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Study ID: RAP-MD-32

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

Statistical Analysis Plan Amendment 1 Date: 22 May 2019

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RAP-MD-32

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

STATISTICAL ANALYSIS PLAN AMENDMENT

Original SAP Date: February 12, 2019

Amendment 1 Date: May 22, 2019

1.0 TABLE OF CONTENTS

LIST OF TABLES

[redacted]

LIST OF FIGURES

2.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
[redacted]	[redacted]
DBTP	double-blind treatment period
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DxV	Diagnostic Validation
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
[redacted]	[redacted]
ET	early termination
ICF	informed consent form
IP	investigational product
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

MMRM	mixed-effects model for repeated measures
[redacted]	[redacted]
[redacted]	[redacted]
PCS	potentially clinically significant
PID	patient identification
PK	pharmacokinetic
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]
[redacted]	[redacted]
SE	Standard Error
SFUP	Safety Follow-up Period
SI	*Le Système International d'Unités* (International System of Units)
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

3.0 HISTORY OF CHANGE

Section No.	Section Name	Description
General Notes		The following changes are implemented in the statistical sections of protocol amendment 1 (dated May 22, 2019): 1. The gatekeeping serial testing procedure was replaced by the graphical testing procedure to adjust for multiple comparisons in the primary and secondary efficacy parameters for both rapastinel doses versus placebo. The section of "interim analysis" was added based on the proposal agreed by the FDA (response dated dd May 2019). 2. The section of "determination of sample size" was revised to reflect the associated changes in the significance level and associated power for the final primary efficacy analyses due to the addition of interim analysis. These changes are now implemented in Sections 10.2 (KEY SECONDARY EFFICACY PARAMETERS), 13.0 (INTERIM ANALYSIS) and 14.0 (DETERMINATION OF SAMPLE SIZE) of this SAP amendment. In addition, other revisions were documented in this history of change and implemented in this SAP amendment.
10.2	KEY SECONDARY EFFICACY PARAMETERS	The gatekeeping testing procedure was replaced by the graphical testing procedure to adjust for multiple comparisons in the primary and secondary efficacy parameters for both rapastinel doses versus placebo.
11.3	VITAL SIGNS	The orthostatic hypotension was specified to be summarized for pre-dose, post-dose and other visits without IP administration separately for the DBTP.
13.0	INTERIM ANALYSIS	The blinded sample-size re-estimation was replaced by an unblinded interim analysis in order to identify early signs of futility.
14.0	DETERMINATION OF SAMPLE SIZE	The sample size estimation was revised to reflect a reduced significance level (from 0.05% to 0.049%) and associated power for the final primary efficacy analyses due to the addition of interim analysis.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4.0 INTRODUCTION

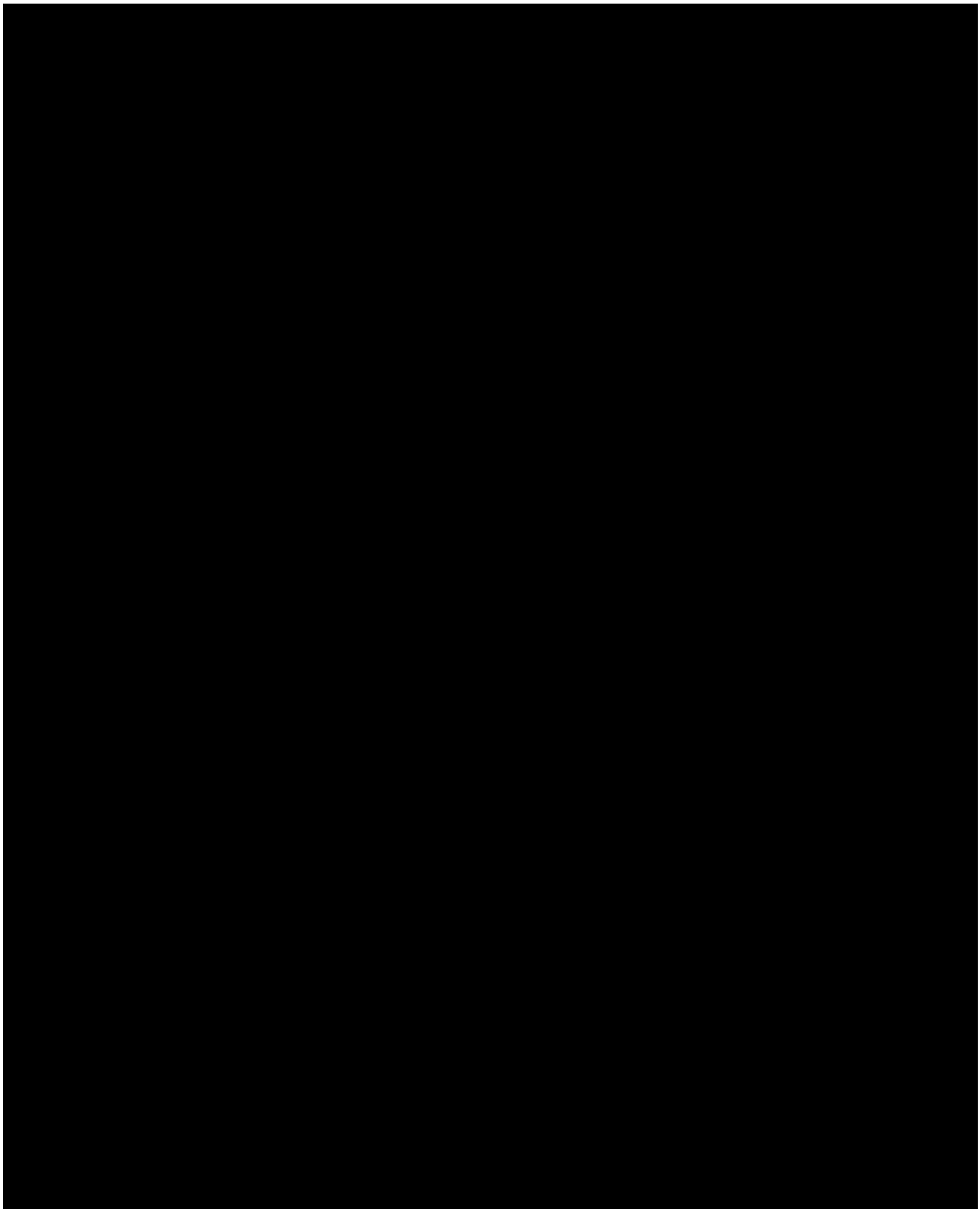
This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined in the Study RAP-MD-32 protocol amendment 1 (dated May 22, 2019). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic, pharmacodynamic and/or health economics and outcomes research data (if applicable) will be prepared separately.

