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Study ID: RAP-MD-33

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

Statistical Analysis Plan Date: 26 Aug 2019

RAP-MD-33

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

STATISTICAL ANALYSIS PLAN

SAP Date: August 26, 2019

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1.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
CRF	case report form
[redacted]	[redacted]
[redacted]	[redacted]
DBTP	double-blind treatment period
ECG	electrocardiogram, electrocardiographic
ET	early termination
ICF	informed consent form
IP	investigational product
IV	intravenous
IWRS	Interactive Web Response System
ITT	intent-to-treat
[redacted]	[redacted]
MDD	major depressive disorder
NEAE	newly emergent adverse event

PCS	potentially clinically significant
PID	patient identification
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]
SE	standard error
SOC	system organ class
SI	*Le Système International d'Unités* (International System of Units)
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent 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 of Study RAP-MD-33 (version dated 02MAY2018).

Study RAP-MD-33 is a Phase 3, multicenter, randomized-withdrawal, parallel-group, placebo-controlled, maintenance study to evaluate the efficacy, safety, and tolerability of rapastinel in the prevention of relapse in patients with major depressive disorder (MDD) who completed one of the rapastinel lead-in studies including RAP-MD-30 and RAP-MD-32. The RAP-MD-31 study was terminated before any patient was enrolled. Thus, there is no patient rolled-over from the RAP-MD-31 study to RAP-MD-33 study.

The study will be conducted in the following periods:

- An 8- to 16-week open-label treatment period (OLTP) where patients receive rapastinel 225 or 450 mg IV weekly

- A randomized double-blind treatment period (DBTP) of at most 52 weeks of treatment duration where patients are randomized 1:1:1 to either rapastinel 225 or 450 mg weekly, rapastinel clinically driven schedule (IV, 225 or 450 mg, variable interval, placebo on intervening weeks) or placebo

- A 2-week safety follow-up period

In order for patients to transition from the OLTP and be randomized into the DBTP, the patient must meet the stability 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 six consecutive weeks.

2) An observed MADRS total score ≤ 12 for at least two consecutive visits prior to randomization.

The OLTP starts with the first dose of open-label treatment and ends with one of the following: the first dose of double-blind treatment for patients who enter the DBTP or Visit 69/Week 52 End-of-Treatment/Early Termination (ET) assessments for patients who do not enter the DBTP.

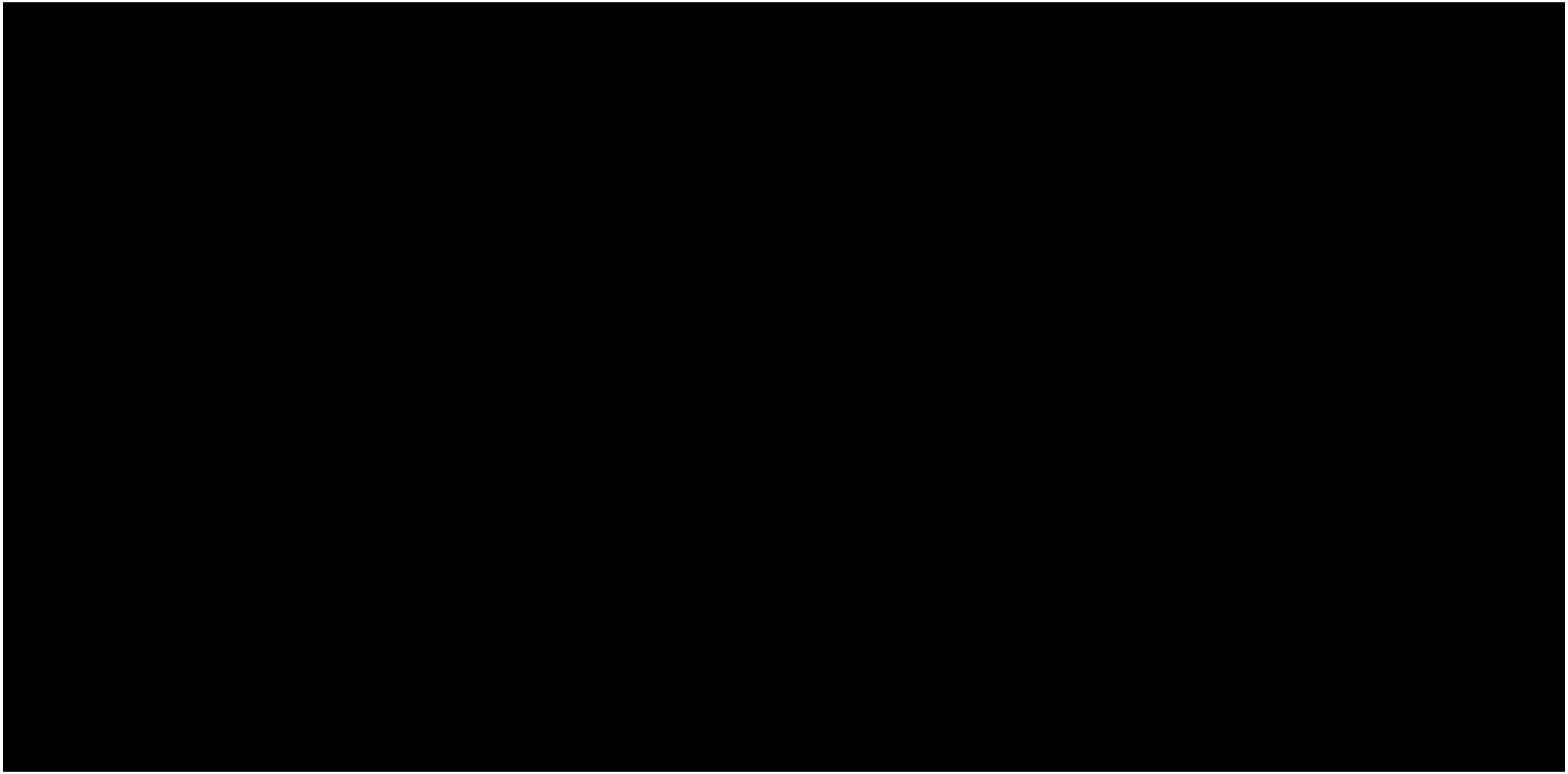
The double-blind treatment period starts when the first dose of double-blind treatment is administered and ends when the patient meets relapse criteria, completes 52 weeks of double-blind treatment, or discontinues for other reasons.

