CLINICAL STUDY PROTOCOL

A multicenter, randomized, open-label, 2-arm, 2-period crossover trial to investigate the effects of food on the pharmacokinetics of a single dose of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

A food effects trial of the pharmacokinetics of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

NCT Number: NCT06036108
Protocol No. 331-102-00151
Version Date: 29 Aug 2024 (Version 1.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A multicenter, randomized, open-label, 2-arm, 2-period crossover trial to investigate the effects of food on the pharmacokinetics of a single dose of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

A food effects trial of the pharmacokinetics of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

Protocol No. 331-102-00151

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	1
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	Office of Pharmacovigilance Operations, Department of Pharmacovigilance [redacted]
Amendment 1 Approval:	29 Aug 2024 (English Translation: 25 Sep 2024)
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List of Abbreviations

Abbreviation	Definition
5-HT_{1A}	5-hydroxytryptamine 1A
5-HT_{2A}	5-hydroxytryptamine 2A
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_%Extrap	percentage of AUC due to extrapolation from t_{last} to infinity [$(AUC_\infty - AUC_t)/AUC_\infty \times 100$]
AUC_∞	area under the concentration-time curve from time zero to infinity
AUC_τ	area under the concentration-time curve during a dosing interval (τ) at steady-state
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
BMI	body mass index
CGI-I	Clinical Global Impression - Global Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CL/F	apparent clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
CPK	creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DIEPSS	Drug Induced Extra-Pyramidal Symptoms Scale
DNA	deoxyribonucleic acid
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EM	extensive metabolizer
FBR	Future Biospecimen Research
FDA	(United States) Food and Drug Administration
FT_4	free thyroxine
GCP	Good Clinical Practice
IB	investigator brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IM	intermediate metabolizer
IRE	immediately reportable event
IWRS	interactive web response system
LSMD	least square mean difference
λ_z	apparent terminal-phase disposition rate constant (first-order)
OD	orally disintegrating
OROS	osmotic-controlled release oral delivery system

Abbreviation	Definition
PANSS	Positive and Negative Syndrome Scale
PM	poor metabolizer
PQC	product quality complaint
QTc	corrected QT interval
QTcI	individually corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	quaque (once) weekly
$t_{1/2,z}$	terminal-phase elimination half life
TEAE	treatment-emergent adverse event
t_{last}	time of last measurable (positive) concentration
t_{max}	time to maximum plasma concentration
TSH	thyroid-stimulating hormone

1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)

Protocol No.: 331-102-00151

Protocol Title:

A multicenter, randomized, open-label, 2-arm, 2-period crossover trial to investigate the effects of food on the pharmacokinetics of a single dose of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

Protocol Lay Person Short Title:

A food effects trial of the pharmacokinetics of brexpiprazole once-weekly (QW) formulation in patients with schizophrenia

Clinical Phase/Trial Type:

Phase 1/clinical pharmacology trial

Planned Treatment/Indication:

Schizophrenia

Trial Rationale:

Brexpiprazole conventional tablets, a once-daily oral formulation, has demonstrated efficacy and safety in the treatment of schizophrenia in clinical trials in subjects with schizophrenia conducted in Japan, the US, and Europe and is approved in Japan and overseas as a treatment for schizophrenia. In the treatment of schizophrenia, maintenance of drug compliance is thought to be instrumental in alleviating symptoms and achieving favorable outcomes; however, in comparison with other chronic diseases, schizophrenia is generally associated with poor drug adherence due mainly to lack of consciousness of disease and cognitive impairment. Long-acting drugs have been introduced into clinical practice as a measure to improve patient adherence to medication, but currently the only commercially available long-acting antipsychotics are all injectable formulations, thus reflecting an unmet medical need for more easy-to-use long-acting antipsychotics. Otsuka is now developing a once-weekly (QW) formulation, utilizing the same less invasive route of administration as conventional brexpiprazole, namely the oral route, but with a different formulation to enable reduced dosing frequency.

Otsuka has conducted clinical pharmacology trials to investigate the pharmacokinetics (PK), tolerability, and safety of the brexpiprazole QW formulation administered as single and multiple oral doses in Japanese patients with schizophrenia and confirmed the tolerability and safety of the drug. Based on the PK results, Otsuka has made dose selection and is currently conducting a phase 3 confirmatory trial to investigate the efficacy and safety of the brexpiprazole QW formulation in patients with acute schizophrenia.

According to "Clinical Pharmacokinetic Studies of Pharmaceuticals" (Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau [PMSB/ELD] Notification No. 796, dated 01 Jun 2001), "Drug Interaction Guidelines for Drug Development and Proper Informatics," (Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau [PSEHB/PED] Notification No. 0723-6, dated 23 Jul 2018), and "Guidelines for Design and Evaluation of Sustained-Release (Oral) Preparations" (Notification. No. 5 of the First Evaluation and Registration Division, PAB dated 11 Mar 1988), there is a requirement to investigate the effects of food on the final drug product, and therefore it was decided to evaluate food effects in this trial. Additionally, the design of this trial was made with reference to various guidance and guidelines, and tests and endpoints are items that are commonly performed.

Based on the above, the conduct of the planned trial based on this protocol is judged to be scientifically and ethically appropriate.

Objectives and Endpoints:

To investigate the effect of food on the PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia and to confirm safety under those conditions.

Objectives	Endpoints
Primary objective: To investigate the effect of food on PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia	Primary pharmacokinetic endpoint: Geometric mean ratio and two-sided 90% confidence interval of C_{max}, AUC_{∞}, and AUC_t of brexpiprazole in plasma after administration in a fed state versus administration in a fasting state Secondary pharmacokinetic endpoints: • Plasma concentrations of brexpiprazole and metabolite [redacted] • Pharmacokinetic parameters of brexpiprazole and metabolite [redacted] in plasma

Objectives	Endpoints
Secondary objective: To confirm safety of the brexpiprazole QW formulation in patients with schizophrenia	Safety endpoints: • Adverse events (AEs) • Clinical laboratory tests • Vital signs (body temperature, blood pressure, and pulse rate) • Physical examination findings • Body weight • Body mass index (BMI) • 12-Lead electrocardiography (ECG) • Drug Induced Extrapyramidal Symptoms Scale (DIEPSS) • Columbia-Suicide Severity Rating Scale (C-SSRS) Other endpoints: • Clinical Global Impression-Severity of Illness (CGI-S) • Clinical Global Impression - Global Improvement (CGI-I) • Bowel-movement investigation

Trial Design:

Multicenter, randomized, open-label, 2-arm, 2-period crossover trial

Trial Population:

Patients at least 18 years of age and below the age of 65 with a diagnosis of schizophrenia based on the diagnostic criteria proposed in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5®)

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the specified assessment time points:

1) Patients at least 18 years of age and below the age of 65 at the time of informed consent
2) Patients with a diagnosis of schizophrenia based on DSM-5® at the time of informed consent
3) Patients who are able to be hospitalized for the protocol-defined hospitalization period
4) Patients with a body mass index [BMI = body weight (kg)/height $(m)^2$] of 18.5 kg/m^2 or higher and lower than 35.0 kg/m^2 at screening

5) Patients who provide written informed consent before commencement of any trial-related procedures and whom the investigator judges to be capable of following all the conditions of this trial
6) Patients who, in the judgment of the investigator, have stable psychotic symptoms maintained by administration of an antipsychotic within the dosing range indicated below, before commencement of investigational medicinal product (IMP) administration

   [Upper limit of dose and regimen]

   - Antipsychotic medication comprising no more than 2 active components, and
   - A daily dose equivalent to ≤ 600 mg/day of chlorpromazine

     * If multiple antipsychotics are taken in the same day, this is to be the combined equivalent dose.

