CLINICAL STUDY PROTOCOL

A Randomized, Multi-center, Double-blind, Placebo-controlled, Parallel-group Comparison Trial to Assess Efficacy and Safety of OPC-64005 in Patients With Major Depressive Disorder

NCT Number: NCT04244253
PRT NO.: 277-102-00027
Version Date: 31 Mar 2020

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-64005

REVISED CLINICAL PROTOCOL

A Randomized, Multi-center, Double-blind, Placebo-controlled, Parallel-group Comparison Trial to Assess Efficacy and Safety of OPC-64005 in Patients With Major Depressive Disorder

A Phase 2 Trial of OPC-64005 for Major Depressive Disorder

Protocol No. 277-102-00027

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event	Pharmacovigilance Operations, Pharmacovigilance Email: IRE_277-102-00027@otsuka.jp
Amendment 1 Approval:	31 Mar 2020
Original Approval:	20 Dec 2019
(Date of Translation:	15 Nov 2021)

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1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product:

OPC-64005

Protocol No.:

277-102-00027

Protocol Title:

A Randomized, Multi-center, Double-blind, Placebo-controlled, Parallel-group Comparison Trial to Assess Efficacy and Safety of OPC-64005 in Patients With Major Depressive Disorder

Protocol Lay Person Short Title:

A Phase 2 Trial of OPC-64005 for Major Depressive Disorder

Clinical Phase/Trial Type:

Phase 2/Exploratory trial

Treatment/Indication:

Patients with major depressive disorder

Objectives and Endpoints:

The objective of the trial is to compare the efficacy of OPC-64005 at 20 mg vs placebo and to assess the safety and pharmacokinetics of OPC-64005 at 10 and 20 mg in patients with major depressive disorder (MDD). The primary endpoint is the mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6 of the double-blind treatment period in the OPC-64005 20-mg group compared with the placebo group.

Trial Design:

A multi-center, randomized, double-blind, placebo-controlled, parallel-group comparison trial

Trial Population:

270 male and female patients ≥ 20 to < 65 years of age (at time of informed consent) diagnosed with either "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

Key Inclusion/Exclusion Criteria:

Key inclusion criteria
At informed consent and at screening (Visit 1):

- Patients with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" with the current episode persisting for ≥ 4 weeks to ≤ 1 year

At start of placebo lead-in period (Visit 2):

- Patients with a total score of ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D) based on evaluation performed at start of the placebo lead-in period

At baseline (Visit 3):

- Patients with a HAM-D 17-item total score of ≥ 18 based on evaluation performed at baseline

Key exclusion criteria

At informed consent and at screening (Visit 1):

- Patients with a diagnosis of any of the following diseases according to DSM-5: Neurocognitive disorders, history or complication of schizophrenia spectrum or other psychotic disorder, history or complication of bipolar and related disorders, feeding and eating disorders, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, personality disorders, neurodevelopmental disorders, substance-related and addictive disorders (within 180 days prior to the date of informed consent)
- Patients exhibiting mood-incongruent psychotic features in the current major depressive episode
- Patients who, in the opinion of the investigator, are judged to have treatment-resistant depression, ie, a certain degree of therapeutic effect is not obtained by administration of 2 or more antidepressants having different mechanisms of action at sufficient doses for at least 6 weeks for the current major depressive episode
- Patients receiving augmentation treatment, such as antipsychotics, for the current major depressive episode (excluding the use of sulpiride for depression/depressive state or gastric/duodenal ulcer)

At start of placebo lead-in period (Visit 2):

- Patients with a MADRS Self-assessment (MADRS-S) total score of < 8.5 based on evaluation performed at the start of the placebo lead-in period

At baseline (Visit 3):

- Patients with a MADRS-S total score of < 8.5 based on evaluation performed at baseline or with ≥ 25% reduction in MADRS-S total score at baseline compared with at the start of the placebo lead-in period

Trial Site(s):

Approximately 100 sites in Japan

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Dose Group	Placebo Lead-in Period (Single-blind With Subjects Blinded to Treatment Received)	Double-blind Treatment Period	Double-blind Tapering Period
OPC-64005 10-mg group	Two placebo tablets administered orally once daily for 1 week	One placebo tablet and one OPC-64005 10-mg tablet administered orally once daily for 6 weeks	Two placebo tablets administered orally once daily for 1 week
OPC-64005 20-mg group		One placebo tablet and one OPC-64005 10-mg tablet administered orally once daily for 1 week, followed by two OPC-64005 10-mg tablets for 5 weeks	One placebo tablet and one OPC-64005 10-mg tablet administered orally once daily for 1 week
Placebo group		Two placebo tablets administered orally once daily for 6 weeks	Two placebo tablets administered orally once daily for 1 week

Trial Assessments:

Assessments for efficacy: MADRS, Clinical Global Impression – Improvement (CGI-I), Clinical Global Impression – Severity of Illness (CGI-S), HAM-D, MADRS-S, and Apathy Scale

Assessments for pharmacokinetics, pharmacogenomics, and future biospecimen research: Plasma PK assessment, cytochrome P450 (CYP) 2D6 genetic testing, and blood sampling for DNA storage

Assessments for safety: Laboratory tests, vital signs, physical examination, height, body weight, waist circumference, 12-lead electrocardiogram (ECG), pregnancy test, Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse events (AEs)

Screening/Other: Medical and treatment history, etc

Data Monitoring Committee: No

Statistical Methods:

Statistical Methods for Primary Endpoint:
The primary endpoint is the change from baseline in MADRS total score at Week 6 of the double-blind treatment period.

For the primary analysis, mixed-model repeated-measure (MMRM) analysis will be performed using the observed cases dataset of the full analysis set.

The MMRM will include treatment group (OPC-64005 10-mg group, OPC-64005 20-mg group, and placebo group), timepoint (double-blind treatment period Weeks 1, 2, 3, 4, 5, and 6), and interaction between treatment group and timepoint as factors, and baseline and interaction between baseline and timepoint as covariates. An unstructured error variance-covariance structure will be assumed. For degree-of-freedom approximation, the Kenward-Roger method will be used. The statistical comparison will be performed based on differences in the least square means at double-blind treatment period Week 6 between the OPC-64005 20-mg group and the placebo group.

For each timepoint, the least square mean of each treatment group and the differences in the least square means between each OPC-64005 group and the placebo group, as well as the two-sided 95% confidence intervals, will be determined.

Rationale for target number of subjects:
As no clinical trials of OPC-64005 in patients with major depressive disorder have been previously conducted, the target number of subjects was determined based on the results from another antidepressant clinical trial using MADRS score as the primary endpoint.

In the phase 3 clinical trial of escitalopram conducted outside Japan,[1] the mean change (± SE) from baseline in MADRS total score at the final timepoint of Week 8 (8 weeks after start of administration) determined using last observation carried forward analysis of covariance was −9.4 ± 0.9 in the placebo group (n = 119), −12.0 ± 0.9 in the citalopram 40-mg group (n = 125), −12.8 ± 0.8 in the escitalopram 10-mg group (n = 118), and −13.9 ± 0.8 in the escitalopram 20-mg group (n = 123). Referring to those results, in the present trial it is assumed that the difference between the OPC-64005 20-mg group and the placebo group in the change from baseline in MADRS total score at Week 6 of the double-blind treatment period will be −4 with a standard deviation of 11. To ensure a power of 80% in a two-sided test with a significance level of 0.05, 120 subjects each are required for the OPC-64005 20-mg group and the placebo group. For the OPC-64005 10-

mg group, the number of subjects was set at 30 without statistical consideration. The planned number of subjects to be randomized for the trial was therefore set at 270.

Trial Duration:

- Screening period: ≤ 4 weeks
- Placebo lead-in period (Single-blind with subjects blinded to treatment received): 1 week
- Double-blind treatment period: 6 weeks
- Double-blind tapering period: 1 week
- Post-treatment observation period: 2 weeks

The overall trial period from the time informed consent is obtained from the first subject until completion of the last observation of the last subject is planned to be 21 months.

1.2 Schema

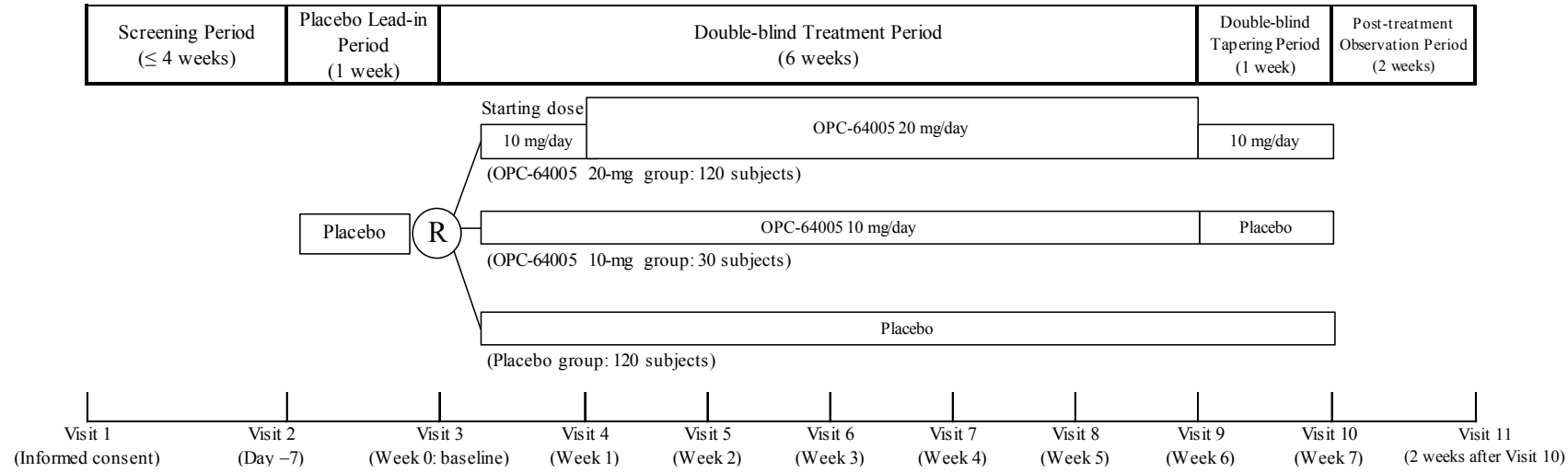

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period	Screening	Placebo Lead-in[a]	Double-blind Treatment							Double-blind Tapering	Post-treatment Observation[j]	At Discontinuation[k]
Visit	Visit 1	Visit 2 (Week −1)	Visit 3 (Baseline)	Visit 4 (Week 1)	Visit 5 (Week 2)	Visit 6 (Week 3)	Visit 7 (Week 4)	Visit 8 (Week 5)	Visit 9 (Week 6)	Visit 10 (Week 7)	Visit 11 (2 weeks after Visit 10 or the final dosing)	
Day ± allowable window	Day −35 to the day before Visit 2	Day −7 ± 1 day	Day 1	Day 8 ± 1 day	Day 15 ± 2 days	Day 22 ± 2 days	Day 29 ± 2 days	Day 36 ± 2 days	Day 43 ± 2 days	Day 50 ± 2 days	14 days ± 7 days after Visit 10 or the final dosing	
Informed consent	●											
Demographics	●											
Concomitant medications/therapies	◄											►
Eligibility assessment	●	●	●									
Randomization			●									
MADRS	●	●	●	●	●	●	●	●	●			●
CGI-I				●	●	●	●	●	●			●[l]
CGI-S	●	●	●	●	●	●	●	●	●			●
HAM-D	●	●	●						●			●
MADRS-S	●	●	●	●	●	●	●	●	●			●
Apathy Scale			●						●			●
Laboratory tests[b]	●		●						●			●
Vital signs[c]	●	●	●	●	●	●	●	●	●	●		●
Physical examination	●	●	●	●	●	●	●	●	●	●	●	●
Height[d] and body weight, waist circumference	●		●						●			●
12-lead ECG	●		●		●		●		●			●

Table 1.3-1 Schedule of Assessments

Period	Screening	Placebo Lead-in[a]	Double-blind Treatment							Double-blind Tapering	Post-treatment Observation[j]	At Discontinuation[k]
Visit	Visit 1	Visit 2 (Week −1)	Visit 3 (Baseline)	Visit 4 (Week 1)	Visit 5 (Week 2)	Visit 6 (Week 3)	Visit 7 (Week 4)	Visit 8 (Week 5)	Visit 9 (Week 6)	Visit 10 (Week 7)	Visit 11 (2 weeks after Visit 10 or the final dosing)	
Day ± allowable window	Day −35 to the day before Visit 2	Day −7 ± 1 day	Day 1	Day 8 ± 1 day	Day 15 ± 2 days	Day 22 ± 2 days	Day 29 ± 2 days	Day 36 ± 2 days	Day 43 ± 2 days	Day 50 ± 2 days	14 days ± 7 days after Visit 10 or the final dosing	
Pregnancy test[e]	•	•								•		•
C-SSRS	•	•	•	•	•	•	•	•	•	•	•	•
AEs	←											→
Blood sampling for plasma PK assessment[f]				•	•		•		•			
Blood sampling for CYP2D6 genetic testing			•[h]									
Blood sampling for DNA storage[g]			•[h]									
IMP dispensing[i]		•	•	•	•	•	•	•	•			•
IMP compliance			•	•	•	•	•	•	•	•		•

[a]The placebo lead-in period is conducted in a single-blind manner with subjects blinded to treatment received.

[b]Blood will be withdrawn under fasting conditions (fasting [including juices and other sugar-containing beverages] for at least 8 hours) at Visit 3 and Visit 9. Blood will be withdrawn under fasting conditions wherever possible at Visit 1, Visit 11, and discontinuation.

[c]Body temperature, systolic/diastolic blood pressure, pulse rate (blood pressure and pulse rate in the supine, sitting, and standing positions), and respiratory rate (sitting position) will be measured.

[d]Height will be measured at screening only.

[e]A urine pregnancy test will be performed. If the urine pregnancy test is positive, a serum pregnancy test will be performed.

[f]Blood sampling time is not specified for blood sampling for plasma PK assessment.

[g]Blood sample will be collected from subjects who consented blood sampling for DNA storage.

[h]If blood samples cannot be collected or blood samples need to be recollected for some reason, blood samples should be collected during the trial.

