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Study ID: RAP-MD-99

Title: An Open-label, Long-Term Extended Access Protocol for Rapastinel as Adjunctive or Monotherapy Treatment in Patients with Major Depressive Disorder

Protocol Date: 03 July 2018

1.0

TITLE PAGE

**An Open-label, Long-term Extended Access Protocol for Rapastinel as Adjunctive
or Monotherapy Treatment in Patients with Major Depressive Disorder**

RAP-MD-99

(3106-399-008)

IND # 107,974 and 136,870

Original Protocol Date: 03 Jul 2018

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2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

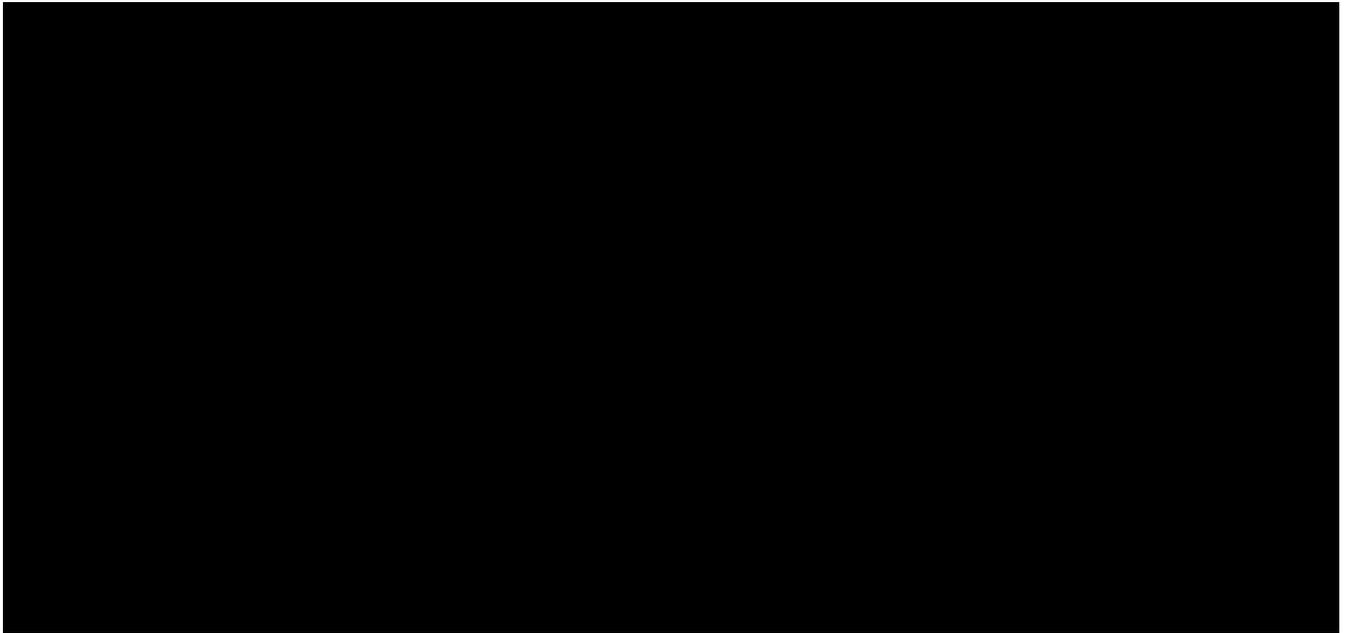
CLINICAL TREATMENT PROTOCOL SYNOPSIS: Treatment protocol RAP-MD-99	
Protocol Number	RAP-MD-99 (3106-399-008)
Title of Protocol	An Open-label, Long-term Extended Access Protocol for Rapastinel as Adjunctive or Monotherapy Treatment in Patients with Major Depressive Disorder
Study Centers (Country)	Approximately 225 study centers
Development Phase	3
Objective	To provide continued access to rapastinel for patients with major depressive disorder (MDD) who have completed specified prior rapastinel studies
Methodology	<p>Multicenter, open-label, long-term extended access treatment protocol in adult patients with a primary diagnosis of MDD. Patients must enter RAP-MD-99 after completion of prespecified rapastinel studies (henceforth referred to as lead-in studies) including RAP-MD-04, RAP-MD-05 (GLYX13C203), RAP-MD-06, and RAP-MD-33.</p> <p>The final visit from the lead-in study may serve as the first visit in RAP-MD-99 and, after obtaining informed consent, open-label rapastinel may be administered to ensure continuity of treatment. Patients may also enter RAP-MD-99 at a visit independent of the lead-in study occurring within approximately 1 month after completion of the lead-in study (with the exception of patients who are entering after completion of RAP-MD-06 in which case there specified time limit).</p> <p>This treatment protocol consists of an open-label treatment period (OLTP) of indeterminate duration. During the OLTP, patients will return to the study center for visits at which administration of rapastinel and wellness check for collection of adverse event (AE) and concomitant medication information are conducted. Visits should typically be spaced weekly or biweekly but may be up to 4 weeks apart (based on investigator discretion). Appropriate safety follow-up upon discontinuation of patients from treatment will be at the discretion of the investigator.</p>
Number of Patients	Up to approximately 1800 patients are planned to be enrolled

