Title: A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects

NCT Number: NCT03437564

Protocol Approve Date: 15-Feb-2018

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

Takeda Pharmaceutical Company Limited

PROTOCOL

A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects

A Bioequivalence Study of the Lu AA21004 20 mg and 2×10 mg Tablets

Study Number: Vortioxetine-1001

Compound: Lu AA21004

Date: 15 February 2018

Version/Amendment Number: Amendment 1

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1.0 STUDY SUMMARY

Clinical Study Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** Lu AA21004
Study Number: Vortioxetine-1001	**Phase:**1
Study Title: A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects	
Study Design: This is a 2 x 2 crossover, open-label, comparative study in Japanese healthy adults to evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing, and also to evaluate the safety of a single oral dose of Lu AA21004 20 mg. Subjects will be randomized in a 1:1 ratio to either treatment sequence A or B. This study consists of the screening period, Period 1, and Period 2. Subjects will receive one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets on Day 1 of Period 1 and Period 2. The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks. If bioequivalence is not demonstrated with the initially planned number of subjects, an add-on subject study may be conducted in accordance with the "Partial Revision of Guideline for Bioequivalence Studies of Generic Products".	
Primary Objective: To evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing in Japanese healthy adults **Secondary Objective:** To evaluate the safety of a single dose of Lu AA21004 20 mg in Japanese healthy adults	
Subject Population: Japanese healthy adult subjects	
Planned Number of Subjects: 28 (14 per treatment sequence) If an add-on subject study is conducted, the maximum number of additional subjects will be 28 (14 per treatment sequence).	**Planned Number of Sites:** 1 site
Dose Levels: A single dose of either one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets will be given under fasted conditions on Days 1 in Period 1 and Period 2.	**Route of Administration:** Oral
Duration of Treatment: Single dose × 2 periods (The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.)	**Planned Study Period:** Screening period: Day -28 to Day -1 Period 1 and Period 2: Day 1 to Day 25 (when the period between dosing of Period 1 and Period 2 is set as 3 weeks)
Inclusion Criteria: In order to be eligible for participation in this trial, the subject must: 1. Be a healthy Japanese adult volunteer. 2. Understand the contents of the study and be capable of providing written consent to participate in the study. 3. Be willing to comply with all study procedures and restrictions. 4. Aged between ≥20 and ≤45 years at the time of screening. 5. Have a BMI of ≥18.5 and ≤24.9 (kg/m^2) and a body weight of ≥50 kg at the time of screening. 6. Be a extensive metabolizer (EM) based on CYP2D6 genotyping at the time of screening. 7. A female subject of childbearing potential with a non-sterilized male partner must agree to routinely use appropriate contraception during the study from the time of signing informed consent until 4 weeks after last dosing of the study drug.	
Exclusion Criteria: The subject must be excluded from participating in the trial if the subject: 1. Has received any investigational drugs within 90 days before screening for this study. 2. Previously received Lu AA21004 before participation in this study. 3. Is an employee of the sponsor or the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be coerced to provide consent. 4. Has uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality which may affect study participation or study results. 5. Has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription drugs, OTC drugs, or foods.	

6. Has a positive pregnancy test at the time of screening or Day −1.
7. Is a pregnant or lactating female.
8. Has a positive urine drug test at the time of screening or Day −1.
9. Has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
10. Consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day.
11. Is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the Period 1 study drug administration.
12. Used any of the excluded drugs, dietary products or foods during the period specified in the table in Section 7.3, or will need any of them during the study period.
13. Has any current or a history of gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn), or any surgical intervention (gastrectomy, cholecystectomy etc.).
14. Has a history of cancer.
15. Has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
16. Has poor peripheral venous access.
17. Has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of Period 1 study drug administration.
18. Has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of Period 1 study drug administration.
19. Has undergone blood component collection within 2 weeks (14 days) prior to the start of Period 1 study drug administration.
20. Has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or on Day −1 of Period 1.
21. Has abnormal laboratory test values at screening or on Day −1 of Period 1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×ULN.
22. Is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

Criteria for Evaluation:

<Primary endpoints>

· AUC from time 0 to the last quantifiable time point (AUC_{last}) of Lu AA21004

· Maximum plasma concentration (C_{max}) of Lu AA21004

<Secondary endpoints>

· AUC_{∞}, t_{max}, MRT, λ_z , and $t_{1/2z}$

· Safety: adverse events (AEs), vital signs (sitting blood pressure, sitting pulse rate, body temperature (axillary)), resting 12-lead electrocardiograms (ECGs), and laboratory test results

Statistical Considerations:

1) Plasma concentration and pharmacokinetic parameters

The descriptive statistics for plasma concentration of Lu AA21004 will be provided for each formulation (Lu AA21004 20 mg tablet and 10 mg tablet) by visit and the mean and standard deviation of plasma concentration will be plotted for both formulations on the same graph. The descriptive statistics for PK parameter will be provided for each formulation.

2) Bioequivalence assessment

The bioequivalence of Lu AA21004 20 mg tablet and 2× 10 mg tablets is evaluated.

The log-transformed (natural log) PK parameters AUC_{last} and C_{max} of Lu AA21004 will be analysed separately using analysis of variance (ANOVA) with dosing formulation, treatment sequence, administration period as fixed effects and the two-sided 90% confidence interval (CIs) for the differences between the formulations and between the periods will be provided. The log-transformed (natural log) PK parameters AUC_{∞}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004 and t_{max} of Lu AA21004 will be analysed separately using ANOVA in the same manner (confidence coefficient 90%, 95%).

Rational for the Sample Size:

Planned number of subjects is 28 (14 per treatment sequence).

The planned sample size was calculated based upon the analysis of logarithmically transformed AUC_{last} and C_{max}. If the 90% CIs for the ratios of Lu AA21004 20 mg tablets and 2× Lu AA21004 10 mg tablets (2× Lu AA21004 10 mg tablets/ Lu AA21004 20 mg tablet) geometric mean value of AUC_{last} and C_{max} are both be within the limits of 80.00% to 125.00%, bioequivalence can be verified. It is hypothesize that there is no interaction between dosing formulation and administration period at AUC_{last} and C_{max}. Based on data from previous studies, the largest estimate of the within-subject coefficient of variation (CV) of AUC_{last} and C_{max}were up to 9.5% and 14.3% and a sample size of 24 would then provide a power of 99.8% and 91.5% for each correctly concluding bioequivalence even if the true ratio is 1.1. Given that the 90% CIs for the ratio of the geometric means for AUC_{last} and C_{max} must both be contained in 80.00% to 125.00% in order to conclude bioequivalence between the two treatments, 24 subjects provided an overall power of at least 91.3%, assuming that the two endpoints AUC_{last}

and C_{max} are independent.

Taking into account possible occurence of dropouts, planned number of subjects is 28.

In case bioequivalence cannot be demonstrated with the number of subjects initially planned due to the insufficiency of the number of subjects, an add-on subject study will be conducted in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products, if applicable. The maximum number of additional subjects in the add-on subject study is 28 (14 per treatment sequence), which is determined based on study feasibility, but is not on statistical consideration.

2.0 SCHEMATIC OVERVIEW OF THE STUDY

The overview of the study design is shown in Figure 2.a.

Figure 2.a Study Design Overview

Treatment sequence	Period 1		Period 2
	Day 1 to 4	Day 5 to 21[a]	Day 1 to 4
A	One Lu AA21004 20 mg tablet Single dose under fasted condition	Washout	Two Lu AA21004 10 mg tablets Single dose under fasted condition
B	Two Lu AA21004 10 mg tablets Single dose under fasted condition		One Lu AA21004 20 mg tablet Single dose under fasted condition

Period	Screening period		Administration term							
			Period 1					Period 2		
Day[b]	−28 to −2	−1	1	2 to 3	4	5 to 20	21	1	2 to 3	4
Days from the Period 1 study drug dossing [a]	-	-	1	2 to 3	4	5 to 20	21	22	23 to 24	25
Inpatient/Outpatient	Outpatient	Inpatient				No visit	Inpatient			
Procedure	Informed consent, screening	Admission	Study drug administration		Discharge		Admission	Study drug administration		Discharge

(a) When the interval between the Period 1 dosing and the Period 2 dosing of the study drug is 3 weeks.
(b) Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2, with the day before Period 1 study drug administration referred to as Day −1 and the day before Period 2 study drug administration as Day 21.

3.0 STUDY SCHEDULE

	Screening period		Administration term									
			Period 1						Period 2			
			Treatment period				Washout period		Treatment period			
Day[1)]	Screening -28 to -2	-1	1	2	3	4 [9)]	5 to 20	21	1	2	3	4 [9)]
Days from Period 1 study drug administration[2)]	-	-	1	2	3	4	5 to 20	21	22	23	24	25
Informed consent	X											
Demographic data, Height	X											
Medical history, concurrent medical conditions, prior medication	X											
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events monitoring[3)]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4)]	X	X		X		X		X		X		X
Body weight	X	X										
Vital signs[5)]	X	X		X		X		X		X		X
12-lead ECG[6)]	X					X						X
Laboratory tests[7)]	X	X				X		X				X
Pharmacokinetic blood sampling[8)]			X	X	X	X			X	X	X	X
CYP2D6 genotyping blood sampling	X											
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X				X		X				X
Study drug administration			X						X			
Hospitalization		In				Out		In				Out

1) Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2, with the day before Period 1 study drug administration referred to as Day −1 and the day before Period 2 study drug administration as Day 21.
2) When the interval between the Period 1 dosing and the Period 2 dosing of the study drug is 3 weeks.
3) AEs will be collected continuously from the time of signing of informed consent until the end of Period 2.
4) Physical examination will be performed at 24 and 72 hours postdose.
5) Vital signs will be measured at 24 and 72 hours postdose.
6) A 12-lead ECG will be performed at 72 hours postdose.
7) Immunology tests will be performed only at screening. Urine drug tests and pregnancy test will be performed only at screening, Day −1 and Day 21. Pregnancy test will be performed only in female subjects of childbearing potential.
8) Pharmacokinetic blood samples will be collected at Day 1 predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours postdose.
9) Or at discontinuation.

4.0 INTRODUCTION

4.1 Background

Lu AA21004 (generic name: vortioxetine hydrobromide) is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter (5-HTT) inhibitor. This novel antidepressant with a different profile from existing medications has been under development.

Depression is a mental disease mainly characterized by a depressed mood and a loss of interest or pleasure, and is additionally characterized by thought or concentration difficulties, an appetite decrease or increase, anxiety, a feeling of worthlessness or guilt, and thoughts related to suicide (suicidal ideation) as well as somatic symptoms including sleep disturbances and fatigability.[1][2]

The course of depression varies from only 1 episode in a lifetime to a lifelong disorder with recurrent episodes, and some patients suffer from long-term depressive symptoms despite treatments. Depression is therefore a significant mental and social burden and economic loss for not only patients but also their family, which treatment is necessary.[3]

Depression is mainly treated with pharmacotherapy and psychotherapy, and these treatments are selected according to the severity and pathological condition.[3] As pharmacotherapy in patients with moderate to severe depression, antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants have been widely used. These antidepressants, however, have problems such as patients with inadequate response and adverse effects; therefore, development of an antidepressant with a novel profile can broaden treatment options and optimize treatment for depression.

From the results of the clinical pharmacology studies, following pharmacokinetic profiles were shown. Lu AA21004 was slowly absorbed with t_{max} of approximately 7 to 11 hours, and the absolute bioavailability of Lu AA21004 was approximately 75%. Lu AA21004 was extensively metabolized in the liver, and CYP2D6 was shown to be the primary enzyme in metabolism of Lu AA21004 to the major metabolite Lu AA34443. The $t_{1/2z}$ of Lu AA21004 was approximately 66 hours, and two-thirds of its metabolites were excreted in urine, and one-third were excreted in feces.Based on the results of the clinical studies, treatment with Lu AA21004 at doses of 5 to 20 mg/day was safe and effective. As of December 2017, Lu AA21004 has been approved for marketing as a drug for the treatment of MDD in countries including the U.S., Europe and Australia.

In Japan, Lu AA21004 is being developed for treatment of major depression disorder and has been evaluated in four clinical pharmacology studies of CPH-001, CPH-002, CPH-003, and CPH-004 conducted in healthy adults or elderly individuals; two placebo-controlled short-term studies of CCT-002 and CCT-003 conducted in patients with major depressive disorder; and a long-term extension study of OCT-001 in patients who completed CCT-003. In all these studies, Lu AA21004 was well-tolerated without major safety issues. Currently, CCT-004 study is being conducted as a short-term placebo-controlled study for major depressive disorder patients.

4.2 Rationale for This Study

In the dissolution tests, the different strengths (10 mg and 20 mg) of commercial formulations in Japan showed different dissolution behaviors and did not meet bioequivalence criteria. Consequently, this study has been planned to evaluate the bioequivalence between Lu AA21004 20 mg tablet and 2× Lu AA21004

10 mg tablets in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products.[4]

4.3 Benefits/Risks

Subjects in this study will not benefit from this study.

In the clinical pharmacology studies conducted to date in Japanese healthy adults or elderly individuals (ie, CPH-001, CPH-002, CPH-003 and CPH-004) and clinical studies including Japanese major depressive disorder patients (ie, CCT-002, CCT-003 and OCT-001), Lu AA21004 at a dose of 2.5 to 40 mg was well-tolerated without major safety issues. Further detailed safety data on Lu AA21004 are provided in the Investigator's Brochure.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study is planned on the basis of the following hypothesis:

Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets will be shown to be bioequivalent.

5.2 Objectives

5.2.1 Primary Objective

To evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing in Japanese healthy adults.

5.2.2 Secondary Objective

To evaluate the safety of a single dose of Lu AA21004 20 mg in Japanese healthy adults.

5.3 Endpoints

5.3.1 Primary Endpoints

- AUC_{last} of Lu AA21004
- C_{max} of Lu AA21004

5.3.2 Secondary Endpoints

- AUC_{∞}, t_{max}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004
- Adverse events, vital signs, 12-lead ECG, and laboratory test values

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

1) Study design

This is a 2 x 2 crossover, open-label, comparative study in Japanese healthy adults to evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing, and also to evaluate the safety of a single oral dose of Lu AA21004 20 mg.

Subjects will be randomized in a 1:1 ratio to either treatment sequence A or B.

This study consists of the screening period, Period 1, and Period 2. Subjects will receive one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets on Days 1 of Period 1 and Period 2. The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.

If bioequivalence is not demonstrated with the initially planned number of subjects, an add-on subject study may be conducted in accordance with the "Partial Revision of Guideline for Bioequivalence Studies of Generic Products".

2) Planned number of subjects

The planned number of subjects is 28 (14 per treatment sequence). If an add-on subject study is conducted, the maximum number of additional subjects will be 28 (14 per treatment sequence).

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale for Study Design

A 2-period, 2-treatment, cross-over design, which allows bioequivalence evaluation with minimal effect on inter-subject variation, was selected for this study in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products.

Open-label design is adopted because the primary objective of the study is to evaluate the pharmacokinetic profile and to assess bioequivalence of Lu AA21004 tablets which is an objective indicator.

To eliminate all biases arising from arbitrary assignment of subjects, subjects will be randomized to receive the two treatments in either treatment sequence.

6.2.2 Rationale for Dose

Based on clinical data obtained so far, the clinical doses of Lu AA21004 for the treatment of major depression in Japanese patients are expected to be 10-20 mg/day, and 10 mg and 20 mg commercial tablets have been developed. For this study designed to evaluate the bioequivalence between Lu AA21004 20 mg tablet and 2× 10 mg tablets, one Lu AA21004 20 mg tablet and two Lu AA21004 10 mg tablets will be used.

6.2.3 Rationale for Washout Period

In CPH-004 study ('A Phase 1, Open-Label, Single-Dose, 2-Period Crossover Study to Assess Pharmacokinetics of Lu AA21004 and Effect of Food on the Pharmacokinetics after Oral Administration of Lu AA21004 in Healthy Male Subjects'), in which 14 days interval between the Period 1 dosing and the Period 2 dosing of the study drug, plasma unchanged Lu AA21004 concentration at Period 2 predose was

higher than 11% of C_{max} value of the Period 1 in the subject with the highest plasma unchanged Lu AA21004 level in Period 1. Based on these results, it is set that the interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks in order for the plasma concentration at Period 2 predose to be decreased below 5% of C_{max} in Period 1. Also, the Partial Revision of Guideline for Bioequivalence Studies of Generic Products recommends that there should be a washout period at least 5 times longer than the apparent half-life of the investigational drug. The 3 weeks interval between the Period 1 dosing and the Period 2 dosing of the study drug in this study is longer than 5 times of the apparent elimination half-life of Lu AA21004(about 66 hours) thus meets this guideline.

