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Study ID: RAP-MD-04

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

Statistical Analysis Plan: 13 Dec 2018

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RAP-MD-04

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

STATISTICAL ANALYSIS PLAN

Final: 13 December 2018

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1.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BP	blood pressure
bpm	beats per minute
[redacted]	
CI	confidence interval
CPK	creatine phosphokinase
CRF	case report form
[redacted]	
DBTP	double-blind treatment period
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	
ET	early termination
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
ICF	informed consent form
IND	Investigational New Drug (application)
IP	investigational product
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale

MDD	major depressive disorder
mITT	modified Intent-to-Treat
NEAE	newly emergent adverse event
OLTP	open-label treatment period
PCS	potentially clinically significant
PID	patient identification
PK	pharmacokintetic
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{1/3}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	
SD	standard deviation
[redacted]	
SFU	Safety Follow-up
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UDS	urine drug screen
ULN	upper limit of normal

2.0 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the methodology that will be used to summarize the statistical analyses of the efficacy and safety data for the final protocol Amendment 2 of Study RAP-MD-04 (version dated 13 Nov 2018).

Study RAP-MD-04 is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of rapastinel as long-term maintenance treatment for patients with major depressive disorder (MDD) who completed 1 of the rapastinel lead-in studies (RAP-MD-01, RAP-MD-02, or RAP-MD-03). While the protocol was written to accommodate the potential recruitment of *de novo* patients, there were no *de novo* patients enrolled. Consequently, all analysis in this document pertains specifically to roll-over patients only.

The study will be conducted for the roll-over patients in the following periods:

- An 8- to 16-week, open-label treatment period (OLTP) where patients receive rapastinel 450 mg IV weekly
- A randomized, double-blind treatment period (DBTP) of at least 26 weeks (and up to 104 weeks) where patients are randomized 1:1:1 to either rapastinel 450 mg weekly, rapastinel 450 mg biweekly or placebo
- A 2-week safety follow-up period (for patients who do not enter the RAP-MD-06 extension study only)

In order for patients to transition from the OLTP and be randomized into the DBTP, the patient must meet the stable responder criterion sometime after 8 weeks (and up to 16 weeks) during the OLTP. A patient will be considered a stable responder upon achieving both criteria (1) and (2) below:

1) An observed Montgomery-Asberg Depression Rating Scale (MADRS) total score ≤ 12 with no more than one modest MADRS excursion (MADRS total score > 12 but ≤ 16) for at least 6 consecutive weeks.
2) An observed MADRS total score ≤ 12 for at least 2 consecutive visits prior to randomization.

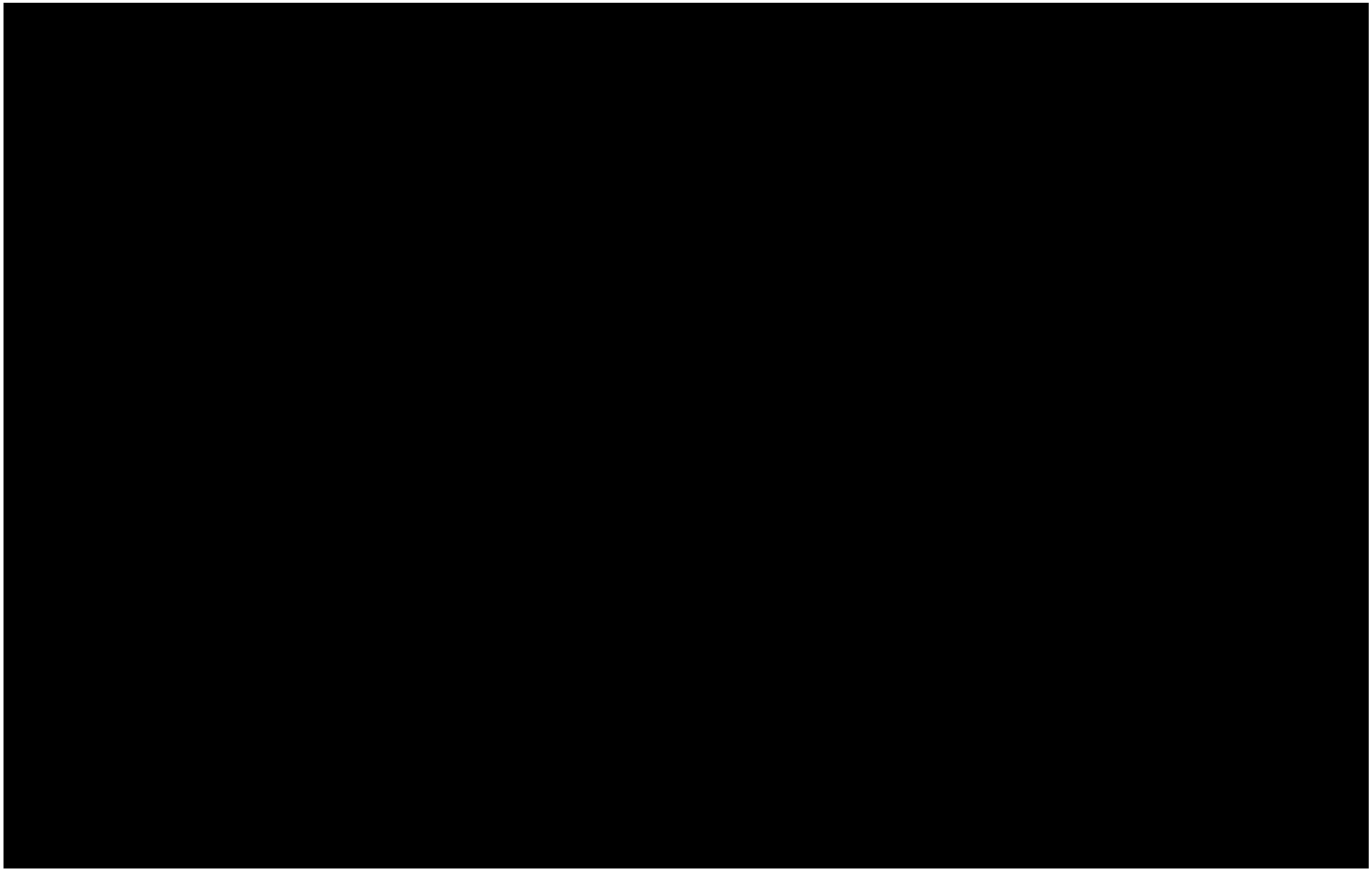
To meet these criteria a patient must have no missing MADRS assessments within the last 6 consecutive weeks prior to randomization.

