STATISTICAL ANALYSIS PLAN

A single center, open-label, randomized, 3-arm, 3-way crossover trial to investigate the bioequivalence of brexpiprazole (OPC-34712) orally disintegrating tablets in healthy adult males

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Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug Brexpiprazole (OPC-34712)

Protocol No. 331-14-002

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Statistical Analysis Plan

Version: 1.0
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
BE	Bioequivalence
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
IMP	Investigational medicinal product
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
OD	Orally disintegrating
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
WHODD	World Health Organization Drug Dictionary
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_%Extrap	Ratio of area under the concentration-time curve from t_{last} to infinity versus AUC_{∞}
CL/F	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	Apparent clearance of drug from plasma after extravascular administration per body weight
C_{max}	Maximum (peak) plasma concentration of the drug
λ_z	Terminal elimination rate constant
λ_z (Rsq)	Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z
λ_z (point)	Number of points used in computing λ_z
λ_z (upper)	Upper limit of time for values to be included in the calculation of λ_z
λ_z (lower)	Lower limit on time for values to be included in the calculation of λ_z
$t_{1/2,z}$	Terminal-phase elimination half-life
t_{last}	Time of the last measureable concentration
t_{max}	Time to maximum (peak) plasma concentration

1 Introduction

This statistical analysis plan (SAP) describes the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis in 331-14-002 trial.

2 Trial Objectives

The purpose of the present trial is to investigate the bioequivalence of brexpiprazole ODT 2 mg and brexpiprazole conventional tablet 2 mg.

3 Trial Design

3.1 Type/Design of Trial

This is a single center, open-label, randomized, 3-arm, 3-way crossover trial in 21 healthy adult male subjects. Subjects will be hospitalized to the trial site 3 times during the trial (Days −1 to 8, Days 20 to 28, and Days 40 to 48) and will be discharged at the end of each period of hospitalization (on Days 8, 28, and 48) after completion of safety evaluation and blood collection for pharmacokinetic assessment.

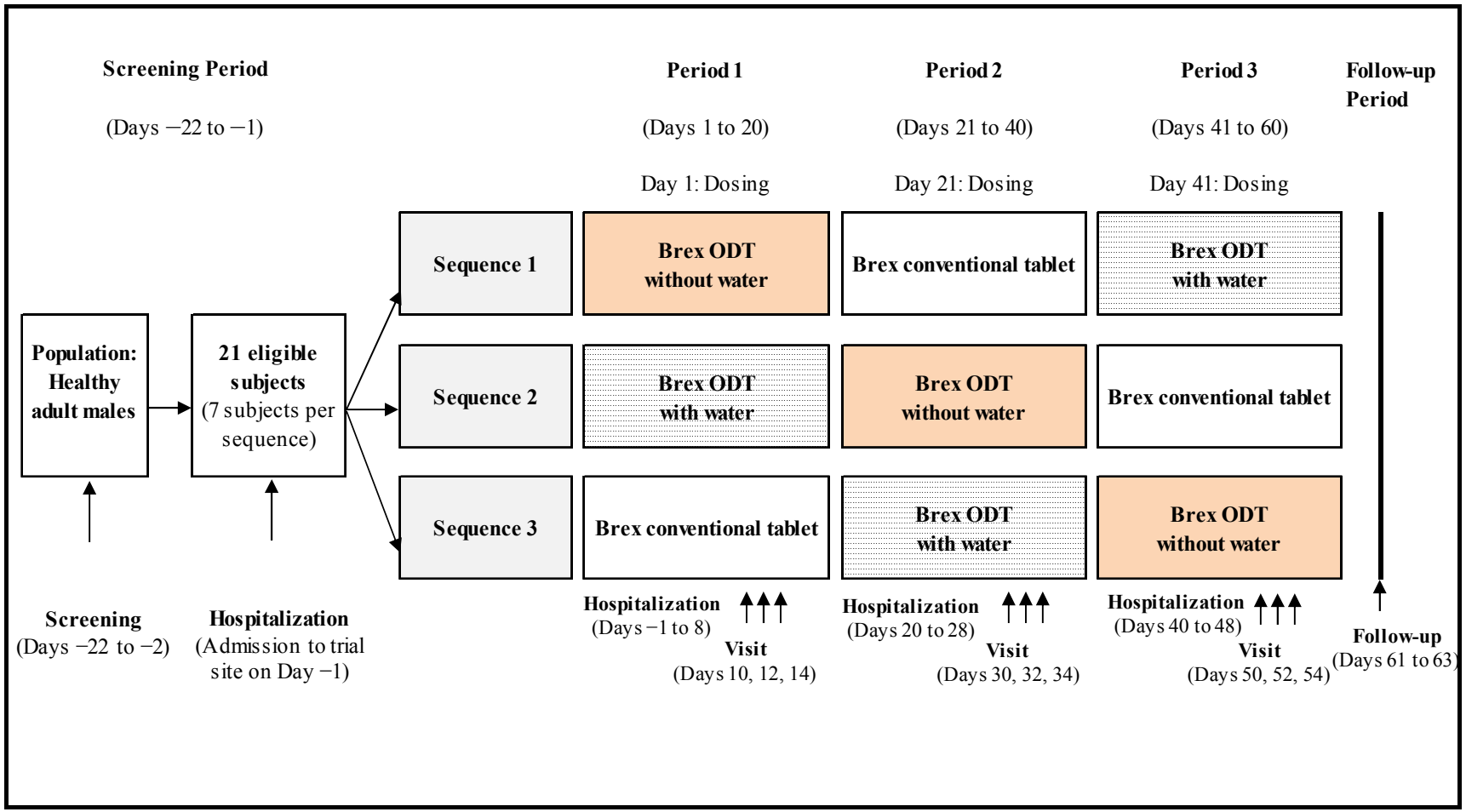
A 2-mg dose of brexpiprazole will be administered to each subject as either an ODT or a conventional tablet on Days 1, 21, and 41, and ODT will be administered either with water or without water, according to the randomized administration schedule.