6.2.4 Rationale for Endpoints

6.2.4.1 Rationale for Pharmacokinetic Endpoints

AUC_{last} and C_{max} of unchanged Lu AA21004 will be evaluated in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products. Since the apparent elimination half-life of unchanged Lu AA21004 is very long (about 66 hours), the plasma concentration of Lu AA21004 will be evaluated until 72 hours postdose, in accordance with "Partial Revision of Guideline for Bioequivalence Studies of Generic Products".

6.2.4.2 Rationale for Safety Endpoints

Safety measures will include those commonly used in clinical pharmacology studies (Adverse events, Vital signs, Clinical laboratory tests, and 12-lead ECG assessment).

6.2.5 Important Procedures based on Study Objectives: Time Points of the Procedures

Blood sample collection for pharmacokinetic evaluation is the important procedure in this study.

- For all time points of evaluation after administration of the study drug, the blood samples for pharmacokinetic evaluation should be collected at a time as closest as possible to the scheduled time.
- If blood sample collection and other procedures are scheduled for the same time, blood sample collection should be prioritized, with implementation of other procedures within the allowable window (Appendix C).
- The priority order of procedures may be changed based on agreement between the investigator and the sponsor.
- Any unscheduled procedure required for emergency assessment for safety concerns must be prioritized over any scheduled procedures.

6.3 Start and End/Completion of the Study

6.3.1 Definition of the Start of the Study

The time of the start of the entire study is defined as the time when the first subject has signed the informed consent form.

6.3.2 Definition of the Completion of the Study

The time of the completion of the entire study is defined as the time when the last subject has completed the last planned or follow-up visit (or last contact related to a planned visit [possibly a telephone contact]), has been discontinued from the study, or has become lost to follow-up (ie, not reachable by the investigator).

6.3.3 Definition of Study Termination

Study termination for reasons other than safety are defined, such as below:

- When the study is terminated for non-safety reasons on the basis of certain findings on this study drug from nonclinical or other clinical studies with administration of this study drug (eg, findings on pharmacokinetics, pharmacodynamics, efficacy, or biological target).
- When the study is terminated for non-safety reasons on the basis of certain data that became available regarding another drug in the same class as this study drug or the same study methodology as this study.
- When the study is terminated for non-scientific and non-safety reasons, such as delay in subject enrollment.

Study termination for safety reasons are defined, such as below:

- When the study is prematurely terminated because of unexpected safety concerns for subjects, raised from any clinical or nonclinical study of this study drug, another drug in the same class as this study drug, or the same study methodology as this study.

6.3.4 Criteria for Suspension or Termination of the Entire Study

6.3.4.1 Criteria for Suspension or Termination of the Study

The study will be temporarily suspended or prematurely terminated if one or both of the following criteria are met:

- New information or other evaluation has been obtained regarding the safety or efficacy of the study drug that alters the known risk/benefit profile of Lu AA21004, and the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) has occurred that compromises the ability to achieve the primary study objective or compromises the safety of subjects.

6.3.4.2 Procedures for Suspension or Termination of the Study

In the event that the sponsor, institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor. The procedure will be followed by the applicable study site during the course of termination or study suspension.

6.3.5 Criteria for Suspension or Termination of a Study Site

6.3.5.1 Criteria for Suspension or Termination of a Study Site

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise is permitted by the contractual agreement.

6.3.5.2 Procedures for Suspension or Termination of Participation of a Study Site

In the event that the sponsor, IRB, or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by the applicable study site during the course of termination or study suspension.

7.0 CRITERIA FOR SELECTION AND DISCONTINUATION OF SUBJECTS

All inclusion/exclusion criteria, including test results, need to be confirmed prior to the study drug administration in Period 1.

7.1 Inclusion Criteria

In order to be eligible for participation in this study, the subject must fulfill the following criteria:

1. Be a healthy Japanese adult volunteer.
2. Understand the contents of the study and be capable of providing written consent to participate in the study.
3. Be willing to comply with all study procedures and restrictions.
4. Aged between ≥20 and ≤45 years at the time of screening.
5. Have a BMI of ≥18.5 and ≤24.9 (kg/m^2) and a body weight of ≥50 kg at the time of screening.
6. Be a extensive metabolizer (EM) based on CYP2D6 genotyping at the time of screening.
7. A female subject of childbearing potential* with a non-sterilized male partner* must agree to routinely use appropriate contraception* during the study from the time of signing informed consent until 4 weeks after last dosing of the study drug (*see Appendix B).

7.1.1 Rationale for the Inclusion Criteria

Inclusion criteria 1, 2, 3, 4 and 7:

These are the standard inclusion criteria used in clinical pharmacology studies in healthy adults.

Inclusion criterion 5:

The body weight criterion is set because collecting 400 mL of whole blood from people weighing less than 50.0 kg has harmful effect on health, according to the "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products" (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare in 1956). [5]

The BMI criterion is set to correspond to the normal body weight range according to the diagnostic criteria for obesity proposed by the Japan Society for the Study of Obesity. [6]

Inclusion criterion 6:

This criterion is set because the "Partial Revision of Guideline for Bioequivalence Studies of Generic Products" recommends that, if polymorphism is involved in clearance of the test drug, bioequivalence studies of the drug should be conducted in subjects with greater clearance.

7.2 Exclusion Criteria

The subject meeting any of the following criteria will be excluded from the study:

1. Has received any investigational drugs within 90 days before screening for this study.
2. Previously received Lu AA21004 before participation in this study.
3. Is an employee of the sponsor or the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be coerced to provide consent.

4. Has uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality which may affect study participation or study results.
5. Has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription drugs, OTC drugs, or foods.
6. Has a positive pregnancy test at the time of screening or Day −1.
7. Is a pregnant or lactating female.
8. Has a positive urine drug test at the time of screening or Day −1.
9. Has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
10. Consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day .
11. Is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the Period 1 study drug administration.
12. Used any of the excluded drugs, dietary products or foods during the period specified in the table in Section 7.3, or will need any of them during the study period.
13. Has any current or a history of gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn), or any surgical intervention (gastrectomy, cholecystectomy etc.).
14. Has a history of cancer.
15. Has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
16. Has poor peripheral venous access.
17. Has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of Period 1 study drug administration.
18. Has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of Period 1 study drug administration.
19. Has undergone blood component collection within 2 weeks (14 days) prior to the start of Period 1 study drug administration.
20. Has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or on Day −1 of Period 1.
21. Has abnormal laboratory test values at screening or on Day −1 of Period 1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN).

22. Is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

7.2.1 Rationale for the Exclusion Criteria

Exclusion criterion 1:

This is set to secure the safety of the subjects, with reference to the "General Considerations for Clinical Trials". [7]

Exclusion criteria 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16 and 22:

These are set as the standard exclusion criteria used in clinical pharmacology studies in healthy adults and also to secure the safety of the subjects.

Exclusion criteria 5, 20 and 21:

These are set to secure the safety of the subjects.

Exclusion criterion 13:

This is set to secure the safety of the subjects, and also to avoid possible effects on pharmacokinetic assessments.

Exclusion criteria 17, 18 and 19:

These are set in line with "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products" (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare in 1956). [5]

7.3 Excluded Medications, Dietary Products, and Foods

Excluded medications, dietary products, and foods are shown in Table 7.a.

Use of the concomitant drugs (prescribed or over-the-counter [OTC] drugs) and consumption of dietary products, or foods listed in Table 7.a is prohibited from the specified time point until discharge in Period 2 to avoid possible effects on the safety and pharmacokinetics. However, the use will be allowed when judged by the investigator or sub-investigator to be necessary for certain reasons such as onset of an adverse event.

Table 7.a Excluded Medications, Dietary Products, and Foods

From Period 1 Day −28 through the end of the study period	From Period 1 Day -14 through the end of the study period	From Period 1 Day -3 through the end of the study period
All prescription drugs	Vitamins	Alcohol-containing products
All OTC drugs	Foods and beverages containing grapefruit, Sweetie, Seville orange, shaddock, or other citrus fruits that inhibit CYP3A4	Caffeine-containing products
Dietary products (ie, products containing St. John's wort, ginseng, kava kava, ginkgo, Chinese traditional medicines, or melatonin)		
Nicotine containing product		

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator or sub-investigator.

7.4 Other Restrictions / Diet, Fluid, Activity Control

7.4.1 Foods and Beverages

On the day before blood collection for laboratory tests, the subjects must finish the last meal by 21:00 and then fast until blood collection in the next morning. If the examination (eg, screening examination) is performed in the afternoon, the blood collection will be performed after at least 10 hours of fasting from the last meal.

During hospitalization, the subjects take given meals and are not allowed to take any other food. Meal menus will be same for each period.

The subjects must fast from at least 10 hours before the study drug administration.

The subjects must fast until 4 hours after the study drug administration. If a meal and a test or blood collection are scheduled for the same time, the meal will be taken after the test/blood collection.

Excessive drinking and eating should be avoided during the entire study period.

Liquid intake will be prohibited from 1 hour before study drug administration until 4 hours postdose, with the exception of water (150 mL) to take the study drug.

7.4.2 Daily Activities

Smoking is not allowed during the study period.

Supine position is not allowed for 4 hours after the study drug administration, unless it is required for examinations. During hospitalization, light exercise will be performed for about 15 minutes a day.

Excessive exercise is not allowed during the study period. The subjects will be instructed not to change the lifestyle between Periods 1 and 2 and lead a regular life even during the washout period.

Blood donation is not allowed for at least 12 weeks after the final examination of this study. The investigator or sub-investigator will instruct the subjects on the prohibition of blood donation.

If a subject visits another medical institution during the study period, the subject should inform the investigator or sub-investigator in advance whenever possible. After the visit, the subject should inform the investigator or sub-investigator of the circumstance and treatment details. Also, the investigator or sub-investigator will contact the medical institution to notify that the subject is participating in this study.

7.5 Documentation of Subject Withdrawal Before Study Treatment

The investigator or sub-investigator will account for all subjects who signed informed consent. If a subject is withdrawn from the study before the study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF) with the information.

The primary reason for subject withdrawal is recorded in the eCRF using the following categories:

- Death
- AE
- Screen failure (failed to meet the inclusion criteria or did meet the exclusion criteria) <specify reason>
- Protocol deviation

- Lost to follow-up
- Voluntary withdrawal <specify reason>
- Study terminated by sponsor
- Pregnancy
- Sample size sufficient
- Other <specify reason >

Subject identification codes assigned to subjects who discontinued the study before the study drug administration should not be reused.

7.6 Criteria for Withdrawal of a Subject

The primary reason for subject withdrawal is recorded in the eCRF using the following categories by the investigator or sub-investigator. If the subject is withdrawn from the study before the study drug administration, see Section 7.5.

1. Death
   The subject has died during the study period.
   Note: If a subject died during the study period, this event will be handled as a serious adverse event (SAE). For the reporting procedures, see Section 10.2.9.3.
2. Adverse event (AE)
   The subject has experienced an AE that requires discontinuation from the study because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
   - Liver function test abnormalities
     If any liver function test abnormality meeting the criteria below occurs during study drug administration, the study drug administration will be immediately discontinued, and appropriate follow-up testing will be performed until the subject's laboratory profile has returned to normal or baseline (see Section 9.2.9.1):
     - ALT or AST >8 × ULN, or
     - ALT or AST >5 × ULN and persists for ≥2 weeks, or
     - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
     - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Protocol deviation
   After the start of study drug administration, the subject is found not to fulfil the eligibility criteria or not to comply with protocol requirements, and continued participation in the study poses an unacceptable risk to the subject's health.

4. Lost to follow-up
   The subject did not return to the study site, and attempts to contact the subject have been unsuccessful. The attempts to contact the subject should be recorded in the subject's source document.
5. Voluntary withdrawal
   The subject requested to withdraw from the study. The reason for withdrawal, if obtained, will be recorded in the eCRF.
   Note: Every effort should be made to determine the reason for the withdrawal where possible (withdrawal due to an AE is not categorized as "Voluntary withdrawal").
6. Discontinuation of the entire study by the sponsor
   The sponsor has decided to terminate the study.
7. Pregnancy of a subject
   Note: If a subject was found to be pregnant, the subject will be immediately withdrawn from the study. For the procedures, see Appendix B.
8. Other
   Note: Specific details should be recorded in the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for Early Termination Visit if possible.

7.8 Reserve Subjects

For Period 1, some of the subjects who are assessed to be eligible based on the screening results may stand by as reserve subjects. If a subject scheduled to receive the study drug does not receive the study drug for certain reasons before study drug administration in Period 1, a reserve subject may be enrolled in the study to replace that subject.

Subjects who discontinued after study drug administration will not be replaced by reserve subjects.

7.9 Replenishment of Subjects Whose Study Was Discontinued after Initiation of Study Drug Administration

If a subject who discontinued the study after the initiation of study drug administration, it is possible to newly incorporate another subject after consultation between the investigator and the sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug

[Drug products]

The study drugs are shown in Table 8.a.

Table 8.a Study Drug

Formulation	Active ingredient	Dosage form	Strength
Lu AA21004 10 mg tablet	1-[2-(2,4-Dimethylphenylsulfanyl)phenyl] piperazine hydrobromide	Tablet	10 mg
Lu AA21004 20 mg tablet			20 mg

[Packaging]

Fifteen tablets of 10 mg of Lu AA21004 tablet or 20 mg of Lu AA21004 tablet are placed in one bottle and the bottle is placed in an outer box.

8.1.1 Study Drug Labeling

Each outer box of the study drug is labeled with the following information: statement that the drug is for clinical trial use only, sponsor's name and address, study drug name, lot number, storage condition and expiration date.

8.1.2 Study Drug Storage and Management

The study drugs should be stored at room temperature (1 to 30°C).

The study drugs must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor, or its designee for destruction. The study drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Study Drug Blinding

This is an open-label study.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

The study drug storage manager will receive the written procedures for handling, storage, and management of the study drugs prepared by the sponsor, and will appropriately manage the drugs in accordance with the procedures. The written procedures will be provided to the investigator as well. The written procedures will specify the procedures that are necessary to ensure appropriate receipt, handling, storage, management, and dispensing of the sponsor-supplied drugs, as well as retrieval of unused drugs from the subjects and their return to the sponsor or destruction.

The study drug storage manager will promptly return unused drugs to the sponsor after the study is closed at the study site.

9.0 STUDY PROCEDURES

The following sections describe the study procedures and data to be collected by the investigator or sub-investigator. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site personnel in principle. The study schedule is shown in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained from each subject prior to any study procedures. Informed consent requirements are described in Section 13.2.

9.1.1.1 Subject Identification Codes

A unique subject identification code will be assigned to each subject at the time that informed consent is explained. This subject identification code will be used throughout the study.

9.1.1.2 Assignment of Subjects

The subjects in ascending order of the subject identification code will be randomized to either treatment sequence in accordance with the assignment list.

Each subject will be assigned with a subject number (4 digit number). This subject number will be used by the study site and the pharmacokinetic laboratory to identify the pharmacokinetic samples. The test tubes for pharmacokinetic measurements sent to the laboratory must be labeled with the subject numbers. The laboratory will use the subject numbers when reporting the measurement results. These subject numbers should not be replaced by the subject identification codes. If a subject is replaced by a reserve subject, the treatment sequence assigned to the original subject will be used for the reserve subject.

If a subject is withdrawn from the study after the start of study drug administration, and if a new subject is enrolled as a result of discussion between the investigator and the sponsor, the investigator will check with the sponsor regarding the newly enrolled subject's subject number and treatment sequence.

The assignment list will be prepared by the sponsor, and provided to the investigator before the start of the study, while the sponsor will retain its copy. Information on the assignment will be kept in a secure place with limited access to authorized personnel.

