form FDA 1572 or Investigator’s Information & Agreement in lieu of FDA 1572 must be completed and returned to the sponsor
- A fully executed contract
- The curricula vitae for the investigator and all subinvestigators listed on Form FDA 1572 Investigator’s Information & Agreement in lieu of FDA 1572, including a copy of each physician’s license
- A copy of the original IRB/EC 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/EC, as stated in Section 5.1.
- A copy of the IRB/EC-approved ICF
- A copy of the HIPAA authorization form, or other applicable local privacy forms
- A list of the IRB/EC 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
- Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after 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 (or equivalent). 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

- Participants will be assigned a unique identifier (PID). Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.0 **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol (RAP-MD-30, dated 17 Apr 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, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Signed informed consent will be obtained from each patient participating in a clinical research study. This consent must include the following items:

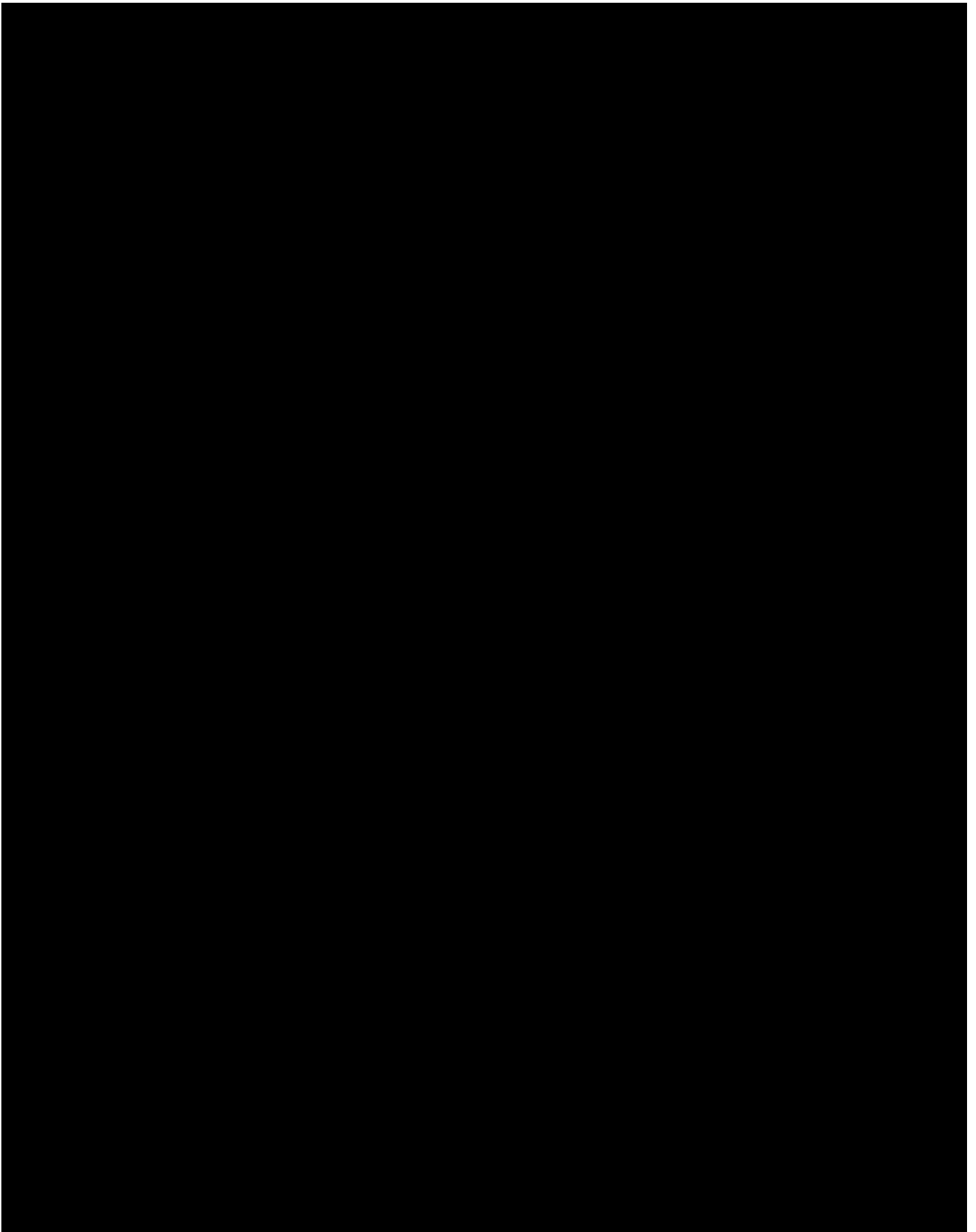
- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, the sponsor, the IRB/EC, 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/EC 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