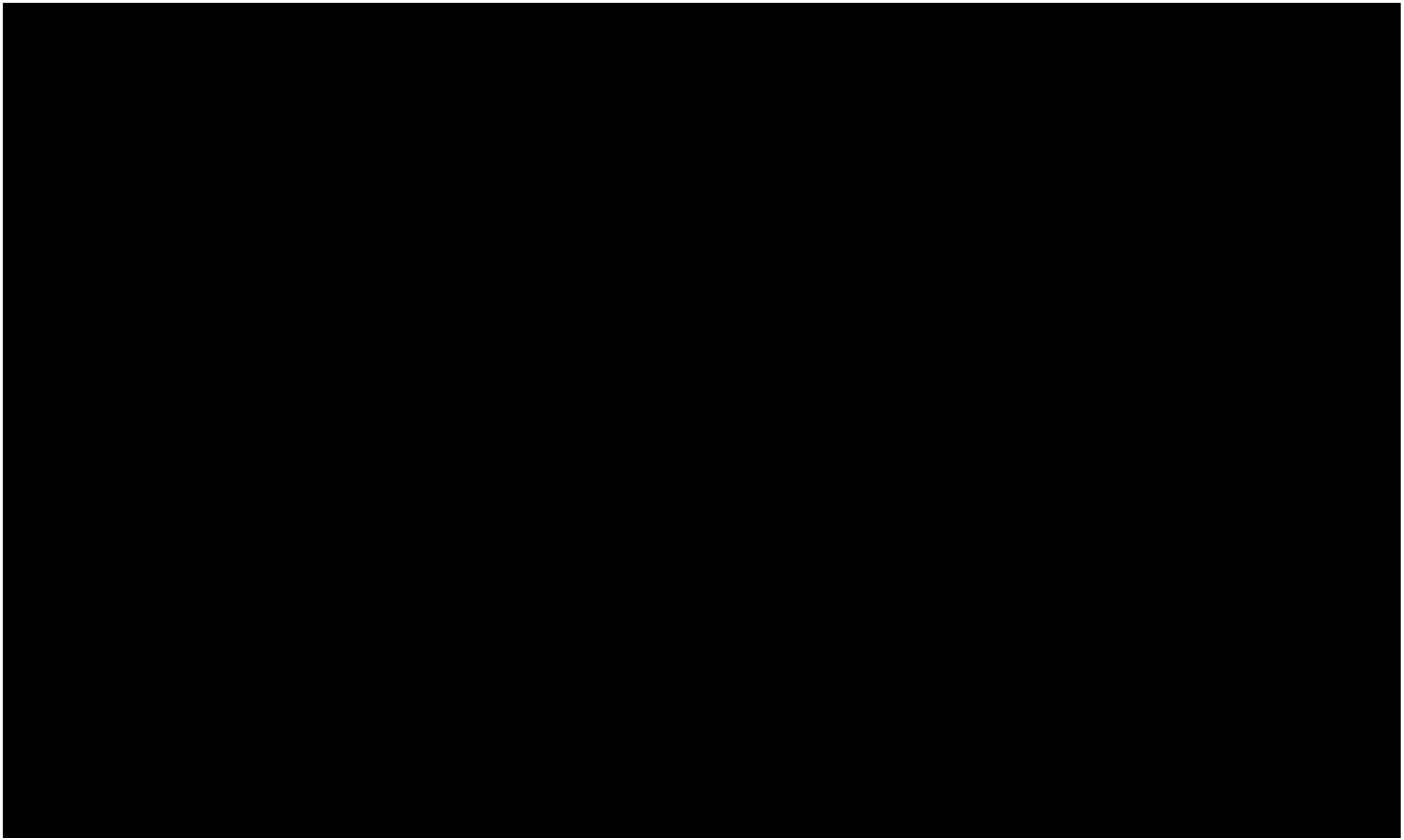
The safety follow-up (SFU) period starts after completion of the last scheduled assessment (or ET) and ends with the last available assessment.