9.1.2 Eligibility Assessment

Each subject will be assessed based on the inclusion and exclusion criteria shown in Section 7.0.

9.1.3 Medical History and Demographic Data

Demographic data to be obtained will include date of birth, sex, race (as reported by the subjects), height, body weight, caffeine and alcohol consumption, and smoking status.

Medical history to be obtained will include clinically relevant diseases and symptoms that resolved or disappeared within 1 year before signing of informed consent. Ongoing diseases and symptoms are regarded as concurrent medical conditions. Prior medication data to be obtained will include all drugs relevant to the eligibility criteria and safety assessments that stopped within 4 weeks (28 days) before signing of informed consent.

9.1.4 Concomitant Medication

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. Subjects will be asked whether they have used any medication other than the study drug (from signing of informed consent through the end of the study), and detailed use of all medications, including vitamins, OTC medications, and Chinese traditional medicines, must be recorded in the eCRF. The documentation for the drug should include its nonproprietary name, route of administration, start and end dates, and reason for use.

9.2 Study Procedures and Assessments

9.2.1 Physical Examination

Physical examination will consist of the following body systems:
(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

9.2.2 Height and Body Weight

Height and body weight will be measured. Height (unit: cm) will be rounded to the nearest integer. Body weight (unit: kg) will be measured to the first decimal place.

9.2.3 BMI

BMI will be calculated using the following formula:

Metrics: BMI = Body weight (kg) / Height $(m)^2$

BMI will be rounded to the first decimal place. Eligibility assessment will use the rounded BMI value.

9.2.4 Vital Signs

Vital signs will be measured in terms of body temperature (axillary), sitting blood pressure (systolic and diastolic) after resting for at least 5 minutes, and sitting pulse rate (beats per minute).

9.2.5 12-lead ECG

A 12-lead ECG will be recorded. Subjects will rest for at least 5 minutes in a supine position before each 12-lead ECG.

The investigator or sub-investigator (or a specialist physician at the study site) will assess the ECG findings using one of the following categories: within normal or abnormal. If abnormal, then the investigator or sub-investigator (or a specialist physician at the study site) will determine whether the abnormality is clinically relevant. The time of 12-lead ECG will be recorded. The following parameters will be collected from the subject's 12-lead ECG tracing, and recorded in the eCRF: heart rate, RR interval, PR interval, QT interval, QRS interval and QTcF interval (corrected using Fridericia's formula).

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

C-SSRS will be conducted at the time specified in the study schedule. The investigator or sub-investigator will assess the risk of suicide in study subjects based on the information obtained from C-SSRS and if

suicidal ideation or suicidal behavior is observed during the study period, it should be recorded in the eCRF as an AE.

9.2.7 Study Drug Administration

One Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets will be orally administered on Days 1 in Period 1 and Period 2. Subjects will fast from at least 10 hours before study drug administration until 4 hours postdose. With the exception of water (150 mL) to ingest the study drug, beverage intake will be prohibited from 1 hour before study drug administration until 4 hours postdose.

The dose and mode of administration are shown in Table 9.a.

Table 9.a Dose and Mode of Administration

Treatment sequence	Period 1		Period 2
	Day 1 to Day 4	Day 5 to 21	Day 1 to Day 4
A	One Lu AA21004 20 mg tablet Single dose under fasted condition[(a)]	Washout period	Two Lu AA21004 10 mg tablets Single dose under fasted condition[(a)]
B	Two Lu AA21004 10 mg tablets Single dose under fasted condition[(a)]		One Lu AA21004 20 mg tablet Single dose under fasted condition[(a)]

(a) Oral administration with 150 mL of water under fasted condition (after fasting for at least 10 hours)

9.2.8 Assessment of AEs

Assessment of AEs will be started at the time of signing of informed consent. For details of AE collection and related procedures, see Section 10.2.

9.2.9 Laboratory Test Procedures and Assessment

The following laboratory tests will be performed at the study site. Samples for laboratory tests will be collected after fasting for at least 10 hours according to the study schedule shown in Section 3.0. The blood collection volume is shown in Appendix D.

The investigator or sub-investigator will be responsible for assessing and retaining the results of laboratory tests. The investigator will retain a copy of the reference values of laboratory tests.

9.2.9.1 Laboratory Tests

Hematology tests

The following hematology tests will be performed.

Red blood cell count	White blood cell count and differential (lymphocytes, neutrophils, eosinophils , basophils, monocytes)
Hemoglobin	Hematocrit
Platelet count	

Blood chemistry tests

The following blood chemistry tests will be performed.

Albumin	ALT
ALP	AST
GGT	Total bilirubin

Direct bilirubin	Total protein
Creatinine	Creatine kinase
BUN	Potassium
Sodium	Chloride
Calcium	Inorganic phosphorus
Glucose	Total cholesterol
HDL-cholesterol	LDL-cholesterol
Triglyceride	Uric acid

Urinalysis

The following urinalysis will be performed.

pH	Specific gravity
Qualitative tests for protein, glucose, occult blood, urobilinogen, and ketone bodies	

Other

Immunology tests
HBsAg, HCV antibody, HIV antigen/antibody, serological test for syphilis
Urine drug tests
Phencyclidine, benzodiazepines, cocaine, antihypnotic agents, cannabinoids, morphine-like narcotics, barbiturates, and tricyclic antidepressants
Pregnancy test (Only in female subjects of childbearing potential)
Urinary human chorionic gonadotropin

Note: For immunology and urine drug tests, the investigator or sub-investigator will directly return the results to the subjects. The sponsor will not receive detailed results of these tests for the subjects (including reserve subjects) selected to be given the study drug, but will check the overall test results only (ie, presence or absence of positive results).

If subjects experienced ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, ALP, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

For liver function test abnormalities as SAEs, the criteria for reporting are described in Section 10.2.9.4, and the criteria for withdrawal of the subject are described in Section 7.6.

9.3 Samples for Pharmacokinetics and CYP2D6 Polymorphism Assessments

The samples for pharmacokinetic analysis and CYP2D6 genotyping will be collected at the study site according to the study schedule shown in Section 3.0. The blood collection volume is shown in Appendix D. The samples for measurements are specified in Table 9.b.

Table 9.b Samples for Measurements

Name of sample	Matrix	Purpose of sample collection	Mandatory/ Optional
Pharmacokinetic sample	Plasma	Pharmacokinetic analysis	Mandatory
CYP2D6 genotyping sample	Whole blood	CYP2D6 genotyping	Mandatory

9.3.1 Pharmacokinetic Measurements

The pharmacokinetic parameters will be calculated from plasma concentrations of unchanged Lu AA21004 in the pharmacokinetic analysis set.

Term	Definition
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration Calculation Formula:Time 0 is taken as t_1, and the last time point when the concentration exceeding the lower limit of quantification (C_{last}) is taken as $t_n(= t_{last})$ $AUC_{last}=\sum_{i=2}^{n}\frac{(C_i + C_{i-1})}{2}(t_i - t_{i-1})$
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity Calculation Formula:$AUC_{\infty}=AUC_{last}+ C_{last}/\lambda_z$
C_{max}	Maximum plasma concentration (Observed value)
t_{max}	Time to reach C_{max} (Observed value)
$t_{1/2z}$	Apparent elimination half-life
$MRT_{\infty,ev}$	Mean residence time Calculation Formula:$MRT_{\infty,ev}=AUMC_{\infty}/AUC_{\infty}$
$MRT_{last,ev}$	The average residence time from 0 hour to time of the last quantifiable concentration Calculation Formula:$MRT_{last,ev}=AUMC_{last}/AUC_{last}$
λz	Apparent elimination rate constant
$AUMC_{\infty}$	Area under the first moment time curve from 0 hour to infinity Calculation Formula:$AUMC_{\infty}=AUMC_{last} + C_{last}\times t_{last}/\lambda_z + C_{last}/\lambda_z^2$
$AUMC_{last}$	Area under the first moment time curve from 0 hour to final determinable（By the trapezoidal method）

9.3.1.1 Pharmacokinetic Samples

The blood samples for pharmacokinetic analysis of unchanged Lu AA21004 will be collected according to Table 9.c.

The time of each sample collection will be recorded in the source documents and eCRF.

Table 9.c Collection of Pharmacokinetic Samples (in Both Period 1 and Period 2)

Analyte	Matrix	Time points of sample collection
Unchanged Lu AA21004	Plasma	Predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours postdose

9.3.2 CYP2D6 Genotyping

Blood samples for CYP2D6 genotyping will be collected.

9.4 Hospitalization Period

In both Period 1 and Period 2, the subjects will be admitted to the study site on the day before study drug administration, and hospitalized for 5 days. During the hospitalization period, the investigator or sub-investigator will perform assessments and observations of the subjects according to the study schedule shown in Section 3.0. The subjects will be discharged from the study site, after no clinically relevant abnormalities in the physical condition was confirmed based on physical examination in 4 days after study drug administration in both Period 1 and Period 2.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical trial subject who provided informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment (including the study drug) or study participation.

An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory values), symptom, or disease temporally associated with the study participation whether or not it is considered related to the treatment (including the study drug) or study procedures.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent manifestations of a pre-existing condition or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or sub-investigator for any reason.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant by the investigator or sub-investigator (ie, if a certain action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value or finding is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), only the diagnosis should be reported as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline examinations , observations and evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences worsening of a concurrent medical condition (worsening after signing of informed consent), the worsening should be recorded appropriately as an AE. The investigator or sub-investigator should ensure that the event term recorded captures the worsening in the condition (eg, “worsening of…”).

- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition from baseline (eg, "worsening of…").
- If a subject has a pre-existing chronic concurrent medical condition (eg, cataract, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition (eg, "worsening of…").

Worsening of AEs:

- If an AE which occurred before study drun administration was worsened after initial dosing of the study drug or an AE was worsened after any change in study treatment, the worsening should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to a change in study treatment, the event should be captured once with the maximum severity recorded.

Preplanned procedures (surgeries or therapies):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective procedures (surgeries or therapies):

- Elective procedures performed where there is no change in the subject's medical condition (surgeries or therapies) should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as the known intentional or accidental administration of the study drug or ingestion by the subject in an amount higher than the protocol-specified amount. Whether the episode is an overdose or not will be determined by the investigator or sub-investigator after discussion with the sponsor.
- All episodes of overdose (irrespective of occurrence of AEs) will be recorded on the Overdose page of the eCRF, so that important safety information on overdose can be entered into the database in a consistent manner. AEs associated with overdose will be recorded on the AE page of the eCRF as described in Section 10.0.
- Serious AEs (SAEs) associated with overdose will be reported according to the procedures described in Section 10.2.9.
- If an overdose of the study drug has occurred, the subject should be treated according to the symptoms.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that:

1. Results in death.
2. Is life threatening.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Leads to a congenital anomaly.
6. Is a significant medical event that satisfies any of the following:
   - May require intervention to prevent the items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/Acute respiratory distress syndrome (ARDS)	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure (including convulsion and epilepsy)	Pulmonary fibrosis (including interstitial pneumonia)
Agranulocytosis	Neuroleptic malignant syndrome / malignant hyperthermia
Aplastic anaemia	Spontaneous abortion / stillbirth and fetal death
Toxic epidermal necrolysis / Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxic shock

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Significant Medical Events" satisfying SAE reporting requirements.

10.2 AE-related Procedures

10.2.1 Assessment of the Severity of AEs

The severity of AEs is categorized/defined as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.2.2 Assessment of the Causality of AEs

The causality of each AE to the study drug will be assessed using the following categories/definitions:

Related:	An AE that follows a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the drug), or for which possible involvement of the drug is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the relevant study drug (control drug), such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the relevant study drug (control drug) and/or that can reasonably be explained by other factors, such as underlying disease, concurrent disease, concomitant medication, or concurrent treatment.

10.2.3 Relationship to Study Procedures

A causal relationship between the adverse event and study procedures will be assessed.

The causal relationship is assessed as "Related" if the investigator or sub-investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality is assessed as "Not Related"

10.2.4 Start Date

The start date of an AE is the date on which signs or symptoms of the event were first noted by the subject or the investigator or sub-investigator.

10.2.5 Stop Date

The stop date of an AE is the date on which the event resolved (including resolution with sequelae) or the subject died.

10.2.6 Intermittent or Continuous AEs

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous."

10.2.7 Action Taken with Study Drug

- Drug withdrawn – the study drug administration was stopped due to the particular AE.
- Dose not changed – the particular AE did not require a change in the study drug dose.
- Unknown –it has not been possible to determine what action has been taken after the AE onset.
- Not Applicable – the study drug administration was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE, or an AE was seen prior to administration of the study drug.

10.2.8 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the severity is lowered by one or more categories; the diagnosis/sign/symptom has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died not directly from the AE while the AE was "recovering/resolving".
- Not recovered/Not resolved – there is no change in the diagnosis/sign/symptom; the severity of the diagnosis/sign/symptom or laboratory value at last observation is worse than that at onset; the event is

an irreversible congenital anomaly; the subject died not directly from the AE while the AE was "Not recovered/not resolved".

- Resolved with sequelae – the subject recovered from the acute AE with remaining permanent or clinically significant impairment (eg, recovered from a cardiovascular accident but with persisting paralysis).
- Fatal – the AE was directly related to the death.
- Unknown – the course of the AE could not be determined at the end of the subject's participation in the study for certain reasons such as hospital change or residence change.

10.2.9 Collection and Reporting of AEs, SAEs and Liver Function Test Abnormalities

10.2.9.1 Collection Period

Collection of AEs (AEs, SAEs, AEs of special interest, and liver function test abnormalities) will be started at the time of the subject's signing of informed consent and continued until the end of Period 2. For subjects decided to be withdrawn from the study before initial dosing of the study drug, AEs will be collected until that time point.

10.2.9.2 AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" will be asked, and subjects will report any AEs occurring during the study. Subjects experiencing any SAE before first dosing of the study drug must be monitored until the SAE resolves and clinically relevant laboratory abnormalities return to baseline or there is a satisfactory explanation for the observed change. Non-serious AEs occurring before first dosing of the study drug, whether or not related to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs after first dosing of the study drug, whether or not related to the study drug, must be monitored until the symptoms resolve and clinically relevant laboratory abnormalities return to baseline or until there is a satisfactory explanation for the observed change. All AEs will be documented on the AE page of the eCRF, whether or not the investigator or sub-investigator concludes that the event is related to the study drug. The following information will be documented for each event:

- Event term
- Start and stop date and time
- Frequency
- Severity
- Investigator's or sub-investigator's opinion of the causal relationship to the study drug (related or not related).
- Investigator's or sub-investigator's opinion of the causal relationship to study procedures, including details of the suspected procedure
- Action taken with the study drug

- Outcome of event
- Seriousness
- Timing of occurrence (after study drug administration)

10.2.9.3 SAE Reporting

When an SAE occurs during the AE collection period, it should be reported according to the following procedure:

An SAE should be reported by the investigator or sub-investigator to the sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit the detailed SAE Form to the sponsor within 10 calendar days. The information should be completed as fully as possible and contain the following at a minimum:

- A brief description of the event and the reason why the event is categorized as serious
- Subject identification code
- Investigator's or sub-investigator's name
- Name of the study drug
- Causality assessment

Any SAE spontaneously reported to the investigator or sub-investigator after the end of the AE collection period should be reported to the sponsor if considered related to the subject's study participation.

Reporting of SAEs occurring before initial dosing of the study drug will follow the procedure described for SAEs occurring during study treatment.

Follow-up of SAEs

If information not available at the time of the first report becomes available on a later date, the investigator or sub-investigator should complete a follow-up SAE form copy or provide other written documentation and promptly submit it to the sponsor. Copies of any relevant data from the hospital notes (eg, ECG, laboratory test values, discharge summary, postmortem results) should be sent to the sponsor, if requested.

All SAEs should be followed by the investigator or sub-investigator until resolution or final outcome confirmation of the event.

10.2.9.4 Reporting of Liver Function Test Abnormalities

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator or sub-investigator will contact the study monitor and investigate the subject details and possible alternative etiologies (eg, acute viral hepatitis A or B, other acute liver disease). Follow-up tests described in Section 9.2.9 will also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all serious unexpected suspected adverse reactions (SUSARs) and any other SAEs for expedited reporting to the regulatory authorities, investigators, and IRBs. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs

will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also perform expedited reporting of other significant safety information that may greatly affect the current benefit-risk profile of the study drug or require a change to the study treatment or overall conduct of the study. The study site also will forward a copy of all expedited reports to the IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis sets, analysis variables and analysis methodology to address all study objectives.

