CLINICAL STUDY PROTOCOL

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

NCT Number: NCT03902574

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

CLINICAL PROTOCOL

(Translation of Japanese Original)

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

Protocol No. 331-14-002

CONFIDENTIAL - PROPRIETARY INFORMATION

Clinical Development Phase:	1
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	Pharmacovigilance Department 3-2-27 Otedori, Chuo-ku, Osaka 540-0021, Japan E-mail: IRE_331-14-002@otsuka.jp
Issue Date:	18 Jan 2019
Protocol Version Number:	1.0
(Date of Translation:	10 May 2019)

Protocol Synopsis

<table>
<tr><td colspan="2">Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.
Name of Investigational Medicinal Product:
Brexpiprazole (OPC-34712)</td><td>Protocol No.: 331-14-002</td></tr>
<tr><td>Protocol Title:</td><td colspan="2">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</td></tr>
<tr><td>Clinical Phase:</td><td colspan="2">Phase 1</td></tr>
<tr><td>Treatment Indication:</td><td colspan="2">Schizophrenia</td></tr>
<tr><td>Objective(s):</td><td colspan="2">To investigate the bioequivalence of brexpiprazole 2-mg orally disintegrating tablet (ODT) formulation and brexpiprazole 2-mg conventional tablet</td></tr>
<tr><td>Trial Design:</td><td colspan="2">This is a single center, open-label, randomized, 3-arm, 3-way crossover trial.

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 according to the randomized administration schedule.
<table>
<tr><th>Dose</th><th>Sequence</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td rowspan="3">2 mg</td><td>1</td><td>ODT without water</td><td>Conventional tablet</td><td>ODT with water</td></tr>
<tr><td>2</td><td>ODT with water</td><td>ODT without water</td><td>Conventional tablet</td></tr>
<tr><td>3</td><td>Conventional tablet</td><td>ODT with water</td><td>ODT without water</td></tr>
</table>
Subjects will be admitted 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 (on Days 8, 28, and 48) after completion of safety evaluation and pharmacokinetic (PK) blood sampling.</td></tr>
<tr><td>Subject Population:</td><td colspan="2">A total of 21 healthy Japanese male subjects at least 20 years of age and below 40 years of age, will be enrolled.</td></tr>
<tr><td>Inclusion/Exclusion Criteria:</td><td colspan="2"><u>Inclusion Criteria:</u>
1) Healthy Japanese male subjects at least 20 years of age and below 40 years of age, at the time of informed</td></tr>
</table>

consent.

2) Subjects with a body mass index (BMI: weight [kg] ÷ height $[m]^2$) within the range of 18.5 to < 25.0 kg/m^2 (to be checked also at the time of screening).
3) Subjects capable of providing written informed consent prior to initiation of any trial-related procedures, and able, in the opinion of the investigator or subinvestigator, to comply with all requirements of the trial.

Exclusion Criteria:

1) Clinically significant abnormality at the time of screening (eg, significant deviation from reference ranges) or in medical history that, in the opinion of investigator, subinvestigator, or sponsor may place the subject at risk or interfere with outcome variables, including drug absorption, distribution, metabolism, and excretion.
2) Subjects who have supine blood pressure, after resting for at least 3 minutes, higher than 140 mmHg or lower than 100 mmHg (systolic blood pressure) or higher than 90 mmHg or lower than 50 mmHg (diastolic blood pressure) and who have a reduction in blood pressure upon standing of ≥ 20 mmHg (based on the difference between standing and sitting systolic blood pressure) at the time of screening.
3) Subjects who have a supine pulse rate, after resting for at least 3 minutes, outside the range of 40 to 90 bpm at the time of screening.
4) Clinically relevant electrocardiogram (ECG) findings in the 12-lead ECG tests performed at screening or at admission to the trial site in Period 1, such as atrioventricular block, QRS interval > 120 msec, or QTcF interval ≥ 450 msec.
5) Subjects who meet any of the following for hepatitis:

- History of or current hepatitis B, or current hepatitis C. Positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (anti-HCV) at the time of screening.
- History of or current alcoholic hepatitis or nonalcoholic steatohepatitis.

6) History of or current acquired immunodeficiency syndrome (AIDS). Positive test result for human immunodeficiency virus (HIV) at the time of screening.
7) History of serious mental disorder.
8) History of drug or alcohol abuse within 2 years prior to screening.
9) Positive alcohol test or urine drug screen for substance abuse at screening or at admission to trial site in each period.
10) Sexually active males who cannot or will not practice 2 different methods of birth control or remain abstinent during the trial and until 30 days after the final administration of the investigational medicinal product (IMP), or will not refrain from sperm donation from the screening visit until 30 days after the final administration of IMP.
11) History of any significant drug allergy.
12) Any history of significant bleeding or hemorrhagic tendency.
13) Blood collection (blood donation, etc) exceeding 200 mL within 30 days or 400 mL within 90 days prior to the first administration of IMP, or blood collection (blood donation, etc) exceeding 1200 mL in total within 1 year prior to first administration of IMP.
14) History of difficulty in donating blood
15) Use of another investigational drug within 120 days prior to the first administration of IMP.
16) Previous exposure to brexpiprazole.

	17) Use of tobacco products or daily exposure to secondhand smoke within 2 months prior to screening, or positive urine cotinine test (urine cotinine concentration of > 200 ng/mL) at screening. 18) Consumption of grapefruit, grapefruit products, Seville orange, Seville orange products, star fruit, or star fruit products within 72 hours prior to first administration of IMP, or consumption of alcohol within 72 hours prior to administration of IMP. 19) Use of prescription, over-the-counter (OTC), or herbal medication, or vitamin supplements, or consumption of food or beverages containing St. John's Wort within 14 days prior to the first administration of IMP, or use of antibiotics within 30 days prior to the first administration of IMP. The sponsor may allow use only if the medication used is considered unlikely to impact PK assessment. 20) History of major surgery of the digestive tract (excluding appendectomy). 21) Occupational exposure to pesticides or organic solvents within 30 days prior to screening. 22) Any subject visiting other hospitals or departments or planning to visit other hospitals or departments during the trial period. 23) Any subject who, in the judgment of the investigator or subinvestigator, should not participate in the trial.
Trial Site:	Medical Co. LTA Hakata Clinic

<table>
<tr><td>Investigational Medicinal Product, Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:</td><td>[Investigational medicinal product: Brexpiprazole ODTs]
<table>
<tr><th>Active ingredient (content per tablet)</th><th>per dose</th><th>Regimen</th></tr>
<tr><td>Brexpiprazole 2 mg</td><td>1 tablet</td><td><u>With water</u>: IMP will be administered with 150 mL of ordinary-temperature water after at least 10 hours of fasting.
<u>Without water</u>: After at least 10 hours of fasting, IMP will be allowed to disintegrate in the mouth (on the tongue), and will then be promptly swallowed with saliva.</td></tr>
</table></td></tr>
<tr><td>Reference Product, Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:</td><td>[Reference product: Brexpiprazole conventional tablets]
<table>
<tr><th>Active ingredient (content per tablet)</th><th>per dose</th><th>Regimen</th></tr>
<tr><td>Brexpiprazole 2 mg</td><td>1 tablet</td><td>IMP will be administered with 150 mL of ordinary-temperature water after at least 10 hours of fasting.</td></tr>
</table></td></tr>
<tr><td>Trial Assessments:</td><td>[Primary endpoints]
C_{max} and AUC_t of brexpiprazole
[Secondary endpoints]
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}
[Safety endpoints]
Adverse events (AEs), clinical laboratory values, vital signs (body temperature, blood pressure, pulse rate, respiratory rate), body weight, 12-lead ECG, physical examination, and Columbia-Suicide Severity Rating Scale (C-SSRS)</td></tr>
<tr><td>Statistical Methods:</td><td>[Statistical methods for the primary endpoints]
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 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.
[Rationale for target sample size]
Based on the Guideline for Bioequivalence Studies of Generic</td></tr>
</table>

	Products, 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 bioavailability 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 at 7 for each sequence and 21 in total.
Trial Duration:	The total duration of the trial for each subject will be up to 85 days, including the following trial periods: • Screening period: Days −22 to −1 • Period 1: Days 1 to 20 (Day 1 dosing) • Period 2: Days 21 to 40 (Day 21 dosing) • Period 3: Days 41 to 60 (Day 41 dosing) • Follow-up period: Days 61 to 63 Trial Duration: March 2019 to June 2019

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT_{1A}	5-Hydroxytryptamine 1A
5-HT_{2A}	5-Hydroxytryptamine 2A
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{24h}	Area under the concentration-time curve from time zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_%Extrap	Percentage of AUC due to extrapolation from t_{last} to infinity $[(AUC_{\infty} - AUC_t) / AUC_{\infty} \times 100]$
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Science
CL/F	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	CL/F normalized in body weight
C_{max}	Maximum (peak) plasma concentration of the drug
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
D_2	Dopamine D_2
EDC	Electronic data capture
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRE	Immediately reportable event
λ_z	Apparent terminal-phase disposition rate constant (first-order)
LDH	Lactic dehydrogenase
LSMD	Least square mean difference
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
OD	Orally disintegrating
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PQC	Product quality complaint
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
QTcI	Individually corrected QT interval
RBC	Red blood cell count
SAE	Serious adverse event
$t_{1/2,z}$	Terminal-phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{last}	Time of last measurable [positive] concentration
t_{max}	Time to maximum (peak) plasma concentration
WBC	White blood cell count

1 Introduction

Brexpiprazole (OPC-34712) is a new compound synthesized by Otsuka Pharmaceutical Co., Ltd. that exhibits partial agonistic action against serotonin 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptors,[1] antagonistic action against serotonin 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$) receptors,[2] and partial agonistic action against dopamine D_2 (D_2) receptors.[2] Compared with aripiprazole, brexpiprazole has the optimized intrinsic activity against D_2 receptors and enhanced actions on the serotonergic system. Therefore, a reduction in adverse drug reactions including akathisia and insomnia, and improvement of positive symptoms, negative symptoms, and cognitive impairment, which were problems associated with aripiprazole treatment, are expected.

