CLINICAL STUDY PROTOCOL

A Single-center, Open-label, Randomized, Two-treatment, Two-period Crossover Trial to Investigate Bioequivalence Between Single Administration of ASC-01 (Aripiprazole/Sertraline Combination Drug) and Concomitant Single Administration of Aripiprazole and Sertraline and Food Effect on Pharmacokinetics of ASC-01 in Healthy Male Adults

NCT Number: NCT03342963
PRT NO.: 031-102-00214
Version Date: 23 October 2017 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

ASC-01

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Protocol No.: 031-102-00214

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	I
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event Contact	PV Operation Office, Pharmacovigilance Department, Otsuka Pharmaceutical Co., Ltd. Phone: 3-2-27, Otedori, Chuo-ku, Osaka 541-0021 Email: IRE_031-102-00214@otsuka.jp
Release Date:	23 Oct 2017
Version No.:	1.0

Synopsis

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<tr><td colspan="2">Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.
Name of Investigational Medicinal Product: ASC-01 (Aripiprazole/Sertraline Combination Drug)</td><td>Protocol No.: 031-102-00214</td></tr>
<tr><td>Protocol Title:</td><td colspan="2">A Single-center, Open-label, Randomized, Two-treatment, Two-period Crossover Trial to Investigate Bioequivalence Between Single Administration of ASC-01 (Aripiprazole/Sertraline Combination Drug) and Concomitant Single Administration of Aripiprazole and Sertraline and Food Effect on Pharmacokinetics of ASC-01 in Healthy Male Adults</td></tr>
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<tr><td>Indication:</td><td colspan="2">Depression/depressed state (Administration should be limited to patients who showed an inadequate response to existing antidepressant therapy)</td></tr>
<tr><td>Objectives:</td><td colspan="2">[Cohort 1: Bioequivalence] To investigate bioequivalence for aripiprazole between administration of one ASC-01 tablet and concomitant administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets
[Cohort 2: Food effect] To investigate the effect of food on the plasma pharmacokinetics of aripiprazole and sertraline following single oral administration of ASC-01 under a fasting or fed condition</td></tr>
<tr><td>Trial Design:</td><td colspan="2">A single-center, open-label, randomized, two-treatment, two-period crossover trial will be conducted in two cohorts.
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<tr><td>Concomitant administration (B-1)</td><td>Concomitant single administration of aripiprazole and sertraline</td><td>Single administration of ASC-01</td></tr>
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<tr><td>Group receiving the following administration first</td><td>Period I</td><td>Period II</td></tr>
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</table>
Note) There will be a wash-out period of at least 35 days between each period.</td></tr>
</table>

Trial Population:	Fifty-four and 20 healthy male adult subjects aged 20 to 40 years, inclusive, will be enrolled in Cohort 1 (bioequivalence) and Cohort 2 (food effect), respectively.
Key Inclusion/Exclusion Criteria:	[Common to both cohorts] Inclusion Criteria 1) Healthy male subjects aged 20 to 40 years, inclusive, at time of informed consent 2) Subjects with a body mass index (BMI = body weight [kg]/height [m]^2) of ≥18.5 and <25.0 kg/m^2 at screening 3) Subjects capable of providing written, informed consent prior to initiation of any trial-related procedures, and, in the opinion of the investigator or subinvestigator, of complying with all requirements of the trial Key Exclusion Criteria 1) Subjects who have clinically significant abnormal medical history or abnormalities in physical findings at screening that in the investigator's or subinvestigator's opinion or in the sponsor's opinion may place the subject at risk or interfere with outcome variables, including drug absorption, distribution, metabolism, and excretion 2) Subjects who have a supine blood pressure of >140/90 mmHg or <100/50 mmHg after ≥3 minutes of rest and an orthostatic blood pressure decline (difference between sitting and standing systolic blood pressure) of ≥20 mmHg at screening (the sponsor may accept such subjects exceptionally only if the findings are considered clinically insignificant) 3) Subjects who have a supine pulse rate outside the range of 40 to 90 bpm after ≥3 minutes of rest at screening (the sponsor may accept such subjects exceptionally only if the findings are considered clinically insignificant) 4) Subjects who have a history or complication of hepatitis or acquired immunodeficiency syndrome or who have tested positive for hepatitis B surface antigen, hepatitis C virus antibody, or HIV antigen or antibody 5) Subjects who are judged by the investigator or subinvestigator to be ineligible to participate in the trial due to a history of serious psychiatric

disease

6) Subjects who have a history of clinically significant drug or alcohol abuse prior to screening examination
7) Subjects who test positive in a breath alcohol test or a urine drug test for substance abuse performed at the visit for screening examination or hospitalization at the trial site
8) Subjects who are sexually active and who are unable or unwilling to practice two kinds of contraception or remain abstinent during the trial and for 30 days after final investigational medicinal product (IMP) administration or who plan to provide sperm during the period from the visit for screening examination until 30 days after final IMP administration
9) Subjects who have a history of significant drug allergy
10) Subjects who have a history of significant bleeding or hemorrhagic diathesis
11) Subjects who have provided >200 mL of blood or >600 mL of plasma within 30 days prior to the first IMP administration
12) Subjects who have undergone blood collection (blood donation, etc.) of >1200 mL in total within 1 year prior to the first IMP administration
13) Subjects who have difficulty with blood collection
14) Subjects who have received any IMP within 120 days prior to the first IMP administration
15) Subjects who have smoked or been routinely exposed to secondhand smoke within 2 months prior to screening or who tested positive in urine cotinine test performed at the visit for screening or hospitalization at the trial site
16) Subjects who have consumed food or drink containing St. John's Wort within 14 days prior to IMP administration in each treatment period or who have consumed grapefruit, Seville orange, star fruit, or any food or drink containing these items within 7 days prior to IMP administration in each treatment period. Subjects who have consumed alcohol within 3 days prior to IMP administration in each treatment period
17) Subjects who have taken any prescription or nonprescription medicines, Chinese medicines, or vitamins within 14 days or any antibiotics within 30 days prior to the first IMP administration

18) Subjects who have undergone major gastrointestinal surgery (other than an appendectomy)
19) Subjects who have been occupationally exposed to an insecticide or organic solvent within 30 days prior to screening
20) Subjects who have a family history of long QT syndrome
21) Subjects who are visiting another hospital or department or who plan to visit another hospital or department during the trial period
22) Subjects with no fixed address
23) Subjects determined by the investigator or subinvestigator to be inappropriate for participation in this trial

Trial Site: Fukuoka Mirai Hospital

Investigational Medicinal Products, Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

[IMP: ASC-01 Combination Tablets]

Cohort	Active Ingredient (Content Per Tablet)	Single Dose	Dose Regimen
1	Aripiprazole 3 mg/sertraline 100 mg	1 tablet	To be administered with approximately 150 mL of water after subjects have fasted for at least 10 hours. (Single oral administration under a fasting condition)
2			To be administered with approximately 150 mL of water either after subjects have fasted for at least 10 hours or at 30 minutes after the start of breakfast (Single oral administration under a fasting or fed condition)

[Reference formulation, etc: Aripiprazole tablets, sertraline tablets]

Cohort	Active Ingredient (Content Per Tablet)	Single Dose	Dose Regimen
1	Aripiprazole 3-mg tablet	1 tablet	To be administered with approximately 150 mL of water after subjects have fasted for at least 10 hours (single oral administration under a fasting condition)
	Sertraline 50-mg tablet	Two tablets	

Test Items:	[Common to both cohorts] Pharmacokinetics: Blood collection for plasma drug concentration measurement Safety: Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and temperature), 12-lead electrocardiography, body weight, Columbia-Suicide Severity Rating Scale (C-SSRS), and concomitant medications and therapies Screening and others: Medical history, drug history, breath alcohol test, urine drug test, immunological test, etc.
Endpoints:	Primary: [Cohort 1: Bioequivalence] C_{max} and AUC_{168h} of aripiprazole [Cohort 2: Food effect] C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline Secondary: [Cohort 1: Bioequivalence] 1) Plasma concentration of aripiprazole 2) Pharmacokinetic parameters of aripiprazole 3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, MRT_∞, and λ_z of aripiprazole following administration of ASC-01 to those following concomitant administration of aripiprazole and sertraline, and difference in the t_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline (t_{max} for ASC-01 administration minus t_{max} for concomitant administration) [Cohort 2: Food effect] 1) Plasma concentrations of aripiprazole and sertraline 2) Pharmacokinetic parameters of aripiprazole and sertraline 3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, and CL/F of aripiprazole and sertraline for administration under a fed condition to those for administration under a fasting condition, and difference in the t_{max} of aripiprazole and sertraline between administration under a fed condition and administration under a fasting condition (t_{max} for a fasting condition minus t_{max} for a fed condition) Safety (common to both cohorts) Adverse events, clinical laboratory tests, physical examination, vital signs

	(blood pressure, pulse rate, and temperature), 12-lead electrocardiography, body weight, and C-SSRS
Statistical Methods:	Statistical Methods for Primary Endpoints In Cohort 1 (bioequivalence), analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max} and AUC_{168h} of aripiprazole-using group (group receiving administration of ASC-01 first or group receiving concomitant administration of aripiprazole and sertraline first), treatment (ASC-01 or concomitant administration of aripiprazole and sertraline), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max} and AUC_{168h} of aripiprazole between ASC-01 administration and concomitant administration of aripiprazole and sertraline will be calculated. If the 90% confidence intervals are within the range of ln(0.8) to ln(1.25), single administration of ASC-01 and single concomitant administration of aripiprazole and sertraline will be judged to be bioequivalent for aripiprazole. If an add-on subject study is conducted, bioequivalence will be assessed based on the combined results of the trial and the add-on subject study using the same criteria. In Cohort 2 (food effect), analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline using group (group receiving ASC-01 under a fasting condition first or group receiving ASC-01 under a fed condition first), treatment (administration under a fasting condition or under a fed condition), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline between administration under a fasting condition and administration under a fed condition will be obtained. If there are any subjects in each cohort from whom evaluable parameters cannot be obtained in both Periods I and II, sensitivity analysis including those subjects will also be performed. Rationale for the Target Sample Size For Cohort 1 (bioequivalence), the sample size was determined by the method of Diletti as the number of subjects required for the 90% confidence intervals for the differences in the log-converted mean C_{max} and AUC_{168h} of aripiprazole between single administration of ASC-01 and concomitant single administration of aripiprazole and sertraline to be within the acceptable range

	for bioequivalence of ln(0.8) to ln(1.25) based on the Guideline for Bioequivalence Studies of Generic Products. In the results of a pharmacokinetic trial conducted to examine the bioavailability of ASC-01 (031-11-004), the ratios of the geometric mean C_{max} and AUC_{168h} of aripiprazole were respectively 1.12 and 1.05 and the within-subject variances were 0.029 and 0.006. The proportion of subjects excluded from the pharmacokinetic analysis due to vomiting or withdrawal was approximately 40%. Assuming the ratio of the geometric mean C_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline and the within-subject variance to be, respectively, 1.1 and 0.029, the number of subjects required to ensure a statistical power of 90% or higher is 16 per group (32 subjects in total). Assuming a 40% rate of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 1 is set at 27 subjects per group (54 subjects in total). For Cohort 2 (food effect), referring to FDA guidance, the sample size required for the analysis of food effect on the pharmacokinetics of ASC-01 is 6 subjects per group (12 subjects in total). In consideration of the possibility of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 2 is set at 10 subjects per group (20 subjects in total).
Trial Duration:	Trial Duration: November 2017 to July 2018 Duration of trial participation for each subject: Up to 64 days with a wash-out period of 35 days ([Common to both cohorts] Screening [21 to 2 days before the start of administration], 8 days in Period I [5 days of hospitalization followed by 2 outpatient visits], 35 days or longer wash-out period, 8 days in Period II [5 days of hospitalization followed by 2 outpatient visits])

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Abbreviations	Definitions
5-HT_{1A}	5-hydroxytryptamine 1A
5-HT_{2A}	5-hydroxytryptamine 2A
AE	Adverse event
AUC_{168h}	Area under the concentration-time curve from 0 to 168 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum (peak) plasma concentration of the drug
CYP	Cytochrome P450
C-SSRS	Columbia-suicide severity rating scale
FDA	Food and Drug Administration
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRE	Immediately reportable event
MRT_{∞}	Mean residence time from time 0 to infinity
PQC	Product quality complaint
λ_z	Terminal elimination rate constant
SNRI	Serotonin-noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
$t_{1/2,z}$	Terminal-phase elimination half-life
t_{max}	Time to maximum (peak) plasma concentration

1 Introduction

ASC-01 is a combination drug of aripiprazole and sertraline.

Aripiprazole, an antipsychotic drug developed by Otsuka Pharmaceutical Co., Ltd., is primarily pharmacologically characterized by dopamine D_2 receptor partial agonist action; additionally, it induces serotonin 5-HT_{1A} receptor partial agonist action and serotonin 5-HT_{2A} receptor antagonist action. Aripiprazole was approved for the treatment of schizophrenia in the United States in 2002 and has been widely used in the European Union and Asian countries including Japan, etc.[1] As for depression/depressed state, the first approval for the indication of "Adjunctive Treatment of Major Depressive Disorder" was obtained in November 2007 in the United States,[2] and the approval for the indication of "depression, depressed state (Administration should be limited to patients who showed an inadequate response to existing antidepressant therapy)" was obtained in June 2013 in Japan.