     However, this does not include administration of antipsychotic medication at doses equivalent to less than 100 mg/day of chlorpromazine, which are not expected to have any antipsychotic effect.
7) Patients who are able to finish the high-fat meal specified in this protocol within 20 minutes

Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the specified assessment time points:

<Regarding medical history and complications>

1) Patients with a concurrent mental disorder besides schizophrenia who are judged by the investigator to be unsuitable for participation in the trial
2) Patients who have met the DSM-5® diagnostic criteria for substance-related or addictive disorder, including alcohol and benzodiazepines but excluding caffeine and tobacco, within 180 days before commencement of IMP administration
3) Patients with a positive drug test at screening

   However, patients who tested positive for a drug other than cocaine may be included if their condition is not diagnosed as any substance-related or addictive disorder, according to the DSM-5® diagnostic criteria.
4) Patients who fall under any of the following criteria regarding suicidal ideation and suicidal behavior
   - Patients who answered “yes” to Question 4 “Active Suicidal Ideation with Some Intent to Act, without Specific Plan” or Question 5 “Active Suicidal Ideation with Specific Plan and Intent” regarding C-SSRS suicidal ideation at screening (for the past 6 months) or at the Period 1 baseline examination (since the last assessment)
   - Patients who exhibited suicidal behavior on C-SSRS at screening (for the past 2 years) or at the Period 1 baseline examination (since the last assessment)
   - Patients who present a serious risk of suicide based on the judgment of the investigator

5) Patients who have previously undergone gastrointestinal surgery that could affect PK evaluation
6) Patients who have undergone major surgery or blood transfusion or who have made a blood donation (whole blood or blood plasma) within 30 days before the acquisition of informed consent
7) Patients who have a clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorder.
   Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not interfere with safety and PK assessments.
8) Patients with any of the following laboratory or ECG values at screening (according to the results from the central laboratory or the central ECG laboratory)

Platelets: ≤ 75000/mm^3(/μL)	Hemoglobin: ≤ 9 g/dL
Neutrophils, absolute: ≤ 1000/mm^3	Aspartate aminotransferase (AST): > 2 × upper limit of normal (ULN)
Alanine aminotransferase (ALT): > 2 × ULN	Creatine phosphokinase (CPK): > 3 × ULN
Creatinine: ≥ 2 mg/dL	QT interval corrected for heart rate using Fridericia's formula (QTcF): > 450 milliseconds

9) Patients who fall under any of the following criteria at screening
   - Inadequately controlled hypertension (supine or sitting diastolic blood pressure of > 95 mmHg)
   - Symptomatic hypotension
   - Orthostatic hypotension, defined as a decrease of ≥ 30 mmHg in systolic blood pressure or a decrease of ≥ 20 mmHg in diastolic blood pressure after standing for at least 3 minutes compared with the supine values prior to standing
10) Patients meeting any of the following criteria
   - Patients with type 1 diabetes mellitus or patients with type 2 diabetes mellitus being treated with insulin
   - Patients with type 2 diabetes mellitus who have not been maintained on a stable regimen of anti-diabetic medication(s) or undergone diet/exercise therapy for at least 28 days prior to screening
   - Patients meeting either of the following criteria for poor blood glucose control at screening
     – Glycosylated hemoglobin (HbA1c) of ≥ 7.0% according to the global standard value
     – Fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL

11) Patients with a complication of hypothyroidism or hyperthyroidism (except in cases where the condition has been kept stable for at least 90 days at the time of screening through drug therapy) or patients who show abnormal values for thyroid-stimulating hormone (TSH) and free thyroxin (FT_4) in at screening
12) Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (whether controlled or uncontrolled), or with a history of angioplasty, stenting, or coronary artery bypass surgery
13) Patients with a history or complication of epilepsy or seizures, except for childhood febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, etc
14) Patients with a history or a complication of neuroleptic malignant syndrome
15) Patients with a history or a complication of paralytic ileus
16) Patients with a history or a complication of water intoxication
17) Patients with a history or a complication of rhabdomyolysis
18) Patients with a history or a complication of pulmonary embolism

<Prohibited concomitant medications/therapies>

19) Patients who are using clozapine at the time of informed consent
20) Patients who fail to meet the specified requisite washout periods for the prohibited concomitant drugs and foods (see Section 5.3 and Section 6.5.1) before commencement of IMP administration, or patients who are anticipated to take any of the prohibited drugs or foods during the trial
21) Patients whose clinical symptoms have worsened to the point where use of prohibited concomitant therapy or medication is required during the washout period for prior medication

<Allergies or drug reactions>

22) Patients who have allergy or hypersensitivity to brexpiprazole conventional tablet, orally disintegrating tablet (OD tablet), or brexpiprazole QW formulation, or patients for whom there are known safety concerns
23) Patients to whom brexpiprazole is contraindicated in the package insert
    - Patients with coma
    - Patients under marked influence of CNS depressants such as barbiturates or anesthetics
    - Patients receiving adrenaline
24) Patients with a history of allergy to more than one medication

<Pregnancy>

25) Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP
26) Sexually active males or females of childbearing potential (FOCBP), or their partners, who do not agree to practice 2 different approved methods of birth control or remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods] or withdrawal are not acceptable methods of contraception) during the trial and for 28 days after the last dose of

IMP. If employing birth control, 2 of the following approved methods must be used: [vasectomy, tubal ligation, intrauterine device, birth control pill, or condom (all of which are approved or certified in Japan)]. A definition of childbearing potential can be found in Section 10.3.

<Others>

27) Patients who are involuntarily hospitalized under the Mental Health and Welfare Law of Japan, or prisoners

28) [redacted].

29) Patients whose cytochrome P450 2D6 (CYP2D6) phenotype is judged to be either poor metabolizers (PM) or Unknown based on the results of CYP2D6 genetic testing at screening

30) Patients judged by the investigator to be unsuitable for participation in the trial

31) Patients with a history of unexplained loss of consciousness

Trial Site(s):

Approximately 25 sites in Japan

Trial Intervention(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

[Screening period]

Only brexpiprazole-naive subjects will be administered the following to verify that they have no acute hypersensitivity to brexpiprazole. Brexpiprazole conventional tablet and OD tablet used in this administration are classified as drugs used in the clinical trial other than the IMP (predosing products).

1) Predosing products: Brexpiprazole conventional tablet (1 mg), OD tablet (0.5 mg or 1 mg)
2) Dose and regimen

   Brexpiprazole-naive subjects will undergo and complete oral administration of brexpiprazole conventional tablet 1 mg (1 mg × 1 tablet) or OD tablet 1 mg (1 mg × 1 tablet or 0.5 mg × 2 tablets) for 2 consecutive days no later than 20 days prior to commencement of brexpiprazole QW formulation administration in Period 1.

[IMP administration period (Period 1 and Period 2)]

Subjects who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be randomized at a 1:1 ratio to either the fasting-state-administration-first group or the fed-state-administration-first group on the day before administration of the IMP in Period 1 (or on the day of IMP administration if preparation of the high-fat meal is completed in time) and will receive the IMP in Period 1 and Period 2 as follows. To the extent possible, the IMP will be administered at approximately the same time of day in both Period 1 and Period 2. [redacted] Administration of IMP should be performed at least 48 hours after symptoms of diarrhea have disappeared. For administration in the fed state in Period 1 or Period 2, if the high-fat meal cannot be eaten completely during the period specified in Section 5.3.1, the date of IMP administration may be postponed once only, after consultation with the subject.

1) IMP: brexpiprazole QW formulation 24 mg tablet
2) Dose and regimen

   Fasting-state-administration-first group

   In Period 1, a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water following at least 10 hours of fasting. In Period 2, following at least 10 hours of fasting, the subject will consume a high-fat meal within 20 minutes, after which a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water within 10 minutes of finishing the meal.

   Fed-state-administration-first group

   In Period 1, following at least 10 hours of fasting, the subject will consume a high-fat meal within 20 minutes, after which a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water within 10 minutes of finishing the meal. In Period 2, a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water following at least 10 hours of fasting.

Trial Assessments:

Assessments for Efficacy: None

Assessments for Safety: Adverse event (AE), clinical laboratory tests, vital signs, physical examination findings, body weight, 12-lead ECG, DIEPSS, C-SSRS

Assessments for Pharmacokinetics: Plasma drug concentration

Other: Height, CGI-S, CGI-I, bowel-movement investigation, CYP2D6 genetic testing, deoxyribonucleic acid (DNA) storage (optional)

Data Monitoring Committee: No

Statistical Methods:

Analysis of primary efficacy endpoint

The natural log-transformed C_{max}, AUC_{∞}, and AUC_t of brexpiprazole in plasma will be analyzed using a linear mixed-effects model with group (fasting-state-administration-first group or fed-state-administration-first group), meal condition (fasting or fed), and period (Period 1, Period 2) as fixed effects, and within-group subjects as a random effect, and the differences in means of natural log-transformed values between meal conditions (fed-state administration − fasting-state administration) and their two-sided 90% confidence intervals will be calculated. The differences in the mean natural log-transformed values (fed-state administration − fasting-state administration) and their two-sided 90% confidence intervals will be inverse-transformed to calculate the ratio of geometric mean values (fed-state administration/fasting-state administration) and two-sided 90% confidence interval.