In the US, brexpiprazole received manufacturing and marketing approval as monotherapy for schizophrenia and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in July 2015. Brexpiprazole is currently being developed for treating other mental disorders. In Japan, brexpiprazole has undergone a placebo-controlled double-blind trial (331-10-002) and a long-term study (331-10-003) in schizophrenia patients, received manufacturing and marketing approval in January 2018, and has been available for clinical use as monotherapy for schizophrenia since April of the same year. Clinical investigations of brexpiprazole as an adjunctive therapy for major depressive disorder and as a treatment for agitation associated with dementia of the Alzheimer's type are currently ongoing.

In the treatment of mental disorders such as schizophrenia, it is important that the patient continue to take antipsychotic medication; however, among patients who require such treatment are those who suffer from dysphagia or for whom it is not possible to take medication in a hard form such as a tablet when their condition is critical, while there are others who are unable to comprehend the need for treatment due to lack of knowledge of their disease or cognitive dysfunction, resulting in decreased adherence or a tendency to refuse to take their medication. For these reasons, orally disintegrating tablets (ODTs) that can be taken without water are being developed so that the treatment method that best suits a patient's condition can be selected. This will enable a more appropriate response to the needs that are seen in clinical practice and will widen the selection of treatments available.

1.1 Nonclinical Data

Data from preclinical studies have shown that brexpiprazole has high binding affinity for D_2 receptors,[2] 5-HT_{1A} receptors,[1] and 5-HT_{2A} receptors[2] and also has partial agonistic action against dopamine D_2 receptors and serotonin 5-HT_{1A} receptors and antagonistic action against serotonin 5-HT_{2A} receptors, suggesting that the drug has a favorable profile as an antipsychotic treatment.

For detailed information regarding relevant data from preclinical animal studies, including Pharmacokinetics (PK) and toxicology studies, refer to the current version of the investigator's brochure.

1.2 Clinical Data

No clinical trials of the brexpiprazole ODTs used in the present trial have been conducted.

As reference, the results of a single-dose trial of conventional tablets and a bioavailability (BA) study using ODTs with a different formulation/manufacturing method in healthy adult Japanese subjects, and the results of a QT/QTc study in schizophrenia patients in the US are outlined below. For detailed information, refer to the current version of the investigator's brochure.

1.2.1 Phase 1 Single-dose Trial in Healthy Adult Subjects (Japanese Study 331-07-002)

A single rising dose trial of brexpiprazole (0.2, 0.5, 1, 2, 4, 6, 10, 15, 20, and 30 mg) was conducted in healthy adult male subjects. An adverse event (AE; blood pressure decreased) that occurred in the 6 mg group was assessed as an AE meeting the criteria for stopping dose escalation, resulting in dose discontinuation at a dose of 6 mg. A total of 10 subjects were included in each of the dose groups: 8 subjects in the brexpiprazole group (6 subjects in the 4 mg group) and 2 subjects in the placebo group.

The C_{max}, AUC_{∞}, and AUC_t of brexpiprazole at single doses of brexpiprazole (0.2 to 6 mg) increased dose-proportionally. The result of regression analysis showed that AUC_{∞} was also dose-proportional. The mean cumulative urinary excretion of brexpiprazole at 168 hours postdose was less than 0.4%; the contribution of renal excretion was minimal.

The incidence of AEs was 26.1% (12/46 subjects) in the brexpiprazole group. Adverse events that occurred in 2 or more subjects were nausea (10.9%, 5/46 subjects), dizziness (8.7%, 4/46 subjects), and blood triglycerides increased and somnolence (4.3% each,

2/46 subjects). All AEs were mild or moderate in severity, and no serious adverse events (SAEs) were observed. In this study, the maximum tolerated dose was 4 mg.

1.2.2 BA Study of ODTs and Conventional Tablets in Healthy Adult Subjects (Japanese Study 331-102-00019)

A randomized, 3-arm, 3-way crossover trial to evaluate the BA of a brexpiprazole 4-mg ODT formulation relative to the 4-mg conventional tablet was conducted in 18 healthy adult male subjects. A total of 17 subjects received brexpiprazole 4-mg conventional tablet, 18 subjects received brexpiprazole 4-mg ODT without water, and 16 subjects received brexpiprazole 4-mg ODT with water.

Mean plasma brexpiprazole concentration peaked at 6 hours after administration of conventional tablet, at 5 hours after administration of ODT without water, and at 4 hours after administration of ODT with water, and declined gradually thereafter. The C_{max} following administration of conventional tablet, administration of ODT without water, and administration of ODT with water was 46.1 ± 10.8 ng/mL (mean ± standard deviation, same hereafter), 44.9 ± 13.8 ng/mL, and 47.4 ± 10.0 ng/mL, respectively, AUC_t was 2590 ± 1210 ng·h/mL, 2680 ± 1150 ng·h/mL, and 2750 ± 1380 ng·h/mL, respectively, and AUC_∞ was 2770 ± 1460 ng·h/mL, 2830 ± 1270 ng·h/mL, and 2920 ± 1630 ng·h/mL, respectively. The geometric mean ratios for C_{max}, AUC_t, and AUC_∞, between administration of ODT without water and administration of conventional tablet were 0.9790, 1.0049, and 0.9965, respectively, and their 90% confidence intervals were 0.8842–1.0840, 0.9549–1.0575, and 0.9454–1.0505, respectively. The geometric mean ratios for C_{max}, AUC_t, and AUC_∞, between administration of ODT with water and administration of conventional tablet were 1.0241, 1.0386, and 1.0369, respectively, and their 90% confidence intervals were 0.9231–1.1363, 0.9858–1.0942, and 0.9825–1.0943, respectively.

The incidence of AEs was 52.9% following administration of conventional tablet, 38.9% following administration of ODT without water, and 50.0% following administration of ODT with water. The AEs included orthostatic hypotension (7 events) and nausea (4 events) following administration of conventional tablet; nausea (5 events), orthostatic hypotension (3 events), vomiting (1 event), and headache (1 event) following administration of ODT without water; and nausea (4 events), orthostatic hypotension (4 events), vomiting (1 event), blood creatine phosphokinase increased (1 event), and dizziness (1 event) following administration of ODT with water. All AEs were mild or moderate in severity, and no SAEs were observed.

1.2.3 QT/QTc Study in schizophrenia patients (US Study 331-10-242)

A total of 205 patients with schizophrenia or schizoaffective disorder received 4 mg or 12 mg brexpiprazole, placebo, or moxifloxacin once daily for 11 days. The 12 mg group consisted of 67 subjects.

For a primary endpoint of time-matched QTcI change from baseline corrected for placebo on Day 11 following brexpiprazole treatment, no QTcI prolongation was observed at either dose of 4 mg or 12 mg.

An event of worsening of schizoaffective disorder was reported as an SAE in the brexpiprazole 4 mg/day group and assessed as not related to the study drug. Adverse events leading to discontinuation occurred in 3 subjects in the 4 mg/day group, including vomiting, dermatitis contact, and orthostatic hypotension (1.4%, 1/70 subjects) and 7 subjects in the 12 mg/day group, including dizziness and extrapyramidal disorder (3.0%, 2/67 subjects), akathisia, psychotic disorder, and joint stiffness (1.5%, 1/67 subjects). Of these, orthostatic hypotension (1 subject) in the 4 mg/day group, and extrapyramidal disorder (2 subjects), dizziness (2 subjects), joint stiffness (1 subject), and akathisia (1 subject) in the 12 mg/day group were assessed as related to the study drug.