[i]Follow the instruction of the Interactive Response Technologies (IRT) system. If the dose is tapered after treatment discontinuation, the investigational medicinal product (IMP) will be dispensed according to the instruction of the IRT system because the IMP is administered under double-blind conditions.

[j]Performed in subjects who started IMP administration after Visit 3.

[k]Performed if discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration at Visit 9.

[l]Not performed if discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration at Visit 3.

1.4 Trial Procedures

The investigator will perform the investigations, observations, and examinations according to the schedule of assessments (Table 1.3-1), and record the visit date and results of investigations, observations, and examinations in the source document and electronic case report form (eCRF). The demographic investigation, laboratory tests, and other test items, which the clinical trial associate is allowed to perform, may be performed by the clinical trial associate under the supervision of the investigator.

1.4.1 Visit 1

1.4.1.1 At Informed Consent

Prior to the screening examination, the investigator will obtain written consent from the subject, assign a subject identification (ID) number to the subject, and record the subject ID number and date of informed consent in the subject screening log, source document, and eCRF. It is acceptable to obtain informed consent on a day before Visit 1.

1.4.1.2 Screening Examination

After obtaining informed consent, the investigator will perform Visit 1 observations and examinations, and judge whether the subject is eligible to participate in the trial. At this time, the investigator will record whether the subject is eligible/ineligible for registration, date of registration, and reason for the judgment if ineligible, in the subject screening log.

The investigator will ascertain the following demographic information.

- Date of birth
- Sex
- Childbearing potential (see 10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information for the definition) in female subjects (if no childbearing potential, the reason shall be recorded)
- Race
- Ethnicity
- Country
- DSM-5 diagnosis, severity, and specifiers (with anxious distress, with mixed features, with melancholic features, with atypical features, with mood-congruent psychotic features, with mood-incongruent psychotic features, with catatonia, peripartum onset, seasonal pattern)
- Initial onset of MDD
- Number of major depressive episodes
- Onset timing of the current major depressive episode
- Prior medications (all antidepressants) for the current major depressive episode

- Prior therapies (psychotherapies/somatotherapies performed within 6 weeks before informed consent) for the current major depressive episode
- All prior medications used within 28 days before informed consent, and prior therapies performed within 6 weeks before informed consent
- Medical history (within 2 years of informed consent, however, those related to the inclusion/exclusion criteria are not limited to 2 years)
- Complications

The investigator will register the required information in the Interactive Response Technologies (IRT) system.

If antidepressants are being used at Visit 1, the use of the drug(s) should be discontinued by Visit 2 by appropriately tapering the dose if necessary, taking safety into consideration (the use of antidepressants is permitted until the day before Visit 2) (see Section 6.5.1.2). If the dose of antidepressants is to be tapered, the subject should visit the trial site to confirm safety, where appropriate.

1.4.2 Visit 2

The investigator will perform Visit 2 observations and examinations within 28 days after Visit 1 and confirm the eligibility of the subject. Eligible subjects will be registered in the IRT system with the required information and start investigational medicinal product (IMP) administration (placebo). Ineligible subjects will also be registered in the IRT system with the required information. Visit 2 examinations can be performed on the same day of Visit 1 examinations in subjects who are naive to antidepressants or subjects who need no dose tapering of antidepressants used as prior therapy. In these cases, test values from Visit 1 can be used as test values of Visit 2.

1.4.3 Visit 3

The investigator will perform Visit 3 observations and examinations 7 days (± 1 day) after Visit 2 and confirm the eligibility of the subject. Eligible subjects will be registered in the IRT system with the required information and assigned the IMP. The date of randomization is regarded as Day 1. Ineligible subjects will also be registered in the IRT system with the required information.

1.4.4 Visit 4 Through Visit 9

The investigator will perform the observations and examinations specified for Visits 4, 5, 6, 7, 8, and 9 on Days 8 (± 1 day), 15 (± 2 days), 22 (± 2 days), 29 (± 2 days), 36 (± 2 days), and 43 (± 2 days), respectively. The investigator will register the required information in the IRT system and dispense the IMP.

1.4.5 Visit 10

The investigator will perform Visit 10 observations and examinations on Day 50 (± 2 days). The investigator will register the required information in the IRT system.

1.4.6 Visit 11

The investigator will perform Visit 11 observations and examinations 14 days (± 7 days) after the date of last IMP dose in all subjects who started IMP administration after Visit 3. The investigator will register the required information in the IRT system at the end of the post-treatment observation period for each subject.

1.4.7 At Discontinuation

If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 9, the investigator will perform the examination at discontinuation specified in the schedule of assessments, and record the results and the visit date in the source document and eCRF. The investigator will register the required information in the IRT system.

If discontinuation occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 3, it is not necessary to perform the post-treatment observation (Visit 11) after the examination at discontinuation has been performed.

If discontinuation occurs during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]) after the examination at discontinuation has been performed, and then the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. However, if the investigator judges that the IMP needs to be discontinued due to an adverse event (AE) or if the IMP dose cannot be tapered due to the subject's circumstances such as he/she does not wish to taper the dose, dose tapering is not mandatory, and the examination at discontinuation will be performed followed by the post-treatment observation (Visit 11) 2 weeks after the date of the final dosing.

If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4, dose tapering is not necessary after the examination at discontinuation has been performed, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.

If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 9 and Visit 10, the examination at discontinuation is not necessary, the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.

2 Introduction

OPC-64005 is a serotonin-noradrenaline-dopamine triple reuptake inhibitor (TRI) synthesized by Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as Otsuka Pharmaceutical). It is being developed for the indication of depression/depressed state in Japan.

Please refer to the OPC-64005 investigator's brochure (IB) for more detailed information.

2.1 Trial Rationale

Depression (major depressive disorder [MDD]) is a psychiatric disease with mood/affective disorders such as depressed mood and loss of interest/pleasure as prominent symptoms. While the etiology of MDD has not been fully clarified, one of the most common hypotheses is the monoamine hypothesis, and reduced monoamines (serotonin, noradrenaline, and dopamine) in synaptic clefts is considered to be one of the causes of MDD.

OPC-64005 is a TRI that inhibits reuptake of serotonin, noradrenaline, and dopamine. Nonclinical studies confirmed that OPC-64005 inhibited monoamine reuptake of serotonin, noradrenaline, and dopamine, increased extracellular concentrations of serotonin, noradrenaline, and dopamine in the rat medial prefrontal cortex (mPFC), and increased extracellular dopamine concentrations in the striatum. In addition, OPC-64005 showed significant antidepressant-like effects in a rat forced swimming test and significant anxiolytic-like effects in a rat elevated plus maze test. Furthermore, Japan and overseas phase 1 trials in healthy adults using positron emission tomography (PET)-labeled ligands (PET trials) confirmed that OPC-64005 binds to each intracerebral transporter of serotonin, noradrenaline, and dopamine (SERT, NET, and DAT, respectively) (Trials 277-10-205, 277-13-001, and 277-14-001). It is therefore expected that, based on the mechanism of action, the results of the nonclinical studies, and the results of the PET trials in healthy adults, OPC-64005 may exert therapeutic effects for the treatment of MDD.

In addition, in the Japanese and overseas phase 1 trials in healthy adults, the safety and tolerability of repeated administration of OPC-64005 at a dose of up to 30 mg were confirmed.

Therefore, it was judged appropriate to plan a phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group comparison trial in patients with MDD to assess the efficacy and safety of OPC-64005 in MDD at doses for which safety and tolerability have been confirmed in repeated administration.

See Section 4.2 for the rationale for the trial design.

2.2 Background

2.2.1 History of Development

Major depressive disorder is a psychiatric disorder with mood/affective disorders such as depressed mood and loss of interest/pleasure as prominent symptoms, and accompanies reduced thinking and concentration, decreased or increased appetite, anxiety, feeling of self-worthlessness and self-accusation, suicidal ideation, and sleep disorder. In Japan, the prevalence of MDD among psychiatric disorders is high with its lifetime prevalence reported to be 5.7% and the 12-month prevalence reported to be 2.7%.[2] Furthermore, there are significant socio-economic losses due to decreased social functioning such as absence from work and unemployment due to depression and an increased number of suicides. Therefore, treatment of depression plays a socially important role.

The mainstay of treatment of MDD is pharmacotherapy with antidepressants, with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and mirtazapine recommended as first-line drugs. However, the response rate to treatment with antidepressants is reported to be 50% to 65%,[3] and there are still patients who do not adequately respond to antidepressants. Selective serotonin reuptake inhibitors and SNRIs, which are commonly used as first-line drugs for MDD at present, are drugs based on the monoamine hypothesis, and act on the serotonergic system and the serotonergic system/noradrenergic system, respectively, but their action on the dopaminergic system is weak. When considering drug therapy for MDD based on the monoamine hypothesis, most evidence supports drugs that concurrently act on the serotonergic system, noradrenergic system, and dopaminergic system. Dopamine is known to play a key role in reward, motivation, mood control, working memory, attention, and executive function. Addition of the action on the dopaminergic system to the actions on the serotonergic and noradrenergic systems is expected to alleviate anhedonia, which is one of the core symptoms of MDD that does not adequately respond to SSRIs and SNRIs, and to improve recognition and motivation.[4]

As mentioned above, drugs that simultaneously control the serotonergic system, noradrenergic system, and dopaminergic system are considered to be beneficial antidepressants and are expected to be a new therapeutic option for MDD as drugs with different mechanisms of action from SSRIs or SNRIs. Given this background, we embarked upon the development of OPC-64005, which inhibits reuptake of serotonin, noradrenaline, and dopamine, in patients with MDD.

2.2.2 Results of Nonclinical Studies

OPC-64005 is a TRI that inhibits reuptake of serotonin, noradrenaline, and dopamine, and it has been confirmed to exhibit inhibitory activities on serotonin, noradrenaline, and dopamine reuptake into rat brain synaptosomes (concentration of drug producing 50% inhibition [IC_{50}] is 1.131 nM, 0.9684 nM, and 102.9 nM, respectively). In a microdialysis study, OPC-64005 significantly and dose-dependently increased extracellular concentrations of serotonin, noradrenaline, and dopamine in the mPFC. Moreover, OPC-64005 significantly and dose-dependently increased extracellular dopamine concentrations in the striatum at a dose 10-fold higher than that in the mPFC. Furthermore, in the rat forced swimming test, OPC-64005 showed significant antidepressant-like effects. In the rat elevated plus maze test, OPC-64005 showed significant anxiolytic-like effects.

2.2.3 Results of Clinical Trials

A total of 3 clinical trials in healthy adults (Trials 277-13-001, 277-14-001, and 277-10-205) were conducted in Japan and overseas to evaluate SERT, NET, and DAT occupancy following administration of OPC-64005.

Following a single dose of OPC-64005, plasma OPC-64005 concentrations increased reaching a peak at around 3 hours postdose, and then rapidly decreased. The SERT and NET occupancy increased with an increase in plasma OPC-64005 concentrations. In several models, the maximum effect (E_{max}) on the SERT occupancy, 50% effective concentration (EC_{50}), E_{max} on the NET occupancy, and EC_{50} were estimated to be 73.3% to 84.8%, 5.5 to 8.84 ng/mL, 117%, and 18.8 ng/mL, respectively. Significant binding of OPC-64005 to SERT and NET was also observed at 24 hours postdose, and the SERT and NET occupancy at 24 hours after a single dose of OPC-64005 (60 mg) was > 74% and > 71%, respectively. The pharmacodynamic (PD) data indicated that OPC-64005 administered once daily may continuously occupy the transporters.

Following repeated doses of OPC-64005 (30 mg) once daily for 14 days, the mean DAT occupancy was 27.8% at 2 hours postdose (plasma concentration range: 138 to 257 ng/mL) and 24.4% at 24 hours postdose (plasma concentration range: 60.8 to 127 ng/mL).

2.3 Known and Potential Risks and Benefits

OPC-64005 is a TRI and has the potential to induce symptoms associated with SERT inhibition (eg, gastrointestinal disorder, sexual dysfunction, migraine) and symptoms associated with NET inhibition (eg, tachycardia, tremor) due to its mechanism of

action.[5,6] Worsening of psychiatric symptoms, Parkinsonism, and psychomotor hyperactivity may also develop due to DAT inhibition.[6]

In earlier Japanese and overseas phase 1 trials (Trials 277-10-001, 277-12-001, 277-09-201, 277-13-001, 277-14-001, 277-10-205, 277-10-204, 277-09-202, and 277-10-206), a single dose or repeated doses of OPC-64005 at doses between 1 mg and 60 mg was/were administered to 313 healthy adults. In addition, in overseas, a phase 2 trial in patients with attention-deficit/hyperactivity disorder (AD/HD) (Trial 277-201-00001) was conducted and OPC-64005 (at 20 to 30 mg) was administered to 77 subjects.

In the phase 1 trials in healthy adults, the following AEs were reported in ≥ 5% of the 313 subjects who received OPC-64005: nausea (53 subjects, 16.9%), tachycardia (30 subjects, 9.6%), dizziness (30 subjects, 9.6%), headache (24 subjects, 7.6%), and presyncope (17 subjects, 5.4%). In the phase 2 trial in AD/HD patients, the following AEs were reported in ≥ 5% of the 77 subjects who received OPC-64005: dry mouth (15 subjects, 19.5%), nausea (14 subjects, 18.2%), decreased appetite (13 subjects, 16.9%), fatigue (7 subjects, 9.1%), dizziness (6 subjects, 7.8%), headache (6 subjects, 7.8%), insomnia (6 subjects, 7.8%), constipation (5 subjects, 6.5%), nasopharyngitis (4 subjects, 5.2%), and sedation (4 subjects, 5.2%).

Other than the above AEs, although the incidence is not high, skin eruption (rash) may occur after administration of OPC-64005, and it was reported in 5 healthy adult subjects and 2 AD/HD patients.

In addition, as serious adverse events (SAEs), supraventricular tachycardia was reported in 1 healthy adult subject (relationship to IMP: possibly related) and suicide attempt was reported in 1 AD/HD patient (relationship to IMP: not related).

As described above, there is a risk that AEs reported in the above clinical trials, including AEs that may occur due to inhibition of SERT, NET, and DAT, may occur after administration of OPC-64005. However, AEs other than those mentioned above may occur and careful monitoring is necessary.

