NCT03002077

Study ID: RAP-MD-06

Title: An Open-label, Long-term Safety Study of Rapastinel as Adjunctive Therapy in Patients With Major Depressive Disorder

Statistical Analysis Plan Date: 11 Dec 2018

Naurex, Inc., an indirect subsidiary of Allergan, plc.
5 Giralda Farms
Madison, NJ 07940

RAP-MD-06

An Open-label, Long-Term Safety Study of Rapastinel as Adjunctive Therapy in Adult Patients with Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

Final SAP Date: **11 Dec 2018**

TABLE OF CONTETNS

List of Tables

1.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BP	blood pressure
BPRS+	Brief Psychiatric Rating Scale – Positive Symptoms Subscale
CADSS	Clinician Administered Dissociative States Scale
[redacted]	[redacted]
CPK	creatinine phosphokinase
[redacted]	[redacted]
DBTP	double-blind treatment period
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
[redacted]	[redacted]
ET	early termination
GGT	gamma glutamyl transferase
HDL	high-density lipoprotein
[redacted]	[redacted]
ICF	informed consent form
ITT	intent-to-treat
IP	investigational product

IV	intravenous(ly)
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
mITT	modified Intent-to-Treatment
NEAE	new emergent adverse event
OLTP	open-label treatment period
PCS	potentially clinically significant
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
SCID	Structured Clinical Interview for Diagnostic Statistic Manual of Mental Health Disorders, Fifth Edition
SD	standard deviation
SDC	symbol digit coding
SOC	system organ class
SI	*Le Système International d'Unités* (International System of Units)
TBL	total bilirubin
TEAE	treatment-emergent adverse event

TESAE	treatment-emergent serious adverse event
UDS	urine drug screen
ULN	upper limit of normal

2.0 INTRODUCTION

This statistical analysis plan (SAP) 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 #2 dated 13 Nov 2018.

Study RAP-MD-06 is a Phase 3, multicenter, open-label study to evaluate the long-term safety and tolerability of rapastinel as adjunctive therapy to ADT in adult patients with MDD who either completed the RAP-MD-04 Double-blind Treatment Period (DBTP) at Visit 122 (Week 104, ET) or who do not meet criteria to be randomized into the DBTP of RAP-MD-04 and are therefore discontinued from that study. The protocol made provision for the potential enrollment of patients who did not participate in RAP-MD-04 (identified as *de novo* enrollment patients) at some study centers if enrollment of rollover patients did not meet targeted projections. However, the enrollment of *de novo* patients was never initiated and at the time of SAP writing, there will be no *de novo* patients in the final database. Therefore, statistical analyses related to *de novo* patients will not be addressed in this SAP, but refer to corresponding protocol sections.

The study will be conducted in the following periods:

- Up to 2-week screening period (only for *de novo* patients)
- Up to 52-week Open-Label Treatment Period (OLTP)
- 2-week safety follow-up period