Sample size

The sample size was set as a sufficient number required to achieve a two-sided 90% confidence interval of the geometric mean ratios of C_{max}, AUC_{∞}, and AUC_t following administration in the fed state versus the fasting state within a range of 0.8 to 1.25 under the assumption of absence of any food effects on the brexpiprazole QW formulation.

[redacted]

[redacted]

Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial:

- Screening period: Up to 42 days
- IMP administration period: 57 days (including washout period and follow-up period)

The trial start is defined as the date the first subject signs their informed consent form. Overall, the trial duration from signing of the first informed consent form to the final subject assessment is expected to be 1 year and 7 months.

Known and Potential Risks and Benefits:

[redacted]

[redacted]

Based on the above, it was considered that there are no major safety concerns regarding administration of a single dose of brexpiprazole QW formulation at 48 mg in either a fasting or fed state, and the risk is considered to be manageable by observing the subjects under hospitalization and exercising careful consideration of safety during the first week after administration of the IMP.

Since this trial is a clinical-pharmacology trial to investigate the effect of food on the PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia, no benefit to subjects is expected.

1.2 Schema

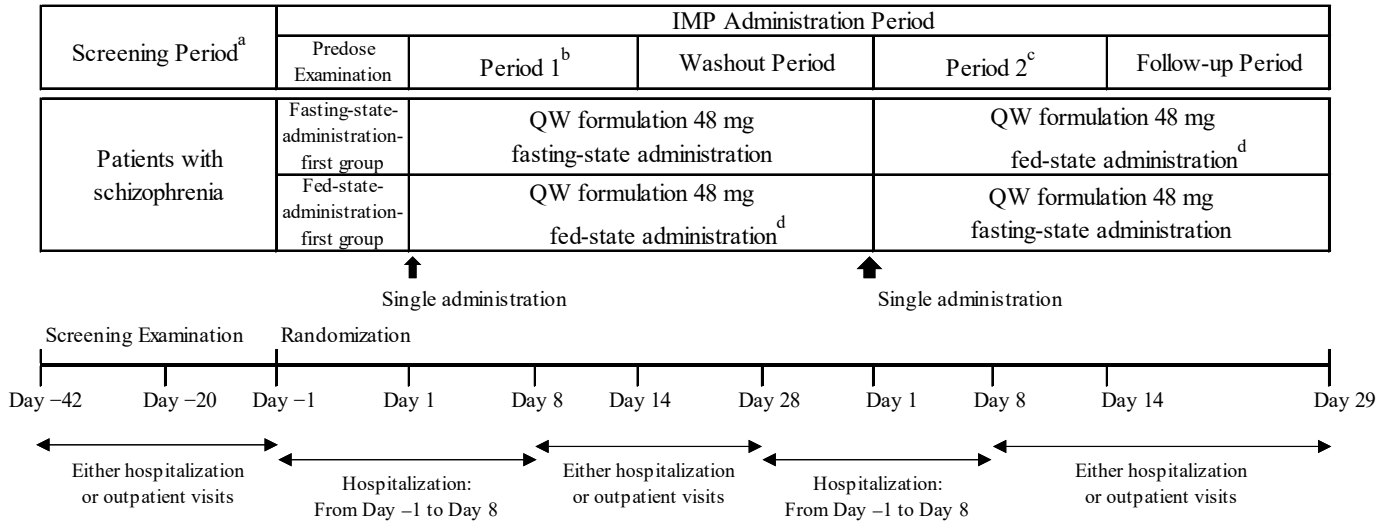


Figure 1.2-1 Trial Design Schematic

[a]Brexpiprazole-naive subjects will undergo and complete oral administration of brexpiprazole conventional tablet 1 mg (1 mg × 1 tablet) or OD tablet 1 mg (1 mg × 1 tablet or 0.5 mg × 2 tablets) for 2 consecutive days no later than 20 days prior to commencement of brexpiprazole QW formulation administration in Period 1, to verify that they have no allergic reaction or hypersensitivity.

[b][redacted].

[c][redacted]

[d]The meal will be a high-fat meal (approximately 900 kcal or more containing approximately 35% or more lipid content). For administration after a meal in Period 1 or Period 2, if the high-fat meal cannot be eaten completely during the period specified in Section 5.3.1, the date of IMP administration may be

postponed once only. The date of IMP administration in Period 1 can be adjusted within a period of 42 days from the start date of screening and, with the date of IMP administration in Period 1 counted as Day 1, the date of IMP administration in Period 2 can be adjusted between Day 30 and Day 36.

1.3 Schedule of Assessments

The schedule of assessments is shown in Table 1.3-1.

Table 1.3-1 Schedule of Assessments

	Screening Period	IMP Administration Period													
		Period 1 Baseline Examination	Period 1 (Administration of QW Formulation 48 mg in a Fasting or Fed State)												Washout[e]
Day (per treatment period)	From −42	−1	1				2		3	4	6	8	11	14	
Hours predose/postdose	—	−24	−2	0	3	9	24	36	48	72	120	168	240	312	
Informed consent[a]	×														
Informed consent for blood sampling for DNA storage (optional)	×														
Inclusion/exclusion criteria	×	×													
Demographic data (including height)	×														
Subject registration	×	×													
Predosing[b]	×														
IMP administration				×[c]											
Blood sampling for CYP2D6 genetic testing[d]	×														
Blood sampling for DNA storage (optional)[f]		×													
Blood sampling for plasma drug concentration measurement			×		×	×	×	×	×	×	×	×	×	×	
Clinical lab tests[g]	×	×[h]							×			×		×	
TSH, FT_4	×														
Urine drug screening	×	×													
Alcohol breath test[i]	×	×													
Pregnancy test (FOCBP only)[j]	×	×												×	
Physical examination	×		×		×	×	×	×	×	×	×	×	×	×	

Table 1.3-1 Schedule of Assessments

	Screening Period	IMP Administration Period												
		Period 1 Baseline Examination	Period 1 (Administration of QW Formulation 48 mg in a Fasting or Fed State)											
Day (per treatment period)	From −42	−1	1				2		3	4	6	8	11	14
Hours predose/postdose	—	−24	−2	0	3	9	24	36	48	72	120	168	240	312
Vital signs (body temperature, pulse rate, blood pressure)[k]	×		×			×	×		×	×		×		×
Body weight	×	×										×		×
12-Lead ECG[k]	×	×[l]				×	×		×			×		×
DIEPSS		×							×			×		×
C-SSRS	×	×					×		×	×	×	×	×	×
CGI-S		×										×		×
CGI-I												×		×
Adverse events	←													
Concomitant medications/therapies	←													
Bowel-movement investigation[m]	←											→		← Washout[e]
Hospitalization period	Outpatient visits permitted	Hospitalization											Outpatient visits permitted	

Table 1.3-1 Schedule of Assessments

	IMP Administration Period														
	Period 2 Baseline Examination	Period 2 (Administration of QW Formulation 48 mg in a Fasting or Fed State)												Examination at Withdrawal[n]	Follow-up Examination
Day (per treatment period)	−1	1				2		3	4	6	8	11	14		28 days after last dose of IMP
Hours predose/postdose	−24	−2	0	3	9	24	36	48	72	120	168	240	312		
Informed consent[a]															
Informed consent for blood sampling for DNA storage (optional)															
Inclusion/exclusion criteria															
Demographic data (including height)															
Subject registration	×													×	×
Predosing[b]															
IMP administration			×[c]												
Blood sampling for CYP2D6 genetic testing[d]															
Blood sampling for DNA storage (optional)[f]															
Blood sampling for plasma drug concentration measurement		×		×	×	×	×	×	×	×	×	×	×	×	
Clinical lab tests[g]	×							×			×		×	×	
TSH, FT_4															
Urine drug screening	×														
Alcohol breath test[i]	×														
Pregnancy test (FOCBP only)[j]	×												×	×	
Physical examination		×		×	×	×	×	×	×	×	×	×	×	×	×
Vital signs (body temperature, pulse rate, blood pressure)[k]		×			×	×		×	×		×		×	×	
Body weight	×										×		×	×	
12-Lead ECG[k]	×				×	×		×			×		×	×	

Table 1.3-1 Schedule of Assessments

	IMP Administration Period														
	Period 2 Baseline Examination	**Period 2 (Administration of QW Formulation 48 mg in a Fasting or Fed State)**												**Examination at Withdrawal[n]**	**Follow-up Examination**
Day (per treatment period)	−1	1				2		3	4	6	8	11	14		28 days after last dose of IMP
Hours predose/postdose	−24	−2	0	3	9	24	36	48	72	120	168	240	312		
DIEPSS	×							×			×		×	×	×
C-SSRS	×					×		×	×	×	×	×	×	×	
CGI-S	×										×		×	×	
CGI-I											×		×	×	
Adverse events	———	———	———	———	———	———	———	———	———	———	———	———	———	———	——— ▶
Concomitant medications/therapies	———	———	———	———	———	———	———	———	———	———	———	———	———	———	——— ▶
Bowel-movement investigation[m]	———	———	———	———	———	———	———	———	———	———	——— ▶				
Hospitalization period	Hospitalization											Outpatient visits permitted			

[a]Before any trial-related tests or treatments, written informed consent will be obtained from subjects themselves (and from their legal representatives in the case of subjects who are hospitalized for reasons of medical protection) prior to the screening examination.