The benefits of participating in the trial include the fact that depressive symptoms may improve, and that during the trial the subjects could receive more detailed tests and examinations by physicians than they could have with just general examinations. As of Oct 2019, no TRIs have been approved for the indication of depression/depressive symptoms in Japan or overseas.

3 Objectives and Endpoints

The objective of the trial is to compare the efficacy of OPC-64005 at 20 mg vs placebo and to assess the safety and pharmacokinetics (PK) of OPC-64005 at 10 and 20 mg in patients with MDD.

The primary endpoint is the mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6 of the double-blind treatment period in the OPC-64005 20-mg group compared with the placebo group.

The secondary endpoints are the MADRS response rate (proportion of subjects with ≥ 50% reduction from baseline in MADRS total score at Week 6 of the double-blind treatment period), MADRS remission rate (proportion of subjects with MADRS total score ≤ 10 and ≥ 50% reduction from baseline in MADRS total score at Week 6 of the double-blind treatment period), Clinical Global Impression – Improvement (CGI-I) improvement rate (proportion of subjects with CGI-I of 1 or 2 at Week 6 of the double-blind treatment period), mean change from baseline in Clinical Global Impression – Severity of Illness (CGI-S), mean change from baseline in the total score of 17 items of the Hamilton Rating Scale for Depression (HAM-D), mean change from baseline in Apathy Scale score, mean change from baseline in the total score of MADRS Self-assessment (MADRS-S), and mean change from baseline in MADRS anhedonia factor score for evaluation of the efficacy of OPC-64005 at 20 mg.

The safety and PK of OPC-64005 at 10 mg and 20 mg will also be assessed in patients with MDD.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To compare the efficacy of OPC-64005 at 20 mg vs placebo administered orally as repeated doses once daily for 6 weeks in patients with MDD	Primary endpoint: Change from baseline in MADRS total score at Week 6 of the double-blind treatment period Secondary endpoints: MADRS response rate, MADRS remission rate, CGI-I improvement rate, mean change from baseline in CGI-S, mean change from baseline in HAM-D 17-item total score, mean change from baseline in Apathy Scale score, mean change from baseline in MADRS-S total score, mean change from baseline in MADRS anhedonia factor score
Secondary: To assess the safety and PK of OPC-64005 administered orally as repeated doses at 10 mg or 20 mg once daily for 6 weeks in patients with MDD	Safety endpoints: Laboratory tests, vital signs, physical examination, height, body weight, waist circumference, 12-lead electrocardiogram (ECG), pregnancy test, Columbia-Suicide Severity Rating Scale (C-SSRS), and AEs PK

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

In this trial, OPC-64005 at 10 mg or 20 mg or placebo will be orally administered as repeated doses once daily for 6 weeks in 270 patients with MDD, and the efficacy, safety, and PK of OPC-64005 will be assessed. This is a phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group comparison trial consisting of 5 periods: screening period, placebo lead-in period (single-blind with subjects blinded to treatment received), double-blind treatment period, double-blind tapering period, and post-treatment observation period.

4.2 Scientific Rationale for Trial Design

The trial was designed with reference to the Guideline for Clinical Evaluation of Antidepressants[7] (hereinafter referred to as the Clinical Evaluation Guideline). The Clinical Evaluation Guideline states that "a double-blind, placebo-controlled comparison trial is necessary for evaluation of efficacy of antidepressants" and "duration of treatment in exploratory and confirmatory trials of antidepressants is generally 6 to 8 weeks." Therefore, this trial was designed as a randomized, double-blind, placebo-controlled, parallel-group comparison trial to appropriately assess the efficacy and safety with a 6-week double-blind treatment period.

The screening period was set as a necessary period to confirm the inclusion/exclusion criteria and wash out prior medications. The placebo lead-in period (single-blind with subjects blinded to treatment received) was set because it is preferable to exclude subjects with significant changes in symptoms for the purpose of appropriately evaluating the efficacy of OPC-64005. Although no AEs related to withdrawal symptoms have been reported after the end of administration of OPC-64005 in previous trials, the double-blind tapering period was set because when antidepressants are discontinued, a gradual reduction in dose is generally recommended. The post-treatment observation period was set to confirm the safety of subjects after administration of the final dose of OPC-64005.

4.3 Dosing Rationale

4.3.1 Rationale for Mode of Administration

The results of the PET trials in healthy adults confirmed that OPC-64005 maintained intracerebral SERT, NET, and DAT occupancy for 24 hours after administration (Trials

277-10-205, 277-13-001, and 277-14-001), and OPC-64005 is expected to be effective when administered once daily. Accordingly, a dosing regimen of once-daily administration was set.

In the overseas phase 2 trial in AD/HD patients (Trial 277-201-00001), OPC-64005 administered at 30 mg once daily for 8 weeks (starting dose: 20 mg/day, 4 days) resulted in a statistically significant improvement in symptoms compared with the placebo.

4.3.2 Rationale for Dose

The dose of OPC-64005 in this trial was determined based on estimated receptor occupancy of each monoamine transporter obtained from a simulation analysis[8] of a PK/PD model, which was newly conducted using the results of the PET trials in healthy adults.[9]

There are many studies on intracerebral monoamine receptor occupancy of antidepressants, and PET trials[10,11,12] of various drugs reported that the ideal monoamine transporter occupancy by TRIs, taking antidepressant effect and safety into account, are ≥ 80% for SERT, 50% to 70% for NET, and ≤ 30% for DAT.[13]

Table 4.3.2-1 shows the estimated maximum occupancy of each monoamine transporter by OPC-64005 in the steady-state after repeated administration of OPC-64005. The SERT occupancy reached approximately 70% at OPC-64005 10 mg. The NET occupancy was > 50% at OPC-64005 10 mg and > 60% at 20 mg. The DAT occupancy reached 25% at OPC-64005 20 mg. OPC-64005 is a TRI expected to be a new therapeutic option for depression. Since OPC-64005 is expected to act on serotonin, noradrenaline, and dopamine at 20 mg based on the estimated occupancy, 20 mg was selected as the dose for assessing efficacy and safety in this trial.

Table 4.3.2-1 Estimated Maximum Occupancy (Median) of Each Monoamine Transporter by OPC-64005 in Steady-state

OPC-64005 Dose	5 mg	10 mg	20 mg	30 mg
SERT	64%	71%	74%	75%
NET	40%	55%	63%	66%
DAT	5%	12%	25%	34%

Estimated by a PK/PD model simulation based on the results of the PET trials (Trials 277-10-205, 277-13-001, and 277-14-001)

In the previous phase 1 repeated-dose trials in healthy adults (Trials 277-12-001 and 277-10-206), tolerability was confirmed at doses up to 30 mg/day. The overseas phase 2 trial in AD/HD patients (Trial 277-201-00001) confirmed that OPC-64005 was safe and tolerable when administered at 20 mg/day for 4 days, followed by a dose increased on

Day 5 to 30 mg/day, which was administered up until Day 56, for a total of 8 weeks. Based on these clinical results, it was judged that there are no significant safety problems in selecting 20 mg as the dose for efficacy assessment in the present trial.

In Trial 277-201-00001, on the other hand, the incidence of AEs that led to discontinuation of the trial in the OPC-64005 group was 23.4% (18/77 subjects) and higher than that in the placebo group (8.5%, 7/85 subjects). Most of these AEs occurred during the early stage of treatment initiation (during treatment at 20 mg). Therefore, in consideration of safety at an early stage of treatment, the starting dose in the present trial was set at 10 mg, which is lower than the starting dose of Trial 227-201-00001.

As of Oct 2019, there are no TRIs approved in Japan or overseas, and the safety profile is unknown. The 10-mg group was also included in the trial because evaluation of safety at the lower dose is beneficial when assessing the safety profile of OPC-64005.

4.4 End of Trial Date Definition

The end of trial date is defined as the date of last observation (Visit 11) of the last subject. For discontinued subjects, the end of trial date is the date of last observation. For subjects lost to follow-up, the end of trial date is the date of final contact attempt.

4.5 Definition of Completed Subjects

The treatment period is defined as the period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether the subject was actually administered all IMP doses. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete Visit 9 (Week 6 of the double-blind treatment period) will be defined as trial completers.

5 Trial Population

The trial population is 270 male and female patients ≥ 20 to < 65 years of age (at time of informed consent) diagnosed with either “major depressive disorder, single episode” or “major depressive disorder, recurrent episode” according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

5.1 Subject Selection and Numbering

Subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number [S + 5 digits] upon providing written consent). The site number will be designated by the sponsor. The subject number will be given in the order of informed consent from S00001 as the serial numbers in the trial sites. Demographic information

(collection date, date of birth, sex, childbearing potential, race, ethnicity, country) and medical history will be recorded in the source document and electronic case report form (eCRF) at screening.

Subjects enrolled in the trial will be registered in the IRT system, and eligible subjects will be assigned a unique randomization number in the IRT system. Results of the eligibility assessment, date of randomization, and randomization number will be recorded in the eCRF.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial by either investigator.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

At informed consent and at screening (Visit 1):

1) Patients of ≥ 20 years to < 65 years of age (at time of informed consent)
2) Male or female patients
3) Patients who have sufficient understanding to provide consent for execution of all observations, examinations, and evaluation items stipulated in the protocol, and are capable of fully understanding the content of the trial and providing written consent
4) Outpatients
5) Patients with DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" with the current episode persisting for ≥ 4 weeks to ≤ 1 year (the Mini-International Neuropsychiatric Interview [M.I.N.I.] method is used for assessment)

At start of placebo lead-in period (Visit 2):

6) Patients with a HAM-D 17-item total score of ≥ 18 based on evaluation performed at the start of the placebo lead-in period

At baseline (Visit 3):

7) Patients with a HAM-D 17-item total score of ≥ 18 based on evaluation performed at baseline

[Rationale for Inclusion Criteria]

1): The lower limit of age for adults is based on legal competency to provide consent. The upper limit of age is < 65 years to appropriately evaluate the safety of OPC-64005 because the elderly generally have reduced physiological function.

2): Depression develops regardless of sex.

3): This criterion was set for ethical considerations.

4): This criterion was set in view of subject safety, as treatment should be prioritized in patients whose condition requires hospitalization.

5) to 7): These criteria were set to appropriately evaluate efficacy.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1). However, if results are not available at the time of tests/assessments, such as laboratory tests values, the results need to be confirmed by baseline.

At informed consent and at screening (Visit 1):

1) Pregnant women, breastfeeding women, and/or women who have a positive urine pregnancy test result at screening
2) Sexually active males or females of childbearing potential (FOCBP), who do not agree to practice 2 different approved methods of birth control or remain fully abstinent during the trial and for 2 weeks after the last dose of the IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, condom (all methods approved or validated in Japan). The definition of childbearing potential is provided in Section 10.3.
   Male patients must also agree not to donate sperm from trial screening through 2 weeks after the last dose of the IMP.
3) Patients with the following DSM-5 diagnosis (diseases that can be confirmed by M.I.N.I. will be evaluated using M.I.N.I.):

- Neurocognitive disorders
- Schizophrenia spectrum and other psychotic disorders (history/complication)
- Bipolar and related disorders (history/complication)
- Feeding and eating disorders
- Obsessive-compulsive disorder
- Panic disorder
- Posttraumatic stress disorder
- Personality disorders

- Neurodevelopmental disorders
- Substance-related and addictive disorders (within 180 days prior to the date of informed consent)

4) Patients exhibiting mood-incongruent psychotic features in the current major depressive episode
5) Patients with complicated hypothyroidism or hyperthyroidism at informed consent (excluding patients whose disease condition has been stabilized by drug therapy for at least 90 days preceding informed consent)
6) Patients who meet any of the following criteria or have any of the following symptoms at screening:

- Inadequately controlled hypertension (diastolic blood pressure [DBP] > 95 mmHg)
- Symptomatic hypotension
- Orthostatic hypotension defined as a fall in systolic blood pressure (SBP) of ≥ 30 mmHg or fall in DBP of ≥ 20 mmHg after the patient has stood for 3 minutes compared with the pressures measured in the supine position before standing

7) Patients with complicated ischemic heart disease, myocardial infarction, or congestive cardiac failure (regardless of whether these conditions are being adequately or inadequately controlled), patients who have undergone angioplasty, stent placement, or coronary artery bypass grafting
8) Patients with a history of neuroleptic malignant syndrome or serotonin syndrome
9) Patients with a history or complication of convulsive disorder except for pediatric isolated febrile convulsion
10) Patients with the following laboratory values or ECG parameters at screening (assessed based on the results of the central laboratory, central ECG facility)

- Platelet count ≤ 75,000/mm^3
- Hemoglobin ≤ 9 g/dL
- Absolute neutrophil count ≤ 1000/mm^3
- Aspartate aminotransferase (AST) > 2-fold the upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2-fold the ULN
- Creatinine ≥ 2 mg/dL
- Glycosylated hemoglobin (HbA1c) ≥ 7% (International Scale [NGSP])
- Fasting blood glucose ≥ 126 mg/dL, or casual blood glucose ≥ 200 mg/dL
- Fridericia's corrected QT (QTcF) interval ≥ 450 msec
- Abnormal values of thyroid-stimulating hormone (TSH) and free thyroxine (FT4)

11) Patient with hypersensitivity to drugs (all drugs including prescription and over the counter [OTC] drugs) and ingredients of OPC-64005 (D-mannitol, corn starch, low substituted hydroxypropylcellulose, pregelatinized starch, magnesium stearate, hypromellose, talc, titanium oxide, yellow ferric oxide) (including history)

12) Patients who, in the opinion of the investigator, are judged to have treatment-resistant depression, ie, a certain degree of therapeutic effect is not obtained by administration of 2 or more antidepressants having different mechanisms of action at sufficient doses for at least 6 weeks for the current major depressive episode
13) Patients receiving augmentation treatment, such as antipsychotics, for the current major depressive episode (excluding the use of sulpiride for depression/depressive state or gastric/duodenal ulcer)
14) Patients who have received electroconvulsive therapy in the past
15) Patients who have embarked upon a new course of psychotherapy (except for supportive psychotherapy generally conducted as part of routine medical practice) within 6 weeks of informed consent
16) Patients who have received OPC-64005 in the past
17) Patients who have participated in any other trials within 60 days of informed consent
18) Patients with a HAM-D Suicide (No. 11) score of ≥ 3 at screening, patients who responded "Yes" to Question 4 or Question 5 of the C-SSRS at screening, or patients who, in the opinion of the investigator, are judged to be at high risk for committing suicide during the trial based on the current psychiatric symptoms and medical history at screening
19) Patients in whom, in the opinion of the investigator, it cannot be ruled out that a possible change in the patient's circumstances (eg, leave of absence, return to work, relocation) may affect the efficacy evaluation of the trial
20) Patients with clinically problematic diseases of the nervous system, liver, kidney, metabolic system, blood system, immune system, cardiovascular system, lung, or gastrointestinal system. However, if the disease is minor and adequately controlled and does not interfere with the safety and efficacy evaluations, the patient can be enrolled.
21) Other patients who, in the opinion of the investigator, should not participate in the trial

