Statistical Analysis Plan: A double-blind, placebo-controlled, fixed dose study of AGN-241751 in adult participants with major depressive disorder, Amendment 2

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1 Title Page

STATISTICAL ANALYSIS PLAN

A Double-Blind, Placebo-Controlled, Fixed-Dose Study of AGN-241751 in Adult Participants with Major Depressive Disorder

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Protocol Number:	3125-201-002
Development Phase:	2a
Product Name:	AGN-241751
Study Statistician:	Ludmyla Rekeda, PhD
Sponsor Name and Legal Registered Address**:**	Naurex, Inc., an indirect subsidiary of Allergan plc, 5 Giralda Farms Madison, NJ 07940 USA

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Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
ANCOVA	analysis of covariance
CFB	change from baseline
CGI-S	Clinical Global Impressions–Severity
C-SSRS	Columbia–Suicide Severity Rating Scale
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
ET	early termination
mITT	modified intent-to-treat
LOCF	last observation carried forward
LS	least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MedDRA	Medication Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
PCS	potentially clinically significant
PK	pharmacokinetic
PID	participant identification
PT	preferred term
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
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4 Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study 3125-201-002 (version dated 02 March 2018) and the most recent amendment (version #1 dated on 08 Jun 2018). Specifications of tables, figures, and data listings are contained in a separate document.

This study is a multicenter, randomized, double-blind (with a single-blind placebo lead-in), placebo-controlled, parallel-group, fixed-dose, 3-week study in participants with major depressive disorder (MDD). The study will include a total of 10 visits and will be approximately 5 weeks in duration:

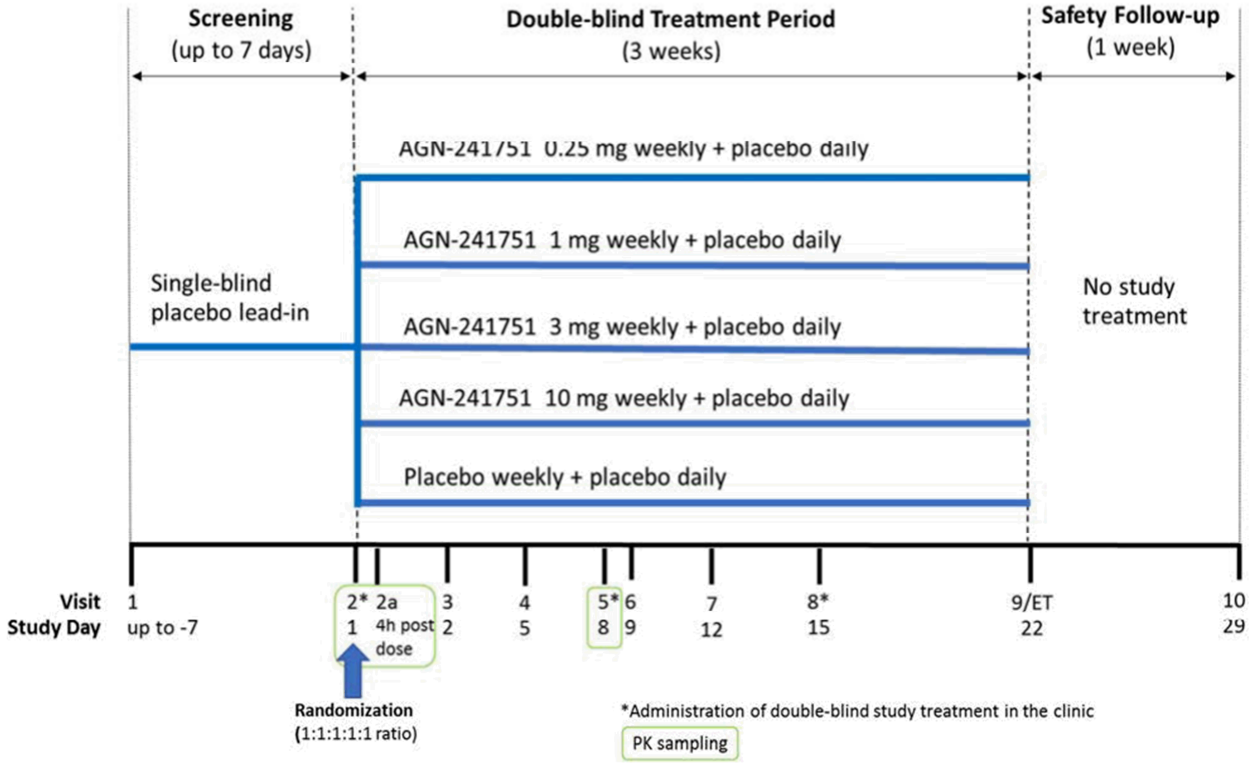
- Up to 1-week screening period
- 3-week double-blind treatment period
- 1-week safety follow-up period