Sertraline has been marketed in Japan for the treatment of "depression/depressive state" and "panic disorder" since July 2006.[3] It has been approved in 110 countries around the world and used for more than 10 years.[4] Moreover, relative to other selective serotonin reuptake inhibitors (SSRIs), sertraline is characterized by a low risk of drug interactions due to its limited effect on hepatic metabolic enzymes (CYPs).[5]

The first-line treatment for MDD is the use of antidepressants. The drugs mainly used are SSRIs, such as paroxetine, fluvoxamine, sertraline, and escitalopram, and SNRIs, such as milnacipran, duloxetine, and venlafaxine. However, remission rates with SSRIs and SNRIs are only 30% to 40%.[6] Unless remission is achieved, social dysfunction continues and causes problems, such as unemployment, school dropout, or divorce.[7]

When response to a first-line drug is inadequate, various guidelines recommend the combination of the first-line drug and an atypical antipsychotic as the next treatment options.[8,9,10] The Japanese Society of Mood Disorders Treatment Guideline lists aripiprazole, quetiapine, olanzapine, and risperidone as atypical antipsychotics to be used in combination with first-line antidepressant augmentation therapy; however, in Japan only aripiprazole is approved as a therapeutic drug for "depression/depressive state."

For patients in whom the combination of a first-line drug and an atypical antipsychotic to be used, a combination drug of aripiprazole and a first-line drug would require fewer number of tablets to be taken than concomitant administration, providing increased convenience for patients, and it was therefore decided to develop this combination drug. Although this combination drug is not intended for patients with central disease, it has

been reported that a decrease in the number of tablets to be taken can be expected to improve medication adherence.[11,12]

1.1 Nonclinical Studies

Detailed information on relevant data from nonclinical studies with aripiprazole and sertraline, including pharmacokinetic and toxicity studies in animals, is presented in the Investigator's Brochure.

1.2 Clinical Studies

In a clinical pharmacology trial in which pharmacokinetics after single administration of ASC-01 tablet (aripiprazole 3 mg/sertraline 100 mg combination) and single concomitant administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets was investigated in healthy male adults (031-11-004), the pharmacokinetics of aripiprazole and sertraline after administration of ASC-01 and that after concomitant administration of aripiprazole and sertraline were similar, with no major safety issues identified.

In a double-blind trial in patients with major depressive disorder (031-12-005), ASC-01 showed a statistically significant improvement in the mean change in MADRS total score, the primary endpoint, compared with sertraline, indicating its efficacy in patients with major depressive disorder who had an inadequate response to sertraline monotherapy. The results of the secondary and other endpoints also supported the efficacy of ASC-01.

Most adverse events in the ASC-01 group were mild or moderate in severity. The incidence of serious adverse events and adverse events leading to discontinuation of the study drug was not significantly different between the ASC-01 group and the sertraline group. For other safety endpoints, there were no safety concerns in the ASC-01 group compared with the sertraline group. There were no notable safety issues and ASC-01 treatment was well tolerated.

The results of this study suggested that ASC-01 is useful for patients with major depressive disorder who have had an inadequate response to sertraline monotherapy.

1.3 Risks and Benefits

In a pharmacokinetic trial to investigate the bioavailability of ASC-01 in healthy male adults (031-11-004), gastrointestinal disorders were observed in half of the subjects after administration of ASC-01 and after concomitant administration of aripiprazole and sertraline. These include nausea (48.0%, 12/25), vomiting (32.0%, 8/25), and diarrhoea (4.0%, 1/25) after administration of ASC-01 and nausea (50.0%, 13/26) and vomiting (30.8%, 8/26) after concomitant administration of aripiprazole and sertraline. In addition

to the frequent gastrointestinal adverse events described above, other adverse events occurring in two or more subjects in either administration group were decreased appetite (12.0%, 3/25) and dizziness (8.0%, 2/25) after administration of ASC-01 and decreased appetite (7.7%, 2/26) after concomitant administration of aripiprazole and sertraline, and all of which were consistent with adverse drug reactions reported for commercially available aripiprazole and sertraline.

Among the adverse events occurring at an incidence of ≥5% in the ASC-01 group in the double-blind trial in patients with major depressive disorder (031-12-005), akathisia was the only one that occurred at an incidence of ≥2 times the incidence in the sertraline group. The incidence was 12.9% (27/209) in the ASC-01 group and 3.4% (7/203) in the sertraline group.

Detailed information on ASC-01, including the risks and adverse reactions, is presented in the Investigator's Brochure.

Since this trial was conducted in healthy subjects, there is no benefit to subjects from participation in the trial.

2 Appropriateness and Objectives of the Trial

2.1 Trial Rationale

2.1.1 Bioequivalence (Cohort 1)

Clinical development of ASC-01 was begun in order to provide a treatment option for patients with major depressive disorder who do not respond completely to sertraline monotherapy and to contribute to improved convenience with an expected increase in compliance by reducing the number of tablets that patients are required to take. A pharmacokinetic trial (031-11-004) was conducted as a bioavailability trial to confirm the appropriateness of this combination drug formulation by comparing pharmacokinetics between single administration of ASC-01 and concomitant single administration of aripiprazole and sertraline in healthy male adults.

Results showed the pharmacokinetic parameters of both aripiprazole and sertraline to be similar between administration of ASC-01 and concomitant administration of the two drugs. Furthermore, the results for sertraline met the bioequivalence criteria specified in “Partial Revisions of the Guideline for Bioequivalence Studies of Generic Products” (Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau, dated 29 Feb 2012)[13] (hereinafter referred to as the BE Guideline).

In view of circumstances that ASC-01 will be interchangeably used with concomitant administration of aripiprazole tablet and sertraline tablet in the clinical setting, it was

considered that the bioequivalence of aripiprazole should also be evaluated in accordance with the BE Guideline.

This trial is designed in accordance with the BE Guideline to investigate bioequivalence between single oral administration of one ASC-01 tablet and concomitant single oral administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets in a crossover manner in healthy male adults.

Bioequivalence will be evaluated only for aripiprazole.

2.1.2 Food Effect (Cohort 2)

As "Clinical Pharmacokinetic Studies on Drugs" (Notification No. 796 of the Evaluation and Licensing Division, PMSB, dated 01 Jun 2001) and "Methods of Studying Drug Interactions" (Notification No. 813 of the Evaluation and Licensing Division, PMSB, dated June 4, 2001) state that it is necessary to examine the effect of food on gastrointestinal absorption using the final formulation for any oral formulation, it was decided to further conduct a food effect trial for ASC-01.

Since no guidelines for the method of studying food effect have been issued in Japan, the guidance for food effect studies issued by the FDA ("Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies")[14] and "Methods of Studying Drug Interactions" were used as references, and to reduce the effect of variation among trial subjects, a crossover method was selected from among the trial designs presented in those documents.

2.2 Dosing Rationale and Regimen

2.2.1 Dose Regimen

[Cohort 1]

As the BE Guideline states that drugs are usually given to subjects with 100 to 200 mL water (normally 150 mL) after fasting for more than 10 hours, the investigational medicinal product (IMP) will be administered with approximately 150 mL of water after subjects have fasted for at least 10 hours.

[Cohort 2]

For administration under a fasting condition, the IMP will be administered after subjects have fasted for at least 10 hours as per the dose regimen in the BE Guideline as above. For administration under a fed condition, the IMP will be administered with approximately 150 mL of water at 30 minutes after the start of breakfast in reference to the FDA Guidance.[14]

2.2.2 Dosage

[Cohort 1]

The BE Guideline states that one dose unit or a clinical usual dose should generally be employed.

One dose unit of aripiprazole in the currently approved dosage and administration for depression/depressed condition is 3 mg, and the dose should not exceed 15 mg per day. As the maximum dose for healthy adults was set at 6 mg due to clinical symptoms such as sleepiness and dizziness being experienced by some subjects in a phase 1 single-dose trial conducted prior to the first new drug application in Japan, and in view of the safety information obtained in bioequivalence trials, for the present trial it was decided to use 3-mg aripiprazole, at which aripiprazole does not induce major effects on subjects, taking the following into consideration:

In clinical pharmacology trials of aripiprazole conducted in healthy adult subjects, 7 doses (0.25, 0.5, 1, 2, 3, 4, and 6 mg) were administered in a cumulative total of 319 subjects (the cumulative total was obtained by counting subjects separately once for each dose or each period [Period I or II]; overall, 187 subjects participated in the trials). Although no subjects experienced vomiting (as an adverse drug reaction) at doses of 0.25 to 2 mg, 1.73% (3/173) of subjects experienced vomiting at 3 mg. At 4 and 6 mg, the incidence of vomiting was 5.26% (3/57) and 6.56% (4/61), respectively, indicating a tendency for the incidence to increase as the dose increased.[15] As it may not be possible to evaluate normal absorption of the IMP in subjects experiencing vomiting, considering the purpose of the present trial, it was concluded that a dose with a low incidence of vomiting is preferable.

Regarding sertraline, one dose unit for the approved dosage regimen is 25 to 100 mg. No specifically significant symptoms were observed in single-dose trials conducted in Japan for sertraline administered at 50, 100, and 200 mg in healthy adult subjects.[16]

The Japanese Society of Mood Disorders Treatment Guideline states that an augmentation therapy should be started if patients with moderate/severe depression show an incomplete response to the first-line monotherapy at a sufficient dose and treatment duration, which should be employed to prevent apparently refractory cases due to insufficient dose and treatment duration. As the target patients for ASC-01 are expected to be patients with depression/depressive state who show an incomplete response to sertraline therapy at a sufficient dose and treatment duration, the dose of sertraline used in the combination drug was set at 100 mg.

Based on the above, subjects will receive either single administration of one tablet of ASC-01 (aripiprazole 3 mg/sertraline 100 mg combination drug) or concomitant single administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets.

[Cohort 2]

For the same reasons as in Cohort 1, subjects will receive single administration of one tablet of ASC-01 (aripiprazole, 3 mg/sertraline, 100 mg combination drug).

2.3 Trial Objectives

2.3.1 Cohort 1

To investigate bioequivalence for aripiprazole between administration of one ASC-01 tablet and concomitant administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets

2.3.2 Cohort 2

To investigate the effect of food on the plasma pharmacokinetics of aripiprazole and sertraline following single oral administration of ASC-01 under a fasting or fed condition

3 Trial Design

3.1 Type/Design of Trial

This is a single-center, open-label, randomized, two-treatment, two-period crossover trial in healthy male adults conducted using 2 cohorts to investigate bioequivalence for aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline and the effect of food on the pharmacokinetics of ASC-01.

The trial design is outlined in Figure 3.1-1.

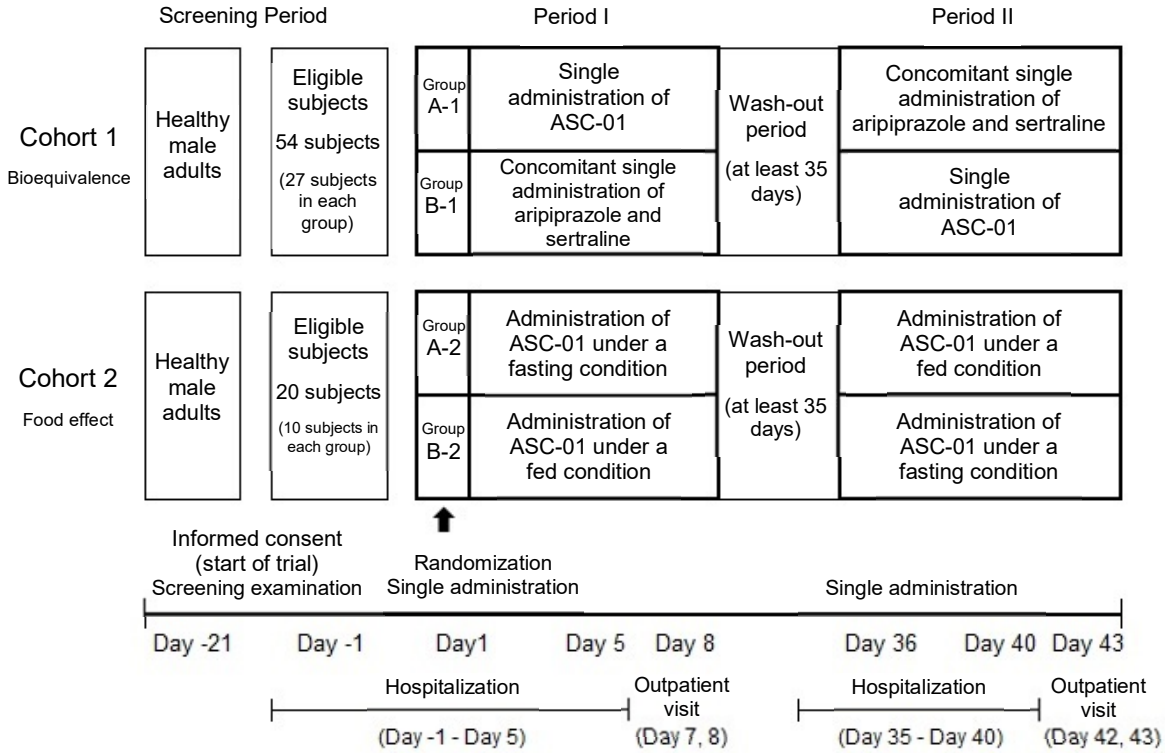

Figure 3.1-1 Trial Design Schematic

There will be a wash-out period of at least 35 days between IMP administration in Periods I and II. The number of days with a wash-out period of 35 days is shown.
Group A-1, group receiving administration of ASC-01 first; Group B-1, group receiving concomitant administration of aripiprazole and sertraline first; Group A-2, group receiving administration of ASC-01 under a fasting condition first; and Group B-2, group receiving administration of ASC-01 under a fed condition first

3.1.1 Cohort 1

A total of 54 healthy male adults will be randomized: 27 subjects into a group receiving administration of ASC-01 first (Group A-1) and 27 subjects into a group receiving concomitant administration of aripiprazole and sertraline first (Group B-1). On the respective administration days in Periods I and II, the IMP will be orally administered once after subjects have fasted for at least 10 hours. Subjects receiving ASC-01 in Period I will receive concomitant administration of aripiprazole and sertraline in Period II, and subjects receiving concomitant administration of aripiprazole and sertraline in Period I will receive ASC-01 in Period II. The plasma concentration of aripiprazole will be measured in each treatment period to examine pharmacokinetics.

