Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Assess the Efficacy and Safety of Lu AA21004 in Patients with Major Depressive Disorder

NCT Number: NCT02389816

Statistical analysis plan Approve Date: 23-May-2018

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

Statistical Analysis Plan

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study to Assess the Efficacy and Safety of Once-daily Oral Dose of Lu AA21004 in Patients with Major Depressive Disorder A Phase III Study of Lu AA21004 in Patients with Major Depressive Disorder
Study Number:	Lu AA21004/CCT-004
Sponsor:	Takeda Pharmaceutical Company Limited

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Version 2: Prepared on 23 May, 2018

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Glossary

- Treatment-emergent adverse event (TEAE): An adverse event which occurs on or after the start of double-blind study drug
- Placebo lead-in adverse event: An adverse event which occurs on or after the start of placebo lead-in study drug before the start of double-blind study drug
- Drug-related adverse event: An adverse event that is considered to be either probable, or possible related to the double-blind study drug will be treated as related.
- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- PCS: Potentially Clinically Significant
- Study Day: The day before the first dose of the double-blind study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1.
- Follow-up Day: The day after the last dose of the double-blind study drug will be defined as Follow-up Day 1.
- Treatment Groups: Placebo, Lu AA21004 10 mg, Lu AA21004 20 mg
- MADRS total score: Sum of the 10 MADRS items
- HAM-D17 total score: Sum of the 17 HAM-D items
- HAM-D21 total score: Sum of the 21 HAM-D items
- SDS total score: Sum of the 3 SDS items
- MADRS response: Percentage of subjects whose MADRS total score decreased by a greater than or equal to 50% from baseline
- MADRS remission: Percentage of subjects whose MADRS total score decreased to 10 or less

Definition of TIME WINDOW

For each test/observation/evaluation item, all evaluable data (non-missing and acceptable according to the "Handling Rules for Analysis Data") will be handled according to the following rules.
For each visit other than Week 8 (LOCF), observation in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. The difference from the scheduled Study Day will be judged based on the Study Day and Follow-up Day.
For Week 8 (LOCF), the last observation obtained in the corresponding time interval will be used.

MADRS, CGI-S

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Screening	Study Day: -22	<= -12	-
Placebo lead-in	Study Day: -8	-11 - -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 1	Study Day: 7	2 - 10	<8
Week 2	Study Day: 14	11 - 21	<8
Week 4	Study Day: 28	22 - 35	<8
Week 6	Study Day: 42	36 - 49	<8
Week 8	Study Day: 56	50 <=	<8
Week 8 (LOCF)	-	2 <=	<8

HAM-D

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Screening	Study Day: -22	<= -12	-
Placebo lead-in	Study Day: -8	-11 - -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 8	Study Day: 56	2 <=	<8
Week 8 (LOCF)	-	2 <=	<8

CGI-I

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: -1	<= 1	-
Week 1	Study Day: 7	2 - 10	<8
Week 2	Study Day: 14	11 - 21	<8
Week 4	Study Day: 28	22 - 35	<8
Week 6	Study Day: 42	36 - 49	<8
Week 8	Study Day: 56	50 <=	<8
Week 8 (LOCF)	-	2 <=	<8

SDS

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Placebo lead-in	Study Day: -8	<= -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 8	Study Day: 56	2 <=	<8
Week 8 (LOCF)	-	2 <=	<8

DSST, PDQ-5

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Placebo lead-in	Study Day: -8	<= -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 1	Study Day: 7	2 - 10	<8
Week 8	Study Day: 56	11 <=	<8
Week 8 (LOCF)	-	2 <=	<8

Laboratory Value, Weight, ECG

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Screening	Study Day: -22	<= -12	-
Placebo lead-in	Study Day: -8	-11 - -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 4	Study Day: 28	2 - 42	<8
Week 8	Study Day: 56	43 <=	<8

Vital Sign, C-SSRS

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Screening	Study Day: -22	<= -12	-
Placebo lead-in	Study Day: -8	-11 - -5	-
Baseline (Week 0)	Study Day: -1	-4 - 1	-
Week 1	Study Day: 7	2 - 10	<8
Week 2	Study Day: 14	11 - 21	<8
Week 4	Study Day: 28	22 - 35	<8
Week 6	Study Day: 42	36 - 49	<8
Week 8	Study Day: 56	50 <=	<8

Others

- Duration of exposure to double-blind study drug (days): date of last dose of double-blind study drug – date of first dose of double-blind study drug + 1
- Double-blind study drug compliance (%): number of double-blind study drugs taken / duration of exposure to double-blind study drug × 100 (rounded off to one decimal place)
- QT_CF interval = (QT interval) / ([QT_CB interval]^2 / [QT interval]^2)$^{0.33}$ (rounded off to the whole number)
- Among the laboratory test items, the following data will not be included if it is from a postprandial specimen.
  Glucose, lipids (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol [Direct method])
-

1 Study Subjects, Demographic, and Other Baseline Characteristics

1.1 Disposition of Subjects

1.1.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	Date First Subject Signed the Informed Consent Form
	MedDRA Version
	WHO Drug Version
	SAS Version Used for Creating the Datasets
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). (1) Display of Analysis Variable(s)

1.1.2 Disposition of All Subjects Who Did Not Enter Placebo Lead-in Period

Analysis Set:	All Subjects Who Did Not Enter the Placebo Lead-in Period	
Analysis Variable(s):	Categories in parentheses ([ ]) (hereinafter the same)	
	Age (years)	[Min<= - <=50, 51<= - <=Max]
	Gender	[Male, Female]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). (1) Frequency distributions for counting values and descriptive statistics for continuous variables	

1.1.3 Subject Eligibility

1.1.3.1 Subject Eligibility at Start of Placebo Lead-in Period

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s):	Eligibility Status	[Eligible for Entrance into the Placebo Lead-in Period, Not Eligible for Entrance into the Placebo Lead-in Period]
	Primary Reason for Subject Not Being Eligible	[Pretreatment Event or Adverse Event (AE), Did Not Meet Inclusion Criteria, Met Exclusion Criteria, Major Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal, Study Termination, Other]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.	
	(1) Frequency Distributions	

1.1.3.2 Subject Eligibility at Start of Double-blind Period

Analysis Set:	All Subjects Who Entered the Placebo Lead-in Period	
Analysis Variable(s):	Eligibility Status	[Eligible for Randomization, Not Eligible for Randomization]
	Primary Reason for Subject Not Being Randomized	[Pretreatment Event or Adverse Event (AE), Did Not Meet Inclusion Criteria, Met Exclusion Criteria, Major Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal, Study Termination, Other]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). When calculating percentages for the primary reasons for subject not being eligible for randomization, the total number of ineligible subjects will be used as the denominator.	
	(1) Frequency Distributions	