Approximately 250 participants are planned for enrollment in the double-blind treatment period (50 participants each in the AGN-241751 and placebo groups). Participants will be randomized in a ratio of 1:1:1:1:1 to 1 of 5 treatment groups: 0.25 mg, 1 mg, 3 mg, 10 mg dose AGN-241751, and placebo.

Aside from the single-blind screening period and double-blind treatment period, there is an additional single-blind element to this study (blinded to the participant). AGN-241751 is being developed for once-weekly dosing; however, in order to minimize participant's expectations and control for placebo response, treatment will be presented to participants as oral daily dosing. Each treatment kit (dispensed once weekly) in the double-blind treatment period will contain 2 bottles: Bottle 1 will contain a single dose of double-blind study treatment and Bottle 2 will contain multiple doses single-blind placebo tablets (blinded to the participant). At Visit 2 (Day 1), Visit 5 (Day 8), and Visit 8 (Day 15), site staff will give the participant the single dose of double-blind study treatment from Bottle 1 to take by oral ingestion in the clinic (ie, the first dose of study treatment for that week). Site staff will give Bottle 2, 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. To maintain consistency, study treatment at Visit 1 (single-blind placebo lead-in) will be dispensed in the same manner; the single dose of single-blind study treatment from Bottle 1 will be given to the participant for oral ingestion in the clinic, and then, Bottle 2 containing single-blind placebo tablets will be dispensed for the participant to take 1 tablet daily by oral ingestion through the remainder of the week.

During the first 2 weeks of the double-blind treatment period, participants will have 3 study visits per week. The visits will occur in the following pattern: in-clinic treatment day, 1 day following the in-clinic treatment day, 4 days following the in-clinic treatment day, and 7 days following the in-clinic treatment day (which is the next in-clinic 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 5 and 6 must be conducted 1 day apart). Visit 8 will be conducted 7 days following the second in-clinic treatment day. All participants who receive study treatment must complete Visit 9/ET. Participants will enter a 1-week safety follow-up period and return for Visit 10. Participants who prematurely discontinue from the study before completing 3 weeks of 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



5 Study Objectives

The primary objective is to evaluate the efficacy, as measured by improvement in MADRS total score, at 1 day post initial oral dose of AGN-241751 compared with placebo in participants with MDD. The key secondary objective is to evaluate the efficacy at Week 3 of AGN-241751 administered orally once a week compared with placebo in participants with MDD.