The trial is designed in accordance with the BE Guideline. Furthermore, the results in the trial will be handled in accordance with the BE Guideline.

Group	Period I		Period II
Group A-1 Group receiving administration of ASC-01 first	Single administration of ASC-01	Wash-out period[a]	Concomitant single administration of aripiprazole and sertraline
Group B-1 Group receiving concomitant administration of aripiprazole and sertraline first	Concomitant single administration of aripiprazole and sertraline		Single administration of ASC-01

[a]: There will be a wash-out period of at least 35 days between IMP administration in Periods I and II.

3.1.2 Cohort 2

A total of 20 healthy male adults will be randomized: 10 subjects into a group receiving administration of ASC-01 under a fasting condition first (Group A-2) and 10 subjects into a group receiving administration of ASC-01 under a fed condition first (Group B-2). On the respective administration days in Periods I and II, the IMP will be orally administered once after subjects have fasted for at least 10 hours (for administration under a fasting condition) or at 30 minutes after the start of breakfast (for administration under a fed condition). Subjects receiving administration under a fasting condition in Period I will receive administration under a fed condition in Period II, and subjects receiving administration under a fed condition in Period I will receive administration under a fasting condition in Period II. The plasma concentrations of aripiprazole and sertraline will be measured in each treatment period to examine pharmacokinetics.

Group	Period I		Period II
Group A-2 Group receiving ASC-01 under a fasting condition first	Administration under a fasting condition	Wash-out period[a]	Administration under a fed condition
Group B-2 Group receiving ASC-01 under a fed condition first	Administration under a fed condition		Administration under a fasting condition

[a]: There will be a wash-out period of at least 35 days between IMP administration in Periods I and II.

3.2 Method of Administration

3.2.1 Cohort 1

3.2.1.1 ASC-01 Tablets

One tablet of ASC-01 (3-mg aripiprazole/100-mg sertraline combination drug) will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.1.2 Aripiprazole Tablets and Sertraline Tablets

One aripiprazole 3-mg tablet and two sertraline 50-mg tablets will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.2 Cohort 2

3.2.2.1 Administration under a fasting condition

One tablet of ASC-01 will be administered once with approximately 150 mL of water after subjects have fasted for at least 10 hours.

3.2.2.2 Administration under a fed condition

One tablet of ASC-01 will be administered once with approximately 150 mL of water at 30 minutes after the start of breakfast.

[Rationale for the duration of treatment]

As the BE Guideline states that in principle, bioequivalence studies should be performed by single-dose studies, a single dose will be administered in the present trial.

3.3 Trial Population

3.3.1 Number of Subjects and Population

Fifty-four healthy male adults aged 20 to 40 years, inclusive, will be enrolled in Cohort 1 and 20 in Cohort 2.

A few reserve subjects may be allowed to stand by until completion of IMP administration in Period I. If a subject to be treated withdraws consent or the investigator or subinvestigator determines that the subject should not be administered the IMP, the subject will be replaced with a reserve subject. Subjects who are withdrawn from the trial after randomization will not be replaced.

3.3.2 Issuance of Subject Identification Number

Subject number (S + in-site serial number [5-digit]) will be assigned at the trial site in the order of consent from 00001 at the time of written consent. At randomization, subjects assigned to Cohort 1 (bioequivalence trial) will be assigned a site number of 101 and subjects assigned to Cohort 2 will be assigned a site number of 201. The [site number (3 digits) + subject number] will be the subject identification number (ID). The trial site will prepare and store a list of all subjects who have given informed consent and their subject IDs.

3.4 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor subinvestigator, nor by the medical advisor.

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects. Consent will be documented by signing the informed consent form. The informed consent form (ICF) will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines[17], and local regulatory requirements.

Investigators or subinvestigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or subinvestigator, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or subinvestigator). If a trial associate has provided a supplemental explanation, the trial associate will also sign and date the consent form. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects,

so that they can make a knowledgeable and voluntary decision on continued trial participation after obtaining sufficient information.

3.4.2 Inclusion Criteria

Subjects must meet all of the inclusion criteria listed in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria (Common to Both Cohorts)	
1	Healthy male subjects aged 20 to 40 years, inclusive, at time of informed consent
2	Subjects with a body mass index (BMI = body weight [kg]/height [m]^2) of ≥18.5 and <25.0 kg/m^2 at screening
3	Subjects capable of providing written, informed consent prior to initiation of any trial-related procedures, and in the opinion of the investigator or subinvestigator, of complying with all requirements of the trial

[Rationale for inclusion criteria]

1. The lower age limit is set at the age at which subjects as legal adults are capable of taking responsibility for providing informed consent, whereas the upper age limit is set at 40 years, considering concerns for the possibility of subjects having a disease or metabolic ability different from younger subjects, in reference to the Guideline for Bioequivalence issued by the American Pharmacists Association. Male subjects are specified in order to avoid the need to consider the possibility of pregnancy.
2. Specified to avoid a possible influence on pharmacokinetics.
3. Specified to ensure that subjects are capable of providing consent and to make it possible for the investigator or subinvestigator to assess whether subjects are capable of observing the protocol.

3.4.3 Exclusion Criteria

Subjects who meet any of the exclusion criteria listed in Table 3.4.3-1 will be excluded.

Table 3.4.3-1 Exclusion Criteria (Common to Both Cohorts)	
1	Subjects who have clinically significant abnormal medical history or abnormalities in physical findings at screening that in the investigator's or subinvestigator's opinion or in the sponsor's opinion may place the subject at risk or interfere with outcome variables, including drug absorption, distribution, metabolism, and excretion. These abnormalities may include, but are not limited to, cardiac, hepatic, renal, neurological, endocrine, gastrointestinal, respiratory, hematological, and immunological diseases/disorders (complications or medical history).
2	Subjects who have a supine blood pressure of >140/90 mmHg or <100/50 mmHg after ≥3 minutes of rest and an orthostatic blood pressure decline (difference between sitting and standing systolic blood pressure) of ≥20 mmHg at screening. The sponsor may accept such subjects exceptionally only if the findings are considered clinically insignificant.
3	Subjects who have a supine pulse rate outside the range of 40 to 90 bpm after ≥3 minutes of rest at screening. The sponsor may accept such subjects exceptionally only if the findings are considered clinically insignificant.
4	Subjects who have a history or complication of hepatitis or acquired immunodeficiency syndrome or who have tested positive for hepatitis B surface antigen, hepatitis C virus antibody, or HIV antigen or antibody
5	Subjects who are judged by the investigator or subinvestigator to be ineligible to participate in the trial due to a history of serious psychiatric disease
6	Subjects who have a history of clinically significant drug or alcohol abuse prior to screening examination
7	Subjects who test positive in a breath alcohol test or a urine drug test for substance abuse performed at the visit for screening examination or hospitalization at the trial site
8	Subjects who are sexually active and who are unable or unwilling to practice two kinds of contraception or remain abstinent during the trial and for 30 days after final IMP administration. If contraception is used, two of the following methods must be used: vasectomy, tubal ligation, intrauterine device, oral contraceptive pill, condom with spermicide, and occlusive cap with spermicide (diaphragm or cervical cap). Subjects who plan to provide sperm during the period from the visit for screening examination until 30 days after final IMP administration
9	Subjects who have a history of significant drug allergy
10	Subjects who have a history of significant bleeding or hemorrhagic diathesis

11	Subjects who have provided >200 mL of blood or >600 mL of plasma within 30 days prior to the first IMP administration
12	Subjects who have undergone blood collection (blood donation, etc.) of >1200 mL in total within 1 year prior to the first IMP administration
13	Subjects who have difficulty with blood collection
14	Subjects who have received any IMP within 120 days prior to the first IMP administration
15	Subjects who have smoked or been routinely exposed to secondhand smoke within 2 months prior to screening or who tested positive in urine cotinine test performed at the visit for screening or hospitalization at the trial site (urine cotinin concentration > 200 ng/mL)

Table 3.4.3-1 Exclusion Criteria (Common to Both Cohorts) (continued)	
16	Subjects who have consumed the following: • Subjects who have consumed food or drink containing St. John's Wort within 14 days prior to IMP administration in each treatment period • Subjects who have consumed grapefruit (including fruit juice), Seville orange (including fruit juice), star fruit, or any food or drink containing these items within 7 days prior to IMP administration in each treatment period • Subjects who have consumed alcohol within 3 days prior to IMP administration in each treatment period
17	Subjects who have taken any prescription or nonprescription medicines, Chinese medicines, or vitamins within 14 days or any antibiotics within 30 days prior to the first IMP administration. Such subjects may be exceptionally eligible if, in the sponsor's opinion, the medication is unlikely to affect pharmacokinetic results.
18	Subjects who have undergone major gastrointestinal surgery (other than an appendectomy)
19	Subjects who have been occupationally exposed to an insecticide or organic solvent within 30 days prior to screening
20	Subjects who have a family history of long QT syndrome
21	Subjects who are visiting another hospital or department or who plan to visit another hospital or department during the trial period
22	Subjects with no fixed address
23	Subjects determined by the investigator or subinvestigator to be inappropriate for participation in this trial

[Rationale for exclusion criteria]

1. Specified to confirm that subjects are healthy.

2 to 7. Specified because such subjects cannot be considered healthy.

8. Specified to ensure the safety of subjects and their partners.

9 to 14. Specified to ensure the safety of subjects.

15 to 17. Specified to avoid a possible influence on pharmacokinetics.

18 and 19. Specified to avoid a possible influence on pharmacokinetics due to exposure to substances considered to stimulate liver microsomal enzymes.

20 to 23. Specified to ensure the safety of subjects.

3.5 Endpoints

3.5.1 Cohort 1

3.5.1.1 Primary Endpoint

- C_{max} and AUC_{168h} of aripiprazole

3.5.1.2 Secondary Endpoints

1) Plasma concentration of aripiprazole
2) Pharmacokinetic parameters of aripiprazole
3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, MRT_∞, and λ_z of aripiprazole following administration of ASC-01 to those following concomitant administration of aripiprazole and sertraline and the difference in the t_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline (t_{max} for ASC-01 administration minus t_{max} for concomitant administration)

3.5.2 Cohort 2

3.5.2.1 Primary Endpoint

- C_{max}, AUCt, AUC_∞, and AUC_{168h} of aripiprazole and sertraline

3.5.2.2 Secondary Endpoints

1) Plasma concentrations of aripiprazole and sertraline
2) Pharmacokinetic parameters of aripiprazole and sertraline
3) Ratios of the C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, and CL/F of aripiprazole and sertraline for administration under a fed condition to those for administration under a fasting condition and the difference in the t_{max} of aripiprazole and sertraline between administration under a fed condition and administration under a fasting condition (t_{max} for a fasting condition minus t_{max} for a fed condition)

3.5.3 Safety (Common to Both Cohorts)

Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and temperature), 12-lead electrocardiography, body weight, and Columbia-Suicide Severity Rating Scale (C-SSRS)

3.6 Measures to Minimize/Avoid Bias

Since the primary endpoint of this trial is based on plasma drug concentrations, there will be no bias without blinding. The trial will therefore be conducted by an open-label, two-treatment, two-period crossover design. In Cohort 1, subjects will be randomly assigned according to the assignment table to two groups, ie, a group receiving administration of ASC-01 first (Group A-1) and a group receiving concomitant administration of one aripiprazole 3-mg tablet and two sertraline 50-mg tablets first (Group B-1). In Cohort 2, subjects will be randomly assigned according to the assignment table to two groups, ie, a group receiving administration of ASC-01 under a fasting condition first (Group A-2) and a group receiving administration of ASC-01 under a fed condition first (Group B-2).

3.7 Study Methods

The schedule of assessments is shown in Table 3.7-1.

Table 3.7-1 Schedule of Assessments (Common to Both Cohorts)

	Screening test[a]	Period I																Wash-out period[b]	Period II																Discontinuation[c]
	Outpatient visit	Hospitalization														Outpatient visit			Hospitalization												Outpatient visit			
(Day)	-21 to -2	-1	1										2	3	4	5	7	8		-1	1									2	3	4	5	7	8	
(h)			predose	0	1	2	3	4	5	6	8	12	24	48	72	96	144	168			predose	0	1	2	3	4	5	6	8	12	24	48	72	96	144	168	
Informed Consent	●																																		
Demographics	●																																		
Height	●																																		
Immunological Test	●																																		
Alcohol Test, Urine Drug and Cotinin Screen	●	●																		●															
Concomitant Medications/Therapies	←																		→																
Dosing				●																		●														
Blood Collection for Plasma Drug Concentration Measurement			●		●	●	●	●	●	●	●	●	●	●	●	●	●	●			●		●	●	●	●	●	●	●	●	●	●	●	●	●	
SAFETY																																			
Adverse Events	←																		→																
Clinical Laboratory Tests	●		●													●		●			●												●		●	●
Physical Examination	●		●													●		●			●												●		●	●
Vital Signs (blood pressure, pulse rate, and temperature)	●		●			●		●			●		●	●	●	●	●	●			●			●		●			●		●	●	●	●	●	●
12-lead Electrocardiography	●		●								●		●					●			●								●					●	●
Body Weight	●		●															●			●								●					●	●
C-SSRS	●		●													●	●	●			●												●	●	●	●

[a] After obtaining informed consent, each test will be performed between 21 and 2 days before the day of IMP administration in Period I.

