NCT03352453

Study ID: RAP-MD-20

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy and Safety Study of Rapastinel for Rapid Treatment of Symptoms of Depression and Suicidality in Adult Patients with Major Depressive Disorder

Statistical Analysis Plan: 20 May 2019

Naurex Inc., an indirect subsidiary of Allergan, plc

5 Giralda Farms
Madison, NJ 07940

RAP-MD-20

A Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy and Safety Study of Rapastinel for Rapid Treatment of Symptoms of Depression and Suicidality in Adult Patients with Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

Version 1.0: 20 May 2019

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[redacted]

LIST OF IN-TEXT FIGURES

1.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BPM	beats per minute
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
DBTP	double-blind treatment period
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ET	early termination
IP	investigational product
IV	intravenous
IWRS	interactive web response system
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MMRM	mixed-effects model for repeated measures

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
SD	standard déviation
[redacted]	[redacted]
SFU	safety follow-up
SI	*Le Système International d'Unités* (International System of Units)
SOC	standard of care
S-STS	Sheehan-Suicidality Tracking Scale
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

2.0 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 and/or specified in the final protocol amendment 2 of RAP-MD-20 (version dated 20 MAY 2019). Specifications of tables, figures, and data listings are contained in a separate document.

RAP-MD-20 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 4-week, fixed-dose study comparing rapastinel with placebo in patients with MDD experiencing suicidality. The study will be approximately 5 to 6 weeks in duration and will include the following periods:

- Approximately 5-day screening period
- 4-week double-blind treatment period (DBTP)
- 1-week safety follow-up period

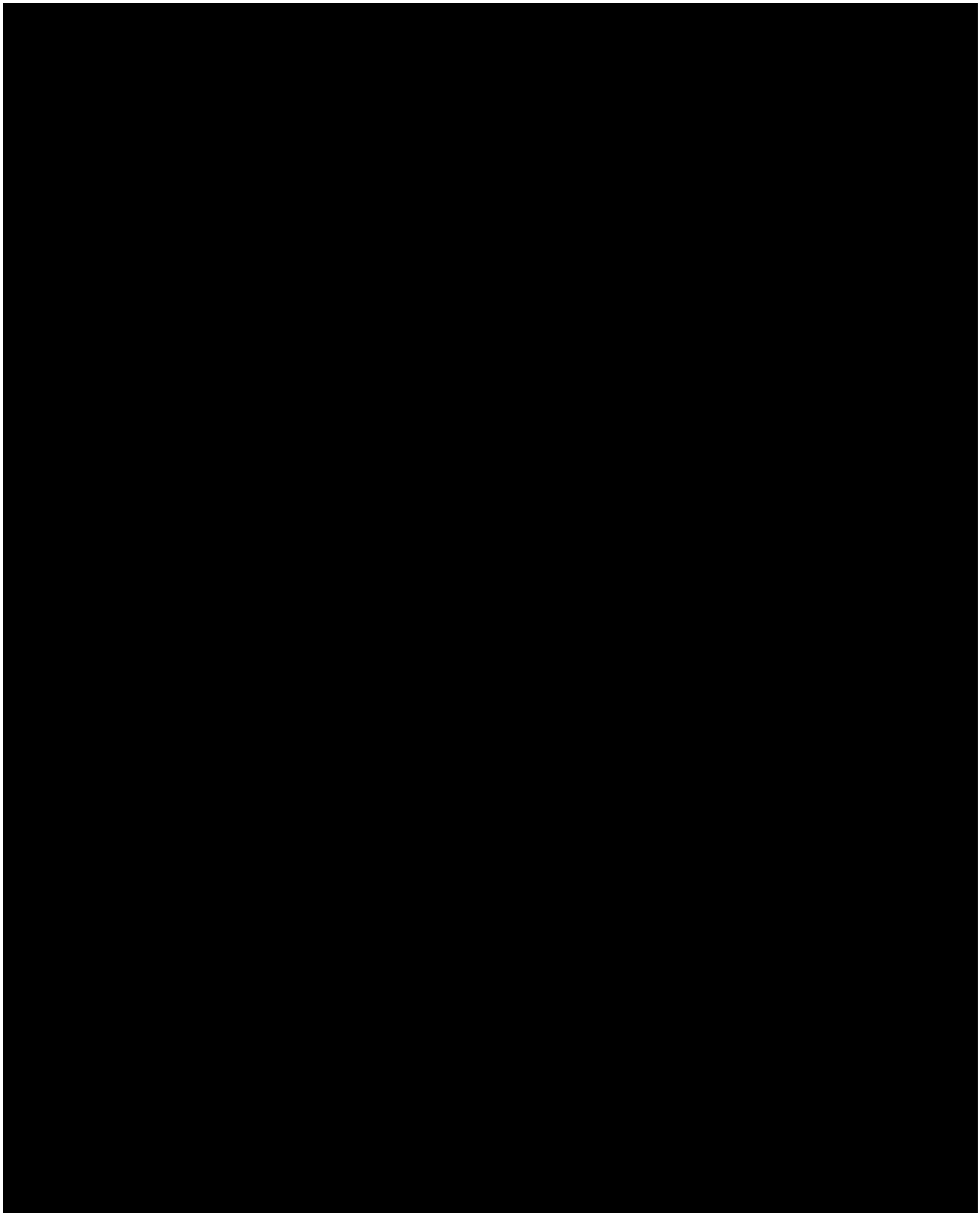
Approximately 300 patients are planned to be randomized in the DBTP (150 patients per treatment group).

