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

Statistical Analysis Plan: 25 Jan 2019

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RAP-MD-02

A Randomized, Double-blind, Placebo-controlled, Multicenter Study of Rapastinel as Adjunctive Therapy in Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

Final Version: 25JAN2019

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[redacted]

1.0 LIST OF ABBREVIATIONS

AE	adverse event
ADT	antidepressant therapy
ATRQ	Antidepressant Treatment Response Questionnaire
[redacted]	
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
[redacted]	
DB	double-blind
DxV	Diagnostic Validation
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
[redacted]	
ET	early termination
ICF	informed consent form
IP	investigational product
IWRS	Interactive Web Response System
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
mITT	Modified Intent to Treat
MMRM	mixed-effects- model for repeated measures
PCS	potentially clinically significant
PID	patient identification
PDMT	protocol deviation management tool
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

SAS	Statistical Analysis System
[redacted]	
SD	standard deviation
[redacted]	
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

2.0 INTRODUCTION

Study RAP-MD-02 is a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study in patients who are 18 to 65 years of age, meet DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for Major Depressive Disorder (MDD), have a minimum score of 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS), and have an ongoing inadequate response to antidepressant therapy (ADT).

The study will consist of up to a 14-day screening and washout period followed by a 1-week placebo lead-in period, a 2-week randomized treatment period, and then a 1 week of safety follow-up period. Both the placebo lead-in period and randomized treatment period will be conducted in a double-blind (DB) manner. Consequently, the combination of these two periods is referred to as the DB treatment period.

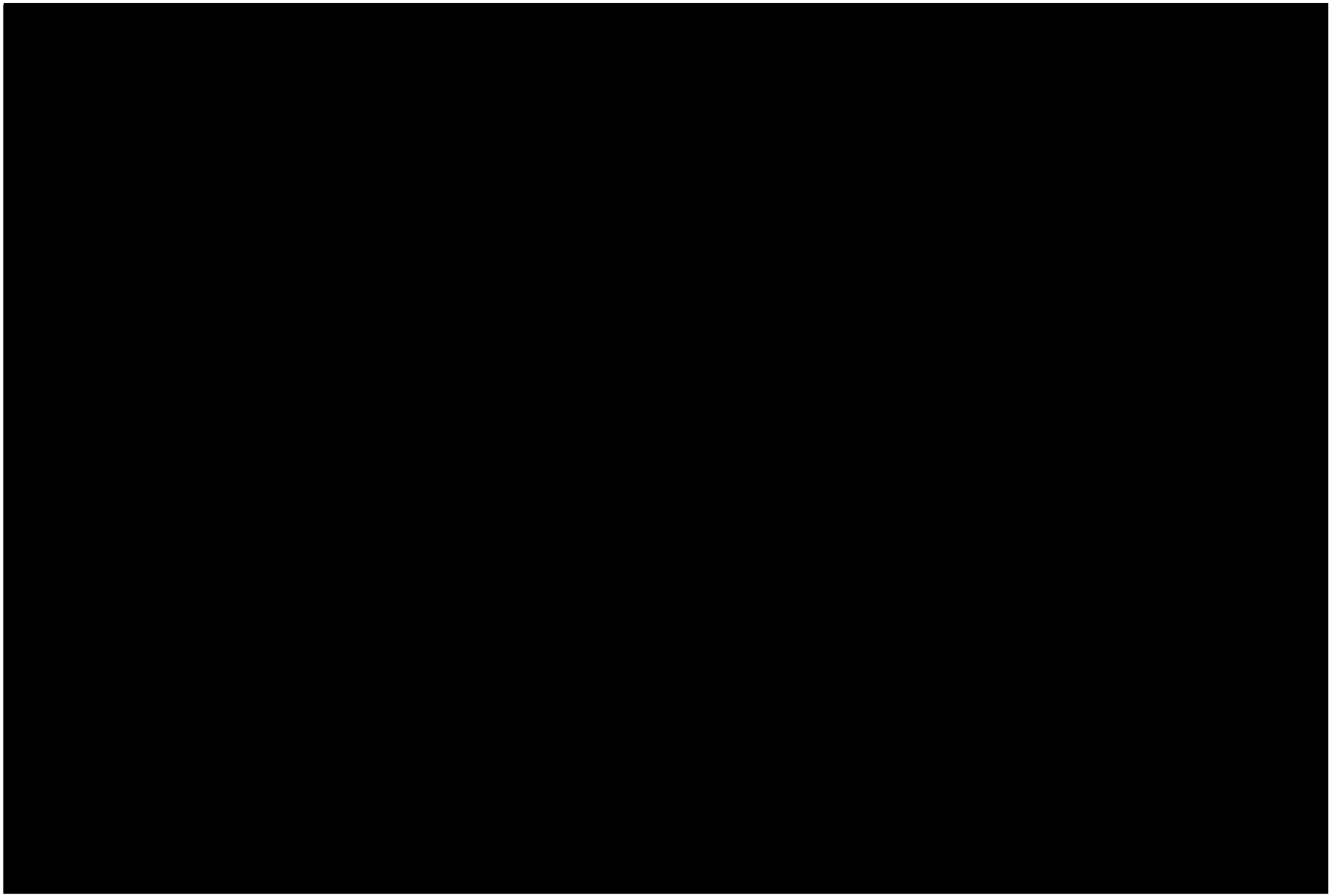
Signed informed consent from the patient or the patient's legally authorized representative will be obtained before any study-related procedures are begun. At the end of the screening period, patients meeting the eligibility criteria for this study will be enrolled into a 1-week, double-blind, placebo lead-in period intended to identify placebo responders. Placebo responders will be defined by meeting at least 1 of the following criteria at any time point during the 1-week double-blind placebo lead-in:

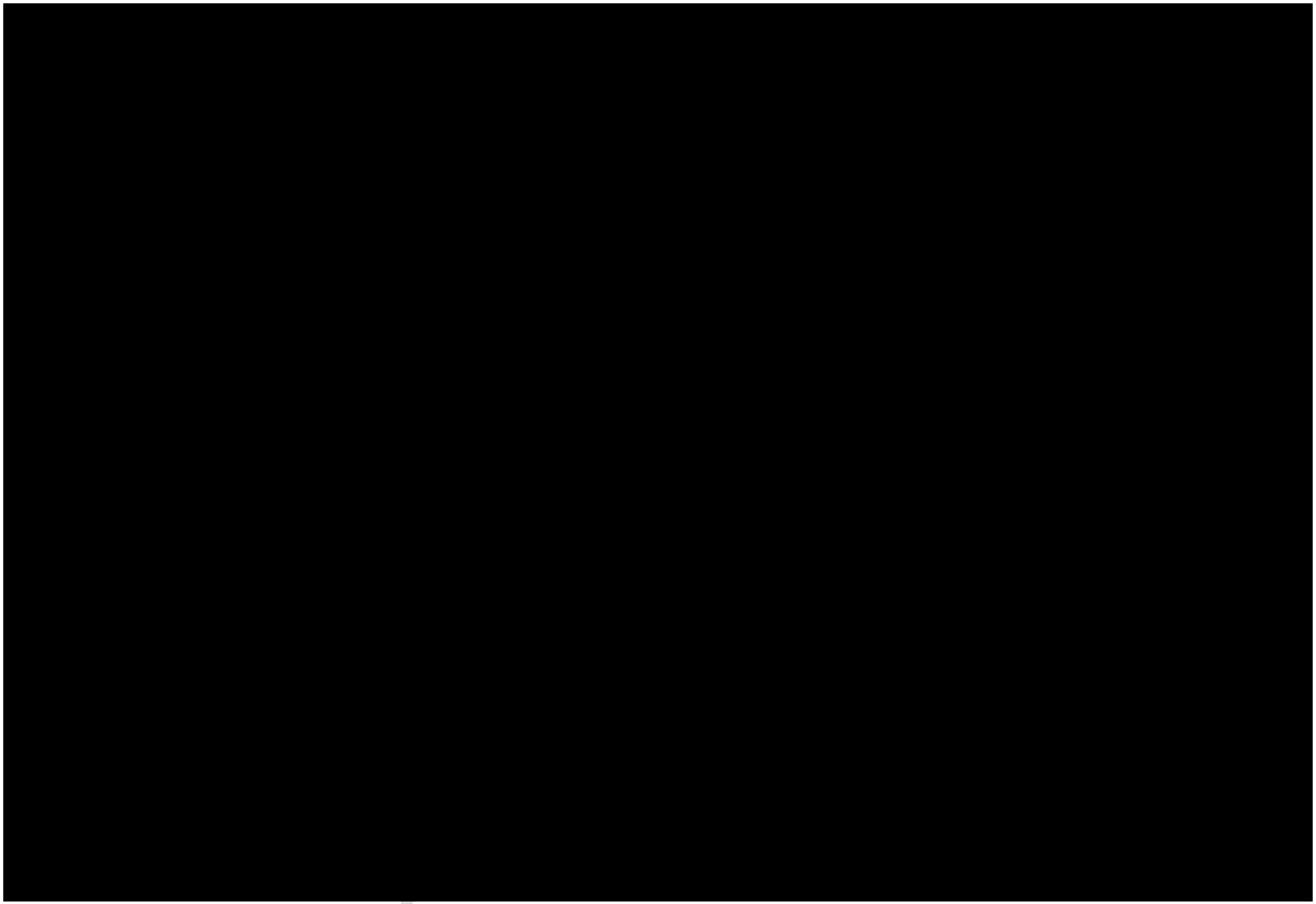
- Patients with ≥ 50% decrease from Day 0 MADRS total score
- Patients achieving a MADRS total score of ≤ 14 points

[redacted]

Upon completion of the lead-in period, patients will be randomized (1:1:1) to one of three treatment groups (either rapastinel 450 mg, rapastinel 225 mg, or placebo) adjunctive to ongoing ADT. Randomization will be stratified by patient's responder status (as placebo non-responder vs. placebo responder) achieved during the end of the placebo lead-in period. The schedule of visits and procedures for study RAP-MD-02 is presented in Table 2-1. The study design is shown graphically in Figure 2–1.