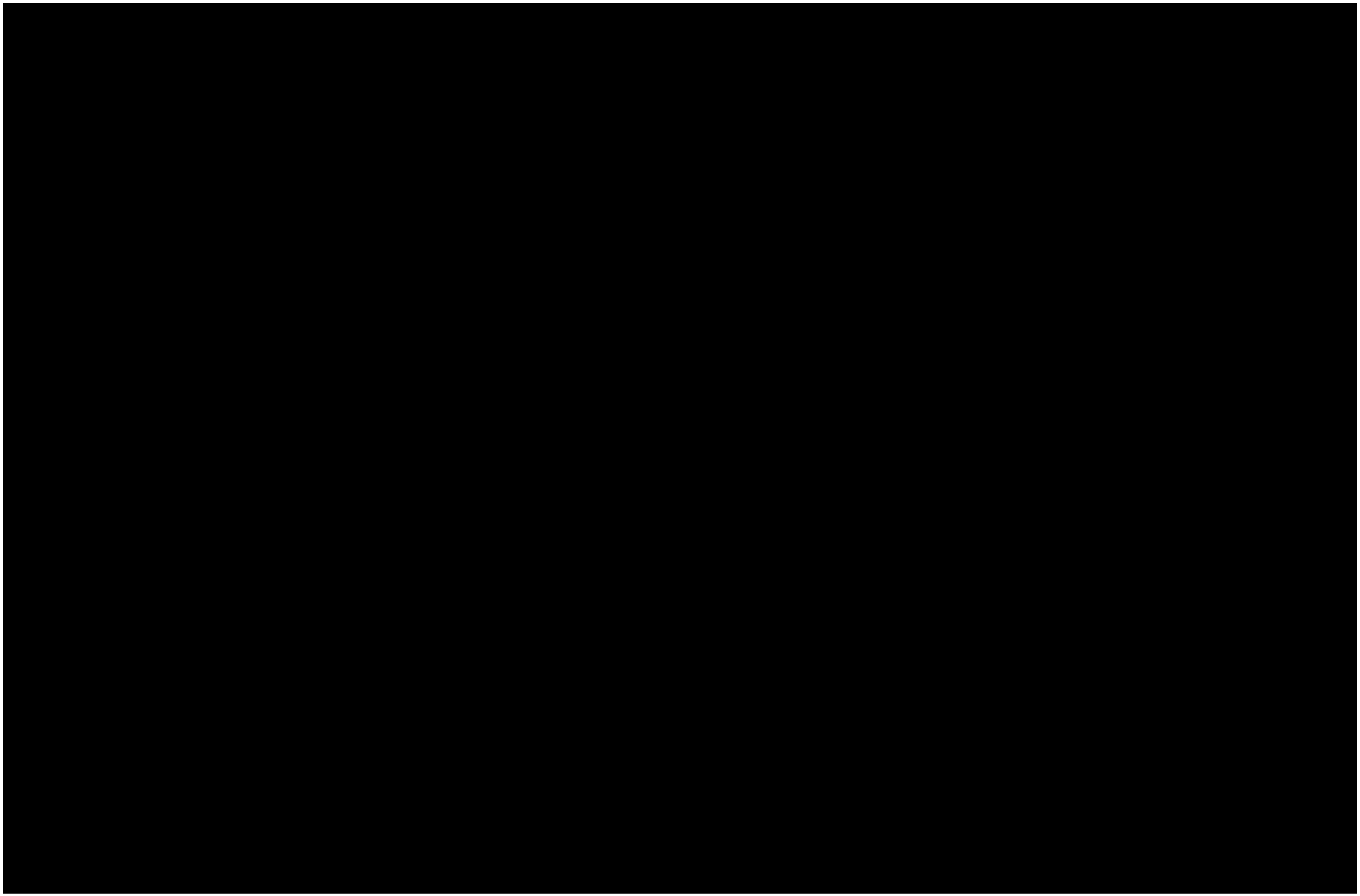
This study is planned to be terminated when 100 patients have completed the 52-week OLTP. The actual sample size is expected to be larger than 100 patients and some patients will have less than 52 weeks of open-label treatment (as many as 500 patients are expected to enter the OLTP of Study RAP-MD-06).

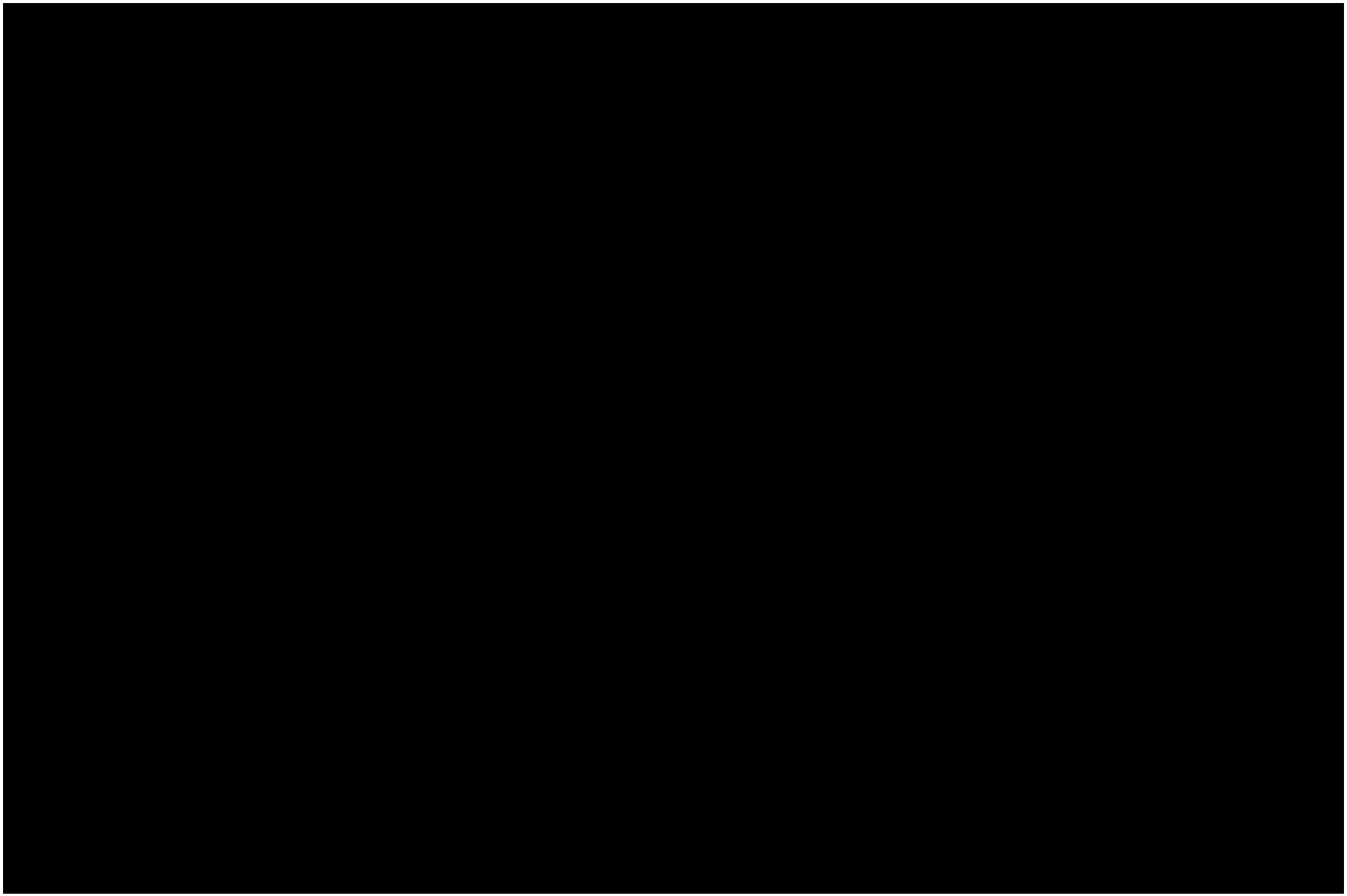
Patients enrolling from study RAP-MD-04 will begin receiving 450 mg intravenous (IV) at OLTP Visit 1.