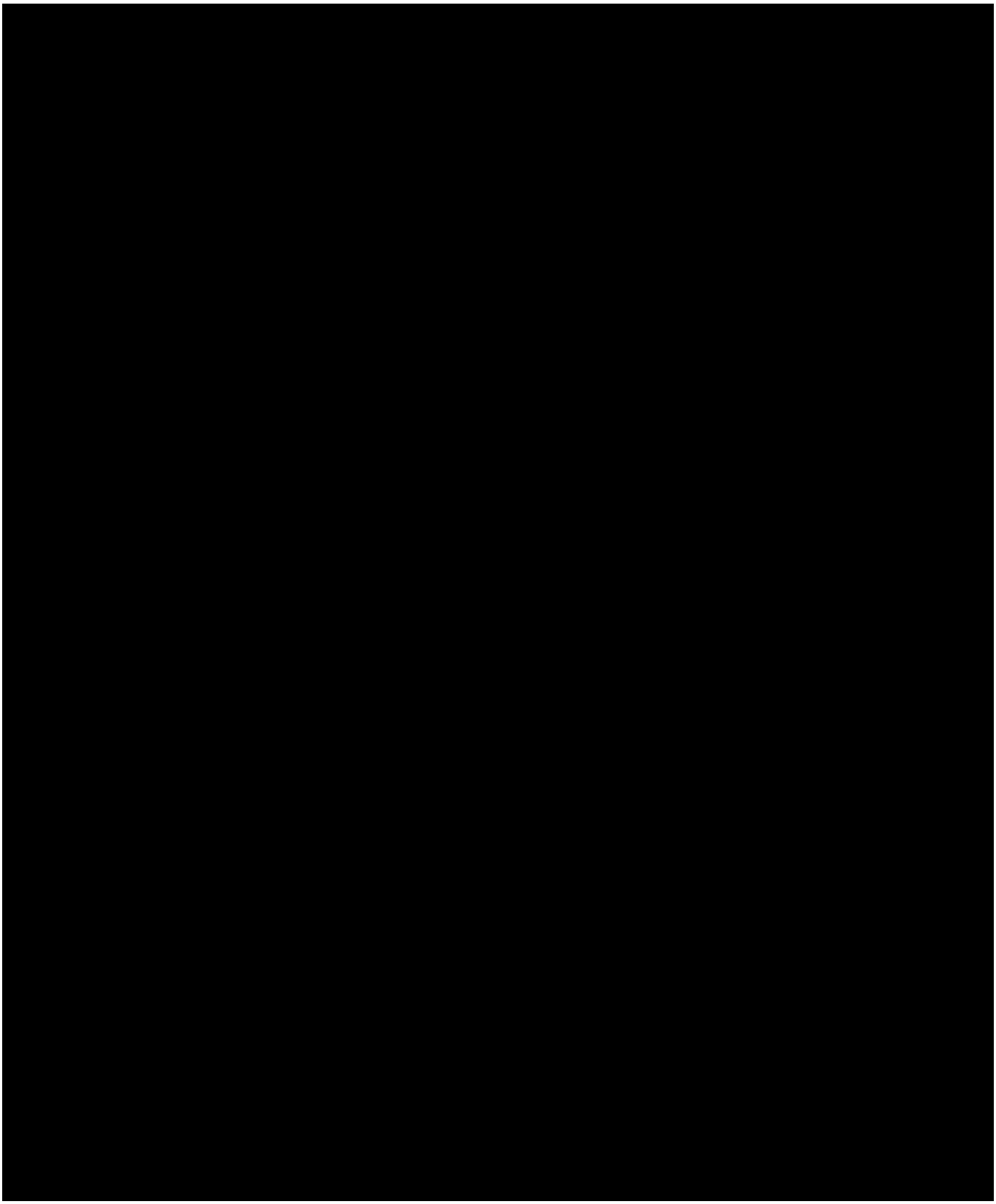
A schematic of the study design is presented in Figure 3–1. The Schedule of Evaluations is provided in Section 3.0.

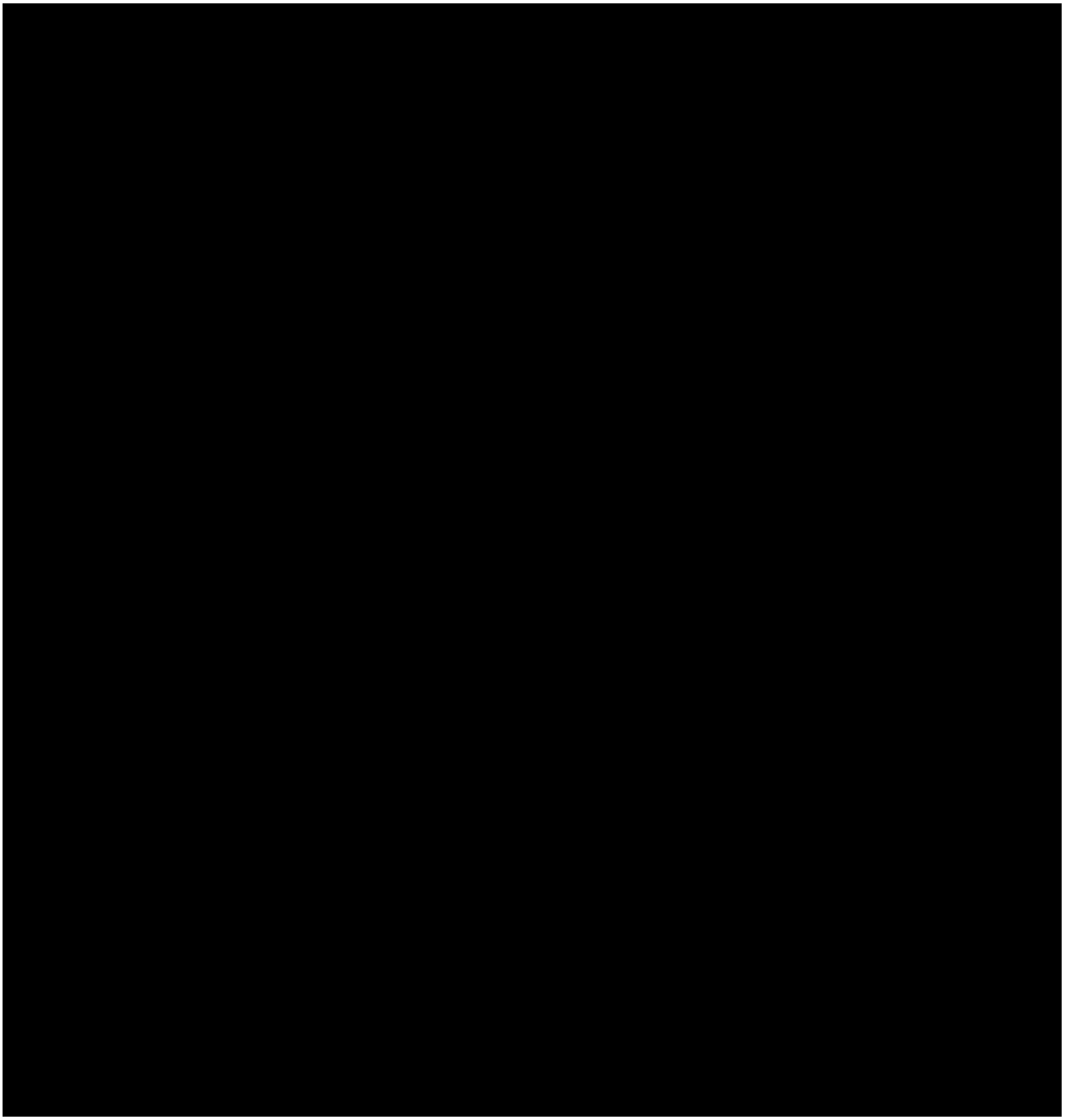
Patients will be randomized in a ratio of 1:1 to 1 of 2 treatment groups in DBTP: rapastinel 450 mg IV weekly injection or placebo IV weekly injection. During participation in the study, patients may be treated per local SOC with limited restrictions and IP will be administered in addition to SOC treatments.

