Statistical Analysis Plan

A Two-Part, Double-Blind, Placebo-Controlled, Single- and Multiple-Dose (Part A) or Twice Daily Dose (Part B) Study of AGN-241751 in Adult Participants with Major Depressive Disorder

STATISTICAL ANALYSIS PLAN for Part A

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1.0 TITLE PAGE

3125-104-002

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STATISTICAL ANALYSIS PLAN for Part A

Final: 7 June 2019

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AE	adverse event
BPRS+	Brief Psychiatric Rating Scale - Positive Symptoms Subscale
CADSS	Clinician Administered Dissociative States Scale
CGI-S	Clinical Global Impressions-Severity
C–SSRS	Columbia–Suicide Severity Rating Scale
ECG	electrocardiogram, electrocardiographic
ET	early termination
ICF	informed consent form
LOCF	last observation carried forward
mITT	modified intent to treat
MMRM	mixed-effects model for repeated measures
MADRS	Montgomery- Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
OC	observed cases
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
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
LLN	lower limit of normal

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data for part A as outlined and/or specified in the final protocol of Study 3125-104-002 and the most recent protocol amendment (Amendment 1 dated 05 March 2019; Amendment 2 dated 03 May 2019). Specifications of tables, figures, and data listings are contained in a separate document.

Part A of study 3125-104-002 is a Phase 1b, multicenter, randomized, double-blind, placebo-controlled, parallel-group (4 arms), weekly and once daily dose, 2-week study of AGN241751 in participants with major depressive disorder (MDD). The study will include a total of 7 visits and will be approximately 5 weeks in duration:

- Up to 2-week screening period
- 2-week double-blind treatment period
- 1-week safety follow-up period

After providing written consent, participants will enter a screening period of up to 14 days. Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate participant and site schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period, including the rater-administered montgomery- asberg depression rating scale (MADRS). Participants meeting the eligibility criteria at the end of Visit 2 (Day 1 of the randomized inpatient treatment) will be assigned a treatment and enter the double-blind treatment period.

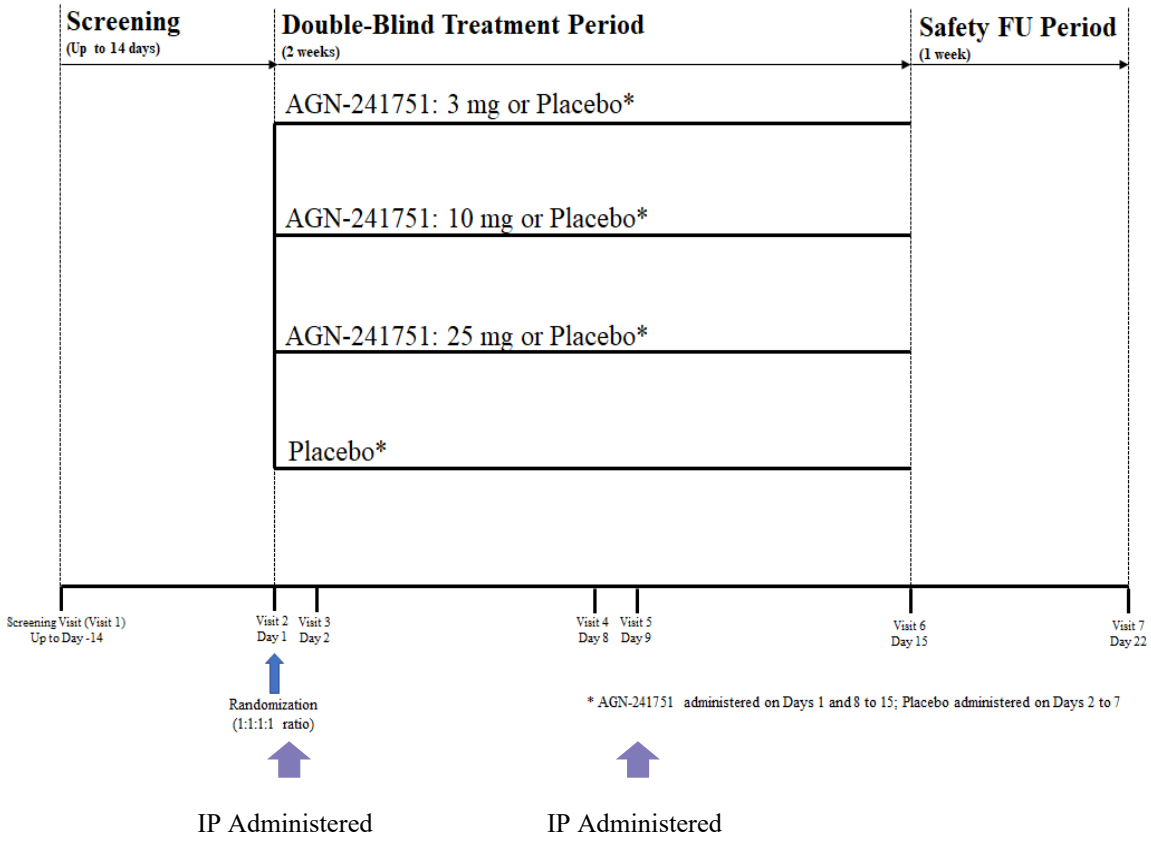
Approximately 100 participants are planned for enrollment in the double-blind treatment period (25 participants each in the AGN-241751 and placebo groups). Participants will be randomized in a ratio of 1:1:1:1 to 1 of 4 treatment groups: 3 mg, 10 mg, and 25 mg dose AGN-241751 and placebo. All participants will be randomized to receive active treatment or placebo (Day 1, and Days 8 to 15) and placebo alone (Days 2 through 7).