All patients will receive open-label rapastinel at 450 mg IV (adjunctive to ADT), either weekly or once every two weeks, based upon the Investigator's discretion in the OLTP. Patents will skip odd-numbered visits (after visit 2) if being treated on a biweekly basis. The once-every-2-weeks schedule can only be initiated on even-numbered visits in order to maintain the appropriate visit schedule. Patients who are on a once-every-2-weeks schedule can be transitioned back to weekly visits at any visit.

Patients completing 52 weeks of open-label treatment or patients prematurely discontinuing will undergo a safety follow-up period of 2 weeks. Additional follow-up visits may be scheduled within 30 days, if necessary, for safety reasons.

Table 2–1 below presents the Schedule of Evaluations for the study.





3.0 OBJECTIVES

The objective of this study is to evaluate the long-term safety and tolerability of rapastinel as adjunctive to ADT in patients with MDD.

Safety Objectives

- To evaluate the safety and tolerability of rapastinel (450 mg IV weekly or once every 2 weeks [biweekly]) as an adjunct to ongoing ADT, as evaluated by AEs, clinical laboratory measures, ECGs, vital signs, and [redacted]

- To evaluate the psychotomimetic effects of rapastinel (450 mg IV weekly or once every 2 weeks) as an adjunct to ongoing ADT, as measured by the change from baseline in BPRS+ at all postdose evaluations

- To evaluate the dissociative effects of rapastinel (450 mg IV weekly or once every 2 weeks) as an adjunct to ongoing ADT, as measured by the change from baseline in CADSS at all postdose evaluations

4.0 PATIENT POPULATIONS

Two populations will be considered in the statistical analysis of the study, as specified in the following subsections. All patients will be combined into one treatment group: Rapastinel 450 mg, for statistical analyses purposes.

4.1 SAFETY POPULATION

The Safety Population will consist of all screened patients who receive at least 1 dose of rapastinel during the OLTP of the study.

4.2 MODIFIED INTENT-TO-TREAT POPULATION

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

5.0 PATIENT DISPOSITION

The number of patients in the 2 analysis populations will be summarized by study center.

The number and percentage of patients who complete the OLTP, who prematurely discontinue from the OLTP, and who complete the safety follow-up period will be summarized overall and by reasons for premature discontinuation for the Safety Population.

5.1 PROTOCOL DEVIATIONS

The number and percentage of patients with significant protocol deviations will be summarized for all patients in the Safety Population. Protocol deviations will be defined in the Protocol Deviation Requirement Specification, including significance classification.

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

Medical and surgical history, psychiatric history, previous treatment with psychotropic medication, and nondrug psychiatric treatment will be summarized for the Safety Population. *Prior medication* will be defined as any medication started before the date of first dose of IP in the first lead-in study. *Concomitant medication* during the OLTP will be defined as any medication taken on or after the date of the first dose of open-label IP during the OLTP.

The use of prior medication will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the Safety Population. Concomitant medications during the OLTP will be summarized by the number and percentage of patients 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. Concomitant medications started after the last visit of the OLTP will not be summarized but will be included in the data listings.