<p>Diagnosis and Main Criteria for Inclusion</p>	<ul style="list-style-type: none"> • Completion of lead-in study: <ul style="list-style-type: none"> ○ RAP-MD-06, regardless of date of completion ○ RAP-MD-04, with date of completion (as a nonrandomized completer or randomized completer) within approximately 1 month prior to Visit 1 ○ RAP-MD-05, with date of completion within approximately 1 month prior to Visit 1 ○ RAP-MD-33, with date of completion within approximately 1 month prior to Visit 1 • Adequate therapeutic benefit in the lead-in study to justify continuation of treatment with rapastinel in the judgment of the investigator
<p>Test Product, Dosage, and Mode of Administration</p>	<p>Patients will receive intravenous (IV) rapastinel (450 mg) generally given weekly or biweekly but up to once every 4 weeks is allowed (based on investigator discretion).</p>
<p>Duration of Participation</p>	<p>Indeterminate. Treatment protocol will be terminated upon drug availability following marketing approval in each participating country, termination of rapastinel development, or if sponsor determines that treatment protocol termination is appropriate for other reasons.</p>
<p>Reference Therapy, Dosage, and Mode of Administration</p>	<p>N/A</p>
<p>Criteria for Evaluation</p>	
<p>Safety Measures</p>	<ul style="list-style-type: none"> • AEs
<p>Statistical Methods</p>	<p>The Open-label Safety Population will consist of all screened patients who receive at least 1 dose of investigational product (IP) during the OLTP. AEs will be analyzed descriptively for the Open-Label Safety Population.</p>

Approval Page

Name of Investigational Product: Rapastinel

Document: RAP-MD-99 Protocol



3.0 **TABLE OF CONTENTS**

1.0	TITLE PAGE	1
2.0	SYNOPSIS AND SCHEDULE OF EVALUATIONS	2
3.0	TABLE OF CONTENTS.....	5
4.0	LIST OF ABBREVIATIONS	8
5.0	ETHICAL CONSIDERATIONS	10
5.1	Institutional Review Board and Independent Ethics Committee	10
5.2	Ethical Conduct of the Treatment protocol.....	10
5.3	Patient Information and Informed Consent.....	11
6.0	INVESTIGATORS AND TREATMENT PROTOCOL ADMINISTRATIVE STRUCTURE	12
7.0	INTRODUCTION	13
8.0	TREATMENT PROTOCOL OBJECTIVES	17
9.0	INVESTIGATIONAL PLAN	18
9.1	Overall Treatment protocol Design and Plan: Description	18
	9.1.1 Open-label Treatment Period.....	18
9.2	Discussion of Treatment protocol Design.....	19
9.3	Selection of Treatment protocol Population	19
	9.3.1 Inclusion Criteria	19
	9.3.2 Exclusion Criteria.....	20
	9.3.3 Removal of Patients from Therapy or Assessment.....	21
	9.3.3.1 Criteria for Required Removal of Patients from Therapy or Assessment	22
	9.3.4 Patient Replacement Procedures	22
9.4	Treatments	23
	9.4.1 Treatments Administered	23
	9.4.2 Identity of Investigational Products.....	23
	9.4.3 Handling of Investigational Products	24
	9.4.4 Method of Assigning Patients to Treatment Groups	24
	9.4.5 Selection of Dosages in the Treatment Protocol.....	25
	9.4.6 Selection and Timing of Dose for Each Patient.....	25
	9.4.6.1 Open-label Treatment Period.....	25
	9.4.7 Blinding.....	25
	9.4.8 Unblinding.....	25
	9.4.9 Prior and Concomitant Therapy	25
	9.4.10 Other Restrictions.....	26
	9.4.10.1 Participation in Clinical Trials.....	26
	Patients may not participate in any other interventional clinical trial while taking part in this treatment protocol.....	26
	9.4.10.2 Alcohol	26
	9.4.10.3 Contraception	26
	9.4.11 Monitoring Treatment Compliance	27
	9.4.12 Treatment After Discontinuation.....	27