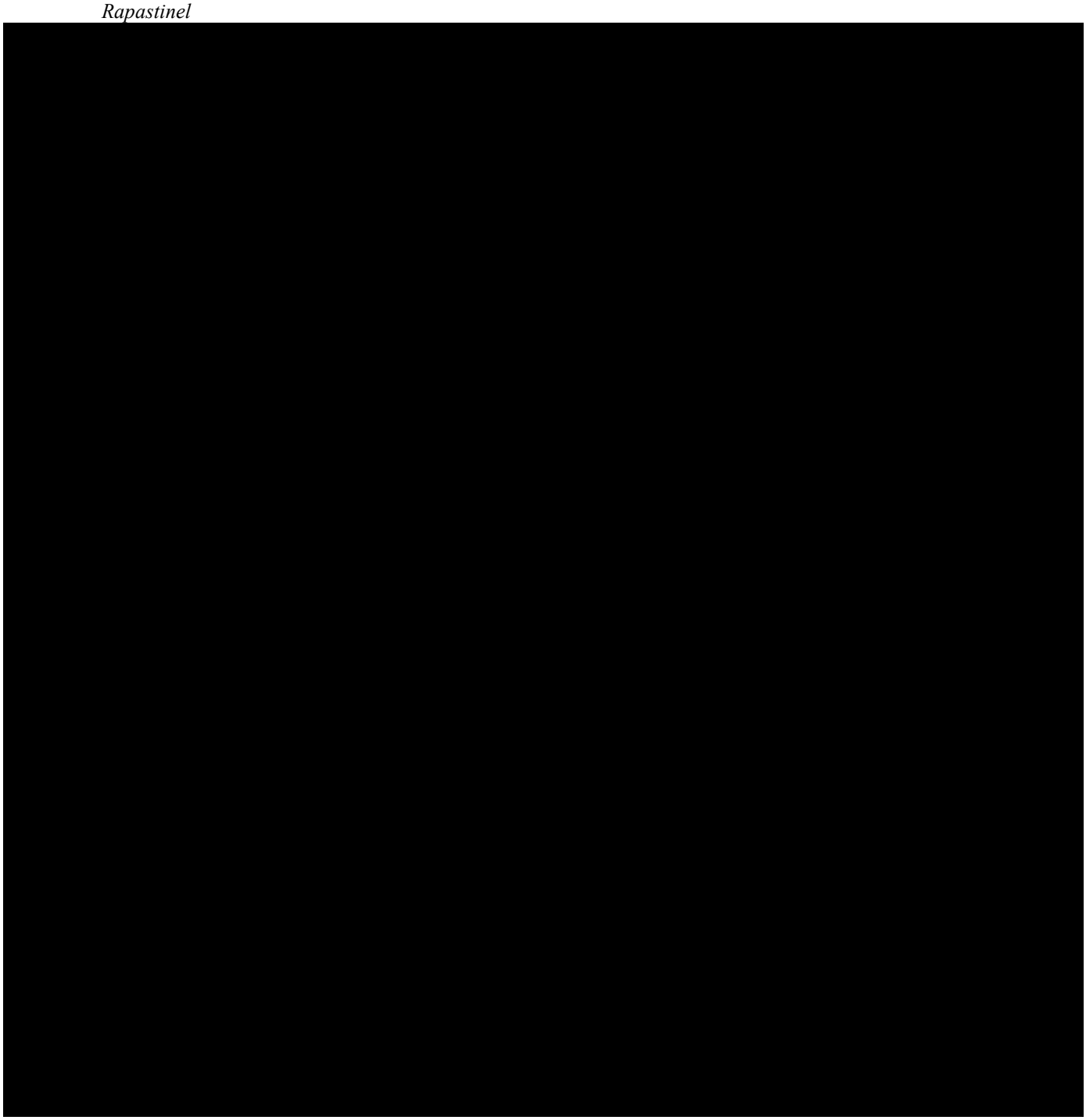
Study RAP-MD-32 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients 18 to 75 years of age who meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder (MDD). The symptoms and severity of MDD will be assessed based on their Montgomery-Åsberg Depression Rating Scale (MADRS) and Clinical [redacted]. All patients will be treatment naive (defined as those who have not received antidepressant, or have received antidepressant but not meeting adequate dose or duration criteria per the Antidepressant Treatment Response Questionnaire [ATRQ]) in the present episode or inadequate response (<50% reduction in depressive symptoms) to 1 to 3 antidepressant therapies (ADTs) given at adequate doses for ≥ 4 weeks during the present episode.

The study will include a total of 10 visits and will be approximately 10 weeks in duration:

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

Signed informed consent from the patient or the patient's legally authorized representative will be obtained before any study-related procedures are begun. Patients will wash out any previous ADT and/or prohibited medications during the screening period. Patients meeting the eligibility criteria at the end of Visit 2 will be randomized in a ratio of 1:1:1 to one of the three treatment arms: rapastinel 900 mg IV weekly, rapastinel 450 mg IV weekly, or placebo IV weekly. The double-blind treatment period (DBTP) starts with the first dose of study treatment. Upon completion of the DBTP, patients may be eligible to enter the extension study. Patients who do not enter the extension study will enter a 2-week safety follow-up period. Efficacy and safety assessments will be conducted at the clinic 1 day following the treatment day in the 1st week and at the ends of weeks 1, 2, 3, 4, 5 and 6 of the DBTP. Patients prematurely discontinuing from the study, regardless of cause, will be seen for a final evaluation. The schedule of evaluations for Study RAP-MD-32 is presented in Table 4–1.