[b] There will be a wash-out period of at least 35 days between IMP administration in Periods I and II.

[c] If a subject refuses to receive examinations at the time of discontinuation, or if the investigator or subinvestigator determines that examinations cannot be performed due to emergency, etc., only feasible observations/examinations among the specified examinations will be performed.

See Table 3.7-2 for the acceptable time windows for observations, examinations, and evaluations after IMP administration.

Table 3.7-2	**Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)**	
Item	Timing	Acceptable Time Window
Blood collection for plasma drug concentration measurement	1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours after the start of administration of IMP	3 minutes before and after each blood collection time
	144 and 168 hours after the start of administration of IMP	1 hour before and after each blood collection time
Confirmation of concomitant medications/therapies	Feasible time	
Adverse Events	Feasible time	
Clinical laboratory tests	96 and 168 hours after the start of administration of IMP	2 hours before and after examination time
Physical Examination	Feasible time on days 5 and 8	
Vital signs (blood pressure, pulse rate, and temperature)	2, 4, 8, 24, 48, 72, and 96 hours after the start of administration of IMP	Within 60 minutes before the time of measurement and before blood collection for pharmacokinetics
	144 and 168 hours after the start of administration of IMP	2 hours before and after examination time
12-lead electrocardiography	8 and 24 hours after the start of administration of IMP	Within 60 minutes before the time of measurement and before blood collection for pharmacokinetics
	168 hours after the start of administration of IMP	2 hours before and after examination time
Body weight	168 hours after the start of administration of IMP	2 hours before and after examination time
C-SSRS	96 hours after the start of administration of IMP	1 hour before and after examination time
	144 and 168 hours after the start of administration of IMP	2 hours before and after examination time

3.7.1 General Procedures During Hospitalization (Common to Both Cohorts)

Subjects will remain seated or in a supine position for 8 hours after IMP administration. However, another position may be used for a short period of time to perform the procedures specified in the protocol. When subjects go to the toilet within 8 hours after administration, it should be monitored and brief (<10 minutes). Subjects should be

monitored to use the toilet within 8 hours after oral administration so that they do not vomit and spit out their oral medication. Subjects may walk from 8 hours after administration; however, they must refrain from strenuous exercise.

3.7.2 Meal Requirements

3.7.2.1 Cohort 1

During hospitalization, subjects should take meals (standard meals) prepared at the trial site at around 9 AM (breakfast), 1 PM (lunch), and 7 PM (dinner), except breakfast on the day of IMP administration. However, food intake will be prohibited from 10 PM on the day before IMP administration to 4 hours after IMP administration because the IMP should be administered after fasting for at least 10 hours. If a meal time overlaps with an examination or blood collection, the meal will be given after the examination or blood collection.

Only meals and beverages provided by the trial site will be allowed during hospitalization. Drinking water will be prohibited for 2 hours before and after IMP administration except for the time of IMP administration. Outside the above period, subjects will basically be allowed to drink water ad libitum.

During hospitalization, meals other than breakfast prior to administration will be the same in Periods I and II, and only meals prepared at the trial site will be taken at predetermined times.

If breakfast is taken on the day of IMP administration, the time of starting breakfast will be recorded in the case report form (CRF).

3.7.2.2 Cohort 2

During hospitalization, subjects should take meals (standard meal, Melander meal) prepared at the trial site at around 9 AM (breakfast), 1 PM (lunch), and 7 PM (dinner) except breakfast on the day of IMP administration.

In case of administration under a fasting condition, food intake will be prohibited from 10 PM on the day before IMP administration to 4 hours after IMP administration. In case of administration under a fed condition, the standard meal provided by the trial site will be used as the breakfast before administration, and the meal will be taken within 30 minutes. If a meal time overlaps with an examination or blood collection, the meal will be given after the examination or blood collection.

Only meals and beverages provided by the trial site will be allowed during hospitalization. Drinking water will be prohibited for 2 hours before and after IMP

administration except for the time of IMP administration. Outside the above period, subjects will basically be allowed to drink water ad libitum.

During hospitalization, meals other than breakfast prior to administration will be the same in Periods I and II, and only meals prepared at the trial site will be taken at predetermined times.

If breakfast is taken on the day of IMP administration, the time of starting breakfast will be recorded in the CRF.

3.7.3 Schedule of Assessments

3.7.3.1 Screening Examination (Common to Both Cohorts)

After obtaining the consent, the following observations, examinations, and evaluations will be performed as screening within 21 days before hospitalization in Period I (Day –21 to Day –2) to determine eligibility for the study. The results of eligibility check will be recorded in the source documents and CRF.

[Examination/investigation items]

- Demographic data (date of birth, sex, race, ethnicity, drinking habit, and medical history)
- Height, body weight, and BMI (Height will be measured in 0.1 cm increments. When measurement is performed to two or more decimal places, the value will be rounded to one decimal place. BMI will be calculated based on height and body weight at screening using the following formula: BMI = body weight [kg]/height $[m]^2$.)
- Immunological tests (HBs antigen, HCV antibody, and HIV antigen/antibody tests)
- Breath alcohol test, urine drug test, and urine cotinine test (the test will be performed according to the procedure specified by the trial site)
- Confirmation of concomitant medications and therapies
- Adverse event assessment
- Clinical laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, and temperature)
- 12-lead electrocardiography
- C-SSRS (to be performed using Appendix 2 "Baseline Assessment Version.")

3.7.3.2 Hospitalization (day before investigational medicinal product administration in each period, common to both cohorts)

Subjects to be treated and reserve subjects will visit the trial site on the day before IMP administration (Day –1) in each period to confirm their intention to participate in the trial

again. The following observations, examinations, and evaluations will be performed to confirm the eligibility of subjects, and subjects will be hospitalized. Subjects will take dinner and fast from around 10 PM. Subjects who completed Period I without discontinuation will proceed to the next period.

- Breath alcohol test, urine drug test, and urine cotinine test (the test will be performed according to the procedure specified by the trial site)
- Confirmation of concomitant medications and therapies
- Adverse event assessment

3.7.3.3 Day of Investigational Medicinal Product Administration (Day 1 of Each Period)

3.7.3.3.1 Enrollment of Subjects and Assignment of Investigational Medicinal Product to Subjects (Period I Only, Common to Both Cohorts)

IMP will be assigned by cohort. Before administration on Day 1 in Period I, eligible subjects will be randomly assigned to each treatment group according to the assignment table. If a subject to be treated withdraws consent or is determined not to be able to receive IMP prior to randomization, a new subject will replace the dropout subject to receive IMP.

Subjects who are not randomized will be discharged from the trial site.

Subjects who are withdrawn from the trial after randomization will not be replaced.

3.7.3.3.2 Within 3 Hours Before Investigational Medicinal Product Administration (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed.

- Blood collection for plasma drug concentration measurement
- Adverse event assessment
- Clinical laboratory tests (samples for chemistry, hematology, and urinalysis will be collected.)
- Physical examination
- Vital signs (blood pressure, pulse rate, and temperature)
- 12-lead electrocardiography
- Body weight
- C-SSRS (to be performed using Appendix 2 "Baseline Assessment Version.")
- Confirmation of concomitant medications and therapies

3.7.3.3.3 Investigational Medicinal Product Administration

3.7.3.3.3.1 Cohort 1

Subjects assigned to the group receiving administration of ASC-01 first (Group A-1) will take one tablet of ASC-01 with approximately 150 mL of water after fasting for at least 10 hours in Period I and one aripiprazole 3-mg tablet and two sertraline 50-mg tablets with approximately 150 mL of water after fasting for at least 10 hours in Period II.

Subjects assigned to the group receiving concomitant administration of aripiprazole and sertraline first (Group B-1) will take one aripiprazole 3-mg tablet and two sertraline 50-mg tablets with approximately 150 mL of water after fasting for at least 10 hours in Period I and one tablet of ASC-01 with approximately 150 mL of water after fasting for at least 10 hours in Period II. The date and time of administration and the drug administered will be recorded in the CRF.

3.7.3.3.3.2 Cohort 2

Subjects assigned to the group receiving administration of ASC-01 under a fasting condition first (Group A-2) will take one tablet of ASC-01 with approximately 150 mL of water after fasting for at least 10 hours in Period I and one tablet of ASC-01 with approximately 150 mL of water 30 minutes after the start of breakfast in Period II.

Subjects assigned to the group receiving administration of ASC-01 under a fed condition first (Group B-2) will take one tablet of ASC-01 with approximately 150 mL of water 30 minutes after the start of breakfast in Period I and one tablet of ASC-01 with approximately 150 mL of water after fasting for at least 10 hours in Period II. The date and time of administration will be recorded in the CRF.

3.7.3.3.4 After Investigational Medicinal Product Administration (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed. Lunch and dinner will be provided.

Examination/Investigation Item	Timing of Implementation (Time After Administration on Day 1)	Acceptable Time Window
Blood collection for plasma drug concentration measurement	1, 2, 3, 4, 5, 6, 8, and 12	Within 3 minutes before and after each blood collection time
Confirmation of concomitant medications and therapies	Feasible time on Day 1	-

Adverse event assessment	Feasible time on Day 1	-
Vital signs (blood pressure, pulse rate, and temperature)	2, 4, and 8	Within 60 minutes before the time of measurement and before blood collection for plasma drug concentration measurement
12-lead electrocardiography	8	Within 60 minutes before the time of measurement and before blood collection for plasma drug concentration measurement

3.7.3.4 Day 2 of Each Period (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed. See "Table 3.7-2 Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)" for acceptable time windows.

- Blood collection for plasma drug concentration measurement (24 hours after IMP administration on Day 1)
- Adverse event assessment
- Vital signs (blood pressure, pulse rate, and temperature)
- 12-lead electrocardiography
- Confirmation of concomitant medications and therapies

3.7.3.5 Day 3 of Each Period (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed. See "Table 3.7-2 Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)" for acceptable time windows.

- Blood collection for plasma drug concentration measurement (48 hours after IMP administration on Day 1)
- Adverse event assessment
- Vital signs (blood pressure, pulse rate, and temperature)
- Confirmation of concomitant medications and therapies

3.7.3.6 Day 4 of Each Period (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed. See "Table 3.7-2 Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts) for acceptable time windows.

- Blood collection for plasma drug concentration measurement (72 hours after IMP administration on Day 1)
- Adverse event assessment
- Vital signs (blood pressure, pulse rate, and temperature)
- Confirmation of concomitant medications and therapies

3.7.3.7 Discharge (Day 5 of Each Period)/Discontinuation (Common to Both Cohorts)

The following observations, examinations, and evaluations will be performed on the day of discharge or at the time of discontinuation. See "Table 3.7-2 Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)" for acceptable time windows.

- Blood collection for plasma drug concentration measurement (96 hours after IMP administration on Day 1)
- Adverse event assessment
- Clinical laboratory tests (samples for chemistry, hematology, and urinalysis will be collected.)
- Physical examination
- Vital signs (blood pressure, pulse rate, and temperature)
- 12-lead electrocardiography (at discontinuation)
- Body weight (at discontinuation)
- C-SSRS (to be performed using Appendix 3 "Since Last Visit Version.")
- Confirmation of concomitant medications and therapies

3.7.3.8 Outpatient Visits (Days 7 and 8 of Each Period, Common to Both Cohorts)

3.7.3.8.1 Day 7 of Each Period

The subjects will visit the trial site as outpatient and the following observations, examinations, and evaluations will be performed. See "Table 3.7-2 Acceptable Time

Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)" for acceptable time windows.

- Blood collection for plasma drug concentration measurement (144 hours after IMP administration on Day 1)
- Adverse event assessment
- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS (to be performed using Appendix 3 "Since Last Visit Version.")
- Confirmation of concomitant medications and therapies

3.7.3.8.2 Day 8 of Each Period

The subjects will visit the trial site as outpatient and the following observations, examinations, and evaluations will be performed. See "Table 3.7-2 Acceptable Time Windows for Observations, Examinations, and Evaluations After Investigational Medicinal Product Administration (Common to Both Cohorts)" for acceptable time windows.

- Blood collection for plasma drug concentration measurement (168 hours after IMP administration on Day 1)
- Adverse event assessment
- Clinical laboratory tests (samples for chemistry, hematology, and urinalysis will be collected.)
- Physical examination
- Vital signs (blood pressure, pulse rate, and temperature)
- 12-lead electrocardiography
- Body weight
- C-SSRS (to be performed using Appendix 3 "Since Last Visit Version.")
- Confirmation of concomitant medications and therapies

3.7.4 Prior and Concomitant Medications (Common to Both Cohorts)

The investigator or subinvestigator will record in the CRF all medications and therapies used by the subject from 14 days prior to signing of informed consent until the end of the evaluation period (defined as the period during which subjects are evaluated for trial objectives). The investigator or subinvestigator will record in the CRF all medications and therapies used by the subject for treatment of an adverse event or which caused an

adverse event until the end of the trial (defined as the last date of contact or the date of final contact attempt).

3.7.5 Safety Assessments (Common to Both Cohorts)

3.7.5.1 Adverse Events

See Section 5 for the methods and timing of assessment, recording, and analysis of adverse events.

3.7.5.2 Clinical Laboratory Assessments

3.7.5.2.1 Clinical Laboratory Assessments

Laboratory data presented in Table 3.7.5.2-1 will be collected as specified in the Schedule of Assessments (Table 3.7-1). Tests will be performed according to the procedures specified by the trial site. The date and time of blood and urine collection will be recorded in the CRF.