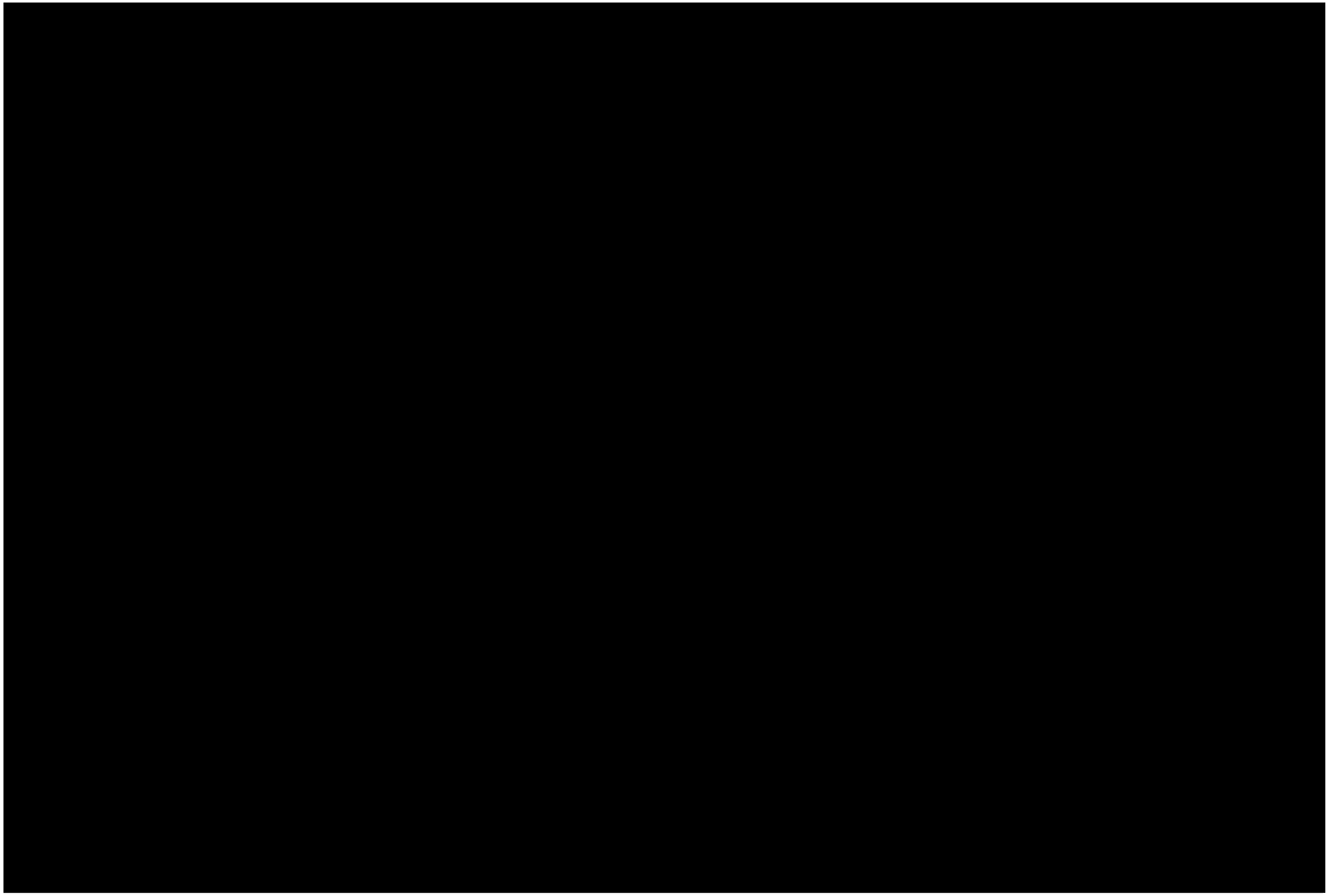
The OLTP starts with the first dose of open-label treatment and ends with 1 of the following: the last scheduled assessment at the Visit 122/Early Termination for patients who do not enter the DBTP; the first dose of double-blind treatment for patients who enter the DBTP.

The double-blind treatment period starts when the first dose of double-blind treatment is administered and ends with the last scheduled assessment at Visit 122 (or ET).

For patients not entering RAP-MD-06, the safety follow-up (SFU) period starts after completion of the last scheduled assessment at Visit 122 (or ET) and ends with the last available assessment.

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





3.0 STUDY OBJECTIVES

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

Efficacy Objectives

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

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

[redacted]

[redacted]

4.0 ANALYSIS POPULATIONS

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

4.1 OPEN-LABEL SAFETY POPULATION

The Open-label Safety Population will consist of all patients who signed the informed consent form (ICF) and received at least 1 dose of open-label rapastinel during the OLTP of the study.

4.2 OPEN-LABEL INTENT-TO-TREAT POPULATION

The Open-label Intent-to-Treat (Open-label ITT) Population will consist of all patients in the Open-label Safety Population who had at least 1 postbaseline assessment of the MADRS during the OLTP of the study. An assessment is considered postbaseline in the OLTP if it was taken after the first dose of open-label rapastinel during the OLTP of the study.

4.3 DOUBLE-BLIND SAFETY POPULATION

The Double-blind Safety Population will consist of all patients in the Open-label Safety Population who were randomized to a treatment group during the DBTP of the study and received at least 1 dose of investigational product (IP) during the DBTP.

For by treatment analyses using the Double-blind Safety Population, patients will be assigned to the treatment groups they were randomized to during the DBTP.

4.4 DOUBLE-BLIND MODIFIED INTENT-TO-TREAT POPULATION

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

For by treatment analyses using the Double-blind mITT Population, patients will be assigned to the treatment groups that they were randomized to during the DBTP.

5.0 PATIENT DISPOSITION

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

The number and percentage of patients who entered the OLTP, who prematurely discontinued from the OLTP, who completed the OLTP, who met or did not meet the criteria to enter the DBTP at the end of the OLTP, and who entered the SFU will be summarized overall and by reasons for premature discontinuation as recorded on the open-label disposition page of the electronic case report forms (eCRF) for the Open-label Safety Population.

Similarly, the number and percentage of patients who completed the DBTP, who prematurely discontinued from the DBTP, and who entered the SFU will be summarized overall, by double-blind treatment group, and by reasons for premature discontinuation as recorded on the double-blind disposition page of the eCRF for the Double-blind Safety Population.

5.1 PROTOCOL DEVIATIONS

The number and percentage of patients with significant protocol deviations during the OLTP will be summarized overall in the Open-label Safety Population. Similarly, the number and percentage of patients with significant protocol deviations during the DBTP will be summarized overall and by double-blind treatment group in the Double-blind Safety Population. Protocol deviations will be defined in the Protocol Deviation Requirement Specification, including significance classification.

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized overall for the Open-label ITT Population and by treatment group for the Double-blind mITT Population.

Medical and surgical history, psychiatric history, previous treatment with psychotropic medication, and nondrug psychiatric treatment will be summarized overall for the Open-label Safety Population and by treatment group for the Double-blind Safety Population.

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

The use of prior and 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. Concomitant medications during the DBTP will be summarized by treatment group by the number and percentage of patients receiving each medication within each therapeutic class for the Double-blind Safety Population. Multiple medication use of the same therapeutic class by a patient will only be counted once. Concomitant medications started after the patient's last study visit during their last treatment period will not be summarized but will be included in the data listings.

Prior ADT treatment in the current episode, as recorded on the ATRQ collected in the lead-in studies, will be summarized by frequency counts and percentages for patients who took each ADT in adequate dose and duration, total number of ADT taken at adequate dose and duration (ie, 1, 2, 3 or more), and percentage of improvement reported (ie, < 25%, 25% to 49%, 50% to 75%, or >75%). For the OLTP, the summaries will be overall for the Open-label Safety Population. For the DBTP, the summaries will be by treatment group for the Double-blind Safety Population.

The *WHO Drug Dictionary Enhanced* will be used to classify prior and concomitant medications by therapeutic class and drug name.

7.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

7.1 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 will be presented.

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

The number of IV doses of rapastinel administered to each patient during the OLTP will be summarized using descriptive statistics for the Open-label Safety Population. Similarly, the number of IV doses administered to each patient during the DBTP will be summarized by treatment group, using descriptive statistics for the Double-Blind Safety Population.