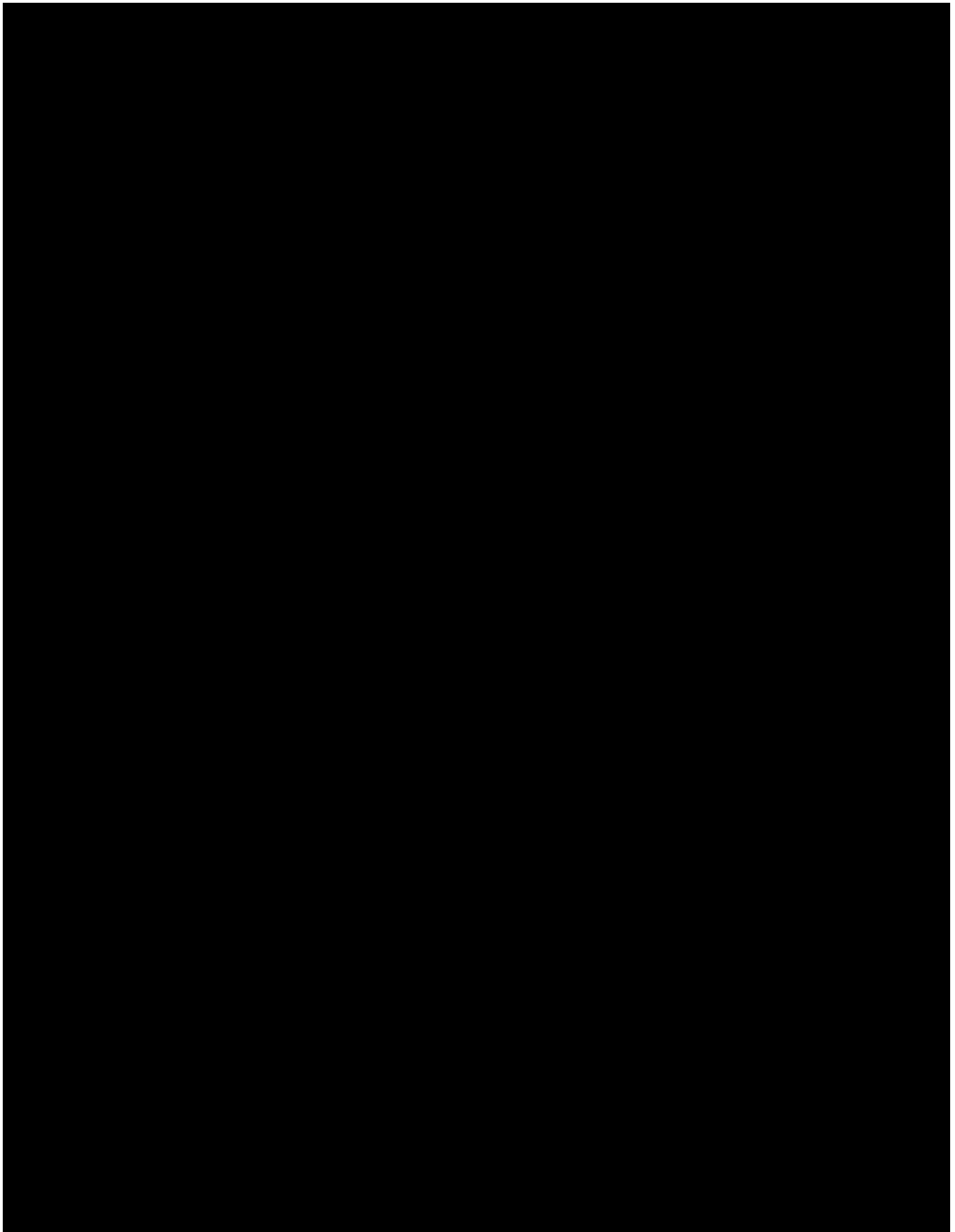
- The expected circumstances for which the patient's participation may be terminated by the investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research 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.

