STATISTICAL ANALYSIS PLAN

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
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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug OPC-64005

Protocol No. 277-102-00027

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

Statistical Analysis Plan

Version: 1.0
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Confidential

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CK (CPK)	Creatinine phosphokinase
CYP	Cytochrome P450
DSM-5	Diagnostic and statistical manual of mental disorders fifth edition
EM	Extensive metabolizer
FAS	Full analysis set
HAM-D	Hamilton Rating Scale for Depression
HDL	High-density lipoprotein
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	Intermediate metabolizer
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
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
MNAR	Missing Not At Random
OC	Observed Cases
PM	Poor metabolizer
PT	Preferred term
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate by Fridericia's formula
SMQ	Standardised MedDRA queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHODD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan documents the details of the statistical analysis methodology to be applied in the protocol of Trial 277-102-00027.

2 Trial Objectives

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 major depressive disorder (MDD).

3 Trial Design

3.1 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.

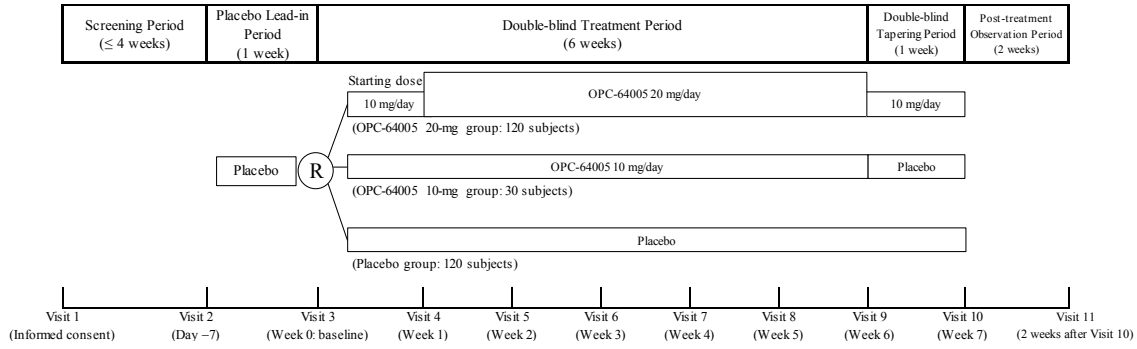

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

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

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

3.2.2 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.

3.2.3 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.

3.2.4 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 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):

- 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.

3.3 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).

3.4 Trial Visit Window

For all endpoints, acceptable windows for analysis are specified, and analysis should take place at the analysis time points regardless of the time points recorded on the case report form.

Acceptable windows for analysis in the double-blind treatment period are shown in Table 3.4-1. Day 1 is defined as the start day of IMP administration in the double-blind treatment period. If multiple data exist within an acceptable window, the last data within the window will be used in analysis. Data obtained 7 days or later after the final IMP administration in the double-blind treatment period will be excluded from analysis performed at any time point in the double-blind treatment period. Data obtained on the day after the start of IMP administration in the double-blind tapering period and thereafter will also be excluded from analysis performed at any time point in the double-blind treatment period.

Table 3.4-1 Acceptable Windows for Analysis in the Double-blind Treatment Period

Week	Target Day	Trial Day Interval
Baseline	1	After the start of IMP administration in the placebo lead-in period to 1
Week 1 in the double-blind treatment period	8	2-11
Week 2 in the double-blind treatment period	15	12-18
Week 3 in the double-blind treatment period	22	19-25
Week 4 in the double-blind treatment period	29	26-32
Week 5 in the double-blind treatment period	36	33-39
Week 6 in the double-blind treatment period	43	40-50

Time points recorded on the case report form will be used in analysis in the double-blind tapering period (Week 7) and the post-treatment observation period.

3.5 Handling of Endpoints

3.5.1 Montgomery Åsberg Depression Rating Scale

The Montgomery-Åsberg Depression Rating Scale (MADRS) total score will be the total score of MADRS Items 1 through 10. The MADRS anhedonia factor score will be the total score of MADRS Items 1, 2, 6, 7, and 8.