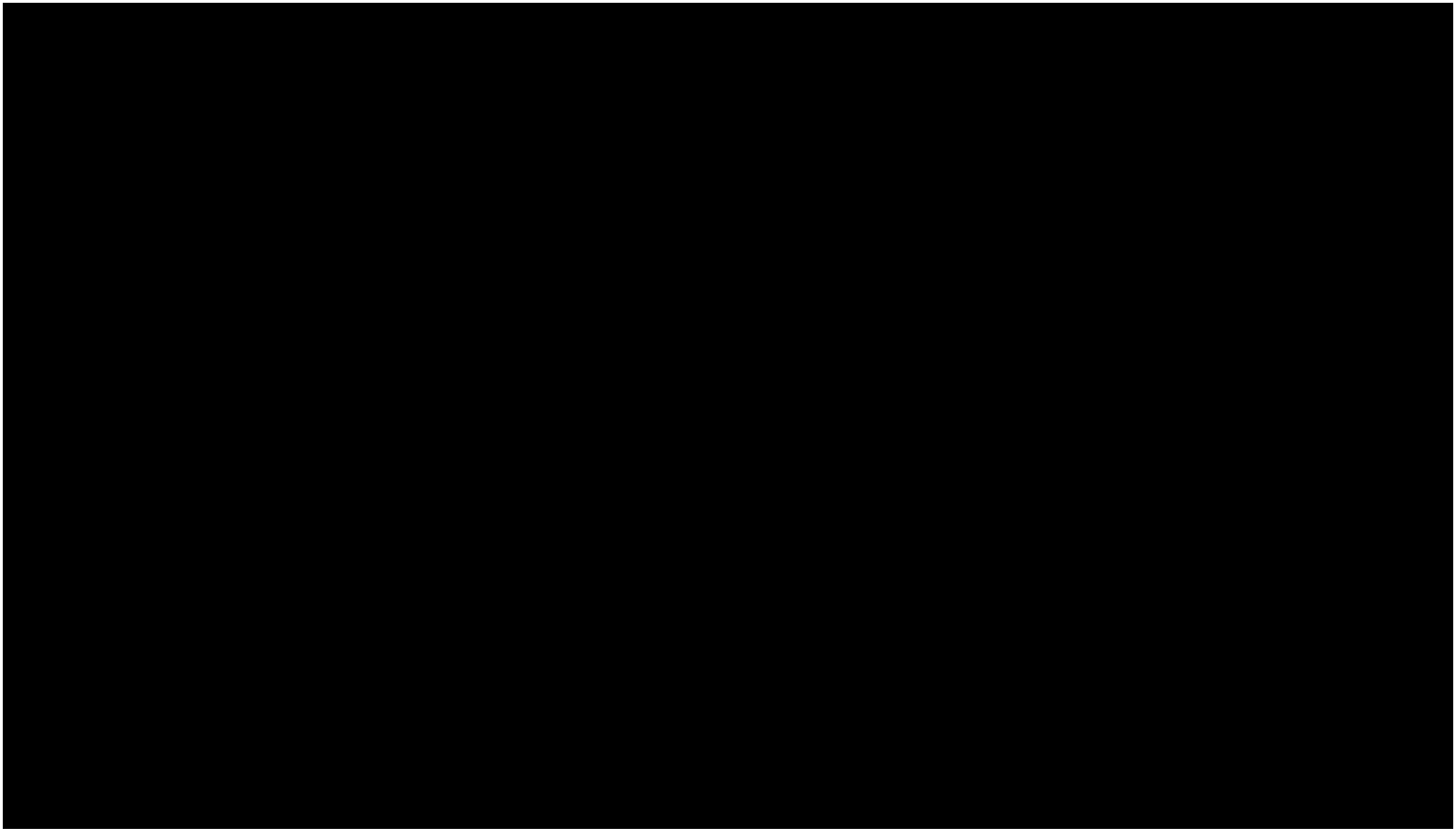
Individual treatment durations will vary. The maximum duration of the study will be 70 weeks.

[redacted]

[redacted]







3.0 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 (225 or 450 mg IV weekly or clinically driven schedule) versus placebo in the maintenance treatment of MDD as a monotherapy, as measured by time to relapse during the first 52 weeks of the DBTP.

[redacted]

4.0 PATIENT 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 MODIFIED INTENT-TO-TREAT POPULATION

The Open-label modified Intent-to-Treat (OL mITT) 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 double-blind IP.

4.4 DOUBLE-BLIND MODIFIED INTENT-TO-TREAT POPULATION

The Double-blind modified Intent-to-Treat (DB mITT) Population will consist of all patients in the Double-blind Safety Population who had at least 1 post-randomization assessment of the MADRS or the CGI-S during the DBTP of the study.

5.0 PATIENT DISPOSITION

The number of patients who were screened for participation in the OLTP from lead-in studies RAP-MD-30 and RAP-MD-32, and who were screen failures and reasons for failing will be summarized.

The number of patients in the Open-label Safety and Open-label mITT Populations will be summarized overall and by study center. The number of patients in the Double-blind Safety and Double-blind mITT Populations will be summarized overall, and by treatment group 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 DBTP will be summarized overall and by reasons for premature discontinuation for all enrolled patients in the OLTP.

Similarly, the number and percentage of patients who completed the DBTP and who prematurely discontinued from the DBTP will be summarized overall, by double-blind treatment group, and by reasons for premature discontinuation for the all randomized patients in the DBTP.

6.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

Medical and surgical history during the past 12 months and psychotropic medication history during the previous 5 years will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or newer. Data will be presented in listings for the Open-label Safety Population.

Psychiatric history will be summarized overall for the Open-label mITT Populations and by treatment group for the Double-blind modified ITT population.

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. Concomitant medication during the DBTP will be defined as any medication taken on or after the date of the first dose of double-blind IP.

Prior and concomitant medications during the OLTP will be listed for the Open-label Safety Population. Concomitant medications during the DBTP will be listed for the Double-blind Safety Population. Concomitant medications started after the patient's last study visit during their last treatment period will be presented in the data listings.

The *World Health Organization Drug Dictionary Enhanced* (WHODDE) 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.

8.0 EFFICACY ANALYSES

8.1 PRIMARY EFFICACY PARAMETERS

The analysis of the primary efficacy parameter will be performed using the Double-blind mITT Population.