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

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

7.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

7.1 EXTENT OF EXPOSURE

Exposure to rapastinel for the Safety Population during the OLTP will be summarized descriptively for treatment duration, calculated as the number of days from the date of the first dose of open-label rapastinel taken to the date of the last dose taken during the OLTP, inclusive.

In addition, dosing frequencies will be summarized. Dosing frequency is defined by number of days between two consecutive visits; weekly dosing is defined as two consecutive visits occurring with 4 to 10 days apart, and biweekly dosing is defined as two consecutive visits occurring with 11 to 17 days apart. Sustained bi-weekly dosing, defined as bi-weekly dosing at least 3 times in a row, will also be summarized. Descriptive statistics will be provided for average doses taken per week. Average doses taken per week are defined as total doses taken during the OLTP divided by the number of weeks till the patients took the last dose.

The number and percentage of patients taking each qualifying ADT in the OLTP will be summarized for the mITT Population. Mean daily dose (calculated as the total dose taken by the patient during a specified study period divided by the patient's treatment duration during that specified study period measured in days) and duration of treatment with each qualifying ADT will be summarized using descriptive statistics in the OLTP for the mITT Population.

7.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the total number of IV doses actually taken by a patient during that period divided by the number of IV doses that were expected to be taken during the same period multiplied by 100. The total number of IV doses actually taken during a specific time period is calculated as the sum of IV doses taken during that study period as obtained from the study medication exposure record. The number of IV doses expected to be taken for a specific study period will be the number of weeks that a patient was prescribed rapastinel IV in that study period. Descriptive statistics for IV compliance will be presented for each week, as well as for the whole OLTP for the Safety Population.

Dosing compliance for the background ADT during a specified period is defined as the doses actually taken by a patient during that period divided by the dose expected to be taken during the same period multiplied by 100. The total ADT dose actually taken during a specific time period is calculated as the sum of ADT dose taken during that study period as obtained from the study medication *Exposure: Background Antidepressant CRFs*. The total ADT dose expected to be taken for a specific study

period will be obtained from the same CRFs. Descriptive statistics for ADT compliance during the OLTP will be presented for each ADT for the mITT Population.

7.3 WEIGHT ADJUSTED DOSE OF RAPASTINEL

The dose of rapastinel for each patient will be divided by corresponding patient's weight assessed at Visit 1 and summarized descriptively overall for Safety Population.

8.0 EFFICACY ANALYSES

The main objective of this study is to evaluate safety and tolerability. All efficacy analyses will be performed using the mITT Population. The Day 0 assessment of the first lead-in study will be used as the baseline. The Day 0 assessment of the first lead-in study is the last non-missing assessment before the first dose of Double-Blind IP during the placebo lead-in period of their respective first lead-in study. All efficacy analysis will be descriptive.

[redacted]:

[redacted]

9.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety assessments collected at an unscheduled visit during the safety follow-up period will be included in the data listing for the corresponding parameter.

The safety parameters will include AEs, clinical laboratory, vital signs, and ECG parameters, and the BPRS+, CADSS, [redacted]. The baseline of the first lead-in study (the last non-missing assessment prior to the first dose of double-blind IP during the placebo lead-in period of their respective first lead-in study) will be used as the baseline for all analyses of that safety parameter, unless stated otherwise.

9.1 ADVERSE EVENTS

AEs will be coded using the *Medical Dictionary for Regulatory Activities (MedDRA)*. An AE (classified by preferred term) that occurs during the OLTP or thereafter will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of IP in the first lead-in study or was present before the first dose of IP in the first lead-in study and increased in severity during the OLTP or thereafter. If more than 1 AE is reported before the first dose of IP in the first lead-in study and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the OLTP or thereafter that were also coded to that preferred term. An AE that occurred more than 30 days after the date of the last dose of open-label IP will not be counted as a TEAE. An AE that becomes serious during the OLTP or thereafter will also be considered as TEAE.

A AE occurring during the OLTP will be considered a newly emergent AE (NEAE) if the AE was not present before the first dose of open-label IP or was present before the first dose of open-label IP but increased in severity during the OLTP. A AE occurring during the safety follow-up period will be considered a newly emergent AE (NEAE) if the AE was not present before Visit 54 or was present before Visit 54 but increased in severity during the safety follow-up period. An AE that becomes serious during the OLTP or thereafter will also be considered as an NEAE for OLTP or thereafter. The number and percentage of patients reporting NEAEs during the OLTP will be summarized by system organ class (SOC) and preferred term. An AE that occurs more than 30 days after the date of the last dose of IP will not be considered an NEAE.

The number and percentage of patients reporting TEAEs will be tabulated by SOC 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 distribution of TEAEs by severity and relationship to the IP will be summarized. An AE that occurs more than 30 days after the date of the last dose of IP will not be summarized.

The incidence of common (in ≥ 2% of patients) TEAEs during the OLTP or thereafter will be summarized by preferred term and will be sorted by decreasing frequency.