At start of placebo lead-in period (Visit 2):

22) Pregnant women, breastfeeding women, and/or women who have a positive urine pregnancy test result at the start of the placebo lead-in period
23) Patients with a MADRS-S total score of < 8.5 based on evaluation performed at the start of the placebo lead-in period
24) Patients with a HAM-D Suicide (No. 11) score of ≥ 3 at the start of the placebo lead-in period, patients who responded "Yes" to Question 4 or Question 5 of the C-SSRS at the start of the placebo lead-in period, or patients who, in the opinion of the investigator, are judged to be at high risk for committing suicide during the trial based on the current psychiatric symptoms and medical history at the start of the placebo lead-in period
25) Patients who required another hospitalization during the screening period due to the current major depressive episode

26) Other patients who, in the opinion of the investigator, should not participate in the trial

At baseline (Visit 3):

27) Patients with a MADRS-S total score of < 8.5 based on evaluation performed at baseline or with ≥ 25% reduction in MADRS-S total score at baseline compared with at the start of the placebo lead-in period
28) Patients with a HAM-D Suicide (No. 11) score of ≥ 3 at baseline, patients who responded "Yes" to Question 4 or Question 5 of the C-SSRS at baseline, or patients who, in the opinion of the investigator, are judged to be at high risk for committing suicide during the trial based on the current psychiatric symptoms and medical history at baseline
29) Patients who required another hospitalization during the placebo lead-in period due to the current major depressive episode
30) Other patients who, in the opinion of the investigator, should not participate in the trial

[Rationale for Exclusion Criteria]

1), 2), 22): These criteria were set for safety considerations because the safety of OPC-64005 during pregnancy and breastfeeding has not been established.

3), 4), 12) to 15), 19), 23), 27): These criteria were set to appropriately evaluate efficacy.

5): This criterion was set to appropriately evaluate efficacy because patients with thyroid disorders may experience depressive symptoms.

6) to 11), 17), 18), 20), 21), 24) to 26), 28) to 30): These criteria were set for safety considerations.

16): This criterion was set to avoid potential influence on the blindness.

5.3 Lifestyle Considerations

The following lifestyle considerations apply for the trial.

5.3.1 Meals and Dietary Restrictions

Consumption of grapefruit, starfruit, Seville orange, and their processed products such as juices is prohibited from 3 days before Visit 2 until the end of the double-blind tapering period. Consumption of St. John's wort-containing foods is prohibited from Visit 2 through Visit 9.

5.3.2 Caffeine, Alcohol, and Tobacco

From Visit 2 through Visit 9, excessive caffeine consumption and smoking should be avoided, and consumption of alcoholic beverages should be avoided wherever possible.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an informed consent form [ICF]), but who is not dispensed the IMP at Visit 2.

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

- Date of informed consent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

Subjects who participate in the trial and subsequently become screen failures can undergo rescreening. When rescreening is performed, separate written consent needs to be obtained and a new subject ID will be assigned prior to the screening examination.

6 Trial Treatments

6.1 Trial Treatments Administered

For information regarding the dose regimen and treatment period, including any follow-up period(s) for each treatment group of the trial, see Section 6.1.1.

6.1.1 Dosage and Administration

6.1.1.1 Placebo Lead-in Period (Single-blind With Subjects Blinded to Treatment Received)

Two placebo tablets will be administered orally once daily for 1 week.

6.1.1.2 Double-blind Treatment Period

- Placebo group

Two placebo tablets will be administered orally once daily for 6 weeks.

- OPC-64005 10-mg group

One placebo tablet and one OPC-64005 10-mg tablet will be administered orally once daily for 6 weeks.

- OPC-64005 20-mg group

One placebo tablet and one OPC-64005 10-mg tablet will be administered orally once daily for 1 week, followed by two OPC-64005 10-mg tablets for 5 weeks.

6.1.1.3 Double-blind Tapering Period

- Placebo group

Two placebo tablets will be administered orally once daily for 1 week.

- OPC-64005 10-mg group

Two placebo tablets will be administered orally once daily for 1 week.

- OPC-64005 20-mg group

One placebo tablet and one OPC-64005 10-mg tablet will be administered orally once daily for 1 week.

6.1.1.4 At Discontinuation

If discontinuation occurs during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (1 week [7 days ± 2 days]) to the following regimens (however, if the investigator judges that the IMP needs to be discontinued due to an AE or if the IMP dose cannot be tapered due to the subject's circumstances such as he/she does not wish to taper the dose, dose tapering is not mandatory):

- Placebo group

Two placebo tablets will be administered orally once daily for 1 week.

- OPC-64005 10-mg group

Two placebo tablets will be administered orally once daily for 1 week.

- OPC-64005 20-mg group

One placebo tablet and one OPC-64005 10-mg tablet will be administered orally once daily for 1 week.

If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4 or between the start of IMP administration after Visit 9 and Visit 10, dose tapering is not necessary. If the IMP dose is tapered after discontinuation, the IMP will be dispensed according to the instructions from the IRT system, as the IMP will be administered under double-blind conditions.

6.1.1.5 Handling of Missed Doses

If the subject realizes that he/she missed taking the IMP the day before, he/she will not take the missed IMP dose from the day before.

6.1.1.6 Investigation on Drug Compliance

The investigator will confirm the drug compliance status between the scheduled visits, and record the daily dose, treatment start date, and treatment end date in the source document and eCRF.

The drug compliance rate will be calculated by the following formula: [Dose (number of tablets) between the scheduled visits] / [number of prescription days between the scheduled visits × 2 tablets] × 100. If the drug compliance rate between the scheduled visits is < 65%, administration will be discontinued (see Section 7.3.3).

6.1.2 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC-64005 IB and a separate manual.

6.2.1 Packaging and Labeling

The IMP will be provided by the sponsor or designated agent to the IMP manager. The IMP will be supplied as blister cards. Each blister card used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, protocol number, sponsor's name and address, route of administration, lot number, expiry date, and storage method, etc.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The IMP manager must maintain an inventory record of the IMP (investigational or placebo) received, dispensed, administered, and returned. The IMP manager may not provide the IMP to any patient not participating in this protocol.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent. All IMP returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return of used IMP containers, unused IMP, and partially-used IMP.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure 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)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor or sponsor's designee by email (destination address: PQC_277-102-00027@otsuka.jp) of the information listed in Section 6.2.5.2 immediately after acknowledging the PQC.

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

6.2.5.2 Information Required for Reporting Product Quality Complaints

- Description of complaint

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

6.2.5.3 Return Process in the Case of Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. The sponsor may provide sample 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.

6.2.5.4 Assessment/Evaluation

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

6.3 Measures to Minimize/Avoid Bias

This trial will be performed as a randomized double-blind trial to minimize bias.

Treatment assignment codes will not be disclosed to the subjects or investigator. Except for designated persons, the treatment assignment code will not be disclosed to the sponsor's trial staff including contract research organizations (CROs) (except for the bioanalytical laboratory and pharmacogenomic [PGx] laboratory) during the trial.

Emergency keys are controlled by the IRT system until the end of the trial. They will be disclosed according to the procedures for breaking the blind when a medical emergency occurs to a subject and it is judged important to identify the treatment assignment code for treatment of the subject. Procedures for breaking the blind can be found in Section 8.8.7.

If the IMP is collected by the sponsor before unblinding, the IMP will be collected in the sealed state.

Subjects will be assigned to the OPC-64005 10-mg group, OPC-64005 20-mg group, or placebo group at a ratio of 1:4:4 using the dynamic allocation method (minimization method). A separate specification will be developed to provide details.

Results of drug concentration measurement and PGx assessment should be retained in a manner that prevents their disclosure until unblinding at the end of the trial. These tests

will be performed by the specified laboratories, and will not be performed at a clinical laboratory of the trial site.

6.4 Subject Compliance

During the trial, subjects will be placed under the management of the investigator. The investigator will instruct subjects to adhere to the following:

- Subjects must adhere to the specified schedule during the trial
- The trial must be discontinued when the drug compliance rate between the scheduled visits is < 65%
- Subjects must practice appropriate contraceptive methods
- Subjects must adhere to the requirements in Section 5.3 and Section 6.5
- Subjects must not disclose information obtained as a result of participation in the trial to third parties
- If a rash develops on the skin after the start of IMP administration, subjects must immediately contact trial site staff and follow the investigator's instructions

6.5 Concomitant Medications or Therapies

The investigator will record all concomitant medications taken by the subject from 28 days prior to informed consent through Visit 10 and all concomitant therapies taken by the subject from 6 weeks prior to informed consent through Visit 10 in the eCRF. The investigator will also record all concomitant medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the date of last observation or date of final contact attempt) in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date and end date.

6.5.1 Prohibited Medications

The use of following medications is prohibited. If it is considered necessary by the investigator, these medications will be tapered off and then stopped. If the dose of antidepressants is to be tapered, the subject should visit the trial site to confirm safety, where appropriate.

6.5.1.1 Fourteen Days Before Visit 2 Through Visit 11

- Monoamine oxidase inhibitors

6.5.1.2 Visit 2 Through Visit 9

- Antidepressants
- Benzodiazepines (except for ultrashort-acting hypnotics and sedatives)
- Drugs that are considered to affect the metabolic/activity systems of serotonin, noradrenaline, or dopamine
- Central nervous system drugs (except for ultrashort-acting hypnotics and sedatives; antipyretic, analgesic and anti-inflammatory agents; and general cold medicines)
- Chinese herbal medicines (drugs indicated for neurosis, anxiety neurosis, neurasthenia, and insomnia)
- Over the counter drugs used as sleeping pills
- Supplements used for improvement of depressive symptoms (St. John's wort, S-adenosylmethionine [SAM-e], ω-3 fatty acid, kava extract, γ-aminobutyric acid [GABA])
- Varenicline

6.5.1.3 Visit 2 Through Visit 10

- Strong cytochrome P450 (CYP) 3A4 inhibitors, CYP1A2 inhibitors, CYP2D6 inhibitors, CYP3A4 inducers, CYP1A2 inducers, CYP2B6 inducers, and CYP2D6 substrates with narrow therapeutic range (except for topical drugs)

6.5.2 Restricted Medications

The use of the following medications is restricted.

6.5.2.1 Visit 2 Through Visit 9

- Antipyretic, analgesic and anti-inflammatory agents, and antihistamines

  The concomitant use of these drugs is permitted if they have been used for treatment of a complication at Visit 2. However, the same dosage and administration should be maintained unless an AE has occurred, or the drug is judged to be no longer necessary due to remission of symptoms. Short-term concomitant use of these drugs for treatment of colds is also permitted. The use of local topical drugs is permitted. Short-term is defined as 1 week in principle. If antipyretic, analgesic and anti-inflammatory agents or antihistamines that were not being used at informed consent are administered for > 2 weeks, or such administration is necessary, the trial will be discontinued according to the reason for discontinuation, "significant protocol deviation."
- Ultrashort-acting hypnotics and sedatives

  The concomitant use of ultrashort-acting hypnotics and sedatives (zolpidem, zopiclone, eszopiclone, triazolam) is permitted. However, the concomitant use is permitted with only 1 of these drugs and 2 or more of them must not be used concomitantly. The same dosage and administration should be maintained wherever possible.

6.5.3 Permitted Medications

All medications that are not specified as prohibited/restricted medications can be used concomitantly. However, the same dosage and administration should be maintained, and no new medications/therapies should be added wherever possible.

6.5.4 Rescue Medications

Not applicable.

6.5.5 Prohibited Therapies

The following therapies are prohibited so that the efficacy and safety of OPC-64005 can be appropriately assessed.

- Somatotherapies (electroconvulsive therapy, bright light therapy, sleep deprivation therapy, transcranial magnetic stimulation)
  The concomitant use of these therapies is prohibited from Visit 1 through Visit 9.
- Psychotherapies (except for supportive psychotherapy generally conducted as part of routine medical practice)
  The concomitant use of psychotherapies is prohibited from Visit 2 through Visit 9.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

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

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, investigator, or IRB if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB of the trial site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

If drug eruption is suspected after IMP administration, IMP administration will be discontinued or interrupted (see Section 8.7.2.1).

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 7.3.5.

If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 9, the examination at discontinuation will be performed. If the subject refuses to undergo any examinations at the time of withdrawal, or if examinations cannot be performed due to an emergency or other circumstances, of the examination items specified for the time of withdrawal, only those items that can be performed will be performed.

If the specified examinations have been already performed on the day of discontinuation, they do not need to be repeated.

If discontinuation occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 3, the post-treatment observation (Visit 11) is not necessary after the examination at discontinuation has been performed.

If discontinuation is decided during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]) wherever possible after the examination at discontinuation has been performed (see Section 6.1.1.4). After the dose tapering, the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.

If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4, dose tapering is not necessary after the examination at discontinuation has been performed, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.

If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 9 and Visit 10, the examination at discontinuation is not necessary. The subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may discontinue the IMP for the reasons listed below:

- 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
  - The investigator judges that the subject is at high risk for committing suicide based on his/her clinical symptoms, MADRS No. 10 "Suicidal Thoughts" score is ≥ 5, HAM-D Suicide (No. 11) score is ≥ 3, or "Yes" to Question 4 or Question 5 of the C-SSRS
  - Symptoms change to manic state
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Occurrence of drug eruption
    - Other potentially IMP-related safety concerns or AEs
- Death
- Lost to follow-up
- Noncompliance with IMP (eg, drug compliance rate between the scheduled visits is < 65%)
- Physician decision
- Pregnancy (see Section 10.3)
- Significant protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject
- Lack of efficacy

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.1 and Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent or Assent

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, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent means a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

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 completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express his/her desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Details on the withdrawal of consent from the Future Biospecimen Research (FBR) substudy are provided in the ICF for FBR.