The number and percentage of patients taking each qualifying ADT in the OLTP will be summarized for the Open-label ITT Population; the number and percentage of patients taking each qualifying ADT in the DBTP will be summarized by double-blind treatment group for the Double-Blind mITT Population. Mean daily dose and duration of previous treatment with each qualifying ADT will be summarized using descriptive statistics for the OLTP and by double-blind treatment group for the DBTP for the respective ITT or mITT populations.

7.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified study period will be 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 that same period multiplied by 100. The total number of IV doses actually received during a specific time period is calculated as the sum of IV doses received during that period as obtained from the study medication record. The number of IV doses expected to be taken for a specific treatment period will be the number of weeks in that period, calculated as $\lceil$(period exit date - period entry date + 1)/7$\rceil$.

Descriptive statistics for IP compliance will be presented overall for the OLTP and by treatment group for the DBTP using the respective safety populations.

Dosing compliance for the background ADT during a specified period is defined as the total dose actually taken by a patient during that period divided by the total dose expected to be taken during the same period multiplied by 100. The total ADT dose actually taken during a specific time period is calculated as the sum of ADT dose taken during that period as obtained from the study medication *Exposure: Background Antidepressant CRFs*. The total ADT dose expected to be taken for a specific treatment period will be obtained from the same CRFs. Descriptive statistics for ADT compliance will be presented overall for the OLTP and by treatment group for the DBTP using the respective ITT or mITT populations.

7.3 WEIGHT-ADJUSTED DOSE OF RAPASTINEL

For the OLTP, the dose of rapastinel will be divided by the corresponding patient's weight assessed at Visit 1 and summarized descriptively overall for the Open-label Safety Population.

For the DBTP, the dose of rapastinel will be divided by the corresponding patient's weight assessed at Visit 18 and summarized descriptively by treatment group for the Double-blind Safety Population.

8.0 EFFICACY ANALYSES

All efficacy analyses for the OLTP will be performed using the Open-label ITT Population. All efficacy analyses for the DBTP will be performed using the Double-blind mITT Population. The baseline Day 0 assessment of the lead-in study will be used as the baseline for the OLTP. The Day 0 assessment is the last non-missing assessment before the first dose of Double-blind IP during the placebo lead-in period of their respective lead-in study. The last non-missing assessment before the first dose of Double-blind IP in the DBTP will be used as the baseline for the DBTP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all CIs will be 2-sided 95% CIs, unless stated otherwise.

The rater-administered MADRS will be used when deriving endpoints for analyses. The computer-administrated MADRS scores will be provided in a listing.

8.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy parameter is the time to first relapse. Relapse during the DBTP is defined as meeting any of the following criteria:

- MADRS total score $\geq$ 18 at 2 consecutive assessments. The 2 MADRS assessments must occur on different calendar dates
- $\geq$ 2 increase in CGI-S score compared with that obtained at randomization
- Risk of suicide as determined by the investigator
- Need for hospitalization due to worsening of depression as determined by the investigator
- Need for alternative treatment of depressive symptoms as determined by the investigator

Further details on the derivation of the relapse criterion are provided in section 15.3.

The primary endpoint is the time to first relapse during the first 52 weeks of the DBTP, defined as relapse date – randomization date + 1. Patients who do not meet the above relapse criteria during the first 52 weeks of the DBTP will be censored at 52 weeks or the time of completion or discontinuation from the study, whichever is earlier.

The primary efficacy analysis is to evaluate the time to first relapse in MDD patients who are stable responders to open-label treatment with rapastinel for MDD.

The primary null hypothesis is that the distribution of the time to first relapse for each of the rapastinel 450 mg weekly and 450 mg biweekly treatment groups is not different from that for the placebo treatment group. The primary alternative hypothesis is that the distribution of the time to first relapse for either of the rapastinel 450 mg weekly and 450 mg biweekly treatment groups is different from that for the placebo treatment group.

The hypothesis testing will compare the time to first relapse between each rapastinel group and the placebo group using the log-rank test for the Double-blind mITT Population. Estimates of the hazard ratio and 95% CIs will be based on the Cox proportional hazards model with treatment group as an explanatory variable. The Kaplan-Meier estimates for the cumulative distribution of the relapse rate for each treatment group will be provided. The proportion of patients who relapse, the Kaplan-Meier estimate of the median, first quartile and third quartile of the time to first relapse and corresponding 95% CI for the median will be presented for each treatment group. Plots of the Kaplan-Meier estimate of the distribution of the time to first relapse will also be provided for each treatment group. The primary reason for relapse, as collected on the *Relapse CRF*, will be tabulated by treatment group.

Three sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis assumes that patients who discontinued without meeting any of the relapse criteria during the first 52 weeks of the DBTP relapsed instead of being censored. The second sensitivity analysis will be based on the delta-adjusted method examined by Zhao et al (2014). The third sensitivity analysis is an extension of the placebo-based pattern mixture model proposed by Lu (2014, 2015). The placebo-based pattern mixture model assumes that patients who discontinued from the rapastinel treatment groups would have disease progression after discontinuation similar to that of placebo. The extended placebo-based pattern mixture model uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring underlying the placebo-based pattern mixture model. The extended placebo-based pattern mixture model sensitivity analysis for time-to-event data is described as follows:

Let $h_0(t)$ denote the baseline hazard function associated with the placebo group. Let β_1 and β_2 denote the treatment effects in terms of log hazard ratios under noninformative censoring for rapastinel 450 mg weekly versus placebo and rapastinel 450 mg biweekly versus placebo, respectively. The hazard functions associated with the rapastinel 450 mg weekly and 450 mg biweekly groups under noninformative censoring are thus given by $h_1(t) = h_0(t) \exp(\beta_1)$ and $h_2(t) = h_0(t) \exp(\beta_2)$, respectively. Consider the extended placebo-based pattern mixture model sensitivity analysis. For the placebo group, we assume that patients with premature discontinuation would have comparable experience after discontinuation to their counterparts without premature discontinuation. For the rapastinel treatment groups, each dropout timepoint for rapastinel patients defines a missing data pattern, and we assume that patients with premature discontinuation would have disease progression after discontinuation somewhere between their counterparts without premature discontinuation and patients in the placebo group. Specifically, we assume that $h_1(t) = h_0(t) \exp((1- \phi)\beta_1)$ and $h_2(t) = h_0(t) \exp((1- \phi)\beta_2)$ for $t > C$, where C denotes the time of premature discontinuation. The sensitivity parameter $\phi \in [0,1]$ characterizes the gradual deviation from the noninformative censoring with $\phi = 0$ toward the informative censoring underlying the placebo-based pattern mixture model with $\phi = 1$. A multiple imputation approach will be used to implement the extended placebo-based pattern mixture model.

Technical details for the implementation of the sensitivity analyses are provided in APPENDIX I.

8.2 SECONDARY EFFICACY ANALYSIS

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

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

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

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

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

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

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

[redacted]

9.1 ADVERSE EVENTS

AEs will be coded 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 lead-in study or was present before the first dose of IP in the lead-in study and increased in severity during the OLTP or thereafter. An AE that becomes serious during the OLTP or thereafter will also be considered as a TEAE. If more than 1 AE is reported before the date of the first dose of IP in the lead-in study and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the OLTP or thereafter that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of IP will not be counted as a TEAE.

An AE (classified by preferred term) that occurs during the OLTP of the study will be considered a newly emergent adverse event (NEAE) if the AE was not present before the first dose of IP in the OLTP or it was present before the first dose of IP in the OLTP and increased in severity during the OLTP. An AE that becomes serious during the OLTP will also be considered as an NEAE. If more than 1 AE is reported before 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.