Subjects randomized to Sequence 1 will receive an ODT without water on Day 1, a conventional tablet on Day 21, and an ODT with water on Day 41.

Subjects randomized to Sequence 2 will receive an ODT with water on Day 1, an ODT without water on Day 21, and a conventional tablet on Day 41.

Subjects randomized to Sequence 3 will receive a conventional tablet on Day 1, an ODT with water on Day 21, and an ODT without water on Day 41.

The trial design schematic is shown in Figure 3-1.



Brex = brexpiprazole; ODT = orally disintegrating tablet

Figure 3-1 Trial Design

3.2 Trial Treatments

3.2.1 Brexpiprazole ODTs (Investigational Medicinal Product)

Subjects will receive one 2-mg brexpiprazole ODT with or without 150 mL of ordinary-temperature water. When administered without water, the subject will be instructed to place the tablet directly on the tongue and keep it there until it disintegrates completely before swallowing. Compliance will be ensured by a mouth check.

All doses will be administered after fasting for at least 10 hours and no food will be allowed until 4 hours postdose. Except as part of the dosing procedure, water will be restricted from 1 hour prior to dosing until 2 hours postdose.

3.2.2 Brexpiprazole Conventional Tablets

Subjects will receive one 2-mg brexpiprazole conventional tablet with 150 mL of ordinary-temperature water. Compliance will be ensured by a mouth check. The IMP will be administered after fasting for at least 10 hours and no food will be allowed until 4 hours postdose. Except as part of the dosing procedure, water will be restricted from 1 hour prior to dosing until 2 hours postdose.

3.3 Trial Population

A total of 21 healthy male subjects at least 20 years of age and below 40 years of age, will be enrolled.

3.4 Trial Visit Window

Nominal time points will be used for summary of safety parameters and plasma concentration. The examinations on withdrawal and unscheduled visits will be not used in the analyses and will be provided in the listings.

4 Sample Size

Based on the BE Guideline[1], the sample size was calculated so that the 90% confidence intervals of geometric mean ratios for brexpiprazole C_{max} and AUC_t between ODT (with or without water) and conventional tablet would fall within the bioequivalence range of 0.8 to 1.25.