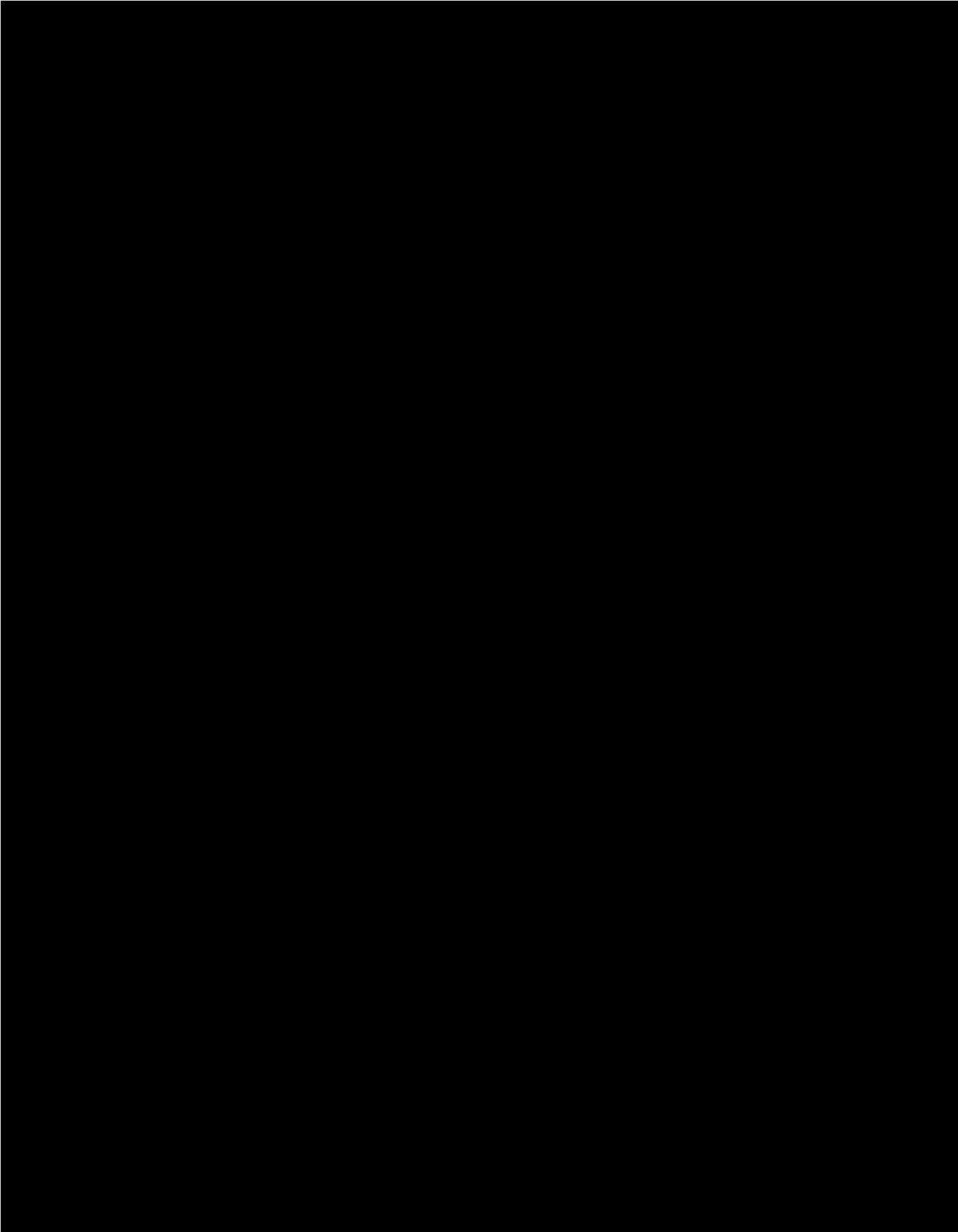
A copy of the signed consent form must be given to the patient.