[b]Brexpiprazole-naive subjects will undergo and complete oral administration of brexpiprazole conventional tablet 1 mg (1 mg × 1 tablet) or OD tablet 1 mg (1 mg × 1 tablet or 0.5 mg × 2 tablets) for 2 consecutive days no later than 20 days prior to commencement of brexpiprazole QW formulation administration in Period 1.

[c]For fasting-state administration, IMP will be administered with approximately 150 mL of water following at least 10 hours of fasting. For administration in the fed state, following at least 10 hours of fasting, the subject will consume a high-fat meal within 20 minutes, after which IMP will be administered with approximately 150 mL of water within 10 minutes of finishing the meal. To the extent possible, the IMP will be administered at approximately the same time of day in both Period 1 and Period 2. [redacted] Administration of IMP should be performed at least 48 hours after symptoms of diarrhea have disappeared. For administration in the fed state in Period 1 or Period 2, if the high-fat meal cannot be eaten completely during the period specified in Section 5.3.1, the date of IMP administration may be postponed once only. The date of IMP administration in Period 1 can be adjusted within a period of 42 days from the start date of screening and, with the date of IMP administration in Period 1 counted as Day 1, the date of IMP administration in Period 2 can be adjusted between Day 30 and Day 36.

[d]Samples collected will be delivered to the central laboratory no later than 16 working days (excluding Saturdays, Sundays, and public holidays) before the scheduled date of administration of the IMP. Given that approximately 16 working days are required to obtain evaluation results, the schedule of IMP administration, etc, will be adjusted.

[e] [redacted]

[f] A blood sample should preferably be collected at the Period 1 baseline examination, but may be collected at any time during the trial. If repeat blood sampling is necessary, a blood sample will be collected at any feasible time during the trial.

[g] Clinical laboratory tests comprise hematology, blood chemistry, and urinalysis. Blood sampling should be performed after at least 8 hours of fasting, to the extent possible.

[h] It is not necessary to perform this examination if fasting blood sampling was performed at screening (after at least 8 hours of fasting) and IMP administration is started within 14 days after screening examination.

[i] Performed before any other examinations. If the test result is positive, then whether the trial can be continued without any problems will be determined, and only after a repeat alcohol breath test is negative will the other examinations be performed.

[j] If a urine test is positive, then a serum test will be performed.

[k] If performed on the same day as blood collection, performing vital sign measurement and 12-lead ECG immediately after blood collection should be avoided and they should be performed prior to blood collection if at all possible.

[l] It is not necessary to perform this examination if IMP administration is started within 14 days after screening examination.

[m] From Day −3 to Day 8 of Period 1 and Period 2, subjects will keep a record of the date and time of bowel movements (with multiple entries if there are multiple bowel movements) and the condition of the stool.

[n] Performed only when withdrawal occurs during the period from administration of the IMP to completion of the Day 14 examination in Period 1 and Period 2. If the subject refuses to undergo the examination at the time of withdrawal or if the investigator decides that the examination cannot be performed due to an emergency or for other reasons, only feasible observations and tests will be performed.

Table 1.3-2 Acceptable Windows	
Standard Examination Time Point	**Acceptable Windows for All Observations, Tests, and Assessments**
Predose	Blood sampling for plasma drug concentration measurement, physical examination, vital signs: within 2 hours predose Other: within 24 hours predose
3 hours postdose	±30 minutes
9 hours postdose	±30 minutes 12-lead ECG only: ±60 minutes
24, 36, 48, 72, and 120 hours postdose	±2 hours
168 hours postdose	±4 hours
240 and 312 hours postdose	±24 hours
Follow-up examination	+7 days at maximum

1.3.1 General Inpatient Procedures

Subjects will remain in either a seated or half-seated position for the first 4 hours following IMP administration except during brief periods where protocol-related procedures need to be performed. In addition, to prevent self-induced emesis resulting in loss of the oral dose, the subject's restroom visits must be supervised and should be brief (< 10 minutes). Following the 4-hour postdose period, the subjects will be allowed to ambulate, but should not exercise strenuously.

1.3.2 Schedule of Assessments

1.3.2.1 Screening Period

Prior to any trial-related procedures, the investigator will explain information on the procedure and characteristics of the trial to subjects, obtain their written informed consent (as well as the consent of their parent/legal guardian if subjects are hospitalized for reasons of medical protection), and record the following subject information in the source documents and electronic case report form (eCRF). Subjects from whom informed consent has been obtained will also be registered in the interactive web response system (IWRS).

- Date of informed consent
- Subject identifier (ID)
- Previous subject ID, if the subject was rescreened
- Date of informed consent for DNA storage (optional)*

*Informed consent will be obtained before blood sampling for DNA storage (optional).

After informed consent is obtained, the following observations, tests, and assessments will be performed as screening procedures, and will be recorded together with the date of

conduct in the source documents and eCRF. Subjects' eligibility to participate in the trial will be assessed. A screening examination will be performed within 42 days before IMP administration. The IMP does not necessarily have to be administered within 42 days after acquisition of informed consent.

[Items]

- Result of eligibility assessment
- Demographics (date of investigation, date of birth, sex at birth, possibility of pregnancy, race, ethnicity, country [Japan])
- Date of initial diagnosis of schizophrenia
- Complications (at the time of informed consent)
- Medical and surgical histories (within 2 years before informed consent; however, all histories relating to inclusion/exclusion criteria should be obtained)
- Height and body weight
- Urine drug screening
- Alcohol breath test (Performed before any other examinations. If the test result is positive, then whether the trial can be continued without any problems will be determined, and only after a repeat alcohol breath test is negative will the other examinations be performed.)
- Pregnancy test (Only for female subjects of childbearing potential. If a urine test is positive, then a serum test will be performed.)
- Clinical laboratory tests (including TSH and FT_4 only at screening)
- Blood sampling for CYP2D6 genetic testing (Samples collected will be delivered to the central laboratory no later than 16 working days [excluding Saturdays, Sundays, and public holidays] before the scheduled date of administration of the IMP. Given that approximately 16 working days are required to obtain evaluation results, the schedule of IMP administration, etc, will be adjusted.)
- Physical examination
- Vital signs (body temperature, pulse rate, and blood pressure) (If vital signs are measured on the same day as blood collection, measurement immediately after blood collection should be avoided and measurement should be carried out prior to blood collection if at all possible. Pulse rate and blood pressure will be measured in the supine position [performed first], sitting position, and standing position after each position is maintained for at least 3 minutes [blood pressure and pulse rate measurements in the supine and standing positions will take place only at screening].)
- 12-Lead ECG (If performed on the same day as blood collection, performing 12-lead ECG immediately after blood collection should be avoided and it should be performed prior to blood collection if at all possible.)
- C-SSRS
- AEs

- Concomitant medications/therapies (all prior medications/therapies administered from 30 days prior to informed consent)
- Administration status of predosing product

Brexpiprazole-naive subjects will undergo and complete oral administration of brexpiprazole conventional tablet 1 mg (1 mg × 1 tablet) or OD tablet 1 mg (1 mg × 1 tablet or 0.5 mg × 2 tablets) for 2 consecutive days no later than 20 days prior to commencement of brexpiprazole QW formulation administration in Period 1 to verify that they have no acute hypersensitivity to brexpiprazole.