Patients completing the DBTP and patients who prematurely discontinue from the study before completing 4 weeks of double-blind treatment should enter the 1-week safety follow-up period.

Additional follow-up visits may be scheduled within 30 days of last dose of IP or last study visit, if necessary for safety reasons.







4.0 STUDY OBJECTIVES

The objectives of this study are to evaluate the efficacy, safety and tolerability of rapastinel as a rapid treatment of symptoms of depression and suicidality in adult patients with MDD who are at imminent risk of suicide.

Primary Efficacy Objectives

- To evaluate the efficacy of rapastinel (450 mg IV) versus placebo as a rapid treatment of MDD symptoms in adult patients with MDD who are at imminent risk of suicide, as measured by the change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) total score at 1 day after first dose of investigational product (IP)

- To evaluate the efficacy of rapastinel (450 mg IV) versus placebo as a rapid treatment of suicidality symptoms in adult patients with MDD who are at imminent risk of suicide, as measured by the change from baseline on the Sheehan-Suicidality Tracking Scale (S-STS) total score at 1 day after first dose of IP

Key Secondary Efficacy Objectives:

- To evaluate the efficacy of rapastinel (450 mg IV) versus placebo in the treatment of MDD symptoms, as measured by change from baseline MADRS at 28 Days after first dose of IP.

- To evaluate the efficacy of rapastinel (450 mg IV) versus placebo in the treatment of suicidality symptoms, as measured by the change from baseline on the S-STS total score at 28 Days after first dose of IP.

[redacted]

5.0 ANALYSIS POPULATIONS

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

5.1 Randomized Population

The Randomized Population will consist of all screened patients who are randomized to a treatment group in the study.

5.2 Safety Population

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of randomized IP.

5.3 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 postbaseline assessment of the MADRS total score or S-STS total score.

6.0 PATIENT DISPOSITION

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

Screen failures (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 during the same period and who enter the safety follow-up period will be presented for each treatment group and pooled across treatment groups for the randomized population. The reasons for premature discontinuation from the DBTP as recorded on the disposition pages of the eCRFs will be summarized (number and percentage) by treatment group for the randomized population.

6.1 Protocol Deviations

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

7.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

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.

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.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use of the same therapeutic class by a patient will only be counted once.

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

8.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Extent of Exposure

The number and percentage of patients who received 1, 2, 3, and 4 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.

Exposure to the IP for the 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.

8.2 Measurement of Treatment Compliance

Dosing compliance is defined as the total number of IV doses actually taken by a patient during the DBTP divided by the number of IV doses that were expected to be taken during the DBTP multiplied by 100. Descriptive statistics for IP compliance will be presented by treatment group for each week for the Safety Population.

8.3 Weight-Adjusted Dose of Rapastinel

The dose of rapastinel will be divided by patient baseline weight and summarized descriptively by treatment group for the Safety Population.

9.0 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 treatment during DBTP.

For efficacy analyses in which 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. These pseudo-centers will be used for all efficacy analyses when the model is adjusted for study center. 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. 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 participant, only the last assessment will be used in the analysis.

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.

9.1 Primary Efficacy Analysis

The primary efficacy parameters will be the change from baseline in MADRS total score and the change from baseline in S-STS total score at 1 day after first dose of treatment. The primary analysis for both primary efficacy parameters will be performed using analysis of covariance (ANCOVA) models with terms for treatment, study center, and baseline. The analysis will be performed based on postbaseline scores using only the observed cases without imputation of missing values. The treatment difference for rapastinel versus placebo will be estimated and reported along with the corresponding 95% CI and the p-value for superiority testing.

9.2 Secondary Efficacy Analysis

The two key secondary efficacy parameters are:

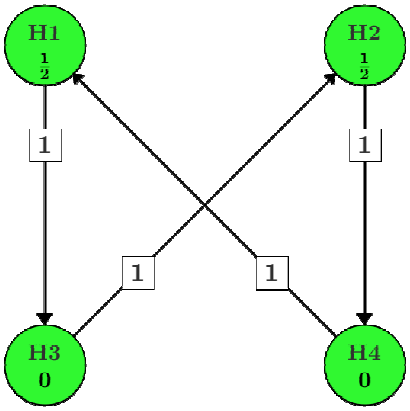
- Change from baseline in MADRS total score at 28 days after first dose of treatment
- Change from baseline in S-STS total score at 28 days after first dose of treatment

Analysis of change from baseline in MADRS total scores and change from baseline in S-STS total score will be performed using mixed-effects model for repeated measures (MMRM) with terms for treatment, study center, visit, 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). The treatment difference for rapastinel versus placebo at selected timepoints will be estimated and reported along with the corresponding 95% CI and the p-value for superiority testing.

In the case that the MMRM 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 model still does not converge after using those initial values, simplified covariance structures will be used to fit the model in the following order: (1) ante-dependence, (2) heterogeneous autoregressive, (3) Toeplitz, and (4) compound symmetry. If MMRM still fails to converge, by visit ANCOVA model similar to the primary efficacy analysis will be used for the analysis.