1.1.4 Number of Subjects by Site

1.1.4.1 Number of Subjects Who Entered the Placebo Lead-in Period by Site

Analysis Set:	All Subjects Who Entered the Placebo Lead-in Period	
Analysis Variable(s):	Status of Entrance into the Placebo Lead-in Period	[Entered]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s) for each stratum. (1) Frequency Distributions	

1.1.4.2 Number of Subjects Randomized by Site

Analysis Set:	Randomized Set	
Analysis Variable(s):	Randomization Status	[Randomized]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s):	Frequency distributions will be provided for each treatment group and overall for each stratum. (1) Frequency Distributions	

1.1.5 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variable(s):	Double-blind Study Drug Administration Status	[Not Treated]
	Reason for Not Being Treated	[Pretreatment Event or Adverse Event (AE, Liver Function Abnormalities, Major Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Non Compliance with IMP, Other]
	Double-blind Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Pretreatment Event or Adverse Event (AE), Liver Function Abnormalities, Major Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Non Compliance with IMP, Other]
Analytical Method(s):	Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator. (1) Frequency Distributions	

1.1.6 Protocol Deviations and Analysis Sets

1.1.6.1 Protocol Deviations

Analysis Set:	All Subjects Who Entered the Placebo Lead-in Period Randomized Set	
Analysis Variable(s):	Protocol Deviations	[Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk, Other Deviations]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). When the randomized set is analyzed, the frequency distribution will be provided for each treatment group and overall. The number of subjects who have protocol deviations will be counted, and the disposition of deviations are shown after classifying the contents of deviations into the above categories. A subject who has several deviations that can be classified into several categories will be counted once in each appropriate category (overlapping). (1) Frequency Distributions	

1.1.6.2 Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variable(s):	Handling of Subjects and Subject Data	[Categories are based on the specifications in Handling Rules for Analysis Data]
	Analysis Sets	
	Full Analysis Set	[Included]
	Per Protocol Set	[Included]
	Safety Analysis Set	[Included]
Analytical Method(s):	Frequency distributions will be provided by treatment group for (1) and (2), and by treatment group and overall for (3). For (1) and (2), a subject who has several reasons for exclusion will be counted once in each appropriate category (overlapping).	

(1) Frequency Distributions for Subjects Excluded from Analysis Sets
(2) Frequency Distributions for Subject Data Excluded from Analysis Sets
(3) Frequency Distributions for Number of Included Subjects in Analysis Sets

1.2 Demographics and Other Baseline Characteristics

1.2.1 Summary of Demographics and Other Baseline Characteristics

Analysis Set:	Randomized Set	
	All Subjects Who Entered the Placebo Lead-in Period	
	All Subjects Who Entered the Placebo Lead-in Period, but Not Randomized	
Analysis Variable(s):	Age (years)	[Min<= - <=50, 51<= - <=Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) at Baseline	
	BMI (kg/m^2) at Baseline	
	Smoking Classification	[The subject is a current smoker, The subject is an ex-smoker, The subject has never smoked]
	History of Alcohol Consumption	[Never, Once monthly or less often, Once a week, 2 to 6 times/week, Daily]
	Symptoms for Major Depressive Episode	
	1. Depressed mood almost all day long or almost every day shown by that person's own statement (e.g., sorrow or feeling of emptiness) or other person's observation (e.g., that person looks crying)	[Yes, No]
	2. Markedly diminished interest or pleasure almost all day long, almost every day, or in almost all activities (shown by that person's own statement or other person's observation)	[Yes, No]
	3. Significant weight loss or decrease despite of no dietary	[Yes, No]

therapy (e.g., not less than 5% change of weight in a month) or decreased or increased appetite almost every day	
4. Insomnia or hypersomnia almost every day	[Yes, No]
5. Psychomotor agitation or retardation almost every day (which can be observed by other persons but not subjective sensation, e.g., that person is simply restless or has become sluggish)	[Yes, No]
6. Fatigue or loss of energy almost every day	[Yes, No]
7. Feelings of worthlessness, or excessive or inappropriate guilt almost every day (which could be delusive but not simply blaming oneself or a sense of guilt toward becoming ill)	[Yes, No]
8. Diminished ability to think or concentrate, or indecisiveness almost every day (shown by that person's own statement or other person's observation)	[Yes, No]
9. Recurrent thoughts of death (not only fear of death), recurrent suicidal ideation or actual attempt with no special plan, or clear plan for suicide	[Yes, No]
MADRS Total Score at Placebo Lead-in	[Min<= - <=30, 31<= - <=Max]
MADRS Total Score at Baseline	[Min<= - <=30, 31<= - <=Max]
Percent Chang in MADRS Total Score from Placebo Lead-in at Baseline	[Min<= - <=-25, -25< - <25, 25<= - <=Max]

HAM-D17 Total Score at Placebo Lead-in

HAM-D17 Total Score at Baseline

CGI-I Score at Baseline

CGI-S Score at Placebo Lead-in [Min<= - <=4, 5<= - <=Max]

CGI-S Score at Baseline [Min<= - <=4, 5<= - <=Max]

SDS Total Score at Placebo Lead-in

SDS Total Score at Baseline

DSST Score at Placebo Lead-in

DSST Score at Baseline

PDQ-5 Score at Placebo Lead-in

PDQ-5 Score at Baseline

Analytical Method(s): The following summaries will be provided for the above analysis variable(s). When the randomized set is analyzed, the frequency distribution will be provided for each treatment group and overall. However, weight, BMI, and efficacy endpoints (MADRS total score, HAM-D17 total score, CGI-I score, CGI-S score, SDS total score, DSST score, and PDQ-5 score) will target only the randomized set.

(1) Frequency distributions for counting values and descriptive statistics for continuous variables

1.2.2 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s): Medical History

Concurrent Medical Conditions

Analytical Method(s): Frequency distributions will be provided for each treatment group and overall. Analysis variables will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically, and PT will be sorted in decreasing frequency.

(1) Frequency distributions for medical history by SOC and PT

(2) Frequency distributions for concurrent medical conditions by SOC and PT

The frequency distribution will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A

subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History and Concomitant Medications

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Medication History Concomitant Medications
Analytical Method(s):	Frequency distributions will be provided for each treatment group and overall. Analysis variables will be coded using WHO Drug dictionary and will be summarized using generic names. They will be sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same generic name will be counted only once for that generic name. (1) Frequency distributions for medication history (2) Frequency distributions for concomitant medications

1.3 Treatment Compliance

1.3.1 Study Drug Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Duration of Exposure to Double-blind Study Drug (days)	[1<= - <=7, 8<= - <=14, 15<= - <=28, 29<= - <=42, 43<= - <=56, 57<= - <=Max]
	Double-blind Study Drug Compliance (%)	[Min<= - <70.0, 70.0<= - <90.0, 90.0<= - <=100.0, 100.0< - <=Max]
Analytical Method(s):	Frequency distributions will be provided for each treatment group and overall. (1) Frequency distributions for counting values and descriptive statistics for continuous variables	

2 Efficacy Analysis

The full analysis set that has been defined in the protocol and the Handling Rules for Analysis Data will be the main analysis set used. The per protocol set will be used for an analysis performed secondarily on the primary endpoint in order to examine the robustness of the results from the perspective of sensitivity analysis.