1.3.2.2 IMP Administration Period: Period 1 Baseline Examination

The investigator will perform the observations, tests, and assessments indicated in Table 1.3-1, determine subject eligibility, and register subjects in IWRS. Subjects judged to be eligible will be randomized to either the fasting-state-administration-first group or the fed-state-administration-first group on the day before administration of the IMP (or on the day of IMP administration if preparation of the high-fat meal is completed in time) and will receive the IMP in either a fasting or fed state. [redacted] The date of IMP administration can be adjusted within a period of 42 days from the start date of screening, and administration of IMP should be performed at least 48 hours after symptoms of diarrhea have disappeared. If IMP administration is postponed, the observations, tests, and assessments for Day −1 and Day 1 shown in Table 1.3-1 will be repeated before administration of the IMP (although blood sampling for DNA storage does not need to be repeated). The starting date of hospitalization, the results of eligibility assessment, the date of randomization, the outcome of randomization (fasting-state-administration-first group or fed-state-administration-first group), and the results of observations, tests, and assessments will be recorded together with the date of conduct in the source documents and eCRF. From 3 days before IMP administration (Day −3) to 7 days after IMP administration (Day 8), subjects will keep a record of the date and time of bowel movements (with multiple entries if there are multiple bowel movements) and the condition of the stool. If IMP administration cannot be adjusted within a period of 42 days from the start date of screening and has to be discontinued, re-screening and re-randomization of the subject are possible. In such a case, the subject must once again provide written informed consent and be assigned a new subject ID prior to the screening examination.

1.3.2.3 IMP Administration Period: Period 1 Postdose

The investigator will perform the observations, tests, and assessments shown in Table 1.3-1 and will record them together with the date of conduct in the source documents and eCRF.

1.3.2.4 IMP Administration Period: Period 2 Baseline Examination

The investigator will perform the observations, tests, and assessments shown in Table 1.3-1, and will record them together with the date of conduct and the starting date of hospitalization in the source documents and eCRF. The investigator will also determine the appropriateness of transitioning to IMP administration in Period 2 and will register subjects in IWRS. If administration is performed in the fasting state in Period 1, then administration will be performed in the fed state in Period 2. If administration is performed in the fed state in Period 1, then administration will be performed in the fasting state in Period 2. [redacted] If IMP administration is postponed, the observations, tests, and assessments for Day −1 and Day 1 shown in Table 1.3-1 will be repeated before administration of the IMP. From 3 days before IMP administration (Day −3) to 7 days after IMP administration (Day 8), subjects will keep a record of the date and time of bowel movements (with multiple entries if there are multiple bowel movements) and the condition of the stool.

1.3.2.5 IMP Administration Period: Period 2 Postdose

The investigator will perform the observations, tests, and assessments shown in Table 1.3-1 and will record them together with the date of conduct in the source documents and eCRF.

1.3.2.6 Withdrawal

When withdrawal occurs during the period from administration of the IMP to completion of the Day 14 examination in Period 1 and Period 2, the investigator will perform the observations, tests, and assessments shown in Table 1.3-1 as soon as possible after a decision is made to withdraw the subject, ideally on the day of withdrawal, and will

record them together with the date of conduct in the source documents and eCRF. If the subject refuses to undergo the examination at the time of withdrawal or if the investigator decides that the examination cannot be performed due to an emergency or for other reasons, only feasible observations and tests will be performed. Subjects who withdraw during the period from administration of the IMP in Period 1 to completion of the Day 14 examination in Period 2 will be registered in IWRS.

1.3.2.7 Follow-up Examination

The investigator will perform the observations, tests, and assessments shown in Table 1.3-1 at 28 days (acceptable window: +7 days) after the date of the last dose of IMP and will record them together with the date of conduct in the source documents and eCRF, and will also record those subjects who completed the follow-up examination in the IWRS.

2 Introduction

Brexpiprazole is a chemical entity that works through a combination of partial agonist activity at dopamine D2 receptors and serotonin 1A ($5\text{-}HT_{1A}$) receptors and antagonist activity at serotonin 2A ($5\text{-}HT_{2A}$) receptors.[1] The brexpiprazole once-weekly (QW) formulation is a once-weekly oral formulation and is currently under development as a treatment for schizophrenia.

Please refer to the brexpiprazole (OPC-34712) Investigator's Brochure (IB) for more detailed information.

2.1 Trial Rationale

Brexpiprazole conventional tablets, a once-daily oral formulation, has demonstrated efficacy and safety in the treatment of schizophrenia in clinical trials in subjects with schizophrenia conducted in Japan, the US, and Europe and is approved in Japan and overseas as a treatment for schizophrenia. In the treatment of schizophrenia, maintenance of drug compliance is thought to be instrumental in alleviating symptoms and achieving favorable outcomes; however, in comparison with other chronic diseases, schizophrenia is generally associated with poor drug adherence due mainly to lack of consciousness of disease and cognitive impairment. Long-acting drugs have been introduced into clinical practice as a measure to improve patient adherence to medication, but currently the only commercially available long-acting antipsychotics are all injectable formulations, thus reflecting an unmet medical need for more easy-to-use long-acting antipsychotics. Otsuka is now developing a once-weekly (QW) formulation, utilizing the same less invasive

route of administration as conventional brexpiprazole, namely the oral route, but with a different formulation to enable reduced dosing frequency.

Otsuka has conducted clinical pharmacology trials to investigate the pharmacokinetics (PK), tolerability, and safety of the brexpiprazole QW formulation administered as single and multiple oral doses in Japanese patients with schizophrenia and confirmed the tolerability and safety of the drug. Based on the PK results, Otsuka has made dose selection and is currently conducting a phase 3 confirmatory trial to investigate the efficacy and safety of the brexpiprazole QW formulation in patients with acute schizophrenia.

According to "Clinical Pharmacokinetic Studies of Pharmaceuticals" (Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau [PMSB/ELD] Notification No. 796, dated 01 Jun 2001), "Drug Interaction Guidelines for Drug Development and Proper Informatics," (Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau [PSEHB/PED] Notification No. 0723-6, dated 23 Jul 2018), and "Guidelines for Design and Evaluation of Sustained-Release (Oral) Preparations" (Notification. No. 5 of the First Evaluation and Registration Division, PAB dated 11 Mar 1988), there is a requirement to investigate the effects of food on the final drug product, and therefore it was decided to evaluate food effects in this trial. Additionally, the design of this trial was made with reference to various guidance and guidelines,[2,3,4] and tests and endpoints are items that are commonly performed.

Based on the above, the conduct of the planned trial based on this protocol is judged to be scientifically and ethically appropriate.

2.2 Background

2.2.1 Treatment of Schizophrenia

Schizophrenia is a condition primarily characterized by positive symptoms such as hallucinations and delusions and negative symptoms such as apathy, lack of spontaneity, and social withdrawal, and is likely to have a chronic course. The prevalence of schizophrenia in the world is reported to be around 0.5%, though this percentage varies depending on the country.[5,6] In the acute phase characterized by hallucinations, delusions, and psychomotor agitation, impulsive behaviors and positive symptoms should be controlled, while in the maintenance phase, it is vital to prevent recurrence/relapse of symptoms, maintain the alleviated condition, and improve cognitive function or at least not impair cognitive function in the course of treatment. It is recommended that pharmacotherapy should be performed as the mainstay of treatment in the acute phase,

should be continued for at least 6 months in the recovery phase, in which patients are recovering from acute psychotic conditions,[7] and should be further continued for at least 1 year, and perhaps permanently, in the maintenance phase.[7,8] In either treatment phase, it has been noted that absence of medication is associated with the persistence of symptoms[9,10] and an increase in the incidence of relapse and risks of hospitalization and suicide.[11] Continuous treatment for an appropriate period is considered to contribute to the alleviation of symptoms as well as to good outcomes by preventing recurrence/relapse from occurring.[9] However, in comparison with other chronic diseases, schizophrenia is generally associated with poor drug adherence due mainly to lack of consciousness of disease and cognitive impairment on the part of patients.[7,8,9,12]

As a measure to improve patient adherence to medication, long-acting drugs have been introduced into clinical practice. However, it is known that long-acting drugs are associated with the risk of causing injection site reactions (pain, swelling, itching, and induration), which are adverse reactions not caused by oral medications, as well as the risk of exacerbating or prolonging symptoms even after treatment discontinuation due to adverse reactions, because long-acting drugs remain in the body for a prolonged period instead of being rapidly excreted after administration.[13] Some patients resist receiving injectable drugs out of fear of injection site reactions or injections themselves.[13] Under these circumstances, it may be considered that there is an expectation for the development of long-acting formulations that are easier to use and contribute to continuation of treatment.