An AE (classified by preferred term) that occurs during the DBTP of the study will be considered an NEAE if the AE was not present before the first dose of IP in the DBTP or it was present before the first dose of IP in the DBTP and increased in severity during the DBTP. An AE that becomes serious during the DBTP will also be considered as an NEAE. If more than 1 AE is reported before the first dose of IP in the DBTP and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the DBTP that were also coded to that preferred term.

An AE (classified by preferred term) that occurs during the SFU of the study will be considered an NEAE if the AE was not present before or at Visit 122 or it was present before or at Visit 122 and increased in severity during the SFU. An AE that becomes serious during the SFU will also be considered as an NEAE. If more than 1 AE is reported before or at Visit 122 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 SFU 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 counted as an NEAE.

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

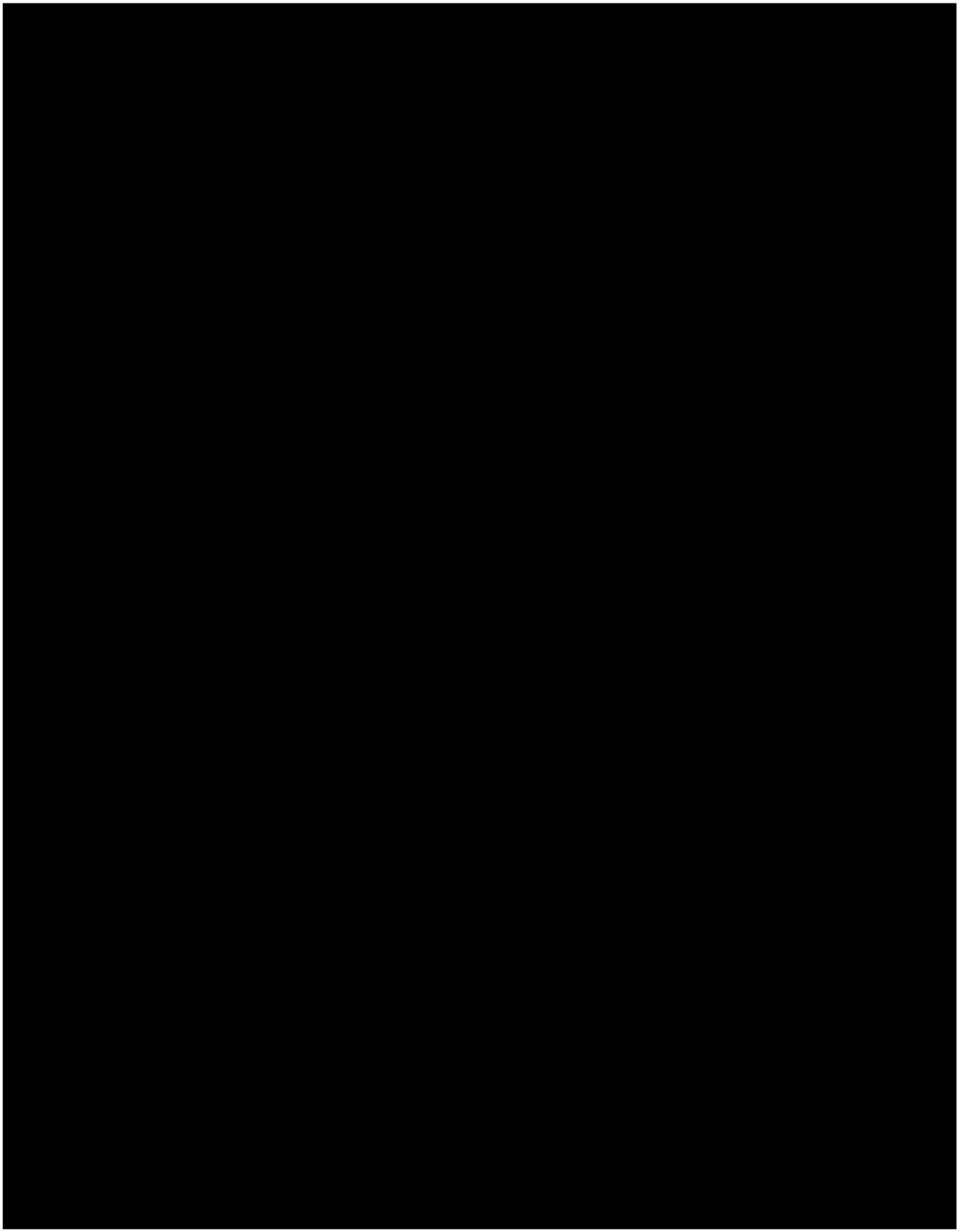
The incidence of common ($\geq$ 2% of patients in any treatment group) TEAEs and NEAEs during the OLTP will be summarized overall by preferred term. Similarly, the incidence of common TEAEs and NEAEs during the DBTP and during the SFU will be summarized by preferred term and treatment group and will be sorted by decreasing frequency starting with the weekly rapastinel group followed by the biweekly rapastinel group.

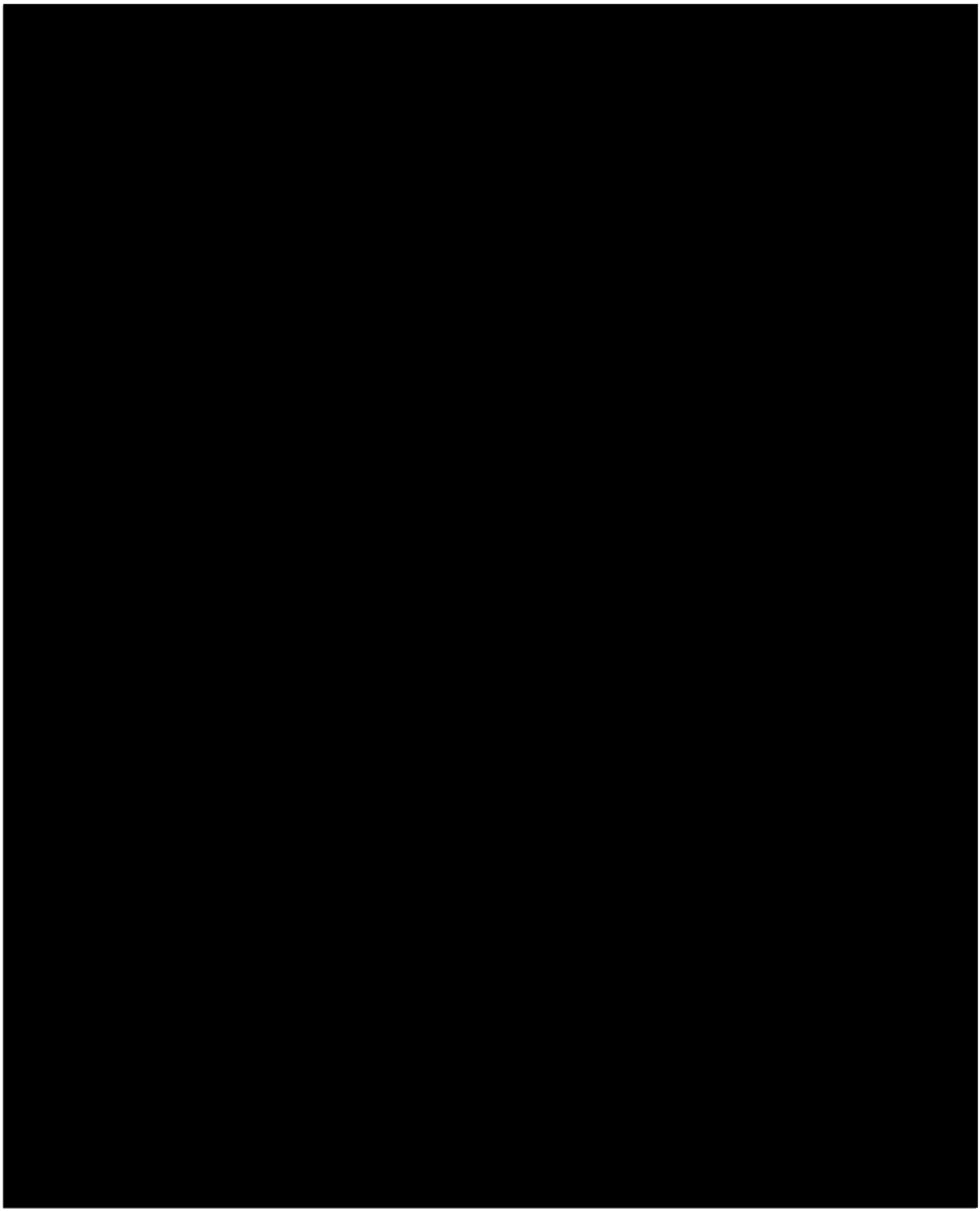
An SAE that occurred between the date of the first dose of IP in the OLTP and 30 days after the date of the last dose of IP, inclusive, will be considered a treatment-emergent SAE (TESAE). The number and percentage of patients who had TESAEs during the OLTP will be summarized overall by preferred term and sorted by decreasing frequency. The number and percentage of patients who had TESAEs during the DBTP and during the SFU will be summarized by treatment group and preferred term and will be sorted by decreasing frequency starting with the weekly rapastinel group followed by the biweekly rapastinel group.