AGN-241751 is being developed for once-weekly dosing; however, the impact of repeated administration of AGN-241751 requires testing. In order to minimize participant's expectations and control for placebo response while changing dosing regimens, all treatments will be presented to participants as oral daily dosing throughout the study. On Day 1, all participants will be randomized to receive the first treatment (ie, 4 treatment groups: 3 mg, 10 mg, and 25 mg dose AGN-241751 or placebo), followed by blinded placebo on Days 2 through 7. Starting on Day 8, participants will then start 7 consecutive days of randomized treatment, administered once daily through Day 15.

On Day 1, site staff will give the participant the single dose of double-blind study treatment from Bottle 1 (for applicable visit) to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will then give Bottle 2 (for applicable visits), which contains the single-blind placebo tablets, to the participant with the instruction to take 1 tablet daily by oral ingestion for the remainder of that week (Days 2 through 7). On Day 8, site staff will give the participant the single dose of double-blind study treatment from Bottle 1 (for applicable visit) to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will then give Bottle 2 (for applicable visits), which contains double-blind study treatment, to the participant with the instruction to take 1 tablet daily by oral ingestion for the remainder of that week (Days 9 through 15).

Participants will have 7 study visits during the study. The first 6 visits will occur in the following pattern: the Screening Visit (Visit 1; up to Day -14); at Visit 2 (Day 1 of the randomized inpatient treatment); at Visit 3 (1 day following the inpatient treatment day); at Visit 4 (7 days following the first inpatient treatment day, which is the second inpatient treatment day); at Visit 5 (1 day following the second inpatient treatment day); and at Visit 6 (7 days following the second inpatient treatment day). If necessary, study visits may be conducted up to 2 days before or after the scheduled visits with the exception of visits that are 1 day apart (ie, Visits 2 and 3 must be conducted 1 day apart; and Visits 4 and 5 must be conducted 1 day apart). Participants will enter a 1week safety follow-up period and return for Visit 7. Participants who prematurely discontinue from the study before completing the double-blind treatment should enter the 1-week safety follow-up period. Additional follow-up visits may be scheduled within 30 days, if necessary for safety reasons.

Figure 4-1 Study Design Diagram



FU = follow-up; IP = investigational product.

All treatments will be presented to participants as oral once daily dosing throughout the study.

At Visit 2 (Day 1 of the randomized inpatient treatment), all participants will be randomized to receive the first treatment, followed by blinded placebo on Days 2 through 7.

Starting at Visit 4 (Day 8), participants will then start 7 consecutive days of double blinded randomized treatment, administered once daily through Day 15.

The schedule of activities for Study 3125-104-002 is presented in Table 4-1. The double-blind treatment period starts with the first dose of study (Day 1) treatment and ends with the last dosing day (Day 15).