In a brexpiprazole 4-mg ODT BA study conducted in Japan (331-102-00019) and brexpiprazole bioequivalence studies conducted outside Japan (331-10-243 and 331-13-209), the within-subject variance for natural log-transformed C_{max} and AUC_t values was greatest for C_{max} in Trial 331-13-209 (at 0.035).

Assuming a geometric mean ratio of 1.0 for brexpiprazole C_{max} between ODT (with and without water) and conventional tablet, and a within-subject variance of 0.035 for natural log-transformed C_{max}, to achieve at least 90% power will require 6 subjects in each sequence, 18 in total. Considering the possibility of some subjects being excluded from analysis due to discontinuation, etc, the number of subjects was set as 7 for each sequence and 21 in total.

4.1 Judgment for Conduct of Add-on Subject Study

If bioequivalence cannot be demonstrated in the initial study because of an insufficient number of subjects, an add-on subject study can be performed in accordance with this protocol.

The add-on subject study will be performed using not less than half the number of subjects in the initial study. No add-on subject study will be performed in the following cases:

1) If the results of the initial study show that the point estimates of the geometric mean ratios for AUC_t and C_{max} between ODT and conventional tablet do not fall within the range of 0.8 to 1.25, and
2) If the required number of subjects for the add-on subject study estimated from the results of the initial study is considered to be a sample size that is ethically or scientifically infeasible.

5 Statistical Analysis Sets

5.1.1 Bioequivalence Analysis Set

All subjects who provided C_{max} or AUC_t through Period 1, Period 2, and Period 3

5.1.2 Safety Population

All subjects who received at least one dose of IMP

5.1.3 Handling of Missing Data

There will be no imputation for missing data.

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

C_{max} and AUC_t of brexpiprazole

6.2 Secondary Outcome Variables

1) Plasma concentration-time profiles of brexpiprazole

2) Brexpiprazole AUC_{∞}, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, and t_{last}

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of screened subjects will be presented. The number and percentage of randomized subjects, completed subjects, and discontinued subjects will be presented by sequence. The number and percentage of discontinued subjects by primary reason for discontinuation will also be presented by sequence. The denominators of percentages will be randomized subjects.

The number and percentage of subjects included in each analysis set will be provided by sequence for the randomized subjects.

7.2 Demographic and Baseline Characteristics

For the bioequivalence analysis set and safety analysis set, the descriptive statistics (n, mean, SD, min, median and max) of age, height, weight (screening period) and BMI will be presented overall and by sequence. The frequency distribution of gender, race, ethnicity, country, medical history and current symptoms will be presented overall and by sequence.

7.3 Treatment Compliance

Not applicable.

7.4 Prior and Concomitant Medication

The medications will be coded by World Health Organization Drug Dictionary (WHODD) version March 1, 2019 Global. The previous and concomitant medications will be listed.

7.5 Protocol Deviations

The major protocol deviations will be listed.

8 Efficacy Analyses

Not applicable.

9 Safety Analyses

Safety analysis will be conducted upon the safety analysis set for each formulation and administration method (conventional tablet, ODT without water, ODT with water). Baseline is defined as the last measurement immediately before each dosing (for 12-lead ECG parameters, the mean value of three measurements on the day before IMP administration will be used).

9.1 Extent of Exposure

Subjects who received the IMP will be summarized by each formulation and administration method.

9.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 will be used to code AEs. TEAEs in each period are defined as adverse events occurred on or after the IMP administration in each period to before the IMP administration in next period or the end of study. If multiple occurrences of the same event are observed in the same subject during the same period, the highest severity will be used for analysis.

The incidence of the following events will be summarized by system organ class, preferred term (the denominators will be subjects who administered by each formulation and administration method).

- TEAEs
- TEAEs by severity

The incidence of the following events will be summarized (the denominators will be subjects who administered by each formulation and administration method).

- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

TEAEs potentially causally related to the IMP will also be summarized in the same way.