Analysis will be performed after database lock using the data obtained so far. Also, when an additional study is performed, another analysis will be performed using combined data of the first study with data of the additional study.

11.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: pharmacokinetics analysis set and safety analysis set.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data prior to database lock.

11.1.1.1 Safety Analysis Set

The "safety analysis set" will be defined as all the subjects who received at least one dose of the study drug.

11.1.1.2 Pharmacokinetics Analysis Set

The "pharmacokinetics analysis set" is a subset of all treated subjects who had no major protocol violations, have completed the minimum element of the protocol, and had evaluable pharmacokinetic data.

11.1.2 Analysis of Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the pharmacokinetic analysis set and the safety analysis set.

11.1.3 Pharmacokinetic Analysis

1. Endpoints and their analytical method

[Endpoint]

Primary endpoints

- AUC_{last} of Lu AA21004
- C_{max} of Lu AA21004

Secondary endpoints

- AUC_{∞}, t_{max}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004

[Analytical method]

The following analyses will be based on the pharmacokinetic analysis set.

1) Plasma concentration and pharmacokinetic parameters

The descriptive statistics for plasma concentration of Lu AA21004 will be provided for each formulation (Lu AA21004 20 mg tablet and 10 mg tablet) by visit and the mean and standard deviation of plasma

concentration will be plotted for both formulations on the same graph. The descriptive statistics for PK parameter will be provided for each formulation.

2) Bioequivalence assessment

The bioequivalence of Lu AA21004 20 mg tablet and 2× 10 mg tablets is evaluated.

The log-transformed (natural log) PK parameters AUC_{last} and C_{max} of Lu AA21004 will be analysed separately using analysis of variance (ANOVA) with dosing formulation, treatment sequence, administration period as fixed effects and the two-sided 90% confidence interval (CIs) for the differences between the formulations and between the periods will be provided. The log-transformed (natural log) PK parameters AUC_{∞}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004 and t_{max} of Lu AA21004 will be analysed separately using ANOVA in the same manner (confidence coefficient 90%, 95%).

Bioequivalence for Lu AA21004 will be assessed based on "Guideline for Bioequivalence Studies of Generic Products". Formulations are considered to be bioequivalent if any of the following criteria are met.

If bioequivalence cannot be verified, it will be considered adding additional subjects.

- For the primary endpoints (AUC_{last} and C_{max}), the two-sided 90% CIs of the difference in the mean values of logarithmic parameters to be assessed between two treatments is within the acceptable range of ln(0.80) to ln(1.25).

3) Methods of data transformation and handling of missing data

For plasma concentrations, values below the lower limit of quantification will be treated as Zero. Subjects with any missing pharmacokinetic data for some reasons (e.g., discontinuation, inadequate measurement) will be excluded from the pharmacokinetic analysis set, however, the PK parameters, such as $t_{1/2z}$, will be calculated, as far as possible.

4) Significance level and confidence coefficient

- Significance level: 5% (one-sided test)
- Confidence coefficient : 90% (two-sided)
  : 95% (two-sided)

11.1.4 Safety Analysis

The following analyses will be based on the Safety Analysis Set.

11.1.4.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of the study drug. Analyses will be performed for the following TEAE parameters by formulation. TEAEs will be coded using MedDRA dictionary. The frequency distribution will be provided using system organ class and preferred term for each formulation.

- All TEAE
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs

- TEAEs leading to study drug discontinuation
- Serious TEAEs

11.1.4.2 Assessment of Laboratory Data

For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each formulation.

11.1.4.3 Vital Signs

For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics.

11.1.4.4 Other Safety Parameters

The following analyses will be provided for 12-lead ECGs. For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each formulation.

11.2 Determination of Sample Size

Planned number of subjects is 28 (14 per treatment sequence).

The planned sample size was calculated based upon the analysis of logarithmically transformed AUC_{last} and C_{max}. If the 90% CIs for the ratios of Lu AA21004 20 mg tablets and 2× Lu AA21004 10 mg tablets (2× Lu AA21004 10 mg tablets/ Lu AA21004 20 mg tablet) geometric mean value of AUC_{last} and C_{max} are both be within the limits of 80.00% to 125.00%, bioequivalence can be verified. It is hypothesize that there is no interaction between dosing formulation and administration period at AUC_{last} and C_{max}. Based on data from previous studies, the largest estimate of the within-subject coefficient of variation (CV) of AUC_{last} and C_{max} were up to 9.5% and 14.3% and a sample size of 24 would then provide a power of 99.8% and 91.5% for each correctly concluding bioequivalence even if the true ratio is 1.1. Given that the 90% CIs for the ratio of the geometric means for AUC_{last} and C_{max} must both be contained in 80.00% to 125.00% in order to conclude bioequivalence between the two treatments, 24 subjects provided an overall power of at least 91.3%, assuming that the two endpoints AUC_{last} and C_{max} are independent.

Taking into account possible occurence of dropouts, planned number of subjects is 28.

In case bioequivalence cannot be demonstrated with the number of subjects initially planned due to the insufficiency of the number of subjects, an add-on subject study will be conducted in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products, if applicable. The maximum number of additional subjects in the add-on subject study is 28 (14 per treatment sequence), which is determined based on study feasibility, but is not on statistical consideration.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made by the sponsor or its designee (contract research organization [CRO]) periodically during the study to ensure that all aspects of the protocol are followed in the conduct of the study. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site will guarantee access to source documents by the sponsor or its designee and the IRB.

Study documents will be subject to reviews by the sponsor or its designee (as long as blinding is not jeopardized), including the Investigator's Binder, study drug, subjects' medical records, and informed consent documentation, for verification that the study is appropriately conducted in accordance with the protocol. In addition, consistency between eCRFs and related source documents will be checked. It is important that the investigator, sub-investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviation

The investigator or sub-investigator may deviate and change from the protocol only for medically unavoidable reasons, for example to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from the IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from the IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site will guarantee access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her absence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent form must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives the notification, no protocol activities including screening may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that the subject is free to withdraw at any time without giving a reason and without prejudice to further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given: (1) opportunity to inquire about details of the study and (2) ample time to decide whether or not to participate in the study. If the subject has decided to participate in the study, then the informed consent form must be signed and dated by the subject before participation in the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

The investigator or sub-investigator will retain the original signed informed consent form. The investigator or sub-investigator will document the date the subject signs the informed consent in the subject's medical record. A copy of the signed informed consent form shall be given to the subject.

If the informed consent form is revised, the investigator or sub-investigator will obtain re-consent of the subject in the same manner as the initial informed consent. The date of the re-consent will be recorded in the subject's medical record, and a copy of the revised informed consent form shall be given to the subject.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification code. As permitted by all applicable laws and regulations, limited subject attributes such as sex, age, or date of birth may be used to identify the subject and check the validity of the subject's identification code.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents may be provided to the sponsor only after removal of the subject's personally identifiable information (ie, subject name, address, and other personal identifiers not recorded on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator will provide the sponsor with all results and all data obtained from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site

agreement, public disclosure related to the protocol or study results (including publicly accessible websites) is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. The investigator or sub-investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all Takeda-sponsored interventional clinical trials conducted anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with study site's name, city, country, and recruiting status will be registered and available for public viewing.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If required locally, the sponsor or sponsor's designee will take out an insurance policy to prepare for possible compensation for health injury to study subjects. Subjects with health injury will be compensated and treated as stated in the study site agreement. If the investigator or sub-investigator has questions regarding compensation, he or she should contact the sponsor or sponsor's designee.

14.0 STUDY ADMINISTRATIVE INFORMATION AND RELATED INFORMATION

14.1 Study Administrative Information

14.1.1 Study-related Contact Information

Each study site will be provided with a list of contact information (Protocol Annex 1).

14.1.2 Investigator Agreement

Each study site will be provided with the investigator agreement form.

14.1.3 Study-related Roles and Responsibilities

Each study site will be provided with a list of contact information (Protocol Annex 1).

14.1.4 List of Abbreviations

Term	Definition
5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
EM	extensive metabolizer
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HDL	high-density lipoprotein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
OTC	over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SUSARs	serious unexpected suspected adverse reactions
TEAE	treatment emergent adverse event

15.0 DATA MANAGEMENT AND RECORD KEEPING

The full details of procedures for data management will be documented in the Data Management Plan. AEs and medical history including concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

15.1 eCRF

The investigator or sub-investigator will complete eCRFs for all subjects who signed the informed consent form.

The sponsor or its designee will supply the study site with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. The eCRFs are used to transmit the information collected in the conduct of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify any inconsistent dates, missing data, questionable values, or other erroneous entries. Queries may be issued by the sponsor or its designees and will be answered by the study site.

Changes or corrections to the eCRF are to be recorded in an audit trail designed to capture the data before and after the change/correction, person making the change/correction, date of the change/correction, and reason for the change/correction.

The investigator will review the eCRFs for completeness and accuracy, and electronically sign the designated page of the eCRFs. The investigator will take full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded directly into the eCRFs.

- Laboratory test results
- Drug concentration measurement results

After the study database lock, any change, correction, or addition to the entries in the eCRF by the investigator or sub-investigator will require the eCRF change/correction record (Data Clarification Form). The investigator will review the Data Clarification Form for completeness and accuracy, and electronically sign the form.

The sponsor or its designee will review the eCRFs for accuracy and completeness at the study site during periodic visits. The sponsor or its designee will review the subjects' medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and any information in the eCRFs should not be made available by the investigator or sub-investigator to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

To allow for inspections or audits by the regulatory authorities and the sponsor or its designees, the investigator and the head of the study site will agree to retain the following documents, including the records stipulated in Section 15.1 and study-specific documents. These documents include the subject

screening log, medical records, original signed and dated informed consent forms, electronic copies of eCRFs including the audit trail, and drug accountability record.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site will discuss the record retention period and method with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or, if the drug development is discontinued, 3 years after the date of receipt of its notification).
2. 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site will retain the essential documents until the time of receipt of a sponsor-issued notification stating that the retention is no longer required.

16.0 REFERENCES

[1] Nakane Y, Arima K. Cause and Symptoms of Depression. Journal of Practical Pharmacy. 2000;51(2):826-34.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Translated by Takahashi S, Ono Y, Someya T. Igaku-Shoin. 2004.

[3] Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated November 16, 2010).

[4] Guideline for Bioequivalence Studies of Generic Products (Notification No. 0229-10 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated February 29, 2012).

[5] Act on Securing a Stable Supply of Safe Blood Products (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare, dated June 25, 1956).

[6] Japan Society for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity. 2011;10(Suppl).

[7] General Considerations for Clinical Trials (ICH-E8 guideline; Notification No. 380 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the study appropriately in accordance with the protocol and GCP, while respecting the human rights, safety, and wellbeing of the subjects.
2. When part of important tasks related to the study are delegated to the sub-investigator or clinical research coordinator, prepare the lists of tasks to be delegated and responsible personnel, submit the lists to the head of the study site in advance and receive approval.
3. Prepare a written informed consent form, and update it as needed.
4. Confirm the contents of the clinical study agreement.
5. Provide the sub-investigators, clinical research coordinators, and other study staff with sufficient information about the protocol, drugs, and each person's tasks, and give guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide explanation about the study in writing, and obtain written consent.
7. Assume responsibility for all medical judgments related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical treatment will be provided to subjects for all clinically significant adverse events related to the study, throughout and after the period of the subject's participation in the study.
9. If a subject is being treated at any other medical institution or department, with agreement of the subject, notify the physician of the other medical institution or department of the subject's participation in the study, as well as completion/discontination of the study in writing, and document such records.
10. If expedited reporting of SAEs etc. is required, immediately notify the head of the study site and the sponsor in writing.
11. Determine the need for unblinding of emergency key code for a subject in case of emergency (only for double-blind studies).
12. Prepare correct and complete eCRFs, electronically sign them, and submit them to the sponsor.
13. Check and confirm the entries in the eCRFs completed by the sub-investigator or transcribed from source data by the clinical research coordinator, electronically sign them, and submit them to the sponsor.
14. Discuss any proposals from the sponsor, including protocol amendments.
15. Notify the head of the study site of the completion of the study in writing.

Appendix B Pregnancy and Contraception

Female subjects and their male partners

From signing informed consent, throughout the duration of the study and for 4 weeks after last dose of the study drug, female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use a method of contraception as described below .

In addition, they must be advised not to donate ova during this period.

* A woman of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least one year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Appropriate contraception are defined as the following methods;

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation: Combined pill.
- Intrauterine device (IUD).
- Intrauterine Contraceptive System (IUS)
- Bilateral tubal occlusion.
- Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success).
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose and 4 weeks after last dose.
- Male condom

Subjects will be provided with information on appropriate methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study and up to 4 weeks after last dose of the study drug.

During the course of the study, pregnancy tests (Urinary human chorionic gonadotropin) will be performed only for female subjects of childbearing potential and all subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:

- contraceptive requirements of the study

- assessment of subject compliance through questions such as
  - · Have you used the contraception consistently and correctly since the last visit?
  - · Have you forgotten to use contraception since the last visit?
  - · Are your menses late (even in female subjects with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
  - · Is there a chance you could be pregnant?

In addition to a negative pregnancy test (Urinary human chorionic gonadotropin) at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative pregnancy test prior to receiving any dose of study medication. In addition, subjects must also have a negative pregnancy test (Urinary human chorionic gonadotropin) for one day before receiving the investigational drug at Period 2.

Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the female subject agrees to the primary care physician (obstetrician and gynecologist) being informed, the investigator or sub-investigator should notify the primary care physician that she was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

If any subject is found to be pregnant during the study or up to 4 weeks after last dose of the study drug, all pregnancies will be followed up to final outcome and the outcome, including any premature termination, Investigator or sub-investigator must report to the sponsor using the pregnancy form under the agreement of the female subjects. An evaluation after the birth of the child will also be conducted.

Appendix C Time Windows for Study Procedures

For both Period 1 and Period 2

Test/Observation Item	Scheduled Time	Allowable Time Window
Screening examination [(a)]	Screening (Day -28 to Day -2)	Same as left
Physical examination	Day -1, Day 21	Between 24 hours before administration and just before dosing on Day 1
	24 and 72 hours postdose	±1 hour
Body weight	Day -1	Same as left
Vital signs	Day -1, Day 21	Same as left
	24 and 72 hours postdose	±1 hour
12−lead ECG	72 hours postdose	±1 hour
Laboratory tests	Day -1, Day 21	Same as left
	72 hours postdose	±1 hour [(b)]
Pharmacokinetic blood sampling	Predose on Day 1	Between rising and just before dosing on Day 1
	1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose	±5 minutes
	24, 36, 48, and 72 hours postdose	±10 minutes
C-SSRS	Day -1, Day 21	Same as left
	Day 4	Same as left

Day -1 is defined as the day before the Period 1 study drug administration. Day 21 is defined as the day before the Period 2 study drug administration. Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2.

(a) Height, physical examination, body weight, vital signs, 12-lead ECG, laboratory test, blood collection for CYP2D6 genotyping and C-SSRS.

(b) For urinalysis, from the time of rising up to +1 hour of the scheduled time.