The primary efficacy parameter is the time to first relapse during the 52 weeks of the DBTP, defined as the number of days from the randomization date of DBTP to the relapse date (ie., relapse date – randomization date + 1). Relapse during the DBTP is defined as meeting any of the following criteria:

- Rater-administered MADRS total score ≥ 18 at 2 consecutive visits
- ≥ 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

Patients who did not meet the above relapse criteria during the 52 weeks of the DBTP, the time to relapse will be censored at the time of completion or discontinuation from the study, or 52 weeks, whichever is earlier.

The primary efficacy analysis will be presented by the cumulative distribution function of time to relapse characterized by the Kaplan-Meier curve for each treatment group.

[redacted]

[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 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 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 a newly emergent adverse event (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 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 a newly emergent adverse event (NEAE) if the AE was not present before or at Visit 70 or it was present before or at Visit 70 and increased in severity during the SFU. An AE that becomes serious during the SFU will also be considered as NEAE. If more than 1 AE is reported before or at Visit 70 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.

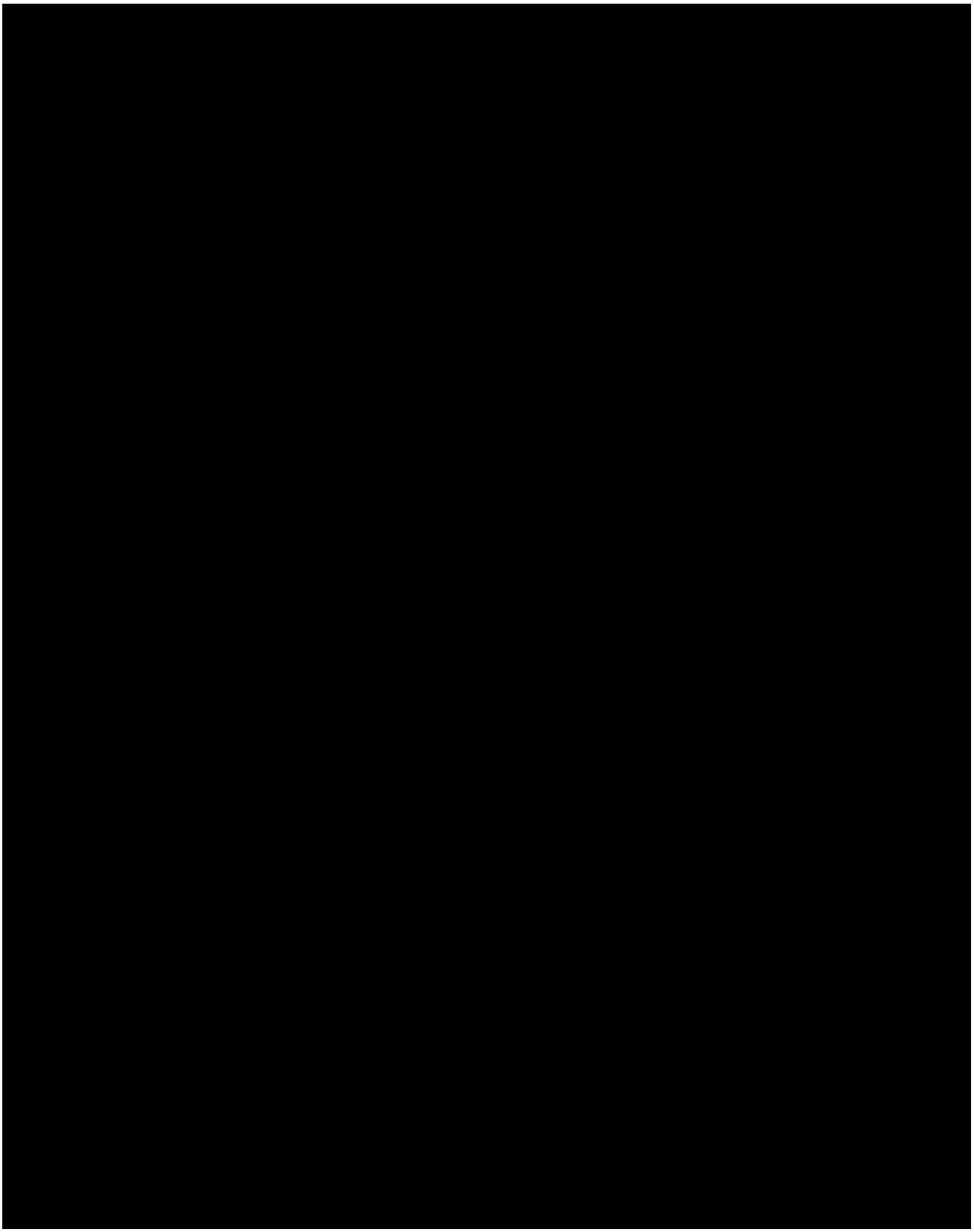
An SAE that occurred between the date of the first dose of IP in the OLTP and 30 days after the date of the last dose of IP, inclusive, will be considered a treatment-emergent SAE (e.g., TESAE).