3.5.2 Clinical Global Impression - Improvement

"0. Not assessed" will be handled as missing data.

3.5.3 Clinical Global Impression - Severity of Illness

"0. Not assessed" will be handled as missing data.

3.5.4 Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (HAM-D) 17-item total score will be the total score of HAM-D Items 1 through 17.

3.5.5 Montgomery Åsberg Depression Rating Scale Self-assessment

The Montgomery Åsberg Depression Rating Scale Self-assessment (MADRS-S) total score will be the total score of MADRS-S Items 1 through 9.

3.5.6 Apathy Scale

The Apathy Scale score will be the total score of Apathy Scale Items 1 through 14.

4 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, the mean change (± SE) from baseline in MADRS total score at the final time point 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.

5 Statistical Analysis Datasets

5.1 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 time point after the start of double-blind treatment.

5.2 Safety Analysis Set

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

5.3 Handling of Missing Data

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.

The secondary endpoint analyses (MADRS response rate, MADRS remission rate, Clinical Global Impression – Improvement [CGI-I] improvement rate, CGI-I score, mean change from baseline in HAM-D 17-item total score, and mean change from baseline in Apathy Scale total score) and the safety analysis (body weight, body mass index [BMI], and waist circumference) will be performed using data imputed with the last data after the start of double-blind IMP administration (last observation carried forward [LOCF]).

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

The primary endpoint is the change from baseline in MADRS total score at Week 6 of the double-blind treatment period, and the mean change in the OPC-64005 20-mg group will be compared with that in the placebo group.

6.2 Secondary Outcome Variables

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), 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 HAM-D 17-item total score, mean change from baseline in Apathy Scale score, mean change from baseline in the total score of MADRS-S (total score of Items 1 through 9), and mean change from baseline in MADRS anhedonia factor score for evaluation of the efficacy of OPC-64005 at 20 mg.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The numbers and proportions of subjects from whom informed consent was obtained, screen failures, those treated with IMP in the placebo lead-in period, those who completed the placebo lead-in period, those who discontinued treatment in the placebo lead-in period, and those who discontinued treatment in the placebo lead-in period by reason for discontinuation will be summarized.

The numbers and proportions of randomized subjects in the double-blind treatment period, those treated with IMP in the double-blind treatment period, those who completed the double-blind treatment period, those who discontinued treatment in the double-blind treatment period, those who discontinued treatment in the double-blind treatment period by reason for discontinuation, and those included in each analysis set will be summarized for overall, for each treatment group, and for the overall OPC-64005 group.

The numbers of subjects treated with IMP in the double-blind tapering period in the all subjects, in those who completed the double-blind tapering period, and in those who discontinued treatment in the double-blind treatment period will be summarized for overall, for each treatment group, and for the overall OPC-64005 group.

The numbers and proportions of subjects who completed the double-blind treatment period will be summarized by time point (Day) (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, and > 42), for overall, for each treatment group, and for the overall OPC-64005 group.

7.2 Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, minimum, median, and maximum; hereinafter the same applies) of age, height, body weight, waist circumference, and BMI and frequency distribution of sex, race, ethnicity, country, medical history (yes or no), complications (yes or no), and cytochrome P450 (CYP) 2D6 genotype (phenotype) will

be determined for overall, for each treatment group, and for the overall OPC-64005 group in each analysis set in the double-blind treatment period. Baseline values will be used for body weight, waist circumference, and BMI.