Table 4-1 Schedule of Activities (SoA)							
		Double-blind Treatment Period					**Safety Follow-up Period**
Visit	***Screening (1)***	***2***	***3***	***4***	***5***	***6/ET[a]***	***7***
Study Day	**up to -14 days**	**1**	**2**	**8**	**9**	**15**	**22**
Informed consent	x						
Medical (surgical, neurologic) and psychiatric histories	x						
Prior medication history	x						
Inclusion/exclusion	x	x					
Randomization assessment		x					
Clinical laboratory determinations[b]	x	x				x	
Urine drug screen	x					x	
Serum pregnancy test	x					x	
Pharmacogenomics consent and sample[c]	x						
Vital signs[d]	x	x	x	x	x	x	x
ECG	x					x	
Physical examination	x					x	
SCID	x						
MADRS	x	x	x	x	x	x	x
CGI-S	x	x	x	x	x	x	
BPRS+	x		x	x	x	x	
CADSS	x		x	x	x	x	

C-SSRS	x	x	x	x	x	x	x
		Double-blind Treatment Period					**Safety Follow-up Period**
Visit	***Screening (1)***	***2***	***3***	***4***	***5***	***6/ET[a]***	***7***
Study Day	**up to -14 days**	**1**	**2**	**8**	**9**	**15**	**22**
HAM-A[e]		x	x	x		x	
AEs		x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x
Study treatment administration in the clinic		x		x			
Study treatment compliance		x		x	x	x	

Screening procedures may be conducted on up to 2 separate dates where necessary to accommodate participant and site schedule; however, every effort should be made to conduct all procedures as early as possible in the screening period.

If necessary, study visits may be conducted up to 2 days before or after the scheduled visits except for visits that are 1 day apart (ie, Visits 2 and 3 must be conducted 1 day apart, and Visits 4 and 5 must be conducted 1 day apart).

[a] Performed for all participants, including those prematurely discontinued after randomization. Clinically significant findings upon termination should be followed until the condition returns to prestudy status or can be explained as unrelated to study treatment. If necessary, additional follow-up visits can be scheduled.

[b] Participants will be requested to fast overnight or for at least 8 hours before arriving at the study center for appointments involving the collection of clinical laboratory blood tests. Clinical laboratory tests can be done at any visit for safety reasons at the discretion of the investigator.

[c] A separate ICF must be signed before the pharmacogenomic blood sample is taken. Participation is optional. This ICF may be signed at any visit during the study; however, the sample should be collected at any visit after the participant has been randomized.

[d] Height will only be measured at Visit 1 (Screening); pulse rate, blood pressure, temperature, and body weight will be assessed at every visit. Blood pressure and pulse will be assessed while the participant is supine and standing.

[e]. HAM-A will be assessed predose at Visits 2, 3, 4, and 6/ET. The HAM-A will be collected only from participants entering the study after the amendment has been IRB approved.

5.0 OBJECTIVES

The primary objective is to evaluate the efficacy, as measured by improvement in MADRS total score, at 1 day after the initial single oral dose of AGN-241751 compared with placebo in participants with MDD. The key secondary objectives are to evaluate the efficacy at Day 8, Day 9 after single oral dose, at Day 15 after repeated dose, and at Day 22, 7 days after the completion of AGN-241751 dosing, when administered orally once daily compared with placebo in participants with MDD.

6.0 PARTICPANT POPULATIONS

6.1 MODIFIED INTENT-TO-TREAT POPULATION

The modified intent to treat (mITT) population includes all randomized participants who received at least 1 administration of study treatment and have a baseline MADRS total score and at least 1 postbaseline assessment for the MADRS total score during the double-blind treatment period. Participants will be summarized according to the randomized study treatment.

6.2 SAFETY POPULATION

The safety population includes all participants who received at least 1 administration of study treatment. Participants will be summarized according to the study treatment they actually received.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in 2 of the study populations (Safety and mITT) will be summarized by treatment group and study center; the number of participants screened will be summarized overall only by study center.

Screen-failure participants (i.e., participants screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the all screened participants. The number and percentage of participants who enter the double-blind treatment period, complete the double-blind treatment period and of participants who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group. Similar disposition information to the double-blind treatment period will be presented for the safety follow-up period. The end of the study is defined as the completion of enrollment and completion of all periods of the study. All participants who prematurely discontinue during the double-blind treatment period or the safety follow-up period will be listed by discontinuation reason.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group (<20, 20-29, 30-39, 40-49, 50-59, and >=60); race; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be summarized descriptively by treatment group for the Safety and mITT populations. Continuous variables will be summarized by number of participants and mean, SD, median, Q1 (25 percentile), Q3 (75 percentile), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term 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 study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of study treatment.

Both prior and concomitant medications will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by the number and percentage of participants in each treatment group for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participants would be counted only once for the coded drug name or therapeutic class.

Formulations (including salts, esters, etc) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the course of the study and may be pooled under a single coded drug name for analyses.

The number and percentage of participants taking each antidepressant therapy (ADT) and the number of ADTs (0, 1, 2, and >2) received in current episodes of major depressive disorder prior to randomization will be summarized by treatment group for the Safety Population. ADT medication selection criteria is included in Table 8-1.