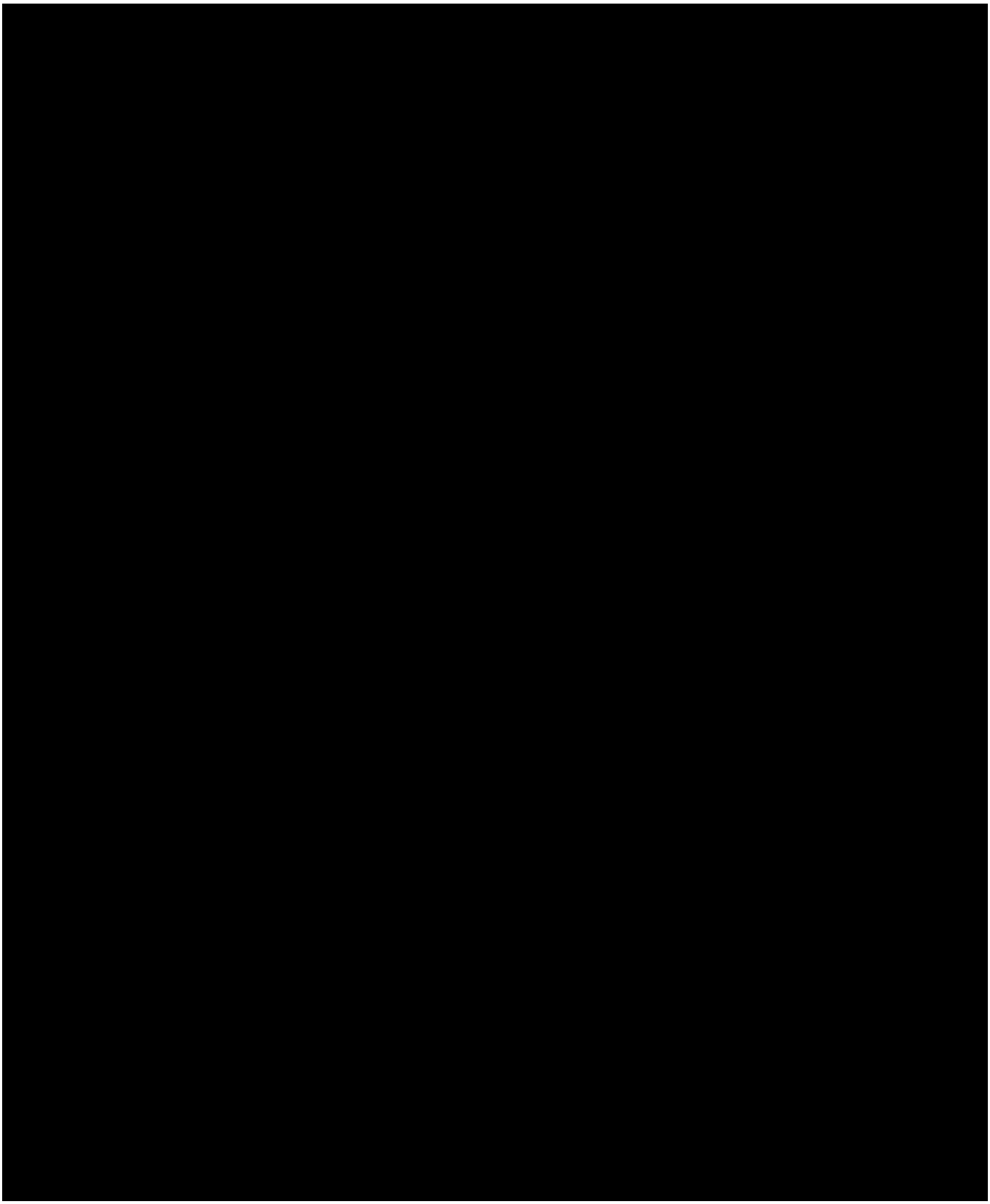
The overall number and percentage of patients with TEAEs, NEAEs, death, TESAEs, TEAEs leading to study discontinuation and TEAEs related to study drug during the OLTP will be tabulated overall, and during the DBTP and the SFU by treatment group.