- 9.5 Efficacy and Safety Assessments.....27
 - 9.5.1 Diagnostic and Efficacy Assessments27
 - 9.5.2 Safety Assessments27
 - 9.5.2.1 Adverse Events.....27
 - 9.5.2.2 Immediate Reporting of Serious Adverse Events31
 - 9.5.2.3 Reporting of Pregnancies Occurring During the Treatment Protocol32
 - 9.5.3 Investigational Product Concentration Measurements33
 - 9.5.4 Health Economic and Outcomes Research Assessments.....33
- 9.6 Data Quality Assurance35
 - 9.6.1 Data Monitoring35
 - 9.6.2 Data Recording and Documentation.....35
- 9.7 Statistical Methods and Determination of Sample Size36
 - 9.7.1 Analysis Populations36
 - 9.7.1.1 Open-label Safety Population36
 - 9.7.2 Patient Disposition36
 - 9.7.3 Demographics and Other Baseline Characteristics.....36
 - 9.7.4 Extent of Exposure and Treatment Compliance37
 - 9.7.4.1 Extent of Exposure37
 - 9.7.4.2 Prior and Concomitant Medication.....37
 - 9.7.4.3 Measurement of Treatment Compliance.....37
 - 9.7.5 Efficacy Analyses.....37
 - 9.7.6 Safety Analyses37
 - 9.7.6.1 Adverse Events38
 - 9.7.7 Interim Analysis38
 - 9.7.8 Determination of Sample Size.....38
 - 9.7.9 Statistical Software.....39
- 9.8 Data and Safety Monitoring Board39
- 9.9 Changes in the Conduct of the Treatment protocol or Planned Analyses.....39
- 9.10 Protocol Deviations40
- 10.0 TREATMENT PROTOCOL SPONSORSHIP41
 - 10.1 Treatment protocol Termination.....41
 - 10.2 Reporting and Publication41
- 11.0 INVESTIGATOR OBLIGATIONS.....42
 - 11.1 Documentation.....42
 - 11.2 Performance.....43
 - 11.3 Use of Investigational Materials43
 - 11.4 Case Report Forms43
 - 11.5 Retention and Review of Records.....43
 - 11.6 Patient Confidentiality44
- 12.0 INVESTIGATOR’S STATEMENT45
- 13.0 APPENDICES46
 - Appendix I. Elements of Informed Consent.....46
 - Appendix II. Contact Information.....48

14.0 LITERATURE CITED49

SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event

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 treatment protocol 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 treatment protocol, the investigator will provide timely and accurate reports to the IRB on the progress of the treatment protocol, 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 protocol, informed consent form (ICF), information sheet, advertisements (as 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 treatment protocol 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 treatment protocol begins, the study centers will require approval from an EC/IRB and government agency. During the course of the treatment protocol, the sponsor or authorized representative will provide timely and accurate reports to the EC/IRB on the progress of the treatment protocol, at intervals not exceeding 1 year (or as appropriate) and will notify the EC/IRB of SAEs or other significant safety findings. The 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 TREATMENT PROTOCOL**

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

This treatment protocol 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 treatment protocol and before participating in any treatment protocol procedures, each patient must provide written informed consent that meets the requirements of 21 CFR 50 (where applicable), local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC 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 treatment protocol at any time.