Table 3.7.5.2-1 Clinical Laboratory Assessments

Hematology	Serum Chemistry
White blood cell (WBC) count and absolute and differential	Alanine aminotransferase (ALT)
Red blood cell (RBC) count	Alkaline phosphatase (ALP)
Hematocrit	Aspartate aminotransferase (AST)
Hemoglobin	Total Bilirubin
Platelets	Blood urea nitrogen (BUN)
	Calcium
	Chloride
	Total cholesterol
Urinalysis	Creatinine
Bilirubin	Creatinine phosphokinase
Glucose	Gamma-glutamyl transferase (GGT)
Ketones	Glucose
Urinary occult blood	Lactate dehydrogenase (LDH)
Protein	Inorganic phosphorus
Urobilinogen	Potassium
pH	Total protein
	Sodium
	Uric acid
	Triglycerides

3.7.5.2.2 Immunological Test

The following data will be collected on the days specified in the Schedule of Assessments (Table 3.7-1). Tests will be performed according to the procedures specified by the trial site. The date and time of blood collection will be recorded in the CRF.

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C virus antibody (HCV antibody)
- Human immunodeficiency virus (HIV antigen/antibody)

3.7.5.2.3 Breath Alcohol Test, Urine Drug Test, and Urine Cotinine Test

The following data will be collected on the days specified in the Schedule of Assessments (Table 3.7-1). Tests will be performed according to the procedures specified by the trial site. The date and time of the test, date and time of urine collection, and test results will be recorded in the CRF.

- Breath alcohol
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine
- Opiates
- Phencyclidine
- Urine cotinine

3.7.5.3 Physical Examination and Vital Signs

3.7.5.3.1 Physical Examination

A complete medical history will be obtained at the screening visit. Physical examination will be performed at screening, admission, discharge/discontinuation, and outpatient visits. Physical examination will include head, ears, eyes, nose, throat, chest, abdomen, genitourinary tract, extremities, nerves, and skin and mucosal sites. The investigator or subinvestigator will be primarily responsible for the assessment of physical findings. The same individual should perform all physical examinations for an individual subject whenever possible. For the screening examination and the examination before IMP administration in each period, the date of assessment and the results of assessment will be recorded in the CRF. For Days 5 and 8 (or at discontinuation) in each period, only the date of assessment will be recorded in the CRF. Any clinically significant physical findings not present at baseline but observed after IMP administration will be recorded as an adverse event and monitored until its outcome has been sufficiently evaluated.

3.7.5.3.2 Vital Signs (Blood Pressure, Pulse Rate, and Temperature)

Vital signs will be measured and recorded according to the schedule presented in Section 3.7.3. Blood pressure and pulse rate will be measured after the subject has maintained the supine position for at least 3 minutes. Standing and sitting blood pressure will be measured at screening only. Body temperature will be measured in the supine position. At screening, the standing and sitting position blood pressure will as well be obtained, and the difference in systolic blood pressure between the standing and sitting position will be calculated. Vital signs will be obtained at each scheduled time point and prior to blood collection for pharmacokinetics (if applicable). The date, time, and results of the assessment will be recorded in the CRF.

3.7.5.4 Electrocardiogram

Electrocardiograms will be performed and recorded according to the schedule presented in Section 3.7.3. Electrocardiograms will be obtained prior to blood collection for pharmacokinetics at each scheduled time point (if applicable). A resting (at least 10 minutes) 12-lead electrocardiogram will be recorded in the supine position. The date of examination, time of measurement, heart rate, PR interval, QRS time, QT interval, and QTc (Fridericia correction method [QTcF] and Bazzett correction method [QTcB]) will be recorded in the CRF. The investigator or subinvestigator will assess each electrocardiogram data, investigate whether the data are normal or abnormal, and record the assessment results and findings in the CRF. The original 12-lead electrocardiogram tracing will be retained in the medical record or investigator file.

3.7.5.5 Body Weight

Body weight will be measured to the nearest 0.1 kg at specified times and on the same scale throughout the trial. The date, time, and results of measurements will be recorded in the source documents and CRF.

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

The C-SSRS assessment will be performed at screening and prior to administration in each period using the Baseline Version according to the schedule presented in Section 3.7.3 of this protocol. On Days 5, 7, and 8 (or at discontinuation) in each period, the C-SSRS assessment will be performed using the Since Last Visit Version with the start day of administration in each period as the base point. The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The Baseline Version of C-SSRS (Baseline Columbia-Suicide Severity Rating Scale) is attached in Appendix 2, and the Since Last Visit Version of C-SSRS (Since Last Visit Columbia-Suicide Severity Rating Scale) is attached in Appendix 3. The date and results of the assessment will be recorded in the CRF.

3.7.6 Pharmacokinetic Assessments

3.7.6.1 Pharmacokinetic Assessments

Cohort 1

Plasma concentrations of aripiprazole will be measured.

Cohort 2

Plasma concentrations of aripiprazole and sertraline will be obtained.

3.7.6.2 Timing of Blood Collection

Samples will be collected before and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 144, and 168 hours after administration on Day 1 in each period. The date and time of blood collection will be recorded in the CRF.

3.7.6.3 Pharmacokinetic Plasma Samples

Venous blood will be collected via an indwelling catheter or direct venipuncture into a blood collection tube containing heparin sodium. When an indwelling catheter is used, it will be filled with saline or heparin as needed for placement. The collected blood will be mixed by inversion and plasma will be separated by centrifugation. All plasma samples will be shipped to the drug concentration measurement facility as described in Appendix 1. Detailed instructions for sample handling and shipment are provided in Appendix 1.

The results of measurement will be reported directly from the drug concentration measurement facility to the sponsor. Therefore, recording in the CRF is not required.

3.7.6.4 Pharmacokinetic Urine Samples

Urine samples for measurement will not be collected.

3.7.7 Genetic Testing

No genetic testing will be performed in this trial.

3.7.8 Future Biospecimen Research Samples

No future biospecimen research is planned for this trial.

3.7.9 End of Trial

The visit on Day 8 in Period II or the time of discontinuation will be considered as the "end of trial date," which will be the "last date of visit or contact" or the "date of final contact attempt."

3.8 Discontinuation Criteria and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

3.8.2 Discontinuation at Individual Sites

The sponsor, investigator, or institutional review board reserves the right to terminate a particular trial site's participation as necessary for medical, safety, regulatory, ethical, or other reasons in accordance with applicable laws, regulations, and GCP as well as for reasons such as no enrollment of subjects and noncompliance with the protocol. The sponsor will be notified promptly if the trial is terminated by the investigator or the IRB at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to adverse events (AEs), required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. Subjects who discontinue treatment will be withdrawn from the trial. Subjects who discontinue will be encouraged to undergo all the examinations at discontinuation and follow-up examinations, and the examinations at discontinuation should be performed as soon as possible after treatment discontinuation.

3.8.3.2 Documenting Reasons for Treatment Interruption or Discontinuation

All subjects may withdraw consent from the trial at any time, and the investigator or subinvestigator may terminate a subject's participation in the trial at any time if medically necessary. Additionally, subjects must be withdrawn from the trial for any of the following reasons:

- Reason related to adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, cases with IMP-related safety concern)
    - Serious adverse event (SAE)

    - Other potentially IMP-related safety concerns or AEs
- Death
- Reason unrelated to medical condition (provide details and confirm history of the subject's adverse event)
- Withdrawal of consent (full written consent withdrawal)
- Lost to follow-up
- Discontinuation of the whole or part of the trial by the sponsor

If the subject (temporarily interrupts or) discontinues IMP due to an adverse event, the investigator or subinvestigator or other trial personnel will make every effort to follow the event until it resolves or stabilizes or the subject is lost to follow-up or has died. The procedures in "3.8.3.1 Treatment Discontinuation" must be followed.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial and can only withdraw consent for future participation.

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be understood, documented, and managed to protect the rights of the subject and the integrity of the trial.

Subjects who discontinue will be encouraged to undergo all the examinations at discontinuation and follow-up examinations, and the examinations at discontinuation should be performed as soon as possible after treatment discontinuation.

3.9 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing, but who is not randomized or assigned trial treatment.

If a subject meets the definition of a screen failure in this trial, the following information will be recorded in the CRF:

- Date of informed consent
- Date of investigation
- Sex
- Birth date
- Race
- Ethnicity

- Country
- Whether or not the subject met the inclusion criteria (If the subject did not meet the inclusion criteria, the item numbers should also be recorded.)
- Whether or not the subject met the exclusion criteria (If the subject met the exclusion criteria, the item numbers should also be recorded.)
- Screen failure date
- Reason for screen failure

3.10 Definition of Completed Subjects

The evaluation period is defined as the time period during which the subject is evaluated for trial objectives, regardless of whether or not the IMP is administered. Subjects who have undergone the last scheduled evaluation during the evaluation period are defined as having completed the trial. In this trial, subjects who have undergone the evaluation on Day 8 in Period II are defined as having completed the trial.

3.11 Definition of Subjects Lost to Follow-up

If a subject cannot be reached on or before Day 8 in Period II and the reason for discontinuation (eg, withdrawal of consent or onset of adverse events) is unknown, the reason for discontinuation will be regarded as lost to follow-up except for the subjects who completed the trial as defined in Section 3.10.

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a “lost to follow-up” status.

3.12 Subject Compliance

The administration time and dose of each IMP will be recorded in the source documents and CRF. Further, information regarding missed or inappropriate doses will be recorded in the source documents and CRF. The oral cavity will be checked at the time of oral administration to make sure the subject takes the IMP.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, IMP dispensing or subject dosing error, violation of concomitant medication criteria), the investigator or subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator, medical advisor, and sponsor will come as quickly as possible to a joint decision regarding the subject’s

continuation in the trial. This decision will be documented by the investigator or subinvestigator and the sponsor and reviewed by the medical advisor.

The investigator or subinvestigator will record all protocol deviations in the source documents.

The investigator or subinvestigator will enter specified items among protocol deviations in the CRF according to the procedure for preparing the CRF prepared by the sponsor.

4 Restrictions (Common to Both Cohorts)

4.1 Prohibited Medications or Therapies

No medications other than the planned IMP may be taken during the trial. The use of prescription, over-the-counter, or herbal medications, vitamin supplements, or St. John's wort within 14 days prior to the first dosing and during the trial, and antibiotics within 30 days prior to the first dosing and during the trial is prohibited. Compassionate use must be discussed with the sponsor on a case-by-case basis and the reason must be documented.

4.2 Other Restrictions

4.2.1 Hospitalization of Subjects

Subjects will be hospitalized from the day before IMP administration in each period until completion of the examinations on Day 5 of IMP administration. The investigator or subinvestigator will confirm that there is no problem in the safety of subjects and then discharge the subjects.

4.2.2 Restriction of Food Intake and Prohibition of Blood Donation

Subjects will be prohibited from taking any food or drink containing St. John’s wort from 14 days before IMP administration to the completion of blood collection at 168 hours after administration on Day 8 in each treatment period.

Grapefruits, grapefruit products, Seville oranges, Seville orange products, starfruits, and star fruit products will be prohibited from 7 days before IMP administration to the completion of blood collection at 168 hours after administration on Day 8 in each treatment period.

Subjects will be prohibited from taking alcohol from 3 days before IMP administration to the completion of blood collection at 168 hours after administration on Day 8 in each treatment period.

Ingestion of food and beverages containing methylxanthine (eg, caffeinated coffee, tea, carbonated beverages, and chocolate) will be prohibited from the time of hospitalization to the completion of blood collection at 168 hours after administration on Day 8 in each treatment period.

Blood donation will be prohibited during the trial.

4.2.3 Posture and Behavior

For 8 hours after administration on the day of IMP administration, rapid change of body position should be avoided, except when necessary for examination, etc., and subjects should sit in a chair or lie in a supine position. Subjects may walk from 8 hours after administration; however, they will be instructed to avoid strenuous exercise.

Irregular activities such as strenuous exercise, overeating and overdrinking, and staying up late should be avoided during the trial because they may affect the safety evaluation.

5 Adverse Event Reporting

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with the IMP. Adverse events would not include information recorded as complications at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred.

An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. “Suspected adverse reaction” implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant disability/incapacity
- Requires inpatient hospitalization or prolongs hospitalization.

  - Hospitalization itself should not be reported as a serious treatment-emergent AE (TEAE); whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered serious TEAEs.
- Congenital anomaly/birth defect
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious AE."

Immediately Reportable Event (IRE) includes any event that results in any of the following outcomes:

- Any SAE
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4 Potential Serious Hepatotoxicity).
- Pregnancy in the partner of a male subject. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will be recorded in the adverse event section of the CRF only if there is a complication or an abnormality in the newborn.

Clinical Laboratory Test Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. The investigator or subinvestigator should ascertain whether each abnormal laboratory value is an abnormal change (ie, a clinically significant change) from baseline for that subject. It does not necessarily have to be determined when an abnormal value is observed for the first time. In addition, the investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically significant by the investigator or subinvestigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale below and reported as indicated in the CRF.

1 =Mild:	Discomfort noticed, but no disruption to daily activity.
2 =Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 =Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator must assess or examine the subject for the occurrence of adverse events. Adverse event information will be followed until the end of the trial specified in Section 3.7.9. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you been feeling?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRF provided by the sponsor. Since this is a crossover trial, changes from baseline in Period II will be evaluated for adverse events in Period II. The following items will be recorded in the CRF in accordance with the procedure for preparing the CRF prepared by the sponsor.