This SAP provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety data as outlined and/or specified in the final study Protocol Amendment 1 (version dated 10OCT2016), Amendment 2 (version dated 10DEC2018), the Restricted Access Addendum Amendment 1 (version dated 10OCT2016), and Amendment 2 (version dated 10DEC2018). Specifications of tables, figures, and data listings are contained in a separate document.





3.0 OBJECTIVES

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

Efficacy Objectives

The "baseline" referred in the following efficacy objectives is defined as the last measurement prior to the first dose of randomized IP.

- Primary efficacy objective: To evaluate the efficacy of rapastinel (450 mg IV, 225 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline to Day 21 in MADRS total score.

- Key secondary efficacy objectives:

    - To evaluate the efficacy of rapastinel (450 mg IV, 225 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline to Day 8 in MADRS total score (1 Day after the first randomized treatment).

    - To evaluate the efficacy of rapastinel (450 mg IV, 225 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline to Day 21 in MADRS total score for placebo non-responders.

    - To evaluate the efficacy of rapastinel (450 mg IV, 225 mg IV) versus placebo in the treatment of MDD as an adjunct to ongoing ADT, as measured by the change from baseline to Day 8 in MADRS total score (1 Day after the first randomized treatment) for placebo non-responders.

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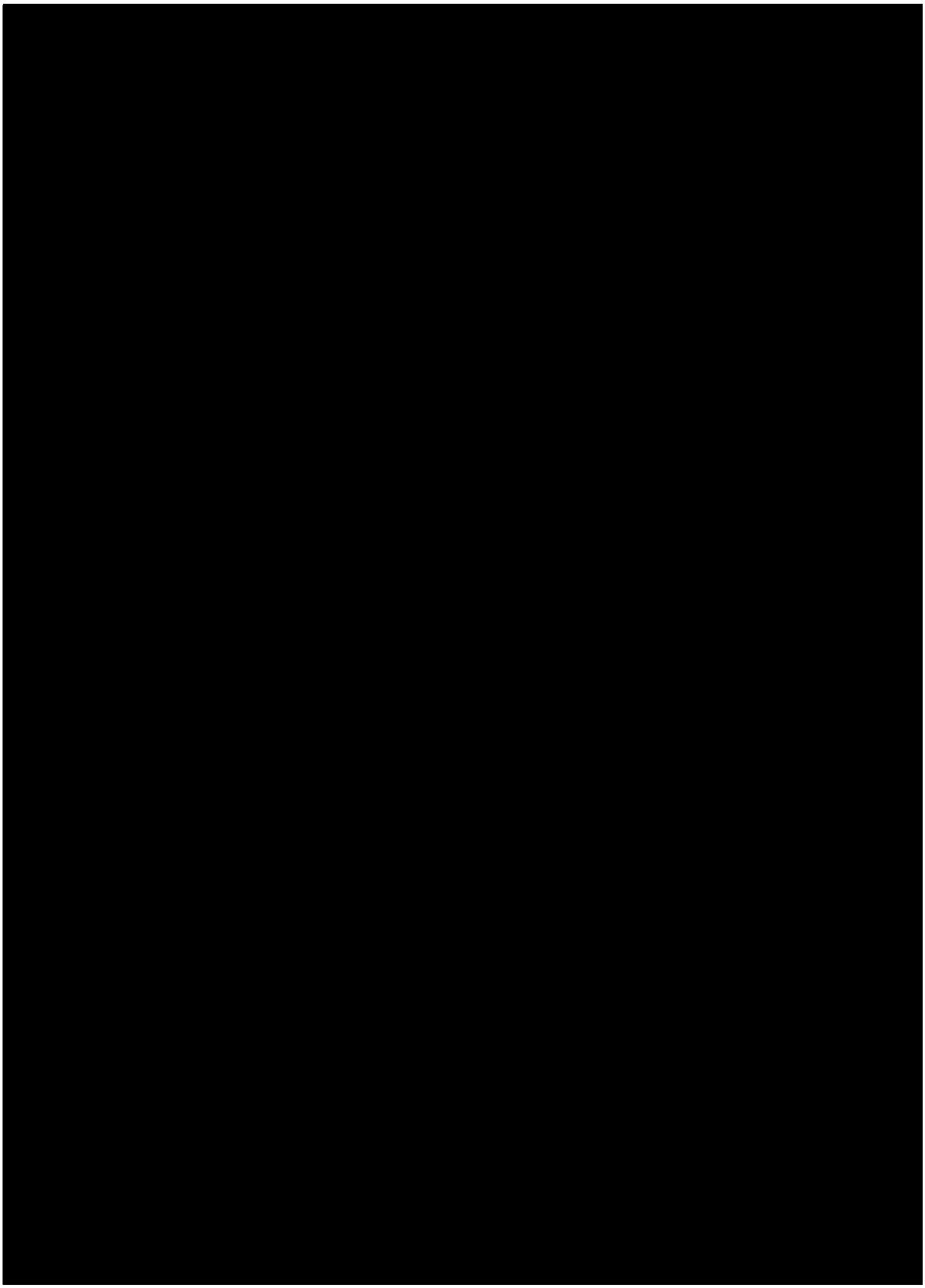


4.0 ANALYSIS POPULATIONS

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

4.1 ENROLLED POPULATION

The Enrolled Population will consist of all patients who signed informed consent, received a patient identification number, entered into screening and received 1 dose of investigational product (IP) during the double-blind treatment period.

4.2 SAFETY POPULATION

The Safety Population will consist of all patients who were randomized and received at least 1 dose of IP during the randomized treatment period.

4.3 MODIFIED INTENT-TO-TREAT POPULATION

The modified Intent-to-Treat (mITT) Population will consist of all patients who were randomized, received at least 1 dose of IP during the randomized treatment period, and had at least 1 post-randomization assessment of the MADRS total score.

5.0 PATIENT DISPOSITION

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

Screen-failure patients (ie, patients screened but not included in the enrolled population) and their associated reasons for failure to enroll will be tabulated overall for all screened patients.

The number and percentage of patients in the mITT population who complete the randomized treatment period, of patients who prematurely discontinue during the same period and who entered the safety follow-up period will be presented for each treatment group and pooled across treatment groups for placebo lead-in period responders and non-responders both separately and combined. The reasons for premature discontinuation during the randomized treatment period as recorded on the disposition pages of the electronic case report forms (eCRFs) will be summarized by treatment group and placebo lead-in period responder status for the mITT Population.

5.1 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 the Enrolled Population. A listing of all significant protocol deviations will be provided.

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and other baseline characteristics (eg, age, race, ethnicity, sex, weight, height, body mass index) will be summarized for all patients combined using the Enrolled Population, mITT Population, placebo responders of mITT Population, and placebo non-responders of mITT Population. An analogous analysis will be performed for baseline efficacy assessments.

Medical and surgical history, psychiatric history, previous treatment with psychotropic medication, and nondrug psychiatric treatment will be summarized by treatment group for the Safety Population.

The *World Health Organization (WHO) Drug Dictionary Enhanced* will be used to classify prior and concomitant medications by therapeutic class. *Prior medication* is defined as any medication taken before the date of the first dose of DB IP during the placebo lead-in period. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of DB IP which is during the placebo lead-in period. If a medication started prior to the first dose of DB IP and continued into the placebo lead-in period, then this medication will be included in the analysis of prior and concomitant medications separately.

The number and percentage of patients with prior and concomitant medication use will be summarized by treatment group and Anatomical Therapeutic Chemical code for the Safety Population.

Multiple medications used by a patient in the same category will be counted only once in the summary tables. Concomitant medications started after the last visit of the randomized treatment period will not be summarized but will be included in the data listings.

Prior ADT treatment in the current episode, as recorded on ATRQ, 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 >3), and percentage of improvement reported (ie., < 25%, 25% to 49%, 50% to 75%, or >75%).

7.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

7.1 EXTENT OF EXPOSURE OF STUDY TREATMENT

The number and percentage of patients who received 1 or 2 randomized IV doses 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, increase in suicidality based on clinical evaluation, and perceptual disturbance 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.

7.2 EXTENT OF EXPOSURE OF BACKGROUND ADT

The number and percentage of patients taking each qualifying ADT will be summarized by treatment group for the mITT Population. The mean daily dose for a patient over a study period is defined as the total daily dose administered by a patient during that study period as captured on the CRF, divided by the duration the patient participants in that study period, measured in days. The mean daily dose for each ADT will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) by treatment group for the mITT Population.

7.3 TREATMENT COMPLIANCE OF BACKGROUND ADT

Dosing compliance for the background ADT during a specified period is defined as the total daily dose received by a patient during that period divided by the total daily dose prescribed during the same period as recorded in the eCRF multiplied by 100 regardless if a patient discontinued from the study. Descriptive statistics for ADT compliance will be presented for each ADT and overall by the treatment group for the randomized treatment period for the mITTPopulation.

7.4 WEIGHT ADJUSTED DOSE OF RAPASTINEL

The dose of rapastinel will be divided by patient baseline weight and summarized by descriptive statistics including total number of patients who received rapastinel, mean, standard deviation, minimum and maximum for the Safety Population.