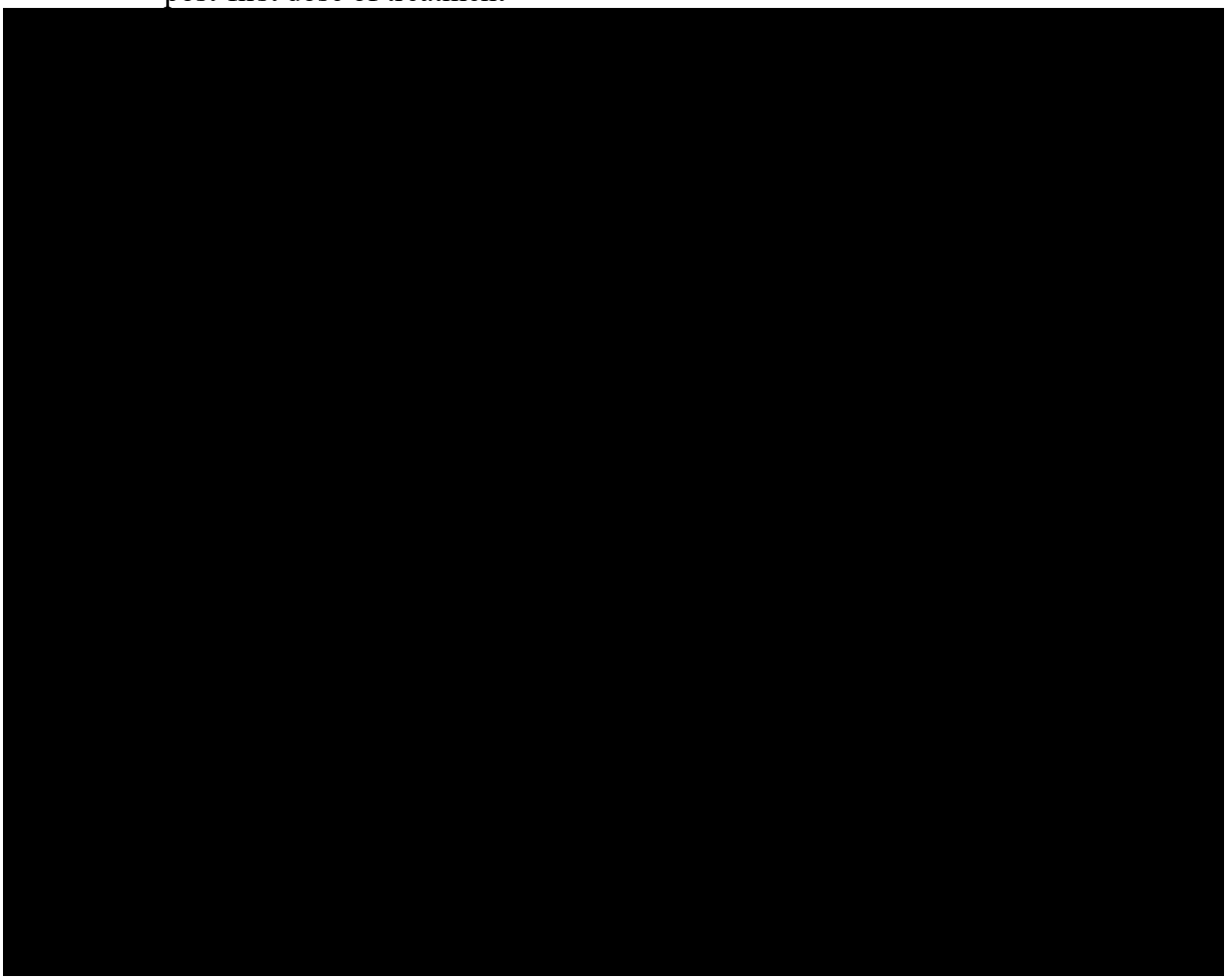
5.0 OBJECTIVES

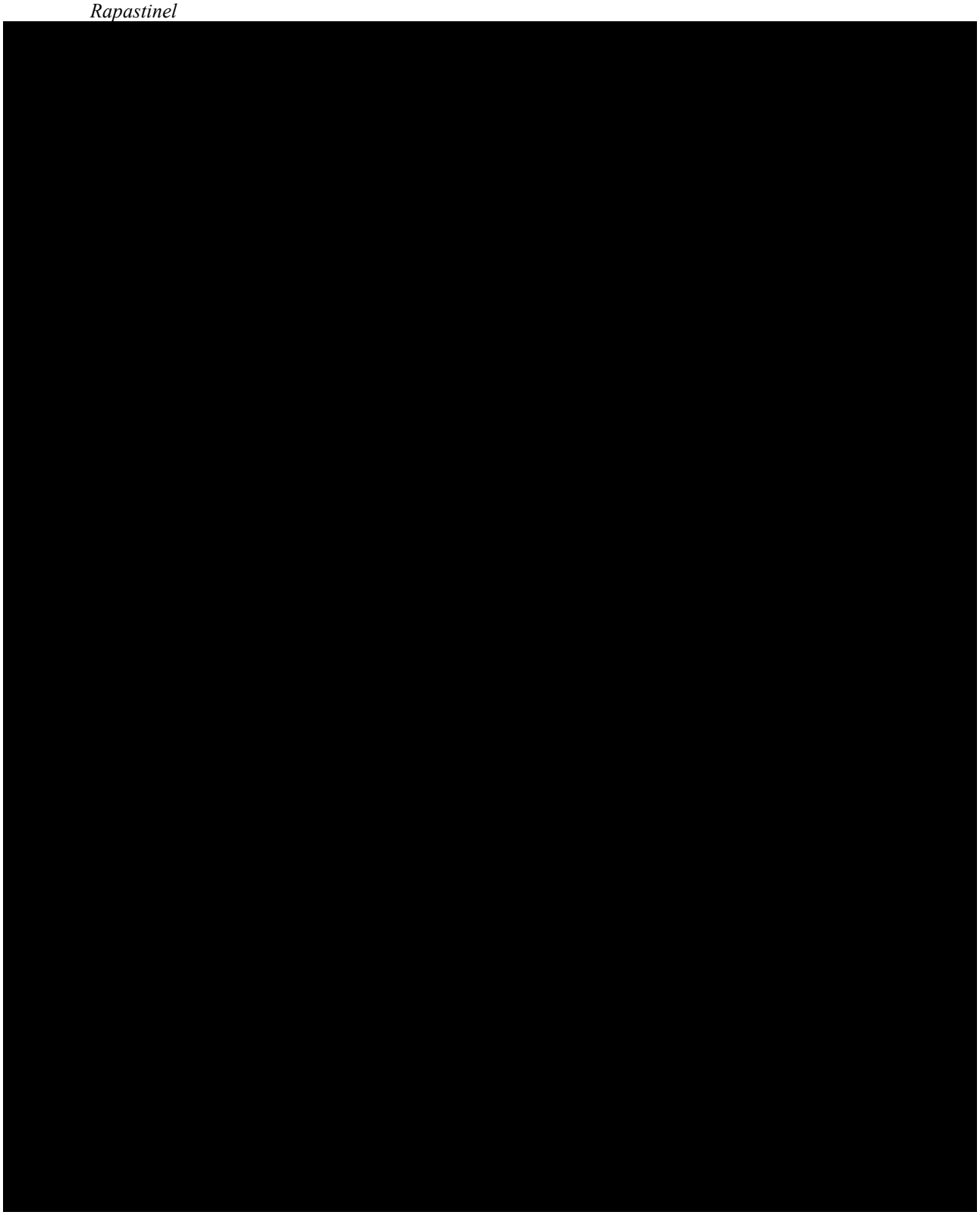
The objectives of this study are to evaluate the efficacy, safety, and tolerability of rapastinel as monotherapy treatment in patients with MDD.

Efficacy Objectives

- Primary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo and rapastinel (900 mg IV) versus placebo in the treatment of MDD, as measured by the change from baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score at end of treatment (end of Week 6)

- Key secondary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV) versus placebo and rapastinel (900 mg IV) versus placebo in the treatment of MDD, as measured by the change from baseline MADRS total score at 1 day post-first dose of treatment





6.0 PATIENT POPULATIONS

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

6.1 SAFETY POPULATION

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

6.2 MODIFIED INTENT-TO-TREAT POPULATION

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

7.0 PATIENT DISPOSITION

The number and percentage of patients in the mITT and Safety populations will be summarized by treatment group and by study center respectively.

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

7.1 PROTOCOL DEVIATIONS

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including the classification of significance vs. non-significance. The number and percentage of patients with significant protocol deviations will be summarized by treatment group for all randomized patients. A listing for all significant protocol deviations will be provided.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; race; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group for the mITT population.

Medical and surgical histories, and psychiatric history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by treatment group for the Safety Population.

Prior medication is defined as any medication taken before the date of the first dose of randomized IP. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of randomized IP. Concomitant medications started after the last visit of the DBTP will not be included in the summaries. If any medication is taken before the date of the first dose of randomized IP and continues after initiation of randomized IP, it will be considered as both a prior and concomitant medication. The *World Health Organization (WHO) Drug Dictionary Enhanced* will be used to code medications.

Both prior and concomitant medication use, and previous treatment with psychotropic medication will be summarized by treatment group and Anatomical Therapeutic Chemical (ATC) code for the Safety Population.

Nondrug psychiatric treatment will be summarized by treatment group for the Safety Population.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

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

IV administration notes including site reaction at placement of IV, reaction to adhesive, infusion interruption, failure of administration device, perceptual disturbances or other conditions based on mental status assessment are collected. For each item, the number and percentage of patients who had a 'yes' response will be summarized by treatment group and visit for the Safety Population.

Duration of follow-up during the DBTP will be summarized in terms of treatment duration, calculated as the number of days from the date of the first dose of randomized IP received to the date of the last dose received, inclusive. Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented by treatment group.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for the DBTP is defined as the total number of IV doses actually received by a patient during that period divided by the number of IP doses that were expected to be received during the period, multiplied by 100, regardless if a patient discontinued from the study. The number of expected doses for a patient is defined as the number of the days from the first dose to the exit visit divided by 7 and rounded up the next integer with the upper limit of 6.