1.3 Pharmacokinetics

Data from clinical trials in healthy adult subjects conducted in the US indicate that brexpiprazole has linear PKs in the steady state when administered as single oral doses of 0.2 to 8 mg or repeated oral doses of 0.5 to 2 mg. The terminal-phase elimination half-life ($t_{1/2,z}$) of brexpiprazole following single oral doses of 0.2 to 8 mg was 48.3 to 80.8 hours and the median t_{max} was 2 to 6 hours.[3] Investigation of the median C_{max}, AUC_t, AUC_∞, and t_{max} values of brexpiprazole following single administration after a high-fat meal showed no food effects on the rate or extent of absorption.[4] The C_{max} and AUC_t values observed in repeated oral administration of brexpiprazole to healthy adult subjects at doses of 0.5 to 2 mg showed that the cumulative coefficient was almost four-fold.[5] Data from a drug interaction trial indicate that brexpiprazole is metabolized by CYP3A4 and CYP2D6 isozymes.[6]

Data from a clinical trial in healthy adult Japanese subjects indicate that brexpiprazole has linear PKs following single oral doses of 0.2 to 6 mg. The $t_{1/2,z}$ of brexpiprazole was 43.9 to 66.6 hours, and the median t_{max} was 3 to 7 hours.[7] Brexpiprazole also showed linear PKs in the steady state with repeated oral administration at doses of 1, 4, and 6 mg

in Japanese patients with schizophrenia. Brexpiprazole reached steady state on Day 10, and the cumulative coefficient was 2.5 to 5.5, based on C_{max} and AUC_{24h}.[8]

1.4 Risks and Benefits

Non-Japanese phase 1 trials using brexpiprazole conventional tablets indicated that brexpiprazole had good safety and tolerability when administered to healthy adult subjects at single doses of 0.2 to 6 mg and at a repeated dose of 2 mg/day.[3,5,9] Repeated-dose trials conducted in the US indicate that brexpiprazole had good tolerability when administered to patients with schizophrenia or schizoaffective disorder at doses of up to 12 mg/day.[10] In addition, a phase 1 single-dose trial conducted in Japan indicated good tolerability at doses of up to 4 mg/day in healthy adult subjects,[7] and a phase 1 repeated-dose trial indicated good tolerability at doses of up to 6 mg/day in schizophrenia patients.[8]

If this trial is conducted within the dose range for which tolerability has been demonstrated in trials conducted to date and, as a result, ODTs become available in clinical practice, this will broaden the selection of available drug formulations, leading to improved adherence.

For detailed information regarding brexpiprazole and possible risks and adverse reactions, refer to the current version of the investigator's brochure.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Brexpiprazole tablets received manufacturing and marketing approval for treatment of schizophrenia in Japan in January 2018, and have been available for clinical use since April of the same year.

Because ODTs can be taken without water, they provide an easy-to-use option for patients with dysphagia and patients who are unable to take medication in a hard form such as a tablet when their condition is critical. The marketing of the ODT formulation in addition to the conventional tablet is considered to be extremely significant as it will provide patients with a choice of formulations to match their various circumstances, thereby leading to improved treatment adherence.

The results of a phase 1 single-dose trial in healthy adult Japanese subjects (331-07-002) have demonstrated the tolerability of single doses up to 4 mg, and therefore it will be possible to ensure subject safety by conducting this clinical trial with a dose of 2 mg. It is

considered appropriate to conduct this trial to investigate the bioequivalence of the ODTs in accordance with the Guideline for Bioequivalence Studies of Generic Products[11] (hereinafter "BE Guideline").

2.2 Dosing Rationale

2.2.1 Regimen

According to the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms Q&A (Attachment 3),[12] a bioequivalence study conducted when applying for approval of dosage forms different from conventional tablets, from the characteristics of ODT formulation, should be basically conducted as a bioequivalence study of "conventional tablets administered with water" and "proposed formulation administered without water," and a bioequivalence study of "conventional tablets administered with water" and "proposed formulation administered with water," and therefore administration both with and without water was decided. In addition, according to the BE Guideline,[11] study drugs should be taken, as a rule, with a certain amount of water, between 100 to 200 mL (typically 150 mL) after fasting for at least 10 hours, and it was therefore decided that the amount of water for administration of investigational medicinal products (IMPs) would be 150 mL.

2.2.2 Dose

According to the BE Guideline,[11] one dose unit or clinical usual dose should generally be employed. Including the starting dose, a single dose unit of the approved dose of Brexpiprazole in Japan is either 1 mg or 2 mg; however, in the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (Attachment 2),[13] it states that if there are several dose formulations of the original drug product, in principle, the high-dose formula of the original drug product should be used as the standard formulation for the conduct of a bioequivalence study.

Based on the above, it was decided to perform single oral administrations of ODTs and conventional tablet at 2 mg.

2.3 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.

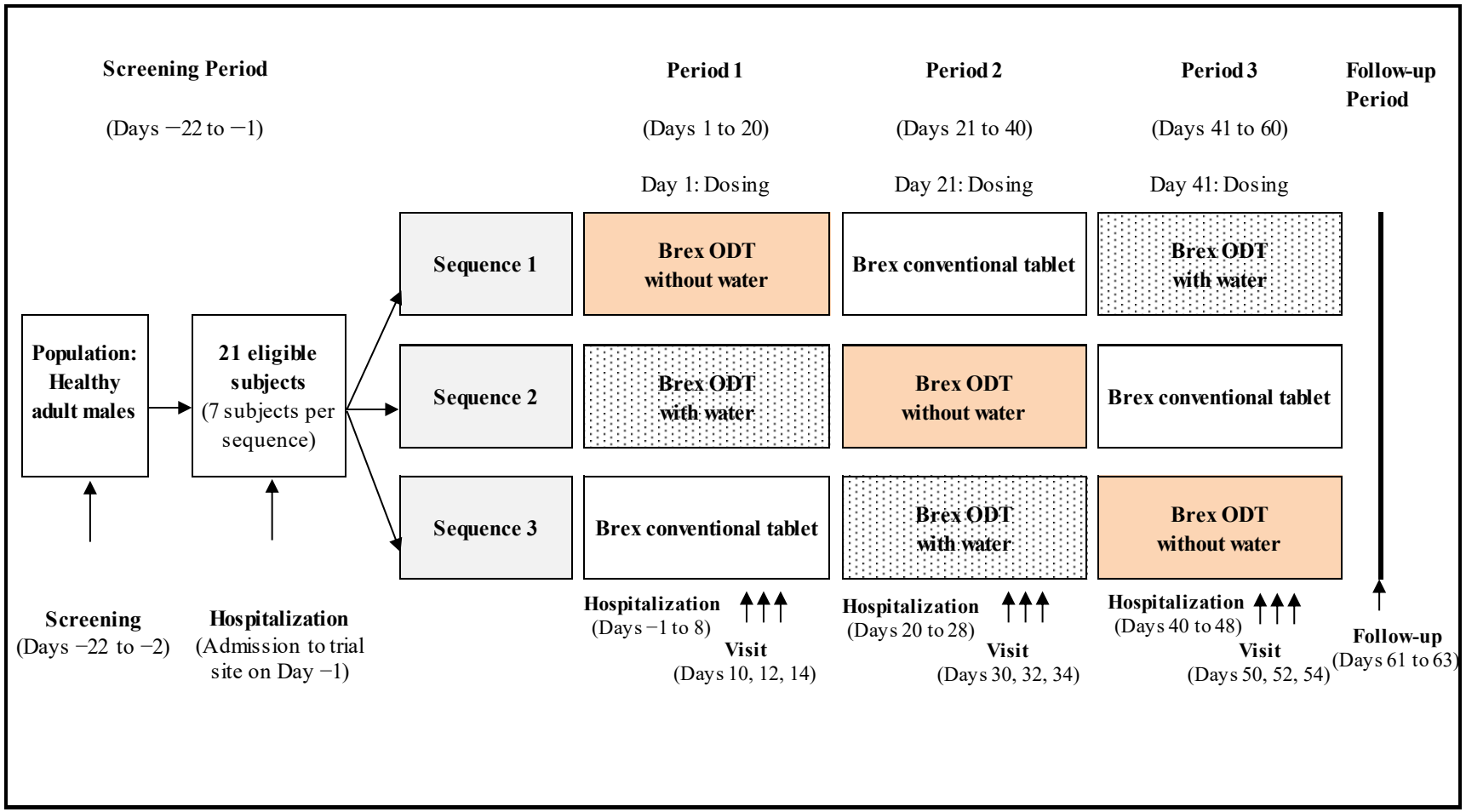
A 2-mg dose of brexpiprazole will be administered to each subject as either an ODT or a conventional tablet on Days 1, 21, and 41, and ODT will be administered either with water or without water, according to the randomized administration schedule.

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 3.1-1.



Brex = brexpiprazole; ODT = orally disintegrating tablet

Figure 3.1-1 Trial Design

3.2 Trial Treatments

3.2.1 Investigational Medicinal Product

3.2.1.1 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.

3.2.1.2 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.

3.2.2 Treatment Period

After single oral administration of the Period 1 IMP, there will be a washout period of 20 days, after which subjects will receive single oral administration of the Period 2 IMP (a different combination of drug formulation and administration method than that of Period 1). After single oral administration of the Period 2 IMP, there will be another washout period of 20 days, after which subjects will receive single oral administration of the Period 3 IMP (a different combination of drug formulation and administration method than those of Period 1 and Period 2).

[Rationale for treatment period]

According to the BE Guideline,[11] studies should be conducted based on single dosing, as a rule.

[Rationale for washout period]

From the results of a Japanese single-dose trial (331-07-002), the mean elimination half-life of brexpiprazole was 66.6 hours in the 4 mg treatment group, for which the elimination half-life was longest. According to the BE Guideline, “Washout periods

should usually be more than 5 times the elimination half-life of the unchanged active ingredient or active metabolites to be measured." This suggests that the washout period should be more than 333 hours (more than 14 days), which is 5 times the elimination half-life. The results of the Japanese bioequivalence study (331-10-005) showed that the blood drug concentration prior to the dosing for Period 2 after a washout period of 20 days was less than 5% of C_{max} in all subjects, and therefore the washout period following trial drug administration is set to be 20 days.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

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

Any subjects scheduled for IMP administration who withdraw their consent or are judged to be unable to receive the IMP before the first administration will be replaced by reserve subjects, without re-randomization of treatment allocations.

There will be no addition or replacement of subjects if any subjects withdraw from the trial after the first randomized administration.