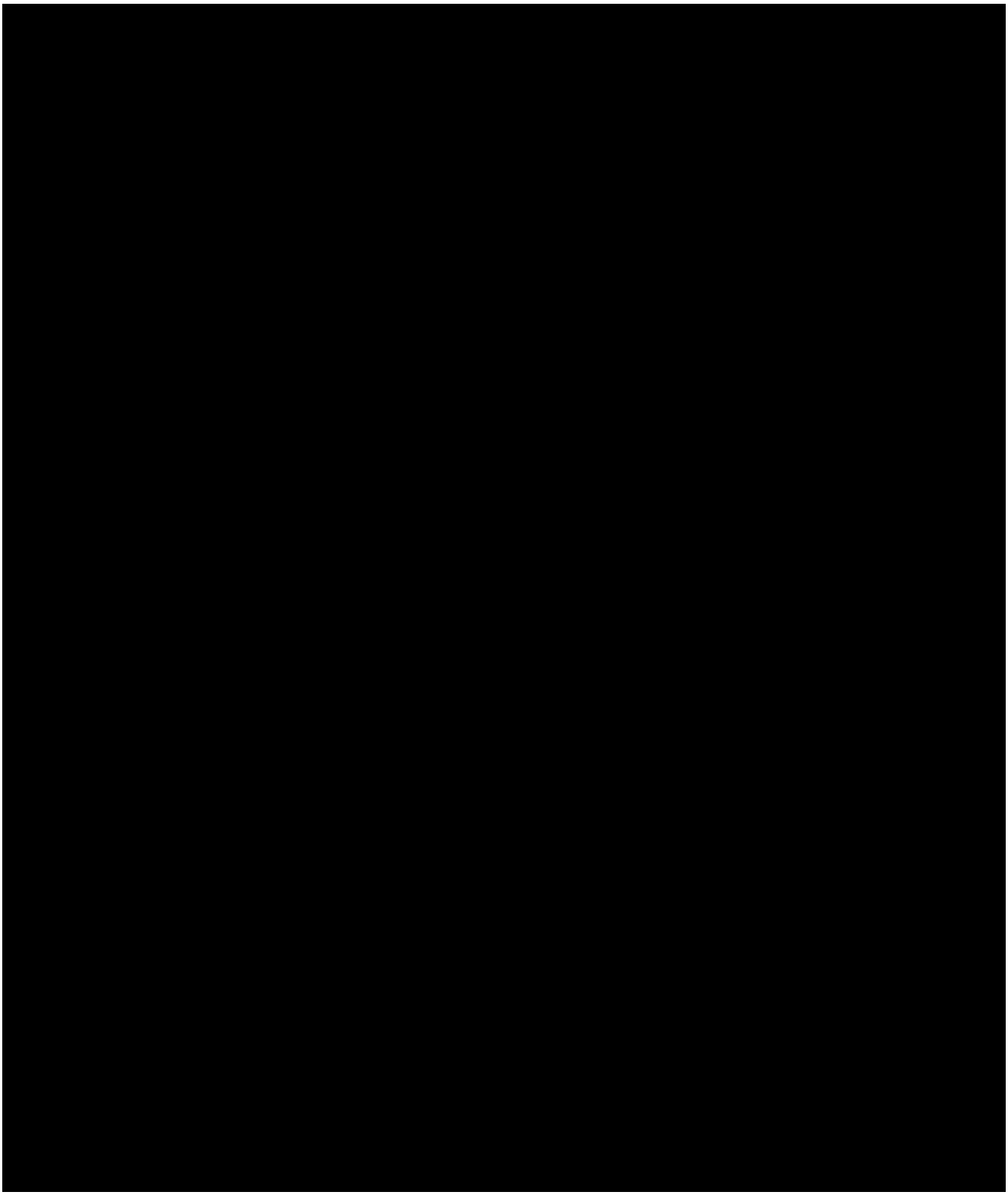
The incidence of common (≥ 2% of patients in any treatment group) TEAEs and NEAEs during the OLTP will be summarized overall by preferred term. Similarly, the incidence of common TEAEs and NEAEs during the DBTP and during the SFU will be summarized by preferred term and treatment group and will be sorted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

Listings will be presented for all patients with AEs and patients who died (if any).

[redacted]







[redacted]

11.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

12.0 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 1400 patients need to be enrolled in this study if 50% of patients are qualified for randomization.

13.0 STATISTICAL SOFTWARE

Statistical analyses will be performed [redacted]

14.0 DATA HANDLING CONVENTIONS

14.1 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

14.2 VISIT TIME WINDOWS

Tables 15.2–1 and 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 14.2–1. OLTP Visit Time Windows

Derived Visit	Target Day	Analysis Visit Window
Baseline		<= Day 0 [a]
Open-label Treatment Period (OLTP)		
Day 1	Day 1	Day 1
Day 7	Day 7	**Start:** Day 2
		End: the Day 7 dosing (Visit 2) date or Day 10 (if no Day 7 dosing)[b]
Week 2	Day 14	**Start:** 1 day after the Day 7 window ends
		End: the Week 2 (Visit 3) dosing date or Day 17 (if no Week 2 dosing)[b]
Week 3	Day 21	**Start:** 1 day after the Week 2 window ends
		End: the Week 3 (Visit 4) dosing date or Day 24 (if no Week 3 dosing) [b]
Week 4	Day 28	**Start:** 1 day after the Week 3 window ends
		End: the Week 4 (Visit 5) dosing date or Day 31 (if no Week 4 dosing)[b]
Week 5	Day 35	**Start:** 1 day after the Week 4 window ends
		End: the Week 5 (Visit 6) dosing date or Day 38 (if no Week 5 dosing)[b]

Week 6	Day 42	**Start:** 1 day after the Week 5 window ends
		End: the Week 6 (Visit 7) dosing date or Day 45 (if no Week6 dosing)[b]
Week 7	Day 49	**Start:** 1 day after the Week 6 window ends
		End: the Week 7 (Visit 8) dosing date or Day 52 (if no Week 7 dosing)[b]
Week 8	Day 56	**Start:** 1 day after the Week 7 window ends
		End: the Week 8 (Visit 9) dosing date or Day 59 (if no Week 8 dosing)[b]
Week 9	Day 63	**Start:** 1 day after the Week 8 window ends
		End: the Week 9 (Visit 10) dosing date or Day 66 (if no Week 9 dosing)[b]
Week 10	Day 70	**Start:** 1 day after the Week 9 window ends
		End: the Week 10 (Visit 11) dosing date or Day 73 (if no Week 10 dosing)[b]
Week 11	Day 77	**Start:** 1 day after the Week 10 window ends
		End: the Week 11 (Visit 12) dosing date or Day 80 (if no Week 11 dosing)[b]
Week 12	Day 84	**Start:** 1 day after the Week 11 window ends
		End: the Week 12 (Visit 13) dosing date or Day 87 (if no Week 12 dosing)[b]
Week 13	Day 91	**Start:** 1 day after the Week 12 window ends
		End: the Week 13 (Visit 14) dosing date or Day 94 (if no Week 13 dosing)[b]
Week 14	Day 98	**Start:** 1 day after the Week 13 window ends
		End: the Week 14 (Visit 15) dosing date or Day 101 (if no Week 14 dosing)[b]
Week 15	Day 105	**Start:** 1 day after the Week 14 window ends
		End: the Week 15 (Visit 16) dosing date or Day 108 (if no Week 15 dosing)[b]
Week 16	Day 112	**Start:** 1 day after the Week 15 window ends
		End: End of OLTP (Randomization Date or Date of Early Termination Visit)