Table 8-1 Criteria for ADT medication

ADT Class	Medication List
Atypical	BUPROPION
	MIRTAZAPINE
	VILAZODONE and/or VILAZODONE HYDROCHLORIDE
	VORTIOXETINE and/or VORTIOXETINE HYDROBROMIDE
SNRI	DESVENLAFAXINE and/or DESVENLAFAXINE SUCCINATE
	DULOXETINE and/or DULOXETINE HYDROCHLORIDE
	LEVOMILNACIPRAN and/or LEVOMILNACIPRAN HYDROCHLORIDE
	VENLAFAXINE and/or VENLAFAXINE HYDROCHLORIDE
SSRI	CITALOPRAM and/or CITALOPRAM HYDROBROMIDE
	ESCITALOPRAM and/or ESCITALOPRAM OXALATE
	FLUVOXAMINE
	FLUOXETINE and/or FLUOXETINE HYDROCHLORIDE
	PAROXETINE and/or PAROXETINE HYDROCHLORIDE
	SERTRALINE

World Health Organization (WHO) Drug Dictionary, March 2017, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Data for medical history with onset dates prior to the Screening visit will be tabulated and presented using the Safety population. An overall total will be provided for the study as well as by treatment group. Medical history data will be coded using the MedDRA version 22.0 dictionary. No statistical comparisons will be performed.

A significant protocol deviations listing will be provided for protocol deviations for the Randomized Participants. Protocol deviations will be defined in a separate document, including importance classification.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to the study treatment for the Safety Population during the double-blind treatment period will be summarized by treatment group (placebo, 3mg, 10mg and 25mg). Descriptive statistics (number of participants, mean, SD, median, Q1 (25 percentile), Q3 (75 percentile), minimum, and maximum) will be presented for each study day from Day 1 to Day 15.

The following parameters for the study treatment will also be summarized using descriptive statistics by treatment group:

- Treatment duration overall and by treatment regimen intervals (Day 1, Day 2-Day 7, Day 8-Day 15). Treatment duration will be calculated as the number of days from the date of the first dose of study treatment to the date of the last dose of study treatment, inclusive.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for the double-blind treatment period is defined as the number of tablets actually taken by a participant during that period divided by the number of days the participants are expected to be taken during the same period multiplied by 100. If a participant achieved 80 to 120 percent compliance, then participant is considered as a compliant. Descriptive statistics (number and percentage) will be used to summarize compliant rates.

10.0 EFFICACY ANALYSES

The efficacy analyses will be based on the mITT Population. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study treatment. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

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

1. Based on the number of mITT participants, 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.
2. 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.
3. 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 that 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.

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

The rater-administered MADRS will be used for the efficacy analyses.

10.1 PRIMARY EFFICACY PARAMETER

The primary efficacy parameter will be the change from baseline in MADRS total score at 1 day after first dose and will be analyzed using a mixed-effects model for repeated measures (MMRM) model with treatment group, visit, pooled study center, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant scores. If the model fails to converge based on the unstructured covariance matrix, then structures of Heterogenous Toeplitz, Toeplitz, and Compound Symmetry will be applied, in the specified order, until the model converges. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997). These analyses will be performed based on all postbaseline scores using only the observed cases (OC) without imputation of missing values. MADRS assessments at all study visits will be included in the MMRM model. Primary endpoint descriptive statistics and associated statistical testing results from the MMRM model will be presented.

10.2 SECONDARY EFFICACY PARAMETER

The secondary efficacy parameter will be the change from baseline in MADRS total score at Day 8 and Day 9 after single oral dose, on Day 15 after repeated dose, and on Day 22, 7 days after the completion of AGN-241751 dosing. The primary analysis for the secondary endpoints will be performed using an MMRM with treatment group, visit, pooled study center, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger 1997). These analyses will be performed based on all postbaseline scores using only the OCs without imputation of missing values. The Day 1 predose MADRS will be used as baseline for all analysis. MADRS assessments at all study visits will be included in the MMRM model. Key secondary endpoint descriptive statistics and associated statistical testing results from the MMRM model will be presented by visit.

In addition, a sensitivity analysis using the multiple imputation (MI) approach under missing not at random (MNAR) assumptions will be performed on the primary and key secondary efficacy parameters.

For the sensitivity analysis of the primary endpoint, change from baseline in MADRS totals score at 1-day post Day 1 and secondary endpoint, change from baseline in MADRS totals score at Day 8, Day 9, Day 15, and Day 22, the following steps will be followed to generate datasets and analyze the data:

1. Generate the imputed datasets:

The implementation of the pattern-mixture model (PMM) with control-based pattern imputation of Ratitch and O'Kelly (2011) will be used to impute missing data under the MNAR assumption.