10.0 EFFICACY ANALYSES

All efficacy analyses will be based on the mITT Population, unless stated otherwise. The baseline for each specific efficacy endpoint is defined as the last non-missing measurement prior to the first dose of randomized IP. All statistical hypothesis tests will be performed at the 2-sided significance level of 5% for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

For efficacy analyses in which pooled study center is a factor, a small center will be defined as a center with < 2 patients in ≥ 1 treatment group in the mITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes ≥ 2 mITT patients within the center. Pooling will be done using the following algorithm:

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

The efficacy analyses using the mITT population will be performed based on the treatment to which the patient is randomized regardless of the actual treatment received.

The efficacy analyses of MADRS assessments will be based on the rater-administered MADRS.

10.1 PRIMARY EFFICACY PARAMETER

The primary efficacy parameter will be the change from baseline in MADRS total score at the end of treatment (end of Week 6). The MADRS contains 10 items that assess depression, with scores for each item ranging from 0 (absence of symptoms) to 6 (symptoms of maximum severity). The MADRS total score is the sum of the 10 individual items. If more than 2 items are missing, the total score will be set to missing. If there are multiple assessments of MADRS total score for the same day visit of a patient, only the last assessment will be used in the analysis.

The primary parameter will be analyzed using a mixed model for repeated measures (MMRM) with terms for treatment, pooled study center, visit (Day 1 visit and the weekly visits from Week 1 to Week 6), baseline, and treatment-by-visit and baseline-by-visit interactions. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward et al, 1997). This analysis will only use the observed postbaseline scores without imputation of missing values. The treatment differences for rapastinel 450 mg versus placebo and rapastinel 900 mg versus placebo will be estimated and reported along with the corresponding 95% CIs and p-values.

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

To assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption, a sensitivity analysis will be conducted.

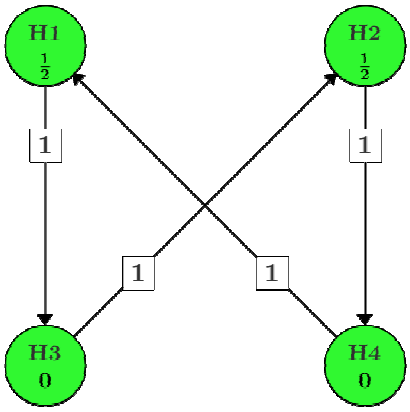
The sensitivity analysis will use a pattern-mixture model based on non-future dependent missing value restrictions (Kenward et al, 2003). The pattern for the pattern-mixture model will be defined by the patient's last visit with observed value. The observed MADRS total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The missing values will be imputed under the assumption that the distribution of the missing observations differs from the observed only by a shift parameter value Δ. The dataset with observed and imputed values will be analyzed using the same model as the primary analysis for between-treatment group comparisons at the end of the treatment. The imputation of missing values and the analysis will be performed 20 times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values of Δ will be selected as 0 to 8.

10.2 KEY SECONDARY EFFICACY PARAMETERS

The key secondary efficacy parameter will be the change from baseline in MADRS total score at 1 day after first dose of randomized IP. The key secondary efficacy parameter will be analyzed in the same MMRM model for the primary efficacy parameter. The treatment differences for rapastinel 450 mg versus placebo and rapastinel 900 mg versus placebo will be estimated and reported along with the corresponding 95% CIs and p-values.

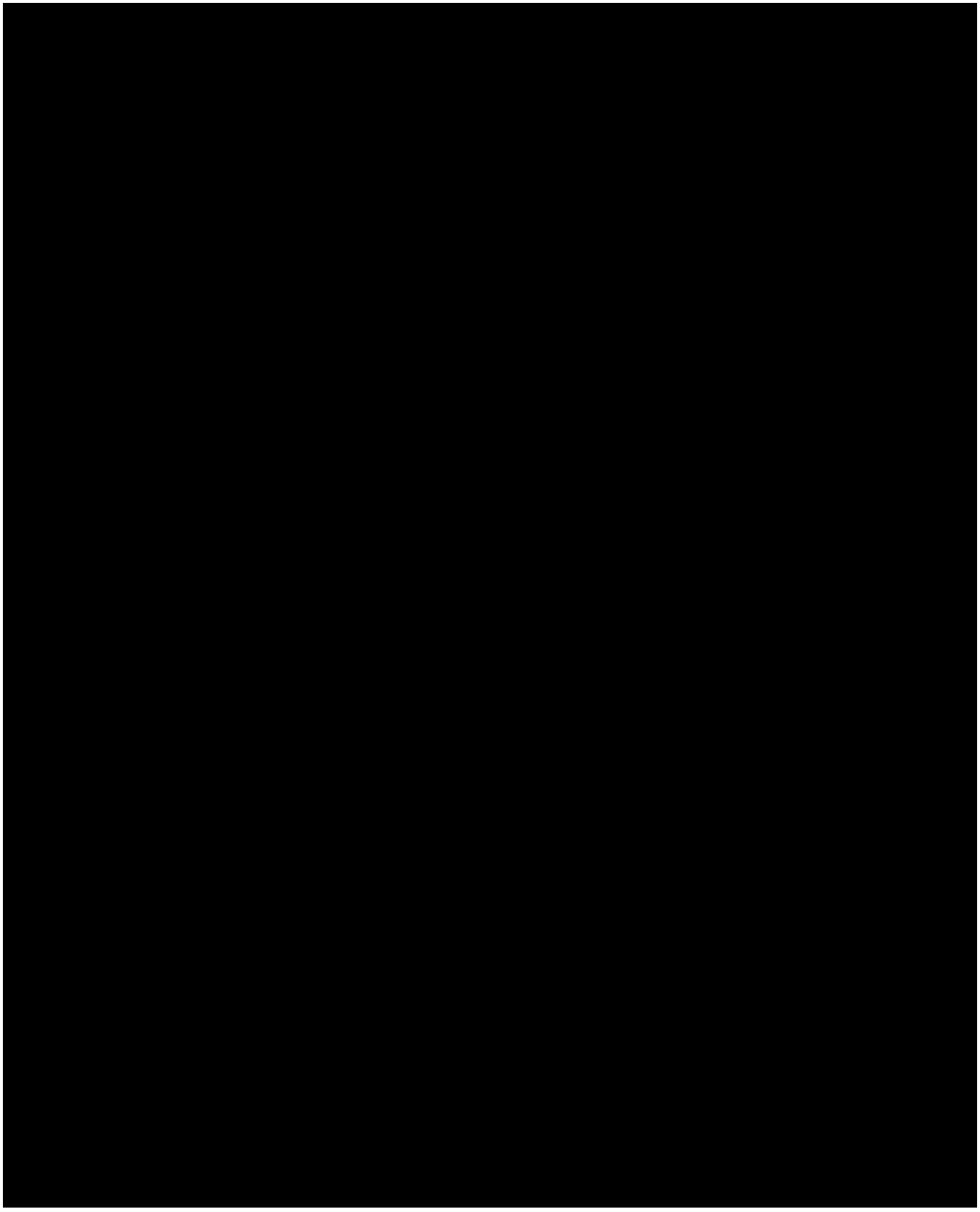
Let H1 and H2 represent the treatment effect comparing rapastinel 450 mg versus placebo and rapastinel 900 mg versus placebo in regards to the primary efficacy parameter of change from baseline in MADRS total score at end of treatment (end of Week 6), respectively; and let H3 and H4 represent the treatment effect comparing rapastinel 450 mg versus placebo and rapastinel 900 mg versus placebo in regards to the secondary efficacy parameter of change from baseline in MADRS total score at 1 day after first dose of treatment. The graphical procedure displayed in Figure 10-1 will be employed to control the overall familywise error rate at $\alpha = 0.049$.