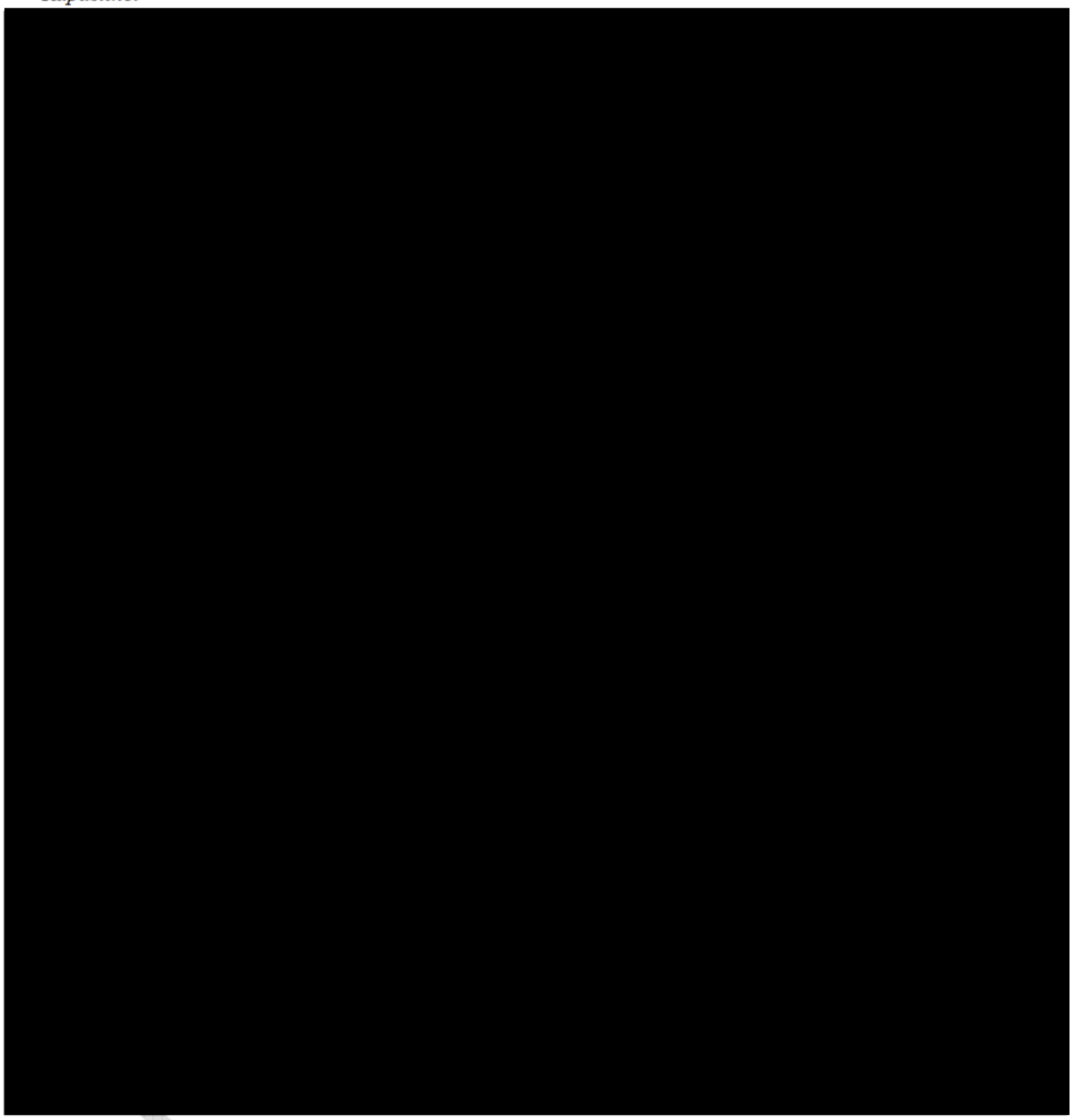
The number and percentage of patients who had fatal TESAEs during the OLTP will be summarized overall by preferred term and sorted by decreasing frequency. The number and percentage of patients who had fatal TESAEs during the DBTP and during the SFU will be summarized by treatment group and preferred term and sorted by decreasing frequency starting with the weekly rapastinel group followed by the biweekly rapastinel group.