Table 5-1 Schedule of Activities (SoA)

	Single-blind Placebo Run-In Period	Double-blind Treatment Period									Safety Follow-up Period
Visit	***1 (Screening)***	***2 (Baseline)***	***2a***	***3***	***4***	***5***	***6***	***7***	***8***	***9/ET[a]***	***10***
Study Day	**up to -7 days**	**1**	**4 hrs post dose**	**2 (1 day post dose)**	**5**	**8**	**9**	**12**	**15**	**22**	**29**
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	
Urine drug screen	x									x	
Serum pregnancy test	x									x	
Vital signs[c]	x	x	x	x	x	x	x	x	x	x	x
ECG	x									x	
Physical examination	x									x	
DxV	x										
SCID	x										
MADRS	x	x	x	x	x	x	x	x	x	x	
CGI-S	x	x	x	x	x	x	x	x	x	x	
BPRS+	x	x				x				x	
CADSS	x	x				x				x	
C-SSRS	x	x	x	x	x	x	x	x	x	x	x
SDC	x									x	
C-VISA	x										

	Single-blind Placebo Run-In Period	Double-blind Treatment Period									Safety Follow-up Period
Visit	***1 (Screening)***	***2 (Baseline)***	***2a***	***3***	***4***	***5***	***6***	***7***	***8***	***9/ET[a]***	***10***
Study Day	**up to -7 days**	**1**	**4 hrs post dose**	**2 (1 day post dose)**	**5**	**8**	**9**	**12**	**15**	**22**	**29**
AEs		x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
PK sampling		x (1 hr, 2 hrs, and 4 hrs post dose)				x 1 sample (15 min to 3 hrs post dose)					
Study treatment administration in the clinic	x (single-blind placebo)	x				x			x		
Study treatment compliance		x		x	x	x	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. The rater-administered MADRS and computer-administered MADRS must be collected on the same date. At Visit 1 (Screening), the computer-administered MADRS will be conducted prior to the rater- administered MADRS. At all other visits, the rater-administered MADRS will be conducted first.

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 5 and 6 must be conducted 1 day apart).

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; C-VISA = Clinical Validation Inventory for Study Admission; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; DxV = Diagnostic Validation; ECG = electrocardiogram; ET = Early Termination; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; SCID = Structured Clinical Interview for DSM disorders; SDC = Symbol Digit Coding

[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] 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.

[d] PK sampling is optional. For participants who consent to participate, samples will be collected at Visit 2/2a (Day 1) at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) post dose. At Visit 5 (Day 8), a single sample will be collected any time from 15 minutes to 3 hours post dose; site staff should record the time of the prior meal taken by the participant before the PK sample collection, whenever possible.

6 Analysis Populations

The analysis populations will consist of participants as defined below:

- 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.

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

7 Patient Disposition

The number and percentage of participants in Safety and mITT Populations 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 (ie, 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. A participant is considered to have completed the study if he/she has completed the double-blind treatment period of the study. 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. The percentage is relevant to the total number of randomized participants. Similar disposition information to the double-blind treatment period will be presented for the safety follow-up period. All randomized participants who prematurely discontinue during the double-blind treatment period or the safety follow-up period will be listed by discontinuation reason.

8 Demographic 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, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Medical and surgical history, psychiatric history, non-drug psychiatric treatment history, and other psychiatric history will also be summarized by double-blind treatment group for the Safety Population.

Prior medication is defined as any medication taken before the first dose of double-blind study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of the double-blind study treatment. Any medications started after the last visit of double-blind treatment period will not be summarized but will be included in listings.

Both prior and concomitant medication use will be summarized by the number and proportion of participants in each treatment group receiving each medication within each therapeutic class for the double-blind treatment period for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings.

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

The number and percentage of participants with important protocol deviations will be summarized by treatment group for randomized participants. Deviations related to the following categories will be included:

- Inclusion or exclusion criteria
- Withdrawal criteria
- Treatment or dose
- Concomitant medications

These and any additional important protocol deviations will be reviewed and documented before database lock and unblinding of treatment codes.

9 Extent of Exposure and Treatment Compliance

9.1 Extent of Exposure

The number and percent of participants who received 1, 2, and 3 double-blind study treatment (tablet) will be summarized by treatment group for the Safety Population.