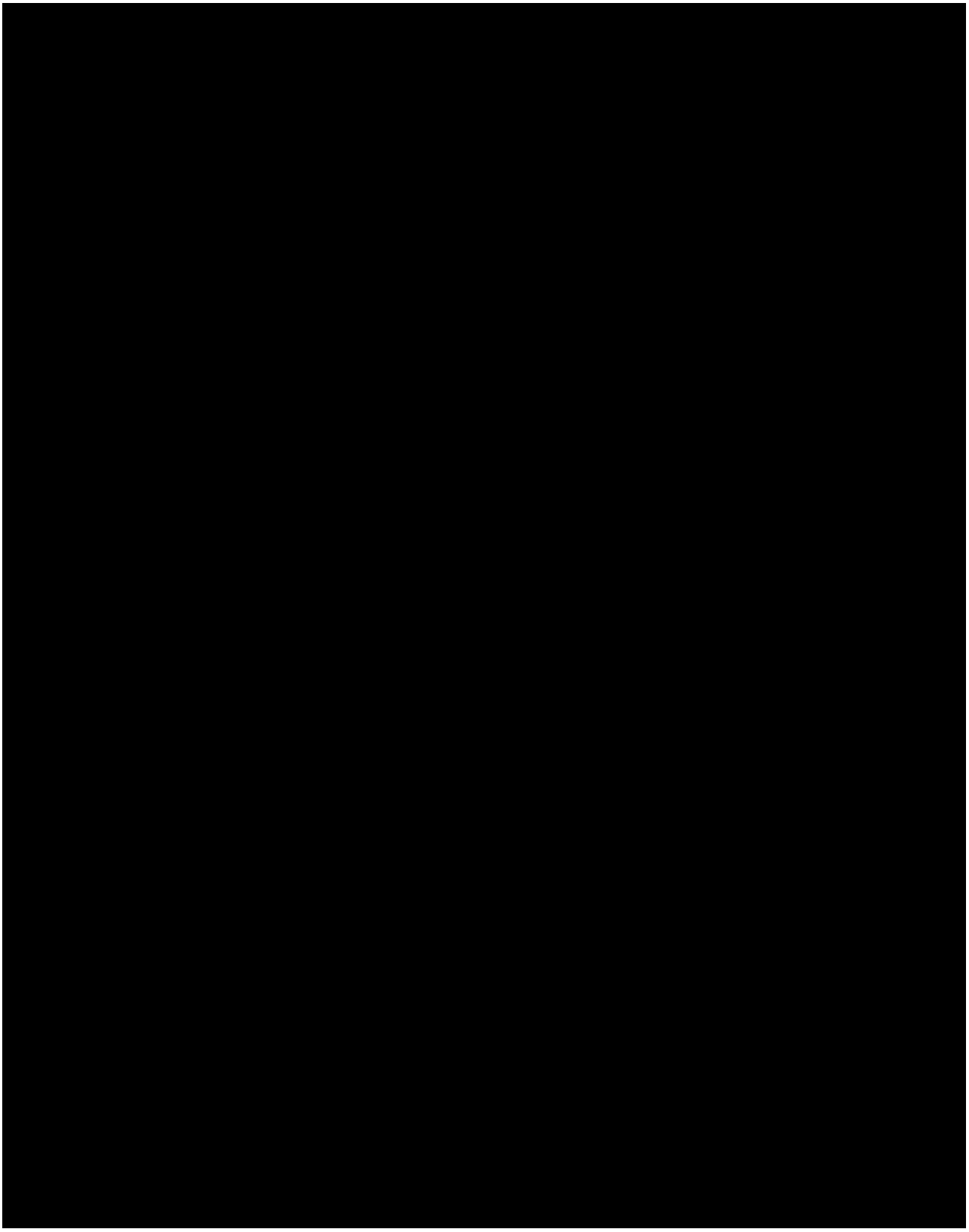
Let H1 and H2 represent the treatment effect comparisons of rapastinel with placebo in regards to the primary efficacy parameters of change from baseline in MADRS total score and change from baseline in S-STS total score at 1 day after first dose of treatment, respectively; and let H3 and H4 represent the treatment effect comparisons of rapastinel with placebo in regards to the secondary efficacy parameters of change from baseline in MADRS total score and change from baseline in S-STS total score at 28 days after first dose of treatment. The graphical procedure displayed in Figure 9.2-1 will be employed to control the overall familywise error rate at α=0.049.

Figure 9.2-1. Graphical Testing Procedure



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

[redacted]



[redacted]

[redacted]

10.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* and reported separately for DBTP and Safety Follow-up (SFU).

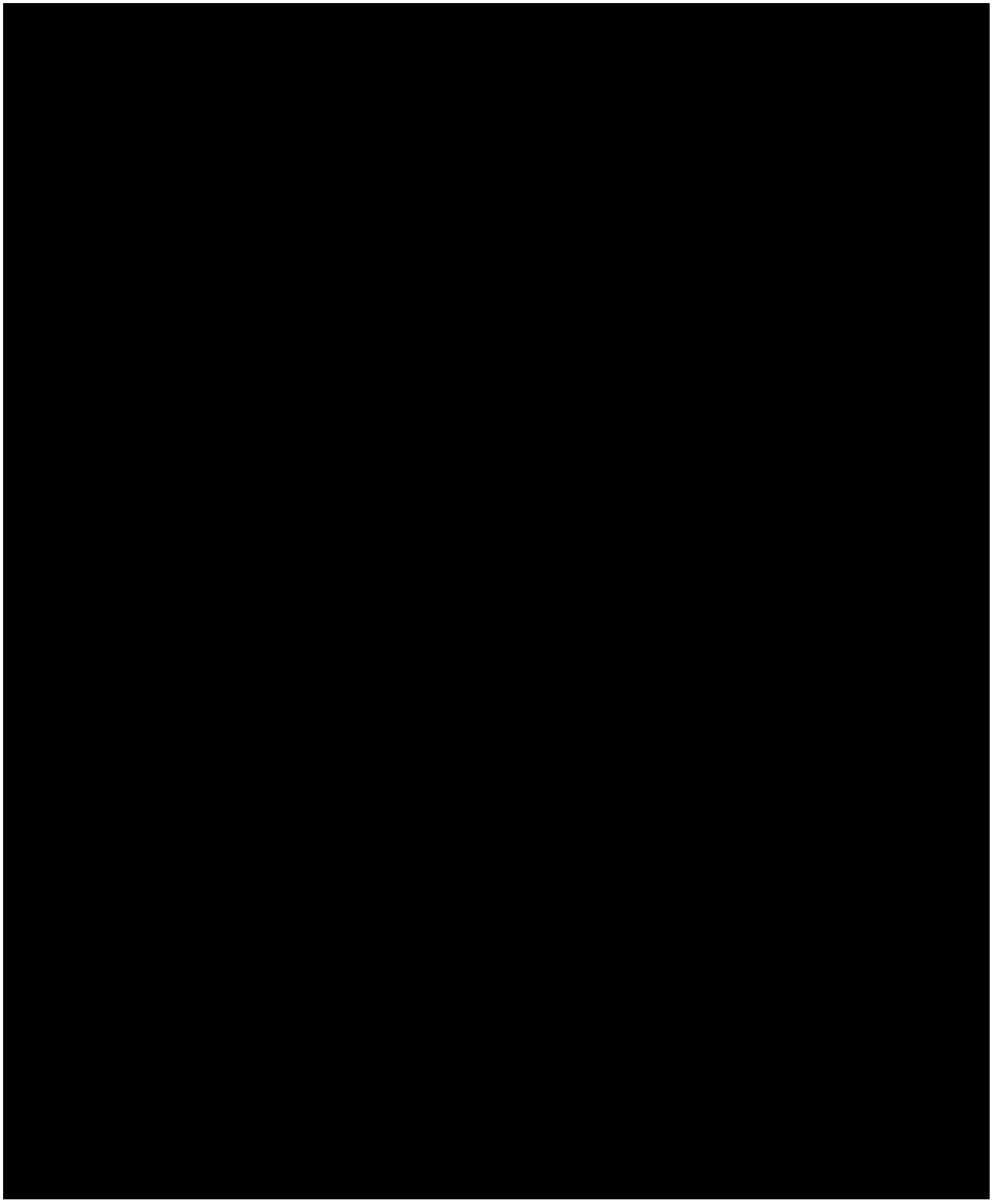
An AE (classified by preferred term) will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of DB IP or was present before the date of the first dose of DB IP and increased in severity after the first dose of DB IP. An AE that becomes serious after the 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 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 (≥ 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 SFU, and patients discontinuing because of AEs occurring before the start of IP will be included in these listings.