9.3 Clinical Laboratory Data

For each clinical laboratory parameter except for qualitative urinalysis, the descriptive statistics of measured values and of changes from baseline will be calculated by time point. For qualitative parameters of clinical laboratory urinalysis, shift tables versus baseline at each time point will be produced. For the clinical laboratory parameters except for qualitative urinalysis, measured values will be classified as Within Reference Range,

Lower Than Reference Range, and More Than Reference Range, using the reference range of the trial site, and shift tables versus baseline at each time point will be produced.

9.4 Vital Sign Data

For each vital sign, the descriptive statistics of measured values and of changes from baseline will be presented by time point.

9.5 Physical Examination Data

For physical examination, listing of physical findings will be presented by each subject.

9.6 Electrocardiogram Data

For each 12-lead ECG parameter, the descriptive statistics of measured values and of changes from baseline will be calculated by time point. For 12-lead ECG assessment of normality/abnormality, shift tables versus baseline at each time point will be produced. For QTcF and QTcB, categorical analysis of measured values and of changes from baseline at each time point will be performed to calculate the number and percentage of subjects. The number and percentage of subjects with actual measurements of corrected QT interval (QTcF, QTcB) at each time point being > 450 msec, > 480 msec, and > 500 msec will be determined. The number and percentage of subjects with changes from baseline being > 30 msec and > 60 msec will be also determined.

9.7 Other Safety Data

9.7.1.1 Body Weight

For body weight, the descriptive statistics of measured values and of changes from baseline will be presented.

9.7.1.2 The Columbia-Suicide Severity Rating Scale

C-SSRS data for individual subjects will be listed.

10 Pharmacokinetic Analyses

10.1 Statistical Analyses of Primary Pharmacokinetic Endpoints

The following analysis will be performed on the bioequivalence analysis set:

The C_{max} and AUC_t of brexpiprazole will be analyzed using the natural log-transformed values in a mixed effect model with sequence (1, 2, and 3), formulation and administration method (conventional tablet, ODT without water, ODT with water), and period (Period 1, Period 2, and Period 3) as fixed effects and the subjects within each

sequence as a random effect. The Kenward–Roger method will be used to estimate the degrees of freedom in the mixed effect model analysis. The 90% confidence intervals of geometric mean ratios for brexpiprazole C_{max} and AUC_t between ODT (with or without water) and conventional tablet will be calculated. If the 90% confidence intervals are within the range of 0.8 to 1.25, the 2 formulations and administration methods will be judged to be bioequivalent.

If an add-on subject study is conducted, bioequivalence will be assessed on the same basis from the result of combining the initial study and the add-on subject study by including study as a fixed effect in the above mixed effect model.

If there are any subjects who had no evaluable parameters through Period 1, Period 2, and Period 3, analysis in which those subjects are included will be performed.

10.2 Pharmacokinetic Methods

10.2.1 Pharmacokinetic Analysis

The PK parameters of brexpiprazole ［C_{max}, AUC_t, AUC_∞, t_{max}, $t_{1/2,z}$, λ_z, t_{last}, CL/F, CL/F/BW, AUC_%Extrap, λ_z (point), λ_z (lower), λ_z (upper) and λ_z (Rsq)］ will be calculated through a noncompartmental PK analysis. CL/F/BW will be calculated by dividing CL/F by the body weight (kg) before IMP administration in each period.

10.2.2 Handling of Data

- If vomiting occurs at a time point less than twice the median t_{max}, the data for the subject who experienced vomiting will be excluded from the bioequivalence analysis set. The median t_{max} that is referenced for that judgment is the median t_{max} of the same group calculated excluding the vomiting case.
- If blood sampling is conducted outside the time window (refer to PRT Table 3.7.3-1), the data will be excluded from the calculation of descriptive statistics for plasma concentrations at that time point. However, it will be used for the calculation of pharmacokinetic parameters, and if the calculation is determined to be unsuitable, the parameter will not be adopted.
- If prohibited medications that may affect the pharmacokinetics of IMP are used, data points after the use of prohibited medications in the relevant subjects will be excluded from the calculation of descriptive statistics for plasma concentrations.

However, it will be used for the calculation of pharmacokinetic parameters, and if the calculation is determined to be unsuitable, the parameter will not be adopted.