9.2 Measurement of Treatment Compliance

Dosing compliance for double-blind study medication for a specified period is defined as the total number of double-blind study medications actually taken by a participant during that period divided by the number of double-blind study medications that were expected to be taken during the same period multiplied by 100. Descriptive statistics for double-blind study medication dosing compliance will be presented by treatment group for each week, as well as for the whole double-blind treatment period of the study for the Safety Population.

Dosing compliance for placebo tablet during a specified period is defined as the doses actually taken by a participant during that period divided by the doses expected to be taken during the same period multiplied by 100. Descriptive statistics for placebo dose compliance during the double-blind treatment period will be presented by treatment group for the Safety Population.

10 Efficacy Analyses

The efficacy analyses will be based on the mITT population. The last-observation-carried-forward (LOCF) approach will be used to impute missing postbaseline values. 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 for main effects. 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 5 participants in the mITT Population. All the small centers will be pooled to form a pseudo-center. If the pseudo-center is still a small center, it will be pooled with the smallest non-small center. If there is more than one smallest non-small center, the small pseudo-center will be pooled with the smallest non-small center that has the largest center number.

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

10.1 Primary and Key Secondary Efficacy Endpoints

Primary efficacy endpoint:

- Change from baseline in MADRS total score at 1 day after first dose

Key secondary efficacy endpoint:

- Change from baseline in MADRS total score at Week 3

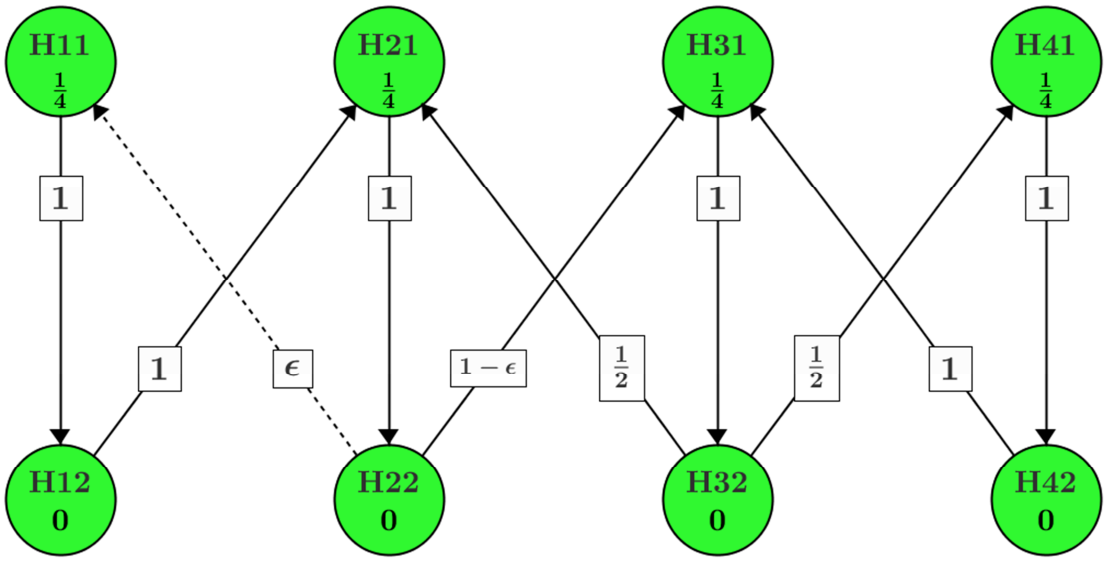
The primary analysis for the primary and key secondary endpoints will be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, visit, pooled study center, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit as 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.

In addition, a sensitivity analysis using the LOCF approach will be performed on the primary efficacy and key secondary parameters. The between-treatment group comparisons will be performed by means of an analysis-of-covariance (ANCOVA) model with treatment group and study center as factors and the baseline MADRS total score as the covariate. 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.