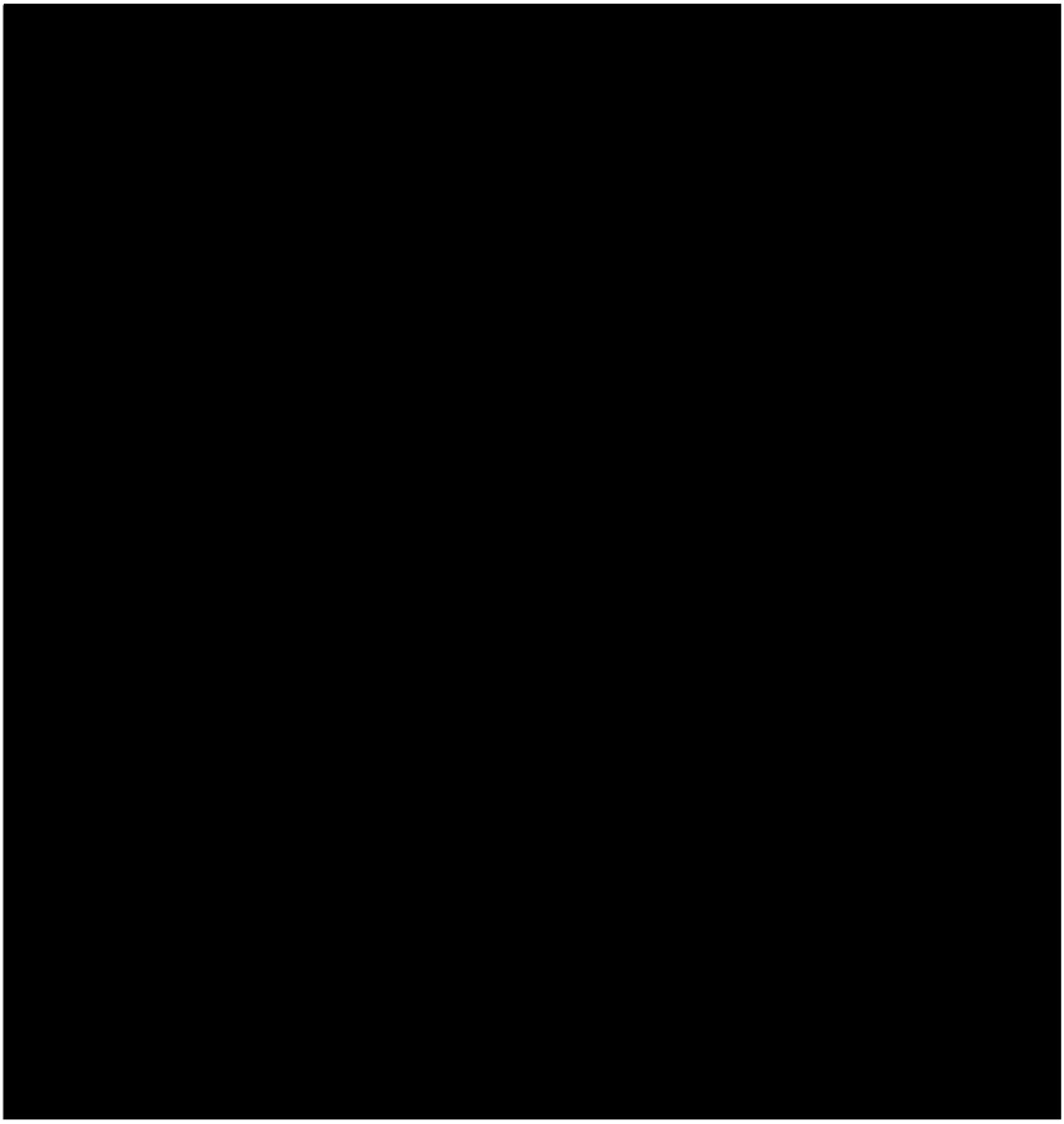
The incidence of TEAEs leading to premature discontinuation of IP during the OLTP will be summarized overall by preferred term and will be sorted by decreasing frequency. The incidence of AEs leading to premature discontinuation of IP during the DBTP will be summarized by preferred term and treatment group and will be sorted by decreasing frequency starting with the weekly rapastinel group followed by the biweekly rapastinel group.

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









11.0 INVESTIGATIONAL PRODUCT PLASMA CONCENTRATION PARAMETERS

Analyses of plasma concentrations of rapastinel will be summarized in a separate document governing the PK analysis.

12.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

13.0 DETERMINATION OF SAMPLE SIZE

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

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed [redacted]

15.0 STATISTICAL AND DATA HANDLING CONVENTIONS

15.1 SUMMARY STATISTICS

The following statistical summaries will be presented for each type of data:

- Continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation (SD), median, minimum, and maximum values).
- Categorical variables will be summarized by frequency distributions (counts and percentages).
- Time-to-event data will be summarized by showing the number of patients, number of patients experiencing the event of interest, estimates of the median, first quartile and third quartile using the Kaplan Meier estimate as well as a 95% CI for the median

15.2 VISIT TIME WINDOWS

Table 15.2–1 and Table 15.2–2 present visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur for the OLTP and DBTP respectively.

Table 15.2–1. Visit Time Windows for Screening and OLTP

OLTP Visit Timepoint	*Visit Number (AVISIT)*	*Target Day for Rollover Patients Relative to the First IP Dose during the OLTP (ADY)*	*Window for Rollover Patients*
Screening	Visit 1	1	1
Week 0	Visit 2	8	[2, 11]
Week 1	Visit 3	15	[12, 18]
Week 2	Visit 4	22	[19, 25]
Week 3	Visit 5	29	[26, 32]
Week 4	Visit 6	36	[33, 39]
Week 5	Visit 7	43	[40, 46]
Week 6	Visit 8	50	[47, 53]*
Week 7	Visit 9	57	[54, 60]*
Week 8	Visit 10	64	[61, 67]*
Week 9	Visit 11	71	[68, 74]*
Week 10	Visit 12	78	[75, 81]*
Week 11	Visit 13	85	[82, 88]*
Week 12	Visit 14	92	[89, 95]*

Table 15.2–1. Visit Time Windows for Screening and OLTP

OLTP Visit Timepoint	*Visit Number (AVISIT)*	*Target Day for Rollover Patients Relative to the First IP Dose during the OLTP (ADY)*	*Window for Rollover Patients*
Week 13	Visit 15	99	[96, 102]*
Week 14	Visit 16	106	[93, 109]*
Week 15**	Visit 17	113	> 109*
Week 16	Visit 18		NA
Early Termination	Visit 122	NA	NA

* If rollover patients meet stabilization criteria at Visits 9-17, Visit 18/Week 16 assessments should be completed at that visit.

** Rollover patients who do not meet stability criteria by Visit 17/Week 15 will undergo the End-of-Treatment/Early Termination assessments (Visit 122/Week 104/ET, as shown on the DBTP Schedule of Evaluations).

Table 15.2–2. Visit Time Windows for DBTP and SFU

DBTP Visit Timepoint	*Visit Number (AVISIT)*	*Target Day Relative to the First IP Dose during the DBTP (ADY)*	*Window*
Week 0	Visit 18	0	0
Week 1	Visit 19	7	[1, 10]
Week 2	Visit 20	14	[11, 17]
Week X^a	Visit "18+X^a"	$7\times X^a$	$[7\times X^a - 3, 7\times X^a + 3]$
Final/Early Termination	Visit 122	NA	NA
Safety Follow-up	Visit 123	$Y^b + 14$	$> Y^b$

[a] X is an integer from 3 to 104.

[b] Y is the study day of the Final/ET visit.

If a patient has 2 or more values for a given endpoint within the same window, the value with collection date closest to the scheduled day will be used for analysis; if there are 2 values whose collection dates are equidistant from the scheduled day, the value corresponding to the later date will be used for analysis.

With the exception of endpoints recorded pre or post IP dose and Visit 122/ET MADRS assessments, in the event there are multiple values of the same endpoint on the same date, the last value will be taken as the value for that date. For endpoints reported pre IP dose, in the event there are multiple values of the same endpoint prior to IP dose, the last value prior to the IP dose is taken as the predose value for that date. Similarly, for endpoints reported post IP dose, in the event there are multiple values of the same endpoint after IP dose, the last value will be taken as the postdose value for that date. For multiple MADRS assessments on the same date for Visit 122/ET, the last MADRS assessment prior to Visit 122/ET on that date will be taken as the value for that date.