8.0 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 measurement prior to the first dose of randomized treatment. The Day 0 measure for each specific efficacy endpoint is defined as the last measurement prior to the first dose of double-blind IP in the placebo lead-in period. The analyses for the placebo lead-in period will be presented for all patients combined and separately for the placebo responders vs. non-responders using the Enrolled Population. All statistical hypothesis tests will be performed at the 2-sided 5% significance level for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

For efficacy analyses in which study center is a factor, a *small center* will be defined as a center with less than 2 placebo non-responder patients in at least 1 treatment group in the mITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes at least 2 placebo non-responder patients within the center for the mITT population. Pooling will be done using the following algorithm:

Based on the number of placebo non-responder 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 number to the smallest center number. 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 more than 1 smallest pseudo-center, the pseudo-center with the smallest center number 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 more than 1 smallest non-small center, the one with the smallest center number will be selected.

If any, the centers with only placebo responder patients will be ordered from largest to the smallest by the number of patients. The smallest pooled center (based on placebo non-responder as defined in the previous paragraph) will be combined with largest center with only placebo responder patients; the second smallest pooled center (based on placebo non-responder as defined in the previous paragraph) will be combined with the second largest center with only placebo responder patients; the remaining centers with only placebo responder patients will be combined similarly. Centers with same number of patients will be further ordered by the center code.

The final pooled pseudo-centers will be used for all efficacy analyses when the model is adjusted for study center.

The efficacy analyses of MADRS assessments will be based on the rater-administered MADRS. 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. If a patient is randomized based on an incorrect stratum, then this patient will be analyzed according to the stratum to which the patient should have been assigned per the electronic data capture system, instead of the stratum per the randomization system of IWRS.

8.1 PRIMARY EFFICACY PARAMETER

The primary efficacy parameter will be the change from baseline to Day 21 in MADRS total score for the mITT population. The MADRS total score is the sum of the 10 individual items. If more than 2 items are missing, then the total score will be set to missing. If there are multiple assessments of MADRS total score for the same nominal visit of a patient, only the last assessment will be used in the analysis.

The primary efficacy parameter will be analyzed using a mixed model for repeated measures (MMRM) with treatment group, pooled study center, visit, placebo responder status at Day 7, and treatment group-by-visit interaction as the fixed effects, and Day 0 MADRS total score, baseline MADRS total score, Day 0 MADRS total score-by-visit and baseline MADRS total score-by-visit interactions as covariates. An unstructured covariance matrix is used to model the covariance of change in scores within patients. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward et al, 1997). The analysis will be performed based on all post-randomization data using only the observed cases without imputation of missing 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 term for study center will be used to find the initial values of the covariance parameters. In the rare event that the 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 using a pattern-mixture model based on non-future dependent missing value restrictions (Kenward et al, 2003) will be performed. 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 missing values will be analyzed using the same model as the primary analysis for between-treatment group comparisons. The imputation of missing values and the analysis will be performed multiple times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values for Δ will be selected as 0 to 8.

8.2 KEY SECONDARY EFFICACY PARAMETERS

There are 3 key secondary efficacy parameters as listed below:

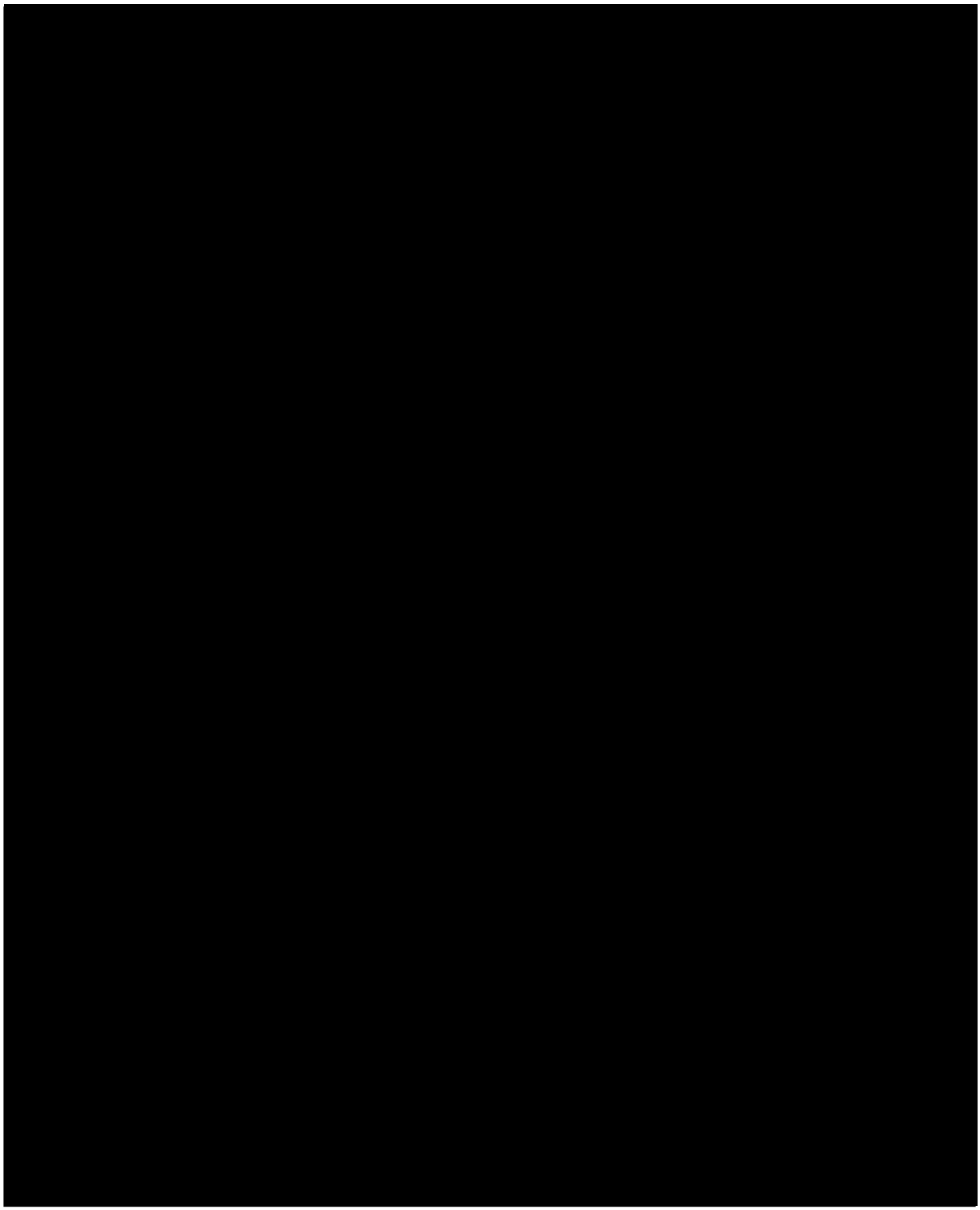
1. Change from baseline to Day 8 (1 Day after the first randomized treatment) in MADRS total score for mITT population
2. Change from baseline to Day 21 in MADRS total score for the placebo non-responders of mITT population
3. Change from baseline to Day 8 in MADRS total score for the placebo non-responders of mITT population

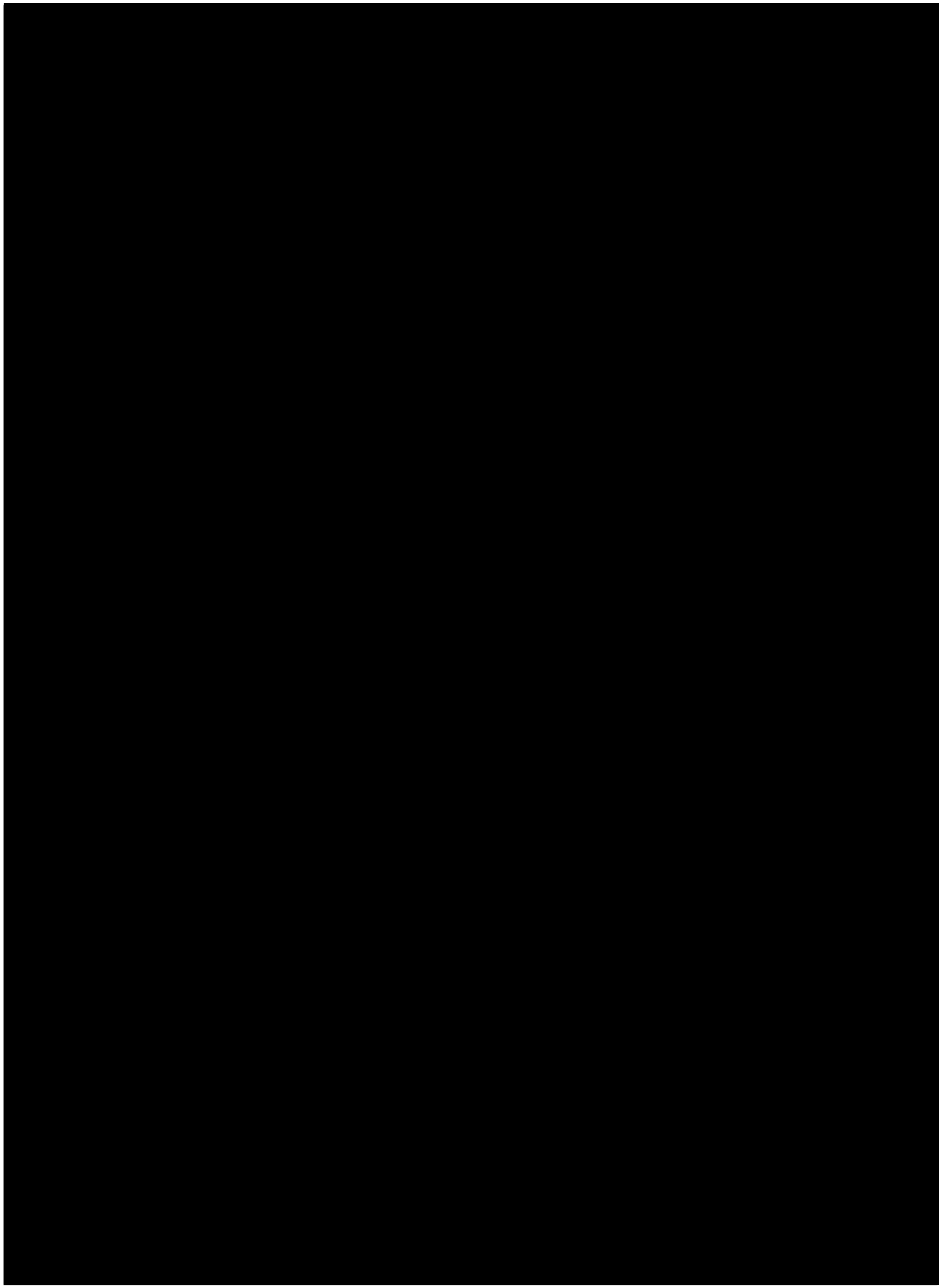
The key secondary parameters will be analyzed using the same MMRM model as for the primary efficacy parameter, except the placebo responder status at Day 7 will be excluded for the analyses of the 2nd and 3rd key secondary efficacy parameters listed above. A sequential testing procedure will be used to control the overall type I error rate at 5% for the multiple comparisons of treatment difference in primary and key secondary efficacy parameters in the order listed below:

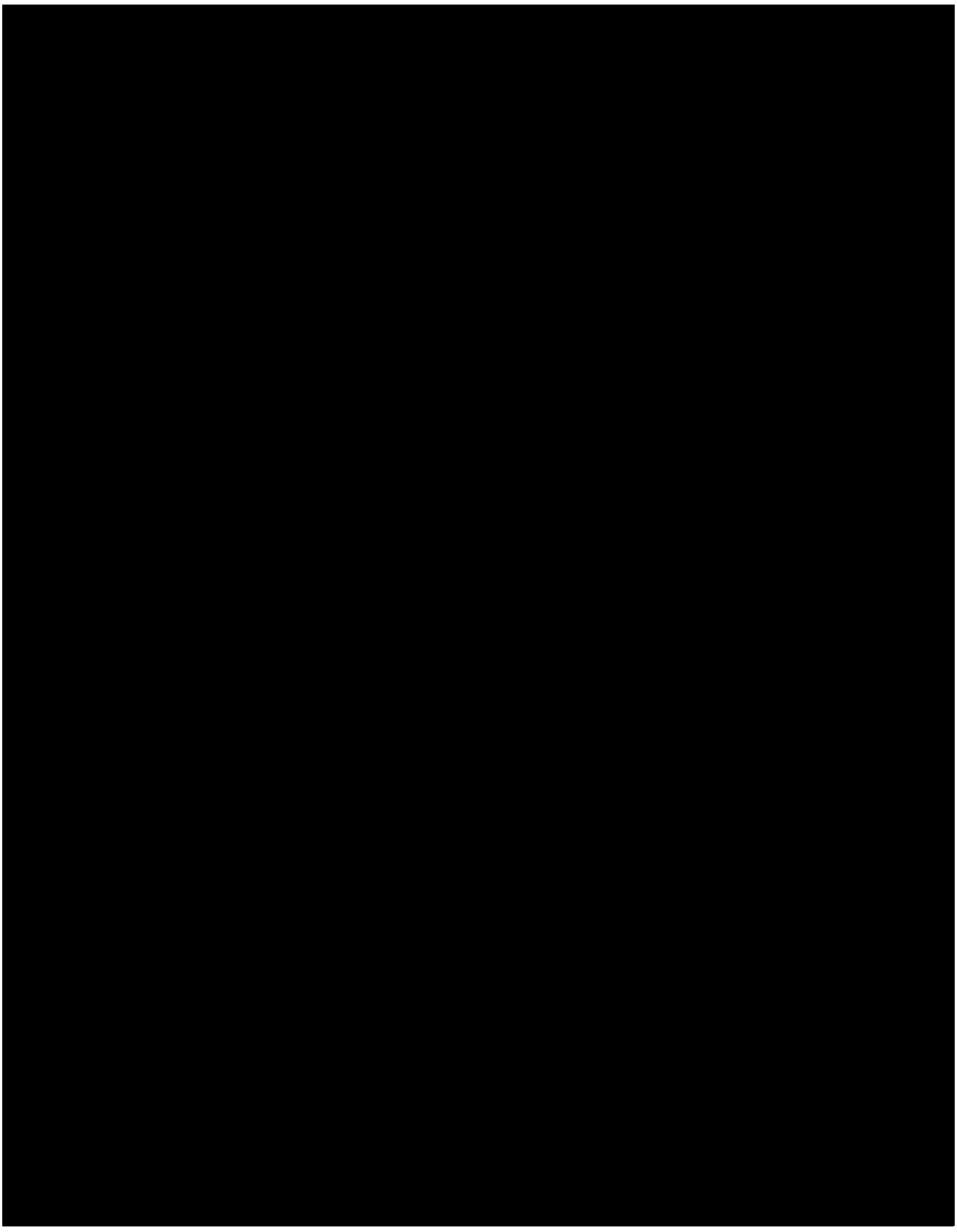
i) Primary - Rapastinel 450 mg vs. placebo
ii) Secondary 1 - Rapastinel 450 mg vs. placebo
iii) Secondary 2 - Rapastinel 450 mg vs. placebo
iv) Secondary 3 - Rapastinel 450 mg vs. placebo
v) Primary - Rapastinel 225 mg vs. placebo
vi) Secondary 1 - Rapastinel 225 mg vs. placebo
vii) Seconday 2 - Rapastinel 225 mg vs. placebo
viii) Secondary 3 - Rapastinel 225 mg vs. placebo

Each between-treatment comparison will be tested at the significance level of 0.05. The between-treatment comparisons will be performed sequentially as long as the treatment effect is statistically significant in the preceding test.

Plots of fitted (least squares) mean values and their standard errors based on the MMRM model for the change in MADRS total score will be presented by treatment group and by visit.







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9.1 ADVERSE EVENTS

AEs will be coded using the *Medical Dictionary for Regulatory Activities* and reported separated for placebo lead-in, randomized treatment, and safety follow-up periods.

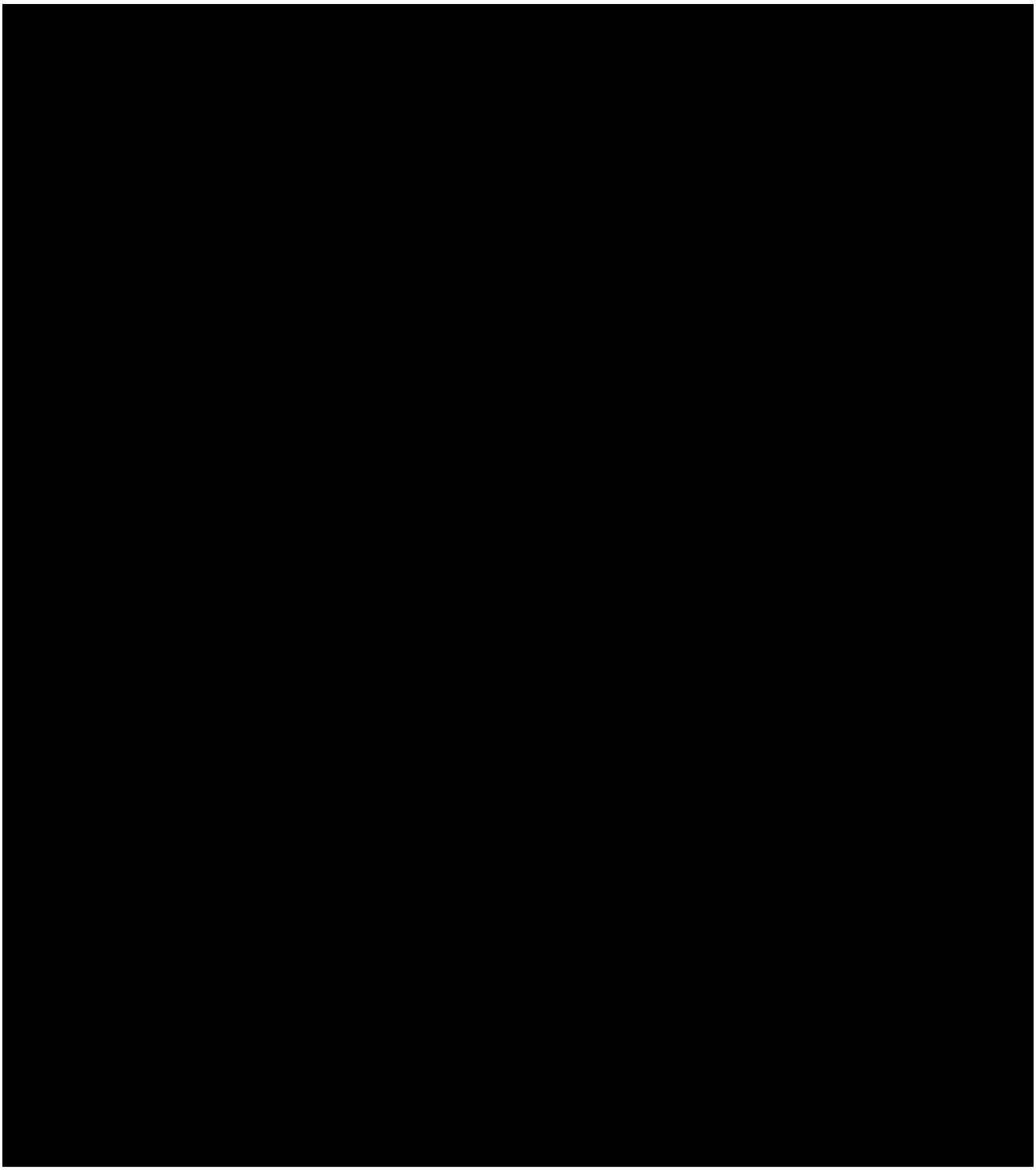
An AE (classified by preferred term) will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of DB IP (i.e. the first IP during the placebo lead-in period) or was present before the date of the first dose of DB IP and increased in severity after the first dose of DB IP. An AE that becomes serious after the date of the first dose of DB IP will also be considered as TEAE. If more than 1 AE was reported before the first dose of DB IP and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during each study period analyzed. An AE that occurred more than 30 days after the date of the last dose of DB IP (including the randomized IP) will not be considered as a TEAE.