[redacted]

[redacted]

[redacted]

[redacted]

10.6 Interim Analysis

An unblinded interim analysis will be conducted to identify early signs of futility. An internal, but separate, fire-walled 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. To maintain the scientific reliability of statistical analyses after the final database lock, preserve the integrity of study conduct, and guard from introducing any potential bias into the conduct of the study and/or analysis of its results, individuals in these two groups will not be involved in any operational aspects of the trial. 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 2-sided, respectively) 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 validity, team structures, and responsibilities, are documented within a separate Data Review Committee Charter.

11.0 DETERMINATION OF SAMPLE SIZE

This study will randomize approximately 300 patients to the rapastinel 450 mg and placebo groups in a 1:1 ratio. The sample size is determined based on the primary efficacy endpoint of the change from baseline in the MADRS total score at 1 day after the first dose of treatment. Assuming the SD of the change from baseline in the MADRS total score is 10 points, a sample size of 150 patients per treatment group will provide about 90% power to detect a difference of 3.76 points for a rapastinel dose versus placebo at a 2-sided significance level of 4.9%.

With respect to S-STS total score, 150 patients per arm will provide approximately 88% power for a treatment difference of 4 between rapastinel 450 mg and placebo and estimated standard deviation of 11 based on the blinded analysis in April 2019 at a 2-sided significance level of 4.9%.

12.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using [redacted].

13.0 STATISTICAL AND DATA HANDLING CONVENTIONS

13.1 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, 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.

13.2 Visit Windows

Table 13.2–1 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 13.2–1. Visit Windows

Analysis Visit	Target Date	Analysis Window (Based on Date)
Day 0 (Baseline)	IndexA[a]	Last record on or before IndexA[a]
Hour 4	IndexA[a]	(IndexA[a], 6 hours after IndexA[a]]
Day 1	IndexA[a]+1	(6 hours after IndexA[a], IndexA[a]+1]
Day 4	IndexA[a]+4	[IndexA[a]+2, IndexB[b]-1]
Day 7	IndexB[b]	IndexB[b]
Day 8	IndexB[b]+1	[IndexB[b]+1, IndexC[c]-1]
Day 14	IndexC[c]	[IndexC[c], IndexD[d]-1]
Day 21	IndexD[d]	[IndexD[d], IndexD[d]+3]
Day 28	IndexD[d]+7	[IndexD[d]+4, day of final double-blind visit or early-termination visit occurring after IndexD[d]+3]
Day 35	IndexD[d]+14	Within the safety follow-up phase

a IndexA: Date of the first dose

b IndexB: Date of the second dose or IndexA+7 if the second dose was not administered

c IndexC: Date of the third dose or IndexB+7 if the third dose was not administered or IndexA+14 if both the second and the third dose were not administered

d IndexD: Date of the fourth dose or IndexC+7 if the fourth dose was not administered or IndexB+14 if both the third and the fourth dose were not administered or IndexA+21 if the second, third and fourth dose were not administered

e [redacted], the visit windows for Days 0 and 7 will be extended to cover the next dosing day (IndexB and IndexC, respectively); the visit window for Day 21 will be IndexD to the last double-blind visit, inclusively.

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.

13.3 Derived Efficacy and Safety Variables

The total score of each variable including MADRS, [redacted] at a particular visit will be calculated using (sum of nonmissing items) × (total number of items) / (number of non-missing 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.

Specifically, if more than 2 items are missing for MADRS, then the total score will be set to missing; [redacted]

Derivation of S-STS total score is detailed in Appendix II.

13.4 Repeated or Unscheduled Assessments of Safety Parameters

If a patient has repeated assessments before the start of the first treatment, the results from the last non-missing assessment made prior to the start of the IP 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.

13.5 Missing Severity Assessment for Adverse Events

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

13.6 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 IP, a causality of yes will be assigned. The imputed values for causal relationship to IP will be used for the incidence summary; the values will be shown as missing in the data listings.

13.7 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 IP, the month and day of the first dose of 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 IP, *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 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 start date are the same as the month and year of the first dose of IP, the day of the first dose of 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 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 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 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 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 IP, the date of the first dose of IP will be assigned to the missing start date.

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

13.8 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. 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 non-imputed start date), the start date will be the imputed stop date.

13.8.1 Incomplete Start Date

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

Missing month and day

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

13.8.2 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 last dose of IP, the month and day of the last dose of 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 IP, *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 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 last dose of IP, the day of the last dose of 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 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 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 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 IP, the first day of the month will be assigned to the missing day.

[redacted]

14.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the final protocol Amendment 2 (version dated 20 MAY 2019).