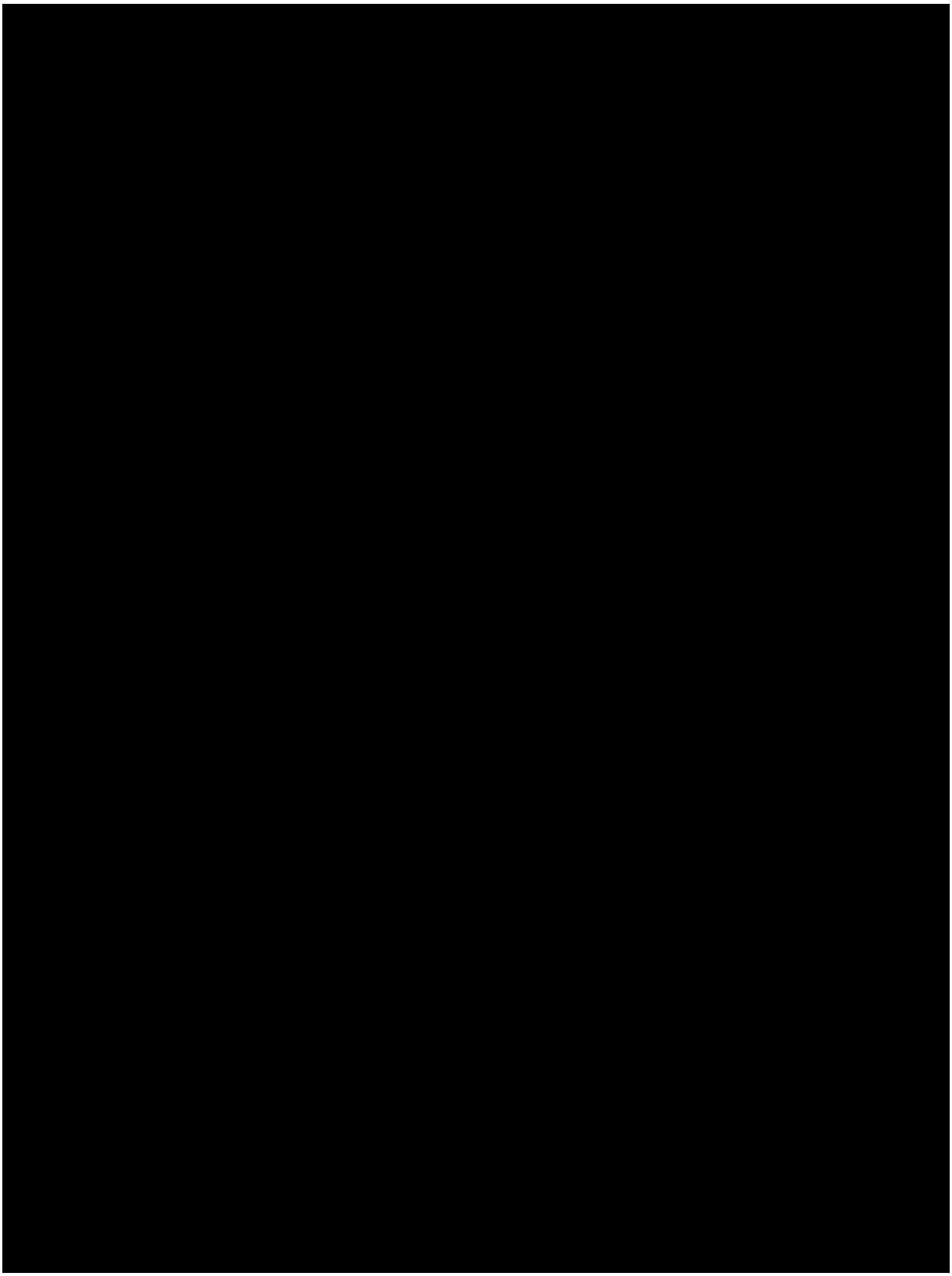
Figure 10-1 **Graphical Testing Procedure**



Specifically, H1 and H2 will be tested at $\alpha = 0.0245$ separately. If H1 is rejected, H3 will then be tested at $\alpha = 0.0245$. If H2 is rejected, H4 will then be tested at $\alpha = 0.0245$. If H3 is rejected but H2 is not rejected, H2 will be further tested at $\alpha = 0.049$. If H2 is rejected at $\alpha = 0.049$, H4 will be further tested at $\alpha = 0.049$. Similarly, if H4 is rejected but H1 is not rejected, H1 will be further tested at $\alpha = 0.049$. If H1 is rejected at $\alpha = 0.049$, H3 will be further tested at $\alpha = 0.049$.

[redacted]





[redacted]

[redacted]

[redacted]

11.1 ADVERSE EVENTS

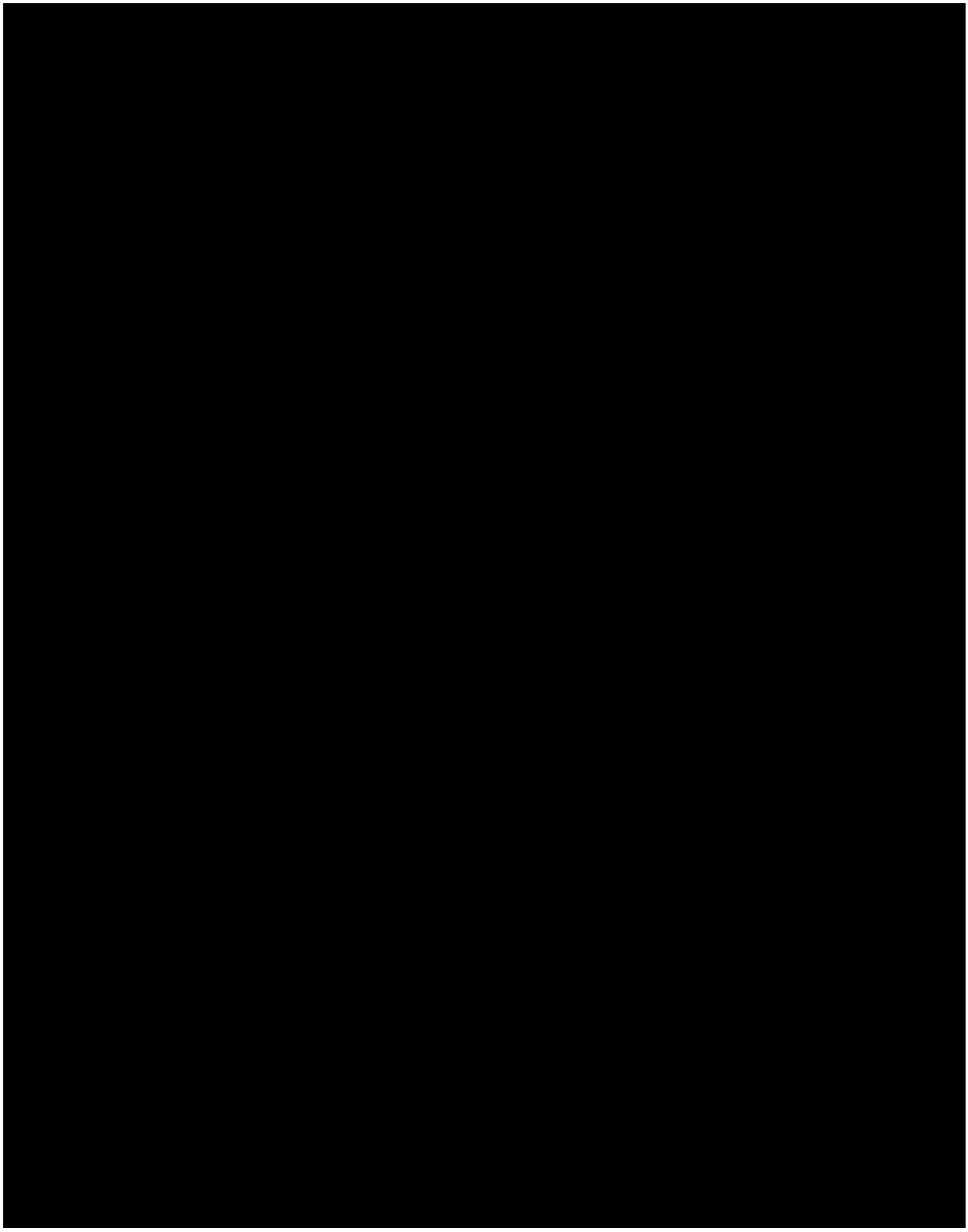
Adverse events will be coded using the *Medical Dictionary for Regulatory Activities* and summarized separately for the DBTP and SFUP.