7.3 Baseline Disease Evaluation

Descriptive statistics of the duration (in months) of the current major depressive episode, age at initial onset, duration (in months) of major depression from initial onset, MADRS total score, HAM-D 17-item total score, CGI-S, Apathy Scale total score, MADRS-S total score, and MADRS anhedonia factor score and frequency distribution of DSM-5 diagnosis (single episode, recurrent episode), DSM-5 severity (mild, moderate, severe), specifiers (not applicable, applicable, applicable if [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]), number of major depressive episodes (1, 2, 3, 4, ≥ 5), MADRS total score (< 30, ≥ 30), prior medications (antidepressants) for the current major depressive episode, prior medications (antianxiety agents), and prior medications (hypnotic agents) will be determined for overall, for each treatment group, and for the overall OPC-64005 group in each analysis set in the double-blind treatment period.

Baseline values will be used for MADRS total score, HAM-D 17-item total score, CGI-S, Apathy Scale total score, MADRS-S total score, and MADRS anhedonia factor score.

The duration of the current major depressive episode and the duration of major depression from initial onset will be determined using the following formula: Duration (in months) = (date of demographic assessment – date of onset + 1) /30. Any unknown month or day of onset will be replaced with June or 15, respectively.

7.4 Treatment Compliance

The compliance rate (the number of days that the subject took medication / the number of days for which the IMP was prescribed) in the double-blind treatment period will be classified into < 70%, ≥ 70% to < 80%, ≥ 80% to < 90%, and ≥ 90%, and frequency distribution of the compliance rate will be determined for overall, for each treatment group, and for the overall OPC-64005 group in FAS. The same tabulation will be performed for the placebo lead-in period and double-blind tapering period. Subjects without dose tapering will be classified as “not applicable” in tabulation for double-blind tapering period.

7.5 Prior and Concomitant Medications

The number and proportion of subjects who used prior medications (antidepressants) for the current major depressive episode will be determined by drug for overall, for each treatment group, and for the overall OPC-64005 group in the safety analysis set.

The numbers and proportions of subjects who used medications before, during, and after the double-blind treatment period will be determined by drug class and preferred term of the World Health Organization Drug Dictionary (WHODD) version September 1, 2019 for overall, for each treatment group, and for the overall OPC-64005 group in the safety analysis set.

7.6 Protocol Deviations

The number and proportion of randomized subjects with major deviations from the protocol will be determined by deviation category (IMP administration, eligibility criteria, failure to discontinue the trial when the subject meets the withdrawal criteria, procedural deviation that may affect primary endpoint evaluation, prohibited concomitant medications, and overall) and trial site for overall, for each treatment group, and for the overall OPC-64005 group.

The same tabulation will be performed for all subjects who are not randomized.

8 Efficacy Analysis

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.

8.1 Primary Efficacy Endpoint

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

8.1.1 Primary Efficacy Analysis

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), time point (double-blind treatment period Weeks 1, 2, 3, 4, 5, and 6), and interaction between treatment group and time point as factors, and baseline and interaction between baseline and time point 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 between the OPC-64005 20-mg group and the placebo group will be performed based on differences in the least square means at Week 6 of the double-blind treatment period between the 2 groups. 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 time point, 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 (CIs), will be determined.

The time course of the least square means of the change from baseline in MADRS total score and standard errors will be plotted for each treatment group.

8.1.2 Sensitivity Analyses

8.1.2.1 Sensitivity Analysis for Handling of Missing Data

As a sensitivity analysis for handling of missing data, placebo multiple imputation and tipping point analysis on MNAR assumption will be performed using a pattern-mixture model with multiple imputation.

Multiple imputation analysis will be performed according to the following procedure. The number of imputations will be 100.

1) The Markov Chain Monte Carlo (MCMC) method will be used to impute intermittent missing data to produce a monotone missing data pattern.
2) The monotone regression method will be used to impute monotone missing data.
3) The same MMRM as that of the primary efficacy analysis will be used to analyze the multiple-imputed datasets.
4) The MIANALYZE procedure will be used to integrate the analysis results of the multiple-imputed datasets, and the estimate of the difference between the OPC-64005 20-mg group and the placebo group at Week 6 in the double-blind treatment period and its 95% CI and p-value will be determined.