3.3.2 Assignment of Subject Identification Number

Subjects who provided written informed consent will be given a unique subject identification number (site number [3 digits] + subject number [S + 5 digits]). Site number will be assigned by the sponsor. Subject numbers will be assigned as site serial numbers, in the order informed consent is obtained, beginning with S00001.

3.4 Eligibility Criteria

3.4.1 Informed Consent

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

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[14] and local regulatory requirements.

The investigator or subinvestigator 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 prior to initiation of any procedures that are performed

solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

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

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

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Healthy Japanese male subjects at least 20 years of age and below 40 years of age, at the time of informed consent.
2.	Subjects with a body mass index (BMI: weight [kg] ÷ height $[m]^2$) within the range of 18.5 to < 25.0 kg/m^2 (to be checked also at the time of screening).
3.	Subjects capable of providing written informed consent prior to initiation of any trial-related procedures, and able, in the opinion of the investigator or subinvestigator, to comply with all requirements of the trial.

[Rationale]

1. The lower age limit is the age at which subjects are capable of taking responsibility for providing informed consent as legal adults, and the upper age limit is set because subjects older than 40 years are more likely to have complications and their metabolism may differ from that of younger subjects. The subject population is restricted to males to eliminate the need to consider the possibility of pregnancy or the effects of menstruation.
2. Specified to reduce the inter-individual variability in pharmacokinetics due to obesity.
3. Specified to ensure that subjects are capable of providing informed consent and to allow the investigator or subinvestigator to judge whether subjects are able to comply with the protocol.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria	
1.	Clinically significant abnormality at the time of screening (eg, significant deviation from reference ranges) or in medical history that, in the opinion of investigator, subinvestigator, or sponsor may place the subject at risk or interfere with outcome variables, including drug absorption, distribution, metabolism, and excretion. This includes, but is not limited to, history of or concurrent cardiac, hepatic, renal, neurologic, gastrointestinal, respiratory, hematologic, and immunologic disease.
2.	Subjects who have supine blood pressure, after resting for at least 3 minutes, higher than 140 mmHg or lower than 100 mmHg (systolic blood pressure) or higher than 90 mmHg or lower than 50 mmHg (diastolic blood pressure) and who have a reduction in blood pressure upon standing of ≥ 20 mmHg (based on the difference between standing and sitting systolic blood pressure) at the time of screening.
3.	Subjects who have a supine pulse rate, after resting for at least 3 minutes, outside the range of 40 to 90 bpm at the time of screening.
4.	Clinically relevant electrocardiogram (ECG) findings in the 12-lead ECG tests performed at screening or at admission to the trial site in Period 1, such as atrioventricular block, QRS interval > 120 msec, or QTcF interval ≥ 450 msec.
5.	Subjects who meet any of the following for hepatitis: • History of or current hepatitis B, or current hepatitis C. Positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (anti-HCV) at the time of screening. • History of or current alcoholic hepatitis or nonalcoholic steatohepatitis.
6.	History of or current acquired immunodeficiency syndrome (AIDS). Positive test result for human immunodeficiency virus (HIV) at the time of screening.
7.	History of serious mental disorder.
8.	History of drug or alcohol abuse within 2 years prior to screening.
9.	Positive alcohol test or urine drug screen for substance abuse at screening or at admission to trial site in each period.
10.	Sexually active males who cannot or will not practice 2 different methods of birth control or remain abstinent during the trial and until 30 days after the final administration of the IMP, or will not refrain from sperm donation from the screening visit until 30 days after the final administration of IMP. If employing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, oral contraceptive, or condom containing sponge with spermicide.
11.	History of any significant drug allergy.
12.	Any history of significant bleeding or hemorrhagic tendency.
13.	Blood collection (blood donation, etc) exceeding 200 mL within 30 days or 400 mL within 90 days prior to the first administration of IMP, or blood collection (blood donation, etc) exceeding 1200 mL in total within 1 year prior to first administration of IMP.
14.	History of difficulty in donating blood.
15.	Use of another investigational drug within 120 days prior to the first administration of IMP.
16.	Previous exposure to brexpiprazole.
17.	Use of tobacco products or daily exposure to secondhand smoke within 2 months prior to screening, or positive urine cotinine test (urine cotinine concentration of > 200 ng/mL) at screening.

Table 3.4.3-1 Exclusion Criteria	
18.	Consumption of grapefruit, grapefruit products, Seville orange, Seville orange products, star fruit, or star fruit products within 72 hours prior to first administration of IMP, or consumption of alcohol within 72 hours prior to administration of IMP.
19.	Use of prescription, over-the-counter (OTC), or herbal medication, or vitamin supplements, or consumption of food or beverages containing St. John's Wort within 14 days prior to the first administration of IMP, or use of antibiotics within 30 days prior to the first administration of IMP. The sponsor may allow use only if the medication used is considered unlikely to impact PK assessment.
20.	History of major surgery of the digestive tract (excluding appendectomy).
21.	Occupational exposure to pesticides or organic solvents within 30 days prior to screening.
22.	Any subject visiting other hospitals or departments or planning to visit other hospitals or departments during the trial period.
23.	Any subject who, in the judgment of the investigator or subinvestigator, should not participate in the trial.

QTcF = QT interval corrected for heart rate by Fridericia's formula

[Rationale]	
1 to 4	Specified to confirm that subjects are healthy.
5 to 9	Specified because such subjects cannot be considered healthy.
10	Specified to ensure the safety of subjects and their partners.
11 to 15	This criterion was set to ensure the safety of subjects. (13: Specified in reference to the criteria for blood donation of the New Blood Program Advisory Committee. 15: Specified in reference to "Criteria for Period of Suspending Participation in Clinical Studies" of the Japan Association of Contract Institutes for Clinical Trials.)
16	This criterion was set to ensure the safety of subjects and to avoid possible effects of previous exposure to brexpiprazole on PK and safety assessments.
17	Specified to confirm that subjects are healthy.
18 to 20	Specified to avoid possible effects on PK.
21	Specified to avoid possible effects on PK due to exposure to any substances known to stimulate hepatic microsomal enzymes.
22	This criterion was set to ensure the safety of subjects.
23	Specified to allow the investigator or subinvestigator to make judgments on subjects' eligibility, taking subjects' compliance into account.

Re-entry of subjects who fail a screening examination will not be permitted. If the investigator or subinvestigator judges that a clinical laboratory test or other test should be repeated, a record is to be kept according to the procedures of the trial site.

3.5 Endpoints

3.5.1 Primary Endpoints

C_{max} and AUC_t of brexpiprazole

3.5.2 Secondary Endpoints

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}

3.5.3 Safety Endpoints

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

3.6 Measures to Minimize/Avoid Bias

The primary endpoints of the present trial are based on plasma drug concentrations, not producing bias without blinding, and therefore this trial will be conducted as an open-label, randomized, 3-arm, 3-way crossover study.

3.7 Trial Procedures

Participation in this trial will be for a total of up to 85 days, including the screening period, 3 periods of hospitalization and outpatient visits, and the follow-up period. Subjects will provide consent and be screened between Days −22 and −2 prior to dosing. Subjects who meet the inclusion criteria and do not fulfill any of the exclusion criteria will be admitted to the trial site on Day −1. Subjects will receive the IMP on Day 1. The washout period following trial drug administration will be 20 days. Subjects will remain hospitalized for 1 week from the day after IMP administration, during which they will undergo observation and examination. Subjects will be discharged on Day 8 after completion of safety evaluation and PK blood sampling. After discharge, subjects will return to the trial site 3 times for examinations and observations on an outpatient basis. For hospitalization in Period 2 and Period 3, subjects will again be hospitalized on the day before IMP administration (on Days 20 and 40), and will undergo IMP administration and observation and examination as with hospitalization in Period 1. The post-treatment follow-up will be performed by trial site visit or telephone between 20 and 22 days after the final IMP administration (between Days 61 and 63). If an AE is suspected as a result of information obtained in a telephone call, the subject will be asked to come to the trial site for further confirmation.

Subjects who discontinue participation should complete the same assessments as are performed at discharge.