10.2 Multiple Comparisons Procedure

Let H11, H21, H31, H41 represent the comparisons of AGN-241751 0.25 mg, 1 mg, 3 mg, and 10 mg, respectively with placebo in regarding to the primary efficacy parameter; and let H12, H22, H32, and H42 represent the comparisons of AGN-241751 0.25 mg, 1 mg, 3 mg, and 10 mg, respectively with placebo in regarding to the key secondary efficacy parameter, the graphical procedure as displayed in Figure 10-1 will be employed to control the overall familywise error rate (FWER) at $\alpha = 0.05$. The ϵ in the figure represents a small positive number less than 0.0001.

Figure 10-1 **Graphical Procedure for Primary and Key Secondary Hypotheses**



10.3 Additional Efficacy Endpoints

Additional efficacy endpoints:

- Change from baseline in MADRS total score at 7 days after first dose of treatment
- Change from baseline in Clinical Global Impressions-Severity (CGI-S) at 1 day and 7 days after first dose of double-blind study treatment, and end of double-blind study treatment period (end of Week 3)
- Rate of MADRS sustained responders during treatment
- Rate of MADRS and CGI-S responders at 1 day and 7 days after first dose of double-blind study treatment, and end of double-blind study treatment period (end of Week 3)
- Rate of MADRS sustained remitters during treatment
- Rate of MADRS remitters at 1 day and 7 days after first dose of double-blind study treatment, and end of double-blind study treatment period (end of Week 3)
- Time to first response
- Time to first sustained response
- Time to first remission
- Time to first sustained remission

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

During the randomized treatment period, 4 types of events for MADRS total score will be defined based on the following criteria:

- Responder: ≥ 50% reduction from baseline MADRS total score
- Sustained responder: meet responder criteria at ≥ 2 consecutive visits and continued through to final assessment
- Remitter: MADRS total score ≤ 10
- Sustained remitter: meet remitter criteria at ≥ 2 consecutive visits and continued through to final assessment

MADRS total score is the sum of the 10 items from the MADRS. If more than 2 items of MADRS are missing, then the total score will be set to missing.

Additional quantitative efficacy parameters will be analyzed in the following way:

Analysis of change from baseline in MADRS total score and CGI-S score will be performed using a similar MMRM for the primary and key secondary endpoints. Baseline CGI-S score will be used as a covariate for the analysis of CGI-S score. In addition, these parameters will be analyzed using ANCOVA (with LOCF imputation) as used for the analysis of primary efficacy parameters.

Additional categorical efficacy parameters will be analyzed in the following way:

Rates for categorical parameters (response and remission) will be reported by treatment group and by visit; 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 the corresponding baseline score as explanatory variables.

Additional time to event efficacy parameters will be analyzed in the following way:

For the time to event type of endpoints, the log-rank test will be performed to compare the treatment arms. Kaplan-Meier curves will be plotted for each treatment arm.

11 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), BPRS+, CADSS, C-SSRS, and SDC parameters. For each safety parameters, except AEs, the last nonmissing safety assessment before the first dose of double-blind 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, 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 21.0 or newer.

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 double-blind study treatment. However, an AE that occurs more than 30 days after the last dose of double-blind study treatment will not be counted as a TEAE. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore TEAEs can be identified as those AEs with recorded onset date on or after the date of the first dose of double-blind study treatment and within 30 days after the last dose of double-blind study treatment. For participants who enter the double-blind treatment period, but did not enter the safety follow-up period, any AE that occurred up to 30 days after the date of the last dose of double-blind study treatment, is considered as TEAEs for the double-blind treatment period. For participants who entered the safety follow-up period, AEs that occurred on or after the date of Visit 9/ET will be considered as TEAEs for the safety follow-up period.

An AE will be considered a treatment-emergent serious AE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

Summaries of TEAEs/AEs will be presented separately for the double-blind treatment period and safety follow-up period.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term. In addition, the number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class, preferred term, and severity for the double-blind treatment period. The number and percentage of participants reporting treatment related TEAEs in each treatment group will be tabulated by system organ class and preferred term for the double-blind treatment period.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe for the summarizations by severity.