The ICF contains all the elements of informed consent listed in [Appendix I](#) of this treatment 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 TREATMENT PROTOCOL ADMINISTRATIVE STRUCTURE**

This treatment protocol will be performed at approximately 225 study centers in North America, Europe, and Asia.

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 treatment protocol and/or prior to participating in any treatment protocol-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 treatment protocol's conduct and the study center 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 treatment protocol investigational plan. The investigator at each study center will be responsible for the management of the treatment protocol conduct, including maintaining the study center 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](#)). In contrast to ketamine, rapastinel has not shown a high likelihood to induce psychotomimetic or dissociative effects in humans so far.

The data available to date demonstrated a favorable safety and tolerability profile of rapastinel. Multiple requests have been received from study centers participating in ongoing studies for establishment of a continued access mechanism for patients who are completing participation of clinical trials of rapastinel. Investigators have indicated several anecdotal instances where patients have reported dramatic improvements in MDD symptoms as well as in their functioning.

The purpose of this treatment protocol is to provide continued access to rapastinel for patients with major depressive disorder (MDD) who have completed specified prior rapastinel studies.

8.0 **TREATMENT PROTOCOL OBJECTIVES**

The objective of this treatment protocol is to provide continued access to rapastinel for patients with MDD who have completed specified prior rapastinel studies.

9.0 **INVESTIGATIONAL PLAN**

9.1 **OVERALL TREATMENT PROTOCOL DESIGN AND PLAN: DESCRIPTION**

Treatment Protocol RAP-MD-99 is a multicenter, open-label extended access treatment protocol in adult patients with MDD who completed lead-in studies RAP-MD-04, RAP-MD-05 (GLYX13C203), or RAP-MD-33 within approximately 1 month of Visit 1, or RAP-MD-06 at any time prior to Visit 1. The final visit from the lead-in study may serve as the first visit of protocol RAP-MD-99 where practical to maintain continuity of treatment. In other cases the first visit of RAP-MD-99 may be conducted independent of the final visit of the lead-in study.

This treatment protocol will be conducted as an Open-label Treatment Period (OLTP) of indeterminate duration.

There is no predetermined limit specified for the number of patients that may be enrolled in the OLTP.

The treatment protocol will be terminated upon drug availability following marketing approval in each participating country, termination of rapastinel development, or if sponsor determines that treatment protocol termination is appropriate for other reasons.

9.1.1 **Open-label Treatment Period**

Patients will enroll from RAP-MD-04, RAP-MD-05, RAP-MD-06, or RAP-MD-33. The final visit from the lead-in study may serve as the initial visit of protocol RAP-MD-99. Following consent at the initial visit, patients will be screened and those who meet entry criteria may enter the OLTP and receive the first dose of open-label treatment (rapastinel). Consent, screening and dosing may all be conducted in a single visit at the discretion of the investigator to facilitate continuity of treatment. Patients may also enter RAP-MD-99 at a visit independent of the lead-in study occurring within approximately 1 month after completion of the lead-in study (with the exception of patients entering from RAP-MD-06 for whom there is no specified time limit [see Inclusion Criterion 2]).

During the OLTP, patients will return to the study center for visits at which administration of rapastinel and wellness check are conducted, including the capture of AEs and concomitant medications. Visits should typically be spaced weekly or biweekly but may be up to 4 weeks apart (based on investigator discretion).

Each patient will be treated until the investigator discontinues them from the treatment protocol at their discretion, the patient discontinues for other reasons, or until the treatment protocol or study center is terminated by the sponsor.

Appropriate safety follow-up upon discontinuation of patients from treatment will be at the discretion of the investigator.

9.2 DISCUSSION OF TREATMENT PROTOCOL DESIGN

This multicenter, open-label, treatment protocol was designed taking into account prior studies that established rapastinel efficacy and safety in adult patients with MDD.