- Name of event
- Date of onset (time should also be recorded during hospitalization whenever possible) and date of resolution
- Severity
- Seriousness (if applicable, the details should be recorded)
- Causal relationship with the IMP
- Outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown)

Collection of adverse events and serious adverse events will commence after the subject has signed the informed consent form and will continue until the last date of observation.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Any change in severity or seriousness of a reported adverse event must be reported as a new adverse event on the CRF.

In addition, the sponsor must be notified immediately by telephone or e-mail of any IREs according to the procedure outlined in "Section 5.3 Immediately Reportable Events (IRE)." Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events (IRE)

After the investigator or subinvestigator, or designee becomes aware of any serious adverse event, potential serious hepatotoxicity, drug-induced liver injury, or confirmed pregnancy, the investigator or subinvestigator must immediately report the event. The investigator or subinvestigator should complete the immediately reportable event form (IRE form) and e-mail or overnight courier to the sponsor (see protocol title page for contact information). (Note that the IRE form is a dedicated form provided by the sponsor and not the adverse event section of the CRF.)

Subjects with serious adverse events should be followed as described in Section 5.7.2. The investigator or subinvestigator should give appropriate treatment to the subject and promptly report the latest information on the subject's condition to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE in the CRF.

5.5 Pregnancy

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures

(ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject or their partner is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or agrees to remain abstinent during the trial, 2 of the following approved methods of birth control must be used: (vasectomy, tubal ligation, intrauterine device, birth control pill, condom with spermicide, or occlusive cap [vaginal diaphragm or cervical cap] with spermicide). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the CRF. Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.

Before enrolling males in this clinical trial, investigators or subinvestigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

All subjects must be instructed to contact the investigator or subinvestigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for at least 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator or subinvestigator for monitoring the outcome of the pregnancy.

The investigator or subinvestigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy,

including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

Not applicable.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE CRF with the current status (ongoing or resolved/recovered) noted. For subjects who have an adverse event or have not recovered from an adverse event at the end of the trial (last date of observation), a post-treatment follow-up visit should be scheduled at least every 4 weeks until the adverse event resolves or stabilizes or the subject is lost to follow-up or has died. This follow-up information will be documented in the subject's medical record. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. All nonserious events that are ongoing at the end of the trial (last date of observation) will be recorded as "ongoing" in the CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

5.7.2 Follow-up of Serious Adverse Events

Any serious adverse event that is ongoing at the end of the trial (last date of observation) must be recorded on the adverse event page of the CRF and reported to the sponsor as described in Section 5.3. Reportable events include previously reported serious adverse events that have not resolved or new serious adverse events. All serious adverse events that are ongoing at the end of the trial (last date of observation) must be recorded as "ongoing" in the CRF. The investigator or subinvestigator will continue to follow up to the point these serious adverse events have resolved or stabilized, or the subject is lost to follow-up, or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor on the IRE form up to the point the serious adverse event has resolved or stabilized, or the subject is lost to follow-up, or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After the End of the Trial (Last Date of Observation)

Any new serious adverse events reported by a subject to the investigator or subinvestigator which occur after the end of the trial (last date of observation) and are determined by the investigator or subinvestigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include serious adverse events that are captured on follow-up telephone contact or at any other time point after the defined trial period. For serious adverse events identified after the end of the trial (last date of observation), the investigator or subinvestigator will follow up the event until it resolves or stabilizes or the subject is lost to follow-up or has died and report crucial follow-up information to the sponsor using the immediately reportable event form (IRE form).

6 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic Analysis

6.1 Pharmacokinetic Analysis Methods

6.1.1 Cohort 1

In Cohort 1, blood samples for measurement of aripiprazole will be collected before and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 144, and 168 hours after administration in each period. The pharmacokinetic parameters (C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, λ_z, t_{last}, CL/F, AUC_%Extrap, and MRT_∞) of aripiprazole will be calculated by non-compartmental pharmacokinetic analysis. Descriptive statistics of plasma concentrations and pharmacokinetic parameters of aripiprazole will be presented by treatment (ASC-01 or concomitant administration of aripiprazole and sertraline).

6.1.2 Cohort 2

In Cohort 2, blood samples for measurement of aripiprazole and sertraline will be collected before and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 144, and 168 hours after administration in each period. The pharmacokinetic parameters (C_{max}, AUC_t, AUC_∞, AUC_{168h}, t_{max}, $t_{1/2,z}$, λ_z, t_{last}, CL/F, AUC_%Extrap, and MRT_∞) of aripiprazole and sertraline will be calculated by non-compartmental pharmacokinetic analysis. Descriptive statistics of plasma concentrations and pharmacokinetic parameters of aripiprazole and sertraline will be presented by treatment (administration under a fasting condition or under a fed condition).

6.2 Pharmacodynamic Analysis Methods

Pharmacodynamic endpoints will not be examined.

6.3 Pharmacokinetic/Pharmacodynamic Analysis Methods

No pharmacokinetic/pharmacodynamic analyses are planned.

6.4 Pharmacogenomic Analysis Methods

No pharmacogenomic analyses are planned.

7 Statistical Analyses

7.1 Sample Size

For Cohort 1, the sample size was determined by the method of Diletti[18] as the number of subjects required for the 90% confidence intervals for the differences in the log-converted mean C_{max} and AUC_{168h} of aripiprazole between single administration of ASC-01 and concomitant single administration of aripiprazole and sertraline to be within the acceptable range for bioequivalence of ln(0.8) to ln(1.25) based on the BE Guideline.[13]

In the results of a pharmacokinetic trial conducted to examine the bioavailability of ASC-01 (031-11-004), the ratios of the geometric mean C_{max} and AUC_{168h} of aripiprazole were respectively 1.12 and 1.05 and the within-subject variances were 0.029 and 0.006. The proportion of subjects excluded from the pharmacokinetic analysis due to vomiting or withdrawal was approximately 40%.

Assuming the ratio of the geometric mean C_{max} of aripiprazole between administration of ASC-01 and concomitant administration of aripiprazole and sertraline and the within-subject variance to be, respectively, 1.1 and 0.029, the number of subjects required to ensure a statistical power of 90% or higher is 16 per group (32 subjects in total). Assuming a 40% rate of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 1 is set at 27 subjects per group (54 subjects in total).

For Cohort 2, referring to the FDA guidance,[14] the sample size required for the analysis of food effect on the pharmacokinetics of ASC-01 is 6 subjects per group (12 subjects in total). In consideration of the possibility of exclusion from analysis due to withdrawal or vomiting, the sample size for Cohort 2 is set at 10 subjects per group (20 subjects in total).

7.2 Datasets for Analysis

7.2.1 Pharmacokinetic Analysis Set

Subjects who received the IMP and whose plasma concentration was measured

7.2.2 Bioequivalence Analysis Set

Subjects from whom C_{max} and AUC_{168h} were obtained in both Periods I and II in Cohort 1

7.2.3 Food Effect Analysis Set

Subjects from whom C_{max}, AUC_t, AUC_∞, and AUC_{168h} were obtained in both Periods I and II in Cohort 2

7.2.4 Safety Analysis Set

Subjects who received at least one dose of IMP

7.3 Handling of Missing Data

Missing data will not be imputed.

7.4 Primary and Secondary Endpoint Analysis

The following analyses will be performed on the bioequivalence analysis set for Cohort 1 and the food effect analysis set for Cohort 2.

7.4.1 Primary Endpoint Analysis

In Cohort 1, analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max} and AUC_{168h} of aripiprazole using group (group receiving administration of ASC-01 first or group receiving concomitant administration of aripiprazole and sertraline first), treatment (ASC-01 or concomitant administration of aripiprazole and sertraline), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max} and AUC_{168h} of aripiprazole between ASC-01 administration and concomitant administration of aripiprazole and sertraline will be calculated. If the 90% confidence intervals are within the range of ln(0.8) to ln(1.25), single administration of ASC-01 and single concomitant administration of aripiprazole and sertraline will be judged to be bioequivalent for aripiprazole.

If an add-on subject study is conducted, bioequivalence will be assessed based on the combined results of this trial and the add-on subject study using the same criteria.

In Cohort 2, analysis of variance will be performed on log-converted (natural logarithm) values for the C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline using group (group receiving ASC-01 under a fasting condition first or group receiving ASC-01 under a fed condition first), treatment (administration under a fasting condition or under a fed condition), subjects within group, and treatment period as factors. The 90% confidence intervals for the differences in the mean C_{max}, AUC_t, AUC_∞, and AUC_{168h} of aripiprazole and sertraline between administration under a fasting condition and administration under a fed condition will be calculated.

If there are any subjects in each cohort from whom evaluable parameters cannot be obtained in both Periods I and II, sensitivity analysis including those subjects will also be performed.

7.4.2 Secondary Endpoint Analysis

Described in "6.1 Pharmacokinetic Analysis Methods."

7.5 Analysis of Demographic and Other Baseline Characteristics

Frequency distributions or descriptive statistics for age, height, body weight (screening period), BMI, past history or present illness will be generated for each randomized group and for the entire population in the bioequivalence analysis set in Cohort 1 and in the food effect analysis set in Cohort 2. Similar summarizations will be performed for other analysis sets by cohort as necessary.

7.6 Safety Analysis

Safety analysis will be performed by cohort and treatment in the safety analysis set. Baseline will be the value immediately before IMP administration in each period.

7.6.1 Adverse Events

All AEs will be coded by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of the following events will be summarized:

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs

Additionally, TEAEs related to the IMP will be summarized in the same manner.

7.6.2 Clinical Laboratory Data

For each clinical laboratory parameter other than urine qualitative test parameters, descriptive statistics of the measured values at each time point and change from baseline will be determined. For qualitative urinalysis parameters in clinical laboratory tests, shift tables from baseline to each time point will be generated. Clinical laboratory parameters other than qualitative urinalysis parameters will be classified as "within reference range," "below reference range," or "above reference range" using institutional reference values, and shift tables from baseline to each time point will be generated.

7.6.3 Physical Examination and Vital Signs Data

For physical examination, physical findings of individual subjects will be listed.

For vital signs, descriptive statistics of measured values and changes from baseline will be presented by time.

7.6.4 Electrocardiogram Data

For each parameter of 12-lead electrocardiography, descriptive statistics of the measured values at each time point and change from baseline will be determined. For normal/abnormal assessment of 12-lead electrocardiography, a shift table from baseline to each time point will be prepared. Categorical analysis will be performed for the measured values of corrected QT interval (Fridericia correction method [QTcF] and Bazzett correction method [QTcB]) and their changes from baseline at each time point, and the number and percentage will be calculated.

7.6.5 Other Safety Data

7.6.5.1 Body Weight

For body weight, descriptive statistics will be provided for measured values and changes from baseline.

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

The C-SSRS of individual subjects will be presented in a listing.

7.7 Pharmacodynamic Analysis

No pharmacodynamic analyses are planned.

7.8 Decision to Conduct Add-on Subject Study

For Cohort 1, if bioequivalence cannot be demonstrated in this trial due to an insufficient number of subjects, an add-on subject study may be performed once in the same manner

as the trial. However, the add-on subject study should be conducted using at least half the number of subjects included in the trial. The add-on subject study will not be conducted in the following cases:

- The difference in the mean log-converted C_{max} and AUC_{168h} between administration of ASC-01 and concomitant administration of aripiprazole and sertraline does not fall within the range of ln(0.8) to ln(1.25) as a result of this trial.
- The number of subjects required for the add-on subject study calculated from the results of the trial is considered unfeasible from an ethical or scientific point of view.

When data from the add-on subject study are pooled and analyzed with the data from the trial, study will also be included as a variable factor in the analysis.

8 Management of Investigational Medicinal Product

ASC-01 is a test formulation and will be provided as an IMP. Aripiprazole 3-mg tablets will be provided as a reference formulation, and sertraline 50-mg tablets will be provided as a reference formulation, etc., for consistency of conditions.

Refer to the Investigator's Brochure and the Clinical Operations Manual for details of management of IMP and reference formulation, etc.

8.1 Packaging and Labeling

The IMP will be provided to the IMP manager by the sponsor or a designated contractor.

Each package box to be used during the treatment period will be labelled to state “For clinical trial use only” as well as the protocol number, IMP code or generic name, quantity, lot number, expiration date, storage conditions, sponsor’s name and address, and precautions for use.

8.2 Storage

The IMP and reference formulation, etc., will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager. The IMP administrator must not provide the IMP and reference formulation, etc., to subjects not participating in this trial.

The IMP and reference formulation, etc., will be stored at room temperature.

The trial site staff will measure and record the temperature in the drug storage area at least once a working day.

8.3 Accountability

. The IMP manager maintain an inventory record of IMP and reference formulation received, dispensed, administered, and returned (or destroyed).

8.4 Returns and Destruction

At the completion or termination of the trial, all unused or partially used IMP and reference formulation, etc., must be returned to the sponsor.

All IMPs and reference formulations, etc., to be returned to the sponsor must be accompanied by documentation of storage and the protocol number and site number must be clearly identified on the outermost portion of the shipping container. Returned IMP and reference formulation, etc. should be in the original containers. The monitor in charge will support the return of unused or partially used IMP and reference formulation, etc.

8.5 Reporting of Product Quality Complaints

A product quality complaint (PQC) is any deficiency or complaint related to the identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, efficacy, or function of an IMP or medical device that is reported in writing, electronically, or orally by a healthcare professional, consumer, subject, medical representative, competent authority, regulatory authority, partner company, affiliate, or another third party after it is provided for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under-fill, over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or subinvestigator or designee must record each PQC identified through any means from the receipt of the IMP from the sponsor or sponsor’s designee, including subject dosing, through and including last confirmation and up to destruction. The

investigator or subinvestigator or designee must immediately notify the sponsor (or designee) of the PQC by e-mail or telephone as indicated below.