- Intermittent (non-monotone) missing data in both treatment groups are imputed using the Monte-Carlo Markov chain (MCMC) method under the MAR assumption.

- Remaining monotone missing data are imputed using a PMM approach using a sequential regression imputation model estimated based on data from the placebo arm only. 50 imputed datasets will be generated.

2. Model based key estimates LSMean difference between treatment group and standard error) will be obtained for the change from baseline in MADRS total score at day 2 (1 day after first dose), Day 8, Day 9, Day 15, and Day 22 for each imputed dataset using the same MMRM.

3. Calculation of the combined mean difference, 95% CI, and p-value for the change from baseline in MADRS total score at day 2 (1 day after first dose), Day 8, Day 9, Day 15, and Day 22 will be done using the method proposed by Rubin (1987) via PROC MIANALYZE.

10.3 ADDITIONAL EFFICACY PARAMETERS

Additional efficacy parameters are as follows:

- Change from baseline in Clinical Global Impressions-Severity (CGI-S) at Day 2 (1 day after first dose), Day 8, Day 9 and Day 15
- MADRS responder status at Day 2 (1 day after first dose), Day 8, Day 9, Day 15 and Day 22
- CGI-S responder status at Day 2 (1 day after first dose), Day 8, Day 9 and Day 15
- MADRS remitter status at Day 2 (1 day after first dose), Day 8, Day 9, Day 15 and Day 22
- Time to first response
- Time to first remission

Analysis of change from baseline in CGI-S score will be performed using a similar MMRM to that used for the key secondary parameter. Multiple comparison procedure will not be applied to the above additional efficacy parameters.

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

CGI-S responder is defined as participants achieving a score of ≤ 2 on the CGI-S of Illness scale.

During the randomized treatment period, 2 types of events for MADRS total score will be defined based on the following criteria:

- Responder: ≥ 50% reduction from baseline MADRS total score
- Remitter: MADRS total score ≤ 10

Rates of responders and remitters will be reported by treatment group for each timepoint (Days 2, 8, 9, 15, and 22 after first dose of randomized treatment). A logistic regression model with LOCF imputation will be used to model the probability of a response or the probability of a remission as a function of a treatment group and baseline MADRS or CGI-S total score. The LOCF approach will be used to impute missing postbaseline values, provided that at least 1 postbaseline assessment is available. Missing values between the baseline and the first nonmissing postbaseline will be imputed with the baseline value. If all the postbaseline values are missing, the baseline value will not be carried forward. Only the total score of a parameter will be imputed using the LOCF approach; individual item scores will not be carried forward. Bar charts for the rates of responders and remitters in MADRS total score will be presented by treatment group and by study day.

Descriptive statistics for the first three additional endpoints and their associated statistical testing results from the MMRM models and logistic regression will be respectively presented by visit.

The time to onset of first event (i.e. first response or first remission) is defined as the number of days from the first randomized dosing to the first event. The time to onset in days will be calculated for each type of event (first response or first remission) in person level. Participants who do not meet the criteria for respective type of event will be censored at the time of their last MADRS assessment during the treatment period.

For each type of event, the proportion of participants with onset of first events, Kaplan-Meier estimate in terms of the median time to onset of first event, and its 95% CI will be presented for each treatment group. Plots of the Kaplan-Meier estimate of the distribution of the time to onset of events will also be provided for each treatment arm. Log-rank tests comparing the time to onset of event distribution between each AGN-241751 dose and placebo will be conducted.

11.0 SAFETY ANALYSES

The safety analysis will be performed using the safety population. The safety parameters will include adverse events (AEs), clinical laboratory including, vital signs, electrocardiographic (ECG), C-SSRS, BPRS+, and CADSS parameters. The last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, Q1 (25 percentile), Q3 (75 percentile), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study medication. However, an AE that occurs more than 30 days after the last dose of study medication will not be counted as a TEAE. Per case report form instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore TEAEs can simply be identified as those AEs with recorded onset date on or after the date of the first dose of study intervention and within 30 days after the last dose of study intervention.

The number and percentage of participants reporting TEAEs in each treatment group will be summarized overall and weekly. The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. 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 total number of TEAEs by system organ class and preferred term; system organ class, preferred term, and severity; system organ class, preferred term, and causal relationship to the study treatment will be summarized by treatment group.