Listings of SAEs and AEs leading to discontinuation by participant will be presented.

11.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group for the following laboratory parameters:

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

In addition, descriptive statistics for 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 11-1.

Table 11-1 List of Selected Parameters Reported in Conventional Unit

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) *(This lab parameter could be the same as #11)*	mg/dL
13	Cholesterol, Total	mg/dL
14	Creatine Kinase	U/L
15	Creatinine	mg/dL
16	Glucose	mg/dL
17	Insulin	uIU/mL
18	Triglycerides	mg/dL

Number	*Laboratory Parameter*	*Conventional Unit*
19	Uric Acid	mg/dL
20	Hemoglobin	G/dL

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 11-2. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group for the double-blind treatment period. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind treatment period. 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.

The number and percentage of participants meeting potential Hy's Law criteria (elevation of alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3x ULN with total bilirubin ≥ 2x ULN and alkaline phosphatase < 2x ULN in a 24-hour period) will be tabulated by double-blind treatment group starting from the first dose of double-blind study treatment to within 30 days after the last dose of double-blind study treatment for the Safety Population. A supportive listing will also be provided.

Table 11-2 Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criterion*[b] *Low Value*	*PCS Criterion*[b] *High Value*
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
Absolute neutrophil count	$\times 10^9$/L	1	1000/µL	< 1.0	—
Platelet count	$\times 10^9$/L	1	1000/µL	≤ 75	≥ 700
White blood cell count	$\times 10^9$/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
Alanine aminotransferase	U/L	1	U/L	—	≥ 3 × ULN

Table 11-2 Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criterion*[b] *Low Value*	*PCS Criterion*[b] *High Value*
(ALT)					
Aspartate aminotransferase (AST)	U/L	1	U/L	—	≥ 3 × ULN
Gamma-glutamyl transferase (GGT)	U/L	1	U/L	—	≥ 3 × ULN
Lactate dehydrogenase (LDH)	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen or Urea	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
Total cholesterol	mmol/L	38.6698	mg/dL	—	> 1.3 × ULN
High-density lipoprotein (HDL) cholesterol	mmol/L	39	mg/dL	< 0.8 × LLN	—
Low-density lipoprotein (LDL) cholesterol	mmol/L	39	mg/dL	—	> 1.2 × ULN
Creatine phosphokinase (CPK)	U/L	1	U/L	—	> 1.5 × ULN
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose, fasting	mmol/L	18.018	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	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Triglycerides, fasting	mmol/L	88.4956	mg/dL	—	> 1.2 × ULN
Uric acid or Urate	µmol/L	0.0168	mg/dL	—	> 1.1 × ULN
Urinalysis					
Protein	—	—	—	—	At least 2 +
Glucose	—	—	—	—	At least 2 +
Blood	—	—	—	—	At least 2 +

a Conversion factor from SI units to conventional (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 laboratory reference range.

11.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, and weight) values at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed

value criterion or the change from baseline value criterion that will be detailed in Table 11-3. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study treatment for each assessment. The percentages will be calculated relative to the number of participants who have available baseline or non-PCS baseline (for parameters with only the observed value criterion) values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 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%

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 Electrocardiograms

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

ECG parameter values are considered PCS if ECG values meeting *either* the actual value or change from baseline PCS high criteria listed in Table 11-4. The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment. The percentages

will be calculated relative to the number of participants with an available non-PCS baseline value and at least one postbaseline assessment. The numerator will be the total number of participants with an 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.

Table 11-4 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.

A listing of all AEs for participants with PCS ECG values will also be provided.

A shift table from baseline to the end of double-blind treatment period 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.