15.0 REFERENCES

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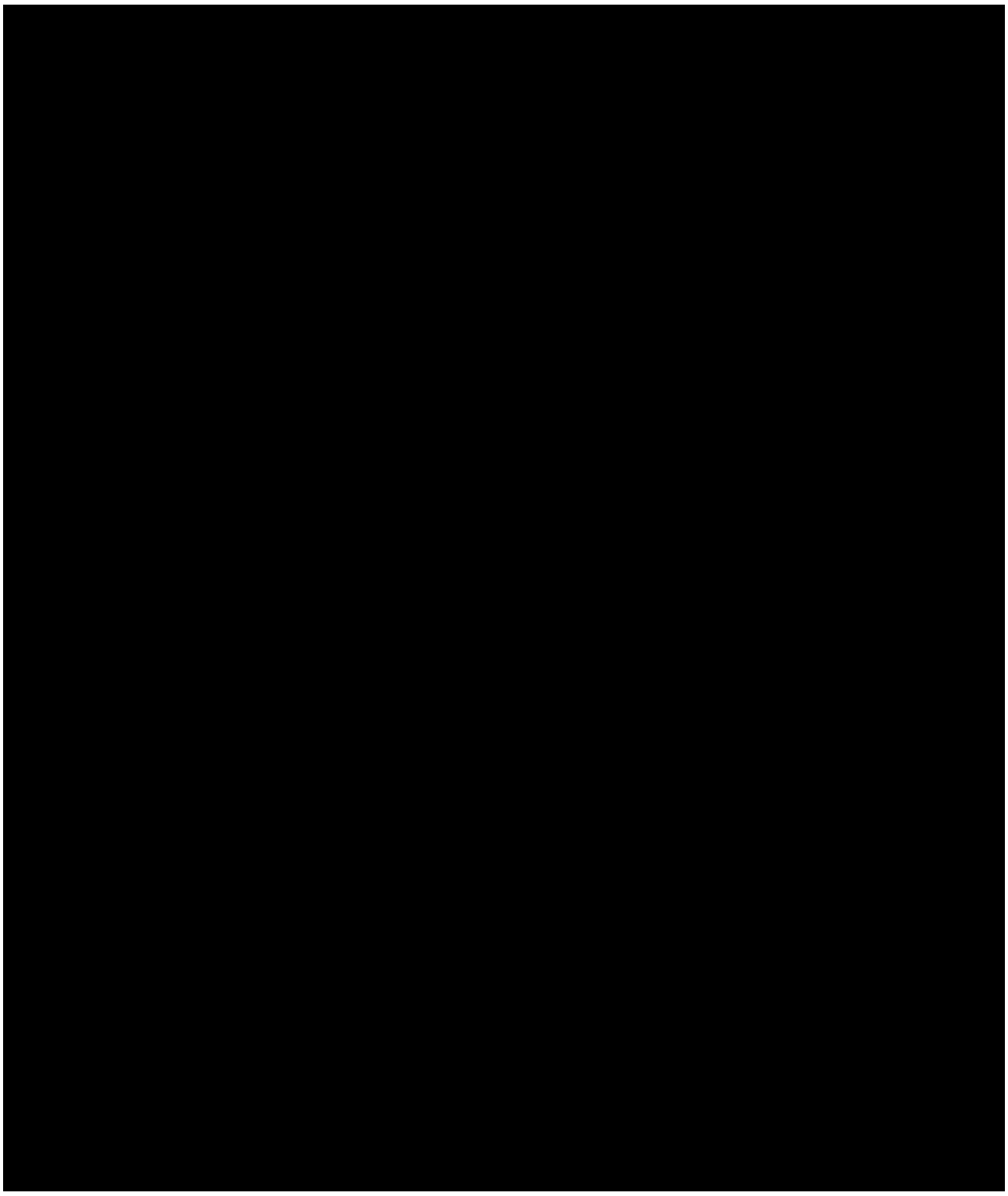