2.1 Primary Endpoint(s) and Analytical Methods

2.1.1 Primary Analysis

Analysis Set: Full Analysis Set

Analysis Variable(s): Change from baseline in the MADRS total score at Week 8 of treatment with double-blind study drug

Analytical Method(s): Primary efficacy analysis will be performed based on a mixed model for repeated measurements (MMRM) analysis of covariance with change from baseline in MADRS total score at each post-dose visit as a dependent variable, and visit, treatment group, visit-by-treatment group interaction, baseline MADRS total score-by-visit interaction as fixed effects. Comparisons between each Lu AA21004 group and the Placebo group will be performed at Week 8 of treatment with double-blind study drug. For the adjustment of freedom degree, Satterthwaite method will be used. For covariance structure analysis among the subjects, the same, unstructured covariance matrix is assumed.

[Model]

Change from baseline in the MADRS total score = Visit + Treatment group + Treatment group × Visit + baseline MADRS total score × Visit

Holm adjustment will be used for multiplicity for the comparison. That is,

$$H_{01}: \mu_{Placebo} = \mu_{10\ mg}$$
$$H_{02}: \mu_{Placebo} = \mu_{20\ mg}$$

A p-value for each null hypothesis will be set to be P_1 and P_2. A test will be performed according to the following procedures after setting P_1 and P_2 in an ascending order as $P^{(1)}$ and $P^{(2)}$ and setting the corresponding null hypotheses as $H^{(1)}$ and $H^{(2)}$.

Step 1: In the case of $P^{(1)} > 0.025$, end the test procedures by holding null hypotheses $H^{(1)}$ and $H^{(2)}$. In the case of $P^{(1)} \leq 0.025$, reject null hypothesis $H^{(1)}$ and proceed to Step 2.

Step 2: In the case of $P^{(2)} > 0.05$, hold null hypothesis $H^{(2)}$. In the case of $P^{(2)} \leq 0.05$, reject null hypothesis $H^{(2)}$.

2.1.2 Secondary Analysis (1)

Analysis Set:	Per Protocol Set
Analysis Variable(s):	Change from baseline in the MADRS total score at Week 8 of treatment with double-blind study drug
Analytical Method(s):	To check the robustness of the results depending on handling of subjects and subject data, the same analyses as section 2.1.1 “Primary Analysis” will be performed using the per protocol set.

2.1.3 Secondary Analysis (2)

Analysis Set:	Full Analysis Set
Analysis Variable(s):	Change from baseline in the MADRS total score at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline)
Visit:	Week 8 (LOCF)
Analytical Method(s):	Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the MADRS total score at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline) by treatment group. The change from baseline in the MADRS total score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and the baseline MADRS total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

2.2 Secondary Endpoint(s) and Analytical Methods

Analysis Set: Full Analysis Set

Analysis Variable(s):
MADRS response at Week 8 (LOCF) of treatment with double-blind study drug
MADRS remission at Week 8 (LOCF) of treatment with double-blind study drug
Change from baseline in the HAM-D17 total score at Week 8 (LOCF) of treatment with double-blind study drug
CGI-I score at Week 8 (LOCF) of treatment with double-blind study drug
Change from baseline in the CGI-S score at Week 8 (LOCF) of treatment with double-blind study drug
Change from baseline in the SDS total score at Week 8 (LOCF) of treatment with double-blind study drug
Change from baseline in the DSST score at Week 8 (LOCF) of treatment with double-blind study drug
Change from baseline in the PDQ-5 score at Week 8 (LOCF) of treatment with double-blind study drug

Visit: Week 8 (LOCF)

Analytical Method(s):
(1) MADRS response at Week 8 (LOCF) of treatment with double-blind study drug

Frequency distributions will be provided by treatment group along with point estimates and the two-sided 95% confidence intervals for MADRS response at Week 8 (LOCF) of treatment with double-blind study drug. Odds ratios of each Lu AA21004 group to the placebo group (each Lu AA21004 group / placebo group) and the two-sided 95% confidence intervals will be provided and tested for treatment differences using a logistic regression model. The logistic regression model will include MADRS response at Week 8 (LOCF) of treatment with double-blind study drug as a dependent variable, and treatment group and baseline MADRS total score as independent variables.

(2) MADRS remission at Week 8 (LOCF) of treatment with double-blind study drug

Frequency distributions will be provided by treatment group along with point estimates and the two-sided 95% confidence intervals at Week 8 (LOCF) of treatment with double-blind study drug. Odds ratios of each Lu AA21004 group to the placebo group (each Lu AA21004 group / placebo group) and the two-sided 95% confidence intervals will be provided and tested for treatment

differences using a logistic regression model. The logistic regression model will include MADRS remission at Week 8 (LOCF) of treatment with double-blind study drug as a dependent variable, and treatment group and baseline MADRS total score as independent variables.

(3) Change from baseline in the HAM-D17 total score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the HAM-D17 total score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The change from baseline in the HAM-D17 total score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline HAM-D17 total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(4) CGI-I score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the CGI-I score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The CGI-I score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline CGI-S score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(5) Change from baseline in the CGI-S score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the CGI-S score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The change from baseline in the CGI-S score at Week 8 (LOCF) of treatment with

double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline CGI-S score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(6) Change from baseline in the SDS total score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the SDS total score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The change from baseline in the SDS total score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline SDS total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(7) Change from baseline in the DSST score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the DSST score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The change from baseline in the DSST score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline DSST score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(8) Change from baseline in the PDQ-5 score at Week 8 (LOCF) of treatment with double-blind study drug

Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the change from baseline in the PDQ-5 score at Week 8 (LOCF) of treatment with double-blind study drug by treatment group. The change from baseline in the PDQ-5 score at Week 8 (LOCF) of treatment with double-blind study drug (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline PDQ-5 score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

2.3 Other Analysis/Additional Endpoint(s) and Analytical Methods

Analysis Set:	Full Analysis Set
Analysis Variable(s):	MADRS total score, MADRS single item MADRS response, MADRS remission HAM-D17 total score, HAM-D single item, HAM-D21 total score CGI-I score, CGI-S score, SDS total score, SDS single item DSST score, PDQ-5 score, PDQ-5 single item
Visit:	[MADRS total score, MADRS single item, CGI-S score] Screening, Placebo Lead-in, Baseline, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 8 (LOCF) [MADRS response, MADRS remission, CGI-I score] Week 1, Week 2, Week 4, Week 6, Week 8, and Week 8 (LOCF) [HAM-D17 total score, HAM-D single item, HAM-D21 total score] Screening, Placebo Lead-in, Baseline, Week 8, and Week 8 (LOCF) [SDS total score, SDS single item] Placebo Lead-in, Baseline, Week 8, and Week 8 (LOCF) [DSST score, PDQ-5 score, PDQ-5 Single item] Placebo Lead-in, Baseline, Week 1, Week 8, and Week 8 (LOCF)

Analytical Method(s):

(1) MADRS total score

MADRS total score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the MADRS total score at each post-dose visit by treatment group. The change from baseline in the MADRS total score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline MADRS total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(2) MADRS single item

MADRS single item will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the changes from baseline (each post-dose visit - Baseline) in the MADRS single item at each post-dose visit by treatment group. The point estimates of the mean differences in the changes from baseline between each Lu AA21004 group and the placebo group (each Lu AA21004 treatment group – placebo group) and the two-sided 95% confidence intervals will be provided.