Appendix D Blood Volume Table

The total blood collection volume collected from each subject is shown below;

Sample Type	Sample Volume per each time(mL)	Number of Samples			Total Volume (mL)
		Screening period	Period 1	Period 2	
Laboratory tests					
Hematology	2	2	2	1	10
Serum chemistry	7	2	2	1	35
Immunology	10	1	0	0	10
CYP2D6 genotyping	5	1	0	0	5
PK assessment	4	0	14	14	112
Total volume					172 mL

Takeda Pharmaceutical Company Limited

PROTOCOL

A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects

A Bioequivalence Study of the Lu AA21004 20 mg and 2×10 mg Tablets

Study Number: Vortioxetine-1001

Compound: Lu AA21004

Date: 28 December 2017

Version/Amendment Number: First Version

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1.0 STUDY SUMMARY

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Takeda Pharmaceutical Company Limited</td><td>Compound:
Lu AA21004</td></tr>
<tr><td>Study Number: Vortioxetine-1001</td><td>Phase: 1</td></tr>
<tr><td colspan="2">Study Title:
A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects</td></tr>
<tr><td colspan="2">Study Design:
This is a 2 x 2 crossover, open-label, comparative study in Japanese healthy adults to evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing, and also to evaluate the safety of a single oral dose of Lu AA21004 20 mg.
Subjects will be randomized in a 1:1 ratio to either treatment sequence A or B.
This study consists of the screening period, Period 1, and Period 2. Subjects will receive one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets on Day 1 of Period 1 and Period 2. The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.
If bioequivalence is not demonstrated with the initially planned number of subjects, an add-on subject study may be conducted in accordance with the “Partial Revision of Guideline for Bioequivalence Studies of Generic Products”.</td></tr>
<tr><td colspan="2">Primary Objective:
To evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing in Japanese healthy adults
Secondary Objective:
To evaluate the safety of a single dose of Lu AA21004 20 mg in Japanese healthy adults</td></tr>
<tr><td colspan="2">Subject Population: Japanese healthy adult subjects</td></tr>
<tr><td>Planned Number of Subjects:
28 (14 per treatment sequence)
If an add-on subject study is conducted, the maximum number of additional subjects will be 28 (14 per treatment sequence).</td><td>Planned Number of Sites:
1 site</td></tr>
<tr><td>Dose Levels:
A single dose of either one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets will be given under fasted conditions on Days 1 in Period 1 and Period 2.</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
Single dose × 2 periods (The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.)</td><td>Planned Study Period:
Screening period: Day -28 to Day -1
Period 1 and Period 2: Day 1 to Day 25 (when the period between dosing of Period 1 and Period 2 is set as 3 weeks)</td></tr>
<tr><td colspan="2">Inclusion Criteria:
In order to be eligible for participation in this trial, the subject must:
1. Be a healthy Japanese adult volunteer.
2. Understand the contents of the study and be capable of providing written consent to participate in the study.
3. Be willing to comply with all study procedures and restrictions.
4. Aged between ≥20 and ≤45 years at the time of screening.
5. Have a BMI of ≥18.5 and ≤24.9 (kg/m^2) and a body weight of ≥50 kg at the time of screening.
6. Be a extensive metabolizer (EM) based on CYP2D6 genotyping at the time of screening.
7. A female subject of childbearing potential with a non-sterilized male partner must agree to routinely use appropriate contraception during the study from the time of signing informed consent until 4 weeks after last dosing of the study drug.</td></tr>
<tr><td colspan="2">Exclusion Criteria:
The subject must be excluded from participating in the trial if the subject:
1. Has received any investigational drugs within 90 days before screening for this study.
2. Previously received Lu AA21004 before participation in this study.
3. Is an employee of the sponsor or the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be coerced to provide consent.
4. Has uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality which may affect study participation or study results.
5. Has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or</td></tr>
</table>

significant intolerance to prescription drugs, OTC drugs, or foods.

6. Has a positive pregnancy test at the time of screening or Day −1.
7. Is a pregnant or lactating female.
8. Has a positive urine drug test at the time of screening or Day −1.
9. Has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
10. Consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day.
11. Is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the Period 1 study drug administration.
12. Used any of the excluded drugs, dietary products or foods during the period specified in the table in Section 7.3, or will need any of them during the study period.
13. Has any current or a history of gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn), or any surgical intervention (gastrectomy, cholecystectomy etc.).
14. Has a history of cancer.
15. Has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
16. Has poor peripheral venous access.
17. Has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of Period 1 study drug administration.
18. Has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of Period 1 study drug administration.
19. Has undergone blood component collection within 2 weeks (14 days) prior to the start of Period 1 study drug administration.
20. Has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or on Day −1 of Period 1.
21. Has abnormal laboratory test values at screening or on Day −1 of Period 1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×ULN.
22. Is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

Criteria for Evaluation:

<Primary endpoints>

· AUC from time 0 to the last quantifiable time point (AUC_{last}) of Lu AA21004

· Maximum plasma concentration (C_{max}) of Lu AA21004

<Secondary endpoints>

· AUC_{∞}, t_{max}, MRT, λ_z , and $t_{1/2z}$

· Safety: adverse events (AEs), vital signs (sitting blood pressure, sitting pulse rate, body temperature (axillary)), resting 12-lead electrocardiograms (ECGs), and laboratory test results

Statistical Considerations:

1) Plasma concentration and pharmacokinetic parameters

The descriptive statistics for plasma concentration of Lu AA21004 will be provided for each formulation (Lu AA21004 20 mg tablet and 10 mg tablet) by visit and the mean and standard deviation of plasma concentration will be plotted for both formulations on the same graph. The descriptive statistics for PK parameter will be provided for each formulation.

2) Bioequivalence assessment

The bioequivalence of Lu AA21004 20 mg tablet and 2× 10 mg tablets is evaluated.

The log-transformed(natural log) PK parameters AUC_{last} and C_{max} of Lu AA21004 will be analysed separately using analysis of variance (ANOVA) with dosing formulation, treatment sequence, administration period as fixed effects and the two-sided 90% confidence interval (CIs) for the differences between the formulations and between the periods will be provided. The log-transformed(natural log) PK parameters AUC_{∞}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004 and t_{max} of Lu AA21004 will be analysed separately using ANOVA in the same manner (confidence coefficient 90%, 95%).

Rational for the Sample Size:

Planned number of subjects is 28 (14 per treatment sequence).

The planned sample size was calculated based upon the analysis of logarithmically transformed AUC_{last} and C_{max}. If the 90% CIs for the ratios of Lu AA21004 20 mg tablets and 2× Lu AA21004 10 mg tablets (2× Lu AA21004 10 mg tablets/ Lu AA21004 20 mg tablet) geometric mean value of AUC_{last} and C_{max} are both be within the limits of 80.00% to 125.00%, bioequivalence can be verified. It is hypothesize that there is no interaction between dosing formulation and administration period at AUC_{last} and C_{max}. Based on data from previous studies, the largest estimate of the within-subject coefficient of variation (CV) of AUC_{last} and C_{max}were up to 9.5% and 14.3% and a sample size of 24 would then provide a power of 99.8% and 91.5% for each correctly concluding bioequivalence even if the true ratio is 1.1. Given that the 90% CIs for the ratio of the geometric means for AUC_{last} and C_{max} must both be contained in 80.00% to 125.00% in order to conclude bioequivalence

between the two treatments, 24 subjects provided an overall power of at least 91.3%, assuming that the two endpoints AUC_{last} and C_{max} are independent.

Taking into account possible occurence of dropouts, planned number of subjects is 28.

In case bioequivalence cannot be demonstrated with the number of subjects initially planned due to the insufficiency of the number of subjects, an add-on subject study will be conducted in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products, if applicable. The maximum number of additional subjects in the add-on subject study is 28 (14 per treatment sequence), which is determined based on study feasibility, but is not on statistical consideration.

2.0 SCHEMATIC OVERVIEW OF THE STUDY

The overview of the study design is shown in Figure 2.a.

Figure 2.a Study Design Overview

Treatment sequence	Period 1		Period 2
	Day 1 to 4	Day 5 to 21[a]	Day 1 to 4
A	One Lu AA21004 20 mg tablet Single dose under fasted condition	Washout	Two Lu AA21004 10 mg tablets Single dose under fasted condition
B	Two Lu AA21004 10 mg tablets Single dose under fasted condition		One Lu AA21004 20 mg tablet Single dose under fasted condition

Period	Screening period		Administration term							
			Period 1					Period 2		
Day[b]	−28 to −2	−1	1	2 to 3	4	5 to 20	21	1	2 to 3	4
Days from the Period 1 study drug dossing [a]	-	-	1	2 to 3	4	5 to 20	21	22	23 to 24	25
Inpatient/Outpatient	Outpatient	Inpatient				No visit	Inpatient			
Procedure	Informed consent, screening	Admission	Study drug administration		Discharge		Admission	Study drug administration		Discharge

(a) When the interval between the Period 1 dosing and the Period 2 dosing of the study drug is 3 weeks.
(b) Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2, with the day before Period 1 study drug administration referred to as Day −1 and the day before Period 2 study drug administration as Day 21.

3.0 STUDY SCHEDULE

	Screening period		Administration term									
			Period 1						Period 2			
			Treatment period				Washout period		Treatment period			
Day[1)]	Screening -28 to -2	-1	1	2	3	4 [9)]	5～20	21	1	2	3	4 [9)]
Days from Period 1 study drug administration[2)]	-	-	1	2	3	4	5～20	21	22	23	24	25
Informed consent	X											
Demographic data, Height	X											
Medical history, concurrent medical conditions, prior medication	X											
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events monitoring[3)]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4)]	X	X		X		X		X		X		X
Body weight	X	X										
Vital signs[5)]	X	X		X		X		X		X		X
12-lead ECG[6)]	X					X						X
Laboratory tests[7)]	X	X				X		X				X
Pharmacokinetic blood sampling[8)]			X	X	X	X			X	X	X	X
CYP2D6 genotyping blood sampling	X											
Study drug administration			X						X			
Hospitalization		In				Out		In				Out

1) Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2, with the day before Period 1 study drug administration referred to as Day −1 and the day before Period 2 study drug administration as Day 21.
2) When the interval between the Period 1 dosing and the Period 2 dosing of the study drug is 3 weeks.
3) AEs will be collected continuously from the time of signing of informed consent until the end of Period 2.
4) Physical examination will be performed at 24 and 72 hours postdose.
5) Vital signs will be measured at 24 and 72 hours postdose.
6) A 12-lead ECG will be performed at 72 hours postdose.
7) Immunology tests will be performed only at screening. Urine drug tests and pregnancy test will be performed only at screening, Day −1 and Day 21. Pregnancy test will be performed only in female subjects of childbearing potential.
8) Pharmacokinetic blood samples will be collected at Day 1 predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours postdose.
9) Or at discontinuation.

4.0 INTRODUCTION

4.1 Background

Lu AA21004 (generic name: vortioxetine hydrobromide) is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and 5-HT transporter (5-HTT) inhibitor. This novel antidepressant with a different profile from existing medications has been under development.

Depression is a mental disease mainly characterized by a depressed mood and a loss of interest or pleasure, and is additionally characterized by thought or concentration difficulties, an appetite decrease or increase, anxiety, a feeling of worthlessness or guilt, and thoughts related to suicide (suicidal ideation) as well as somatic symptoms including sleep disturbances and fatigability.[1][2]

The course of depression varies from only 1 episode in a lifetime to a lifelong disorder with recurrent episodes, and some patients suffer from long-term depressive symptoms despite treatments. Depression is therefore a significant mental and social burden and economic loss for not only patients but also their family, which treatment is necessary.[3]

Depression is mainly treated with pharmacotherapy and psychotherapy, and these treatments are selected according to the severity and pathological condition.[3] As pharmacotherapy in patients with moderate to severe depression, antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors , and noradrenergic and specific serotonergic antidepressants have been widely used. These antidepressants, however, have problems such as patients with inadequate response and adverse effects; therefore, development of an antidepressant with a novel profile can broaden treatment options and optimize treatment for depression.

From the results of the clinical pharmacology studies, following pharmacokinetic profiles were shown. Lu AA21004 was slowly absorbed with t_{max} of approximately 7 to 11 hours, and the absolute bioavailability of Lu AA21004 was approximately 75%. Lu AA21004 was extensively metabolized in the liver, and CYP2D6 was shown to be the primary enzyme in metabolism of Lu AA21004 to the major metabolite Lu AA34443. The $t_{1/2z}$ of Lu AA21004 was approximately 66 hours, and two-thirds of its metabolites were excreted in urine, and one-third were excreted in feces.Based on the results of the clinical studies, treatment with Lu AA21004 at doses of 5 to 20 mg/day was safe and effective. As of December 2017, Lu AA21004 has been approved for marketing as a drug for the treatment of MDD in countries including the U.S., Europe and Australia.

In Japan, Lu AA21004 is being developed for treatment of major depression disorder and has been evaluated in four clinical pharmacology studies of CPH-001, CPH-002, CPH-003, and CPH-004 conducted in healthy adults or elderly individuals; two placebo-controlled short-term studies of CCT-002 and CCT-003 conducted in patients with major depressive disorder; and a long-term extension study of OCT-001 in patients who completed CCT-003. In all these studies, Lu AA21004 was well-tolerated without major safety issues. Currently, CCT-004 study is being conducted as a short-term placebo-controlled study for major depressive disorder patients.

4.2 Rationale for This Study

In the dissolution tests, the different strengths (10 mg and 20 mg) of commercial formulations in Japan showed different dissolution behaviors and did not meet bioequivalence criteria. Consequently, this study has been planned to evaluate the bioequivalence between Lu AA21004 20 mg tablet and 2× Lu AA21004

10 mg tablets in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products.[4]

4.3 Benefits/Risks

Subjects in this study will not benefit from this study.

In the clinical pharmacology studies conducted to date in Japanese healthy adults or elderly individuals (ie, CPH-001, CPH-002, CPH-003 and CPH-004) and clinical studies including Japanese major depressive disorder patients (ie, CCT-002, CCT-003 and OCT-001), Lu AA21004 at a dose of 2.5 to 40 mg was well-tolerated without major safety issues. Further detailed safety data on Lu AA21004 are provided in the Investigator's Brochure.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study is planned on the basis of the following hypothesis:

Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets will be shown to be bioequivalent.

5.2 Objectives

5.2.1 Primary Objective

To evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing in Japanese healthy adults.

5.2.2 Secondary Objective

To evaluate the safety of a single dose of Lu AA21004 20 mg in Japanese healthy adults.

5.3 Endpoints

5.3.1 Primary Endpoints

- AUC_{last} of Lu AA21004
- C_{max} of Lu AA21004

5.3.2 Secondary Endpoints

- AUC_{∞}, t_{max}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004
- Adverse events, vital signs, 12-lead ECG, and laboratory test values

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

1) Study design

This is a 2 × 2 crossover, open-label, comparative study in Japanese healthy adults to evaluate the bioequivalence between the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet after single dosing, and also to evaluate the safety of a single oral dose of Lu AA21004 20 mg.

Subjects will be randomized in a 1:1 ratio to either treatment sequence A or B.

This study consists of the screening period, Period 1, and Period 2. Subjects will receive one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets on Days 1 of Period 1 and Period 2. The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.

If bioequivalence is not demonstrated with the initially planned number of subjects, an add-on subject study may be conducted in accordance with the "Partial Revision of Guideline for Bioequivalence Studies of Generic Products".

2) Planned number of subjects

The planned number of subjects is 28 (14 per treatment sequence). If an add-on subject study is conducted, the maximum number of additional subjects will be 28 (14 per treatment sequence).

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale for Study Design

A 2-period, 2-treatment, cross-over design, which allows bioequivalence evaluation with minimal effect on inter-subject variation, was selected for this study in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products.

Open-label design is adopted because the primary objective of the study is to evaluate the pharmacokinetic profile and to assess bioequivalence of Lu AA21004 tablets which is an objective indicator.

To eliminate all biases arising from arbitrary assignment of subjects, subjects will be randomized to receive the two treatments in either treatment sequence.

6.2.2 Rationale for Dose

Based on clinical data obtained so far, the clinical doses of Lu AA21004 for the treatment of major depression in Japanese patients are expected to be 10-20 mg/day, and 10 mg and 20 mg commercial tablets have been developed. For this study designed to evaluate the bioequivalence between Lu AA21004 20 mg tablet and 2× 10 mg tablets, one Lu AA21004 20 mg tablet and two Lu AA21004 10 mg tablets will be used.

6.2.3 Rationale for Washout Period

In CPH-004 study ('A Phase 1, Open-Label, Single-Dose, 2-Period Crossover Study to Assess Pharmacokinetics of Lu AA21004 and Effect of Food on the Pharmacokinetics after Oral Administration of Lu AA21004 in Healthy Male Subjects'), in which 14 days interval between the Period 1 dosing and the Period 2 dosing of the study drug, plasma unchanged Lu AA21004 concentration at Period 2 predose was

higher than 11% of C_{max} value of the Period 1 in the subject with the highest plasma unchanged Lu AA21004 level in Period 1. Based on these results, it is set that the interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks in order for the plasma concentration at Period 2 predose to be decreased below 5% of C_{max} in Period 1. Also, the Partial Revision of Guideline for Bioequivalence Studies of Generic Products recommends that there should be a washout period at least 5 times longer than the apparent half-life of the investigational drug. The 3 weeks interval between the Period 1 dosing and the Period 2 dosing of the study drug in this study is longer than 5 times of the apparent elimination half-life of Lu AA21004 (about 66 hours) thus meets this guideline.