The incidence of common (≥ 2% of participants in any treatment group) TEAEs will be summarized by preferred term and treatment group and sorted by decreasing frequency for the test treatment highest dose. It will be reported for Safety population overall.

The number and percentage of participants in the Safety Population who have AEs leading to premature discontinuation of the study treatment will be summarized by preferred term and treatment.

The number and percentage of participants who have TESAEs (treatment-emergent serious adverse event) will be summarized by preferred term and treatment group. An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria. Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 2 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for the following laboratory parameters, measured at Screening and Visit 6/ET:

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, total protein, alkaline phosphatase, albumin, bilirubin (total; direct; indirect), ALT, AST, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides
Urinalysis:	Specific gravity, pH, protein, glucose, ketones, and blood
Urine drug screen (UDS):	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine
Pregnancy at Screening and Visit 6/ET:	Serum β-hCG

The following clinical laboratory levels will be measured at Screening only:

Clinical laboratory screening tests:	HbA1c, fasting insulin, TSH, T3, and free T4
Hepatitis screening:	HCV antibody, hepatitis–B surface antigen, and hepatitis-B core antibody total will be tested. Reflex hepatitis-B core antibody IgM will be performed for all hepatitis–B core antibody total positive or reactive results. Positive test results will be sent for confirmation testing.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11-1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline value and at least one postbaseline assessment. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

Table 11-1 Criteria for Potentially Clinically Significant Clinical Laboratory Tests

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Traditional Unit*	*PCS Criteria*[b] *Low Values*	*PCS Criteria*[b] *High Values*
Hematology					
Hemoglobin	g/L	0.1	g/dL	< 0.9 × LLN	—
Hematocrit	volume fraction	100	%	< 0.9 × LLN	—
Eosinophils	%	1	%	—	> 10
Neutrophils	%	1	%	< 30	> 90
Basophils	%	1	%	—	> 6
Monocytes	%	1	%	—	> 20
Lymphocytes	%	1	%	< 10	> 60
Abs Neutrophils (ANC)	10^9/L	1	1000/µL	< 1.0	—
Platelet count	10^9/L	1	1000/µL	≤ 75	≥ 700
White cell count	10^9/L	1	1000/µL	≤ 2.5	≥ 15
Chemistry					
Albumin	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Alkaline phosphatase	U/L	1	U/L	—	≥ 3 × ULN
ALT (SGPT)	U/L	1	U/L	—	≥ 3 × ULN
AST (SGOT)	U/L	1	U/L	—	≥ 3 × ULN
Gamma-glutamyl transferase (GGT)	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen (BUN)	mmol/L	2.8011	mg/dL	—	> 1.2 × ULN
Calcium	mmol/L	4.008	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	1	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Cholesterol	mmol/L	38.6698	mg/dL	—	> 1.3 × ULN
High-density lipoprotein (HDL) cholesterol	mmol/L	39	mg/dL	< 0.8 × LLN	—

Laboratory Parameter	***SI Unit***	***Conversion Factor[a]***	***Traditional Unit***	***PCS Criteria[b] Low Values***	***PCS Criteria[b] High Values***
Low-density lipoprotein (LDL) cholesterol	mmol/L	39	mg/dL	—	> 1.2 × ULN
CPK	u/L	1	mg/dL	—	> 1.5 × ULN
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose, fasting	mmol/L	18	mg/dL	< 0.8 × LLN	> 1.2 × ULN
Magnesium	mmol/L	2	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 1.5 × ULN
Total protein	g/L	—	—	< 0.9 × LLN	> 1.1 × ULN
Triglycerides, fasting	mmol/L	88.6	mg/dL	—	> 1.2 × ULN
Urinalysis					
Protein	—	—	—	—	At least 2 +
Glucose	—	—	—	—	At least 2 +
Blood	—	—	—	—	At least 2 +

a Conversion factor from SI units to traditional units.

b Criteria refer to SI units.

Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.

LLN = lower limit of normal; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal of laboratory reference range.

In addition, descriptive statistics for clinical laboratory values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Table 11-2.