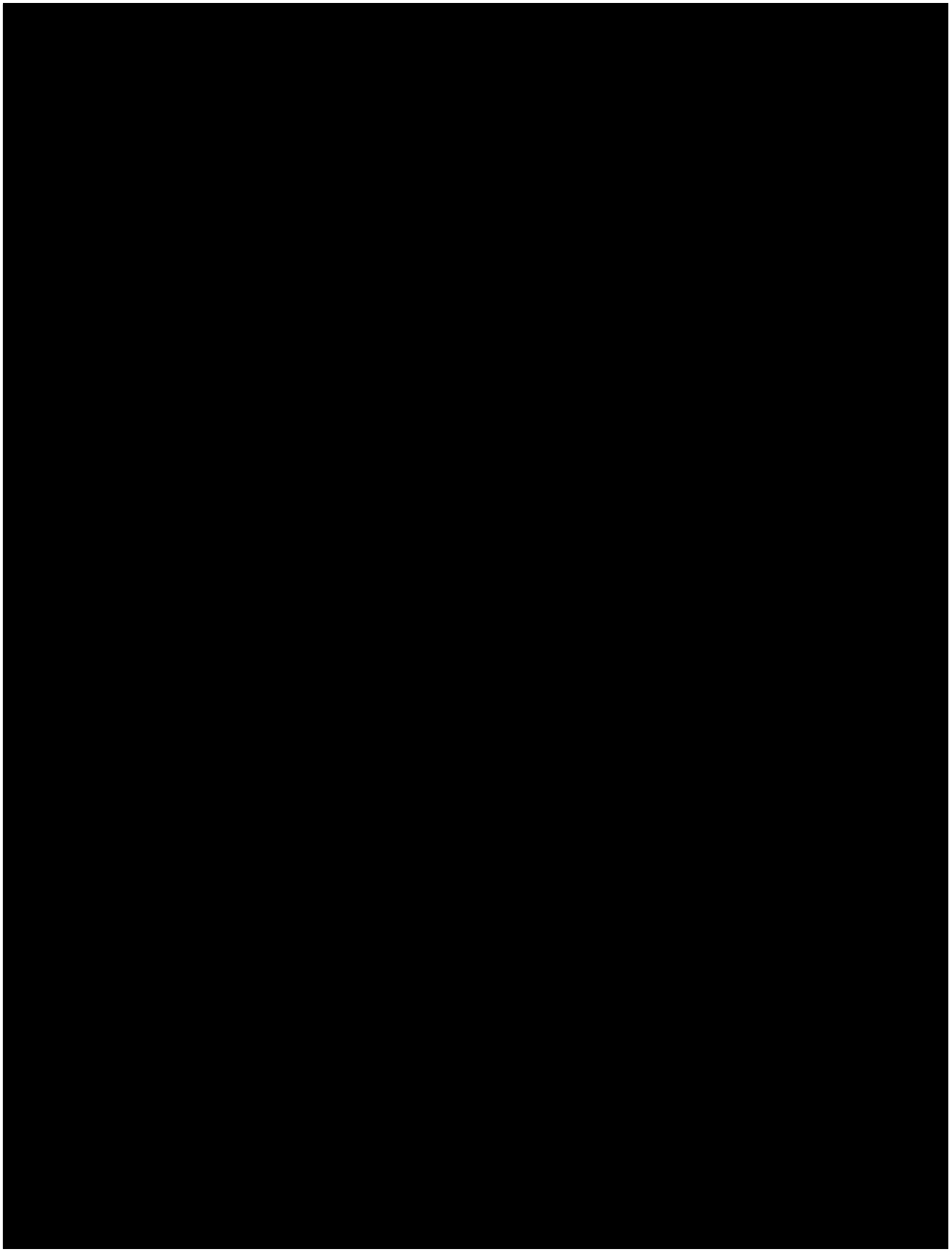
The number and percentage of patients reporting TEAEs and TEAEs leading to study discontinuation in each treatment group will be tabulated by system organ class and preferred term and further categorized by severity and causal relationship to the IP. If more than 1 AE is coded to the same preferred term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

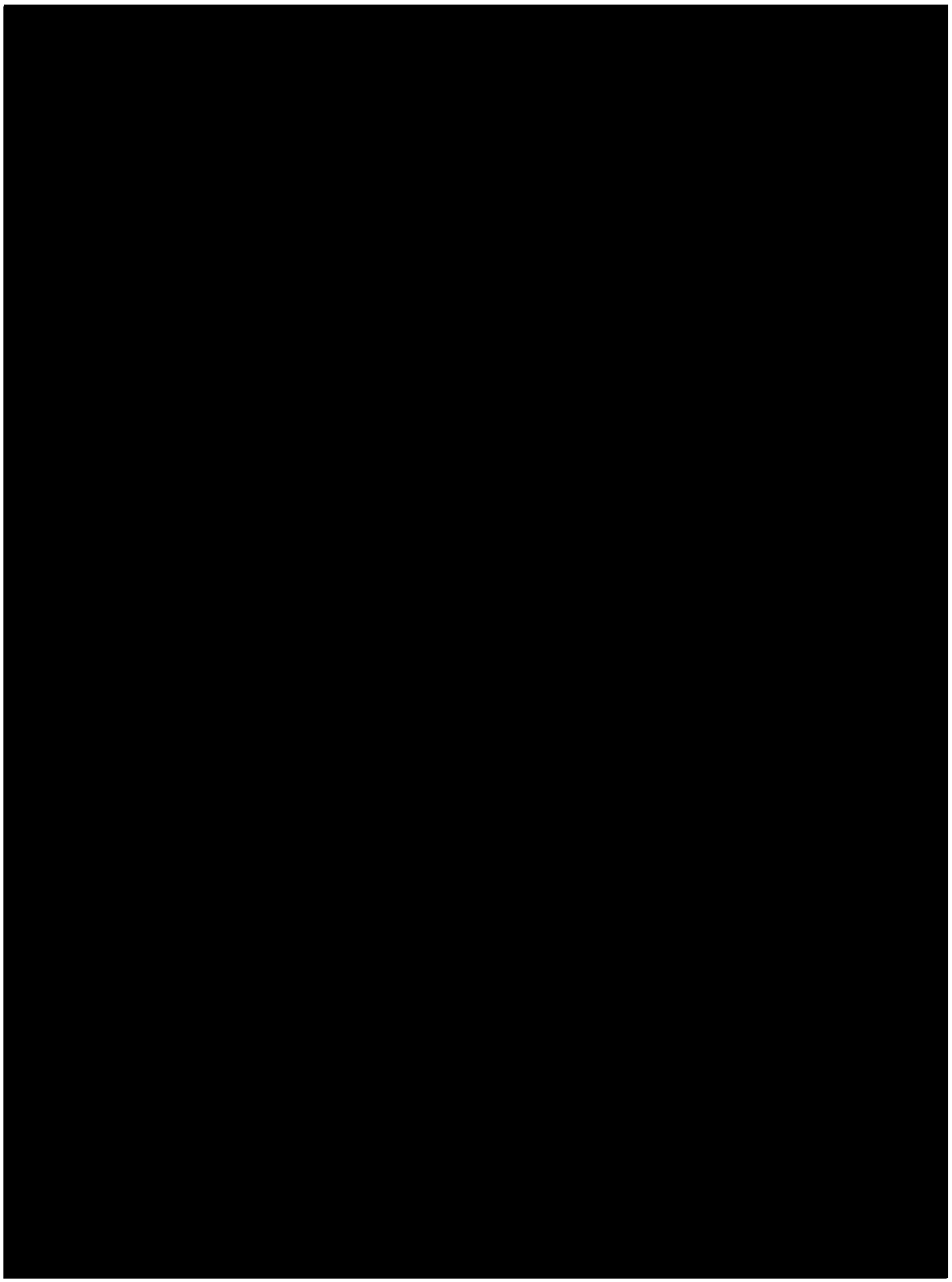
The incidence of common ($\geq$ 2% of patients in any treatment group) TEAEs will be summarized by preferred term and treatment group and sorted by decreasing frequency for the test treatment.