6.2.4 Rationale for Endpoints

6.2.4.1 Rationale for Pharmacokinetic Endpoints

AUC_{last} and C_{max} of unchanged Lu AA21004 will be evaluated in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products. Since the apparent elimination half-life of unchanged Lu AA21004 is very long (about 66 hours), the plasma concentration of Lu AA21004 will be evaluated until 72 hours postdose, in accordance with "Partial Revision of Guideline for Bioequivalence Studies of Generic Products".

6.2.4.2 Rationale for Safety Endpoints

Safety measures will include those commonly used in clinical pharmacology studies (Adverse events, Vital signs, Clinical laboratory tests, and 12-lead ECG assessment).

6.2.5 Important Procedures based on Study Objectives: Time Points of the Procedures

Blood sample collection for pharmacokinetic evaluation is the important procedure in this study.

- For all time points of evaluation after administration of the study drug, the blood samples for pharmacokinetic evaluation should be collected at a time as closest as possible to the scheduled time.
- If blood sample collection and other procedures are scheduled for the same time, blood sample collection should be prioritized, with implementation of other procedures within the allowable window (Appendix C).
- The priority order of procedures may be changed based on agreement between the investigator and the sponsor.
- Any unscheduled procedure required for emergency assessment for safety concerns must be prioritized over any scheduled procedures.

6.3 Start and End/Completion of the Study

6.3.1 Definition of the Start of the Study

The time of the start of the entire study is defined as the time when the first subject has signed the informed consent form.

6.3.2 Definition of the Completion of the Study

The time of the completion of the entire study is defined as the time when the last subject has completed the last planned or follow-up visit (or last contact related to a planned visit [possibly a telephone contact]), has been discontinued from the study, or has become lost to follow-up (ie, not reachable by the investigator).

6.3.3 Definition of Study Termination

Study termination for reasons other than safety are defined, such as below:

- When the study is terminated for non-safety reasons on the basis of certain findings on this study drug from nonclinical or other clinical studies with administration of this study drug (eg, findings on pharmacokinetics, pharmacodynamics, efficacy, or biological target).
- When the study is terminated for non-safety reasons on the basis of certain data that became available regarding another drug in the same class as this study drug or the same study methodology as this study.
- When the study is terminated for non-scientific and non-safety reasons, such as delay in subject enrollment.

Study termination for safety reasons are defined, such as below:

- When the study is prematurely terminated because of unexpected safety concerns for subjects, raised from any clinical or nonclinical study of this study drug, another drug in the same class as this study drug, or the same study methodology as this study.

6.3.4 Criteria for Suspension or Termination of the Entire Study

6.3.4.1 Criteria for Suspension or Termination of the Study

The study will be temporarily suspended or prematurely terminated if one or both of the following criteria are met:

- New information or other evaluation has been obtained regarding the safety or efficacy of the study drug that alters the known risk/benefit profile of Lu AA21004, and the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) has occurred that compromises the ability to achieve the primary study objective or compromises the safety of subjects.

6.3.4.2 Procedures for Suspension or Termination of the Study

In the event that the sponsor, institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor. The procedure will be followed by the applicable study site during the course of termination or study suspension.

6.3.5 Criteria for Suspension or Termination of a Study Site

6.3.5.1 Criteria for Suspension or Termination of a Study Site

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise is permitted by the contractual agreement.

6.3.5.2 Procedures for Suspension or Termination of Participation of a Study Site

In the event that the sponsor, IRB, or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by the applicable study site during the course of termination or study suspension.

7.0 CRITERIA FOR SELECTION AND DISCONTINUATION OF SUBJECTS

All inclusion/exclusion criteria, including test results, need to be confirmed prior to the study drug administration in Period 1.

7.1 Inclusion Criteria

In order to be eligible for participation in this study, the subject must fulfill the following criteria:

1. Be a healthy Japanese adult volunteer.
2. Understand the contents of the study and be capable of providing written consent to participate in the study.
3. Be willing to comply with all study procedures and restrictions.
4. Aged between ≥20 and ≤45 years at the time of screening.
5. Have a BMI of ≥18.5 and ≤24.9 (kg/m^2) and a body weight of ≥50 kg at the time of screening.
6. Be a extensive metabolizer (EM) based on CYP2D6 genotyping at the time of screening.
7. A female subject of childbearing potential* with a non-sterilized male partner* must agree to routinely use appropriate contraception* during the study from the time of signing informed consent until 4 weeks after last dosing of the study drug (*see Appendix B).

7.1.1 Rationale for the Inclusion Criteria

Inclusion criteria 1, 2, 3, 4 and 7:

These are the standard inclusion criteria used in clinical pharmacology studies in healthy adults.

Inclusion criterion 5:

The body weight criterion is set because collecting 400 mL of whole blood from people weighing less than 50.0 kg has harmful effect on health, according to the "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products" (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare in 1956). [5]

The BMI criterion is set to correspond to the normal body weight range according to the diagnostic criteria for obesity proposed by the Japan Society for the Study of Obesity. [6]

Inclusion criterion 6:

This criterion is set because the "Partial Revision of Guideline for Bioequivalence Studies of Generic Products" recommends that, if polymorphism is involved in clearance of the test drug, bioequivalence studies of the drug should be conducted in subjects with greater clearance.

7.2 Exclusion Criteria

The subject meeting any of the following criteria will be excluded from the study:

1. Has received any investigational drugs within 90 days before screening for this study.
2. Previously received Lu AA21004 before participation in this study.
3. Is an employee of the sponsor or the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be coerced to provide consent.

4. Has uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality which may affect study participation or study results.
5. Has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription drugs, OTC drugs, or foods.
6. Has a positive pregnancy test at the time of screening or Day −1.
7. Is a pregnant or lactating female.
8. Has a positive urine drug test at the time of screening or Day −1.
9. Has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
10. Consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day.
11. Is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the Period 1 study drug administration.
12. Used any of the excluded drugs, dietary products or foods during the period specified in the table in Section 7.3, or will need any of them during the study period.
13. Has any current or a history of gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn), or any surgical intervention (gastrectomy, cholecystectomy etc.).
14. Has a history of cancer.
15. Has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
16. Has poor peripheral venous access.
17. Has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of Period 1 study drug administration.
18. Has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of Period 1 study drug administration.
19. Has undergone blood component collection within 2 weeks (14 days) prior to the start of Period 1 study drug administration.
20. Has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or on Day −1 of Period 1.
21. Has abnormal laboratory test values at screening or on Day −1 of Period 1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN).
22. Is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

7.2.1 Rationale for the Exclusion Criteria

Exclusion criterion 1:

This is set to secure the safety of the subjects, with reference to the "General Considerations for Clinical Trials". [7]

Exclusion criteria 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16 and 22:

These are set as the standard exclusion criteria used in clinical pharmacology studies in healthy adults and also to secure the safety of the subjects.

Exclusion criteria 5, 20 and 21

These are set to secure the safety of the subjects.

Exclusion criterion 13:

This is set to secure the safety of the subjects, and also to avoid possible effects on pharmacokinetic assessments.

Exclusion criteria 17, 18 and 19:

These are set in line with "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products" (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare in 1956). [5]

7.3 Excluded Medications, Dietary Products, and Foods

Excluded medications, dietary products, and foods are shown in Table 7.a.

Use of the concomitant drugs (prescribed or over-the-counter [OTC] drugs) and consumption of dietary products, or foods listed in Table 7.a is prohibited from the specified time point until discharge in Period 2 to avoid possible effects on the safety and pharmacokinetics. However, the use will be allowed when judged by the investigator or sub-investigator to be necessary for certain reasons such as onset of an adverse event.

Table 7.a Excluded Medications, Dietary Products, and Foods

From Period 1 Day −28 through the end of the study period	From Period 1 Day -14 through the end of the study period	From Period 1 Day -3 through the end of the study period
All prescription drugs	Vitamins	Alcohol-containing products
All OTC drugs	Foods and beverages containing grapefruit, Sweetie, Seville orange, shaddock, or other citrus fruits that inhibit CYP3A4	Caffeine-containing products
Dietary products (ie, products containing St. John's wort, ginseng, kava kava, ginkgo, Chinese traditional medicines, or melatonin)		
Nicotine containing product		

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator or sub-investigator.

7.4 Other Restrictions/Diet, Fluid, Activity Control

7.4.1 Foods and Beverages

On the day before blood collection for laboratory tests, the subjects must finish the last meal by 21:00 and then fast until blood collection in the next morning. If the examination (eg, screening examination) is

performed in the afternoon, the blood collection will be performed after at least 10 hours of fasting from the last meal.

During hospitalization, the subjects take given meals and are not allowed to take any other food. Meal menus will be same for each period.

The subjects must fast from at least 10 hours before the study drug administration.

The subjects must fast until 4 hours after the study drug administration. If a meal and a test or blood collection are scheduled for the same time, the meal will be taken after the test/blood collection.

Excessive drinking and eating should be avoided during the entire study period.

Liquid intake will be prohibited from 1 hour before study drug administration until 4 hours postdose, with the exception of water (150 mL) to take the study drug.

7.4.2 Daily Activities

Smoking is not allowed during the study period.

Supine position is not allowed for 4 hours after the study drug administration, unless it is required for examinations. During hospitalization, light exercise will be performed for about 15 minutes a day.

Excessive exercise is not allowed during the study period. The subjects will be instructed not to change the lifestyle between Periods 1 and 2 and lead a regular life even during the washout period.

Blood donation is not allowed for at least 12 weeks after the final examination of this study. The investigator or sub-investigator will instruct the subjects on the prohibition of blood donation.

If a subject visits another medical institution during the study period, the subject should inform the investigator or sub-investigator in advance whenever possible. After the visit, the subject should inform the investigator or sub-investigator of the circumstance and treatment details. Also, the investigator or sub-investigator will contact the medical institution to notify that the subject is participating in this study.

7.5 Documentation of Subject Withdrawal Before Study Treatment

The investigator or sub-investigator will account for all subjects who signed informed consent. If a subject is withdrawn from the study before the study drug administration, the investigator or sub-investigator should complete the electronic case report form (eCRF) with the information.

The primary reason for subject withdrawal is recorded in the eCRF using the following categories:

- Death
- AE
- Screen failure (failed to meet the inclusion criteria or did meet the exclusion criteria) <specify reason>
- Protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify reason>
- Study terminated by sponsor
- Pregnancy

- Sample size sufficient
- Other <specify reason >

Subject identification codes assigned to subjects who discontinued the study before the study drug administration should not be reused.

7.6 Criteria for Withdrawal of a Subject

The primary reason for subject withdrawal is recorded in the eCRF using the following categories by the investigator or sub-investigator. If the subject is withdrawn from the study before the study drug administration, see Section 7.5.

1. Death
   The subject has died during the study period.
   Note: If a subject died during the study period, this event will be handled as a serious adverse event (SAE). For the reporting procedures, see Section 10.2.9.3.
2. Adverse event (AE)
   The subject has experienced an AE that requires discontinuation from the study because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
   - Liver function test abnormalities
     If any liver function test abnormality meeting the criteria below occurs during study drug administration, the study drug administration will be immediately discontinued, and appropriate follow-up testing will be performed until the subject's laboratory profile has returned to normal or baseline (see Section 9.2.8.1):
     – ALT or AST >8 × ULN, or
     – ALT or AST >5 × ULN and persists for ≥2 weeks, or
     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
     – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Protocol deviation
   After the start of study drug administration, the subject is found not to fulfil the eligibility criteria or not to comply with protocol requirements, and continued participation in the study poses an unacceptable risk to the subject's health.
4. Lost to follow-up
   The subject did not return to the study site, and attempts to contact the subject have been unsuccessful. The attempts to contact the subject should be recorded in the subject's source document.
5. Voluntary withdrawal
   The subject requested to withdraw from the study. The reason for withdrawal, if obtained, will be recorded in the eCRF.
   Note: Every effort should be made to determine the reason for the withdrawal where possible (withdrawal due to an AE is not categorized as "Voluntary withdrawal").

6. Discontinuation of the entire study by the sponsor
   The sponsor has decided to terminate the study.

7. Pregnancy of a subject
   Note: If a subject was found to be pregnant, the subject will be immediately withdrawn from the study. For the procedures, see Appendix B.

8. Other
   Note: Specific details should be recorded in the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for Early Termination Visit if possible.

7.8 Reserve Subjects

For Period 1, some of the subjects who are assessed to be eligible based on the screening results may stand by as reserve subjects. If a subject scheduled to receive the study drug does not receive the study drug for certain reasons before study drug administration in Period 1, a reserve subject may be enrolled in the study to replace that subject.

Subjects who discontinued after study drug administration will not be replaced by reserve subjects.

7.9 Replenishment of Subjects Whose Study Was Discontinued after Initiation of Study Drug Administration

If a subject who discontinued the study after the initiation of study drug administration, it is possible to newly incorporate another subject after consultation between the investigator and the sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug

[Drug products]

The study drugs are shown in Table 8.a.

Table 8.a Study Drug

Formulation	Active ingredient	Dosage form	Strength
Lu AA21004 10 mg tablet	1-[2-(2,4-Dimethylphenylsulfanyl)phenyl] piperazine hydrobromide	Tablet	10 mg
Lu AA21004 20 mg tablet			20 mg

[Packaging]

Fifteen tablets of 10 mg of Lu AA21004 tablet or 20 mg of Lu AA21004 tablet are placed in one bottle and the bottle is placed in an outer box.

8.1.1 Study Drug Labeling

Each outer box of the study drug is labeled with the following information: statement that the drug is for clinical trial use only, sponsor's name and address, study drug name, lot number, storage condition and expiration date.

8.1.2 Study Drug Storage and Management

The study drugs should be stored at room temperature (1 to 30°C).

The study drugs must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor, or its designee for destruction. The study drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Study Drug Blinding

This is an open-label study.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

The study drug storage manager will receive the written procedures for handling, storage, and management of the study drugs prepared by the sponsor, and will appropriately manage the drugs in accordance with the procedures. The written procedures will be provided to the investigator as well. The written procedures will specify the procedures that are necessary to ensure appropriate receipt, handling, storage, management, and dispensing of the sponsor-supplied drugs, as well as retrieval of unused drugs from the subjects and their return to the sponsor or destruction.

The study drug storage manager will promptly return unused drugs to the sponsor after the study is closed at the study site.

9.0 STUDY PROCEDURES

The following sections describe the study procedures and data to be collected by the investigator or sub-investigator. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site personnel in principle. The study schedule is shown in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained from each subject prior to any study procedures. Informed consent requirements are described in Section 13.2.

9.1.1.1 Subject Identification Codes

A unique subject identification code will be assigned to each subject at the time that informed consent is explained. This subject identification code will be used throughout the study.

9.1.1.2 Assignment of Subjects

The subjects in ascending order of the subject identification code will be randomized to either treatment sequence in accordance with the assignment list.

Each subject will be assigned with a subject number (4 digit number). This subject number will be used by the study site and the pharmacokinetic laboratory to identify the pharmacokinetic samples. The test tubes for pharmacokinetic measurements sent to the laboratory must be labeled with the subject numbers. The laboratory will use the subject numbers when reporting the measurement results. These subject numbers should not be replaced by the subject identification codes. If a subject is replaced by a reserve subject, the treatment sequence assigned to the original subject will be used for the reserve subject.

If a subject is withdrawn from the study after the start of study drug administration, and if a new subject is enrolled as a result of discussion between the investigator and the sponsor, the investigator will check with the sponsor regarding the newly enrolled subject's subject number and treatment sequence.

The assignment list will be prepared by the sponsor, and provided to the investigator before the start of the study, while the sponsor will retain its copy. Information on the assignment will be kept in a secure place with limited access to authorized personnel.

9.1.2 Eligibility Assessment

Each subject will be assessed based on the inclusion and exclusion criteria shown in Section 7.0.