15.3 DERIVED EFFICACY AND SAFETY VARIABLES

The efficacy variables are derived as follows:

- MADRS total score is the sum of the 10 items from the MADRS. If more than 2 items of the MADRS are missing, then the total score will be set to missing
- *Responder* is defined as a patient with ≥ 50% reduction from Day 0 MADRS total score
- *Remitter* in the randomized treatment period is defined as a patient with MADRS total score ≤ 10

[redacted]

For the MADRS [redacted], the total score at a particular visit will be calculated using (sum of nonmissing items) × (total number of items) / (number of nonmissing items) only if the number of missing items is less than the specified number for each variable. Otherwise, the total score will be set to missing.

The primary efficacy parameter was defined in section 8.1. A relapse will be defined programmatically as meeting any of the following criteria:

- An observed MADRS total score ≥ 18 for two consecutive assessments as determined from the MADRS data (not the Relapse CRF). The 2 MADRS assessments must occur on different calendar dates.
- An observed increase in CGI-S score ≥ 2 compared with that obtained at randomization as determined from the CGI-S data (not the Relapse CRF).

- Marked as a relapse on the Relapse CRF with the primary reason for relapse indicating "Risk of Suicide".

- Marked as a relapse on the Relapse CRF with the primary reason for relapse indicating "Need for hospitalization due to worsening of depression".

- Marked as a relapse on the Relapse CRF with the primary reason for relapse indicating "Need for alternative treatment for depressive symptoms".

The first relapse date for a patient is defined as the earliest assessment date in which any of the relapse criteria mentioned above were met, obtained either from the date recorded on the Relapse CRF (for the primary reasons of "Risk of Suicide", "Need for hospitalization due to worsening of depression" or "Need for alternative treatment for depressive symptoms") or the dates of the corresponding MADRS or CGI-S assessments. For the relapses based on MADRS total score $\geq$ 18 at 2 consecutive visits, the relapse date is defined as the assessment date of the first visit of the 2 consecutive assessments.

15.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

15.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of open-label IP, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of open-label IP, a severity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.6 MISSING CAUSAL RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

If the causal relationship to the IP is missing for an AE that started on or after the date of the first dose of open-label IP, a causality of yes will be assigned. The imputed values for causal relationship to randomized treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for an AE is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of open-label IP, the month and day of the first dose of open-label IP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of open-label IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label IP, the day of the first dose of open-label IP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of open-label IP or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of open-label IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of open-label IP or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of open-label IP, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of open-label IP, the date of the first dose of open-label IP will be assigned to the missing start date.

- If the stop date is before the date of the first dose of open-label IP, the stop date will be assigned to the missing start date.

15.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including background ADT, incomplete (ie, partially missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

15.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of open-label IP, the month and day of the first dose of open-label IP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of open-label IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label IP, the day of the first dose of open-label IP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of open-label IP or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of open-label IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of open-label IP or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of open-label IP, the first day of the month will be assigned to the missing day.

15.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, the month and day of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, *01 Jan* will be assigned to the missing fields.

Missing month only

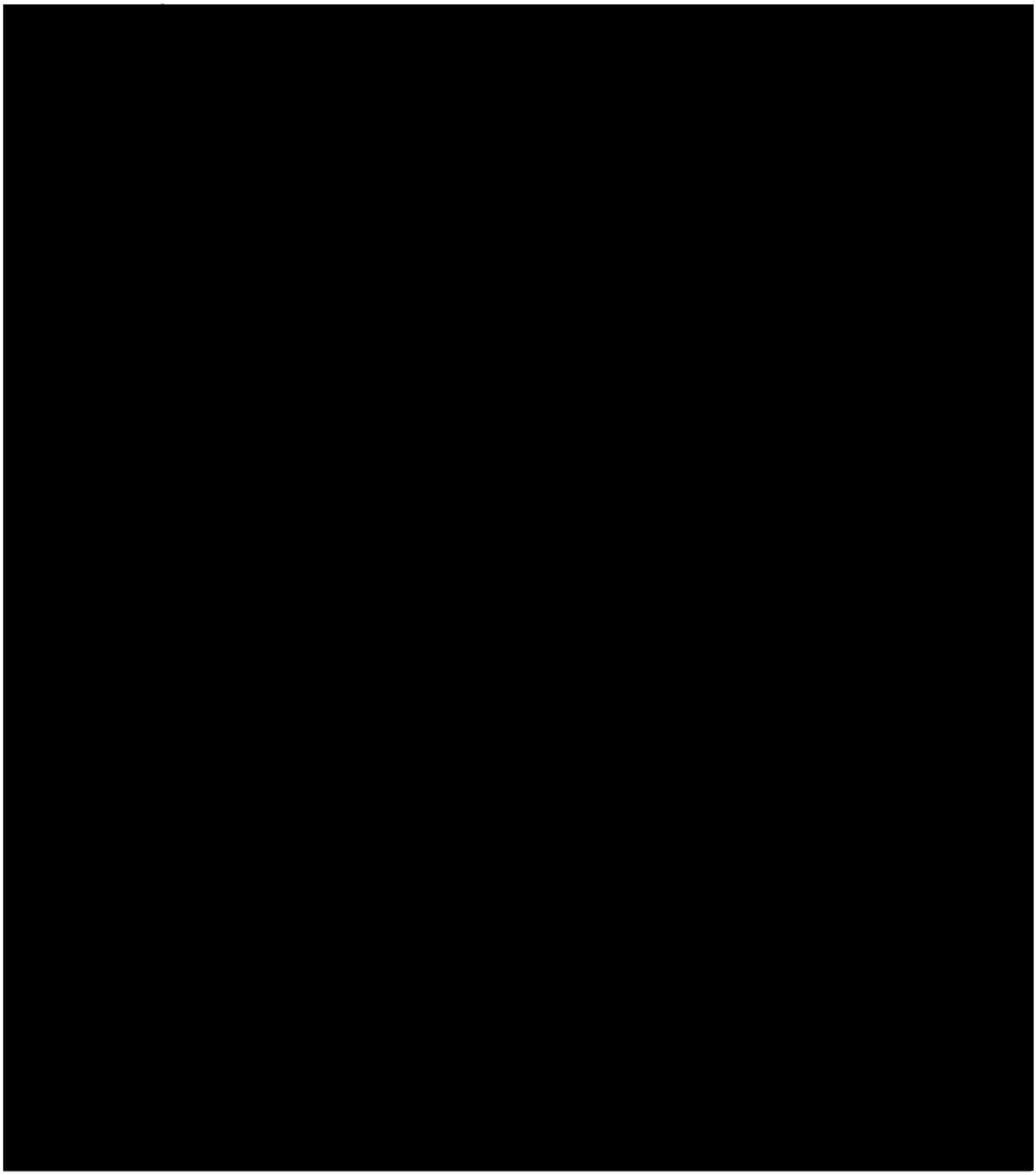
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, the day of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP or if both years are the same but the month of the incomplete stop date is before the month of the date of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete stop date is after the year of the date of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP or if both years are the same but the month of the incomplete stop date is after the month of the later of the date of the last dose of open-label IP and the date of last dose of double-blind IP, the first day of the month will be assigned to the missing day.



15.10 ACTUAL TREATMENT FOR ANALYSIS

If a wrong kit was administered to a patient, the treatment to which a patient was randomized will be used for all the analyses.

15.11 STRATIFICATION HANDLING CONVENTION

Stratification is not being implemented in this study.

16.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the final protocol Amendment 2 (version dated 06 Nov 2018). While there are analyses for endpoints collected during the OLTP that are with respect to Day 0 of the lead-in studies, it was necessary not to explicitly mention this fact in the RAP-MD-04 protocol Amendment 2 in order to protect restricted information pertaining to RAP-MD-01/02/03.