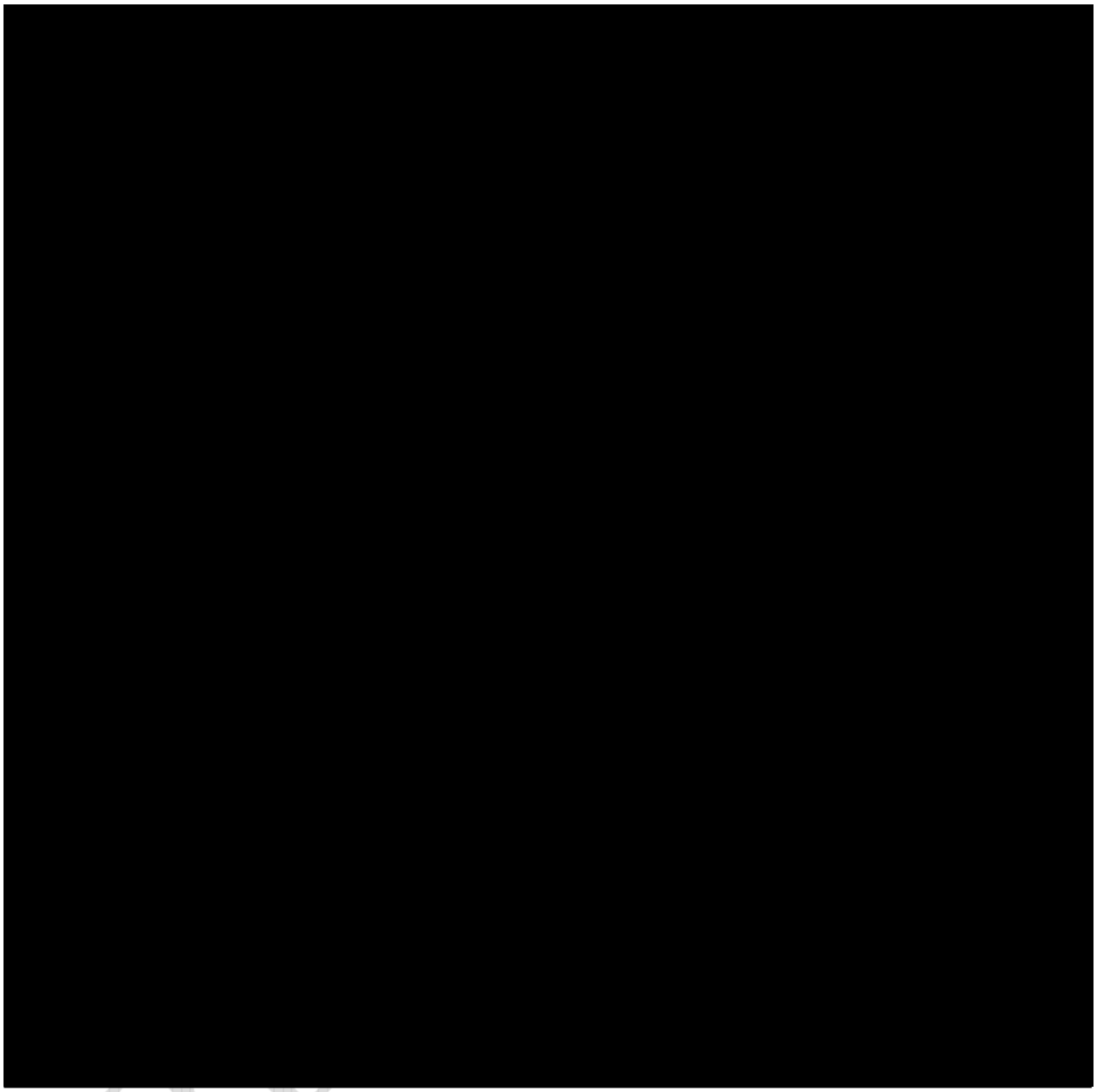
A serious adverse event (SAE) that occurred between the date of the first dose of DB IP and 30 days after the date of the last dose of DB IP, inclusive, will be considered a treatment-emergent SAE (TESAE). The number and percentage of patients who have TESAEs will be summarized by preferred term and treatment group.

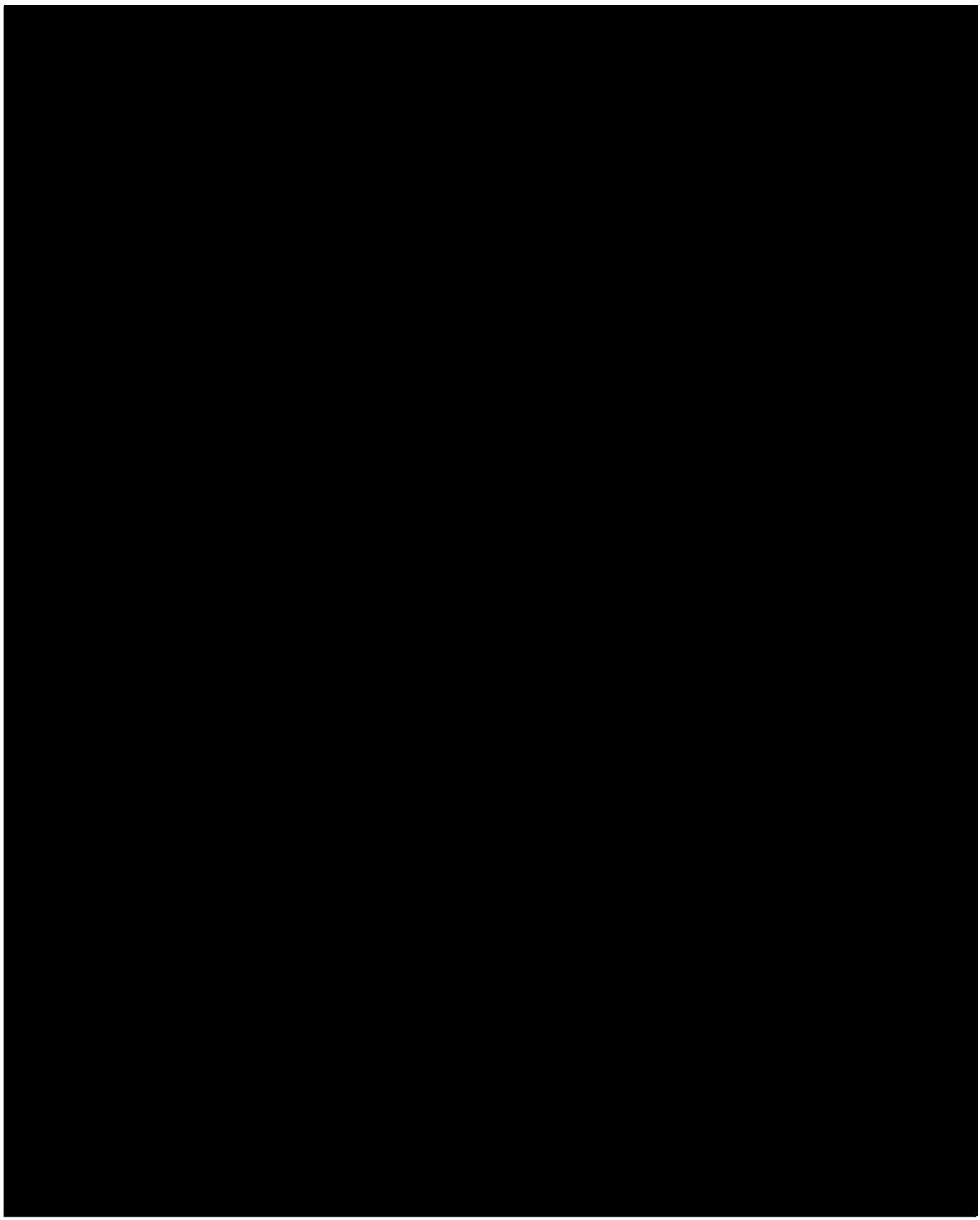
Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any). All patients with SAEs, including SAEs reported during the screening period and the safety follow-up period, and patients discontinuing because of AEs occurring before the start of randomized IP will be included in these listings.











11.0 INTERIM ANALYSIS

At the time of preparation for the Protocol Addendum Amendment 2, a blinded interim analysis was performed as part of data quality review as the study was progressing. In this review, it was observed that the standard deviation for the primary and secondary endpoints were substantially lower than the originally assumed values for sample size calculations. The observed standard deviations in the blinded reviews of this study and other ongoing acute studies at the same time (RAP-MD-01, and RAP-MD-03) were taken into considerations for revising the sample size estimation in next section (Determination of Sample Size).

12.0 DETERMINATION OF SAMPLE SIZE

The originally proposed primary efficacy variable is the change from baseline (ie., Day 7) at Day 8 in MADRS total score and the primary analysis population included the subset of patients who were placebo non-responders during the placebo lead-in period before randomization. Based on that the study was planned to randomize 1050 patients (including both placebo responders and placebo non-responders), assuming standard deviation (SD) of 10 points, which provides 99% power to detect a difference of 3.25 points in MADRS total score between at least 1 of the 2 rapastinel dose groups and placebo at a 2-sided significance level of 0.05.

While the study was ongoing, the primary efficacy variable was revised to be the change from baseline in MADRS score at the last visit, Day 21, and the primary efficacy study population was revised to include all randomized patients (placebo responders and placebo non-responders) based on the feedback by the FDA, EMA, and PDMA. Both of these changes were included in Amendment 2 of the protocol. At the same time of Amendment 2, a blinded data review was conducted for Studies RAP-MD-01, RAP-MD-02, and RAP-MD-03. The pooled SD for the three studies were 7.4, 8.0, and 8.7, respectively, all smaller than the originally assumed 10 points. Sample size was re-calculated using 8.7 as the common SD. The calculation used MMRM model with simulations; it also assumed correlation of 0.5 between the repeated measures and a common drop-out rate of 10% during the randomized treatment period and an additional 5% drop-out rate during the placebo lead-in period for all treatment groups. To have 90% power, the total sample size required is 540 patients. However, the study had already enrolled more than 590 patients with less than 5% of overall drop-out rate, surpassing the re-estimated sample size of 540 patients. The study enrollment will be halted as soon as operationally feasible. The final sample size expected is approximately 630 patients (210 patients per treatment group).