Table 14.2–2. DBTP Visit Time Windows

Derived Visit	Target Day	Analysis Visit Window
Baseline		<= Day/Week 0 [a]
Double Blind Treatment Period (DBTP)		
Day 1	Day 1	Date of first dosing of IP in DBTP (Visit 17)
Day 7	Day 7	**Start:** Day 2
		End: the Day 7 dosing (Visit 18) date or Day 10 (if no Day 7 dosing)[b]
Week 2	Day 14	**Start:** 1 day after the Day 7 window ends
		End: the Week 2 (Visit 19) dosing date or Day 17 (if no Week 2 dosing)[b]
Week 3	Day 21	**Start:** 1 day after the Week 2 window ends
		End: the Week 3 (Visit 20) dosing date or Day 24 (if no Week 3 dosing) [b]
Week 4	Day 28	**Start:** 1 day after the Week 3 window ends
		End: the Week 4 (Visit 21) dosing date or Day 31 (if no Week 4 dosing)[b]
Week 5	Day 35	**Start:** 1 day after the Week 4 window ends
		End: the Week 5 (Visit 22) dosing date or Day 38 (if no Week 5 dosing)[b]
Week 6	Day 42	**Start:** 1 day after the Week 5 window ends
		End: the Week 6 (Visit 23) dosing date or Day 45 (if no Week 6 dosing)[b]
Week 7	Day 49	**Start:** 1 day after the Week 6 window ends
		End: the Week 7 (Visit 24) dosing date or Day 52 (if no Week 7 dosing)[b]
Week 8	Day 56	**Start:** 1 day after the Week 7 window ends
		End: the Week 8 (Visit 25) dosing date or Day 59 (if no Week 8 dosing)[b]
Week 9	Day 63	**Start:** 1 day after the Week 8 window ends
		End: the Week 9 (Visit 26) dosing date or Day 66 (if no Week 9 dosing)[b]
Week 10	Day 70	**Start:** 1 day after the Week 9 window ends
		End: the Week 10 (Visit 27) dosing date or Day 73 (if no Week 10 dosing)[b]
Week 11	Day 77	**Start:** 1 day after the Week 10window ends
		End: the Week 11 (Visit 28) dosing date or Day 80 (if no Week 11 dosing)[b]
Week 12	Day 84	**Start:** 1 day after the Week 11 window ends
		End: the Week 12 (Visit 29) dosing date or Day 87 (if no Week 12 dosing)[b]
Week 13	Day 91	**Start:** 1 day after the Week 12 window ends
		End: the Week 13 (Visit 30) dosing date or Day 94 (if no Week 13 dosing)[b]

Week 14	Day 98	**Start:** 1 day after the Week 13 window ends
		End: the Week 14 (Visit 31) dosing date or Day 101 (if no Week 14 dosing)[b]
Week 15	Day 105	**Start:** 1 day after the Week 14 window ends
		End: the Week 15 (Visit 32) dosing date or Day 108 (if no Week 15 dosing)[b]
Week 16	Day 112	**Start:** 1 day after the Week 15 window ends
		End: the Week 16 (Visit 33) dosing date or Day 115 (if no Week 16 dosing)[b]
Week 17	Day 119	**Start:** 1 day after the Week 16 window ends
		End: the Week 17 (Visit 34) dosing date or Day 122 (if no Week 17 dosing)[b]
Week 18	Day 126	**Start:** 1 day after the Week 17 window ends
		End: the Week 18 (Visit 35) dosing date or Day 129 (if no Week 18 dosing)[b]
Week 19	Day 133	**Start:** 1 day after the Week 18 window ends
		End: the Week 19 (Visit 36) dosing date or Day 136 (if no Week 19 dosing)[b]
Week 20	Day 140	**Start:** 1 day after the Week 19 window ends
		End: the Week 20 (Visit 37) dosing date or Day 143 (if no Week 20 dosing)[b]
Week 21	Day 147	**Start:** 1 day after the Week 20 window ends
		End: the Week 21 (Visit 38) dosing date or Day 150 (if no Week 21 dosing)[b]
Week 22	Day 154	**Start:** 1 day after the Week 21 window ends
		End: the Week 22 (Visit 39) dosing date or Day 157 (if no Week 22 dosing)[b]
Week 23	Day 161	**Start:** 1 day after the Week 22 window ends
		End: the Week 23 (Visit 40) dosing date or Day 164 (if no Week 23 dosing)[b]
Week 24	Day 168	**Start:** 1 day after the Week 23 window ends
		End: the Week 24 (Visit 41) dosing date or Day 171 (if no Week 24 dosing)[b]
Week 25	Day 175	**Start:** 1 day after the Week 24 window ends
		End: the Week 25 (Visit 42) dosing date or Day 178 (if no Week 25 dosing)[b]
Week 26	Day 182	**Start:** 1 day after the Week 25 window ends
		End: the Week 26 (Visit 43) dosing date or Day 185 (if no Week 26 dosing)[b]
Week 27	Day 189	**Start:** 1 day after the Week 26 window ends