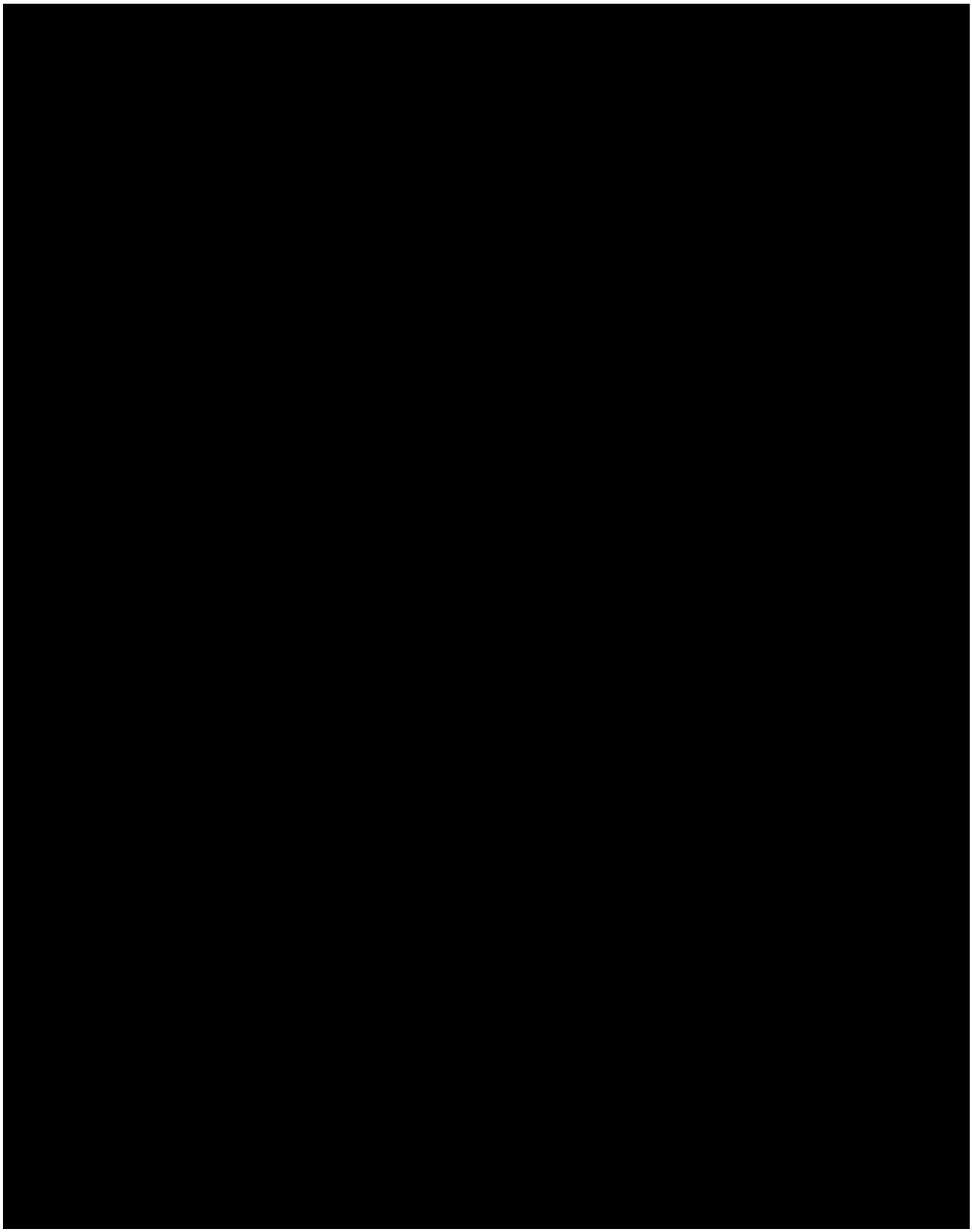

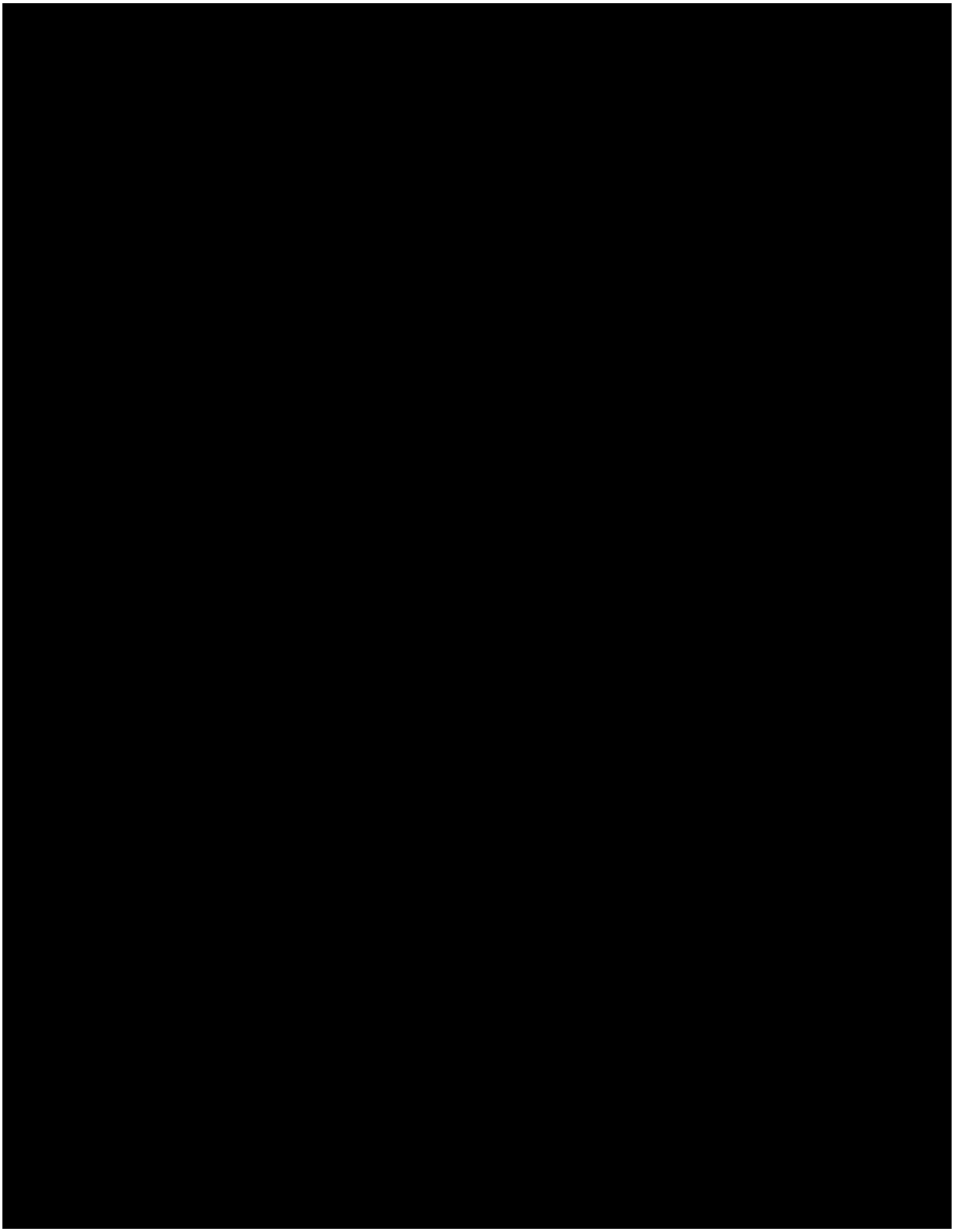

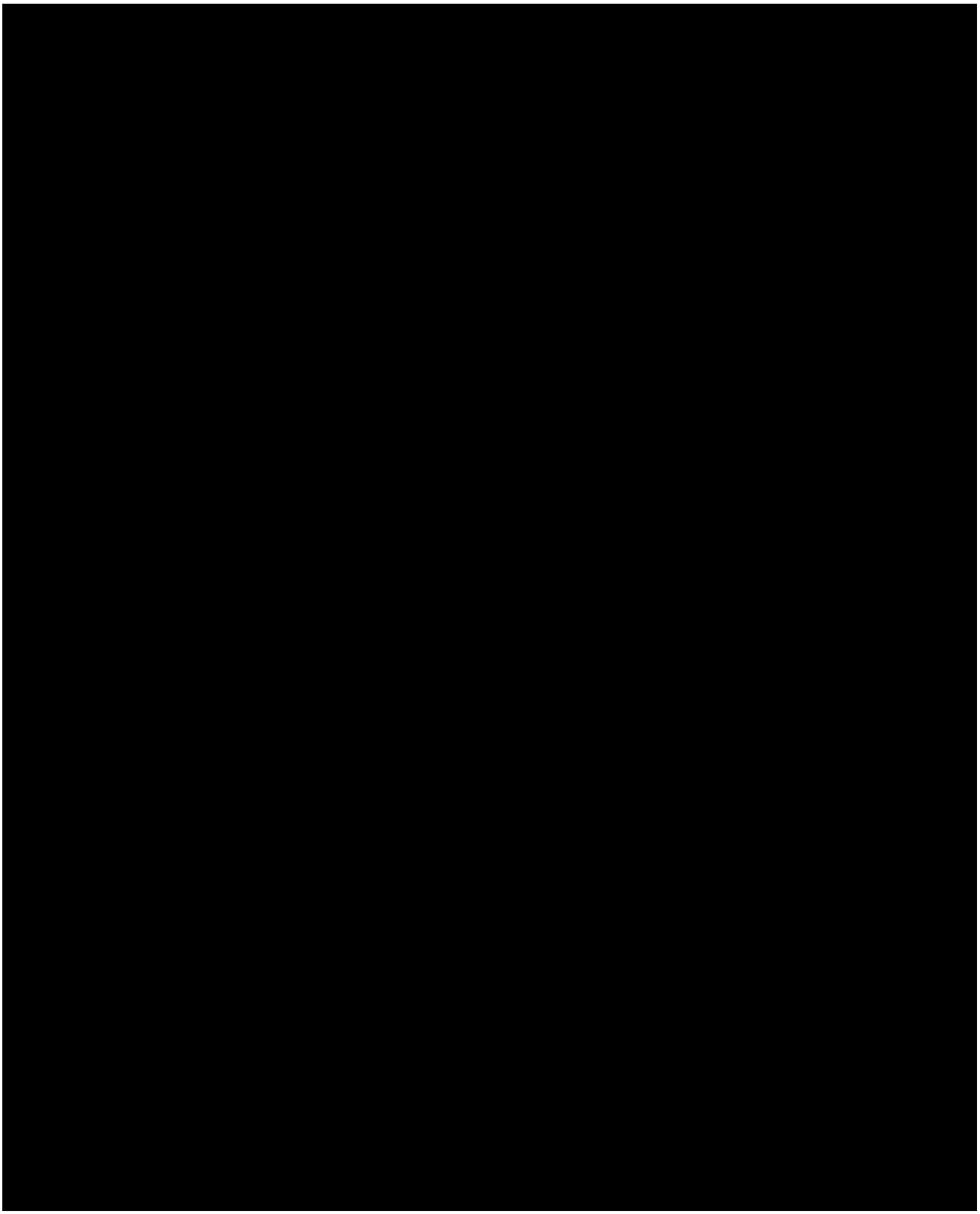