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

			Period 1: Days 1 to 20, Period 2: Days 21 to 40, Period 3: Days 41 to 60										
	Screen -ing	**Admission**	**IMP Administration**	**Postdose Hospitalization Periods**						**Discharge**	**Visit**	**At Discon -tinuation**	**Follow-up[a]**
Day of Conduct	Day −22 to −2	Day −1, 20, 40	Day 1, 21, 41	Day 2, 22, 42	Day 3, 23, 43	Day 4, 24, 44	Day 5, 25, 45	Day 6, 26, 46	Day 7, 27, 47	Day 8, 28, 48	Day 10, 12, 14, 30, 32, 34, 50, 52, 54		Day 61 to 63
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Subject background	X												
Medical history	X												
Hepatitis and HIV screen	X												
Alcohol test and urine drug screen	X	X											
Urine cotinine test	X												
Admission to trial site:													
Admission		X											
Meals		Dinner (followed by fasting from approx 22:00 on Day −1)	Lunch (4 h postdose) and dinner	Breakfast, lunch, dinner									
Discharge										X			
IMP Administration:													
Randomization			Predose on Day 1										
Sequence[b] Sequence 1:			Day 1, 41: Brex ODT 2 mg Day 21: Brex conventional tablet 2 mg										
Sequence 2:			Day 1, 21: Brex ODT 2 mg Day 41: Brex conventional tablet 2 mg										
Sequence 3:			Day 1: Brex conventional tablet 2 mg Day 21, 41: Brex ODT 2 mg										
Record of concomitant drugs and therapies	←					Ongoing							→
Safety:													
Adverse events	←					Ongoing							→
Height	X												
Weight	X	X								X		X	
Physical examination	X	X								X	Day 14, 34, 54	X	
Vital signs[c]	X	X	Predose and 2, 6, 12 h postdose	24 h postdose		72 h postdose		120 h postdose		168 h postdose	216, 264, 312 h postdose	X	
12-lead ECG[d]	X	X (3 consecutive measurements)	2, 6 h postdose	24 h postdose		72 h postdose				168 h postdose		X	
Clinical laboratory tests[e] (Including prolactin concentration)	X	X	Predose							X		X	
C-SSRS	Baseline version		Performed predose using since-last-visit version							Since-last-visit version		Since-last-visit version	
Pharmacokinetics:													
PK blood sampling			Predose and 1, 2, 3, 4, 5, 6, 8, 12 h postdose	16, 24 h postdose	48 h postdose	72 h postdose	96 h postdose	120 h postdose	144 h postdose	168 h postdose	216, 264, 312 h postdose	X	

Brex = brexpiprazole; C-SSRS = Columbia-Suicide Severity Rating Scale; HIV = human immunodeficiency virus; ODT = orally disintegrating tablet

[a] The post-treatment follow-up will be performed by trial site visit or telephone between 20 and 22 days after the final IMP administration.

[b] ODT will be administered with and without water in the following sequences. Sequence 1: Administered without water on Day 1 and with 150 mL of ordinary-temperature water on Day 41. Sequence 2: Administered with 150 mL of ordinary-temperature water on Day 1 and without water on Day 21. Sequence 3: Administered with 150 mL of ordinary-temperature water on Day 21 and without water on Day 41.

[c] Blood pressure and pulse rate will be taken with the subject in the supine (performed first), sitting, and standing positions after remaining for at least 3 minutes in each position. Sitting and standing blood pressure and pulse rate will be measured only at screening. Body temperature and respiratory rate will be measured with the subject in the supine position.

[d] Twelve-lead ECG will be performed after the subject has been supine and at rest for at least 10 minutes. Three consecutive ECG measurements will be taken upon admission in each period and the mean value of those three measurements will be used as the baseline data for each period respectively.

[e] Measurement of prolactin concentration at admission (Days −1, 20, and 40) is not required.

3.7.1 General Inpatient Procedures

On Days 1, 21, and 41, the IMP will be administered after subjects have fasted for at least 10 hours (from approximately 22:00 the day before dosing) and no food will be allowed for 4 hours postdose. Except as part of the dosing procedure, water will be restricted from 1 hour prior to dosing until 2 hours postdose.

Subjects will be instructed to remain either seated or in a semi-recumbent position for the first 4 hours following dosing except during brief periods when protocol-related procedures are performed. Restroom visits must be supervised during the 4 hours postdose and should be brief (< 10 minutes). In addition, during the 4-hour period post oral dosing, the subject's toilet use must be supervised to prevent self-induced emesis resulting in loss of the oral dose.

Following the 4-hour postdose period, the subjects will be allowed to ambulate, but will be instructed not to exercise strenuously.

3.7.2 Dietary Requirements

- From 14 days before the first IMP administration until completion of blood sampling at 312 hours postdose on Day 54

  Consumption of food or beverages containing St. John's Wort is prohibited.
- From 72 hours before the first IMP administration until completion of blood sampling at 312 hours postdose on Day 54

  Consumption of grapefruit, grapefruit products, Seville oranges, Seville orange products, star fruit, or star fruit products is prohibited.
- From 72 hours before each administration until discharge at the end of each hospitalization period

  Consumption of alcohol is prohibited.
- During hospitalization

  Consumption of food or beverages containing methylxanthines (such as caffeinated coffee, caffeinated tea, caffeinated soda, and chocolate) is prohibited.

3.7.3 Schedule of Assessments

Trial days and activities are summarized in Table 3.7.3-1.

Table 3.7.3-1 Trial Days and Activities

Screening (Days −22 to −2)

- Written informed consent
- Confirmation of the inclusion and exclusion criteria
- Subject background survey (date of birth, sex, race, ethnicity, current symptoms, medical history, drinking habit, smoking habit)
- Physical examination
- Vital signs (body temperature, blood pressure, pulse rate, respiratory rate)
  - Blood pressure and pulse rate will be taken with the subject in the supine (performed first), sitting, and standing positions after remaining for at least 3 minutes in each position (sitting and standing blood pressure and pulse rate will be measured only at screening).
  - Body temperature and respiratory rate will be taken with the subject in the supine position.
  - The difference between standing and sitting systolic blood pressure will also be measured.
- Measurement of height, body weight, and BMI
  - Height will be measured to the nearest 0.1 cm.
  - Body weight will be measured in the fasting state.
  - BMI will be calculated based on the body weight and height at screening, by rounding down to the first decimal place.
- Clinical laboratory tests (hematology, biochemistry, urinalysis)
- Prolactin concentration test
- Alcohol test, urine drug screen, urinary cotinine test
- Human immunodeficiency virus (HIV) screen, and hepatitis B surface antigen (HBsAg) and hepatitis C antibodies (anti-HCV) screens
- 12-lead ECG
  - The ECG will be performed after the subject has rested in the supine position for at least 10 minutes.
- Columbia-Suicide Severity Rating Scale (C-SSRS) (use of baseline version)
- Confirmation of concomitant medications and therapies
- Identification/assessment of AEs

Table 3.7.3-1 Trial Days and Activities

Admission (Days −1, 20, and 40)
• Subjects will be admitted to the trial site. • Reconfirmation of the inclusion and exclusion criteria (Note: HIV and hepatitis tests and BMI measurement do not need to be reperformed) • Physical examination • Vital signs (body temperature, blood pressure, pulse rate, respiratory rate) – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. • Body weight • Clinical laboratory tests (hematology, biochemistry, urinalysis) • Alcohol test, urine drug screen • 12-lead ECG – The ECG will be performed after the subject has rested in the supine position for at least 10 minutes. – The mean value of three consecutive ECG measurements taken upon admission in each period will be used as the baseline data for each period respectively. • Confirmation of concomitant medications and therapies • Identification/assessment of AEs • Meals will be provided as follows: dinner, followed by fasting from approximately 22:00.

Table 3.7.3-1 Trial Days and Activities

IMP Administration (Days 1, 21, and 41)
• Eligible subjects will be randomized before IMP administration on Day 1. • If replacement of any subject occurs before the first administration of IMP, a reserve subject will receive the IMP treatment allocated to the dropout subject, without re-randomization of treatment allocations. Subjects who do not receive the IMP treatment will be discharged from the trial site. • Subjects randomized to Sequence 1 will receive one ODT without water on Day 1, one conventional tablet with 150 mL of ordinary-temperature water on Day 21, and one ODT with 150 mL of ordinary-temperature water on Day 41. • Subjects randomized to Sequence 2 will receive one ODT with 150 mL of ordinary-temperature water on Day 1, one ODT without water on Day 21, and one conventional tablet with 150 mL of ordinary-temperature water on Day 41. • Subjects randomized to Sequence 3 will receive one conventional tablet with 150 mL of ordinary-temperature water on Day 1, one ODT with 150 mL of ordinary-temperature water on Day 21, and one ODT without water on Day 41. • The IMP will be administered after fasting for at least 10 hours. • No food will be allowed for 4 hours postdose. Except as part of the dosing procedure, water will be restricted from 1 hour prior to dosing until 2 hours postdose. • Vital signs (body temperature, blood pressure, pulse rate, respiratory rate): predose (within 120 minutes prior to dosing) and 2, 6, and 12 hours postdose. – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. – Except at predose, vital signs should be measured within 60 minutes prior to the designated time and prior to PK blood collection. • Clinical laboratory tests (hematology, biochemistry, urinalysis): predose • Prolactin concentration test: predose • Blood sampling for PK assessments: predose (within 120 minutes prior to dosing) and 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose. – Except at predose, if a sample cannot be taken at the designated time, a window of ± 3 minutes is acceptable for each blood collection. • 12-lead ECG: 2 and 6 hours postdose – The ECG will be performed after the subject has rested in the supine position for at least 10 minutes. – ECGs should be performed within 60 minutes prior to the designated time and prior to PK blood collection. • C-SSRS (use of since-last-visit version): predose • Confirmation of concomitant medications and therapies • Identification/assessment of AEs • Meals will be provided as follows: lunch and dinner.

Table 3.7.3-1 Trial Days and Activities

Postdose Hospitalization Period (Days 2 to 7, Days 22 to 27, and Days 42 to 47)
• Vital signs (body temperature, blood pressure, pulse rate, respiratory rate): 24, 72, and 120 hours postdose[a] – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. – Vital signs should be measured within 60 minutes prior to the designated time and prior to PK blood collection. • Blood sampling for PK assessments: 16, 24, 48, 72, 96, 120, and 144 hours postdose[a] – If a sample cannot be taken at the designated time, a window of ± 3 minutes is acceptable for each blood collection. • 12-lead ECG: 24 and 72 hours postdose – The ECG will be performed after the subject has rested in the supine position for at least 10 minutes. – ECGs should be performed within 60 minutes prior to the designated time and prior to PK blood collection. • Confirmation of concomitant medications and therapies • Identification/assessment of AEs • Meals will be provided as follows: breakfast, lunch, and dinner.