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted before Visit 11, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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.

If the subject was classified as "lost to follow-up", "Were you able to contact the subject?", "Date of contact/Date of final contact attempt" and "Contact method" will be recorded in source documents and eCRF.

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Section 1.3.

8.1 Efficacy Assessments

8.1.1 Montgomery Åsberg Depression Rating Scale

A trained and qualified investigator will evaluate the following 10 depressive symptoms on 7 scales of 0 to 6 using the Structured Interview Guide for MADRS (SIGMA) at the specified evaluation points, and record the date and time of evaluation and evaluation result in the source document and eCRF. The total score of items 1, 2, 6, 7, and 8 will be used as the MADRS anhedonia factor score.

1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep

5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel

9. Pessimistic thoughts 10. Suicidal thoughts

8.1.2 Clinical Global Impression – Improvement

The investigator will evaluate improvement of depressive symptoms on the following 8 scales using the CGI-I at the specified evaluation points. During the double-blind treatment period, improvement will be evaluated in comparison with the subject's condition at Visit 3 (at the start of the double-blind treatment period), and the date and time of evaluation and evaluation result will be recorded in the source document and eCRF.

0. Not assessed 1. Very much improved 2. Much improved 3. Minimally improved

4. No change 5. Minimally worse 6. Much worse 7. Very much worse

8.1.3 Clinical Global Impression - Severity of Illness

The investigator will evaluate the severity of depressive symptoms on the following 8 scales using the CGI-S at the specified evaluation points, and record the date and time of evaluation and evaluation result in the source document and eCRF.

0. Not assessed 1. Normal, not at all ill 2. Borderline mentally ill 3. Mildly ill

4. Moderately ill 5. Markedly ill 6. Severely ill

7. Among the most extremely ill

8.1.4 Hamilton Depression Rating Scale

A trained and qualified investigator will evaluate the following 21 depressive symptoms using the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) at the specified evaluation points: Items No. 1 to 2, 10 to 14, 16 to 17, and 19 on 5 scales of 0 to 4, Items No. 5 and 20 on 4 scales of 0 to 3, and Items No. 3 to 4, 6 to 9, 15, 18, and 21 on 3 scales of 0 to 2. The total score of Items No. 1 to 17 will be calculated, and the date and time of evaluation and evaluation result will be recorded in the source document and eCRF.

1. Depressed mood 2. Work and activities 3. Genital symptoms

4. Somatic symptoms gastrointestinal 5. Loss of weight

6. Insomnia early 7. Insomnia middle 8. Insomnia late

9. Somatic symptoms general 10. Feelings of guilt 11. Suicide

12. Anxiety psychic 13. Anxiety somatic 14. Hypochondriasis

15. Insight 16. Retardation 17. Agitation

18. Diurnal variation 19. Depersonalization and derealization

20. Paranoid symptoms 21. Obsessional and compulsive symptoms

8.1.5 Montgomery Åsberg Depression Rating Scale Self-assessment

All subjects will perform self-assessment on the following 10 items of MADRS-S on the scale of 0 to 3 at the specified evaluation points, and the investigator will record the date and time of evaluation and evaluation result in the source document and eCRF.

Staying power 1. Mood 2. Feelings of unease 3. Sleep 4. Appetite

5. Ability to concentrate 6. Initiative 7. Emotional involvement

8. Pessimism 9. Zest for life

8.1.6 Apathy Scale

All subjects will perform self-assessment for each of the following 14 items on the Apathy Scale on 4 scales at the specified evaluation points.

1. Are you interested in learning new things?

2. Does anything interest you?

3. Are you concerned about your condition?

4. Do you put much effort into things?

5. Are you always looking for something to do?

6. Do you have plans and goals for the future?

7. Do you have motivation?

8. Do you have the energy for daily activities?

9. Does someone have to tell you what to do each day?

10. Are you indifferent to things?

11. Are you unconcerned with many things?

12. Do you need a push to get started on things?

13. Are you neither happy nor sad, just in between?

14. Would you consider yourself apathetic?

8.2 Pharmacokinetic Assessments

Plasma drug concentrations will be determined to calculate the PK parameters of OPC-64005 and its metabolite OPC-144013 in a population PK analysis performed separately.

8.2.1 Pharmacokinetic Plasma Samples

Blood samples for PK analysis will be collected at the time points as shown in Table 1.3-1 (schedule of assessments). The date and time of sample collection and the date and time of IMP administration immediately before blood collection will be recorded in the source document and eCRF.

Blood samples (2 mL) will be collected in vacutainers containing heparin sodium and processed into plasma to determine the concentrations of OPC-64005 and metabolite OPC-144013 by a validated high performance liquid chromatography-tandem mass spectrometry method. Additional metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

All plasma samples will be shipped to the bioanalytical laboratory for analysis. Additional information on the procedures for collection, handling and shipment of samples will be provided in a separate manual.

The bioanalytical laboratory will record the use of the treatment assignment table, and measure drug concentrations of samples collected from the OPC-64005 group only. The content of the treatment assignment table will not be disclosed to any person other than those permitted to perform procedures by the bioanalytical manager, and should be kept under lock and key. The results of drug concentration measurement will be kept under lock and key by the bioanalytical laboratory, and an electronic file will be submitted to the sponsor after unblinding. Therefore, drug concentration data do not need to be recorded in the source document or eCRF.

The residual plasma samples will be stored at the bioanalysis laboratory and disposed of after the clinical study report has been prepared.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Tests on CYP2D6 genotype and phenotype will be performed. CYP2D6 genetic testing is mandatory.

[Rationale for CYP2D6 Genetic Testing]

In vitro evaluation showed that CYP2D6 is involved in OPC-64005 metabolism, and CYP2D6 is known to have genotypes with different enzyme activity. It was judged appropriate for evaluation of the PK of OPC-64005 to perform a test on CYP2D6 genotypes, which could be a potential factor accounting for variations.

8.4.1 Pharmacogenomic Samples

Blood samples for CYP2D6 genetic testing will be collected at the time point described in Table 1.3-1 (schedule of assessments). If blood samples cannot be collected or blood samples need to be recollected for some reason, blood samples should be collected during the trial. The date of sample collection will be recorded in the source document and eCRF.

Blood samples (2 mL) will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) dipotassium. Genomic DNA will be extracted from a blood sample and used to test CYP2D6*1, *2, *4, *5, *10, *14, *18, *21, and *41 alleles. The CYP2D6 genotype of each subject will be determined using the CYP2D6 genotype assessment table (Appendix 4: Genetic Testing), and furthermore, the phenotype will be classified as an extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM), or unknown based on the CYP2D6 genotype. The results of CYP2D6 genetic testing will not be disclosed to the subjects in principle.

All blood samples will be shipped to the PGx laboratory for analysis. Additional information on the procedures for collection, handling, and shipment of samples will be provided in a separate manual.

The PGx laboratory will record the use of the treatment assignment table and extract DNA from blood samples collected from the OPC-64005 group only. Blood samples collected from the placebo group will be disposed of according to the PGx laboratory procedures. The content of the treatment assignment table will not be disclosed to any person other than those permitted to perform procedures by the person responsible of the PGx laboratory, and should be kept under lock and key. The results of CYP2D6 genetic testing will be kept under lock and key by the PGx laboratory, and an electronic file will be submitted to the sponsor after unblinding. Therefore, the test results do not need to be recorded in the source document or eCRF.

The residual DNA samples will be stored at the PGx laboratory and disposed of after the clinical study report has been prepared.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Storage of DNA samples will be conducted to enable future exploratory evaluation of variations in DNA characteristics related to individual differences in the drug response (efficacy, safety, PK, etc) of the drugs used in this trial and/or variations in DNA characteristics related to diseases.

DNA samples will be collected only at trial sites, which approved blood sampling for DNA storage, and only from subjects who provided voluntary written consent for DNA storage.

[Rationale for Sample Storage for Future Biospecimen Research]

Storage of DNA samples will be conducted to enable future genomic/genetic analysis if further explanation other than the results of CYP2D6 genetic testing performed in this trial is required for the PK of OPC-64005, if new information on genetics and PK becomes available, and/or if it is judged that genomic/genetic analysis would be useful for evaluating the drug response (efficacy and safety) of the IMP and diseases. The Ministry of Health, Labour and Welfare (MHLW) states in Q&A 1 of "Regarding Clinical Studies Utilizing Pharmacogenomics (30 Sep 2008, PFSB/ELD Notification No. 0930007)" as follows regarding the collection and storage of DNA samples during trials: It is permissible to obtain samples for genomic/genetic analyses relevant to the evaluation of the study drug (eg, PK, efficacy, and safety) from subjects in a clinical trial in either of the following cases: (1) the target and time of genomic/genetic analysis are already specified at the time of the clinical trial or (2) the target and time of genomic/genetic analysis have not yet been specified but such analysis is planned to be performed in the future for further evaluation of the study drug. The ministry also stated in Q&A 2 that it is permissible to obtain samples for genomic/genetic analyses not related to the evaluation of the study drug from subjects.[14] In addition, in the International Council for Harmonization (ICH) E18 Guideline on Genomic Sampling and Management of Genomic Data, in Section 1.4 General Principles states "With advances in science and increased awareness of the impact of genomics, there is a need and an opportunity to maximize the value of the collected samples and the data generated from them, and therefore, genomic sample acquisition is strongly encouraged in all phases and studies of clinical development."[15]

In addition, sample collection is planned to coincide as much as possible with other trial examinations in order to minimize the burden on subjects and therefore the collection and storage of DNA samples on a voluntary basis is considered appropriate.

8.6.1 Scope of Future Biospecimen Research

Research performed on FBR samples includes genetic analyses (DNA). Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from subjects who have provided appropriate consent. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

8.6.2 Summary of Procedures for Future Biospecimen Research Samples

All subjects enrolled in the clinical trial will be considered for enrollment in the optional FBR substudy.

After obtaining informed consent, the following FBR samples will be obtained at the time point specified in Table 1.3-1 (schedule of assessments). If blood samples cannot be collected or blood samples need to be recollected for some reason, blood samples should be collected during the trial.

- Blood (2 mL, EDTA dipotassium) for DNA analysis

Information whether samples were collected and the date of sample collection will be recorded in the source document and eCRF. Additional information on the procedures for collection, handling, and shipment of samples will be provided in a separate manual. If a FBR substudy is planned, a separate document describing the analysis may be prepared and the results may be reported separately from the clinical study report.

8.6.3 Storage of Samples for Future Biospecimen Research

The samples for biospecimen research will be stored at the biospecimen storage site for future analysis until the earliest of the following time points: 1) when genomic/genetic analysis is considered to be no longer necessary, 2) when 15 years have passed since the first informed consent for DNA storage was obtained in this trial, or 3) when the subject withdraws his/her consent for DNA storage.

8.6.4 Genomic/Genetic Analysis

Genomic/genetic analysis will be performed only if such analysis is judged to be useful for exploratory evaluation of variations in DNA characteristics related to individual

differences in the drug response (efficacy, safety, PK, etc) of the IMP and/or variations in DNA characteristics related to diseases.

If it is decided to perform genomic/genetic analysis, a pharmacogenomic study protocol will be prepared. After approval of the protocol by the sponsor's research review board, the analysis will be performed in compliance with the applicable national laws and regulations.

It is currently impossible to identify the target for genomic/genetic analysis. While it is possible that related genome-wide analyses using a DNA chip, microarray, next-generation sequencer, etc, may be performed, the results of these analyses will never be used for any purpose other than those described above.

The DNA samples for genomic/genetic analysis will be double-coded at the biospecimen storage site prior to being sent to the genomic/genetic analysis laboratory (currently undetermined), and genomic/genetic analysis will be performed with the double coding maintained.

8.6.5 Provision and Withdrawal of Consent for Future Biospecimen Research

A document explaining the DNA storage and the genomic/genetic analyses using stored DNA will be prepared, and signed informed consent will be obtained separately from the informed consent for participation in the clinical trial. The date of informed consent will be recorded in the source documents and the eCRF.

If a subject withdraws his/her consent for DNA storage during the sample storage period, the sponsor will request the biospecimen storage facility to dispose of the subject's samples. The biospecimen storage facility will dispose of the samples with anonymity maintained. However, if it becomes impossible to identify an individual subject's samples for some reason, such as destruction of the data linking the samples to subject information (key code table, etc), it may become impossible to dispose of the samples of a specific subject who has withdrawn his/her consent.

Even if a subject decides to discontinue participation in the clinical trial, participation in DNA storage will not be canceled automatically. In addition, any results of the genomic/genetic analysis that have already been obtained at the time consent is withdrawn will not be disposed of.

8.6.6 Disclosure of Genomic/Genetic Analytical Results to Subjects

Even if findings are obtained as a result of the analysis, such results are considered exploratory in nature or at an early stage of research and their scientific reliability

(accuracy, certainty, etc) will not have been fully confirmed. Since the disclosure of scientifically ambiguous information would provide no benefit to subjects, in principle the sponsor will not disclose the results of the genomic/genetic analysis to the subjects.

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2. The total volume of blood to be collected is approximately 38 mL.

Blood and urine samples will be collected from each subject, and the date and time of blood collection, date of urine collection, and fasting state at the time of blood collection will be recorded in the source document and eCRF. Blood will be withdrawn under fasting conditions (fasting [including juice and other sugar-containing beverages] for at least 8 hours) at Visit 3 and Visit 9. Blood will be withdrawn under fasting conditions wherever possible at Visit 1, Visit 11, and discontinuation. In this trial, the central laboratory selected by the sponsor will be used. Laboratory values determined by the central laboratory will be used for confirmation of eligibility. Appropriate procedures for collection, handling, and shipment of samples will be provided in a separate manual before the trial. The central laboratory will report test results to the investigator. The investigator will confirm the test results, record the date of confirmation of results and sign the laboratory test report so that it will become an official document. Test results will be directly reported from the central laboratory to the sponsor in an electronic file, consequently, they do not need to be recorded in the source document or eCRF.

8.7.2 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1).

The investigator will evaluate physical findings by conducting medical interviews and by other means for the following body sites. At screening, the date of assessment and assessment result will be recorded in the source document and eCRF. After screening, the date of assessment only will be recorded in the source document and eCRF. If clinically significant physical findings compared with screening are observed, they will be recorded as AEs in the source document and eCRF.