An SAE that occurred between the date of the first dose of the open-label IP and 30 days after the date of the last dose of IP, inclusive, will be considered a treatment-emergent SAE (TESAE). The number and percentage of patients who have TESAEs will be summarized by preferred term. In addition, the incidence of TESAEs that led to death will be summarized separately by preferred term.

The incidence of TEAEs leading to premature discontinuation of IP during the OLTP and the safety follow-up period will be summarized by preferred term and will be sorted by decreasing frequency.

Listings will be presented for all 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 IP will be included in these listings.

9.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline values at each assessment timepoint will be presented for the following clinical laboratory parameters.

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point (including the end of the open-label treatment period) will be presented for selected clinical laboratory parameters listed in Appendix I. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix I.

Hematology: Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Sodium, potassium, calcium, chloride, bicarbonate, magnesium, gamma glutamyl transferase, phosphate, glucose, blood urea nitrogen, creatinine, creatine phosphokinase (CPK), total protein, alkaline phosphatase (ALP), albumin, bilirubin (total; direct; indirect), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides

Urinalysis: Specific gravity, pH, protein, glucose, ketones, and blood

Laboratory test values are considered to be potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 9.2–1. The number and percentage of patients with potentially clinically significant (PCS) clinical laboratory values will be summarized for the OLTP. The PCS criteria will be displayed in SI units. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment during the OLTP. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value during the OLTP. In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of study for clinical laboratory parameters will be presented for the following categories: low, normal, and high, which are provided by the laboratory vendor.

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of ALT or AST ≥ 3x ULN, along with total bilirubin (TBL) ≥ 2x ULN and a non-elevated ALP < 2x ULN, all based on blood draws collected within a 24-hour period. Potential Hy's Law criteria without time window is defined by a post baseline elevation of maximum ALT or AST ≥ 3x ULN, along with maximum TBL ≥ 2x ULN.

Patients who meet the potential Hy's Law criteria from the first dose of IP in this study to within 30 days after the last dose of IP will be summarized.

Table 9.2–1. Criteria for Potentially Clinically Significant Laboratory Values in SI Units

Laboratory Parameter	*SI Unit*	*Conventional Unit*	*PCS Criterion[b] Low Value*	*PCS Criterion[b] High Value*
Hematology				
Hemoglobin	g/L	g/dL	< 0.9 × LLN	—
Hematocrit	Volume fraction	%	< 0.9 × LLN	—
Eosinophils	%	%	—	> 10
Neutrophils	%	%	< 30	> 90
Basophils	%	%	—	> 6
Monocytes	%	%	—	> 20
Lymphocytes	%	%	< 10	> 60
Absolute neutrophil count	× 10^9/L	1000/μL	< 1.0	—
Platelet count	× 10^9/L	1000/μL	≤ 75	≥ 700
White blood cell count	× 10^9/L	1000/μL	≤ 2.5	≥ 15
Chemistry				
Albumin	g/L	g/dL	< 0.9 × LLN	> 1.1 × ULN
ALP	U/L	U/L	—	≥ 3 × ULN

Table 9.2–1. Criteria for Potentially Clinically Significant Laboratory Values in SI Units

ALT	U/L	U/L	—	≥ 3 × ULN
AST	U/L	U/L	—	≥ 3 × ULN
Gamma-glutamyl transferase (GGT)	U/L	U/L	—	≥ 3 × ULN
Lactate dehydrogenase (LDH)	U/L	U/L	—	≥ 3 × ULN
Blood urea nitrogen or Urea	mmol/L	mg/dL	—	> 1.2 × ULN
Calcium	mmol/L	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Total cholesterol	mmol/L	mg/dL	—	> 1.3 × ULN
HDL cholesterol	mmol/L	mg/dL	< 0.8 × LLN	—
LDL cholesterol	mmol/L	mg/dL	—	> 1.2 × ULN
CPK	U/L	U/L	—	> 1.5 × ULN
Creatinine	µmol/L	mg/dL	—	> 1.3 × ULN
Glucose, fasting	mmol/L	mg/dL	< 0.8 × LLN	> 1.2 × ULN
Magnesium	mmol/L	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	mEq/L	< 0.9 × LLN	> 1.1 × ULN
TBL	µmol/L	mg/dL	—	> 1.5 × ULN
Total protein	g/L	g/dL	< 0.9 × LLN	> 1.1 × ULN
Triglycerides, fasting	mmol/L	mg/dL	—	> 1.2 × ULN
Uric acid or Urate	µmol/L	mg/dL	—	> 1.1 × ULN
Urinalysis				
Protein	—	—	—	At least 2 +
Glucose	—	—	—	At least 2 +
Blood	—	—	—	At least 2 +

9.3 VITAL SIGNS

Descriptive statistics for vital signs (eg, pulse rate, systolic and diastolic BP, oral or tympanic temperature, and body weight) and changes from baseline values at each visit will be presented. For systolic and diastolic BP, measurements will be taken both before (predose) and after (postdose - approximately 15 minutes after) IP administration if it is scheduled for that visit. Descriptive statistics for the predose, postdose, and difference (postdose value minus predose value) will be presented.