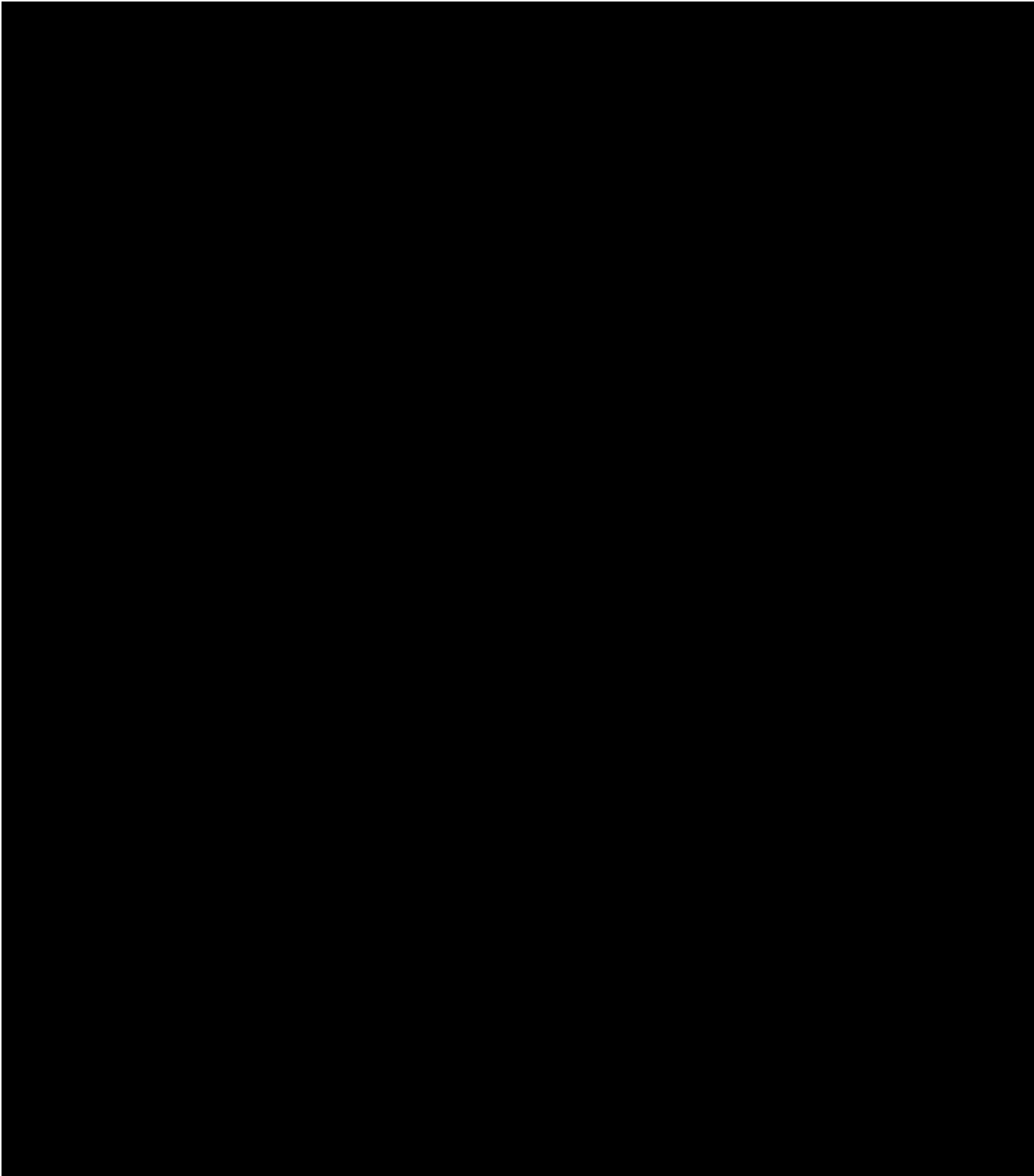
APPENDIX II. CONTACT INFORMATION

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









APPENDIX IV. SCALES AND QUESTIONNAIRES

Please refer to the Study Reference Manual for reference copies of scales and questionnaires.

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