2.2.2 Development History of Brexpiprazole

Brexpiprazole is a new chemical entity discovered by Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as “Otsuka”) that works through a combination of partial agonist activity at dopamine D2 receptors and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.[1]

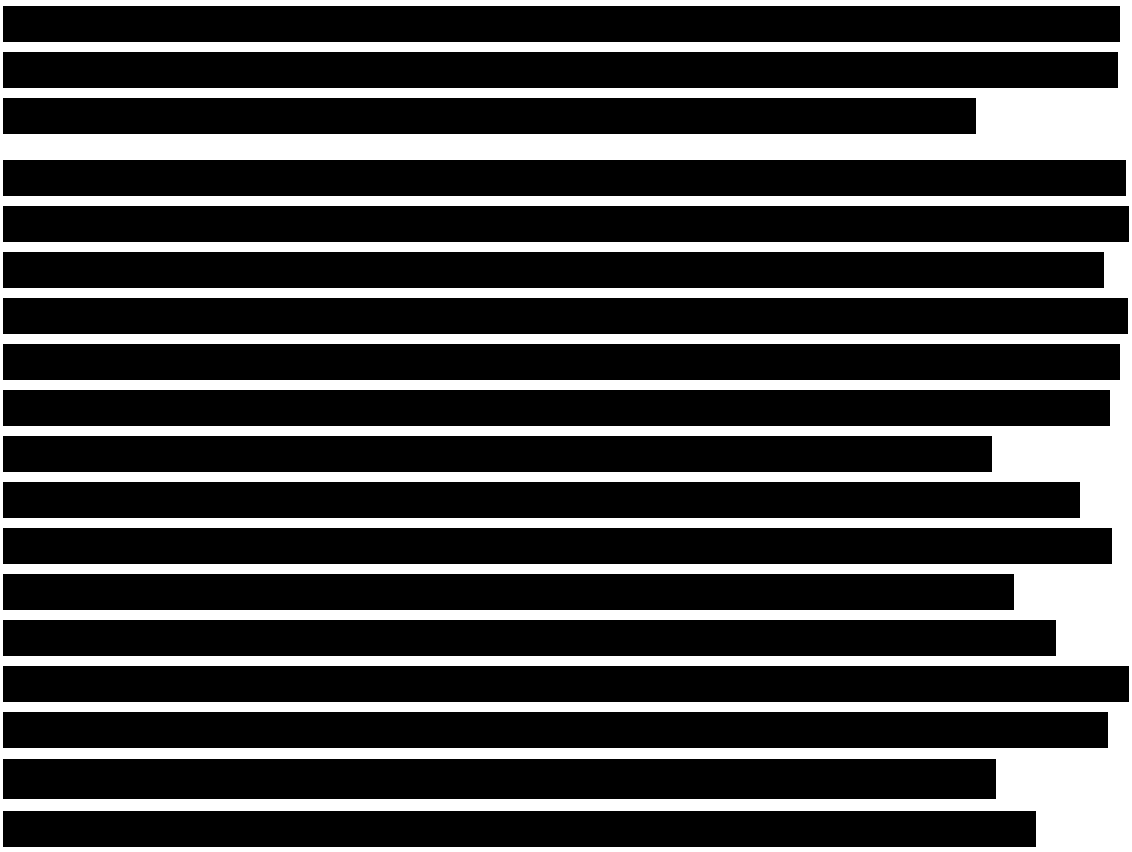
Brexpiprazole was studied in clinical trials in the United States (US) and Europe and was first granted marketing approval in the US in July 2015 as treatment for schizophrenia and an adjunctive therapy to antidepressants for the treatment of major depressive disorder. Further development of this drug for other psychiatric disorders is now ongoing in the US. Brexpiprazole was also proven to be effective and safe in clinical trials in Japanese patients with schizophrenia and was granted marketing approval in Japan in January 2018. The drug is currently undergoing further development for other psychiatric conditions.

The approved regimen for brexpiprazole in Japan and other countries is once-daily oral administration. As stated above, maintenance of drug compliance is considered instrumental in alleviating symptoms and achieving favorable outcomes in the treatment of schizophrenia, but currently the only commercially available long-acting antipsychotics are all injectable formulations. With the goal of improving the current status of pharmacotherapy for schizophrenia, Otsuka is developing an oral brexpiprazole once-weekly formulation (hereinafter referred to as “QW formulation”) that can reduce the dosing frequency with the same “less invasive” route of administration as the existing brexpiprazole.

Otsuka has conducted clinical pharmacology trials to investigate the pharmacokinetics (PK), tolerability, and safety of the brexpiprazole QW formulation administered as single and multiple oral doses in Japanese patients with schizophrenia, and has made dose selection based on the PK results and confirmed the tolerability and safety of the drug. Accordingly, the brexpiprazole QW formulation is currently undergoing further development.

The results of nonclinical and clinical studies related to this drug are summarized below.

2.2.2.1 Nonclinical Data

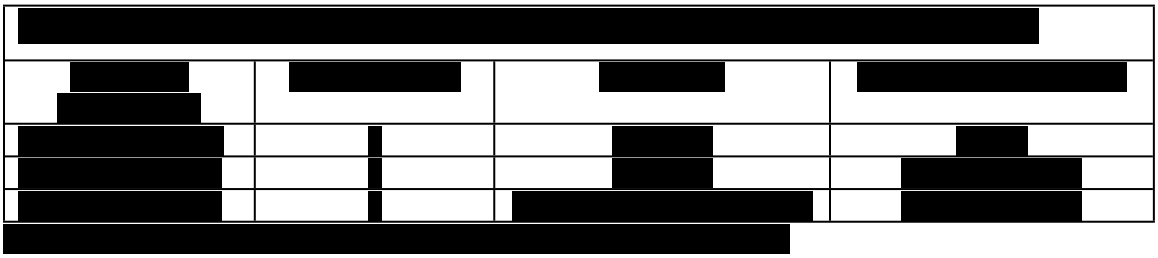


[redacted]

2.2.2.2 Clinical Data

Please refer to the brexpiprazole IB for further information.

[redacted]