The number and percentage of patients with postbaseline PCS vital sign values will be summarized. Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 9.3–1. The percentages will be calculated relative to the number of patients with baseline values and at least 1

postbaseline assessment for the OLTP or the safety follow-up period. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A listing of all AEs occurring in patients who have PCS vital sign values will also be provided.

The number and percentage of patients with orthostatic hypotension will be provided. Orthostatic hypotension is defined as a reduction of ≥ 20 mm Hg in systolic BP or a reduction of ≥ 10 mm Hg in diastolic BP measured after the patient stands up after resting in the supine position. Standing measurements should be taken after a sufficient amount of time has been given to allow the BP to equilibrate in the standing state.

Table 9.3–1. Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	***Flag***	***Criteria[a]***	
		Observed Value	***Change from Baseline***
Supine systolic BP, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Supine diastolic BP, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Supine pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A postbaseline value will be considered a potentially clinically significant value if it meets both criteria for observed value and change from baseline.
bpm = beats per minute.

9.4 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB interval, and QTcF interval) and changes from baseline values at each assessment timepoint will be presented.

ECG parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 9.4–1. The number and percentage of patients with PCS postbaseline ECG values will be tabulated for the OLTP. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the OLTP. The numerator is the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. In addition, a listing showing all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of study in the Investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not

clinically significant; and abnormal, clinically significant.

The number and percentage of patients with change from baseline QTc > 30 msec but not exceeding 60 msec and of patients with an increase > 60 msec will be tabulated. A listing of all AEs will be provided for all patients who have postbaseline QTc changes > 30 msec.

Table 9.4–1. Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	***Unit***	***Higher Limit***
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTcB	msec	> 500
QTcF	msec	> 500

QTc = QT interval corrected for heart rate.
QTcB = QT interval corrected for heart rate using the Bazett formula.
QTcF = QT interval corrected for heart rate using the Fridericia formula.

9.5 OTHER SAFETY PARAMETERS

Other safety parameters comprise the BPRS+, CADSS, [redacted]

Descriptive statistics of actual values and change from baseline for BPRS+ and CADSS total score will be presented at each assessment timepoint during the OLTP. BPRS+ total score is defined as the sum of 4 positive symptoms scales including suspiciousness, unusual thought content, hallucinations, and conceptual disorganization. CADSS total score is defined as the sum of scores for 23 subjective items.

[redacted]

[redacted]

11.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

12.0 DETERMINATION OF SAMPLE SIZE

Approximately 500 patients are expected to enter the OLTP. The study will be terminated when 100 patients have completed the 52-week OLTP.

13.0 COMPUTER METHODS

Statistical analyses will be performed [redacted]

14.0 STATISTICAL AND DATA HANDLING CONVENTIONS

14.1 SUMMARY STATISTICS

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

- Continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum, and maximum values).

- Categorical variables will be summarized by frequency distributions (counts and percentages).

14.2 VISIT TIME WINDOWS

Table 14.2–1 and Table 14.2–2 below present the visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 14.2–1. Visit Time Windows for the Open-label Treatment Period

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Baseline	*Baseline from first lead-in study*	
Visit 1	Day 1	
Visit 2 (Week 0)	Day 8	Days [2, 11]
Visit 3 (Week 1)	Day 15	Days [12, 18]
Visit 4 (Week 2)	Day 22	Days [19, 25]
Visit 5 (Week 3)	Day 29	Days [26, 32]
Visit 6 (Week 4)	Day 36	Days [33, 39]
Visit 7 (Week 5)	Day 43	Days [40, 46]
Visit 8 (Week 6)	Day 50	Days [47, 53]
Visit 9 (Week 7)	Day 57	Days [54, 60]
Visit 10 (Week 8)	Day 64	Days [61, 67]
Visit 11 (Week 9)	Day 71	Days [68, 74]
Visit 12 (Week 10)	Day 78	Days [75, 81]
Visit 13 (Week 11)	Day 85	Days [82, 88]
Visit 14 (Week 12)	Day 92	Days [89, 95]
Visit 15 (Week 13)	Day 99	Days [96, 102]
Visit 16 (Week 14)	Day 106	Days [103, 109]
Visit 17 (Week 15)	Day 113	Days [110, 116]
Visit 18 (Week 16)	Day 120	Days [117, 123]
Visit 19 (Week 17)	Day 127	Days [124, 130]
Visit 20 (Week 18)	Day 134	Days [131, 137]