In placebo multiple imputation, for discontinued subjects in each OPC-64005 group, MNAR will be assumed for missing data after discontinuation and an imputation model based on the placebo group will be used in imputation.

In tipping point analysis, for subjects in each OPC-64005 group who discontinued treatment for any of the following reasons, MNAR will be assumed for missing data after discontinuation.

- Withdrawal for any reason
- Withdrawal due to AEs, a lack of efficacy, or consent withdrawal
- Withdrawal due to AEs or a lack of efficacy

For subjects in each OPC-64005 group who discontinued treatment for reasons assumed as MNAR, the MAR assumption will be used to impute post-discontinuation missing data, add Δ (intergroup differences in MMRM of the primary efficacy analysis) × k% to the imputed value, and increase k until a statistically significant conclusion is reversed ($p > 0.05$).

8.1.2.2 Sensitivity Analysis for Normality Assumption

As a sensitivity analysis for normality assumption, multiple imputation under the MAR assumption will be performed, and the Wilcoxon rank sum test will be used to compare the OPC-64005 20-mg group and the placebo group for each time point, and the Hodges-Lehmann estimator of the intergroup difference will be determined. A robust regression analysis with treatment group as a factor and baseline as a covariate will also be performed for each time point. If between-imputation variance is 0 because of the absence or paucity of missing data, analysis without multiple imputation will be performed.

8.1.3 Technical Computational Details for Primary Efficacy Analysis

The SAS code for the MIXED procedure to perform the primary efficacy MMRM analysis is shown below.

```
proc mixed;
   class treatment visit subjid;
   model change=treatment baseline visit treatment*visit baseline*visit / ddfm=kr;
   repeated visit /type=un subject=subjid;
   lsmeans treatment*visit / diff cl;
   ods output diffs=diffs lsmeans=lsmeans;
run;
```

8.2 Secondary Efficacy Analyses

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. The same analysis will be performed on the OC dataset.

- 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. The same analysis will be performed on the OC dataset.

- Mean change from baseline in CGI-S
- Mean change from baseline in MADRS-S total score (total score of Items 1 through 9)
- 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.

8.3 Subgroup Analyses

For the mean change from baseline in MADRS total score, the same MMRM analysis as that of the primary endpoint will be performed for each of the following subgroups.

For CYP2D6 genotype, all subjects in the placebo group will be included in each subgroup.

- Sex (male, female)
- Age (< 55, ≥ 55)
- Body weight ($\leq$ median, $>$ median)
- BMI ($\leq$ median, $>$ median)

- CYP2D6 genotype (phenotype) (PM, IM, EM)
- Duration (in months) of the current major depressive episode (≤ median, > median)
- Age at initial onset (≤ median, > median)
- Duration (in months) of major depression from initial onset (≤ median, > median)
- Baseline MADRS total score (< 30, ≥ 30)
- Baseline CGI-S (≤ median, > median)
- Baseline HAM-D 17-item total score (≤ median, > median)
- Baseline Apathy Scale total score (≤ median, > median)
- Baseline MADRS-S total score (≤ median, > median)
- Baseline MADRS anhedonia factor score (≤ median, > median)
- DSM-5 diagnosis (single episode, recurrent episode)
- DSM-5 severity (mild, moderate, severe)
- Specifiers (not applicable, applicable, applicable if [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])
- Number of major depressive episodes (1, 2, 3, 4, ≥ 5)
- Prior medications (antidepressants) for the current major depressive episode (yes or no)
- Prior medications (antianxiety agents) (yes or no)
- Prior medications (hypnotic agents) (yes or no)

8.4 Exploratory or Other Analyses

The Cochran Mantel Haenszel (CMH) Row Mean Scores test of CGI-I scores will be performed on LOCF dataset to compare the OPC-64005 20-mg group and the placebo group. The mean in each treatment group and the mean difference between each OPC-64005 group and the placebo group with their two-sided 95% CIs will be determined. The same analysis will be performed on the OC dataset.