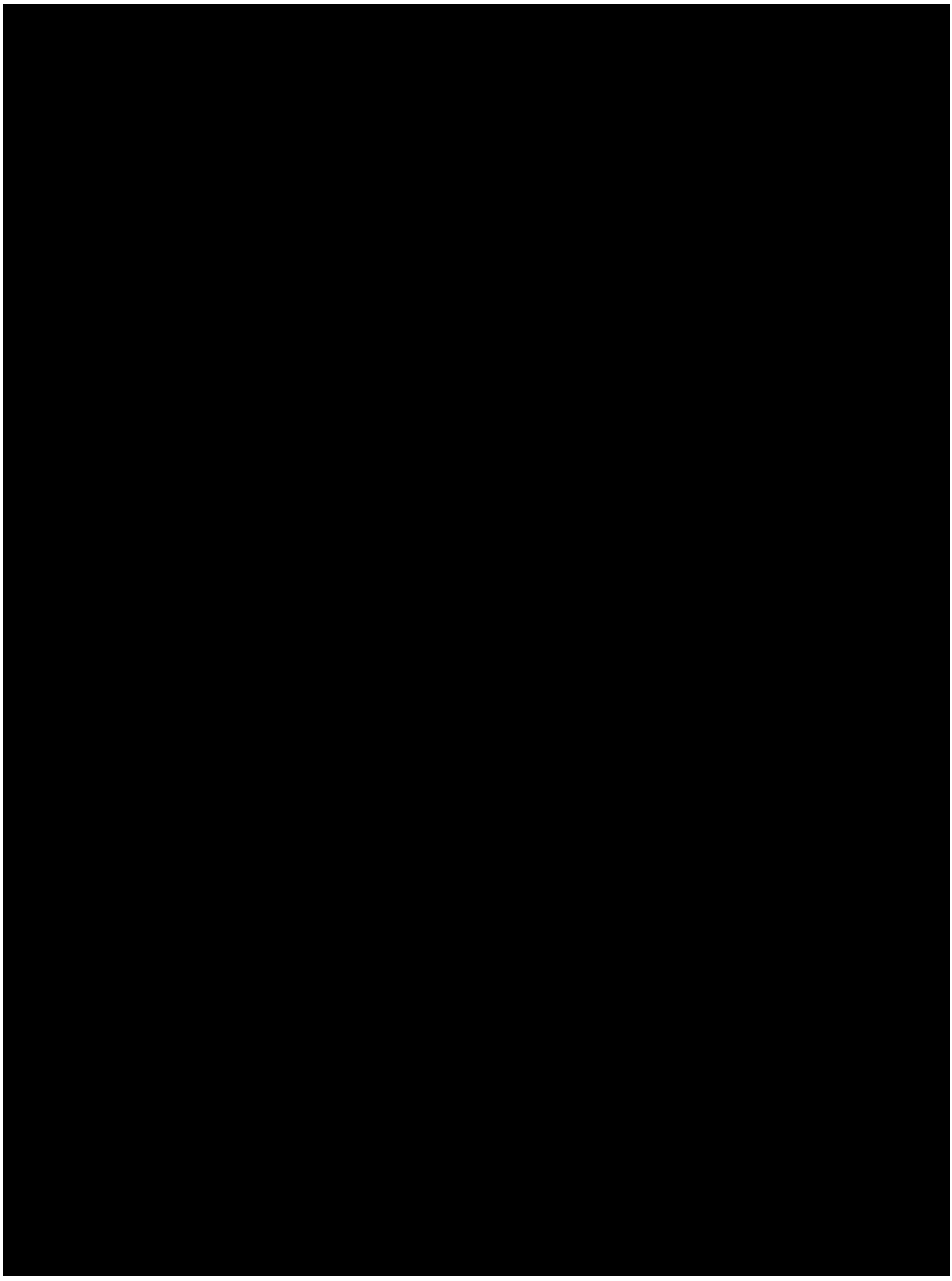
An AE (classified by preferred term) will be considered a treatment-emergent adverse event (TEAE) during the DBTP if it was present after the first dose of IP, or was present before the date of the first dose of IP and increased in severity or became serious after the first dose of IP. If more than 1 AE was reported before the first dose of IP and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the DBTP or safety follow-up period. For patients who complete this study and enters the RAP-MD-33 study, an AE that occurs on or after the last day of the DBTP will not be considered as a TEAE. For patients who do not enter the RAP-MD-33 study, an AE that occurs more than 30 days after the date of the last dose of IP will not be considered as a TEAE.