13.0 STATISTICAL SOFTWARE

Statistical analyses will be performed [redacted]

14.0 DATA HANDLING CONVENTIONS

14.1 VISIT TIME WINDOWS

Table 14.1–1 presents visits assigned and the corresponding range of treatment days (window) during which an actual visit may occur for all safety analyses where baseline is the last nonmissing assessment before the first dose of DB IP in the placebo lead-in period. The visit windows used in the "change from Day 0" or "reduction from Day 0" efficacy analyses will be derived according to this table as well. Termination visit is assigned to the visit window according to the table below.

Table 14.1–1. Visit Time Windows for Change from Day 0 in Efficacy and Change from Baseline in Safety Analyses

Analysis Visit	Target Date	Analysis Window (Based on Date)
Baseline	Index0[a]	Last record on or before Index0[a]
Day 1	Index0[a]+1	Index0[a]+1
Day 4	Index0[a]+4	[Index0[a] +2, IndexA[b]-1]
Day 7	IndexA[b]	IndexA[b]
Day 8[d]	IndexA[b]+1	IndexA[b]+1
Day 11	IndexA[b]+4	[IndexA[b]+2, IndexB[c]-1]
Day 14	IndexB[c]	IndexB[c]
Day 15[d]	IndexB[c]+1	IndexB[c]+1
Day 18	IndexB[c]+4	[IndexB[c]+2, IndexB[c]+5]
Day 21[de]	IndexB[c]+7	Days [IndexB[c]+6, day of final double-blind visit or Early-termination Visit occurring after IndexB[c]+5]
Day 28	IndexB[c]+14	Within the safety follow-up phase

a Index0: Date of placebo dose during the placebo lead-in period

b IndexA: Date of first randomized dose or Index0 + 7 for patients who did not receive any randomized dose

c IndexB: Date of second randomized dose or IndexA +7 if the 2nd dosing of randomized treatment was not administered for patients who were randomized

d For analysis of parameters BPRS+ (Brief Psychiatric Rating Scale) and CADSS (Clinician Administered Dissociative States Scale), the visit windows for Days 1 and 8 will be extended to cover the next dosing day (indexA and indexB, respectively); the visit window for Day 15 will be 1 day after IndexB to Day 19; and the visit window for Day 21 will be Days 20 to the last double-blind visit, inclusively.

For efficacy analysis where baseline is defined as the last measurement prior to the first dose of randomized IP, the assigned visit and the corresponding range of treatment days (window) during which an actual visit may occur is displayed in Table 14.1–1. Termination visit is assigned to the visit window according to the table below.

Table 14.1–2. Visit Time Windows for Change from Baseline in Efficacy Analyses

Analysis Visit	Target Date	Analysis Window (Based on Date)
Day 0	Index0[a]	Last record on or before Index0[a]
Baseline	IndexA[b]	Last record on or before IndexA[b]
Day 8	IndexA[b]+1	IndexA[b]+1
Day 11	IndexA[b]+4	[IndexA[b]+2, IndexB[c]-1]
Day 14	IndexB[c]	IndexB[c]
Day 15	IndexB[c]+1	IndexB[c]+1
Day 18	IndexB[c]+4	[IndexB[c]+2, IndexB[c]+5]
Day 21[e]	IndexB[c]+7	Days [IndexB[c]+6, day of final double-blind visit or Early-termination Visit occurring after IndexB[c]+5]
Day 28	IndexB[c]+14	Within the safety follow-up phase

a Index0: Date of placebo dose during the placebo lead-in period

b IndexA: Date of first randomized dose or Index0 + 7 for patients who did not receive any randomized dose

c IndexB: Date of second randomized dose or IndexA +7 if the 2nd dosing of randomized treatment was not administered for patients who were randomized

If a patient has 2 or more non-missing assessments within the same window, the assessment closest to the target day will be used for analysis; if there are 2 closest assessments with the same number of days from the scheduled day, the later one will be used for analysis.

14.2 DERIVED EFFICACY AND SAFETY VARIABLES

The total score of each variable including MADRS, BPRS+, and CADSS 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.

14.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of DB treatment, the results from the final nonmissing assessment made before the start of the DB IP will be used as baseline. 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.

14.4 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of DB 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 DB IP, 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.

14.5 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 DB 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.

14.6 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). If the patient did not receive any randomized dosing during the study, then the date of first dose of DB IP will be utilized for the purpose of imputation.

Missing month and day

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

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

14.7 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. If the stop date is complete and the imputed start date is after the stop date, the start date will be imputed using the stop date. If the imputed stop date is before the start date (imputed or nonimputed start date), the start date will be the imputed stop date. If the patient did not receive any randomized dosing during the study, then the date of first dose of DB IP will be utilized for the purpose of imputation.

14.7.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date.

Missing month and day

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

14.7.2 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 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 randomized IP, the month and day of the last dose of randomized IP will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the last dose of randomized IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the last dose of randomized 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 last dose of randomized IP, the day of the last dose of randomized IP 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 randomized 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 last dose of randomized 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 last dose of randomized IP 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 randomized IP, the first day of the month will be assigned to the missing day.

15.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

This SAP amendment includes additional analyses listed below. There are no other changes to the analyses specified in the final Protocol Amendment 2 (version dated 12 Oct 2018) and Amendment 3 (version dated 20NOV2018).

- Prior ADT use in current episode recorded on ATRQ (Section 7.0)
- Weight adjusted dose of rapastinel (section 7.4)

[redacted]

16.0 REFERENCES

Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. Biometrika 2003; 90(1): 53-71.

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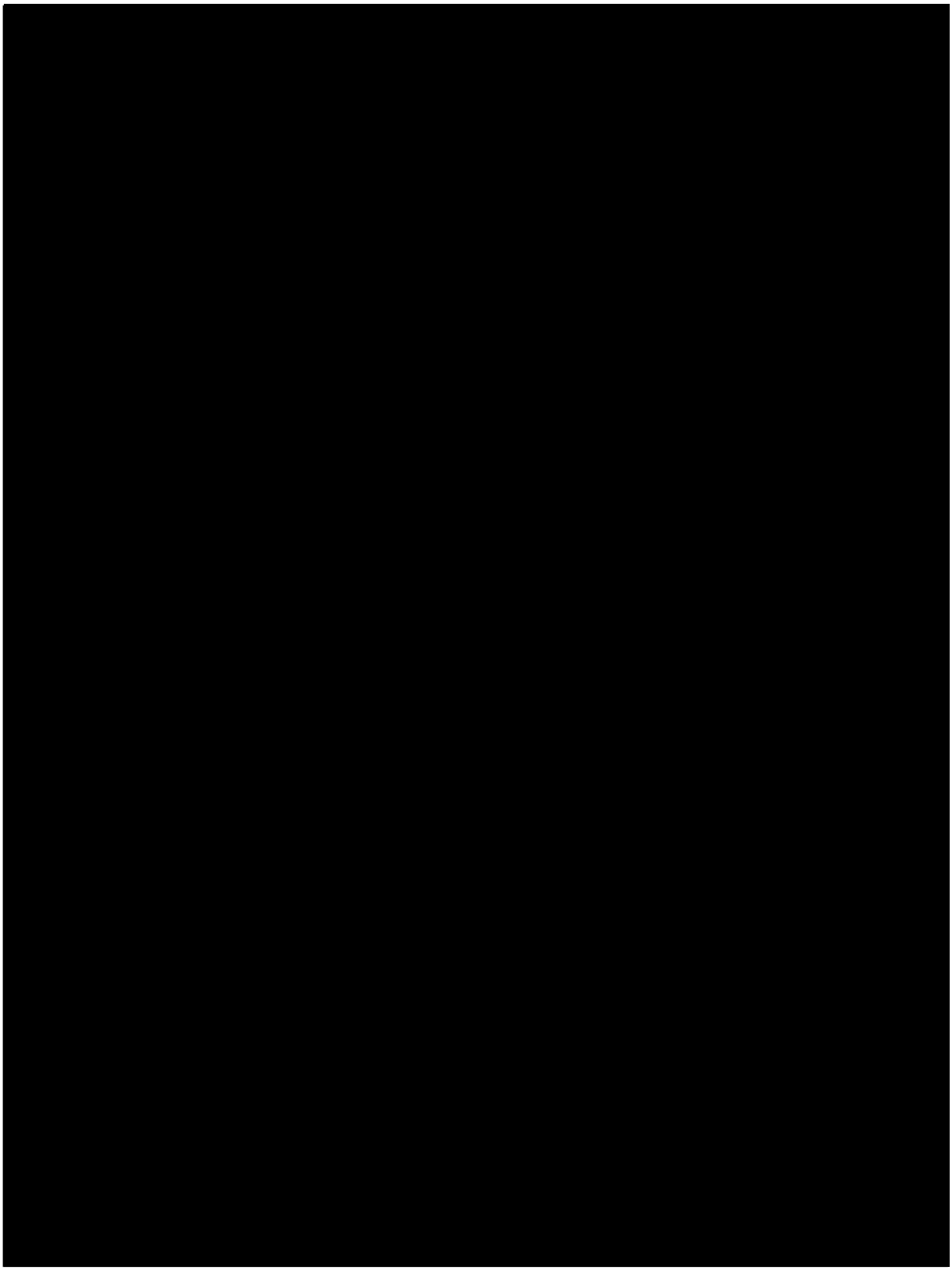
Wang C, Daniels MJ. A note on MAR, identifying restrictions, model comparison, and sensitivity analysis in pattern mixture models with and without covariates for incomplete data. Biometrics, 2011; 67(3):810-818.

17.0 APPENDICES



Appendix II. Pattern-mixture Model Details

For repeated measures under monotone missing, the pattern-mixture model with non-future dependent missing assumption proposed by Kenward et al (2003) provides a feasible solution to accommodate certain missing not at random (MNAR) mechanism. The methodology relies on constructing unidentifiable conditional densities using identifiable densities and borrows techniques from standard multiple imputation.