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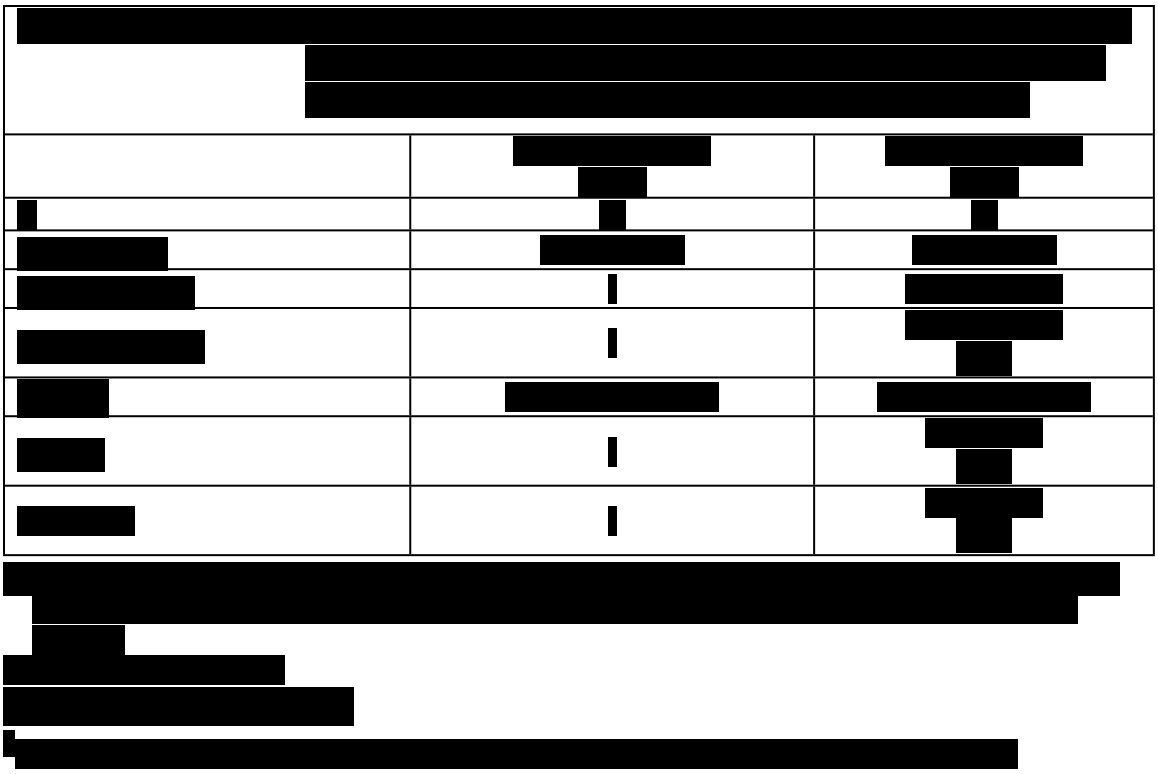
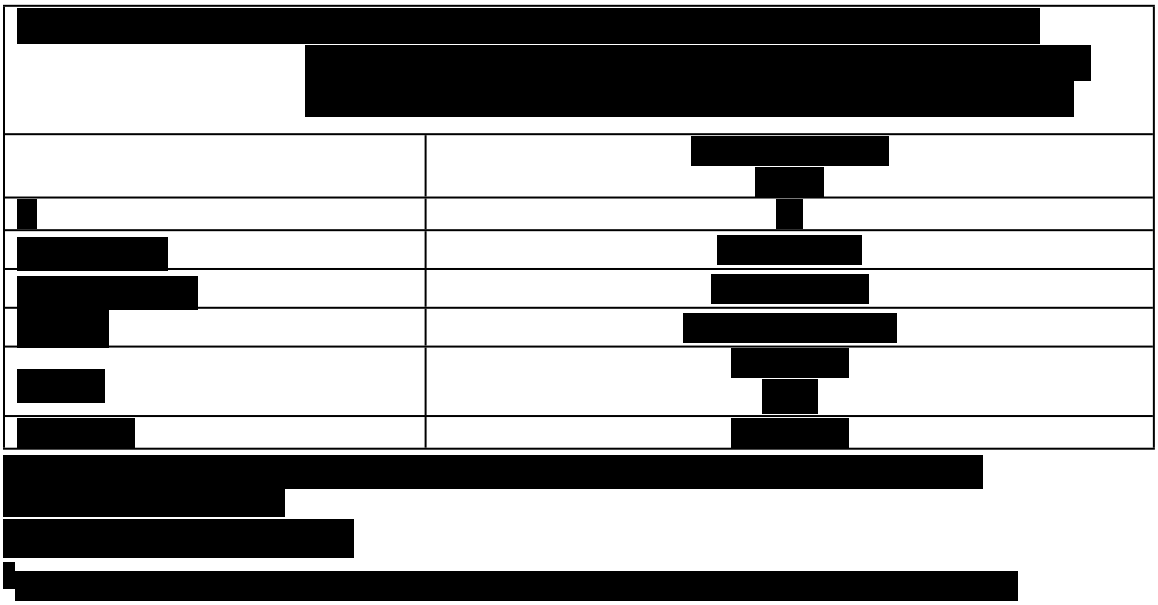
[redacted]





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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

2.3 Known and Potential Risks and Benefits

[redacted]

[redacted]

Since this trial is a clinical-pharmacology trial to investigate the effect of food on the PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia, no benefit to subjects is expected.

Further information on brexpiprazole and information regarding adverse reactions are presented in the IB. Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

To investigate the effect of food on the PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia and to confirm safety under those conditions.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary objective: To investigate the effect of food on PK of a single dose of brexpiprazole QW formulation at 48 mg in patients with schizophrenia	Primary pharmacokinetic endpoint: Geometric mean ratio and two-sided 90% confidence interval of C_{max}, AUC_{∞}, and AUC_t of brexpiprazole in plasma after administration in a fed state versus administration in a fasting state Secondary pharmacokinetic endpoints: • Plasma concentrations of brexpiprazole and metabolite [redacted] • Pharmacokinetic parameters of brexpiprazole and metabolite [redacted] in plasma

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Secondary objective: To confirm safety of the brexpiprazole QW formulation in patients with schizophrenia	Safety endpoints: • AEs • Clinical laboratory tests • Vital signs (body temperature, blood pressure, and pulse rate) • Physical examination findings • Body weight • BMI • 12-Lead ECG • DIEPSS • C-SSRS Other endpoints: • CGI-S • CGI-I • Bowel-movement investigation

BMI = body mass index; CGI-I = Clinical Global Impression - Global Improvement; CGI-S = Clinical Global Impression-Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; DIEPSS = Drug Induced Extrapyramidal Symptoms Scale.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

The trial design schematic is shown in Figure 1.2-1 and the schedule of assessments is shown in Table 1.3-1.

This is a multicenter, randomized, open-label, 2-arm, 2-period crossover trial to investigate the effects of food on the PK of brexpiprazole QW formulation in patients with a diagnosis of schizophrenia (295.90) based on DSM-5®. The trial consists of 2 periods, namely, the screening period and the IMP administration period (including washout period and follow-up period). The IMP administration period comprises Period 1 and Period 2 to investigate the effects of food on the PK of brexpiprazole QW formulation 48 mg, in which a single oral dose of brexpiprazole QW formulation will be administered at 48 mg in a fasting state or within 10 minutes of finishing a high-fat meal employing a 2-arm, 2-period crossover design. The sample size necessary for the trial assessment is a total of 36 subjects as trial completers.

4.2 Scientific Rationale for Trial Design

[redacted]

[redacted]

[redacted]

4.3 Dosing Rationale

4.3.1 Period 1 and Period 2

A single oral dose of brexpiprazole QW formulation at 48 mg will be administered with approximately 150 mL of water in a fasting state (following at least 10 hours of fasting) or within 10 minutes after the completion of a high-fat meal consumed over 20 minutes or less following at least 10 hours of fasting.

[Rationale]

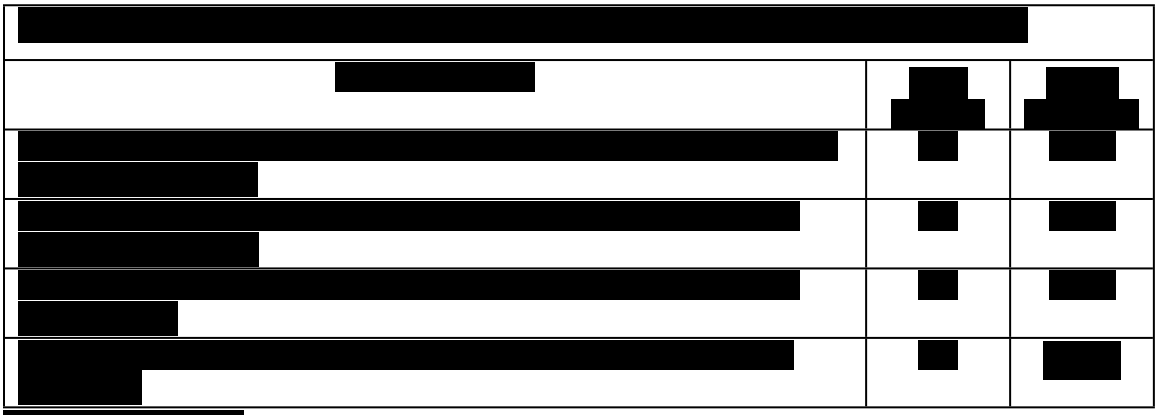
Dosing regimen is based on a commonly adopted dosing regimen for the evaluation of food effects with reference to the Guidelines for Bioequivalence Studies on Generic Drugs[3] and the FDA's guidance on food effect assessment.[2] A high-fat meal, which is considered to have more pronounced food effects, is the type of meal selected.

The dosing unit of the brexpiprazole QW formulation is a 24 mg tablet. With reference to the FDA's guidance on food effect assessment,[2] this trial will use 48 mg. This dose, which is assumed will be the clinically recommended dose of the brexpiprazole QW formulation and which is used in phase 3 trials, is the dose at which the PK of brexpiprazole is likely to be more susceptible to food effects than the 24 mg dose.

[redacted]

[redacted]

[redacted]



[redacted]

4.4 Start and End-of-Trial Definitions

The trial start is defined as the first visit of the first subject, which is the date the first subject signs their informed consent form (ICF). The end-of-trial date is defined as the last date of contact, or the date of final contact attempt as recorded on the post-treatment

follow-up electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For the purposes of this trial, subjects who complete Day 14 blood sampling for plasma drug concentration measurement in Period 2 will be defined as trial completers.