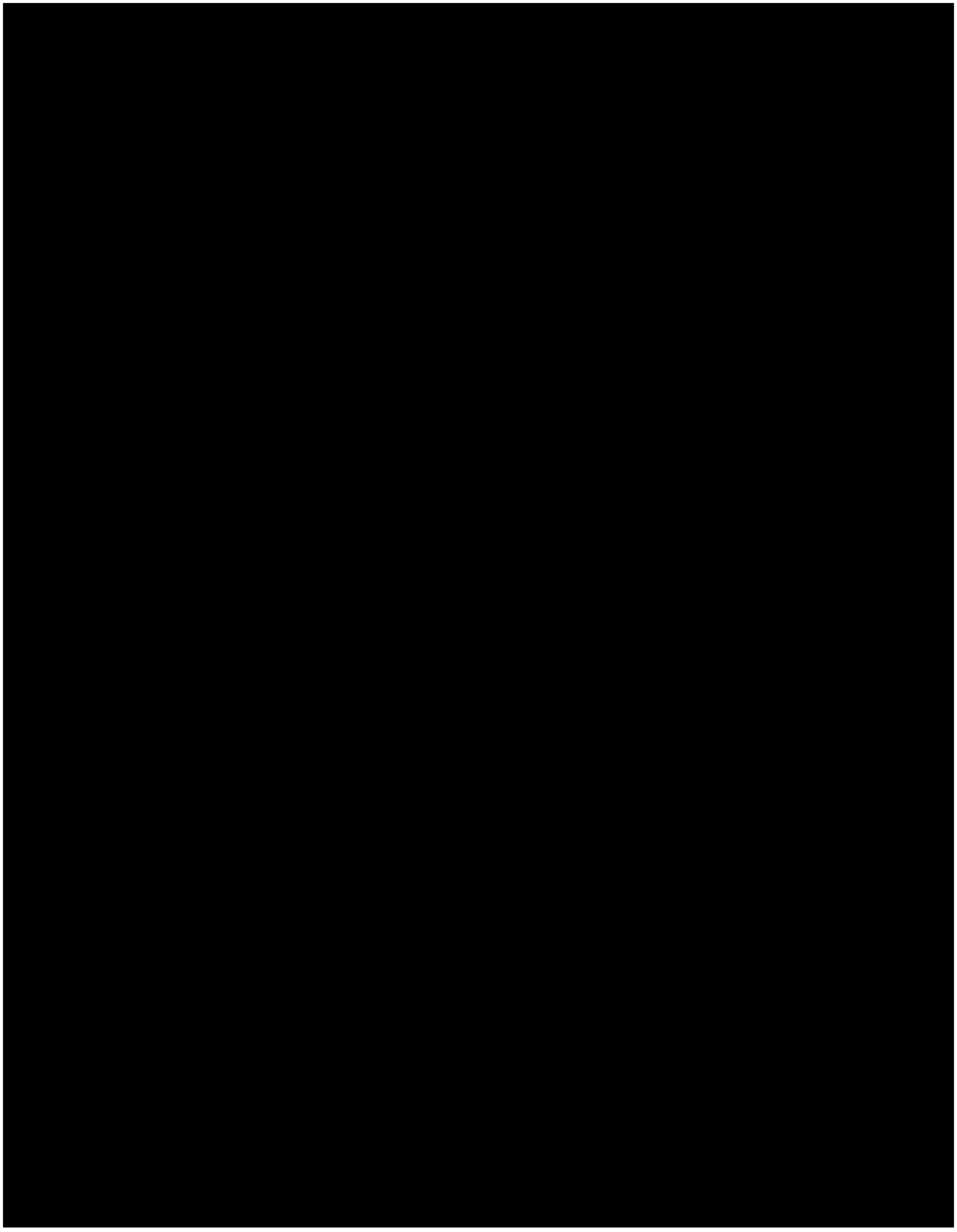
The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term, and further categorized by severity and causal relationship to the IP. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

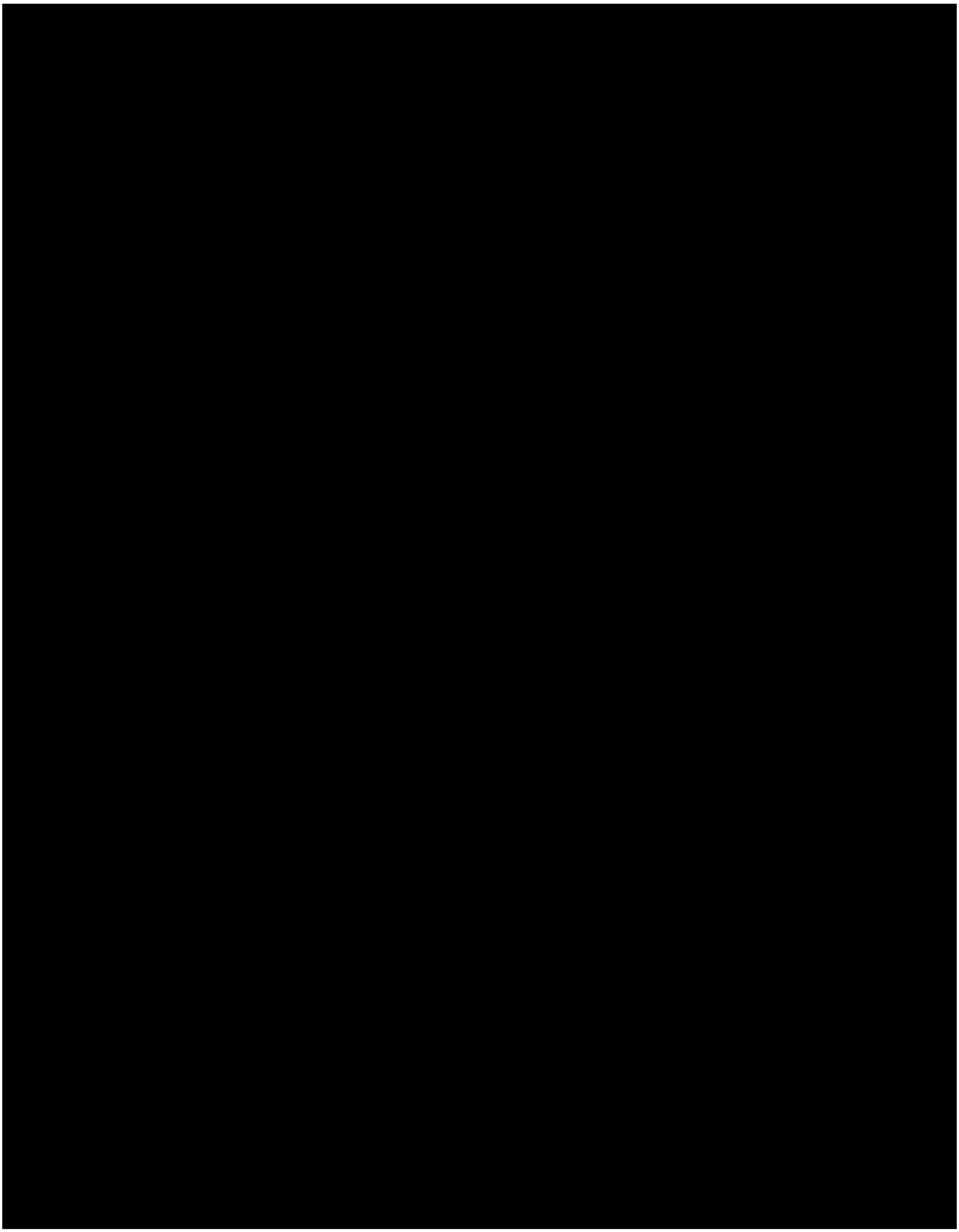
The incidence of common (≥ 2% of patients in any treatment group) TEAEs will be summarized by preferred term and treatment group and sorted by decreasing frequency for the test treatment.