Table 3.7.3-1 Trial Days and Activities

Discharge (Days 8, 28, and 48)
• Physical examination • Vital signs (body temperature, blood pressure, pulse rate, respiratory rate): 168 hours postdose – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. – Vital signs should be measured within 60 minutes prior to the designated time and prior to PK blood collection. • Body weight • Clinical laboratory tests (hematology, biochemistry, urinalysis) • Prolactin concentration test • Blood sampling for PK assessments: 168 hours postdose – If a sample cannot be taken at the designated time, a window of ± 3 minutes is acceptable for each blood collection. • 12-lead ECG: 168 hours postdose – The ECG will be performed after the subject has rested in the supine position for at least 10 minutes. – ECGs should be performed within 60 minutes prior to the designated time and prior to PK blood collection. • C-SSRS (use of since-last-visit version) • Confirmation of concomitant medications and therapies • Identification/assessment of AEs • Subjects will be discharged.

Table 3.7.3-1 Trial Days and Activities

Outpatient Visits (Days 10, 12, 14, 30, 32, 34, 50, 52, and 54)
• Subjects will visit the trial site. • Physical examination: on the third visit day of each period (Days 14, 34, and 54) • Vital signs (body temperature, blood pressure, pulse rate, respiratory rate): 216, 264, and 312 hours postdose[a] – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. – Vital signs should be measured within 60 minutes prior to the designated time and prior to the PK blood sample being taken; however, a window of ± 5 hours is acceptable. • Blood sampling for PK assessments: 216, 264, and 312 hours postdose[a] – If a sample cannot be taken at the designated time, a window of ± 5 hours is acceptable for the blood collection. • Confirmation of concomitant medications and therapies • Identification/assessment of AEs

Table 3.7.3-1 Trial Days and Activities

Discontinuation
• Physical examination • Vital signs (body temperature, blood pressure, pulse rate, respiratory rate) – Blood pressure and pulse rate will be taken after the subject has rested in the supine position for at least 3 minutes. – Body temperature and respiratory rate will be taken with the subject in the supine position. – Vital signs should be measured prior to PK blood collection. • Body weight • Clinical laboratory tests (hematology, biochemistry, urinalysis) • Prolactin concentration test • Blood sampling for PK assessments • 12-lead ECG – The ECG will be performed after the subject has rested in the supine position for at least 10 minutes. – ECGs should be performed prior to PK blood collection. • C-SSRS (use of since-last-visit version) • Confirmation of concomitant medications and therapies • Identification/assessment of AEs
Follow-up (Days 61 to 63)
• Conducted by trial site visit or telephone. • Confirmation of concomitant medications and therapies • Identification/assessment of AEs • If an AE is suspected as a result of information obtained in a telephone call, the subject will be asked to come to the trial site for further confirmation.

[a] Refer to Table 3.7-1 for conduct days.

3.7.4 Safety Assessments

3.7.4.1 Adverse Events

Refer to Section 5 Reporting of Adverse Events for the methods and timing for assessing, recording, and analyzing AEs. This trial is a crossover study, and AEs in each period will be assessed based on a comparison with the subject's status before the IMP administration in the respective periods.

3.7.4.2 Clinical Laboratory Assessments

The data from the clinical laboratory assessments listed in Table 3.7.4.2-1 will be collected on the measurement days specified in the schedule of assessments (Table 3.7-1), and processed according to the procedures specified by the clinical chemistry laboratory. The volume of blood collected will be 10 mL per sampling for hematology and serum biochemistry, 3 mL per sampling for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C antibodies (anti-HCV), and 3 mL per sampling for prolactin concentration. The date and time of each blood and urine collection will be recorded in the case report form (CRF).

Table 3.7.4.2-1 Clinical Laboratory Assessments

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin MCV MCHC Platelet Count Additional Tests: HIV HBsAg anti-HCV Prolactin	Serum Chemistry: ALT Albumin ALP AST Total Bilirubin BUN Calcium Chloride Total Cholesterol Creatinine Creatinine Phosphokinase GGGT Glucose LDH Inorganic Phosphorus Potassium Total Protein Sodium Uric acid Triglycerides
Urinalysis: Color Appearance Bilirubin Glucose Ketones Leukocyte Esterase Nitrites Occult blood Protein Urobilinogen pH Microscopic analysis of RBC/WBC (per high powered field)	Drug Screen (all items in urine except where noted): Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Opiates Phencyclidine Alcohol Test (breath or urine) Urinary Cotinine Test

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HCV = hepatitis C antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGGT = gamma glutamyl transferase; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; LDH = lactic dehydrogenase; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

3.7.4.3 Physical Examination and Vital Sign Assessments

A complete medical history will be taken at the screening visit. A physical examination will be performed in accordance with Section 3.7.3 Schedule of Assessments of this protocol. The physical examination will include an evaluation of the following body systems: head, ears, eyes, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. Whenever possible, all physical examinations for individual subjects should be performed by the same physician (investigator or

subinvestigator) throughout the trial. The date and result of assessment will be recorded in the CRF. Assessments for each period will be made in comparison with the physical condition at the time of admission in each period.

Vital signs (including body temperature, blood pressure, pulse rate, and respiratory rate) will be performed and documented according to Section 3.7.3 Schedule of Assessments of this protocol. Blood pressure and pulse rate will be measured in the order of supine, sitting, and standing after each position has been maintained for at least 3 minutes. If the blood pressure or pulse rate at screening is within the range of exclusion criteria but is not deemed clinically relevant, a total of 3 readings will be taken 10 minutes apart. The subject will be included in the trial if 2 out of 3 readings are outside the range of exclusion criteria. Sitting and standing blood pressure and pulse rate will be measured only at screening, and the difference between standing and sitting systolic blood pressure will be calculated. Body temperature and respiratory rate will be taken with the subject in the supine position. Body temperature will be recorded up to the first decimal place on the CRF. If body temperature is measured to the second decimal place or less, the second decimal place will be rounded. Vital signs will be obtained prior to PK blood collection at the nominal time points, where applicable. Measurement date and time, and measurement result will be recorded in the source document and CRF.

3.7.4.4 Electrocardiogram Assessments

ECGs will be recorded according to the schedule outlined in Section 3.7.3 Schedule of Assessments of this protocol. ECGs will be obtained prior to PK blood collections at either nominal time point, where applicable. Twelve-lead ECGs will be recorded with the subject supine and at rest (for at least 10 minutes), and the original ECG output recording will be retained in the medical record or principal investigator file. The central ECG laboratory will collect and analyze ECG data, and measure heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc (QTcF, QTcB). Three consecutive ECG measurements will be taken upon admission in each period and the mean value of those three measurements will be used as the baseline data for each period respectively. The analysis results will be reported to the investigator or subinvestigator. The investigator or subinvestigator will review the analysis results from the central ECG laboratory, and add their signature and the date of confirmation. The investigator or subinvestigator will determine if a result is normal or abnormal with reference to the analysis results provided by the central ECG laboratory and record measurement date and time, assessment result, and findings in the source documents and CRF.

Analysis results will be directly reported from the central ECG laboratory to the sponsor with the electronic file, and therefore recording in the source documents and CRFs is unnecessary.

3.7.4.5 Body Weight

Body weight will be measured in tenths of a kilogram using the same weight scale throughout the trial in accordance with Section 3.7.3 Schedule of Assessments of this protocol. Measurement date and time, and the measurement result will be recorded in the source documents and CRF.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered in accordance with Section 3.7.3 Schedule of Assessments of this protocol. The C-SSRS captures the occurrence, severity, and frequency of suicide related thoughts and behaviors during the assessment period. This scale consists of a baseline version that is designed to assess of the history of suicide-related events and suicidal ideation that the subject has had at any time in the past, and a since-last-visit version that focuses on any suicidal tendencies that might have arisen since the last assessment. Assessment at screening will be performed using the baseline version, and assessment after that will be performed using the since-last-visit version. A copy of the baseline version of the C-SSRS is presented in Appendix 1, and a copy of the since-last-visit version is presented in Appendix 2. The date and result of assessment will be recorded in the source documents and CRF.

3.7.5 Pharmacokinetic Assessments

3.7.5.1 Pharmacokinetic Plasma Samples

At each time point shown in Table 3.7-1, a 3-mL blood sample will be collected, and plasma concentrations of brexpiprazole will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry method. Additional metabolites that are not identified in the protocol may also be analyzed if new information becomes available. Plasma samples may be used for examination of analysis methods as needed.

The results of drug concentration measurement will be retained by the bioanalytical laboratory, and the electronic file will be submitted to the sponsor. While recording the measurement results in the source documents and CRFs is unnecessary, the date and time of blood sampling will be recorded in the source documents and CRF.

The samples will be shipped to the bioanalytical laboratory, and backup samples will be stored at the trial site and shipped to the bioanalytical laboratory as needed. Detailed handling and shipping instructions are provided in the procedures that have been prepared separately.