Assessed sites: Head, eyes, ears, nose and pharynx, chest, abdomen, urogenital organs, extremities, nerves, skin, and mucous membranes

8.7.2.1 Dermatological Findings

Skin should be carefully observed. If drug eruption occurs after the start of IMP administration, administration of the IMP will be discontinued regardless of its severity, and the event will be reported as an immediately reportable event (IRE) after being assessed as drug eruption (see Section 8.8.3 and Section 8.8.5). The investigator will orally obtain consent from the subject and take pictures of the onset site of drug eruption wherever possible. The pictures (electronic data) will be kept as the source document, and the sponsor will collect copies of the pictures (electronic data). If necessary, the investigator will orally obtain consent from the subject and perform a drug-induced lymphocyte stimulation test (DLST). In addition, depending on the severity, the investigator will instruct the subject to see a dermatologist. If drug eruption is suspected, administration of the IMP will be interrupted, and when drug eruption has been ruled out, administration of the IMP can resume. However, the trial will be discontinued when the drug compliance rate between the scheduled visits is < 65%.

8.7.3 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1).

According to the trial site procedures, body temperature, SBP, DBP, and pulse rate will be measured. Body temperature will be measured after the subject has rested. Systolic blood pressure, DBP, and pulse rate will be measured in the order of supine, sitting, and standing positions after the subject has stayed in each position for at least 3 minutes. The respiratory rate will be measured after the subject has rested for at least 5 minutes in the sitting position. The date and time of measurement, position (for blood pressure and pulse rate), and results will be recorded in the source document and eCRF.

8.7.4 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1).

The investigator will record an ECG using the 12-lead ECG provided by the central ECG facility after the subject has rested for at least 5 minutes in the supine position, assess the ECG (normal or abnormal), and record the date and time the ECG was taken, result of normal/abnormal assessment, and abnormal findings in the source document and eCRF. The original of the 12-lead ECG output will be stored in the medical record or

investigator file. The central ECG facility will collect 12-lead ECG data, measure heart rate, PR interval, RR interval, QRS interval, QT interval, and heart rate corrected QT (QTc) interval (QTcF = QT interval / [RR interval]$^{1/3}$), and the physician of the central ECG facility will perform assessment. The central ECG facility will report analysis results to the investigator, and the investigator will confirm the analysis results, record the date of confirmation of results and sign the analysis result report so that it becomes an official document. The investigator will reconfirm the assessment referring to the "analysis result report" issued by the central ECG facility. Analysis results will be directly reported from the central ECG facility to the sponsor in an electronic file, consequently, they do not need to be recorded in the source document or eCRF.

8.7.5 Suicidality Monitoring

8.7.5.1 Columbia-Suicide Severity Rating Scale

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1).

This scale consists of the C-SSRS Baseline Version, which assesses a lifetime history of suicide-related events and suicidal ideation, and the C-SSRS Since Last Visit Version, which focuses on suicidality since the last visit. At screening, assessment will be performed using the C-SSRS baseline version. After screening, assessment will be performed using the since last visit version. The date and time of assessment and assessment result will be recorded in the source document and eCRF.

"Suicidal ideation" 1 and 2 will be assessed either "Yes" or "No." If 2 is "Yes," "suicidal ideation" 3 to 5 will also be assessed. If "suicidal ideation" 1 or 2 is "Yes," "intensity of ideation" will also be assessed. For "intensity of ideation," "frequency" and "duration" will be rated on 5 scales, and "controllability," "deterrents," and "reason for ideation" will be rated on 6 scales. The following "suicidal behavior" will be assessed either "Yes" or "No," and "total number" will be recorded for each "suicide attempt." If there is any suicide attempt, "actual lethality/medical damage" will be rated on 6 scales. If actual lethality/medical damage is 0, "potential lethality" will be rated on 3 scales.

Suicidal ideation:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan

5. Active suicidal ideation with specific plan and intent

Suicidal behavior: Actual attempt, Non-suicidal self-injurious behavior, Interrupted attempt, Aborted attempt, Preparatory acts or behavior, Suicide (the Since Last Visit Version only)

8.7.6 Other Safety Variables

8.7.6.1 Waist Circumference

Waist circumference will be measured at the time points described in the schedule of assessments (Table 1.3-1).

As few clothes as possible should be worn (lightly dressed with heavy outerwear removed). The positions of the upper coxal bone and upper edge of the right iliac crest will be determined, and the measuring tape will be tightly wrapped around the abdomen along the horizontal plane of the height of the iliac crest. Before reading the measuring tape, the measurer will make sure that the measuring tape is not loose, not pressing on the skin, and is horizontal to the floor. The measurer will measure in units of 1 cm (rounded off to the nearest integer) at the time point where the subject has fully exhaled in a normal manner, and record the date of measurement and result in the source document and eCRF.

8.7.6.2 Height and Body Weight

Height and body weight will be measured at the time points described in the schedule of assessments (Table 1.3-1).

Height and body weight will be measured in units of 0.1 cm and 0.1 kg, respectively, and the date of measurement and result will be recorded in the source document and eCRF. Body weight will be measured using a calibrated and highly reliable weight scale. In the same subject, body weight will be measured using the same weight scale using standard measuring method (shoes off and daily clothes on). If body weight is measured to the second decimal place or below, the figure will be rounded off to the first decimal place.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and

no worsening occurred. An adverse drug 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.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of double-blind IMP treatment. In more detail, TEAEs are all AEs which started after the start of double-blind IMP treatment; or if the event was continuous from baseline and has worsened.

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, 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 incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; 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 SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- 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):

- Any SAE.
- Any AE related to occupational exposure.
- Drug eruption.
- Potential serious hepatotoxicity (see Section 8.8.6).

- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s), etc to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator'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 dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

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.

8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF.

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. If the reported severity, seriousness, or toxicity of an AE changes, the event must be reported as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by e-mail in principle of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date, end date, seriousness, severity, relationship to trial treatment (IMP causality), action taken with trial treatment, and outcome will be recorded on the source document and in the eCRF.

8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, etc, after he/she or site personnel becomes aware of any IRE (SAE, AE related to occupational exposure, drug eruption, potential serious hepatoxicity, or confirmed pregnancy), by e-mail in principle to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Careful attention must be paid to patient privacy when forwarding the IRE form, etc. However, drug eruption, when reported, must be immediately reported (within 24 hours) after the investigator has determined the event to be drug eruption.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

New onset of drug eruption after the start of IMP treatment will be handled as an adverse event of special interest.

8.8.6 Potential Serious Hepatotoxicity

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

8.8.7 Procedure for Breaking the Blind

If an SAE and other events occur and the investigator judges it is necessary to open the subject's treatment assignment code to ensure the safety of the subject, the investigator

can obtain the treatment assignment code of the subject concerned from the IRT system according to the procedure stipulated separately.

Before unblinding, the investigator is encouraged to contact the sponsor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor (ie, the investigator will be able to obtain the code break information independent of the sponsor). The investigator must contact the sponsor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Global Pharmacovigilance Department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

8.8.8 Follow-up of Adverse Events

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. 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).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 2 weeks (Visit 11) after the final dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form, etc. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, etc, according to the appropriate reporting procedures described in Section 8.8.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor. The investigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- 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 does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.8.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

In cases of overdose, estimation of the severity of poisoning is the critical first step. Detailed history and information on the overdose will be collected, and physical examinations will be performed. In addition to symptomatic and supportive therapies, vital signs, ECG, and blood pressure must be monitored until all parameters recover to the predose levels. Gastric lavage and emetics are useful immediately after overdose. It is unknown whether activated carbon and dialysis are effective for the treatment of OPC-64005 overdose. Close medical supervision and monitoring should continue until the patient recovers.

8.10 Subject Assessment Recording

This includes MADRS-S and Apathy Scale (see Section 8.1).

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

The definition of datasets for analysis and the analysis methods for the endpoints are provided below. A detailed analysis plan is provided in a separate statistical analysis plan (SAP). The SAP will be finalized before data lock.

9.1 Sample Size

As no clinical trials of OPC-64005 in patients with MDD have been previously conducted, the target number of subjects was determined based on the results from another antidepressant clinical trial using MADRS score as the primary endpoint. In the phase 3 clinical trial of escitalopram conducted outside Japan,[1] the mean change (± SE) from baseline in MADRS total score at the final timepoint of Week 8 (8 weeks after start of administration) determined using last observation carried forward analysis of covariance was −9.4 ± 0.9 in the placebo group (n = 119), −12.0 ± 0.9 in the citalopram 40-mg group (n = 125), −12.8 ± 0.8 in the escitalopram 10-mg group (n = 118), and −13.9 ± 0.8 in the escitalopram 20-mg group (n = 123). Referring to those results, in the present trial it is assumed that the difference between the OPC-64005 20-mg group and the placebo group in the change from baseline in MADRS total score at Week 6 of the double-blind treatment period will be −4 with a standard deviation of 11. To ensure a power of 80% in a two-sided test with a significance level of 0.05, 120 subjects each are required for the OPC-64005 20-mg group and the placebo group. For the OPC-64005 10-mg group, the number of subjects was set at 30 without statistical consideration. The planned number of subjects to be randomized for the trial was therefore set at 270.

9.2 Datasets for Analysis

9.2.1 Full Analysis Set

The full analysis set (FAS) includes all subjects who were administered at least 1 dose of double-blind IMP and have MADRS total scores at baseline and at least one timepoint after the start of double-blind treatment.

9.2.2 Safety Analysis Set

The safety analysis set includes all subjects who were administered at least 1 dose of double-blind IMP.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analyses

For the primary endpoint analysis, a mixed-model repeated measures (MMRM) analysis will be performed using the observed cases (OC) dataset without imputation of missing data on an assumption of missing at random (MAR). Placebo multiple imputation and tipping point analysis on an assumption of missing not at random (MNAR) will be performed as a sensitivity analysis for handling of missing data. Details will be provided in the SAP.

The secondary endpoint analysis and the safety analysis will be performed using data imputed with data observed immediately before after the start of double-blind treatment (last observation carried forward [LOCF]) if necessary.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

The efficacy analysis will be performed on the FAS. Baseline is the last data obtained after the start of IMP administration in the placebo-lead in period and before the start of double-blind IMP administration.

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary endpoint is the change from baseline in MADRS total score at Week 6 of the double-blind treatment period.

For the primary analysis, an MMRM analysis will be performed using the OC dataset of the FAS.

The MMRM will include treatment group (OPC-64005 10-mg group, OPC-64005 20-mg group, and placebo group), timepoint (double-blind treatment period Weeks 1, 2, 3, 4, 5, and 6), and interaction between treatment group and timepoint as factors, and baseline and interaction between baseline and timepoint as covariates. An unstructured error variance-covariance structure will be assumed. For degree-of-freedom approximation, the Kenward-Roger method will be used. The statistical comparison will be performed based on differences in the least square means at double-blind treatment period Week 6 between the OPC-64005 20-mg group and the placebo group. If any problem occurs in the convergence status in the estimation of variance components, error variance-covariance structures of heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry will be applied in this order, and the first converged structure will be used in the primary analysis. If structures other than unstructured are selected, sandwich estimators of standard error will be used.

For each timepoint, the least square mean of each treatment group and the differences in the least square means between each OPC-64005 group and the placebo group, as well as the two-sided 95% confidence intervals, will be determined.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

Not applicable.

9.4.1.3 Secondary Efficacy Endpoint Analysis

The secondary endpoint analysis will be performed on the FAS.

- MADRS response rate
- MADRS remission rate
- CGI-I improvement rate

The MADRS response rate in the OPC-64005 20-mg group will be compared with that in the placebo group using the χ^2 test in the LOCF dataset. The differences in the response rates between each OPC-64005 group and the placebo group, as well as the two-sided 95% CI (Wald confidence interval), will be determined. The MADRS remission rate and CGI-I improvement rate will be analyzed in the same manner as the MADRS response rate.

- Mean change from baseline in HAM-D 17-item total score
- Mean change from baseline in Apathy Scale score

An analysis will be performed on the mean change from baseline in HAM-D 17-item total score using the analysis of covariance (ANCOVA) model with treatment group as a factor and baseline as a covariate in the LOCF dataset. The least square means of each treatment group and the difference in the least square means between each OPC-64005 group and the placebo group, as well as the two-sided 95% CIs, will be calculated. The mean change from baseline in Apathy Scale total score will be analyzed in the same manner as the mean change from baseline in HAM-D 17-item total score.

- Mean change from baseline in CGI-S
- Mean change from baseline in MADRS-S total score
- Mean change from baseline in MADRS anhedonia factor score (total score of MADRS Items 1, 2, 6, 7, and 8)

The MMRM analysis will be performed in the same manner as that for the primary endpoint.

9.4.1.4 Control of Experiment-wise Type 1 Error

Not applicable because the statistical test for the primary analysis of the primary endpoint is performed only once, which is comparison of the OPC-64005 20-mg group with the placebo group.

9.4.1.5 Other Efficacy Endpoint Analysis

Not applicable.

9.4.2 Safety Analysis

The safety analysis will be performed on the safety analysis set. Baseline is the last data obtained after the start of IMP administration in the placebo lead-in period and before the start of double-blind IMP administration.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and ICH's Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group and for the overall OPC-64005 group:

- TEAEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs of special interest (drug eruption)

Treatment-emergent AEs potentially causally related to the IMP will also be summarized in the same manner.

9.4.2.2 Clinical Laboratory Data

Descriptive statistics of measurement values and changes from baseline at each time point will be calculated by treatment group and for the overall OPC-64005 group for each laboratory test item of continuous data.

Each laboratory test item of continuous data will be classified into below the lower limit of the reference range, within the reference range, or above the upper limit of the reference range based on the reference ranges of the central laboratory, and a shift table from baseline will be generated by treatment group and for the overall OPC-64005 group.

For each laboratory test item of qualitative data, a shift table from baseline will be generated by treatment group and for the overall OPC-64005 group.

The number and proportion of subjects who meet the criteria for clinically significant laboratory value will be determined by treatment group and for the overall OPC-64005 group.

9.4.2.3 Physical Examination and Vital Signs Data

For each item of vital signs (by position for blood pressure and pulse rate), descriptive statistics of measurement values and changes from baseline at each time point will be calculated by treatment group and for the overall OPC-64005 group.