Table 14.2–1. Visit Time Windows for the Open-label Treatment Period

Derived Visit	***Scheduled Visit Day***[a]	***Window***
Visit 21 (Week 19)	Day 141	Days [138, 144]
Visit 22 (Week 20)	Day 148	Days [145, 151]
Visit 23 (Week 21)	Day 155	Days [152, 158]
Visit 24 (Week 22)	Day 162	Days [159, 165]
Visit 25 (Week 23)	Day 169	Days [166, 172]
Visit 26 (Week 24)	Day 176	Days [173, 179]
Visit 27 (Week 25)	Day 183	Days [180, 186]
Visit 28 (Week 26)	Day 190	Days [187, 193]
Visit 29 (Week 27)	Day 197	Days [194, 200]
Visit 30 (Week 28)	Day 204	Days [201, 207]
Visit 31 (Week 29)	Day 211	Days [208, 214]
Visit 32 (Week 30)	Day 218	Days [215, 221]
Visit 33 (Week 31)	Day 225	Days [222, 228]
Visit 34 (Week 32)	Day 232	Days [229, 235]
Visit 35 (Week 33)	Day 239	Days [236, 242]
Visit 36 (Week 34)	Day 246	Days [243, 249]
Visit 37 (Week 35)	Day 253	Days [250, 256]
Visit 38 (Week 36)	Day 260	Days [257, 263]
Visit 39 (Week 37)	Day 267	Days [264, 270]
Visit 40 (Week 38)	Day 274	Days [271, 277]
Visit 41 (Week 39)	Day 281	Days [278, 284]
Visit 42 (Week 40)	Day 288	Days [285, 291]
Visit 43 (Week 41)	Day 295	Days [292, 298]
Visit 44 (Week 42)	Day 302	Days [299, 305]
Visit 45 (Week 43)	Day 309	Days [306, 312]
Visit 46 (Week 44)	Day 316	Days [313, 319]
Visit 47 (Week 45)	Day 323	Days [320, 326]
Visit 48 (Week 46)	Day 330	Days [327, 333]
Visit 49 (Week 47)	Day 337	Days [334, 340]
Visit 50 (Week 48)	Day 344	Days [341, 347]
Visit 51 (Week 49)	Day 351	Days [348, 354]
Visit 52 (Week 50)	Day 358	Days [355, 361]
Visit 53 (Week 51)	Day 365	Days [362, 367]
Visit 54/End of open-label treatment period[b]	Final or termination visit during the open-label treatment period	

a Relative to the date of the first dose of the open-label IP. For example, Day 1 = the date of the first dose of open-label IP.

b Presented in analysis tables for safety parameters, including but not limited to, ECGs, laboratory values, vital signs, and C-SSRS.

Visit Day is calculated as visit date – the first date of open-label IP+1.

Table 14.2–2. Visit Time Windows for the Safety Follow-up Period

Derived Visit	***Scheduled Visit***	***Window***
Visit 55 (Week 54)	Week 54	≥ 1 day after the end of OLTP
End of Safety Follow-up period	Final or termination visit during safety follow-up period	

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

14.3 DERIVED EFFICACY AND SAFETY VARIABLES

For [redacted], BPRS+, and CADSS, the total score at a particular visit will be calculated as (sum of nonmissing items) × (total number of items) / (number of nonmissing items). However, if the number of missing items is more than the specified number for each variable [redacted], 1 for BPRS+, and 4 for CADSS), the total score will be set to missing.

14.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

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

14.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

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

14.6 MISSING RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

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

14.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

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

Missing month and day

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

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

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

Missing month only

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

Missing day only

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

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

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

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

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

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

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

14.8 MISSING DATE INFORMATION FOR 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.

14.8.1 Incomplete Start Date

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

Missing month and day

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

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

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

Missing month only

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

Missing day only

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

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

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

14.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or 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 open-label IP, the month and day of the last dose of open-label 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 open-label 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 open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

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

Missing day only

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

14.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 14.9–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 14.9–1. Examples for Coding of Special Character Values for Clinical Laboratory Parameters

Laboratory Test	***Possible Laboratory Results (in SI Units)***	***Coded Value for Analysis***
Chemistry: ALT	< 5	5
Chemistry: AST	< 5	5
Chemistry: bilirubin, total	< 2	2
Urinalysis: ketones	> 0	Positive
	≤ 0, Negative	Negative
Urinalysis: pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Urinalysis: glucose	≤ 50	0
	(50, 100]	1+
	(100, 250]	2+
	(250, 500]	3+
	(500, 1000]	4+
	≥ 1000	5+

Table 14.9–1. Examples for Coding of Special Character Values for Clinical Laboratory Parameters

Laboratory Test	***Possible Laboratory Results (in SI Units)***	***Coded Value for Analysis***
Chemistry: ALT	< 5	5
Chemistry: AST	< 5	5
Urinalysis: protein	≤ 15	0
	(15, 30]	1+
	(30, 100]	2+
	(100, 500]	3+
	≥ 500	4+

SI = *Le Système International d'Unités* (International System of Units).