3.7.6 End of Trial

The end of trial date is defined as the last date of contact or the date of the final contact attempt from the post-treatment follow-up CRF page for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor prematurely terminates or suspends the trial for safety or unanticipated other reasons, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

The sponsor, investigator, or the IRB has the right to terminate the participation of a particular trial site, if necessary, due to lack of subject enrollment, noncompliance with the protocol, or 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 at the trial site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After the first dose of IMP, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the investigator or subinvestigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects should be encouraged to complete all early termination (ET) and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.8.3.2 Documenting Reasons for Discontinuation

All subjects have the right to withdraw, and the investigator or subinvestigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial (only one reason for discontinuation [the main reason] can be recorded in the CRF):

- AEs
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Lost to follow-up
- Investigator's or subinvestigator's decision (other than AE)
- Pregnancy (see Section 5.5 Pregnancy)
- Protocol deviation (other than non-compliance with IMP)
  - A subject was considered to have not met the inclusion criteria or have met the exclusion criteria.
  - A prohibited concomitant medication was administered or judged to be necessary.
- Termination of all or part of the trial by the sponsor
- Withdrawal of consent by subject (if confirmed not related to an AE)
- Other

If the subject discontinues IMP due to an AE, the investigator or subinvestigator, or other trial personnel, will make every effort to follow the event until the event is resolved or stabilized, or the subject is lost to follow-up or has died. Follow-up procedures in Section 5.7 must be followed. Subjects may be replaced, if withdrawals occur, as described in Section 3.3.1.

3.8.3.3 Withdrawal of Consent

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

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

Subjects who withdraw, should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject signs an ICF), but who is withdrawn from this study before being randomized.

For any subject to whom screen failure applies, the following items will be recorded in the CRF:

- Subject identification number
- Date of informed consent
- Date of visit (date of screening examination)
- Subject background survey (date of survey, date of birth, sex, race, ethnicity)
- Assessment result for eligibility criteria
- Date of assessment of screen failure
- Reason for assessment of screen failure

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for trial objectives irrespective of whether or not the subject actually consumes all doses of IMP. Subjects who are evaluated at the last scheduled visit during the trial period will be defined as trial completers. For purposes of this trial, subjects who complete Day 54 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects with whom contact is lost during the trial period and subjects who do not have a known reason for discontinuation (eg, withdrew consent or AE, etc.) will be classified as lost to follow-up.

The investigator or subinvestigator, or designee 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 investigator or subinvestigator, or designee will attempt to contact the subject via certified mail or an alternative similar method where appropriate, before assigning a “lost to follow-up” status. When a subject is lost to follow-up, presence/absence of contact with the subject, date of contact, and contact method will be recorded in the CRF.

3.12 Subject Compliance

The date and time of each trial drug administration, dosage form, and use or non-use of water when taking medication will be recorded in the source documents and CRF. Information regarding any missed or inappropriately administered doses will also be documented in the source document and in the CRF.

3.13 Protocol Deviations

In the event of a major deviation from the protocol due to an emergency, accident, or mistake (eg, IMP dispensing or subject dosing error or violation of concomitant medication criteria), the investigator or subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator, medical expert, and sponsor will come to a joint decision as quickly as possible regarding the subject’s continuation in the trial. If the decision reached is to allow the subject to continue in the trial, this must be documented by the investigator or subinvestigator, and the sponsor, and approved by the medical expert. All deviations from the written protocol should be recorded in the source documents by the investigator or subinvestigator. If a significant deviation occurs, the date of occurrence of significant deviation and its summary should be recorded in the CRF.

4 Restrictions

4.1 Prohibited Medications

No medications other than planned IMP may be taken during the trial.

- From 14 days before the first IMP administration until completion of follow-up
  Prescription medications, OTC medications, herbal medication, vitamin supplements
- From 30 days before the first IMP administration until completion of follow-up
  Antibiotics

Exceptions to the above may be allowed only in cases where the sponsor judges that administration of the drug is unlikely to influence the pharmacokinetics of brexpiprazole. Exceptions must be discussed with the sponsor on a case-by-case basis and reasons documented.

4.2 Other Restrictions

The following will be prohibited during the specified period.

- From 14 days before the first IMP administration until completion of blood sampling on Day 54 (312 hours postdose in Period 3)
  Food or beverages containing St. John's Wort
- From 72 hours before the first IMP administration until completion of blood sampling on Day 54 (312 hours postdose in Period 3)
  Grapefruit, grapefruit products, Seville oranges, Seville orange products, star fruit, or star fruit products
- From 72 hours before each administration until discharge at the end of each hospitalization period
  Alcohol
- During hospitalization
  Food or beverages containing methylxanthines (such as caffeinated coffee, caffeinated tea, caffeinated soda, and chocolate)
- From 2 months before screening until completion of follow-up
  Smoking
- From the time of informed consent until completion of follow-up
  Blood donation

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as current symptoms at screening for preplanned procedures for which the underlying condition was known and no worsening occurred.

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

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability
- Requires inpatient hospitalization or prolongs hospitalization
  - Hospitalization itself should not be reported as a serious treatment-emergent adverse event (TEAE); whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered serious TEAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Immediately Reportable Event (IRE):

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

Clinical Laboratory Assessment Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator needs to ascertain if this is an abnormal (ie, clinically relevant) change from baseline in each period for that individual subject. This

determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically relevant by the investigator or subinvestigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale.

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 IMP:

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 reasonable relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will assess subjects for the occurrence of AEs. For this trial, information on AEs will be followed until the end of the trial as specified in Section 3.7.6. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How are you feeling?" All AEs (serious and nonserious) reported by the subject must be recorded in the source documents and CRFs provided by the sponsor. The source documents and CRF are to include event name, date and time of onset (recording of time of day is necessary for vomiting and wherever possible for other AEs), date of recovery, seriousness, severity, IMP causality, action taken regarding IMP administration, and outcome. All AE and SAE collections are to begin after a subject has signed the ICF and will continue until the last scheduled contact.

Use medical terminology in 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 there is any change in the severity or seriousness of an AE that has been reported, the AE must be reported as a new AE in the CRF.

In addition, the sponsor must be notified immediately by e-mail, as a rule, of any IREs according to the procedure outlined below in Section 5.3 Immediately Reportable Events. Special attention should be paid to recording hospitalization and concomitant medications

5.3 Immediately Reportable Events

The investigator or subinvestigator, or designee must report any SAE, any AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy, by e-mail to the sponsor, immediately after either the investigator or subinvestigator become aware of the event. An IRE form or other form should be completed and sent by e-mail, in principle, to the sponsor using the contact information on the title page of this protocol. (Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE CRF.)

Subjects experiencing SAEs or IREs should be followed clinically as described in Section 5.7.2. It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

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

5.5 Pregnancy

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

For sexually active subjects with partners who are women of childbearing potential, 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 30 days after the last dose of IMP. Unless the subject or subject's partner is sterile (ie, women who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent during the trial and for 30 days 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 pills, condom with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the CRF. Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.

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

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

Before trial enrollment, subjects 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.

During the trial, all subjects should be instructed to contact the investigator or subinvestigator immediately if they suspect their partners might be pregnant (eg, missed or late menstrual cycle).

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

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject. Other appropriate pregnancy follow-up procedures for a subject's partner

should be considered if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

Not applicable for this open-label trial.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE CRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (excluding IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the CRF. For any AE having been identified throughout the trial, during data 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). The follow-up information after the last scheduled contact will be recorded in the subject's medical record.

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs until the last scheduled contact as specified in Section 3.7.6.

Serious AEs and IREs that are identified or ongoing at the last scheduled contact must be recorded on the AE CRF page. Any new information (eg, Resolved) related to the SAE or IRE obtained from the last scheduled contact of the subject until the last scheduled contact of the last subject in the entire trial must be reported to the sponsor with the IRE form and so on, and the information must be recorded on the AE CRF page. The investigator or subinvestigator must follow SAEs and IREs until the events have resolved or are stabilized, or the subject is lost to follow-up or has died, and report any significant follow-up information to the sponsor with the IRE form and so on. Resolution means the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring After Last Scheduled Contact

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

6 Pharmacokinetic Analysis

6.1 Pharmacokinetic Methods

6.1.1 Primary Endpoints

C_{max} and AUC_t of brexpiprazole

6.1.2 Secondary Endpoints

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}

6.1.3 Datasets for Analysis

The bioequivalence analysis set is defined as the analysis dataset (see Section 7.2.1).

6.1.4 Analysis Methods

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) will be calculated through a noncompartmental PK analysis. The plasma concentrations and estimated PK parameters will be presented with descriptive statistics by formulation and administration method.

6.2 Pharmacodynamic Methods

No pharmacodynamic parameters will be evaluated for this trial.

6.3 Pharmacokinetic/Pharmacodynamic Methods

No pharmacokinetic or pharmacodynamic-related analyses are scheduled for this trial.

6.4 Pharmacogenomic Methods

No pharmacogenomic-related analyses are scheduled for this trial.

7 Statistical Analysis

The definition of analysis sets and analysis method by endpoint are summarized below. The analysis plan will be described in detail in the Statistical Analysis Plan separately. The Statistical Analysis Plan is to be determined before data lock.

7.1 Determination of Sample Size

Based on the BE Guideline, 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.

7.2 Datasets for Analysis

7.2.1 Bioequivalence Analysis Set

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

7.2.2 Safety Population

All subjects who received at least one dose of IMP

7.3 Handling of Missing Data

There will be no imputation for missing data.

7.4 Primary Endpoint Analyses

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 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.

The Kenward–Roger method will be used to estimate the degrees of freedom in the mixed effect model analysis.