Table 11-2 Selected Parameters Reported in Conventional Units

Number	*Laboratory Parameter*	*Conventional Unit*
1	Alanine Aminotransferase (SGPT)	U/L
2	Albumin	G/dL
3	Alkaline Phosphatase	U/L
4	Aspartate Aminotransferase (SGOT)	U/L
5	Bilirubin, Direct (Conjugated)	mg/dL
6	Bilirubin, Indirect (Unconjugated)	mg/dL
7	Bilirubin, Total	mg/dL
8	Blood Urea Nitrogen	mg/dL
9	Calcium	mg/dL
10	Cholesterol, HDL	mg/dL
11	Cholesterol, LDL	mg/dL
12	Cholesterol, LDL direct and calculated (combined) *(may be reported with #11)*	mg/dL
13	Cholesterol, Total	mg/dL
14	Creatine Kinase	U/L

Number	*Laboratory Parameter*	*Conventional Unit*
15	Creatinine	mg/dL
16	Glucose	mg/dL
17	Insulin	uIU/mL
18	Triglycerides	mg/dL
19	Uric Acid	mg/dL
20	Hemoglobin	G/dL

11.3 VITAL SIGNS

Descriptive statistics of actual values and change from baseline for vital signs (systolic and diastolic blood pressures, pulse rate, weight, and temperature) will be presented at each assessment timepoint by treatment.

Vital sign values will be considered PCS if they meet both the observed-value criterion and the change-from-baseline criteria listed in Table 11-3. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants who have available baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline value and at least one PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

Table 11-3 Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***[a]	
		Observed Value	*Change From Baseline*
Supine systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Supine diastolic blood pressure, 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%
Temperature, °C	High	> 38	—
	Low	< 35	—

a A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.

bpm = beats per minute.

11.4 ELECTROCARDIOGRAM

Descriptive statistics of actual values and change from baseline for ECG parameters (ie, heart rate, PR interval, QRS interval, QT interval, and QTc interval according to QTcB and QTcF) will be presented at each assessment timepoint by treatment group.

Electrocardiographic parameter values are considered PCS if they meet the higher-limit PCS criteria listed in Table 11-4 The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline value and at least one postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline value and at least one PCS postbaseline ECG value. A supportive listing of participants with PCS postbaseline values will be provided and will include the participant number and the baseline and postbaseline values. A listing of all AEs for participants with PCS ECG values will also be provided.

A shift table from Screening to Day 15 in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

The number and percentage of participants with a change from baseline QTc > 30 msec but not exceeding 60 msec and of participants with an increase > 60 msec will be tabulated by treatment group. A supportive listing that includes the participant identification number, all QTc values (including change from baseline values), and all AEs will be provided for all participants who have postbaseline QTc changes > 30 msec.

Table 11-4 Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	***Unit***	***Higher Limit***
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTcB, QTcF	msec	>500 or Change from baseline (increase of > 60)

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.

11.5 OTHER SAFETY PARAMETERS

11.5.1 Columbia-Suicide Severity Rating Scale

For the Columbia-Suicide Severity Rating Scale (C-SSRS), the number and percentage of participants with suicidal ideation and suicidal behavior before the double-blind treatment period and during double-blind treatment and safety follow-up periods will be summarized by treatment group for the Safety population. Supportive tabular display of participants with all values will be provided, including study center, PID number, treatment group, visit number, intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior.

11.5.2 Potential Hy's Law

Potential Hy's Law criteria within a 24 hours window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3x ULN, along with total bilirubin (TBL) ≥ 2x ULN and a non-elevated alkaline phosphatase (ALP) < 2x ULN, all based on blood draws collected within a 24 hour period.

Potential Hy's Law criteria without time window (e-DISH) is defined by maximum of post baseline elevation of ALT or AST ≥ 3x ULN, along with maximum of post baseline elevation of TBL ≥ 2x ULN.

Participants who meet the potential Hy's Law criteria from the first dose of study drug to within 30 days after the last dose of study treatment will be summarized. Supportive tabular displays will also be provided.

11.5.3 Brief Psychiatric Rating Scale—Positive Symptoms Subscale

The BPRS+ total score is defined as the sum of 4 positive individual scores including conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Each question is presented on a 7-point Likert scale with a choice for NA as not assessed. If any item were not observed, not assessed, or missing, then the total score was missing.
Descriptive statistics of actual values at baseline, post baseline, and change from baseline for BPRS+ total score as well as for 4 positive individual scores will be presented by

treatment group. Plots of mean values and their standard errors for the BPRS+ total score will be presented by treatment group and by visit for Safety population.

A participant will be considered to have a treatment-emergent symptom in the BPRS scale if any of the following BPRS items scores are ≤ 2 at baseline and > 2 after baseline: conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content. The number and percentage of participants reporting treatment-emergent symptoms in the BPRS scale will be tabulated for each individual item and for all 4 items specified above.

Listings of participants with treatment-emergent symptoms will be provided and will include the participant identification number and baseline and postbaseline values. Listings of all adverse events occurring in participants who have treatment-emergent symptoms will also be provided.