1. Non-Future Dependent Missing Assumption

Assume there are T designed visits in a longitudinal study and let $y_i (i = 1,2,...,T)$ represent patient's measurement at Visit i. When the missing is monotonic, the pattern of missing ***data*** can be defined by the number of measurements (L) actually observed from the patient. Let $f(y_i,..., y_j \mid L = t)$ denote the conditional density of y_i ,... y_j, given ***that*** the last observed measurement at Visit t. Then the overall density function for Pattern t can be written as

$$f(y_1,..., y_T \mid L = t) = f(y_1,..., y_t \mid L = t) f(y_{t+1} \mid y_1,..., y_t, L = t) \times \prod_{s=t+2}^{T} f(y_s \mid y_1,...,y_{s-1}, L = t) \quad (1)$$

Note on the right hand side of (1) the first factor is clearly identifiable from the observed data, while the second and the beyond are not, due to lack of available data. The second factor $f(y_{t+1} \mid y_1,..., y_t, L = t)$ could be identifiable based on an assumed relationship between $f(y_{t+1} \mid y_1,..., y_t, L = t)$ and $f(y_{t+1} \mid y_1,..., y_t, L \geq t+1)$. The third and beyond factors $f(y_s \mid y_1,..., y_{s-1}, L = t)$ (with all $s \geq t+2$) could be identifiable with the help of non-future dependent missing assumption.

For longitudinal data with dropouts, non-future dependent missing (NFD) (Kenward, 2003) assumes that the unidentifiable conditional distributions of y_s $(s \geq t+2)$***, given earlier measurements,*** in Pattern ***t, is set to be equal to the corresponding distribution in pattern L>s-1:***

$$f(y_s \mid y_1,..., y_{s-1}, L = t) = f(y_s \mid y_1,..., y_{s-1}, L \geq s-1) \quad (2)$$

The right hand side of (2) can further be partitioned into

$$f(y_s \mid y_1,...,y_{s-1}, L \geq s-1) = \sum_{j=s-1}^{T} \omega_{s-1,j} \cdot f(y_s \mid y_1,...,y_{s-1}, L = j) \quad (3)$$

where mixture probabilities $\omega_{s-1,j}$ are

$$\omega_{s\text{-}1,j} = \frac{\alpha_j \, f(y_1,\ldots,y_{s\text{-}1} \mid L = j)}{\sum_{t=s\text{-}1}^{T} \alpha_t \, f(y_1,\ldots,y_{s\text{-}1} \mid L = t)} \quad \textbf{(4)}$$

, and α_j represents the fraction of patients from Pattern j.

Each factor of the unidentifiable conditional distribution of y_s ($s \geq t + 2$) on the right side of (1) can be expressed using the following:

- $f(y_s \mid y_1,\ldots,y_{s-1}, L = s-1)$, the unidentifiable conditional distribution of the first missing in pattern s-1,

- $f(y_s \mid y_1,\ldots,y_{s-1}, L = j)$, the identifiable conditional distributions of y_s given $y_1,\ldots,y_{s-1}$ of pattern j ($j \geq s$), and

- α_j, the fraction of patients from pattern j ($j \geq s$ - 1).

So under NFD, all the unidentifiable conditional distributions on the right side of (1) can be estimated and missing values could be therefore imputed based on the assumption for unidentifiable conditional distribution of the first missing ***value***.

We re-formulate the partition in (3), for s ≥ t +2, as the following:

$$f(y_s \mid y_1,\ldots, y_{s\text{-}1}, L = t) = \delta_{s\text{-}1} f(y_s \mid y_1,\ldots, y_{s\text{-}1}, L = s-1) + (1 - \delta_{s\text{-}1}) f(y_s \mid y_1,\ldots, y_{s\text{-}1}, L \geq s) \quad \textbf{(5)}$$

for s ≥ t +2 with $\delta_{s-1} = \omega_{s-1,s-1}$.

Therefore, under monotone missing and NFD assumption, the unidentifiable conditional densities for Visit s in Pattern t (s ≥ t +2) can be expressed as a mixture distribution of $f(y_s \mid y_1,\ldots,y_{s-1}, L = s-1)$ ***- the unidentifiable conditional distribution of the first missing measurement*** y_s ***in Pattern*** $s-1$ ***, and*** $f(y_s \mid y_1,\ldots,y_{s\text{-}1}, L \geq s)$ ***- the identifiable conditional distribution of*** y_s ***from all the patterns with observed data at Visit s or beyond:***

$$f(y_s \mid y_1,\ldots, y_{s\text{-}1}, L \geq s) = \sum_{j=s}^{T} \lambda_{s\text{-}1,j} f(y_s \mid y_1,\ldots, y_{s\text{-}1}, L = j) \quad \textbf{(6)}$$

where the mixture probability

$\lambda_{s\text{-}1,j} = \omega_{s\text{-}1,j} / (1 - \omega_{s\text{-}1,\, s\text{-}1}) =$

$$\frac{\alpha_j f(y_1,\ldots,y_{s-1} \mid L=j)}{\sum_{t=s}^{T} \alpha_t f(y_1,\ldots,y_{s-1} \mid L=t)} \text{ for } j \geq s, \text{ where } \alpha_j \text{ is the fraction of} \quad (7)$$

patients from Pattern j.

The conditional densities for the first missing are selected as:

$$f(y_s \mid y_1,\ldots, y_{s-1}, L = s-1) = f(y_s - \Delta \mid y_1,\ldots, y_{s-1}, L \geq s) \text{ for } s = 2, \ldots, T, \quad (8)$$

Note that the two distributions only differ from a shift (Δ) parameter. When Δ = 0, the missing value y_s in Pattern *s-1* is imputed based on the distribution of all observed data up to Visit *s,* as a result, leading to missing at random (MAR) missingness. When Δ ≠ 0, (***8***) will introduce a scenario of MNAR. ***A*** similar idea was also presented in the recent publication "*The Prevention and Treatment of Missing Data in Clinical Trials*" by the National Academy Press. The selection of the plausible values for the shift parameter (Δ) is discussed in Section 3.

Note that per recommendation in Wang and Daniels (2011), only the observed data within the pattern is assumed to be multivariate normal. The observed data distribution can be expressed in terms of the marginal distribution of baseline measurements and the conditional distributions of postbaseline measurements given earlier measurements. Assuming that these distributions are normal, the linear regression of each observation on prior observations will yield least-squares estimates of model parameters that can be utilized for independent posterior draws of model parameters for observed data. The multiple imputation approach will be used to estimate the overall mean at the final time point.

2. Imputation Procedure

All the missing data will be imputed to create a complete dataset, then statistical analysis can be performed using appropriate techniques such as ***MMRM***. The imputation ***can accommodate*** MNAR ***missing data mechanisms***, based on the theory discussed in the above sections.

The model parameters for each dropout pattern, i.e., the mean, variance and proportions of observations in each pattern, are drawn from their posterior distributions prior to the imputation of missing data for a single imputation.

The details of imputation within a pattern, say Pattern *t,* are as the following:

Step 1. Impute the first missing value y_{t+1} for each patient in Pattern t (t = 1,..., T – 1):

a. Compute estimates of mixture probabilities $\lambda_{s-1,j}$ in (7) with s = t+1 given the posterior draw of proportions of observations in each pattern and the posterior draw of regression parameters for the observed data.

b. Draw a random integer from {s, ..T} to index a component distribution on the right hand side of (6), using mixture probabilities obtained in a). Draw y^*_{t+1} from the identified component normal distribution. Impute the missing y_{t+1} as $\tilde{y}_{t+1} = y^*_{t+1} + \Delta$.

Step 2. Impute the rest of the missing values of $y_{t+2}, y_{t+3}, \ldots, y_T$ for patients in Pattern t:

Starting with imputation for y_{t+2}, first, similar to Step 1, draw y^*_{t+2} from the normal mixture (6) based on the observed $y_1,\ldots,y_t$ and the already imputed $\tilde{y}_{t+1}$ for the patient. Then the missing y_{t+2} is imputed as $\tilde{y}_{t+2} = y^*_{t+2} + \Delta$ with probability δ_{t+1} and as $\tilde{y}_{t+2} = y^*_{t+2}$ with probability $1 - \delta_{t+1}$, where the mixture probability $\delta_{t+1} = \omega_{t+1,t+1}$ is obtained from (4) given the posterior draw of proportions of observations in each pattern and the posterior draw of regression parameters for the observed data.

Missing values of y_{t+3} through y_T can be imputed similarly as y_{t+2}.

To summarize, the imputations of y_{t+1} through y_T is done recursively within each Pattern t (for all t = 1,...,T – 1) to create a complete dataset after imputation is done for all patterns with missing values.

The above imputation procedure is applied to all subjects in each missing data pattern to create a single imputed data set. Repeating the process of drawing parameters from the posterior distribution and imputing missing data given the posterior draw m times will yield m imputed data sets. The observed or imputed values at the final data point are averaged to obtain the overall mean estimate for each imputed data set, and the multiple imputation estimate is obtained by averaging the estimates across m imputations.

In this sensitivity analysis, m is set to equal to 20. The value of m is discussed in the context of imputation efficiency in standard multiple imputation theory (Rubin, 1987, p. 114), and m = 20 would provide at least 96% of relative efficiency as compared with using an large number of imputations (SAS/STAT User's Guide, p. 3796).

3. **Determination of the Shift Parameter Values**

The common shift parameter Δ is the difference between the mean of y_{t+1} among those who drop out at Visit t and those who remain beyond Visit t ($1 \leq t \leq T$ - 1). The exact value of Δ is unknown and can't be estimated from data because of missingness. The magnitude of Δ depends on the medical aspects of the trial. Using relevant historical data, one may select Δ as a proportion of the sample standard deviation or a proportion of observed treatment efficacy.