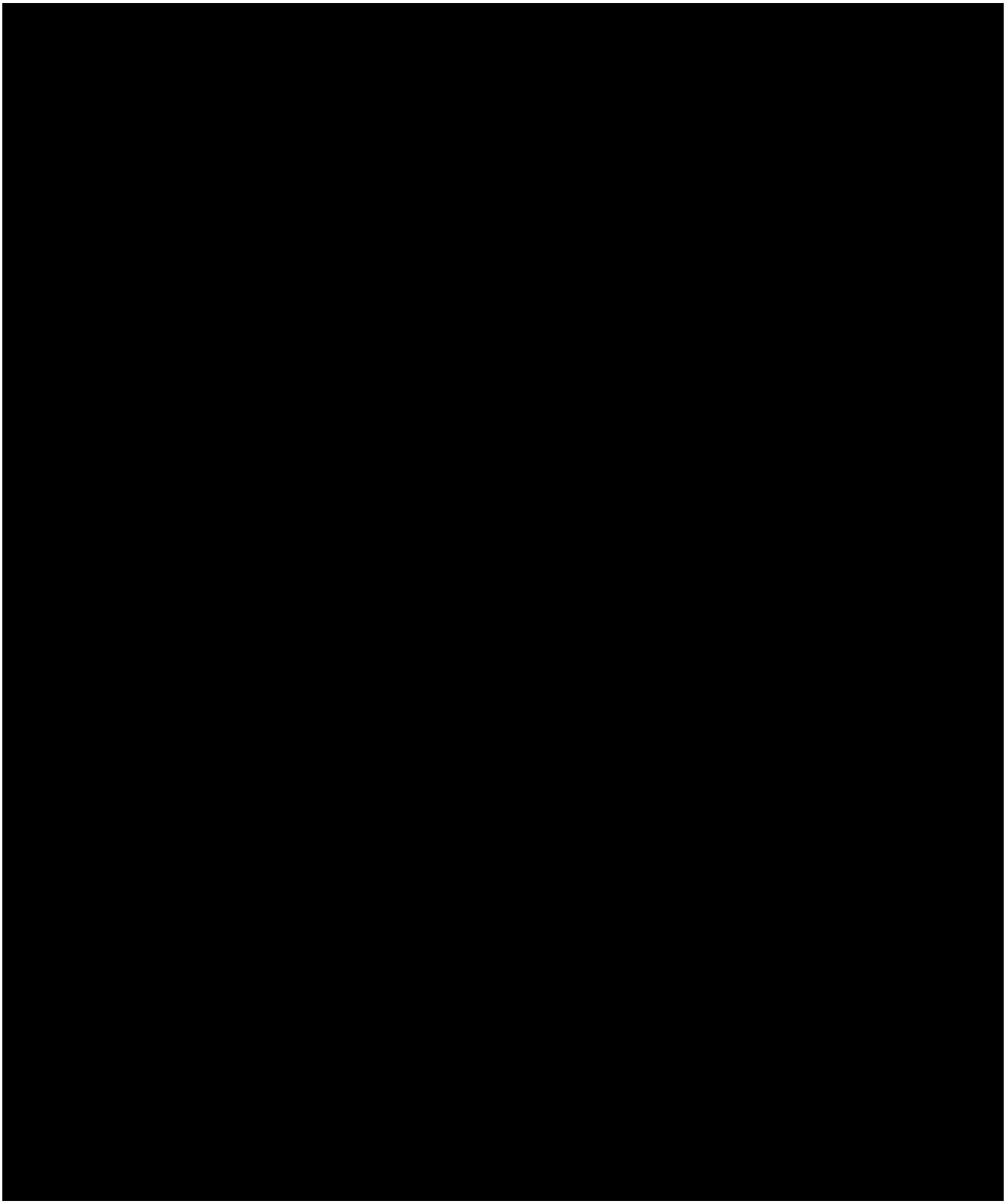

17.0 HISTORY OF CHANGES

Date	Section	Description