For MADRS total score, HAM-D 17-item total score, Apathy Scale total score, CGI-S, MADRS-S total score, and MADRS anhedonia factor score, descriptive statistics of measurement values and changes from baseline at each time point will be calculated for each treatment group in FAS. For CGI-I, descriptive statistics of measurement values at each time point will be calculated for each treatment group in FAS.

For the mean change from baseline in each subscale of MADRS and MADRS-S, the same MMRM analysis as that of the primary endpoint will be performed in FAS. For the mean change from baseline in each subscale of HAM-D 17-item and Apathy Scale, the

same analysis as that of HAM-D 17-item total score will be performed. For each subscale of MADRS, MADRS-S, HAM-D 17-item, and Apathy Scale, descriptive statistics of measurement values and changes from baseline at each time point will be calculated for each treatment group.

9 Safety Analyses

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.

9.1 Extent of Exposure

The frequency distribution of treatment period (in days) in the double-blind treatment period (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, > 42) will be determined by treatment group and for the overall OPC-64005 group.

9.2 Adverse Events

All AEs will be coded by system organ class (SOC) and ICH's Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 preferred term (PT). The incidence of the following events will be summarized by treatment group and for the overall OPC-64005 group. In tabulation by severity, if the same AE occurs more than once in the same subject, the severest event will be used.

- Adverse events occurring after the start of double-blind IMP administration (treatment-emergent adverse events [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)
- TEAEs occurring in at least 2% of subjects in the OPC-64005 20-mg group and more frequently than in the placebo group
- TEAEs by time of initial onset (Day) (1-7, 8-14, 15-21, 22-28, 29-35, 36-42, > 42)

TEAEs of special interest (drug eruption) are defined as IMP-related TEAEs whose coded PTs are included in both Standardised MedDRA Queries (SMQ) "Hypersensitivity" and SOC "skin and subcutaneous tissue disorders."

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

9.3 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 do not meet the criteria for clinically significant laboratory values (Appendix 2) at baseline and meet the criteria after the start of IMP administration will be determined by treatment group and for the overall OPC-64005 group. A listing of these subjects will be provided.

The numbers and proportions of subjects with values for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBL) after the start of IMP administration meeting Hy's Law criteria (ALT or AST $\geq 3 \times$ the upper limit of normal [ULN] and TBL $\geq 2 \times$ ULN) will be determined by treatment group and for the overall OPC-64005 group. A listing of these subjects will be provided.

The numbers and proportions of subjects with a prolactin value not meeting the criteria of $> 1 \times$ ULN, $> 2 \times$ ULN, or $> 3 \times$ ULN at baseline and meeting the criteria after the start of IMP administration will be determined by sex for each treatment group and the overall OPC-64005 group. A listing of these subjects will be provided.

The numbers and proportions of subjects with values of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and blood glucose after the start of IMP administration meeting the criteria for changes in glucose and lipid metabolism-related parameters (Table 9.3-1) will be determined by baseline value for each treatment group and the overall OPC-64005 group. A listing of these subjects will be provided.

Table 9.3-1 Changes in Glucose and Lipid Metabolism-related Parameters		
LAB PARAMETER	**BASELINE**	**ANYTIME POST BASELINE**
LDL Cholesterol, Fasting (mg/dL)	Borderline 100-<160 Normal/Borderline <160 Normal <100 Any Value	High >=160 High >=160 Borderline/High >=100 Increased >=30
HDL Cholesterol, Fasting (mg/dL)	Normal >=40 Any Value	Low <40 Decreased >=20
Triglycerides, Fasting (mg/dL)	Normal <150 Borderline 150-<200 Normal/Borderline <200 Normal <150 Normal/Borderline/High <500 Any Value	High 200-<500 High 200-<500 High 200-<500 Borderline/High/Very High >=150 Very High >=500 Increased >=50
Glucose Fasting, Serum (mg/dL)	Normal <100 Impaired 100-<126 Normal/Impaired <126 Any Value	High >=126 High >=126 High >=126 Increased >=10

The number and proportion of subjects who do not meet the diagnostic criteria for metabolic syndrome (Table 9.3-2) at baseline and meet the criteria after the start of IMP administration will be determined by treatment group and for the overall OPC-64005 group. A listing of these subjects will be provided.