(3) MADRS response

MADRS response will be analyzed for each visit. Frequency distributions will be provided by treatment group along with the point estimates and the two-sided 95% confidence intervals. Odds ratios of each Lu AA21004 group to the placebo group (each Lu AA21004 group / placebo group) and the two-sided 95% confidence intervals will be provided and tested for treatment differences using a logistic regression model. The logistic regression model will include MADRS response as a dependent variable, and treatment group and baseline MADRS total score as independent variables.

(4) MADRS remission

MADRS remission will be analyzed for each visit. Frequency distributions will be provided by treatment group along with the point estimates and the two-sided 95% confidence intervals. Odds ratios of each Lu AA21004 group to the placebo group (each Lu AA21004 group / placebo group) and the two-sided 95% confidence intervals will be provided and tested for treatment differences using a logistic regression model. The logistic regression model will include MADRS remission as a dependent variable, and treatment group and baseline MADRS total score as independent variables.

(5) HAM-D17 total score

HAM-D17 total score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the HAM-D17 total score at each post-dose visit by treatment group. The change from baseline in the HAM-D17 total score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline HAM-D17 total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(6) HAM-D single item

HAM-D single item will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the changes from baseline (each post-dose visit - Baseline) in the HAM-D single item at each post-dose visit by treatment group. The point estimates of the mean differences in the changes from baseline between each Lu AA21004 group and the placebo group (each Lu AA21004 treatment group - placebo group) and the two-sided 95% confidence intervals will be provided.

(7) HAM-D21 total score

HAM-D 21 total score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the changes from baseline (each post-dose visit - Baseline) in the HAM-D21 total score at each post-dose visit by treatment group. The point estimates of the mean differences in the changes from baseline between each Lu AA21004 group and the placebo group (each Lu AA21004 treatment group - placebo group) and the two-sided 95% confidence intervals will be provided.

(8) CGI-I score

CGI-I score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the CGI-I score by treatment group. The CGI-I will be performed based on a mixed model for repeated measurements (MMRM) analysis of covariance with CGI-I score at each post-dose visit (Week 1 to Week 8) as a dependent variable, and visit, treatment group, visit-by-treatment group interaction, baseline CGI-S score-by-visit interaction as fixed effects. Least Square (LS) means and the two-sided 95% confidence intervals at each visit will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 - placebo group) and the two-sided 95% confidence intervals will be provided. The CGI-I score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline CGI-S score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(9) CGI-S score

CGI-S score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the CGI-S score at each post-dose visit by treatment group. The change from baseline in the CGI-S score will be performed based on a mixed model for repeated measurements (MMRM) analysis of covariance with change from baseline (post-dose visit - Baseline) in the CGI-S score at each post-dose visit (Week 1 to Week 8) as a dependent variable, and visit, treatment group, visit-by-treatment group interaction, baseline CGI-S score-by-visit interaction as fixed effects. Least Square (LS) means and the two-sided 95% confidence intervals at each visit will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 - placebo group) and the two-sided 95% confidence intervals will be provided. The change from baseline in the CGI-S score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline CGI-S score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(10) SDS total score

SDS total score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the SDS total score at each post-dose visit score by treatment group. The change from baseline in the SDS total score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline SDS total score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(11) SDS single item

SDS single item will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the changes from baseline (each post-dose visit - Baseline) in the SDS single item at each post-dose visit by treatment group. The point estimates of the mean differences in the changes from baseline between each Lu AA21004 group and the placebo group (each Lu AA21004 treatment group - placebo group) and the two-sided 95% confidence intervals will be provided.

(12) DSST score

DSST score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the DSST score at each post-dose visit by treatment group. The change from baseline in the DSST score will be performed based on a mixed model for repeated measurements (MMRM) analysis of covariance with change from baseline (post-dose visit - Baseline) in the DSST score at each post-dose visit (Week 1 to Week 8) as a dependent variable, and visit, treatment group, visit-by-treatment group interaction, baseline DSST score-by-visit interaction as fixed effects. Least Square (LS) means and the two-sided 95% confidence intervals at each visit will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 - placebo group) and the two-sided 95% confidence intervals will be provided. The change from baseline in the DSST score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline DSST score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group - placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(13) PDQ-5 score

PDQ-5 score will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the change from baseline (each post-dose visit - Baseline) in the PDQ-5 score at each post-dose visit by treatment group. The change from baseline in the PDQ-5 score will be performed based on a mixed model for repeated measurements (MMRM) analysis of covariance with change from baseline (post-dose visit - Baseline) in PDQ-5 score at each post-dose visit (Week 1 to Week 8) as a dependent variable, and visit, treatment group, visit-by-treatment group interaction, baseline PDQ-5 score-by-visit interaction as fixed effects. Least Square (LS) means and the two-sided 95% confidence intervals at each visit will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 – placebo group) and the two-sided 95% confidence intervals will be provided. The change from baseline in the PDQ-5 score at each post-dose visit (dependent variable) will be analyzed using an ANCOVA model with treatment as a fixed effect and the baseline PDQ-5 score as a covariate. Least Square (LS) means and the two-sided 95% confidence intervals will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 group – placebo group) and the two-sided 95% confidence intervals will be provided. The differences in the LS means will be tested for treatment differences.

(14) PDQ-5 single item

PDQ-5 single item will be analyzed for each visit. Descriptive statistics and two-sided 95% confidence intervals of means will be provided for the observed values and the changes from baseline (each post-dose visit - Baseline) in the PDQ single item at each post-dose visit by treatment group. The point estimates of the mean differences in the changes from baseline between each Lu AA21004 group and the placebo group (each Lu AA21004 treatment group - placebo group) and the two-sided 95% confidence intervals will be provided.

(15) The following summaries will be provided if considered appropriate.
For the change from baseline in DSST at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline), divide the therapeutic effect into direct and indirect effect and estimate each percentage. Here, the effect that affects through the change from baseline in the MADRS total score at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline) will be set as an indirect effect and others as a direct effect. Specifically, the following models will be used.
Model 1:
change DSST = alpha1 + gamma1 * treatment + gamma3 * change MADRS + baseline DSST + baseline MADRS + epsilon
Model 2:
change MADRS = alpha2 + gamma2 * treatment + baseline DSST + baseline MADRS + epsilon

2.4 Statistical/Analytical Issues

2.4.1 Adjustments for Covariates

After blind data review, it was decided not to conduct further adjustments for covariates by adding variables.