- Plasma concentrations below lower limit of quantitation (LLOQ) that occur prior to and after the first measurable concentration in each period will be imputed to 0 (ng/mL) and missing.
- LLOQ of brexpiprazole (OPC-34712) is 0.5000 ng/mL.

10.2.3 Calculation of descriptive statistics

Descriptive statistics will be calculated on the bioequivalence analysis set as follows.

1) Plasma drug concentrations

- At each blood collection time point, descriptive statistics will be calculated by conventional tablet, ODT without water and ODT with water.
- Descriptive statistics to be calculated for plasma drug concentrations will be number of analyzed subjects, number of subjects included in the tabulation, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum. However, descriptive statistics will be calculated only at the time point when the number of subjects included in the tabulation exceeds half of the number of analyzed subjects

2) Plasma pharmacokinetic parameters［excluding λ_z, λ_z (lower), λ_z (upper), λ_z (point) and λ_z (Rsq)］

- Descriptive statistics will be calculated for each parameter by conventional tablet, ODT without water and ODT with water.
- Descriptive statistics to be calculated for plasma pharmacokinetic parameters will be number of analyzed subjects, number of subjects included in the tabulation, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum. However, descriptive statistics will be calculated only when the number of subjects included in the tabulation exceeds half of the number of analyzed subjects.

11 Pharmacodynamic Analyses

Not applicable.

12 Pharmacogenomic Analyses

Not applicable.

13 Interim Analysis

Not applicable.

14 Changes in Planned Analysis

The typo in the study protocol is corrected as follows..

Old: TEAEs leading to discontinuation of the IMP

New: Discontinuations due to TEAEs

15 References

1 Guideline for Bioequivalence Studies of Generic Products (PFSB/ELD Notification No. 0229-10 dated 29 Feb 2012).

Appendix 1 List of Summary Tables

CT-1	Subject Disposition
CT-2	Reasons for Discontinuations
CT-3.1	Demographic and Baseline Characteristics - Bioequivalence Analysis Set
CT-3.2	Demographic and Baseline Characteristics - Safety Analysis Set
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CT-10.1.2	Mean Change from Baseline in Clinical Laboratory Test Results - Hematology
CT-10.1.3	Mean Change from Baseline in Clinical Laboratory Test Results - Urinalysis
CT-10.2.1	Shift Tables of Clinical Laboratory Test Results - Serum Chemistry
CT-10.2.2	Shift Tables of Clinical Laboratory Test Results - Hematology
CT-10.2.3	Shift Tables of Clinical Laboratory Test Results - Urinalysis
CT-10.2.4	Listing of Individual Clinically Significant Abnormalities of Laboratory Values
CT-10.3.1	Shift Tables of Clinical Laboratory Test Results - Qualitative Urinalysis
CT-11.1	Mean Change from Baseline in Vital Signs and Weight
CT-12.1	Mean Change from Baseline in Electrocardiogram Results
CT-12.2	Shift Table of Electrocardiogram Findings
CT-12.3	Categorical Analysis of Electrocardiogram Parameters
PKT-1.1.1.1	Individual and Summary of Plasma Concentration Following Single Administration
PKT-1.1.2.1	Individual and Summary of Plasma Pharmacokinetic Parameters Following Single Administration
PKF-1.1.1.1	Mean Plasma Concentrations Following Single Administration
PKF-1.1.16.1	Individual Plasma Concentrations Following Single Oral Administration for Test Group in Comparison to Reference Group
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BE-1.2	Bioequivalence: Analysis of Variance for Pharmacokinetics (Including Subjects With at

Least One evaluable Pharmacokinetic Parameter)

Appendix 2 List of Subject Data Listings

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SUBEX-1	Subjects Excluded From Analysis Set
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PDATA-6.1	Concomitant Medications
PDATA-6.2	Concomitant Therapy
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PDATA-12.1	Electrocardiogram Results at Central Laboratory
PDATA-12.2	Electrocardiogram Results at Trial Site
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PDATA-13.2	Columbia-Suicide Severity Rating Scale (C-SSRS) - Suicidal Behavior
PDATA-13.3	Columbia-Suicide Severity Rating Scale (C-SSRS) - Actual Attempts
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