The number and proportion of subjects who meet the criteria for clinically significant vital signs will be determined by treatment group and for the overall OPC-64005 group.

9.4.2.4 Electrocardiogram Data

For heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc (QTcF), descriptive statistics of measurement values and changes from baseline at each time point will be calculated by treatment group and for the overall OPC-64005 group.

For normal/abnormal assessment of 12-lead ECG, a shift table from baseline will be generated by treatment group and for the overall OPC-64005 group.

For QTc (QTcF) at each time point, the number and proportion of subjects with measurement values after double-blind IMP treatment of > 450 msec, > 480 msec, and > 500 msec, and the number and proportion of subjects with changes from baseline of > 30 msec and > 60 msec will be calculated by treatment group and for the overall OPC-64005 group.

The number and proportion of subjects who meet the criteria for clinically significant ECG will be determined by treatment group and for the overall OPC-64005 group.

9.4.2.5 Other Safety Data

- Body weight, body mass index (BMI) and waist circumference
  For body weight, BMI, and waist circumference, descriptive statistics of measurement values and changes from baseline at each time point will be calculated by treatment group and for the overall OPC-64005 group.
  An analysis of the ANCOVA model with treatment group as a factor and baseline as a covariate will be performed using the LOCF dataset. The least square means of each treatment group and the differences in the least square means between each OPC-64005 group and the placebo group, as well as the two-sided 95% CIs, will be calculated.
  The number and proportion of subjects who meet the criteria for clinically significant body weight will be determined by treatment group and for the overall OPC-64005 group.

- C-SSRS
  The number and proportion of subjects at each time point will be calculated by treatment group and for the overall OPC-64005 group for each item (suicidality, suicidal ideation, suicidal behavior, completed suicide, emergence of suicidal ideation, emergence of serious suicidal ideation, worsening of suicidal ideation, and emergence of suicidal behavior).

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

In each analysis set, descriptive statistics or frequency distribution will be calculated by treatment group and for the overall OPC-64005 group for each demographic and other baseline characteristic.

9.4.3.2 Pharmacokinetic Analysis

For the plasma concentrations of OPC-64005 and OPC-144013, only listings of data will be generated without tabulation.

9.4.3.3 Pharmacodynamic Analysis

No PD analyses are planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analyses are planned.

9.4.3.5 Pharmacogenomic Analysis

For the CYP2D6 genetic testing results, only listings of data will be generated without tabulation.

9.4.3.6 Exploratory Endpoint Analysis

Not applicable.

9.5 Interim Analysis and Adaptive Design

Not applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH Good Clinical Practice (GCP) guideline (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 by an IRB according to regional requirements, and the trial site 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 eCRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a 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 trial site.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH-GCP guideline (E6), and local regulatory requirements. In support of the site's standard process for administering informed consent, this trial will also allow for electronic informed consent form (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators 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 a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator. 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. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

A separate and similar consent process will be followed for PGx testing and FBR. Consent must be obtained before the blood sample is collected. The PGx testing is mandatory, and subjects who do not consent cannot participate in the trial. The FBR is optional and refusal to participate in the FBR does not affect participation in the trial.

10.1.3 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/or 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 eCRF. 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.

10.1.4 Quality Control and Quality Assurance

The sponsor will execute quality management activities for this trial in accordance with ICH E6 (R2). Additional information on the quality management activities will be provided in a separate quality management plan.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guideline (E6), and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) 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 eCRF with source documents, as applicable. The investigator will agree to cooperate with audits.

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) 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 and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 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 records, and recorded data from automated

instruments. All source documents pertaining to this trial will be maintained by the trial sites and made available for direct inspection by authorized persons.

Investigator(s)/trial site(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. Documents (eg, original reports, measurement data) on drug concentration measurement, PGx assessment, and FBR will be retained by the bioanalytical laboratory, PGx laboratory, and biospecimen storage facility, respectively. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations in medical records. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator'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 assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the medical procedures completed;
- The signature (or initials) and date of the investigator (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 progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 CRF Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories and central ECG readers, will be reconciled using key data fields by the sponsor or the CRO with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with ICH GCP guideline E6 Section 8 and as required by applicable local regulations. The institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

The trial sites will maintain all documents and records related to this trial until the following 3 dates, whichever comes later. However, if a longer retention period is required by the sponsor, the retention period and method shall be discussed with the sponsor.

- The date at least 2 years after the date on which approval to market the drug is obtained. If IMP development is discontinued or it is notified that the trial data are not attached to the application dossier, the date at least 3 years after the decision of discontinuation of IMP development or the receipt date of the notification that the trial data are not attached to the application dossier.
- The date at least 3 years after trial discontinuation or completion.
- The date on which the decision to end DNA storage is made.

The trial site 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 trial site 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.

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka Pharmaceutical-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.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Red blood cell (RBC) count White blood cell (WBC) count WBC differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes) Platelets Hemoglobin Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Hematocrit Urinalysis: Occult blood Glucose pH Protein Specific gravity Urobilinogen Ketone body Sediment Urine pregnancy test to FOCBP (if a urine pregnancy test is positive, perform a serum pregnancy test): human chorionic gonadotropin (hCG)	Serum Chemistry: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Total bilirubin Blood urea nitrogen (BUN) Creatinine γ-Glutamyl transpeptidase (γ-GTP) Glucose Lactate dehydrogenase (LDH) Total protein Triglycerides Albumin Cholesterols (total, LDL, HDL) Uric acid Creatinine phosphokinase (CK [CPK]) Serum electrolytes (Ca, K, Na, Cl, Mg, P) Prothrombin time (PT) Activated partial thromboplastin time (APTT) Prothrombin time-international normalized ratio (PT [INR]) Glycosylated hemoglobin (HbA1c) Serum prolactin <At screening only> Free thyroxine (FT4) Thyroid-stimulating hormone (TSH)

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

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

For males and FOCBP, 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 or remains abstinent) to prevent pregnancy during the course of the trial and for 2 weeks after the last dose of IMP. Unless the subject or their partner is of nonchildbearing potential or 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 remains abstinent during the trial and for 2 weeks after the last dose of IMP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, or condom (all methods approved or validated in Japan). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method should be documented in the source document. Male subjects must also agree not to donate sperm from trial screening through 2 weeks after the last dose of IMP.

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

- General information
- ICF
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP 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.

On all FOCBP, urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening and at the start of the placebo lead-in period. If a urine test

is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 2 weeks after the last dose of IMP, and record the event on the IRE form, etc and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator 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.

10.4 Appendix 4: Genetic Testing

CYP2D6 Genotype Assessment Table

	*1	*2	*10	*14B	*41	*4	*5	*14A	*18	*21
*1	E	E	E	E	E	I	I	I	I	I
*2		E	E	E	E	I	I	I	I	I
*10			I	I	I	I	I	I	I	I
*14B				I	I	I	I	I	I	I
*41					I	I	I	I	I	I
*4						P	P	P	P	P
*5							P	P	P	P
*14A								P	P	P
*18									P	P
*21										P

E = EM; I = IM; P = PM

Allele *position								Genotype	Phenotype
100	1758	1846	2573	2850	2988	4125	4180		
del/C	del/G	del/G	del/-	del/C	del/G	del/-	del/G	*1/*5	IM
del/C	del/G	del/G	del/-	del/T	del/G	del/-	del/C	*2/*5	IM
del/T	del/G	del/A	del/-	del/C	del/G	del/-	del/C	*4/*5	PM
del/T	del/G	del/A	del/-	del/C	del/G	del/-	del/G		
del/T	del/G	del/A	del/-	del/T	del/G	del/-	del/C		
del/C	del/G	del/A	del/-	del/C	del/G	del/-	del/G		
del/del	del/del	del/del	del/del	del/del	del/del	del/del	del/del	*5/*5	PM
del/T	del/G	del/G	del/-	del/C	del/G	del/-	del/C	*5/*10	IM
del/T	del/A	del/G	del/-	del/T	del/G	del/-	del/C	*5/*14A	PM
del/C	del/A	del/G	del/-	del/T	del/G	del/-	del/C	*5/*14B	IM
del/C	del/G	del/G	del/-	del/C	del/G	del/9bp	del/G	*5/*18	PM
del/C	del/G	del/G	del/insC	del/T	del/G	del/-	del/C	*5/*21	PM
del/C	del/G	del/G	del/-	del/T	del/A	del/-	del/C	*5/*41	IM
C/C	G/G	G/G	-/-	C/C	G/G	-/-	G/G	*1/*1	EM
C/C	G/G	G/G	-/-	C/T	G/G	-/-	C/G	*1/*2	EM

Allele *position								Genotype	Phenotype
100	**1758**	**1846**	**2573**	**2850**	**2988**	**4125**	**4180**		
C/T	G/G	A/G	-/-	C/C	G/G	-/-	G/G	*1/*4	IM
C/C	G/G	A/G	-/-	C/C	G/G	-/-	G/G		
C/T	G/G	G/G	-/-	C/C	G/G	-/-	C/G	*1/*10	EM
C/C	A/G	G/G	-/-	C/T	G/G	-/-	C/G	*1/*14B	EM
C/T	A/G	G/G	-/-	C/T	G/G	-/-	C/G	*1/*14A	IM
C/C	G/G	G/G	-/-	C/C	G/G	-/9bp	G/G	*1/*18	IM
C/C	G/G	G/G	-/insC	C/T	G/G	-/-	C/G	*1/*21	IM
C/C	G/G	G/G	-/-	C/T	A/G	-/-	C/G	*1/*41	EM
C/C	G/G	G/G	-/-	T/T	G/G	-/-	C/C	*2/*2	EM
C/T	G/G	A/G	-/-	C/T	G/G	-/-	C/C	*2/*4	IM
C/C	G/G	A/G	-/-	C/T	G/G	-/-	C/G		
C/T	G/G	A/G	-/-	T/T	G/G	-/-	C/C		
C/T	G/G	G/G	-/-	C/T	G/G	-/-	C/C	*2/*10	EM
C/C	A/G	G/G	-/-	T/T	G/G	-/-	C/C	*2/*14B	EM
C/T	A/G	G/G	-/-	T/T	G/G	-/-	C/C	*2/*14A	IM
C/C	G/G	G/G	-/-	C/T	G/G	-/9bp	C/G	*2/*18	IM
C/C	G/G	G/G	-/insC	T/T	G/G	-/-	C/C	*2/*21	IM
C/C	G/G	G/G	-/-	T/T	A/G	-/-	C/C	*2/*41	EM
T/T	G/G	A/A	-/-	C/C	G/G	-/-	C/C	*4/*4	PM
T/T	G/G	A/A	-/-	C/C	G/G	-/-	C/G		
T/T	G/G	A/A	-/-	C/T	G/G	-/-	C/C		
C/T	G/G	A/A	-/-	C/C	G/G	-/-	C/G		
T/T	G/G	A/A	-/-	C/C	G/G	-/-	G/G		
T/T	G/G	A/A	-/-	C/T	G/G	-/-	C/G		
C/T	G/G	A/A	-/-	C/C	G/G	-/-	G/G		
T/T	G/G	A/A	-/-	T/T	G/G	-/-	C/C		
C/T	G/G	A/A	-/-	C/T	G/G	-/-	C/G		
C/C	G/G	A/A	-/-	C/C	G/G	-/-	G/G		

Allele *position								Genotype	Phenotype
100	**1758**	**1846**	**2573**	**2850**	**2988**	**4125**	**4180**		
T/T	G/G	A/G	-/-	C/C	G/G	-/-	C/C	*4/*10	IM
T/T	G/G	A/G	-/-	C/C	G/G	-/-	C/G		
T/T	G/G	A/G	-/-	C/T	G/G	-/-	C/C		
T/T	A/G	A/G	-/-	C/T	G/G	-/-	C/C	*4/*14A	PM
C/T	A/G	A/G	-/-	C/T	G/G	-/-	C/C	*4/*14A or *4/*14B	Unknown
T/T	A/G	A/G	-/-	C/T	G/G	-/-	C/G	*4/*14A	PM
C/T	A/G	A/G	-/-	C/T	G/G	-/-	C/G	*4/*14A or *4/*14B	Unknown
T/T	A/G	A/G	-/-	T/T	G/G	-/-	C/C	*4/*14A	PM
C/T	A/G	A/G	-/-	T/T	G/G	-/-	C/C	*4/*14A or *4/*14B	Unknown
C/T	A/G	A/G	-/-	C/T	G/G	-/-	C/G	*4/*14A or *4/*14B	
C/C	A/G	A/G	-/-	C/T	G/G	-/-	C/G	*4/*14B	IM
C/T	G/G	A/G	-/-	C/C	G/G	-/9bp	C/G	*4/*18	PM
C/T	G/G	A/G	-/-	C/C	G/G	-/9bp	G/G		
C/T	G/G	A/G	-/-	C/T	G/G	-/9bp	C/G		
C/C	G/G	A/G	-/-	C/C	G/G	-/9bp	G/G		
C/T	G/G	A/G	-/insC	C/T	G/G	-/-	C/C	*4/*21	PM
C/T	G/G	A/G	-/insC	C/T	G/G	-/-	C/G		
C/T	G/G	A/G	-/insC	T/T	G/G	-/-	C/C		
C/C	G/G	A/G	-/insC	C/T	G/G	-/-	C/G		
C/T	G/G	A/G	-/-	C/T	A/G	-/-	C/C	*4/*41	IM
C/T	G/G	A/G	-/-	C/T	A/G	-/-	C/G		
C/T	G/G	A/G	-/-	T/T	A/G	-/-	C/C		
C/C	G/G	A/G	-/-	C/T	A/G	-/-	C/G		
T/T	G/G	G/G	-/-	C/C	G/G	-/-	C/C	*10/*10	IM
T/T	A/G	G/G	-/-	C/T	G/G	-/-	C/C	*10/*14A	IM
C/T	A/G	G/G	-/-	C/T	G/G	-/-	C/C	*10/*14B	IM
C/T	G/G	G/G	-/-	C/C	G/G	-/9bp	C/G	*10/*18	IM

Allele *position								Genotype	Phenotype
100	**1758**	**1846**	**2573**	**2850**	**2988**	**4125**	**4180**		
C/T	G/G	G/G	-/insC	C/T	G/G	-/-	C/C	*10/*21	IM
C/T	G/G	G/G	-/-	C/T	A/G	-/-	C/C	*10/*41	IM
C/T	A/A	G/G	-/-	T/T	G/G	-/-	C/C	*14A/*14B	IM
C/C	A/A	G/G	-/-	T/T	G/G	-/-	C/C	*14B/*14B	
T/T	A/A	G/G	-/-	T/T	G/G	-/-	C/C	*14A/*14A	PM
C/T	A/G	G/G	-/-	C/T	G/G	-/9bp	C/G	*14A/*18	PM
C/C	A/G	G/G	-/-	C/T	G/G	-/9bp	C/G	*14B/*18	IM
C/T	A/G	G/G	-/insC	T/T	G/G	-/-	C/C	*14A/*21	PM
C/C	A/G	G/G	-/insC	T/T	G/G	-/-	C/C	*14B/*21	IM
C/T	A/G	G/G	-/-	T/T	A/G	-/-	C/C	*14A/*41	IM
C/C	A/G	G/G	-/-	T/T	A/G	-/-	C/C	*14B/*41	
C/C	G/G	G/G	-/-	C/C	G/G	9bp/9bp	G/G	*18/*18	PM
C/C	G/G	G/G	-/insC	C/T	G/G	-/9bp	C/G	*18/*21	PM
C/C	G/G	G/G	-/-	C/T	A/G	-/9bp	C/G	*18/*41	IM
C/C	G/G	G/G	insC/insC	T/T	G/G	-/-	C/C	*21/*21	PM
C/C	G/G	G/G	-/insC	T/T	A/G	-/-	C/C	*21/*41	IM
C/C	G/G	G/G	-/-	T/T	A/A	-/-	C/C	*41/*41	IM
C/T	G/G	A/G	-/-	C/C	G/G	-/-	C/G	*1/*4 or *4/*10	IM
C/T	G/G	A/G	-/-	C/T	G/G	-/-	C/G	*1/*4 or *2/*4	IM

*position: https://www.pharmvar.org/gene/CYP2D6

If the genotype is not determined, it is assessed to be Not determined (ND).