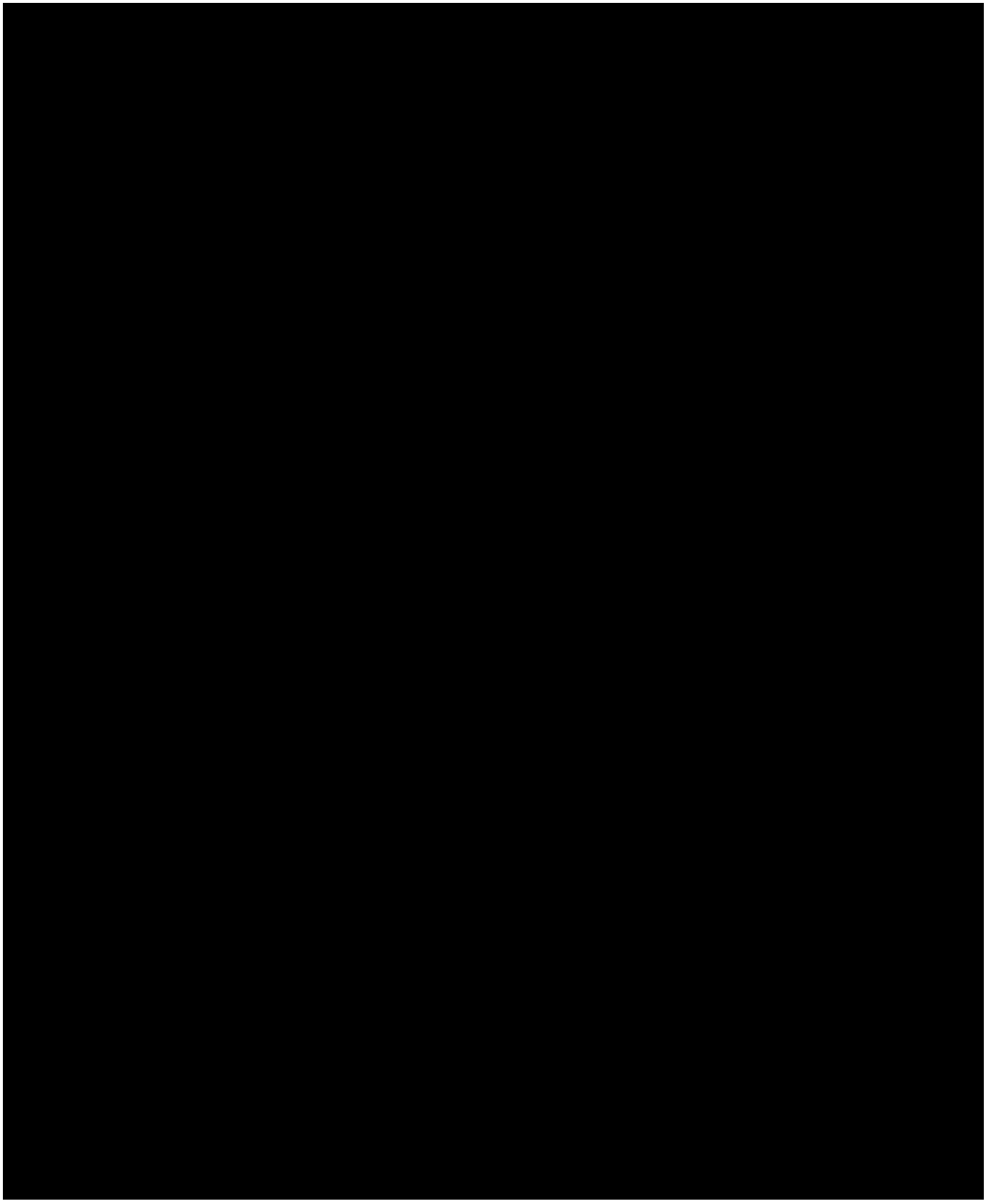
Overall summaries of AEs will be provided on a per-patient basis for categories of all TEAEs, treatment-related TEAEs, death, Treatment-emergent serious AEs (TESAEs), and TEAEs leading to study discontinuation.











13.0 INTERIM ANALYSIS

An unblinded interim analysis will be conducted in order to identify early signs of futility. Separate Statistical Analysis Group and Data Review Committee will be established to conduct the unblinded interim analysis, review the unblinded results, and make recommendations regarding the continuation of the study. In order to maintain the scientific reliability of possible final results and guard from introducing any potential bias into the conduct of the study and/or analysis of its results, individuals in these 2 groups will not be involved in any operational aspect of the study. Additionally, to adjust for multiple comparison issues caused by having several looks at the data, the Bonferroni method will be applied to split the overall Type I Error between the interim and final analysis ($\alpha = 0.001$ and 0.049 two-sided, respectively) in order to further protect the integrity of the study. Further details of the unblinded interim analysis, in particular, its scope, the processes put in place to maintain study integrity, team structures, and responsibilities, are documented in the Data Review Committee Charter.

14.0 DETERMINATION OF SAMPLE SIZE

This study initially planned to randomize approximately 690 patients to the rapastinel 450 mg, rapastinel 900 mg, and placebo groups in a 1:1:1 ratio. The primary efficacy endpoint is the change from baseline in the MADRS total score at the end of Week 6. Assuming the SD is 10 points, within-patient correlation is 0.6, and dropout rate over 6 weeks is 20%, a sample size of 230 patients per treatment group will provide 91% power to detect a difference of 3.5 points for each rapastinel dose versus placebo at a 2-sided significance level of 4.9% originally adjusting for multiple comparisons of 2 rapastinel groups with placebo across the primary and secondary endpoints by using a graphical testing procedure.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version [redacted]

16.0 DATA HANDLING CONVENTIONS

16.1 SUMMARY STATISTICS

The following statistical summaries will be presented for each type of data. Further details are specified in the tables, figures, and listings shells.

- Continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation (SD), median, Q1 and Q3, 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, 1st quartile and 3rd quartile using the Kaplan Meier estimate as well as a 95% CI for the median

16.2 VISIT TIME WINDOWS

Table 16.2-1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16.2–1. Visit Time Windows

Derived Visit	Target Day	Analysis Visit Window
Baseline		<= Day 0 [a] and before the first study IP
Double Blind Treatment Period (DBTP)		
Post First Study IP[c]	Day 0	Post the first study IP on Day 0
Day 1	Day 1	Day 1
Day 7	Day 7	**Start:** Day 2
		End: the Day 7 dosing (Visit 4) 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 5) 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 6) 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 7) dosing date or Day 31 (if no Week 4 dosing)[b]

Table 16.2–1. Visit Time Windows

Week 5	Day 35	**Start:** 1 day after the Week 4 window ends
		End: the Week 5 (Visit 8) 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: End of DBTP (the study exit date of DBTP)
Safety Follow-up Period (SFP)		
Week 8	Day 56	Within the safety follow-up phase
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.

[b] Dosing visit is the nominal visit reported in CRF. A patient is scheduled to receive the 1st dose on day 0, the 2nd dose at week 1, and will be weekly administered until week 5. If a patient skipped a scheduled re-treatment dosing at a week, the dosing date will be treated as missing for that week.

[redacted]

If a patient has 2 or more non-missing assessment within the same window, the assessment closest to the target day will be used for analysis; if the 2 closet assessments are equidistant to the target day, the later one will be used for analysis.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline. 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.

16.4 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, 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 study treatment, an intensity 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.

16.5 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

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

16.6 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., 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 study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *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 start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment 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 study treatment 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 study treatment, 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 study treatment 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 study treatment, 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 study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

16.7 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, incomplete (ie, partly 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.

16.7.1 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 study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *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 start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment 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 study treatment 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 study treatment, 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 study treatment 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 study treatment, the first day of the month will be assigned to the missing day

16.7.2 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 date of the last dose of study treatment is missing, impute it as descripted in Section 16.4. If the imputed stop date is before the start date (imputed or nonimputed 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 last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *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 last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, 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 last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

[redacted]

17.0 REFERENCES

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