17.0 REFERENCES

Lu K. An extension of the placebo-based pattern-mixture model. *Pharmaceutical Statistics* 2014; 13: 103-109.

Lu K., Li D., Koch, G. Comparison between two controlled multiple imputation methods for sensitivity analysis of time-to-event data with possibly informative censoring. *Statistics in Biopharmaceutical Research*, 2015; 7: 199-213.

Zhao, Y., Herring, A. H., Zhou, H., Ali, M.W., and Koch, G. G. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring," *Journal of Biopharmaceutical Statistics*, 2014; 24: 229–253.

18.0 APPENDICES

APPENDIX I. TECHNICAL DETAILS FOR THE IMPLEMENTATION OF THE EXTENDED PLACEBO-BASED PATTERN MIXTURE MODEL VIA MULTIPLE IMPUTATION

The following steps will be taken to implement the extended placebo-based pattern mixture model via multiple imputation:

1. Carry out a Bayesian analysis for the Cox proportional hazards model with treatment group as an explanatory variable and with piecewise constant baseline hazard function. Let $h_0(t;\lambda) = \sum_{j=1}^{J} \lambda_j I(a_{j-1} \le t < a_j)$ denote the piecewise constant baseline hazard function, where $a_0 = 0 < a_1 < \cdots < a_{J-1} < a_J = \infty$ denotes a partition of the time axis. The cut points are chosen to have an approximately equal number of events in each interval. The number of intervals with constant baseline hazard rates, *J,* is set to strike a balance between the approximation to the unknown underlying baseline hazard function and the number of events in each interval. The hazard function for patient *i* is $h(t \mid X_i;\theta) = h_0(t;\lambda)\exp(\beta_1 X_{i1})$, where X_{i1} = 1 if patient *i* is in the rapastinel group.

2. Take a posterior draw of the model parameters, $\tilde{\theta} = (\tilde{\lambda}, \tilde{\beta})$, from the Bayesian analysis.

3. For a patient who prematurely discontinued without meeting any of the relapse criteria during the DBTP, impute the time to relapse after discontinuation, T_i, under the extended placebo-based pattern mixture model with sensitivity parameter ϕ, by equating the conditional survival probability at T_i given that the patient discontinued at C_i to a uniform random variable U_i, that is,

$$\exp\left\{-\int_{C_i}^{T_i} h_0(t;\tilde{\lambda}) e^{(1-\phi)(\tilde{\beta}_1 X_{i1})} dt\right\} = U_i .$$

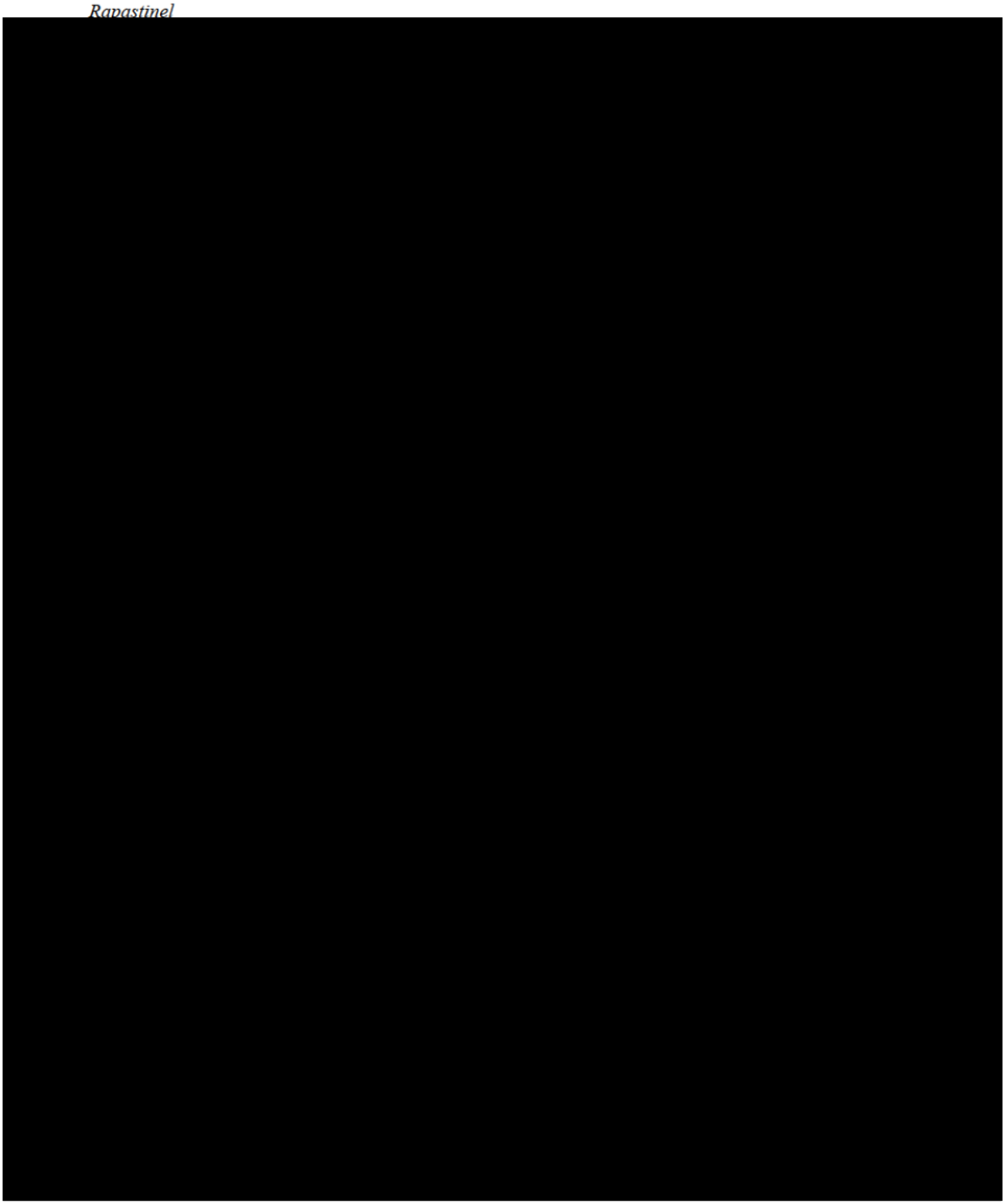
   This equation can be easily solved by noting that the baseline hazard function $h_0(t; \lambda)$ is piecewise constant.

4. If the imputed event time exceeds the planned follow-up time for the patient, we manage the patient as having no event by the end of the planned follow-up time. Thus, the imputed complete data set has no patients with premature discontinuation and has only administrative censoring at the planned follow-up time.

5. Apply the primary analysis model to the complete data set to obtain the parameter estimates and associated covariance matrix for a single imputation. The parameters are the log-rank test statistics for the log-rank test, and the log hazard ratios for the Cox model with treatment group as an explanatory variable.

6. Repeat Step 2 through Step 5 for m times to generate m sets of imputed complete-data parameter estimates and associated covariance matrices. Use the SAS procedure MIANALYZE to combine results from m imputed data sets and draw inference about the treatment effects of both rapastinel groups versus placebo.

7. Vary the value of the sensitivity parameter $\phi \in \{0, 0.2, 0.4, 0.6, 0.8, 1\}$ in Step 3 to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption toward the informative censoring underlying the placebo-based pattern mixture model.



19.0 HISTORY OF CHANGES

Date	Section	Description
11/29/2018	NA	Initial version approval.