14.10 ACTUAL TREATMENT FOR ANALYSIS

Not applicable

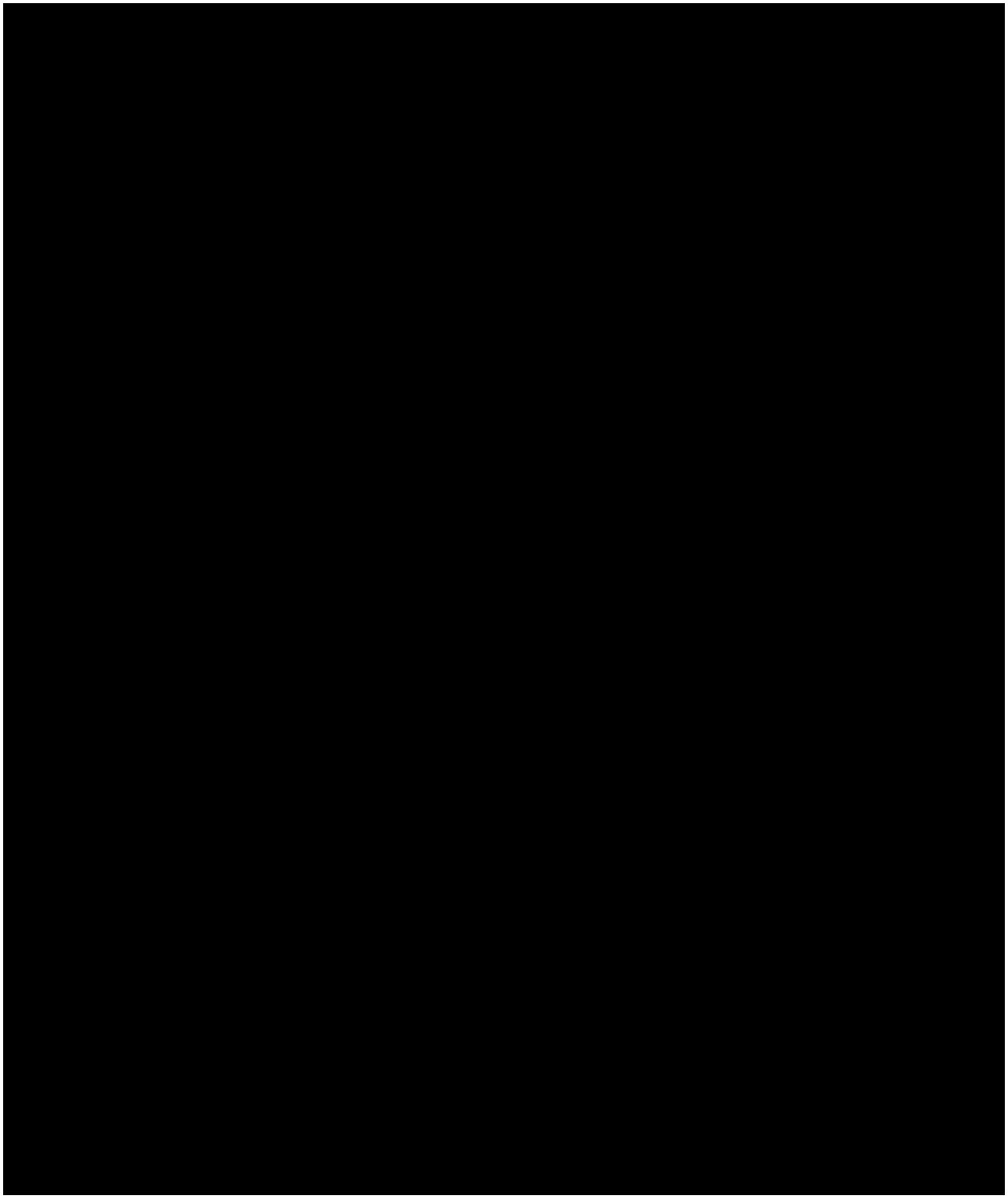
14.11 STRATIFICATION HANDLING CONVENTION

Stratifications not being implemented in this study.

15.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the final protocol Amendment 2 (version dated 13 Nov 2018). The baseline of efficacy analyses is defined as Day 0 of the first lead-in study in the SAP. This was not explicitly mentioned in the RAP-MD-06 final protocol Amendment 2, in order to protect restricted information pertaining to RAP-MD-01/02/03.

16.0 APPENDICES



17.0 HISTORY OF CHANGES

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