Study centers will have experience with the patient population and will be encouraged to apply available guidelines to minimize patient risk or distress. All study centers will have experience with rapastinel in the lead-in studies and all patients will have participated in the lead-in studies.

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

In the event of insufficient therapeutic response or worsening of the patient's initial condition, the IP may be discontinued at the investigator's discretion and an alternative treatment begun.

9.3 SELECTION OF TREATMENT PROTOCOL POPULATION

9.3.1 Inclusion Criteria

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

Criteria to be assessed at Visit 1

1. Written informed consent, obtained from the patient before the initiation of any treatment protocol-specific procedures (Section 5.3)
2. Completion of lead-in study:
 - a. RAP-MD-06 regardless of date of completion
 - b. RAP-MD-04 with date of completion (as a nonrandomized completer or randomized completer) within approximately 1 month prior to Visit 1
 - c. RAP-MD-05 with date of completion within approximately 1 month prior to Visit 1
 - d. RAP-MD-33 with date of completion within approximately 1 month prior to Visit 1

3. Adequate therapeutic benefit in the lead-in study to justify continuation of treatment with rapastinel in the judgement of the investigator
4. Ability to follow treatment protocol instructions and likely to be compliant with protocol requirements

9.3.2 Exclusion Criteria

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

Exclusion criteria to be assessed at Visit 1

Psychiatric and Treatment-Related Criteria

1. Suicide risk, as determined by meeting any of the following criteria:
 - a. A suicide attempt within the past year
 - b. Significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS) at any visit in the lead-in study
 - c. Montgomery-Åsberg Depression Rating Scale (MADRS) Item 10 score ≥ 5 at any visit during participation in the lead-in study where MADRS was conducted.
2. At imminent risk of injuring self or others or causing significant damage to property, as judged by the investigator



[REDACTED]

Other Criteria

[REDACTED]

9.3.3 Removal of Patients from Therapy or Assessment

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

- Screen failure (failure to meet inclusion/exclusion criteria)
- Pregnancy
- Withdrawal of consent
- AE

- Lack of efficacy
- Protocol violation
- Lost to follow-up
- Treatment protocol terminated by sponsor
- Study center terminated by sponsor
- Other

Appropriate safety follow-up upon discontinuation of patients from treatment will be at the discretion of the investigator.

The reason for premature discontinuation from the treatment protocol will be recorded on the Treatment Protocol Disposition Page of the eCRF.

9.3.3.1 *Criteria for Required Removal of Patients from Therapy or Assessment*

Patients who require an alteration of MDD treatment regimen at any point during participation (including but not limited to addition of new therapeutic agent, increase in dose of any background ADT therapy the patient may be taking) due to an inadequate therapeutic response based on the judgment of the investigator should be withdrawn from participation.

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

- A suicide attempt
- Significant risk for suicidal behavior, as judged by the investigator

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 treatment protocol.

9.3.4 *Patient Replacement Procedures*

Patients who prematurely discontinue treatment will not be replaced.

9.4 TREATMENTS

During the OLTP, all eligible patients will receive open-label IV rapastinel (450 mg) typically weekly or biweekly but the interval may be up to 4 weeks at the investigator’s discretion.

9.4.1 Treatments Administered

IP will only be administered to eligible patients by a medically qualified person as per the local and/or 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.

The IP will be administered using the provided prefilled syringes in a “slow bolus” injection to an upper extremity vein within approximately 1 to 2 minutes.

During IP administration and until completion of postadministration evaluation, 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 country and/or local regulations/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 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.

9.4.2 Identity of Investigational Products

Rapastinel 450-mg IV Prefilled Syringes:

[REDACTED]

[REDACTED]

The prefilled syringe will be labeled with the treatment 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 label 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 treatment protocol, 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 Treatment Protocol Reference Manual or contact the sponsor or its designee for further instructions.

At the end of the treatment protocol, all IP must be accounted for. In addition, at the end of the treatment protocol, all unused IP should be returned to the sponsor or the local distributor at the address provided in the Treatment Protocol Reference Manual.