2.4.2 Handling of Dropouts or Missing Data

Missing test results and data determined to be non-evaluable according to the Handling Rules for Analysis Data will not be used for hypothesis testing and estimations. When individual items are missing from a multiple-item assessment, the total score will be set to missing. (MADRS total score, HAM-D17 total score, HAM-D21 total score, SDS total score, and PDQ-5 score)

2.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned in this study.

2.4.4 Multicenter Studies

Although this study is a multicenter study, treatment-by-center interaction will not be explored since the number of subjects for each center is not sufficient for such exploration.

2.4.5 Multiple Comparison/Multiplicity

The main focuses will be placed on the results of the primary analysis performed for the primary endpoint defined as change from baseline in the MADRS total score at Week 8 in the full analysis set. In the primary analyses, each Lu AA21004 group will be compared with the placebo group based on Holm's method to maintain the overall type I error rate below 5%. Other analytical results will be interpreted to support the results of the primary endpoint or to explore the characteristics of the efficacy of Lu AA21004. These results will be considered one measure suggesting the trends or characteristics of the efficacy. Thus, no adjustments for multiplicity will be performed.

2.4.6 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the full analysis set, a secondary analysis will also be performed using the per protocol set to examine the robustness of the results from the perspective of sensitivity analysis.

2.4.7 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable in this study.

2.4.8 Examination of Subgroups

Analysis Set:	Full Analysis Set	
Analysis Variable(s):	Change from baseline in the MADRS total score at Week 8 of double-blind study drug (Week 8 - Baseline)	
Stratum:	Age (years)	[Min<= - <=50, 51<= - <=Max]
	Gender	[Male, Female]
	MADRS Total Score at Baseline	[Min<= - <=30, 31<= - <=Max]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s) for each stratum.	

(1) The same mixed model for repeated measurements (MMRM) analysis of covariance as section "2.1.1 Primary Analysis" will be applied. Least Square (LS) means and the two-sided 95% confidence intervals at each visit will be provided for each treatment group. The point estimates of the differences in the LS means between each Lu AA21004 group and the placebo group (each Lu AA21004 – placebo group) and the two-sided 95% confidence intervals will be provided.

3 Safety Analysis

3.1 Treatment-Emergent Adverse Event

3.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Categories:
- Relationship to Study Drug [Related, Not Related]
- Intensity [Mild, Moderate, Severe]

Analytical Method(s): The following summaries will be provided for each treatment group and overall.

(1) Overview of TEAEs

1) All TEAEs (number of events, number and percentage of subjects)
2) Relationship of TEAEs to study drug (number of events, number and percentage of subjects)
3) Intensity of TEAEs (number of events, number and percentage of subjects)
4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious TEAEs (number of events, number and percentage of subjects)
6) Relationship of serious TEAEs to study drug (number of events, number and percentage of subjects)
7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
8) TEAEs resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

[Number of subjects]

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

3.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Categories:

Intensity	[Mild, Moderate, Severe]
Time of Onset (day)	[1<= - <=7, 8<= - <=14, 15<= - <=28, 29<= - <=42, 43<= - <=56, 57<= - <=Max]

Analytical Method(s): The following summaries will be provided for each treatment group and overall.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically, and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) All TEAEs by SOC and PT

(2) All TEAEs by SOC

(3) All TEAEs by PT

(4) Drug-Related TEAEs by SOC and PT

(5) Intensity of All TEAEs by SOC and PT

(6) Intensity of Drug-Related TEAEs by SOC and PT

(7) TEAEs Leading to Study Drug Discontinuation by SOC and PT

(8) Serious TEAEs by SOC and PT

(9) All TEAEs by SOC and PT Over Time

The frequency distribution will be provided according to the rules below.

[Number of subjects]

- Summary tables other than (5), (6), and (9)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. When calculating percentage of subjects with occurrence of TEAEs, the number of subjects in the safety analysis set will be used as the denominator.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. When calculating percentage of subjects with occurrence of TEAEs, the number of subjects in the safety analysis set will be used as the denominator.

- Summary table for (9)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of subjects with occurrence of TEAEs for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAEs, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of the TEAEs is within the time interval will be used as the numerator.

3.2 Pretreatment Events and Placebo Lead-in Adverse Events

3.2.1 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s): PTE

Analytical Method(s): The following summaries will be provided for the above analysis variable(s). PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically, and PT will be sorted in decreasing frequency.

(1) All PTEs by SOC and PT

(2) Serious PTEs by SOC and PT

The frequency distribution will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

3.2.2 Displays of Placebo Lead-in Adverse Events

Analysis Set: All Subjects Who Received Placebo Lead-in Study Drug

Analysis Variable(s): Placebo lead-in adverse event

Analytical Method(s): The following summaries will be provided for the above analysis variable(s). Placebo lead-in adverse events will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically, and PT will be sorted in decreasing frequency.

(1) All Placebo Lead-in Adverse Events by SOC and PT

(2) Serious Placebo Lead-in Adverse Events by SOC and PT

The frequency distribution will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of run-in AE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of run-in AE within a PT will be counted only once in that PT.

3.3 Laboratory and Other Safety Data

3.3.1 Laboratory Test Results

3.3.1.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s):

Hematology

RBC	WBC	Hemoglobin
Hematocrit	Platelets	

WBC Differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes)

Serum Chemistry

Albumin	AST	ALT
γ-GTP	Alkaline Phosphatase	Total Bilirubin
Direct Bilirubin (Conjugated Bilirubin)	Creatinine	Creatine kinase
Blood Urea Nitrogen	Uric Acid	Glucose
Total Protein	Potassium	Sodium
Calcium	Chloride	Triglycerides
Total Cholesterol	HDL Cholesterol	LDL Cholesterol (Direct Method)

Categories:

Results of judgement based on the reference range: [Low, Normal, or High relative to the normal reference range]

Results based on PCS Criteria: [Meet PCS Criteria, Does not meet PCS Criteria]

Visit: Screening, Placebo Lead-in, Baseline, Week 4, and Week 8

PCS: Baseline (entire pre-dose period), Entire post-dose period

Analytical Method(s): The following summaries will be provided for the above analysis variable(s).

(1) Descriptive statistics for observed values at each visit and changes from baseline at each visit (each post-dose visit [Week 4, Week 8] - Baseline)

(2) Plots over time for each subject

(3) Shift tables at baseline and each post-dose visit of the results of judgement based on the reference range.

(4) Frequency distributions of the results based on PCS Criteria during the entire post-dose period

Refer to the Appendix of this Statistical Analysis Plan if a laboratory parameter has lower or upper PCS Criteria.