7.5 Analysis of Demographic and Baseline Characteristics

For age, height, weight (screening period), BMI, and medical history and current symptoms, the frequency distribution or descriptive statistics will be presented overall and by sequence for the bioequivalence analysis set and safety analysis set.

7.6 Safety Analysis

Safety analysis will be conducted upon the safety analysis set for each formulation and administration method. Baseline is defined as the last measurement immediately before each dosing.

7.6.1 Adverse Events

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

- TEAEs
- TEAEs by severity

- 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.

7.6.2 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.

7.6.3 Physical Examination and Vital Signs Data

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

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

7.6.4 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.

7.6.5 Other Safety Data

7.6.5.1 Body Weight

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

7.6.5.2 The Columbia-Suicide Severity Rating Scale

C-SSRS data for individual subjects will be listed.

7.7 Judgement 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.

7.8 Pharmacodynamic Analysis

No pharmacodynamic-related analyses are scheduled for this trial.

8 Management of Investigational Medicinal Product

2-mg brexpiprazole ODT is the test formulation provided as the IMP, and 2-mg brexpiprazole conventional tablet is provided as the reference product.

For the detailed management of the IMP and reference product, see the investigator's brochure and clinical operation manual.

8.1 Packaging and Labeling

The IMP and reference product will be provided to the IMP manager by the sponsor or designated agent. The IMP will be provided in bottles. Each IMP bottle used will be labeled to clearly disclose the statement "For clinical trial use only," as well as the trial number, IMP name, amount, lot number, expiry date, storage, and sponsor's name and address. The reference product will be provided in commercial product packaging.

8.2 Storage

The IMP and reference product will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager. The IMP manager may not provide IMP or reference product to any subject not participating in this protocol.

The IMP and reference product will be stored at room temperature.

The trial site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The IMP manager must maintain an inventory record of IMP and reference product received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all containers of used IMP and reference product, and all unused and partially used IMP and reference product must be returned to the sponsor or a designated agent.

All IMP and reference products returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number with trial site number on the outermost shipping container. Returned supplies of IMP and reference product should be in the original containers. The assigned trial monitor will facilitate the return of containers of used IMP and reference product, and unused or partially used IMP and reference product.

8.5 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 an IMP, reference product, or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

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

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or subinvestigator, or designee must record all PQCs identified through any means from the receipt of the IMP and reference product from the sponsor, or sponsor's designee, through subject dosing, up to product return, including reconciliation. The investigator or subinvestigator, or designee must notify the sponsor (or sponsor's designee) of the items in Section 8.5.2 Information Required for Reporting Product Quality Complaints by e-mail (e-mail address of the transmission destination: PQC_331-14-002@otsuka.jp) immediately after of becoming aware of the PQC.

Identification of a PQC by the subject should be reported to the investigator or subinvestigator who should then follow one of the reporting mechanisms below.

8.5.2 Information Required for Reporting Product Quality Complaints

The following information is required for reporting purposes:

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

8.5.3 Return Process for Product Quality Complaints

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

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the trial site 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. Materials concerning drug concentration measurement, including the original of the report and measurement data, will be maintained by the bioanalytical laboratory. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding visit or day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's or subinvestigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of all investigators or subinvestigators (or designee) who made an entry in the progress notes.

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.

Any changes to information in the trial progress notes or other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by crossing out the erroneous data, and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be provided in the source document by the investigator or subinvestigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the trial progress notes, the results for clinical laboratory tests, and other source documents will be entered by trial site personnel directly onto eCRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail.

9.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The trial site file will include all source documentation as well as completed CRF data for all subjects screened or enrolled at the trial site. The trial site will take measures to ensure confidentiality and prevent accidental or premature destruction of these documents.

9.4 Record Retention at the Trial Site

The trial site will retain all the trial-related documents and records for one of the two periods of time indicated below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.

- The date 2 years after the date of manufacturing and marketing approval. However, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
- The date 3 years after termination or completion of the trial.

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The trial site shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and relevant regulatory agencies.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, ICH E6 GCP: Consolidated Guidance, 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 (or sponsor designee'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, subinvestigators, and trial site staff will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's (or designee'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 comparison of CRFs with source documents. The investigator agrees to participate with audits.

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

10.3 Protocol Deviations

Due to the complexity of clinical trial protocols and despite training and preventive efforts, deviations from the written protocol may occur and potentially result in harm to subjects, biased or inaccurate results, and possible rejection of all or part of the trial data. Per the ICH E3 guidance on the structure and content of clinical study reports, Section 10.2, protocol deviations should be summarized by site and grouped into different categories such as:

- those who entered the study even though they did not satisfy the entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn
- those for whom there were major IMP dosing errors that may compromise subject safety or PK assessments.
- those who received an excluded concomitant treatment during the course of the trial

Otsuka categorizes clinical protocol deviations as major versus minor. A major deviation is an intentional or accidental action or omission in a trial conduct that could potentially

have a negative impact on the integrity of the trial's primary scientific objectives or has a significant potential to have a negative impact on the safety or efficacy assessments of any trial subject. Major deviations are those that might significantly affect the completeness, accuracy, or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

A minor deviation is an intentional or accidental action or omission during trial conduct in which the protocol is not strictly followed, but which has inconsequential impact on the integrity of the trial as a whole or the safety or efficacy analyses of an individual subject.

All protocol deviations will be categorized as major or minor according to the above definitions and only major deviations will be summarized in the clinical study report.

If the same protocol deviation occurs for multiple subjects, it must be recorded separately for each subject.

The investigator or subinvestigator is expected to document potential protocol deviations as well as their medical assessment regarding continuation of the subject(s) due to the protocol deviation.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH 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. The trial site(s) will seek approval/favorable opinion 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 CRFs, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number or subject identification number will be used to identify each subject.

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

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior

written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

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

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any 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 or subinvestigator will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. However, 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 agency within local applicable timelines.

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

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship

criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

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

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

Investigators or other trial participants 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 participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

1 Koprivica V. In vitro binding and functional characteristics of OPC-34712 at a clone of the human serotonin 5-HT1A receptor. Otsuka Study No. 026010, Otsuka Report No. 020193, 2007.

2 Akazawa H. In vitro receptor binding profiles of OPC-34712 for human dopamine D2, serotonin 5-HT2A, and adrenaline alpha1A receptors. Otsuka Study No. 025637, Otsuka Report No. 020442, 2007.

3 Mallikaarjun S. A phase 1, randomized, double-blind, placebo-controlled study to assess the tolerability, safety, and pharmacokinetics of ascending single oral doses of OPC-34712 in healthy subjects. Otsuka Clinical Study Report for Protocol 331-07-201, issued 07 Dec 2009.

4 Youakim JM. An open-label, randomized, two-way crossover trial of the effect of a high-fat meal on the pharmacokinetics of OPC-34712 in healthy subjects. Otsuka Clinical Study Report for Protocol 331-10-246, issued 10 Oct 2012.

5 Skuban A. A phase 1, open-label, multiple-dose, parallel-group study to assess the pharmacokinetics and safety of oral OPC-34712 in healthy subjects. Otsuka Clinical Study Report for Protocol 331-08-206, issued 19 Feb 2010.

6 Mallikaarjun S. A pilot study to assess the potential for cytochrome P450-mediated and P-glycoprotein-mediated drug interactions with OPC-34712 in healthy subjects. Otsuka Clinical Study Report for Protocol 331-08-207, issued 18 Mar 2010.

[7] Otsuka Pharmaceutical Co, Ltd. A randomized, double-blind, placebo-controlled, single-dose trial of OPC-34712 in healthy adult male subjects. Final Study Report for Protocol 331-07-002, issued 15 Oct 2009.

[8] Otsuka Pharmaceutical Co, Ltd. A repeated-dose trial of OPC-34712 in patients with schizophrenia. Final Study Report for Protocol 331-10-001, issued 08 Jun 2011.

[9] Skuban A. A phase 1, open-label, positron emission tomography (PET) study in healthy subjects following a single oral dose of OPC-34712. Otsuka Clinical Study Report for Protocol 331-07-202, issued 06 Apr 2010.

[10] Skuban A. A phase 1, multi-center, randomized, double-blind, comparator-controlled study to assess the tolerability, safety, efficacy, and pharmacokinetics of ascending multiple oral doses of OPC-34712 in adult subjects with a diagnosis of schizophrenia or schizoaffective disorder. Otsuka Clinical Study Report for Protocol 331-08-205, issued 15 Mar 2010.

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

[12] Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms Q&A (Attachment 3) (Office Communication dated 29 Feb 2012).

[13] Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (Attachment 2) (Office Communication dated 29 Feb 2012).

[14] International Council for Harmonisation (ICH) [homepage on the Internet]. E6(R2): Good Clinical Practice: Integrated Addendum to ICH E6(R1) [finalized 2016 November; cited 2018 Nov 9]. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf.

Appendix 1 Baseline Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline
Version 1/14/09

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?			**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 2 Since Last Visit Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it"*. ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*. ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, brexpiprazole, the concomitant medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where brexpiprazole will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other trial sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the trial site for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementing any amendments made to this protocol. If, however, there is an immediate hazard to subjects, I will implement a deviation or change from the protocol, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse events in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I

understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis can occur, and I consent to be acknowledged in any such cooperative publications that result.

Principal Investigator's Name	Name of Trial Site
Signature	Date