9.4.4 Method of Assigning Patients to Treatment Groups

After a patient signs the consent form at Visit 1, study center personnel will register the patient in the IWRS. [REDACTED]

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

The IP will be labeled with medication kit numbers. The IWRS will provide the study center with the specific medication kit number(s) for each patient at each administration. Study centers will dispense IP according to the IWRS instructions. Study centers will also log on to the IWRS at subsequent visits to obtain an IP 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 treatment protocol source documents.

9.4.5 Selection of Dosages in the Treatment Protocol

The doses of rapastinel in this treatment protocol were selected based on two 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.

9.4.6 Selection and Timing of Dose for Each Patient

9.4.6.1 Open-label Treatment Period

The IP will be administered IV using the assigned single-use prefilled syringes weekly, biweekly, or at intervals up to 4 weeks apart based on the discretion of the investigator. A patient may be switched between treatment frequencies at any time during the OLTP based on clinical presentation and the investigator's discretion.

9.4.7 Blinding

Not applicable

9.4.8 Unblinding

Not applicable

9.4.9 Prior and Concomitant Therapy

Patients should continue any non-IP MDD treatment regimen that was in place upon completion of the lead-in study (including any background ADT treatment for those who were in lead-in studies of the IP as an adjunctive therapy). Patients who require an alteration of MDD treatment regimen at any point during participation (including but not limited to addition of new therapeutic agent, increase in dose of any background ADT therapy the patient may be taking) due to an inadequate therapeutic response based on the judgment of the investigator should be withdrawn from participation.

Investigators should consult the lead-in study protocol from which each patient entered as a source of guidance regarding any other medications/treatments. Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator.

Medication history (psychotropic medication history and all other medications during the past 12 months [to the extent feasible]) will be recorded in the lead-in study in the eCRF. Thereafter, any changes in concomitant medications or any new medications added will be recorded in the eCRF.

9.4.10 Other Restrictions

9.4.10.1 *Participation in Clinical Trials*

Patients may not participate in any other interventional clinical trial while taking part in this treatment protocol.

9.4.10.2 *Alcohol*

It is recommended that patients abstain from alcohol consumption during participation.

9.4.10.3 *Contraception*

For purposes of this protocol, 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 treatment protocol, 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 [IUD], surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), implantable permanent birth control device (ie 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 treatment protocol (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 treatment protocol 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

Not applicable

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 OLTP should discontinue the treatment protocol 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 for MDD must be discontinued from the treatment protocol.

9.5 EFFICACY AND SAFETY ASSESSMENTS

9.5.1 Diagnostic and Efficacy Assessments

Not applicable.

9.5.2 Safety Assessments

Provision for standard of care monitoring and procedures including those described below are the responsibility of the investigator and will not be provided by the sponsor. 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 should be completed at each protocol visit.

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 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 treatment protocol

Please note that medical procedures scheduled prior to consenting, but occurring during the treatment protocol 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 (treatment protocol) 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 posttreatment protocol 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 patient exit from the protocol will be followed until the condition returns to pre-treatment protocol 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 last known dose of IP.

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 center staff until resolution or until the SAE is deemed stable. ***The sponsor may contact the study center to solicit additional information or follow up on the event.***

[Redacted]

[Redacted]

[Redacted]

9.5.2.3 Reporting of Pregnancies Occurring During the Treatment Protocol

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

[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

9.5.3 Investigational Product Concentration Measurements

Not applicable.

9.5.4 Health Economic and Outcomes Research Assessments

Not applicable.

9.5.5 Schedule of Assessments

The descriptions of the procedures to be performed at each visit are provided in the following sections.

[REDACTED]

| [REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]

[REDACTED] [REDACTED]
[REDACTED]
| [REDACTED]

[REDACTED] [REDACTED]
[REDACTED]
| [REDACTED]
| [REDACTED]
| [REDACTED]
[REDACTED]

9.5.5.2 *Unscheduled Visits*

Not applicable.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the treatment protocol, a representative of the sponsor will meet (in person or via telephone) with the investigator and the study center staff to review the procedures to be followed during the treatment protocol. 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 treatment protocol 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 treatment protocol-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 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 treatment protocol 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. Treatment protocol records (eg, copies of eCRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All treatment protocol records must be available for inspection by the sponsor, its authorized representatives, the FDA, or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Analysis Populations

One analysis population will be considered for the statistical analysis of the treatment protocol, as specified in the following subsections.