- PQC_031-102-00214@otsuka.jp

Send the information shown in "8.5.2 Information Required at the Time of Reporting Product Quality Complaints" to the above e-mail address.

Identification of a PQC by the subject should be reported to the investigator or subinvestigator, who should then follow the reporting mechanism above.

8.5.2 Information Required at the Time of Reporting Product Quality Complaints

The following information is required for reporting:

- Description of complaint
- Reporter identification (eg, subject, investigator or subinvestigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- Product name (product or compound name, kit number, or bottle number)
- Clinical protocol reference (number and trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

8.5.3 Procedure for Returning Investigational Medicinal Product If There Is a Product Quality Complaint

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical

records, electronic data, screening logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the site, an investigator or a subinvestigator will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's or subinvestigator's assessment of relationship to IMP must also be recorded;
- Description of medical practice performed
- The signature (or initials) and date of the investigator or subinvestigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record as described above. Any changes to information in medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or subinvestigator. If electronic data systems are used, a full audit trail of the change must be maintained.

Information from medical records and other source documents will be directly entered by investigative site personnel in the sponsor's electronic data capture (EDC). Changes to

the data will be captured by an automatic audit trail. Information recorded in medical records and other source documents will be immediately and clearly transcribed to the CRF and submitted to the sponsor. Any changes to information in paper source documents or CRF will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or subinvestigator.

9.3 File Management at the Trial Site

The head of the trial site will ensure that the files are stored at the trial site in accordance with ICH GCP Guideline E6, Section 8 and applicable local regulations. The files to be stored at the trial site will contain all source documents and data from the completed CRF for all subjects screened or enrolled at the site. The investigator or trial site must take measures to maintain the confidentiality of these records and to prevent their loss or destruction during the required retention period.

9.4 Records Retention at the Trial Site

The trial site will retain all documents and records related to this trial for either of the following 2 periods, whichever comes later. However, if the sponsor requires a longer retention period, the retention period and retention method will be discussed with the sponsor.

- A period of at least 2 years after the date on which approval to market the drug is obtained; However, if a notification is received that development is discontinued or results of the trial will not be attached to the approval application form, the date 3 years after the date of receipt of the notification that development is discontinued or results of the trial will not be attached to the application form.
- Three years after discontinuation or completion of the trial

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator discontinues participation in the trial or in case of discontinuation during the record retention period (eg, due to relocation, retirement, site closure), all trial-

related records must be transferred to a mutually agreed-upon designee for the closure of the trial site within a sponsor-specified time frame. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to carefully follow this trial in accordance with established research principles, ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of an effort to fulfill these obligations (ie, ensure personnel are kept up to date regarding the progress of the trial), the monitor of the sponsor (or representative of the sponsor) will visit the trial site during the course of the trial in addition to regular contacts by phone, e-mail, and written document. In addition, all investigators or subinvestigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The Quality Assurance Unit (or its representative) of the sponsor (or designee) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and a review of the CRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regional regulatory authorities may inspect the investigator site during or after the trial. The investigator will fully cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.3 Protocol Deviations

Due to the complexity of the protocol, protocol deviations may occur despite training and preventative measures, and such deviations may result in harm to subjects, biased or inaccurate results, or rejection of all or part of the trial data. According to Section 10.2 of the ICH E3 “Guideline for Structure and Content of Clinical Study Reports,” protocol deviations should be appropriately summarized by trial site and categorized as follows:

- Subject enrolled in violation of eligibility criteria
- Subject met the withdrawal criteria during the study but were not withdrawn
- Subject received the wrong treatment or incorrect dose
- Subject received an excluded concomitant treatment

Otsuka Pharmaceutical classifies protocol deviations as significant or minor. A significant deviation is any intentional or unintentional act/omission during the conduct of a clinical trial that may have an adverse effect on the integrity of the primary scientific objective of the trial or that may have a significant potential effect on the safety evaluation of subjects. A significant deviation is one that may significantly affect the integrity, accuracy, or reliability of the trial data or that may significantly affect the rights, safety, or welfare of subjects.

A minor deviation is any intentional or unintentional act/omission during the conduct of a clinical trial that is not in strict compliance with the protocol but has minimal impact on the overall integrity of the trial or on the evaluation of safety or efficacy analysis in an individual subject.

All protocol deviations will be classified as significant or minor based on the definitions described above, and only significant deviations will be summarized in the clinical study report.

If the same type of protocol deviation occurs in more than one subject, the deviation must be recorded separately for each subject.

The investigator or subinvestigator will document any suspected protocol deviations and also document medical judgment as to whether or not to continue the subject's participation in the trial due to protocol deviations.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP guidelines (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the CRF, the investigator or subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number or subject ID will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in the CRF. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or subinvestigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). "Administrative" amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, or the sponsor conclude that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

15 References

1 Drug interview form of aripiprazole preparation (ABILIFY® tablets, 1 mg, 3 mg, 6 mg, and 12 mg; OD tablets, 3 mg, 6 mg, 12 mg, and 24 mg; ABILIFY® powder 1%; and ABILIFY® oral solution 0.1%), Mar 2017 (revised version 19)

2 Bristol-Myers Squibb Company, Otsuka America Pharmaceutical, Inc. ABILIFY® (aripiprazole) tablets, ABILIFY DISCMELT® (aripiprazole) orally disintegrating tablets, ABILIFY® (aripiprazole) oral solution, and ABILIFY® (aripiprazole) injection for intramuscular use only. US package insert updated in Dec 2017

3 Package insert of sertraline hydrochloride (Jzoloft tablets, 25 mg, 50 mg, and 100 mg, and OD tablets, 25 mg, 50 mg, and 100 mg), Mar 2015 (revised version 13)

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5 Harada Y, Kohara N, Imaeda T. Pharmacological, pharmacokinetic, and clinical characteristics of sertraline hydrochloride (Jzoloft TM tablets, 25 mg and 50 mg) for the treatment of depression and panic disorder. Folia Pharmacologica Japonica 2006;128:417-26.

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12 Patel BV, Leslie RS, Thiebaud P, Nichol MB, Tang SS, Solomon H, et al. Adherence with single-pill amlodipine/atorvastatine vs a two-pill regimen. Vasc Health Risk Maneg. 2008;4(3):673-81.

13 Guideline for Bioequivalence Studies of Generic Products (Division-Notification 0229 No. 10 of the Pharmaceutical and Food Safety Bureau, dated 29 Feb 2012)

14 Guidance for industory: Food-Effect Bioavailability and Fed Bioequivalence Studies. U.S. department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); 2002

15 Shimada E, Murasaki M, Kawaguchi T, Fukuyama Y. Phase I clinical studies of aripiprazole—safety and pharmacokinetics in healthy adult male volunteers after single and repeated administration. Japanese Journal of Clinical Psychopharmacology 2005;8:695-731.

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Appendix 1 Bioanalytical Sample Handling and Shipment

Handling of Samples

Each storage tube should be labeled securely. The label should include the protocol number, subject number or subject ID, time of administration (eg, Periods I and II), and time of sampling (eg, 8 hours after administration). The actual time of collection, not the scheduled time of collection, should be accurately entered in the CRF.

Plasma Samples

Venous blood should be collected via an indwelling catheter or direct venipuncture into a 2-mL evacuated blood collection tube containing heparin sodium. When an indwelling catheter is used, it should be filled with saline or heparin as needed for placement. After blood sample collection, the tube should be gently inverted several times to mix the contents well. Within 45 minutes after collection, the sample should be centrifuged in a refrigerated centrifuge at about 4°C (1500 to 1800 × G [about 3000 rpm] for about 10 minutes). Approximately equal volumes of plasma should be transferred into two appropriately labeled storage tubes using a standard laboratory technique. Within 90 minutes of collection, the two plasma samples should be stored in a freezer set to – 15°C or colder. Aliquot plasma sample 1 should be sent to Sumika Chemical Analysis Service, Ltd. (SCAS). Aliquot plasma sample 2 should be sent to SCAS separately from aliquot plasma sample 1. Samples should be placed in an airtight container filled with dry ice sufficient for shipment.

Any remaining plasma samples will be stored at SCAS and destroyed after the clinical study report has been prepared.

Appendix 2 Baseline Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale

(C-SSRS)

Baseline Assessment

14 Jan 2009 Version

Posner, K.; Brent, D.;Lucas, C; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.;Mann, J.

Disclaimer:

This scale is intended for use by trained physicians. The questions on the Columbia-Suicide Severity Rating Scale (C-SSRS) are suggested examples of assessment methods.
The final determination of suicidality is left to the physician.

*The definition of suicidal behavior in this scale is based on that used in **The Columbia Suicide History Form**.**

**Development: John Mann, MD, and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103-130, 2003.)*

C-SSRS Baseline-Japan/Japanese-Version of 12 Mar 10-Mapi Research Institute.
ID5353/C-SSRS-Baseline_AU3.0_jpn-JP.doc

Suicidal Ideation	
Ask 1 and 2. If both are no, proceed to the Suicidal Behavior section. *If the answer to 2 is yes, ask 3, 4, and 5. If the answer to 1 or 2 is yes, complete the Degree of Suicidal Ideation section below.*	The time in life when suicidal ideation was most severe
1. Desire to die When the subject acknowledges that he wants to die, not live anymore, or not wake up while asleep. ***Have you ever wanted to die or not wake up while asleep?*** If yes, details	Yes ☐ No ☐
2. Active suicidal ideation - not specific When the subject acknowledges that there was vague and non-specific suicidal ideation (eg, "I have thought about suicide") but the method of suicide, related measures, intent, or plan was not considered. ***Have you actually felt like killing yourself?*** If yes, details	Yes ☐ No ☐
3. Active suicidal ideation with any methods (not plan) without intent to act When the subject acknowledges that he had suicidal ideation and considered at least one suicide method during the evaluation period. This is different from the specific plan (date and time, location, and method) (eg, suicide method was considered but no specific plan was developed). It also includes the answer, "I thought I would die with a drug, but I don't have a concrete plan for when, where, and how to implement it, and I think I never do it." ***Have you thought about how to commit suicide?*** If yes, details	Yes ☐ No ☐
4. Active suicidal ideation with some intent to act, without specific plan When the subject acknowledges that he has suicidal ideation with some intent to act on such thoughts. It is different from the statement, "I have thoughts (of suicide), but I have no intention to do anything." ***Have you ever thought you would like to commit suicide and want to execute it?*** If yes, details	Yes ☐ No ☐
5. Active suicidal ideation with specific plan and intent When the subject has suicidal ideation with a specific plan (complete or partial) and some intent to act. ***Do you have a specific plan for how to commit suicide? Do you intend to implement the plan?*** If yes, details	Yes ☐ No ☐
Degree of Suicidal Ideation	
The following questions rate the most severe suicidal ideation (eg, in 1 to 5 above, 1 represents the least severe ideation and 5 represents the most severe ideation). Ask when suicidal ideation was most severe. ***Most severe suicidal ideation:*** _____ (*Type no. (1 to 5)*) _____ (***Description of suicidal ideation***)	Most severe
Frequency ***How often did you think so?*** (1) Less than once a week (2) Once a week (3) Two to five times a week (4) Every day/almost every day (5) Many times a day	____
Duration ***How long did these thoughts last?*** (1) Several seconds to several minutes/instantaneous (2) Less than 1 hour/for a while (3) 1 to 4 hours/quite a while (4) 4 to 8 hours/most of the day (5) 8 hours or more/continuous	____
Control ***Can/could you suppress thoughts of suicide or thoughts of wanting to die if you want/wanted to?*** (1) Easily able to suppress thoughts (2) Can suppress thoughts although it is a little difficult (3) Some difficulty but can suppress thoughts (4) Very difficult but can suppress thoughts (5) Cannot suppress thoughts (0) Not willing to suppress thoughts	____
Deterrents ***Is there any person or thing (eg, family, religion, pain of dying) that suppressed your thoughts of wanting to die or stopped you from committing suicide?*** (1) Deterrents stopped me from committing suicide (2) Deterrents probably stopped me from committing suicide (3) Not sure if the deterrents stopped me from committing suicide (4) Deterrents probably do not stop me from committing suicide (5) Deterrents do not stop me from committing suicide (0) Not applicable	____
Reasons for Suicidal Ideation ***Why did you want to die or commit suicide? Was it to end the pain or evade the emotions you had at that time (eg, you could not live with such pain or emotions)? Was it to get someone's attention, revenge, or a reaction? Was it both?*** (1) Solely to get someone's attention, revenge, or a reaction (2) Mostly to get someone's attention, revenge, or a reaction (3) Both (50/50) to get someone's attention, revenge, or a reaction and to end the pain (4) Mostly to end the pain (unable to live with the pain or emotions) (5) Solely to end the pain (unable to live with the pain or emotions) (0) Not applicable	____