Table 9.3-2 Diagnostic Criteria for Metabolic Syndrome	
Description	Metabolic Syndrome Criteria (Health, Labour and Welfare Ministry of Japan)
Central obesity	Waist Circumference ≥85 cm (Male), ≥90 cm (Female)
Dyslipidemia	Triglycerides, Fasting ≥150 mg/dL and/or HDL, Fasting <40 mg/dL
Supine blood pressure	Systolic ≥130 mmHg and/or Diastolic ≥85 mmHg
Glucose fasting, serum	≥110 mg/dL
Metabolic syndrome	Met central obesity criteria and 2 of 3 other criteria at a visit

9.4 Vital Sign 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 (Appendix 1) will be determined by treatment group and for the overall OPC-64005 group. A listing of these subjects will be provided.

9.5 Physical Examination Data

Listings of physical examination findings will be provided.

9.6 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), the number and proportion of subjects with measurement values of > 450 msec, > 480 msec, and > 500 msec (ie, subjects who do not meet these criteria before the start of double-blind IMP administration and meet the criteria after the start of double-blind IMP administration) and the number and proportion of subjects with changes from baseline of > 30 msec and > 60 msec will be determined by treatment group and for the overall OPC-64005 group. The number and proportion of subjects with measurement values of > 450 msec and with percent change from baseline of > 10% will also be determined by treatment group and for the overall OPC-64005 group.

The number and proportion of subjects who meet the criteria for clinically significant ECG (Appendix 3) will be determined by treatment group and for the overall OPC-64005 group. A listing of these subjects will be provided.

9.7 Other Safety Data

9.7.1 Body Weight, Body Mass Index, and Waist Circumference

For body weight, BMI, and waist circumference, descriptive statistics of measurement values and changes from baseline at each time point and the last time point (LOCF; Week 6 in the double-blind treatment period) 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. 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 (Appendix 1) will be determined by treatment group and for the overall OPC-64005 group. The same analysis will also be performed by baseline BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30). A listing of subjects who meet the criteria for clinically significant body weight (Appendix 1) will be provided.

9.7.2 Columbia-Suicide Severity Rating Scale

The number and proportion of subjects at each time point and for the entire period after the start of double-blinded IMP administration (including post-treatment observation, discontinuation, and unscheduled visits) will be determined 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). A listing of subjects with emergence of suicidal ideation, emergence of serious suicidal ideation, worsening of suicidal ideation, and emergence of suicidal behavior will be provided. The same tabulation will be performed for each category of suicidal ideation and suicidal behavior.

- Suicidality: "Yes" to any question of suicidal ideation or suicidal behavior
- Suicidal ideation: "Yes" to any question of suicidal ideation
- Suicidal behavior: "Yes" to any question of suicidal behavior
- Emergence of suicidal ideation: Suicidal ideation is absent at baseline and present after baseline.
- Emergence of serious suicidal ideation: Suicidal ideation is absent at baseline and present with an intensity of 4 or 5 after baseline.
- Worsening of suicidal ideation: Increase in the intensity of suicidal ideation after baseline compared with baseline.
- Emergence of suicidal behavior: Suicidal behavior is absent at baseline and present after baseline.

10 Pharmacokinetic Analyses

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

11 Pharmacodynamic Analyses

Not applicable.

12 Pharmacogenomic Analyses

CYP2D6 genotype (phenotype) will be tabulated as specified in Section 7.2 Demographic and Baseline Characteristics.

13 Interim Analysis

No interim analyses are planned.

14 Changes in the Planned Analyses

It has been decided that CYP2D6 phenotype will be tabulated as specified in Section 7.2 Demographic and Baseline Characteristics.

15 References

Not applicable.