9.1.3 Medical History and Demographic Data

Demographic data to be obtained will include date of birth, sex, race (as reported by the subjects), height, body weight, caffeine and alcohol consumption, and smoking status.

Medical history to be obtained will include clinically relevant diseases and symptoms that resolved or disappeared within 1 year before signing of informed consent. Ongoing diseases and symptoms are regarded as concurrent medical conditions. Prior medication data to be obtained will include all drugs relevant to the eligibility criteria and safety assessments that stopped within 4 weeks (28 days) before signing of informed consent.

9.1.4 Concomitant Medication

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. Subjects will be asked whether they have used any medication other than the study drug (from signing of informed consent through the end of the study), and detailed use of all medications, including vitamins, OTC medications, and Chinese traditional medicines, must be recorded in the eCRF. The documentation for the drug should include its nonproprietary name, route of administration, start and end dates, and reason for use.

9.2 Study Procedures and Assessments

9.2.1 Physical Examination

Physical examination will consist of the following body systems:
(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

9.2.2 Height and Body Weight

Height and body weight will be measured. Height (unit: cm) will be rounded to the nearest integer. Body weight (unit: kg) will be measured to the first decimal place.

9.2.3 BMI

BMI will be calculated using the following formula:

Metrics: BMI = Body weight (kg)/Height $(m)^2$

BMI will be rounded to the first decimal place. Eligibility assessment will use the rounded BMI value.

9.2.4 Vital Signs

Vital signs will be measured in terms of body temperature (axillary), sitting blood pressure (systolic and diastolic) after resting for at least 5 minutes, and sitting pulse rate (beats per minute).

9.2.5 12-lead ECG

A 12-lead ECG will be recorded. Subjects will rest for at least 5 minutes in a supine position before each 12-lead ECG.

The investigator or sub-investigator (or a specialist physician at the study site) will assess the ECG findings using one of the following categories: within normal or abnormal. If abnormal, then the investigator or sub-investigator (or a specialist physician at the study site) will determine whether the abnormality is clinically relevant. The time of 12-lead ECG will be recorded. The following parameters will be collected from the subject's 12-lead ECG tracing, and recorded in the eCRF: heart rate, RR interval, PR interval, QT interval, QRS interval and QTcF interval (corrected using Fridericia's formula).

9.2.6 Study Drug Administration

One Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets will be orally administered on Days 1 in Period 1 and Period 2. Subjects will fast from at least 10 hours before study drug administration until 4

hours postdose. With the exception of water (150 mL) to ingest the study drug, beverage intake will be prohibited from 1 hour before study drug administration until 4 hours postdose.

The dose and mode of administration are shown in Table 9.a.

Table 9.a Dose and Mode of Administration

Treatment sequence	Period 1		Period 2
	Day 1 to Day 4	Day 5 to 21	Day 1 to Day 4
A	One Lu AA21004 20 mg tablet Single dose under fasted condition[(a)]	Washout period	Two Lu AA21004 10 mg tablets Single dose under fasted condition[(a)]
B	Two Lu AA21004 10 mg tablets Single dose under fasted condition[(a)]		One Lu AA21004 20 mg tablet Single dose under fasted condition[(a)]

(a) Oral administration with 150 mL of water under fasted condition (after fasting for at least 10 hours)

9.2.7 Assessment of AEs

Assessment of AEs will be started at the time of signing of informed consent. For details of AE collection and related procedures, see Section 10.2.

9.2.8 Laboratory Test Procedures and Assessment

The following laboratory tests will be performed at the study site. Samples for laboratory tests will be collected after fasting for at least 10 hours according to the study schedule shown in Section 3.0. The blood collection volume is shown in Appendix D.

The investigator or sub-investigator will be responsible for assessing and retaining the results of laboratory tests. The investigator will retain a copy of the reference values of laboratory tests.

9.2.8.1 Laboratory Tests

Hematology tests

The following hematology tests will be performed.

Red blood cell count	White blood cell count and differential (lymphocytes, neutrophils, eosinophils , basophils, monocytes)
Hemoglobin	Hematocrit
Platelet count	

Blood chemistry tests

The following blood chemistry tests will be performed.

Albumin	ALT
ALP	AST
GGT	Total bilirubin
Direct bilirubin	Total protein
Creatinine	Creatine kinase
BUN	Potassium
Sodium	Chloride
Calcium	Inorganic phosphorus
Glucose	Total cholesterol
HDL-cholesterol	LDL-cholesterol
Triglyceride	Uric acid

Urinalysis

The following urinalysis will be performed.

pH	Specific gravity
Qualitative tests for protein, glucose, occult blood, urobilinogen, and ketone bodies	

Other

Immunology tests
HBsAg, HCV antibody, HIV antigen/antibody, serological test for syphilis
Urine drug tests
Phencyclidine, benzodiazepines, cocaine, antihypnotic agents, cannabinoids, morphine-like narcotics, barbiturates, and tricyclic antidepressants
Pregnancy test (Only in female subjects of childbearing potential)
Urinary human chorionic gonadotropin

Note: For immunology and urine drug tests, the investigator or sub-investigator will directly return the results to the subjects. The sponsor will not receive detailed results of these tests for the subjects (including reserve subjects) selected to be given the study drug, but will check the overall test results only (ie, presence or absence of positive results).

If subjects experienced ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, ALP, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

For liver function test abnormalities as SAEs, the criteria for reporting are described in Section 10.2.9.4, and the criteria for withdrawal of the subject are described in Section 7.6.

9.3 Samples for Pharmacokinetics and CYP2D6 Polymorphism Assessments

The samples for pharmacokinetic analysis and CYP2D6 genotyping will be collected at the study site according to the study schedule shown in Section 3.0. The blood collection volume is shown in Appendix D. The samples for measurements are specified in Table 9.b.

Table 9.b Samples for Measurements

Name of sample	Matrix	Purpose of sample collection	Mandatory/ Optional
Pharmacokinetic sample	Plasma	Pharmacokinetic analysis	Mandatory
CYP2D6 genotyping sample	Whole blood	CYP2D6 genotyping	Mandatory

9.3.1 Pharmacokinetic Measurements

The pharmacokinetic parameters will be calculated from plasma concentrations of unchanged Lu AA21004 in the pharmacokinetic analysis set.

Term	Definition
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration Calculation Formula:Time 0 is taken as t_1, and the last time point when the concentration exceeding the lower limit of quantification (C_{last}) is taken as $t_n(= t_{last})$ $AUC_{last}=\sum_{i=2}^{n}\frac{(C_i + C_{i-1})}{2}(t_i - t_{i-1})$
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity Calculation Formula:$AUC_{\infty}=AUC_{last} + C_{last}/\lambda_z$
C_{max}	Maximum plasma concentration (Observed value)
t_{max}	Time to reach C_{max} (Observed value)
$t_{1/2z}$	Apparent elimination half-life
$MRT_{\infty,ev}$	Mean residence time Calculation Formula:$MRT_{\infty,ev}=AUMC_{\infty}/AUC_{\infty}$
$MRT_{last,ev}$	The average residence time from 0 hour to time of the last quantifiable concentration Calculation Formula:$MRT_{last,ev}=AUMC_{last}/AUC_{last}$
λz	Apparent elimination rate constant
$AUMC_{\infty}$	Area under the first moment time curve from 0 hour to infinity Calculation Formula:$AUMC_{\infty}=AUMC_{last} + C_{last}\times t_{last}/\lambda_z + C_{last}/\lambda_z^2$
$AUMC_{last}$	Area under the first moment time curve from 0 hour to final determinable (By the trapezoidal method)

9.3.1.1 Pharmacokinetic Samples

The blood samples for pharmacokinetic analysis of unchanged Lu AA21004 will be collected according to Table 9.c.

The time of each sample collection will be recorded in the source documents and eCRF.

Table 9.c Collection of Pharmacokinetic Samples (in Both Period 1 and Period 2)

Analyte	Matrix	Time points of sample collection
Unchanged Lu AA21004	Plasma	Predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours postdose

9.3.2 CYP2D6 Genotyping

Blood samples for CYP2D6 genotyping will be collected.

9.4 Hospitalization Period

In both Period 1 and Period 2, the subjects will be admitted to the study site on the day before study drug administration, and hospitalized for 5 days. During the hospitalization period, the investigator or sub-investigator will perform assessments and observations of the subjects according to the study schedule shown in Section 3.0. The subjects will be discharged from the study site, after no clinically relevant abnormalities in the physical condition was confirmed based on physical examination in 4 days after study drug administration in both Period 1 and Period 2.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical trial subject who provided informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment (including the study drug) or study participation.

An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory values), symptom, or disease temporally associated with the study participation whether or not it is considered related to the treatment (including the study drug) or study procedures.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent manifestations of a pre-existing condition or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or sub-investigator for any reason.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant by the investigator or sub-investigator (ie, if a certain action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value or finding is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), only the diagnosis should be reported as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline examinations , observations and evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences worsening of a concurrent medical condition (worsening after signing of informed consent), the worsening should be recorded appropriately as an AE. The investigator or sub-investigator should ensure that the event term recorded captures the worsening in the condition (eg, “worsening of…”).

- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition from baseline (eg, "worsening of…").
- If a subject has a pre-existing chronic concurrent medical condition (eg, cataract, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition (eg, "worsening of…").

Worsening of AEs:

- If an AE which occurred before study drun administration was worsened after initial dosing of the study drug or an AE was worsened after any change in study treatment, the worsening should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the worsening in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to a change in study treatment, the event should be captured once with the maximum severity recorded.

Preplanned procedures (surgeries or therapies):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective procedures (surgeries or therapies):

- Elective procedures performed where there is no change in the subject's medical condition (surgeries or therapies) should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as the known intentional or accidental administration of the study drug or ingestion by the subject in an amount higher than the protocol-specified amount. Whether the episode is an overdose or not will be determined by the investigator or sub-investigator after discussion with the sponsor.
- All episodes of overdose (irrespective of occurrence of AEs) will be recorded on the Overdose page of the eCRF, so that important safety information on overdose can be entered into the database in a consistent manner. AEs associated with overdose will be recorded on the AE page of the eCRF as described in Section 10.0.
- Serious AEs (SAEs) associated with overdose will be reported according to the procedures described in Section 10.2.9.
- If an overdose of the study drug has occurred, the subject should be treated according to the symptoms.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that:

1. Results in death.
2. Is life threatening.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Leads to a congenital anomaly.
6. Is a significant medical event that satisfies any of the following:
    - May require intervention to prevent the items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/Acute respiratory distress syndrome (ARDS)	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure (including convulsion and epilepsy)	Pulmonary fibrosis (including interstitial pneumonia)
Agranulocytosis	Neuroleptic malignant syndrome / malignant hyperthermia
Aplastic anaemia	Spontaneous abortion / stillbirth and fetal death
Toxic epidermal necrolysis / Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Confirmed or suspected transmission of infectious agent by a medicinal product
	Confirmed or suspected endotoxic shock

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Significant Medical Events" satisfying SAE reporting requirements.

10.2 AE-related Procedures

10.2.1 Assessment of the Severity of AEs

The severity of AEs is categorized/defined as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.2.2 Assessment of the Causality of AEs

The causality of each AE to the study drug will be assessed using the following categories/definitions:

Related:	An AE that follows a reasonable temporal sequence from administration of the study drug (including the course after withdrawal of the drug), or for which possible involvement of the drug is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the relevant study drug (control drug), such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the relevant study drug (control drug) and/or that can reasonably be explained by other factors, such as underlying disease, concurrent disease, concomitant medication, or concurrent treatment.

10.2.3 Relationship to Study Procedures

A causal relationship between the adverse event and study procedures will be assessed.

The causal relationship is assessed as "Related" if the investigator or sub-investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality is assessed as "Not Related"

10.2.4 Start Date

The start date of an AE is the date on which signs or symptoms of the event were first noted by the subject or the investigator or sub-investigator.

10.2.5 Stop Date

The stop date of an AE is the date on which the event resolved (including resolution with sequelae) or the subject died.

10.2.6 Intermittent or Continuous AEs

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous."

10.2.7 Action Taken with Study Drug

- Drug withdrawn – the study drug administration was stopped due to the particular AE.
- Dose not changed – the particular AE did not require a change in the study drug dose.
- Unknown –it has not been possible to determine what action has been taken after the AE onset.
- Not Applicable – the study drug administration was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE, or an AE was seen prior to administration of the study drug.

10.2.8 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the severity is lowered by one or more categories; the diagnosis/sign/symptom has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died not directly from the AE while the AE was "recovering/resolving".
- Not recovered/Not resolved – there is no change in the diagnosis/sign/symptom; the severity of the diagnosis/sign/symptom or laboratory value at last observation is worse than that at onset; the

event is an irreversible congenital anomaly; the subject died not directly from the AE while the AE was "Not recovered/not resolved".

- Resolved with sequelae – the subject recovered from the acute AE with remaining permanent or clinically significant impairment (eg, recovered from a cardiovascular accident but with persisting paralysis).
- Fatal – the AE was directly related to the death.
- Unknown – the course of the AE could not be determined at the end of the subject's participation in the study for certain reasons such as hospital change or residence change.

10.2.9 Collection and Reporting of AEs, SAEs and Liver Function Test Abnormalities

10.2.9.1 Collection Period

Collection of AEs (AEs, SAEs, AEs of special interest, and liver function test abnormalities) will be started at the time of the subject's signing of informed consent and continued until the end of Period 2. For subjects decided to be withdrawn from the study before initial dosing of the study drug, AEs will be collected until that time point.

10.2.9.2 AE Reporting

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" will be asked, and subjects will report any AEs occurring during the study. Subjects experiencing any SAE before first dosing of the study drug must be monitored until the SAE resolves and clinically relevant laboratory abnormalities return to baseline or there is a satisfactory explanation for the observed change. Non-serious AEs occurring before first dosing of the study drug, whether or not related to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs after first dosing of the study drug, whether or not related to the study drug, must be monitored until the symptoms resolve and clinically relevant laboratory abnormalities return to baseline or until there is a satisfactory explanation for the observed change. All AEs will be documented on the AE page of the eCRF, whether or not the investigator or sub-investigator concludes that the event is related to the study drug. The following information will be documented for each event:

- Event term
- Start and stop date and time
- Frequency
- Severity
- Investigator's or sub-investigator's opinion of the causal relationship to the study drug (related or not related).
- Investigator's or sub-investigator's opinion of the causal relationship to study procedures, including details of the suspected procedure
- Action taken with the study drug

- Outcome of event
- Seriousness
- Timing of occurrence (after study drug administration)

10.2.9.3 SAE Reporting

When an SAE occurs during the AE collection period, it should be reported according to the following procedure:

An SAE should be reported by the investigator or sub-investigator to the sponsor within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit the detailed SAE Form to the sponsor within 10 calendar days. The information should be completed as fully as possible and contain the following at a minimum:

- A brief description of the event and the reason why the event is categorized as serious
- Subject identification code
- Investigator's or sub-investigator's name
- Name of the study drug
- Causality assessment

Any SAE spontaneously reported to the investigator or sub-investigator after the end of the AE collection period should be reported to the sponsor if considered related to the subject's study participation.

Reporting of SAEs occurring before initial dosing of the study drug will follow the procedure described for SAEs occurring during study treatment.

Follow-up of SAEs

If information not available at the time of the first report becomes available on a later date, the investigator or sub-investigator should complete a follow-up SAE form copy or provide other written documentation and promptly submit it to the sponsor. Copies of any relevant data from the hospital notes (eg, ECG, laboratory test values, discharge summary, postmortem results) should be sent to the sponsor, if requested.

All SAEs should be followed by the investigator or sub-investigator until resolution or final outcome confirmation of the event.

10.2.9.4 Reporting of Liver Function Test Abnormalities

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator or sub-investigator will contact the study monitor and investigate the subject details and possible alternative etiologies (eg, acute viral hepatitis A or B, other acute liver disease). Follow-up tests described in Section 9.2.8 will also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all serious unexpected suspected adverse reactions (SUSARs) and any other SAEs for expedited reporting to the regulatory authorities, investigators, and IRBs. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs

will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also perform expedited reporting of other significant safety information that may greatly affect the current benefit-risk profile of the study drug or require a change to the study treatment or overall conduct of the study. The study site also will forward a copy of all expedited reports to the IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis sets, analysis variables and analysis methodology to address all study objectives.