Suicidal Behavior *(Tick all that apply. Asked about all types of suicidal behavior listed below.)*	In past life
Suicide attempt: When behavior that may cause self-harm was associated with any desire to die as a result of the behavior. When the behavior was considered to some extent as a means of suicide. This includes cases where the intent to commit suicide is not complete. If the subject has an intent or desire to die as a result of the behavior ***even a little***, it is considered a "suicide attempt." This includes cases where there is a risk of physical damage ***even without actual physical damage***. When a gun is in the mouth and the trigger is pulled, it is considered a "suicide attempt" even if the gun is broken and no physical damage is caused. When suicidal intent is presumed: When suicidal intent can be presumed from the behavior and circumstances even if the subject denies intent or desire to die. For example, when behavior is extremely lethal and obviously not an accident, and its only possible intent is suicide (eg, gunshot to head, jumping from an upper floor). Even if the subject denies intent to commit suicide, the intent to commit suicide can be presumed if the subject believes at the time that his behavior may result in death. ***Have you ever attempted suicide?*** ***Have you done anything to harm yourself?*** ***Have you done any dangerous behavior that could result in death?*** ***What did you do?*** ***Was _____ as a means of suicide?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to die when you _____?*** ***Or, were you aware of the possibility of death when you _____?*** ***Or did you not intend to die when you did it, and did you have another reason (eg, stress relief, feel better, get sympathy, change circumstances)?*** (Self-injurious behavior without suicidal intent) If yes, details	Yes No ☐ ☐ Total number of times _____
Have you had any self-injurious behavior without suicidal intent?	Yes No ☐ ☐
Interrupted suicide attempt: When behavior that might result in self-harm was interrupted (due to external factors) *(if it had not been interrupted, it would have resulted in "suicide attempt").* Drug overdose: The subject took the drug in hand but stopped taking it. Even a small dose is considered a "suicide attempt" rather than an "interrupted suicide attempt." Gun suicide: The subject directed a gun to himself, but someone took the gun away or prevented him from pulling the trigger in some way. When the subject pulls the trigger, even if the gun fails to fire, it is considered a "suicide attempt." Jumping: The subject was in a position to jump down but was pulled down. Hanging: A rope was around the neck but hanging was blocked. ***Have you been stopped by someone else or something after you started to commit suicide and before you actually proceed to behavior that would end your life?*** If yes, details	Yes No ☐ ☐ Total number of times _____
Self-interrupted suicide attempt: When the subject nearly attempted suicide but held back before actually proceeding to self-destructive behavior. This is similar to an example of "interrupted suicide attempt," but it refers to the case where suicide attempt was interrupted by the subject himself and not by something else. ***Have you held back after starting to commit suicide and before actually proceeding to behavior that would end your life?*** If yes, details	Yes No ☐ ☐ Total number of times _____
Preparatory behavior: Any preparation or behavior in preparation for suicide that exceeds the level of verbalizing or thinking about suicide. For example, preparing for suicide means (eg, obtain drugs, purchase weapons) and preparing for death from suicide (eg, release personal belongings, write a suicide note). ***Have you taken any action in preparation for suicide attempt or suicide? (eg, obtain a drug, obtain a weapon, release an important thing, write a suicide note)*** If yes, details	Yes No ☐ ☐
Suicidal behavior: Suicidal behavior was observed during the evaluation period.	Yes No ☐ ☐

Answer only when "suicide attempt" occurred	Date of most recent suicide attempt:	Date of most lethal suicide attempt:	Date of first suicide attempt:
Actual lethality/physical damage: 0. No physical damage or extremely mild physical damage (eg, scratch) 1. Mild physical damage (eg, slurred speech, first-degree burns, mild bleeding, sprain) 2. Moderate physical damage requiring treatment (eg, conscious but lightheaded, somewhat responsive, second-degree burns, bleeding from vessel) 3. Slightly severe physical damage that requires hospitalization and likely to require intensive care (eg, comatose but normal reflexes, third-degree burns of <20%, major bleeding but can recover, major fractures) 4. Severe physical damage requiring hospitalization with intensive care (eg, comatose with reflexes missing, third-degree burns of ≥20%, major bleeding with unstable vital signs, major damage to life-threatening area) 5. Death	Enter code _____	Enter code _____	Enter code _____
Likelihood of Lethality: Answer only if actual lethality/physical damage = 0 The lethality of "suicide attempt" without physical damage. (In the following cases, there is no actual physical damage but extremely high likelihood of lethality: The subject put a gun in the mouth and pulled the trigger, but no physical damage occurred because the gun did not fire. The subject lay on train railway but exited before being run over.) 0 = Suicidal behavior with low potential for physical damage 1 = Suicidal behavior that is likely to cause physical damage but unlikely to result in death 2 = Suicidal behavior that is likely to result in death despite treatment	*Enter code* _____	*Enter code* _____	*Enter code* _____

Appendix 3 Since Last Visit Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale

(C-SSRS)

Since Last Visit

14 Jan 2009 Version

Posner, K.; Brent, D.;Lucas, C; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.;Mann, J.

Disclaimer:

This scale is intended for use by personnel trained in its administration. The questions on the Columbia-Suicide Severity Rating Scale (C-SSRS) are suggested examples of assessment methods.
The final determination on the presence or absence of suicidal ideation or behavior is left to the individual who administered the scale.

The definition of suicidal behavior in this scale is based on that used in ***The Columbia Suicide History Form****.*[*]

[*]*Development: John Mann, MD, and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103-130, 2003.)*

If you wish to copy or reproduce the C-SSRS, please contact the following: Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032
For training or other questions, please contact: posnerk@childpsych.columbia.edu.

C-SSRS Since Last Visit-Japan/Japanese-Version of 10 Jul 15-Mapi.
ID0415933/C-SSRS-SinceLastVisit_AU5.1_jpn-JP.doc

Suicidal Ideation

Ask 1 and 2. If both are no, proceed to the Suicidal Behavior section. If the answer to 2 is yes, ask 3, 4, and 5. If the answer to 1 or 2 is yes, complete the Degree of Suicidal Ideation section below.	Since Last Visit
1. Desire to die When the subject acknowledges that he wants to die, not live anymore, or not wake up while asleep. *Have you ever wanted to die or not wake up while asleep?* If yes, details	Yes ☐ No ☐
2. Active suicidal ideation - not specific When the subject acknowledges that there was vague and non-specific suicidal ideation (eg, "I have thought about suicide") during the evaluation period but the method of suicide, related measures, intent, or plan was not considered. ***Have you actually felt like killing yourself?*** If yes, details	Yes ☐ No ☐
3. Active suicidal ideation with any methods (not plan) without intent to act When the subject acknowledges that he had suicidal ideation and considered at least one suicide method during the evaluation period. This is different from the specific plan (date and time, location, and method) (eg, suicide method was considered but no specific plan was developed). It also includes the answer, "I thought I would die with a drug, but I don't have a concrete plan for when, where, and how to implement it, and I think I never do it." ***Have you thought about how to commit suicide?*** If yes, details	Yes ☐ No ☐
4. Active suicidal ideation with some intent to act, without specific plan When the subject acknowledges that he has suicidal ideation with some intent to act on such thoughts. It is different from the statement, "I have thoughts (of suicide), but I have no intention to do anything." ***Have you ever thought you would like to commit suicide and want to execute it?*** If yes, details	Yes ☐ No ☐
5. Active suicidal ideation with specific plan and intent When the subject has suicidal ideation with a specific plan (complete or partial) and some intent to act. ***Do you have a specific plan for how to commit suicide? Do you intend to implement the plan?*** If yes, details	Yes ☐ No ☐

Degree of Suicidal Ideation

The following questions rate the most severe suicidal ideation (eg, in 1 to 5 above, 1 represents the least severe ideation and 5 represents the most severe ideation). ***Most severe suicidal ideation:*** _____ ***Type no. (1 to 5)*** _____ ***Description of suicidal ideation***	Most severe
Frequency ***How often did you think so?*** (1) Less than once a week (2) Once a week (3) Two to five times a week (4) Every day/almost every day (5) Many times a day	—
Duration ***How long did these thoughts last?*** (1) Several seconds to several minutes/instantaneous (2) Less than 1 hour/for a while (3) 1 to 4 hours/quite a while (4) 4 to 8 hours/most of the day (5) 8 hours or more/continuous	—
Control ***Can/could you suppress thoughts of suicide or thoughts of wanting to die if you want/wanted to?*** (1) Easily able to suppress thoughts (2) Can suppress thoughts although it is a little difficult (3) Some difficulty but can suppress thoughts (4) Very difficult but can suppress thoughts (5) Cannot suppress thoughts (0) Not willing to suppress thoughts	—
Deterrents ***Is there any person or thing (eg, family, religion, pain of dying) that suppressed your thoughts of wanting to die or stopped you from committing suicide?*** (1) Deterrents stopped me from committing suicide (2) Deterrents probably stopped me from committing suicide (3) Not sure if the deterrents stopped me from committing suicide (4) Deterrents probably do not stop me from committing suicide (5) Deterrents do not stop me from committing suicide (0) Not applicable	—
Reasons for Suicidal Ideation ***Why did you want to die or commit suicide? Was it to end the pain or evade the emotions you had at that time (eg, you could not live with such pain or emotions)? Was it to get someone's attention, revenge, or a reaction? Was it both?*** (1) Solely to get someone's attention, revenge, or a reaction (2) Mostly to get someone's attention, revenge, or a reaction (3) Both (50/50) to get someone's attention, revenge, or a reaction and to end the pain (4) Mostly to end the pain (unable to live with the pain or emotions) (5) Solely to end the pain (unable to live with the pain or emotions) (0) Not applicable	—

 C-SSRS–Since Last Visit (14 Jan 2009 Version) Page 1/2

Suicidal Behavior *(Tick all that apply. Asked about all types of suicidal behavior listed below.)*	Since Last Visit
Suicide attempt: When behavior that may cause self-harm was associated with any desire to die as a result of the behavior. This includes cases where the intent to commit suicide is not complete. If the subject has an intent or desire to die as a result of the behavior ***even a little***, it is considered a "suicide attempt." This includes cases where there is a risk of physical damage ***even without actual physical damage***. When a gun is in the mouth and the trigger is pulled, it is considered a "suicide attempt" even if the gun is broken and no physical damage is caused. When suicidal intent is presumed: When suicidal intent can be presumed from the behavior and circumstances even if the subject denies intent or desire to die. For example, when behavior is extremely lethal and obviously not an accident and its only possible intent is suicide (eg, gunshot to head, jumping from an upper floor). Even if the subject denies intent to commit suicide, the intent to commit suicide can be presumed if the subject believes at the time that his behavior may result in death. ***Have you ever attempted suicide?*** ***Have you done anything to harm yourself?*** ***Have you done any dangerous behavior that could result in death?*** ***What did you do?*** ***Was _____ as a means of suicide?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to die when you _____?*** ***Or, were you aware of the possibility of death when you _____?*** ***Did you not intend to die when you did it, and did you have another reason (eg, stress relief, feel better, get sympathy, change circumstances)?*** (Self-injurious behavior without suicidal intent) If yes, details **Have you had any self-injurious behavior without suicidal intent?**	Yes ☐ No ☐ Total number of times _____ Yes ☐ No ☐
Interrupted suicide attempt: When behavior that might result in self-harm was interrupted (due to external factors) (if it had not been interrupted, it would have resulted in "suicide attempt"). Drug overdose: The subject took the drug in hand but stopped taking it. Even a small dose is considered a "suicide attempt" rather than an "interrupted suicide attempt." Gun suicide: The subject directed a gun to himself but someone took the gun away or prevented him from pulling the trigger in some way. When the subject pulls the trigger, even if the gun fails to fire, it is considered a "suicide attempt." Jumping: The subject was in a position to jump down but was pulled down. Hanging: A rope was around the neck but hanging was blocked. ***Have you been stopped by someone else or something after you started to commit suicide and before you actually proceed to behavior that would end your life?*** If yes, details	Yes ☐ No ☐ Total number of times ___
Self-interrupted suicide attempt: When the subject nearly attempted suicide but held back before actually proceeding to self-destructive behavior. This is similar to an example of "interrupted suicide attempt," but it refers to the case where suicide attempt was interrupted by the subject himself and not by something else. ***Have you held back after starting to commit suicide and before actually proceeding to behavior that would end your life?*** If yes, details	Yes ☐ No ☐ Total number of times ___
Preparatory behavior: Any preparation or behavior in preparation for suicide that exceeds the level of verbalizing or thinking about suicide. For example, preparing for suicide means (eg, obtain drugs, purchase weapons) and preparing for death from suicide (eg, release personal belongings, write a suicide note). ***Have you taken any action in preparation for suicide attempt or suicide (eg, obtain a drug, obtain a weapon, release an important thing, write a suicide note)?*** If yes, details	Yes ☐ No ☐
Suicidal behavior: Suicidal behavior was observed during the evaluation period.	Yes ☐ No ☐
Completed suicide:	Yes ☐ No ☐
Answer only when "suicide attempt" occurred	Date of most lethal suicide attempt:
Actual lethality/physical damage: 0. No physical damage or extremely mild physical damage (eg, scratch) 1. Mild physical damage (eg, slurred speech, first-degree burns, mild bleeding, sprain) 2. Moderate physical damage requiring treatment (eg, conscious but lightheaded, somewhat responsive, second-degree burns, bleeding from vessel) 3. Slightly severe physical damage that requires hospitalization and likely to require intensive care (eg, comatose but normal reflexes, third-degree burns of <20%, major bleeding but can recover, major fractures) 4. Severe physical damage requiring hospitalization with intensive care (eg, comatose with reflexes missing, third-degree burns of ≥20%, major bleeding with unstable vital signs, major damage to life-threatening area) 5. Death	*Enter code* ___
Likelihood of Lethality: Answer only if actual lethality/physical damage = 0 The lethality of "suicide attempt" without physical damage (In the following cases, there is no actual physical damage but extremely high likelihood of lethality: The subject put a gun in the mouth and pulled the trigger, but no physical damage occurred because the gun did not fire. The subject lay on train railway but exited before being run over.) 0 = Suicidal behavior with low potential for physical damage 1 = Suicidal behavior that is likely to cause physical damage but unlikely to result in death 2 = Suicidal behavior that is likely to result in death despite treatment	*Enter code* ___