11.5 Other Safety Parameters

11.5.1 Brief Psychiatric Rating Scale—Positive Symptoms Subscale

Descriptive statistics for BPRS+ score and changes from the baseline values at each assessment time point will be presented by treatment group. 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.

11.5.2 Clinician Administered Dissociative States Scale

Descriptive statistics for CADSS score and changes from the baseline values at each assessment time point will be presented by treatment group. CADSS total score is the sum of scores for 23 subjective items. If more than 4 items are missing, then the total score will be set to missing.

11.5.3 Symbol Digit Coding

Descriptive statistics will be presented at each assessment timepoint by treatment for the SDC parameters including the number of symbols completed, the rate of completion (number of symbols completed/time of trial), the number of corrected responses (symbols completed correctly), and the number of errors (symbols completed incorrectly).

11.5.4 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Population. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the participant's lifetime, during the double-blind treatment period, and during the safety follow-up period will also be presented by treatment group. Supportive listings will be provided and will include the PID number, study center number, treatment group, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings. A listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior will also be provided.

12 Health Outcome Analyses

Not Applicable.

13 Interim Analysis

No interim analysis is planned for this study.

14 Determination of Sample Size

The sample size of approximately 50 randomized participants in each of the 5 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 Statistical Software

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

16 Data Handling Convention

16.1 Visit Time windows

Table 16-1 Efficacy and Safety Analysis Visit Definitions

Derived Visit	***Scheduled Visit Day***[a]	***Window***
Baseline	Day 1[d] (visit 2)	Last record on or before Index1[a]
4-hour Post Dose	4-hour Post Dose (visit 2a)	4-hour post dose
Day 2	Day 2 (visit 3)	Index1[a]+1
Day 5	Day 5 (visit 4)	Days [Index1[a] +2, IndexA[b]-1]
Day 8	Day 8[d] (visit 5)	IndexA[b]
Day 9	Day 9 (visit 6)	Day IndexA[b]+1
Day 12	Day 12 (visit 7)	Days [IndexA[b] +2, IndexB[c]-1]
Day 15	Day 15[d] (visit 8)	IndexB[c]
Week 3	Day 22 (visit 9)	Days [IndexB[c]+1, day of final double-blind visit or ET Visit occurring after IndexB[c]+1]
End of double-blind treatment period (end of Week 3)	The last available post-baseline assessment during the double-blind treatment period	
End of safety follow-up period	The last available post-baseline assessment during the safety follow-up period.	

a Index1: Day of first double-blind dose
b IndexA: Day of second double-blind dose, if not received, use Index1 + 7 days
c IndexB: Day of third double-blind dose, if not received, use IndexA + 7 days.
d Study treatment administration in clinic.

16.2 Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of double-blind study treatment. 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.

16.3 Missing Date of the Last Dose of Study treatment

Since participants will receive their double-blind study treatment doses under the direct supervision of study center personnel, the date of the last dose of study treatment will be available, i.e. missing data imputation rule is not applicable.

16.4 Missing Severity Assessment for Adverse Events

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

16.5 Missing Causal Relationship to Study treatment for Adverse Events

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

16.6 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (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 double-blind study treatment, the month and day of the first dose of double-blind 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 double-blind 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 double-blind 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 double-blind study treatment, the day of the first dose of double-blind 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 double-blind 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 double-blind 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 double-blind 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 double-blind 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 double-blind study treatment, the date of the first dose of double-blind study treatment will be assigned to the missing start date
- If the stop date is before the date of the first dose of double-blind study treatment, the stop date will be assigned to the missing start date

16.7 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, 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.

16.7.1 Incomplete Start Date

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

Missing month and day

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

16.7.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as descripted in Section 15.3. 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

16.8 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.

17 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None.

18 REFERENCES

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56 –62.

Bretz, F., Maurer, W. and Hommel, G. (2011), Test and power considerations for multiple endpoint analyses using sequentially rejective graphical procedures. Statistics in Medicine, 30: 1489-1501.