If the genotype is not determined or the phenotype is not estimated to be 1 type, the phenotype is classified as Unknown.

10.5 Appendix 5: Abbreviations

Abbreviation	Definition
AD/HD	Attention-deficit/hyperactivity disorder
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CIOMS	Council for International Organizations of Medical Science
C-SSRS	Columbia-Suicide Severity Rating Scale
CK (CPK)	Creatinine phosphokinase
CYP	Cytochrome P450
DAT	Dopamine transporter
DLST	Drug-induced lymphocyte stimulation test
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EM	Extensive metabolizer
E_{max}	Maximum effect a drug produces
FAS	Full analysis set
FBR	Future Biospecimen Research
FT4	Free thyroxine
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
γ-GTP	γ-Glutamyl transpeptidase
HAM-D	Hamilton Rating Scale for Depression
HbA1c	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
IC_{50}	Concentration of drug producing 50% inhibition
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IRE	Immediately reportable event
IRT system	Interactive Response Technologies system
IM	Intermediate metabolizer

Abbreviation	Definition
LDH	Lactate (lactic acid) dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MADRS	Montgomery Åsberg Depression Rating Scale
MADRS-S	Montgomery Åsberg Depression Rating Scale Self-assessment
MAR	Missing At Random
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I.	Mini-International Neuropsychiatric Interview
MMRM	Mixed-model repeated measures
MNAR	Missing Not At Random
mPFC	Medial prefrontal cortex
NET	Norepinephrine transporter
OC	Observed Cases
OTC	Over the counter
PD	Pharmacodynamic
PET	Positron emission tomography
PK	Pharmacokinetic
PM	Poor metabolizer
PQC	Product quality complaint
PT	Prothrombin time
PT (INR)	Prothrombin time-international normalized ratio
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate by Fridericia's formula
SERT	Serotonin reuptake transporter
SAM-e	S-adenosylmethionine
SIGH-D	Structured Interview Guide for HAM-D
SIGMA	Structured Interview Guide for MADRS
SNRI	Serotonin-noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TRI	Triple Reuptake Inhibitor
TSH	Thyroid-stimulating hormone
21 CFR Part 11	Electronic Records; Electronic Signatures; Final Rule

10.6 Appendix 6: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB. Any permanent 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 will wait for IRB approval 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, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines, as needed.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval 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.

10.6.1 Protocol Amendment(s)/Administrative Change(s)

Amendment 1 Approval Date: 31 Mar 2020

PURPOSE:

To review the trial design schematic because it was targeting only subjects on antidepressants. To review the safety endpoints at and after the end of IMP administration. To clarify the procedures at discontinuation of IMP administration. To review the stipulations for restricted medications. To change the descriptions due to a change in the total volume of blood to be collected in the laboratory tests and a review on the safety endpoints after the finalization of the protocol version 1. To change the calculation method for confidential intervals. To review the stipulations for prohibited medications in consideration of subject safety.

BACKGROUND:

The trial design schematic was amended so that it can be applied to all subjects regardless of the use of antidepressants. The safety endpoints at and after the end of IMP administration were reviewed and amended. The procedures at discontinuation of IMP administration were amended for clarification. The stipulations for restricted medications were amended for clarification. The descriptions were changed based on the change to the total volume of blood to be collected in the laboratory tests and the review of the safety endpoints after the finalization of the protocol version 1. The calculation method for confidence intervals was amended to a method corresponding to differences between the groups. The stipulations for prohibited medications were amended in consideration of subject safety.

MODIFICATIONS TO PROTOCOL:

Location	Before amendment	After amendment
Figure 1.2-1	-	Replacement
Table 1.3-1	-	Visit 10: Addition of vital signs Visit 11: Deletion of the laboratory tests and vital signs Addition of annotations j, k, and l
1.4.6 Visit 11	The investigator will perform Visit 11 observations and examinations 14 days (± 7 days) after the date of last IMP dose in all subjects who have completed or discontinued IMP treatment. The investigator will register the required information in the IRT system at the end of the post-treatment observation period for each subject.	The investigator will perform Visit 11 observations and examinations 14 days (± 7 days) after the date of last IMP dose in all subjects who started IMP administration after Visit 3. The investigator will register the required information in the IRT system at the end of the post-treatment observation period for each subject.
1.4.7 At Discontinuation	If trial discontinuation occurs during the double-blind treatment period or double-blind tapering period, the investigator will perform the examination at discontinuation specified in the schedule of assessments, and record the results and visit date in the source document and eCRF. The investigator will register the required information in the IRT system. If discontinuation occurs during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]), and then the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. However, if the investigator judges that the IMP needs to be discontinued due to an adverse event (AE) or if the IMP dose cannot be tapered due to the subject's circumstances such as he/she does not wish to taper the dose, dose tapering is not mandatory. If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4 or between the start of IMP administration after Visit 9 and Visit 10, dose tapering is not necessary, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.	If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 9, the investigator will perform the examination at discontinuation specified in the schedule of assessments, and record the results and the visit date in the source document and eCRF. The investigator will register the required information in the IRT system. If discontinuation occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 3, it is not necessary to perform the post-treatment observation (Visit 11) 2 weeks after the date of the final dosing after the examination at discontinuation has been performed. If discontinuation occurs during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]) after the examination at discontinuation has been performed, and then the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. However, if the investigator judges that the IMP needs to be discontinued due to an adverse event (AE) or if the IMP dose cannot be tapered due to the subject's circumstances such as he/she does not wish to taper the dose, dose tapering is

		not mandatory, and the examination required at discontinuation will be performed followed by the post-treatment observation (Visit 11) 2 weeks after the date of the final dosing. If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4, dose tapering is not necessary after the examination at discontinuation has been performed, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 9 and Visit 10, the examination at discontinuation is not necessary, the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.
6.5.1 Prohibited Medications 6.5.1.2 Visit 2 Through Visit 9	• Antidepressants • Benzodiazepines (except for ultrashort-acting hypnotics and sedatives) Drugs that are considered to affect the metabolic/activity systems of serotonin, noradrenaline, or dopamine • Strong cytochrome P450 (CYP) 3A4 inhibitors, CYP1A2 inhibitors, CYP2D6 inhibitors, CYP3A4 inducers, CYP1A2 inducers, CYP2B6 inducers, and CYP2D6 substrate with narrow therapeutic range (except for topical drugs) • Central nervous system drugs (except for ultrashort-acting hypnotics and sedatives; antipyretic, analgesic and anti-inflammatory agents; and general cold medicines) • Chinese herbal medicines (drugs indicated for neurosis, anxiety neurosis, neurasthenia, and insomnia) • Over the counter drugs used as sleeping pills • Supplements used for improvement of depressive symptoms (St. John's wort, S-adenosylmethionine [SAM-e], ω-3 fatty acid, kava extract, γ-aminobutyric acid [GABA]) • Varenicline	6.5.1.2 Visit 2 Through Visit 9 • Antidepressants • Benzodiazepines (except for ultrashort-acting hypnotics and sedatives) • Drugs that are considered to affect the metabolic/activity systems of serotonin, noradrenaline, or dopamine • Central nervous system drugs (except for ultrashort-acting hypnotics and sedatives; antipyretic, analgesic and anti-inflammatory agents; and general cold medicines) • Chinese herbal medicines (drugs indicated for neurosis, anxiety neurosis, neurasthenia, and insomnia) • Over the counter drugs used as sleeping pills • Supplements used for improvement of depressive symptoms (St. John's wort, S-adenosylmethionine [SAM-e], ω-3 fatty acid, kava extract, γ-aminobutyric acid [GABA]) • Varenicline 6.5.1.3 Visit 2 Through Visit 10 • Strong cytochrome P450 (CYP) 3A4 inhibitors, CYP1A2 inhibitors, CYP2D6 inhibitors, CYP3A4 inducers, CYP1A2 inducers, CYP2B6 inducers, and CYP2D6 substrate with narrow therapeutic range (except for topical drugs)

6.5.2 Restricted Medications 6.5.2.1 Visit 2 Through Visit 9	• Antipyretic, analgesic and anti-inflammatory agents, and antihistamines The concomitant use of these drugs is permitted if they have been used for treatment of a complication at Visit 2. However, the same dosage and administration should be maintained unless an AE has occurred, or the drug is judged to be no longer necessary due to remission of symptoms. Short-term concomitant use of these drugs for treatment of colds is also permitted. The use of local topical drugs is permitted.	• Antipyretic, analgesic and anti-inflammatory agents, and antihistamines The concomitant use of these drugs is permitted if they have been used for treatment of a complication at Visit 2. However, the same dosage and administration should be maintained unless an AE has occurred, or the drug is judged to be no longer necessary due to remission of symptoms. Short-term concomitant use of these drugs for treatment of colds is also permitted. The use of local topical drugs is permitted. Short-term is defined as 1 week in principle. If antipyretic, analgesic and anti-inflammatory agents or antihistamines that were not being used at informed consent are administered for > 2 weeks, or such administration is necessary, the trial will be discontinued according to the reason for discontinuation, "significant protocol deviation."
7.3.2 Treatment Discontinuation	<Paragraph 2 and onward> If discontinuation of IMP administration occurs, the examination at discontinuation will be performed. If the subject refuses to undergo any examinations at the time of withdrawal, or if examinations cannot be performed due to an emergency or other circumstances, of the examination items specified for the time of withdrawal, only those items that can be performed will be performed. If discontinuation is decided during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]) wherever possible (see Section 6.1.1.4). After dose tapering, the subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4 or between the start of IMP administration after Visit 9 and Visit 10, dose tapering is not necessary, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of	<Paragraph 2 and onward> If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 9, the examination at discontinuation will be performed. If the subject refuses to undergo any examinations at the time of withdrawal, or if examinations cannot be performed due to an emergency or other circumstances, of the examination items specified for the time of withdrawal, only those items that can be performed will be performed. If discontinuation occurs during the period between the start of IMP administration after Visit 2 and the start of IMP administration after Visit 3, the post-treatment observation (Visit 11) 2 weeks after the final dosing is not necessary after the examination at discontinuation has been performed. If discontinuation is decided during the period between the start of IMP administration after Visit 4 and the start of IMP administration after Visit 9, the IMP dose will be tapered (duration: 1 week [7 days ± 2 days]) wherever possible after the examination at discontinuation has been performed (see 6.1.1.4). After dose tapering, the subject will visit the trial site to undergo the

	the final dosing.	same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. If discontinuation occurs during the period between the start of IMP administration after Visit 3 and the start of IMP administration after Visit 4, dose tapering is not necessary after the examination at discontinuation has been performed, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing. If discontinuation of IMP administration occurs during the period between the start of IMP administration after Visit 9 and Visit 10, the examination at discontinuation is not necessary. The subject will visit the trial site to undergo the same examination as scheduled at Visit 10, and the post-treatment observation (Visit 11) will be performed 2 weeks after the date of the final dosing.
8.7.1 Clinically Laboratory Assessments	The total volume of blood to be collected is 68 mL.	The total volume of blood to be collected is approximately 38 mL.
9.4.1.3 Secondary Efficacy Endpoint Analysis	• MADRS response rate • MADRS remission rate • CGI-I improvement rate The MADRS response rate in the OPC-64005 20-mg group will be compared with that in the placebo group using the χ^2 test in the LOCF dataset. The differences in the response rates between each OPC-64005 group and the placebo group, as well as the two-sided 95% CI (Clopper-Pearson confidence interval), will be determined. The MADRS remission rate and CGI-I improvement rate will be analyzed in the same manner as the MADRS response rate.	• MADRS response rate • MADRS remission rate • CGI-I improvement rate The MADRS response rate in the OPC-64005 20-mg group will be compared with that in the placebo group using the χ^2 test in the LOCF dataset. The differences in the response rates between each OPC-64005 group and the placebo group, as well as the two-sided 95% CI (Wald confidence interval), will be determined. The MADRS remission rate and CGI-I improvement rate will be analyzed in the same manner as the MADRS response rate.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

10.7 Appendix 7: Wet-ink Sponsor Signature Page

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPC-64005

REVISED CLINICAL PROTOCOL

A Randomized, Multi-center, Double-blind, Placebo-controlled, Parallel-group Comparison Trial to Assess Efficacy and Safety of OPC-64005 in Patients With Major Depressive Disorder

Protocol No. 277-102-00027

Amendment 1 Approval: 31 Mar 2020

I have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

[redacted]

[redacted]

[redacted]

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