		End: the Week 27 (Visit 44) dosing date or Day 192 (if no Week 27 dosing)[b]
Week 28	Day 196	**Start:** 1 day after the Week 27 window ends
		End: the Week 28 (Visit 45) dosing date or Day 199 (if no Week 28 dosing)[b]
Week 29	Day 203	**Start:** 1 day after the Week 28 window ends
		End: the Week 29 (Visit 46) dosing date or Day 206 (if no Week 29 dosing)[b]
Week 30	Day 210	**Start:** 1 day after the Week 29 window ends
		End: the Week 30 (Visit 47) dosing date or Day 213 (if no Week 30 dosing)[b]
Week 31	Day 217	**Start:** 1 day after the Week 30 window ends
		End: the Week 31 (Visit 48) dosing date or Day 220 (if no Week 31 dosing)[b]
Week 32	Day 224	**Start:** 1 day after the Week 31 window ends
		End: the Week 32 (Visit 49) dosing date or Day 227 (if no Week 32 dosing)[b]
Week 33	Day 231	**Start:** 1 day after the Week 32 window ends
		End: the Week 33 (Visit 50) dosing date or Day 234 (if no Week 33 dosing)[b]
Week 34	Day 238	**Start:** 1 day after the Week 33 window ends
		End: the Week 34 (Visit 51) dosing date or Day 241 (if no Week 34 dosing)[b]
Week 35	Day 245	**Start:** 1 day after the Week 34 window ends
		End: the Week 35 (Visit 52) dosing date or Day 248 (if no Week 35 dosing)[b]
Week 36	Day 252	**Start:** 1 day after the Week 35 window ends
		End: the Week 36 (Visit 53) dosing date or Day 255 (if no Week 36 dosing)[b]
Week 37	Day 259	**Start:** 1 day after the Week 36 window ends
		End: the Week 37 (Visit 54) dosing date or Day 262 (if no Week 37 dosing)[b]
Week 38	Day 266	**Start:** 1 day after the Week 37 window ends
		End: the Week 38 (Visit 55) dosing date or Day 269 (if no Week 38 dosing)[b]
Week 39	Day 273	**Start:** 1 day after the Week 38 window ends
		End: the Week 39 (Visit 56) dosing date or Day 280 (if no Week 39 dosing)[b]
Week 40	Day 280	**Start:** 1 day after the Week 39 window ends
		End: the Week 40 (Visit 57) dosing date or Day 283 (if no Week 40

		dosing)[b]
Week 41	Day 287	**Start:** 1 day after the Week 40 window ends
		End: the Week 41 (Visit 58) dosing date or Day 290 (if no Week 41 dosing)[b]
Week 42	Day 294	**Start:** 1 day after the Week 41 window ends
		End: the Week 42 (Visit 59) dosing date or Day 297 (if no Week 42 dosing)[b]
Week 43	Day 301	**Start:** 1 day after the Week 42 window ends
		End: the Week 43 (Visit 60) dosing date or Day 304 (if no Week 43 dosing)[b]
Week 44	Day 308	**Start:** 1 day after the Week 43 window ends
		End: the Week 44 (Visit 61) dosing date or Day 311 (if no Week 44 dosing)[b]
Week 45	Day 315	**Start:** 1 day after the Week 44 window ends
		End: the Week 45 (Visit 62) dosing date or Day 318 (if no Week 45 dosing)[b]
Week 46	Day 322	**Start:** 1 day after the Week 45 window ends
		End: the Week 46 (Visit 63) dosing date or Day 235 (if no Week 46 dosing)[b]
Week 47	Day 329	**Start:** 1 day after the Week 46 window ends
		End: the Week 47 (Visit 64) dosing date or Day 332 (if no Week 47 dosing)[b]
Week 48	Day 336	**Start:** 1 day after the Week 47 window ends
		End: the Week 48 (Visit 65) dosing date or Day 339 (if no Week 48 dosing)[b]
Week 52	Day 364	**Start:** 1 day after the Week 48 window ends
		End: End of DBTP (Visit 69, the study exit date of DBTP)
Safety Follow-up Period (SFP)		
Week 54	Day 378	Within the safety follow-up phase (Visit 70)
End of SFP: Final or termination visit during SFP		

[a] Day 0 is the date of the first dose of study treatment; baseline is defined as the last non-missing observations prior to first dose of study treatment for the given treatment period.

[b] Dosing visit is the nominal visit reported in CRF. During the OLTP a patient is scheduled to receive the 1st dose on day 0 (Visit 1), the 2nd dose at week 1, and will be weekly administered until week 16. If a patient skipped a scheduled re-treatment dosing at a week, the dosing date will be treated as missing for that week. During the DBTP a patient is schedule to receive the 1st dose on day 0 (Visit 17), the 2nd dose at week 1, and will be weekly administered until relapse criteria are met or for up to 52 weeks (Visit 69) or study termination.

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 69/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 pre-dose 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 post-dose value for that date. For multiple MADRS assessments on the same date for Visit 69/ET, the last MADRS assessment prior to Visit 69/ET on that date will be taken as the value for that date.

[redacted]

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 ≥ 18 at 2 consecutive visits, the relapse date is defined as the assessment date of the first visit of the 2 consecutive assessments.

14.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing 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.

14.5 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.

14.6 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG 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.

14.7 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.

14.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including background ADT, incomplete (i.e. 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.

14.8.1 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.

14.8.2 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, *December 31* 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, *January 1* 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.

[redacted]

14.10 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.

14.11 STRATIFICATION HANDLING CONVENTIONS

Stratification is not being implemented in this study.

15.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Analyses and output have been limited to those needed to support the writing of an abbreviated CSR. The major changes to the analyses specified in the original protocol, dated 02MAY2018, are as follows:

- The primary efficacy analysis will be performed via the Kaplan-Meier curve for the cumulative distribution function of time to relapse for each treatment group.

[redacted]

[redacted]