11.5.4 Clinician Administered Dissociative States Scale

CADSS total score is defined as of 23 non-negative individual scores. Each question is presented on a 5-point Likert scale with 0 meaning “not at all” and 4 meaning “extreme”. If more than 4 items were missing, then the total score was set to missing; if there were 4 or fewer items missing, then the total score is set to the sum of non-missing items multiplied by the total number of items divided by the number of non-missing items.

Descriptive statistics of actual values at baseline, post baseline, and change from baseline for CADSS total score will be presented by treatment group at each assessment timepoint. Plots of mean values and their standard errors for the CADSS total score will be presented by treatment group and by visit for Safety population.

11.5.5 The Hamilton Anxiety Rating Scale

The HAM-A is a clinician-rated scale to rate the severity of anxiety symptoms. The participant tested over 14-questions, and rated on a scale from 0 to 4, with 1 indicating a “not present” response and 4 indicating a “severe” response. The HAM-A will be administered by the investigator or a sub-investigator with extensive professional training and experience in assessing mental illness and qualification standards set by the sponsor and rater training vendor.

The exploratory analysis of HAM-A scores will be performed using the safety population for the double-blind treatment period and for the safety follow-up period, if applicable, P.

The exploratory parameters will include change from baseline in HAM-A total scores at Day 2, 8, and 15. Descriptive statistics of actual values at baseline, post baseline, and change from baseline for HAM-A total score will be presented by treatment group at each assessment timepoint.

12.0 HEALTH OUTCOMES ANALYSES

Not Applicable.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

The sample size of approximately 25 randomized participants in each of the 4 treatment groups is not based on statistical power consideration due to the lack of information of AGN-241751 for the variability of change from baseline to 1 day after first dose in MADRS total score.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 or newer of SAS.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16-1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16-1 Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Baseline	Screening/Day 1 (Visit 2)	last nonmissing assessment before Index1[a]
Day 2	Day 2 (Visit 3)	Days (Index1[a]+1, IndexA[b]-1)
Day 8	Day 8 (Visit 4)	IndexA[b]
Day 9	Day 9 (Visit 5)	Days (IndexA[b] +1, IndexA[b]+4)
Day 15	Day 15 (Visit 6)	Days (IndexA[b]+5, day of final double blind visit or ET Visit occurring after IndexA[b]+5)
End of Double-Blind Treatment	The last available post-baseline assessment (unscheduled assessments) during the double-blind treatment period	
Safety Follow-up (Day 22)	Days [Day after final double-blind visit or ET visit occurring after Day 15 (Visit 6)/Early Termination visit]	

a Index1: Day of first double-blind dose

b IndexA: Day of second double-blind dose, if not received, use Index1 + 7 days

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

If a participant has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis.

16.2 DERIVED VARIABLES

The efficacy variables are derived as follows:

- MADRS total score is the sum of the 10 items from the MADRS. If more than 2 items of the MADRS are missing, the total score will be set to missing
- *Responder on* MADRS is defined as a participant with ≥ 50% reduction from baseline MADRS total score

- *Responder on* CGI-S is defined as participant achieving a score of ≤ 2 on the CGI-S of Illness scale.

- *Remitter on MADRS* is defined as a participant with MADRS total score ≤ 10

- BPRS+ total score is defined as the sum of 4 positive individual scores including suspiciousness, unusual thought content, hallucinations, and conceptual disorganization. If more than 1 item is missing, then the total score will be set to missing

- CADSS total score is defined as the sum of scores for 23 subjective items. If more than 4 items are missing, then the total score will be set to missing.

The total score 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.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study treatment will be used as baseline. If end of double-blind treatment period assessments are repeated or if unscheduled visits occur during the double-blind treatment period, the last nonmissing postbaseline assessment will be used as the end of double-blind treatment period assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6 MISSING CAUSAL RELATIONSHIP TO STUYD DRUG FOR ADVERSE EVENTS

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

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

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

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

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

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

Missing day only

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

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

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

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

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

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

Table 16-2 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[1]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	Yes

[1] Not allowed per database design

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

16.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

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

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

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

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

Missing day only

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

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

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

16.8.2 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 study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

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

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

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

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

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

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

16.9 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 16-3 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16-3 Examples of Coding 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+
Urinalysis: protein	≤ 15	0
	(15, 30]	1+
	(30, 100]	2+
	(100, 500]	3+
	≥ 500	4+

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None

18.0 REFERENCES

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-997.

DOCUMENT HISTORY PAGE

Effect Date	Revision Number	Primary Author	Description of Change