(5) Shift tables of the results based on PCS Criteria at baseline (entire pre-dose period) and during the entire post-dose period

3.3.1.2 Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Protein	[-, +-, 1+, 2+, 3+, 4+]
	Glucose	[-, 1+, 2+, 3+, 4+, 5+]
	Occult blood	[-, +-, 1+, 2+, 3+]
	Urine pH	[Min<= - <=4.9, 5.0<= - <=8.0, 8.1<= - <=Max]
Visit:	Screening, Placebo Lead-in, Baseline, Week 4, and Week 8	
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s).	

(1) Shift tables at baseline and each post-dose visit

3.3.2 Vital Signs, Physical Findings and Other Observations Related to Safety

3.3.2.1 Vital Signs and Weight

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Temperature Systolic Blood Pressure Diastolic Blood Pressure Pulse Rate Weight	
Categories:	Results based on PCS Criteria	[Meet PCS Criteria, Does not meet PCS Criteria]
Visit:	Temperature , Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate: Screening, Placebo Lead-in, Baseline, Week 1, Week 2, Week 4, Week 6, and Week 8 Weight: Screening, Placebo Lead-in, Baseline, Week 4, and Week 8 PCS: Entire post-dose period	
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). (1) Descriptive statistics for observed values at each visit and changes from baseline at each visit (each post-dose visit [Week 1 to Week 8] - Baseline) (2) Plots over time for each subject (3) Frequency distributions of the results based on PCS Criteria during the	

entire post-dose period

Refer to the Appendix of this Statistical Analysis Plan if a vital sign parameter has lower or upper PCS Criteria.

3.3.2.2 12-lead ECG

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	RR Interval	
	PR Interval	
	QT Interval	
	QRS Interval	
	QTcB Interval	
	QTcF Interval	
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Categories:	Results based on PCS Criteria	[Meet PCS Criteria, Does not meet PCS Criteria]
Visit:	Screening, Placebo Lead-in, Baseline, Week 4, and Week 8	
	PCS: Entire post-dose period	

Analytical Method(s): For each variable other than 12-lead ECG interpretations, summaries (1) to (3) will be provided by treatment group.

For 12-lead ECG interpretation, summary (4) will be provided by treatment group.

(1) Descriptive statistics for observed values at each visit and changes from baseline at each visit (each post-dose visit [Week 4, Week 8] - Baseline)

(2) Plots over time for each subject

(3) Frequency distributions of the results based on PCS Criteria during the entire post-dose period

Refer to the Appendix of this Statistical Analysis Plan if a ECG laboratory parameter has lower or upper PCS Criteria.

(4) Shift tables at baseline and each post-dose visit

3.3.2.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	SUICIDAL IDEATION	
	Wish to be Dead	[Yes, No]

Non-Specific Active Suicidal Thoughts	[Yes, No]
Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act	[Yes, No]
Active Suicidal Ideation with Some Intent to Act, without Specific Plan	[Yes, No]
Active Suicidal Ideation with Specific Plan and Intent	[Yes, No]
INTENSITY OF IDEATION	
Most Severe Ideation	[Wish to be dead, Non-specific active suicidal thoughts, Active suicidal ideation with any methods (not plan) without intent to act, Active suicidal ideation with some intent to act, without specific plan, Active suicidal ideation with specific plan and intent]
Frequency	[Less than once a week, Once a week, 2-5 times a week, Every day/almost every day, Several times every day]
Duration	[Several seconds to several minutes/For a moment, Less than 1 hour/For a while, 1-4 hours/For a considerable time, 4-8 hours/Almost all hours of the day, More than 8 hours/Persistent or continuous]
Controllability	[Easy to control, A bit difficult but can control, Somewhat difficult but can control, Relatively difficult but can control, Cannot control, No intention to control]

Deterrents	[Desisted to commit suicide due to deterrent(s), Probably desisted to commit suicide due to deterrent(s), Cannot tell if I desisted to commit suicide due to deterrent(s), Probably did not desist to commit suicide due to deterrent(s), Did not desist to commit suicide due to deterrent(s), Not applicable]
Reasons for Suicidal Ideation	[Only to attract someone's attention, revenge, or gain a response, Almost to attract someone's attention, revenge, or gain a response, Fifty-fifty to attract someone's attention, revenge, or gain a response and end pain, Almost to end pain (could not live to put up with the pain and feelings), Only to end pain (could not live while putting up with the pain and feelings), Not applicable]
SUICIDAL BEHAVIOR	
Actual Attempt	[Yes, No]
Non-Suicidal Self-Injurious Behavior	[Yes, No]
Interrupted Attempt	[Yes, No]
Aborted Attempt	[Yes, No]
Preparatory Acts or Behavior	[Yes, No]
Suicidal Behavior	[Yes, No]
Completed Suicide (other than screening)	[Yes, No]
Answer for Actual Attempts Only	

Most Recent Attempt (Screening Only)	[No physical damage or extremely mild physical damage, Mild physical damage, Moderate physical damage that requires treatment, Slightly severe physical damage that is highly likely to require hospitalization and intensive treatment, Severe physical damage that requires hospitalization and intensive treatment, Death]
Details of no physical damage	[Suicidal behavior that is less likely to bear physical damage, Suicidal behavior that is highly likely to bear physical damage but less likely to die, Suicidal behavior that is highly likely to die even with treatment]
Most Highly Lethal Actual Attempt	[No physical damage or extremely mild physical damage, Mild physical damage, Moderate physical damage that requires treatment, Slightly severe physical damage that is highly likely to require hospitalization and intensive treatment, Severe physical damage that requires hospitalization and intensive treatment, Death]
Details of no physical damage	[Suicidal behavior that is less likely to bear physical damage, Suicidal behavior that is highly likely to bear physical damage but less likely to die, Suicidal behavior that is highly likely to die even with treatment]

	First Attempt (Screening Only)	[No physical damage or extremely mild physical damage, Mild physical damage, Moderate physical damage that requires treatment, Slightly severe physical damage that is highly likely to require hospitalization and intensive treatment, Severe physical damage that requires hospitalization and intensive treatment, Death]
	Details of no physical damage	[Suicidal behavior that is less likely to bear physical damage, Suicidal behavior that is highly likely to bear physical damage but less likely to die, Suicidal behavior that is highly likely to die even with treatment]
Visit:	Screening, Placebo Lead-in, Baseline, Week 1, Week 2, Week 4, Week 6, and Week 8	
Analytical Method(s):	For each variable, summaries (1) will be provided by treatment group. (1) Frequency distributions at each visit	

3.3.2.4 Summary of Columbia-Suicide Severity Rating Scale (C-SSRS)

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Absence of Suicidal Ideation and Suicidal Behavior	[Yes, No]
	Non-Suicidal Self-Injurious Behavior	[Yes, No]
	Presence of Suicidal Ideation or Suicidal Behavior	[Yes, No]
	Suicidal Ideation	[Yes, No]
	Wish to be Dead	[Yes, No]
	Non-Specific Active Suicidal Thoughts	[Yes, No]
	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act	[Yes, No]
	Active Suicidal Ideation with Some Intent to Act, without Specific Plan	[Yes, No]

	Active Suicidal Ideation with Specific Plan and Intent	[Yes, No]
	Suicidal Behavior	[Yes, No]
	Preparatory Acts or Behavior	[Yes, No]
	Aborted Attempt	[Yes, No]
	Interrupted Attempt	[Yes, No]
	Actual Attempt	[Yes, No]
	Completed Suicide	[Yes, No]

Visit: Screening, Baseline (Entire Pre-dose Period), Entire Post-dose Period

Analytical Method(s): For each variable, summaries (1) will be provided by treatment group.