Analysis will be performed after database lock using the data obtained so far. Also, when an additional study is performed, another analysis will be performed using combined data of the first study with data of the additional study.

11.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: pharmacokinetics analysis set and safety analysis set.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data prior to database lock.

11.1.1.1 Safety Analysis Set

The "safety analysis set" will be defined as all the subjects who received at least one dose of the study drug.

11.1.1.2 Pharmacokinetics Analysis Set

The "pharmacokinetics analysis set" is a subset of all treated subjects who had no major protocol violations, have completed the minimum element of the protocol, and had evaluable pharmacokinetic data.

11.1.2 Analysis of Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the pharmacokinetic analysis set and the safety analysis set.

11.1.3 Pharmacokinetic Analysis

1. Endpoints and their analytical method

[Endpoint]

Primary endpoints

- AUC_{last} of Lu AA21004
- C_{max} of Lu AA21004

Secondary endpoints

- AUC_{∞}, t_{max}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004

[Analytical method]

The following analyses will be based on the pharmacokinetic analysis set.

1) Plasma concentration and pharmacokinetic parameters

The descriptive statistics for plasma concentration of Lu AA21004 will be provided for each formulation (Lu AA21004 20 mg tablet and 10 mg tablet) by visit and the mean and standard deviation of plasma

concentration will be plotted for both formulations on the same graph. The descriptive statistics for PK parameter will be provided for each formulation.

2) Bioequivalence assessment

The bioequivalence of Lu AA21004 20 mg tablet and 2× 10 mg tablets is evaluated.

The log-transformed (natural log) PK parameters AUC_{last} and C_{max} of Lu AA21004 will be analysed separately using analysis of variance (ANOVA) with dosing formulation, treatment sequence, administration period as fixed effects and the two-sided 90% confidence interval (CIs) for the differences between the formulations and between the periods will be provided. The log-transformed (natural log) PK parameters AUC_{∞}, MRT, λ_z and $t_{1/2z}$ of Lu AA21004 and t_{max} of Lu AA21004 will be analysed separately using ANOVA in the same manner (confidence coefficient 90%, 95%).

Bioequivalence for Lu AA21004 will be assessed based on "Guideline for Bioequivalence Studies of Generic Products". Formulations are considered to be bioequivalent if any of the following criteria are met.

If bioequivalence cannot be verified, it will be considered adding additional subjects.

- For the primary endpoints (AUC_{last} and C_{max}), the two-sided 90% CIs of the difference in the mean values of logarithmic parameters to be assessed between two treatments is within the acceptable range of ln(0.80) to ln(1.25).

3) Methods of data transformation and handling of missing data

For plasma concentrations, values below the lower limit of quantification will be treated as Zero. Subjects with any missing pharmacokinetic data for some reasons (e.g., discontinuation, inadequate measurement) will be excluded from the pharmacokinetic analysis set, however, the PK parameters, such as $t_{1/2z}$, will be calculated, as far as possible.

4) Significance level and confidence coefficient

- Significance level: 5% (one-sided test)
- Confidence coefficient : 90% (two-sided)
  : 95% (two-sided)

11.1.4 Safety Analysis

The following analyses will be based on the Safety Analysis Set.

11.1.4.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event whose date of onset occurs on or after the start of the study drug. Analyses will be performed for the following TEAE parameters by formulation. TEAEs will be coded using MedDRA dictionary. The frequency distribution will be provided using system organ class and preferred term for each formulation.

- All TEAE
- Drug-related TEAEs
- Intensity of TEAEs

- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs

11.1.4.2 Assessment of Laboratory Data

For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each formulation.

11.1.4.3 Vital Signs

For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics.

11.1.4.4 Other Safety Parameters

The following analyses will be provided for 12-lead ECGs. For continuous variables, the observed values and the changes from baseline will be summarized for each formulation at each visit using descriptive statistics. Case plots will also be presented for the observed values. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each formulation.

11.2 Determination of Sample Size

Planned number of subjects is 28 (14 per treatment sequence).

The planned sample size was calculated based upon the analysis of logarithmically transformed AUC_{last} and C_{max}. If the 90% CIs for the ratios of Lu AA21004 20 mg tablets and 2× Lu AA21004 10 mg tablets (2× Lu AA21004 10 mg tablets/Lu AA21004 20 mg tablet) geometric mean value of AUC_{last} and C_{max} are both be within the limits of 80.00% to 125.00%, bioequivalence can be verified. It is hypothesize that there is no interaction between dosing formulation and administration period at AUC_{last} and C_{max}. Based on data from previous studies, the largest estimate of the within-subject coefficient of variation (CV) of AUC_{last} and C_{max} were up to 9.5% and 14.3% and a sample size of 24 would then provide a power of 99.8% and 91.5% for each correctly concluding bioequivalence even if the true ratio is 1.1. Given that the 90% CIs for the ratio of the geometric means for AUC_{last} and C_{max} must both be contained in 80.00% to 125.00% in order to conclude bioequivalence between the two treatments, 24 subjects provided an overall power of at least 91.3%, assuming that the two endpoints AUC_{last} and C_{max} are independent.

Taking into account possible occurence of dropouts, planned number of subjects is 28.

In case bioequivalence cannot be demonstrated with the number of subjects initially planned due to the insufficiency of the number of subjects, an add-on subject study will be conducted in accordance with the Partial Revision of Guideline for Bioequivalence Studies of Generic Products, if applicable. The maximum number of additional subjects in the add-on subject study is 28 (14 per treatment sequence), which is determined based on study feasibility, but is not on statistical consideration.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made by the sponsor or its designee (contract research organization [CRO]) periodically during the study to ensure that all aspects of the protocol are followed in the conduct of the study. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site will guarantee access to source documents by the sponsor or its designee and the IRB.

Study documents will be subject to reviews by the sponsor or its designee (as long as blinding is not jeopardized), including the Investigator's Binder, study drug, subjects' medical records, and informed consent documentation, for verification that the study is appropriately conducted in accordance with the protocol. In addition, consistency between eCRFs and related source documents will be checked. It is important that the investigator, sub-investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviation

The investigator or sub-investigator may deviate and change from the protocol only for medically unavoidable reasons, for example to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from the IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from the IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site will guarantee access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A.

13.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her absence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent form must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives the notification, no protocol activities including screening may occur.

The study site must adhere to all requirements stipulated by its respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that the subject is free to withdraw at any time without giving a reason and without prejudice to further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given: (1) opportunity to inquire about details of the study and (2) ample time to decide whether or not to participate in the study. If the subject has decided to participate in the study, then the informed consent form must be signed and dated by the subject before participation in the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form prior to subject entering into the study.

The investigator or sub-investigator will retain the original signed informed consent form. The investigator or sub-investigator will document the date the subject signs the informed consent in the subject's medical record. A copy of the signed informed consent form shall be given to the subject.

If the informed consent form is revised, the investigator or sub-investigator will obtain re-consent of the subject in the same manner as the initial informed consent. The date of the re-consent will be recorded in the subject's medical record, and a copy of the revised informed consent form shall be given to the subject.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification code. As permitted by all applicable laws and regulations, limited subject attributes such as sex, age, or date of birth may be used to identify the subject and check the validity of the subject's identification code.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents may be provided to the sponsor only after removal of the subject's personally identifiable information (ie, subject name, address, and other personal identifiers not recorded on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator will provide the sponsor with all results and all data obtained from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site

agreement, public disclosure related to the protocol or study results (including publicly accessible websites) is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. The investigator or sub-investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all Takeda-sponsored interventional clinical trials conducted anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with study site's name, city, country, and recruiting status will be registered and available for public viewing.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If required locally, the sponsor or sponsor's designee will take out an insurance policy to prepare for possible compensation for health injury to study subjects. Subjects with health injury will be compensated and treated as stated in the study site agreement. If the investigator or sub-investigator has questions regarding compensation, he or she should contact the sponsor or sponsor's designee.

14.0 STUDY ADMINISTRATIVE INFORMATION AND RELATED INFORMATION

14.1 Study Administrative Information

14.1.1 Study-related Contact Information

Each study site will be provided with a list of contact information (Protocol Annex 1).

14.1.2 Investigator Agreement

Each study site will be provided with the investigator agreement form.

14.1.3 Study-related Roles and Responsibilities

Each study site will be provided with a list of contact information (Protocol Annex 1).

14.1.4 List of Abbreviations

Term	Definition
5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CYP	cytochrome P450
EM	extensive metabolizer
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HDL	high-density lipoprotein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
OTC	over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SUSARs	serious unexpected suspected adverse reactions
TEAE	treatment emergent adverse event

15.0 DATA MANAGEMENT AND RECORD KEEPING

The full details of procedures for data management will be documented in the Data Management Plan. AEs and medical history including concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

15.1 eCRF

The investigator or sub-investigator will complete eCRFs for all subjects who signed the informed consent form.

The sponsor or its designee will supply the study site with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. The eCRFs are used to transmit the information collected in the conduct of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify any inconsistent dates, missing data, questionable values, or other erroneous entries. Queries may be issued by the sponsor or its designees and will be answered by the study site.

Changes or corrections to the eCRF are to be recorded in an audit trail designed to capture the data before and after the change/correction, person making the change/correction, date of the change/correction, and reason for the change/correction.

The investigator will review the eCRFs for completeness and accuracy, and electronically sign the designated page of the eCRFs. The investigator will take full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded directly into the eCRFs.

- Laboratory test results
- Drug concentration measurement results

After the study database lock, any change, correction, or addition to the entries in the eCRF by the investigator or sub-investigator will require the eCRF change/correction record (Data Clarification Form). The investigator will review the Data Clarification Form for completeness and accuracy, and electronically sign the form.

The sponsor or its designee will review the eCRFs for accuracy and completeness at the study site during periodic visits. The sponsor or its designee will review the subjects' medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and any information in the eCRFs should not be made available by the investigator or sub-investigator to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

To allow for inspections or audits by the regulatory authorities and the sponsor or its designees, the investigator and the head of the study site will agree to retain the following documents, including the records stipulated in Section 15.1 and study-specific documents. These documents include the subject

screening log, medical records, original signed and dated informed consent forms, electronic copies of eCRFs including the audit trail, and drug accountability record.

The investigator and the head of the study site are required to retain essential documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site will discuss the record retention period and method with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or, if the drug development is discontinued, 3 years after the date of receipt of its notification).
2. 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site will retain the essential documents until the time of receipt of a sponsor-issued notification stating that the retention is no longer required.

16.0 REFERENCES

[1] Nakane Y, Arima K. Cause and Symptoms of Depression. Journal of Practical Pharmacy. 2000;51(2):826-34.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Translated by Takahashi S, Ono Y, Someya T. Igaku-Shoin. 2004.

[3] Guideline for Clinical Evaluation of Antidepressants (Notification No. 1116-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated November 16, 2010).

[4] Guideline for Bioequivalence Studies of Generic Products (Notification No. 0229-10 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated February 29, 2012).

[5] Act on Securing a Stable Supply of Safe Blood Products (Ministerial Ordinance No. 22 of the Ministry of Health and Welfare, dated June 25, 1956).

[6] Japan Society for the Study of Obesity. Diagnostic Criteria for Obesity 2011. Journal of Japan Society for the Study of Obesity. 2011;10(Suppl).

[7] General Considerations for Clinical Trials (ICH-E8 guideline; Notification No. 380 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, dated April 21, 1998).

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

1. Conduct the study appropriately in accordance with the protocol and GCP, while respecting the human rights, safety, and wellbeing of the subjects.
2. When part of important tasks related to the study are delegated to the sub-investigator or clinical research coordinator, prepare the lists of tasks to be delegated and responsible personnel, submit the lists to the head of the study site in advance and receive approval.
3. Prepare a written informed consent form, and update it as needed.
4. Confirm the contents of the clinical study agreement.
5. Provide the sub-investigators, clinical research coordinators, and other study staff with sufficient information about the protocol, drugs, and each person's tasks, and give guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide explanation about the study in writing, and obtain written consent.
7. Assume responsibility for all medical judgments related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical treatment will be provided to subjects for all clinically significant adverse events related to the study, throughout and after the period of the subject's participation in the study.
9. If a subject is being treated at any other medical institution or department, with agreement of the subject, notify the physician of the other medical institution or department of the subject's participation in the study, as well as completion/discontination of the study in writing, and document such records.
10. If expedited reporting of SAEs etc. is required, immediately notify the head of the study site and the sponsor in writing.
11. Determine the need for unblinding of emergency key code for a subject in case of emergency (only for double-blind studies).
12. Prepare correct and complete eCRFs, electronically sign them, and submit them to the sponsor.
13. Check and confirm the entries in the eCRFs completed by the sub-investigator or transcribed from source data by the clinical research coordinator, electronically sign them, and submit them to the sponsor.
14. Discuss any proposals from the sponsor, including protocol amendments.
15. Notify the head of the study site of the completion of the study in writing.

Appendix B Pregnancy and Contraception

Female subjects and their male partners

From signing informed consent, throughout the duration of the study and for 4 weeks after last dose of the study drug, female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use a method of contraception as described below.

In addition, they must be advised not to donate ova during this period.

* A woman of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least one year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Appropriate contraception are defined as the following methods;

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation: Combined pill.
- Intrauterine device (IUD).
- Intrauterine Contraceptive System (IUS)
- Bilateral tubal occlusion.
- Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success).
- True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose and 4 weeks after last dose.
- Male condom

Subjects will be provided with information on appropriate methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study and up to 4 weeks after last dose of the study drug.

During the course of the study, pregnancy tests (Urinary human chorionic gonadotropin) will be performed only for female subjects of childbearing potential and all subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:

- contraceptive requirements of the study

- assessment of subject compliance through questions such as
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in female subjects with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
  - Is there a chance you could be pregnant?

In addition to a negative pregnancy test (Urinary human chorionic gonadotropin) at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative pregnancy test prior to receiving any dose of study medication. In addition, subjects must also have a negative pregnancy test (Urinary human chorionic gonadotropin) for one day before receiving the investigational drug at Period 2.

Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the female subject agrees to the primary care physician (obstetrician and gynecologist) being informed, the investigator or sub-investigator should notify the primary care physician that she was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

If any subject is found to be pregnant during the study or up to 4 weeks after last dose of the study drug, all pregnancies will be followed up to final outcome and the outcome, including any premature termination, Investigator or sub-investigator must report to the sponsor using the pregnancy form under the agreement of the female subjects. An evaluation after the birth of the child will also be conducted.

Appendix C Time Windows for Study Procedures

For both Period 1 and Period 2

Test/Observation Item	Scheduled Time	Allowable Time Window
Screening examination [(a)]	Screening (Day -28 to Day -2)	Same as left
Physical examination	Day -1, Day 21	Between 24 hours before administration and just before dosing on Day 1
	24 and 72 hours postdose	±1 hour
Body weight	Day -1	Same as left
Vital signs	Day -1, Day 21	Same as left
	24 and 72 hours postdose	±1 hour
12−lead ECG	72 hours postdose	±1 hour
Laboratory tests	Day -1, Day 21	Same as left
	72 hours postdose	±1 hour [(b)]
Pharmacokinetic blood sampling	Predose on Day 1	Between rising and just before dosing on Day 1
	1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose	±5 minutes
	24, 36, 48, and 72 hours postdose	±10 minutes

Day -1 is defined as the day before the Period 1 study drug administration. Day 21 is defined as the day before the Period 2 study drug administration. Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2.

(a) Height, physical examination, body weight, vital signs, 12-lead ECG, laboratory test and blood collection for CYP2D6 genotyping

(b) For urinalysis, from the time of rising up to +1 hour of the scheduled time.

Appendix D Blood Volume Table

The total blood collection volume collected from each subject is shown below;

Sample Type	Sample Volume per each time (mL)	Number of Samples			Total Volume (mL)
		Screening period	Period 1	Period 2	
Laboratory tests					
Hematology	2	2	2	1	10
Serum chemistry	7	2	2	1	35
Immunology	10	1	0	0	10
CYP2D6 genotyping	5	1	0	0	5
PK assessment	4	0	14	14	112
Total volume					172 mL