9.7.1.1 *Open-label Safety Population*

The Open-label Safety Population will consist of all patients who signed the RAP-MD-99 ICF and who received at least 1 dose of open-label rapastinel during the OLTP of the protocol.

9.7.2 Patient Disposition

The number and percentage of patients who participated in the OLTP, and who prematurely discontinued from the OLTP will be summarized overall and by reasons for premature discontinuation for the Open-label Safety Population.

9.7.3 Demographics and Other Baseline Characteristics

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

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

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

9.7.4.2 Prior and Concomitant Medication

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

The use of prior medication will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Open-label Safety Population. The use of concomitant medications during the OLTP will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Open-label Safety Population.

9.7.4.3 Measurement of Treatment Compliance

Not applicable.

9.7.5 Efficacy Analyses

Not applicable.

9.7.6 Safety Analyses

The safety analyses for the OLTP will be performed using the Open-label Safety Population. The summarization will be overall for the OLTP without consideration for dosing frequency.

Safety parameters will be limited to AEs.

For each safety parameter, the baseline of the lead-in study will be used as the baseline for all analyses of that safety parameter, unless stated otherwise.

9.7.6.1 Adverse Events

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

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

The number and percentage of patients reporting TEAEs during the OLTP will be tabulated by SOC, 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 during the OLTP, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the IP.

The incidence of common ($\geq 2\%$ of patients) TEAEs during the OLTP will be summarized by preferred term and will be sorted by decreasing frequency.

An SAE that occurred between the date of the first dose of the 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 had on-therapy SAEs during the OLTP will be summarized by preferred term and sorted by decreasing frequency.

The number and percentage of patients who had fatal on-therapy SAEs during the OLTP will be summarized by preferred term and sorted by decreasing frequency.

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

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

9.7.7 Interim Analysis

No interim analysis is planned for this treatment protocol.

9.7.8 Determination of Sample Size

Not applicable.

9.7.9 Statistical Software

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

9.8 DATA AND SAFETY MONITORING BOARD

The treatment protocol will be conducted under the supervision of an independent DSMB to be chartered to review safety data at predetermined points during the treatment protocol. 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 treatment protocol and for making recommendations concerning the continuation, modification, and termination of the treatment protocol ([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 treatment protocol. 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 TREATMENT PROTOCOL 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 other applicable oversight bodies 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 unclarity arises with regard to interpretation or conduct of the approved protocol during the conduct of the treatment protocol, 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 treatment protocol 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 treatment protocol 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 treatment protocol data. The IRB/EC must be notified within the time period dictated by the IRB/EC associated with this treatment protocol.

10.0 **TREATMENT PROTOCOL SPONSORSHIP**

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

10.1 **TREATMENT PROTOCOL TERMINATION**

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

10.2 **REPORTING AND PUBLICATION**

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

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 treatment protocol 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 treatment protocol, 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 or 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 treatment protocol. If the treatment protocol 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 (as applicable)
- 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 treatment protocol and for 1 year after completion of the treatment protocol.

11.2 PERFORMANCE

The investigator must demonstrate reasonable efforts to obtain qualified patients for the treatment protocol.

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 treatment protocol 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 treatment protocol 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 treatment protocol 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 treatment protocol, including eCRFs, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all 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 treatment protocol completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the sponsor.

No treatment protocol records shall be destroyed without notifying the sponsor and providing the sponsor the opportunity to arrange long-term storage for such treatment protocol 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 treatment protocol upon request of the sponsor or applicable regulatory authorities. If the investigator for the treatment protocol retires, relocates, or for other reasons withdraws from the responsibility of keeping the treatment protocol 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 treatment protocol-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 treatment protocol in accordance with this protocol (RAP-MD-99, dated 03 Jul 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 treatment protocol. This consent must include the following items:

- A statement that the treatment protocol 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 treatment protocol, 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 treatment protocol
- 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 treatment protocol 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 Treatment Protocol Reference Manual.

14.0 **LITERATURE CITED**

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