(1) Frequency distributions at each visit

4 Significance Level and Confidence Coefficient

- Significance level: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided)

* No statistical testing will be performed if there are less than 5 subjects.

Amendment History (Version Management)

Version	Date	Author	Comments
1	9 June, 2015	PPD	Preparation of Version 1
2	23 May, 2018		Preparation of Version 2

[Appendix 1] Change Comparison Table for Lu AA21004/CCT-004

Page	Before Change	After Change	Reason for Change
Cover	No caption Version 1: Prepared on 9 June, 2015	No caption Version 2: Prepared on 24 May, 2018	
4	Definition of TIME WINDOW -15	Definition of TIME WINDOW -12	Due to error in writing
4	Definition of TIME WINDOW -14 - -5	Definition of TIME WINDOW -11 - -5	Due to error in writing
5	Definition of TIME WINDOW -15	Definition of TIME WINDOW -12	Due to error in writing
5	Definition of TIME WINDOW -14 - -5	Definition of TIME WINDOW -11 - -5	Due to error in writing
6	Definition of TIME WINDOW -15	Definition of TIME WINDOW -12	Due to error in writing
6	Definition of TIME WINDOW -14 - -5	Definition of TIME WINDOW -11 - -5	Due to error in writing
7	Definition of TIME WINDOW -15	Definition of TIME WINDOW -12	Due to error in writing
7	Definition of TIME WINDOW -14 - -5	Definition of TIME WINDOW -11 - -5	Due to error in writing

Page	Before Change	After Change	Reason for Change
7	Others	• QT_CF interval = (QT interval) / ([QT_CB interval]^2 / [QT interval]^2)$^{0.33}$ (rounded off to the whole number) • Among the laboratory test items, the following data will not be included if it is from a postprandial specimen. Glucose, lipids (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol [Direct method])	New addition
13	1.2.1 Summary of Demographics and Other Baseline Characteristics Weight (kg) BMI(kg/m^2)	1.2.1 Summary of Demographics and Other Baseline Characteristics Weight (kg) at Baseline BMI (kg/m^2) at Baseline	To make the time point clear
13	1.2.1 Summary of Demographics and Other Baseline Characteristics Pharmacotherapy for Current Episode	1.2.1 Summary of Demographics and Other Baseline Characteristics (Deleted)	Because it was not an item to be collected in the CRF
15	1.2.1 Summary of Demographics and Other Baseline Characteristics Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.	1.2.1 Summary of Demographics and Other Baseline Characteristics The following summaries will be provided for the above analysis variable(s). When the randomized set is analyzed, the frequency distribution will be provided for each	To make the subjects for distributions clear

Page	Before Change	After Change	Reason for Change
		treatment group and overall. However, weight, BMI, and efficacy endpoints (MADRS total score, HAM-D17 total score, CGI-I score, CGI-S score, SDS total score, DSST score, and PDQ-5 score) will target only the randomized set.	
16	1.2.3 Medication History and Concomitant Medications preferred medication names	1.2.3 Medication History and Concomitant Medications generic names	Due to error in writing

Page	Before Change	After Change	Reason for Change
16	1.2.3 Medication History and Concomitant Medications (1) Medication History by Preferred Medication Name (2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name (3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline by Preferred Medication Name (4) Concomitant Medications That Started After Baseline by Preferred Medication Name (5) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name	1.2.3 Medication History and Concomitant Medications (1) Frequency distributions for medication history (2) Frequency distributions for concomitant medications	Because distributions are no longer necessary

Page	Before Change	After Change	Reason for Change
28	2.3 Other Analysis/Additional Endpoint(s) and Analytical Methods	2.3 Other Analysis/Additional Endpoint(s) and Analytical Methods (15) The following summaries will be provided if considered appropriate. For the change from baseline in DSST at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline), divide the therapeutic effect into direct and indirect effect and estimate each percentage. Here, the effect that affects through the change from baseline in the MADRS total score at Week 8 (LOCF) of treatment with double-blind study drug (Week 8 [LOCF] - Baseline) will be set as an indirect effect and others as a direct effect. Specifically, the following models will be used. Model 1: change DSST = alpha1 + gamma1 * treatment + gamma3 * change MADRS + baseline DSST + baseline MADRS + epsilon Model 2: change MADRS = alpha2 + gamma2 * treatment + baseline DSST + baseline MADRS + epsilon	New addition

Page	Before Change	After Change	Reason for Change
29	2.4.1 Adjustments for Covariates	2.4.1 Adjustments for Covariates After blind data review, it was decided not to conduct further adjustments for covariates by adding variables.	Because there was no covariate to be added as a result under blind data review
30	2.4.8 Examination of Subgroups Pharmacotherapy for Current Episode	2.4.8 Examination of Subgroups (Deleted)	Because it was not an item to be collected in the CRF
35	3.3.1.1 Hematology and Serum Chemistry [Below the lower limit of PCS Criteria or above the upper limit of PCS Criteria]	3.3.1.1 Hematology and Serum Chemistry [Meet PCS Criteria, Does not meet PCS Criteria]	Because it was corrected to an appropriate expression
35	3.3.1.1 Hematology and Serum Chemistry	3.3.1.1 Hematology and Serum Chemistry PCS: Baseline (entire pre-dose period), Entire post-dose period	Because the visit was clearly stated
35	3.3.1.1 Hematology and Serum Chemistry (4) Number and Percentage of Subjects with Potentially Clinically Significant of Laboratory Parameters	3.3.1.1 Hematology and Serum Chemistry (4) Frequency distributions of the results based on PCS Criteria during the entire post-dose period	Because it was corrected to an appropriate expression
36	3.3.1.1 Hematology and Serum Chemistry	3.3.1.1 Hematology and Serum Chemistry (5) Shift tables of the results based on PCS Criteria at baseline (entire pre-dose period) and during the entire post-dose period	New addition

Page	Before Change	After Change	Reason for Change
36	3.3.1.2 Urinalysis Protein [-, +-, 1+, 2+, 3+, 4+, 5+] Glucose [-, +-, 1+, 2+, 3+, 4+, 5+] Occult blood [-, +-, 1+, 2+, 3+, 4+, 5+]	3.3.1.2 Urinalysis Protein [-, +-, 1+, 2+, 3+, 4+] Glucose [-, 1+, 2+, 3+, 4+, 5+] Occult blood [-, +-, 1+, 2+, 3+]	Because they were corrected to reported values
36	3.3.2.1 Vital Signs and Weight [Below the lower limit of PCS Criteria or above the upper limit of PCS Criteria]	3.3.2.1 Vital Signs and Weight [Meet PCS Criteria, Does not meet PCS Criteria]	Because it was corrected to an appropriate expression
36	3.3.2.1 Vital Signs and Weight	3.3.2.1 Vital Signs and Weight PCS: Entire post-dose period	Because the visit was clearly stated
36	3.3.2.1 Vital Signs and Weight (3) Number and Percentage of Subjects with Potentially Clinically Significant of Vital Signs Parameters	3.3.2.1 Vital Signs and Weight (3) Frequency distributions of the results based on PCS Criteria during the entire post-dose period	Because it was corrected to an appropriate expression
37	3.3.2.2 12-lead ECG	3.3.2.2 12-lead ECG Categories: Results based on PCS Criteria [Meet PCS Criteria, Does not meet PCS Criteria]	New addition
37	3.3.2.2 12-lead ECG	3.3.2.2 12-lead ECG PCS: Entire post-dose period	Because the visit was clearly stated
37	3.3.2.2 12-lead ECG	3.3.2.2 12-lead ECG	Because it was corrected to an appropriate

Page	Before Change	After Change	Reason for Change
	(3) Number and Percentage of Subjects with Potentially Clinically Significant of ECG Parameters	(3) Frequency distributions of the results based on PCS Criteria during the entire post-dose period	expression
41		3.3.2.4 Summary of Columbia-Suicide Severity Rating Scale (C-SSRS)	New addition

[Appendix 2]Definition of PCS Criteria

Hematology and Serum Chemistry

Analysis Variable(s):	Unit system	Unit	Definition of PCS
Red blood cells	CV	10^4/uL	Measured value is ≤0.9-fold of LLN or ≥1.1-fold of ULN
	SI	TI/L	Measured value is ≤0.9-fold of LLN or ≥1.1-fold of ULN
White blood cells	CV	/uL	Measured value is ≤2800 or ≥16000
	SI	GI/L	Measured value is ≤2.8 or ≥16
Hemoglobin	CV	g/dL	Measured value is ≤0.9-fold of LLN
	SI	g/L	Measured value is ≤0.9-fold of LLN
Hematocrit	CV	%	Measured value is ≤0.9-fold of LLN
	SI	Fraction of 1	Measured value is ≤0.9-fold of LLN
Platelets	CV	10^4/uL	Measured value is ≤7.5 or ≥70
	SI	GI/L	Measured value is ≤75 or ≥700
Neutrophils	CV	%	Measured value is ≤15
	SI	%	Measured value is ≤15
Eosinophils	CV	%	Measured value is ≥10
	SI	%	Measured value is ≥10
Basophils	CV	%	Measured value is ≥5
	SI	%	Measured value is ≥5
Lymphocytes	CV	%	Measured value is ≤10 or ≥80

	SI	%	Measured value is ≤10 or ≥80
Monocytes	CV	%	Measured value is ≥20
	SI	%	Measured value is ≥20
Albumin	CV	g/dL	Measured value is ≤2.5
	SI	g/L	Measured value is ≤25
AST	CV	U/L	Measured value is ≥3-fold of ULN
	SI	U/L	Measured value is ≥3-fold of ULN
ALT	CV	U/L	Measured value is ≥3-fold of ULN
	SI	U/L	Measured value is ≥3-fold of ULN
ALP	CV	U/L	Measured value is ≥3-fold of ULN
	SI	U/L	Measured value is ≥3-fold of ULN
Total Bilirubin	CV	mg/dL	Measured value is ≥2
	SI	umol/L	Measured value is ≥34.2
Creatinine	CV	mg/dL	Measured value is ≥1.5-fold of ULN
	SI	umol/L	Measured value is ≥1.5-fold of ULN
Creatine Kinase	CV	U/L	Measured value is ≥2-fold of ULN
	SI	U/L	Measured value is ≥2-fold of ULN
Uric Acid	CV	mg/dL	Measured value is ≤0.7-fold of LLN or ≥1.3-fold of ULN

	SI	umol/L	Measured value is ≤0.7-fold of LLN or ≥1.3-fold of ULN
Glucose	CV	mg/dL	Measured value is ≤0.7-fold of LLN or ≥2.5-fold of ULN
	SI	mmol/L	Measured value is ≤0.7-fold of LLN or ≥2.5-fold of ULN
Potassium	CV	mEq/L	Measured value is ≤3.0 or ≥5.5
	SI	mmol/L	Measured value is ≤3.0 or ≥5.5
Sodium	CV	mEq/L	Measured value is ≤125 or ≥155
	SI	mmol/L	Measured value is ≤125 or ≥155
Calcium	CV	mg/dL	Measured value is ≤0.8-fold of LLN or ≥1.2-fold of ULN
	SI	mmol/L	Measured value is ≤0.8-fold of LLN or ≥1.2-fold of ULN
Triglycerides	CV	mg/dL	Measured value is ≥1.5-fold of ULN
	SI	mmol/L	Measured value is ≥1.5-fold of ULN
Total Cholesterol	CV	mg/dL	Measured value is ≥1.5-fold of ULN
	SI	mmol/L	Measured value is ≥1.5-fold of ULN
HDL Cholesterol	CV	mg/dL	Measured value is ≥1.5-fold of ULN
	SI	mmol/L	Measured value is ≥1.5-fold of ULN
LDL Cholesterol	CV	mg/dL	Measured value is ≥1.5-fold of ULN
	SI	mmol/L	Measured value is ≥1.5-fold of ULN

Vital Signs (Blood Pressure, Pulse Rate) and Weight

Analysis Variable(s):	Unit	Definition of PCS
Pulse Rate	bpm	Measured value is ≤50 and change* is ≤-15 or measured value is ≥120 and change* is ≥15
Diastolic Blood Pressure	mmHg	Measured value is ≤50 and change* is ≤-15 or measured value is ≥105 and change* is ≥15
Systolic Blood Pressure	mmHg	Measured value is ≤90 and change* is ≤-20 or measured value is ≥180 and change* is ≥20
Weight	kg	Change rate* is ≤-7% or ≥7%

*: Change or change rate from baseline

Resting 12-lead ECG

Analysis Variable(s):	Unit	Definition of PCS
PR Interval	msec	Measured value is <120 or ≥250
QRS Interval	msec	Measured value is <40 or >150
QT Interval	msec	Measured value is <280 or >500
QTcF Interval	msec	Measured value is <340 and change* is <-60 or measured value is >500 and change* is >60
QTcB Interval	msec	Measured value is <340 and change* is <-60 or measured value is >500 and change* is >60
RR Interval	msec	Measured value is <500 and change* is ≤-200 or measured value is >1200 and change* is ≥200

*: Change from baseline