5 Trial Population

Patients at least 18 years of age and below the age of 65 with a diagnosis of schizophrenia based on the diagnostic criteria proposed in the DSM-5®

5.1 Subject Selection and Numbering

[redacted]

5.2 Eligibility Criteria

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

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the specified assessment time points:

1) Patients at least 18 years of age and below the age of 65 at the time of informed consent
2) Patients with a diagnosis of schizophrenia based on DSM-5® at the time of informed consent
3) Patients who are able to be hospitalized for the protocol-defined hospitalization period
4) Patients with a body mass index [BMI = body weight (kg)/height $(m)^2$] of 18.5 kg/m^2 or higher and lower than 35.0 kg/m^2 at screening

5) Patients who provide written informed consent before commencement of any trial-related procedures and whom the investigator judges to be capable of following all the conditions of this trial
6) Patients who, in the judgment of the investigator, have stable psychotic symptoms maintained by administration of an antipsychotic within the dosing range indicated below, before commencement of IMP administration

   [Upper limit of dose and regimen]

   - Antipsychotic medication comprising no more than 2 active components, and
   - A daily dose equivalent to ≤ 600 mg/day of chlorpromazine
     * If multiple antipsychotics are taken in the same day, this is to be the combined equivalent dose.
     However, this does not include administration of antipsychotic medication at doses equivalent to less than 100 mg/day of chlorpromazine, which are not expected to have any antipsychotic effect.
7) Patients who are able to finish the high-fat meal specified in this protocol within 20 minutes

[Rationale for Inclusion Criteria]

1) The age range is based on epidemiological data on the age of onset and prevalence of schizophrenia. An age of 18 years was set as the lower limit because individuals of this age can take responsibility for their own health and drug therapy as adults and are competent for informed consent. An age of less than 65 years was set as the upper limit so as to exclude the elderly for their safety and because they are more likely to suffer complications, which may have an effect on the safety evaluation. The upper limit of age is also based on the guideline, Studies in Support of Special Populations: Geriatrics (PAB/NDD Notification No. 104, dated 02 Dec 1993), in which the elderly are defined as individuals aged 65 years or older.
2) This criterion was set to identify patients with schizophrenia.
3) This criterion was set in consideration of the effects on PK assessment and subject safety.
4) This criterion was set to minimize interindividual PK variations due to obesity. Since this trial is conducted in patients, the upper limit for obesity or adiposity was set at BMI < 35.0 kg/m^2 based on the criteria proposed by the Japan Society for the Study of Obesity.
5) This criterion was set for ethical reasons.
6) This criterion was set in consideration of subject safety.
7) This criterion was set because this trial is designed to evaluate food effect on PK and meal conditions need to be uniform for appropriate assessment.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the specified assessment time points:

<Regarding medical history and complications>

1) Patients with a concurrent mental disorder besides schizophrenia who are judged by the investigator to be unsuitable for participation in the trial
2) Patients who have met the DSM-5® diagnostic criteria for substance-related or addictive disorder, including alcohol and benzodiazepines but excluding caffeine and tobacco, within 180 days before commencement of IMP administration
3) Patients with a positive drug test at screening

   However, patients who tested positive for a drug other than cocaine may be included if their condition is not diagnosed as any substance-related or addictive disorder, according to the DSM-5® diagnostic criteria.
4) Patients who fall under any of the following criteria regarding suicidal ideation and suicidal behavior
   - Patients who answered "yes" to Question 4 "Active Suicidal Ideation with Some Intent to Act, without Specific Plan" or Question 5 "Active Suicidal Ideation with Specific Plan and Intent" regarding C-SSRS suicidal ideation at screening (for the past 6 months) or at the Period 1 baseline examination (since the last assessment)
   - Patients who exhibited suicidal behavior on C-SSRS at screening (for the past 2 years) or at the Period 1 baseline examination (since the last assessment)
   - Patients who present a serious risk of suicide based on the judgment of the investigator
5) Patients who have previously undergone gastrointestinal surgery that could affect PK evaluation
6) Patients who have undergone major surgery or blood transfusion or who have made a blood donation (whole blood or blood plasma) within 30 days before the acquisition of informed consent
7) Patients who have a clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorder.

   Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not interfere with safety and PK assessments.
8) Patients with any of the following laboratory or ECG values at screening (according to the results from the central laboratory or the central ECG laboratory)

   Platelets: ≤ 75000/mm^3(/μL)　　Hemoglobin: ≤ 9 g/dL

Neutrophils, absolute: ≤ 1000/mm^3	Aspartate aminotransferase (AST): > 2 × upper limit of normal (ULN)
Alanine aminotransferase (ALT): > 2 × ULN	CPK: > 3 × ULN
Creatinine: ≥ 2 mg/dL	QT interval corrected for heart rate using Fridericia's formula (QTcF): > 450 milliseconds

9) Patients who fall under any of the following criteria at screening
   - Inadequately controlled hypertension (supine or sitting diastolic blood pressure of > 95 mmHg)
   - Symptomatic hypotension
   - Orthostatic hypotension, defined as a decrease of ≥ 30 mmHg in systolic blood pressure or a decrease of ≥ 20 mmHg in diastolic blood pressure after standing for at least 3 minutes compared with the supine values prior to standing
10) Patients meeting any of the following criteria
   - Patients with type 1 diabetes mellitus or patients with type 2 diabetes mellitus being treated with insulin
   - Patients with type 2 diabetes mellitus who have not been maintained on a stable regimen of anti-diabetic medication(s) or undergone diet/exercise therapy for at least 28 days prior to screening
   - Patients meeting either of the following criteria for poor blood glucose control at screening
     – Glycosylated hemoglobin (HbA1c) of ≥ 7.0% according to the global standard value
     – fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL
11) Patients with a complication of hypothyroidism or hyperthyroidism (except in cases where the condition has been kept stable for at least 90 days at the time of screening through drug therapy) or patients who show abnormal values for thyroid-stimulating hormone (TSH) and free thyroxin (FT_4) in at screening
12) Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (whether controlled or uncontrolled), or with a history of angioplasty, stenting, or coronary artery bypass surgery
13) Patients with a history or complication of epilepsy or seizures, except for childhood febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, etc
14) Patients with a history or a complication of neuroleptic malignant syndrome
15) Patients with a history or a complication of paralytic ileus
16) Patients with a history or a complication of water intoxication
17) Patients with a history or a complication of rhabdomyolysis

18) Patients with a history or a complication of pulmonary embolism

<Prohibited concomitant medications/therapies>

19) Patients who are using clozapine at the time of informed consent
20) Patients who fail to meet the specified requisite washout periods for the prohibited concomitant drugs and foods (see Section 5.3 and Section 6.5.1) before commencement of IMP administration, or patients who are anticipated to take any of the prohibited drugs or foods during the trial
21) Patients whose clinical symptoms have worsened to the point where use of prohibited concomitant therapy or medication is required during the washout period for prior medication

<Allergies or drug reactions>

22) Patients who have allergy or hypersensitivity to brexpiprazole conventional tablet, OD tablet, or brexpiprazole QW formulation, or patients for whom there are known safety concerns
23) Patients to whom brexpiprazole is contraindicated in the package insert
    - Patients with coma
    - Patients under marked influence of CNS depressants such as barbiturates or anesthetics
    - Patients receiving adrenaline
24) Patients with a history of allergy to more than one medication

<Pregnancy>

25) Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP
26) Sexually active males or females of childbearing potential (FOCBP), or their partners, who do not agree to practice 2 different approved methods of birth control or remain fully abstinent (periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods] or withdrawal are not acceptable methods of contraception) during the trial and for 28 days after the last dose of IMP. If employing birth control, 2 of the following approved methods must be used: [vasectomy, tubal ligation, intrauterine device, birth control pill, or condom (all of which are approved or certified in Japan)]. A definition of childbearing potential can be found in Section 10.3.

<Others>

27) Patients who are involuntarily hospitalized under the Mental Health and Welfare Law of Japan, or prisoners
28) [redacted]

[redacted]

29) Patients whose CYP2D6 phenotype is judged to be either PM or Unknown based on the results of CYP2D6 genetic testing at screening
30) Patients judged by the investigator to be unsuitable for participation in the trial
31) Patients with a history of unexplained loss of consciousness

[Rationale for Exclusion Criteria]

1) though 4), 7) through 19), 21) through 27), and 29): These criteria were set based on safety considerations.

5) This criterion was set to ensure appropriate PK assessment.

6), 20), 28), and 30): These criteria were set to ensure appropriate PK assessment and in consideration of safety.

31) This criterion is specified to exclude patients who, although they have not received a diagnosis such as ventricular tachycardia or ventricular fibrillation, nevertheless have the potential risk of sudden death.

Subjects must agree to the restrictions specified in Section 5.3 and Section 6.5.1.

5.3 Lifestyle Considerations

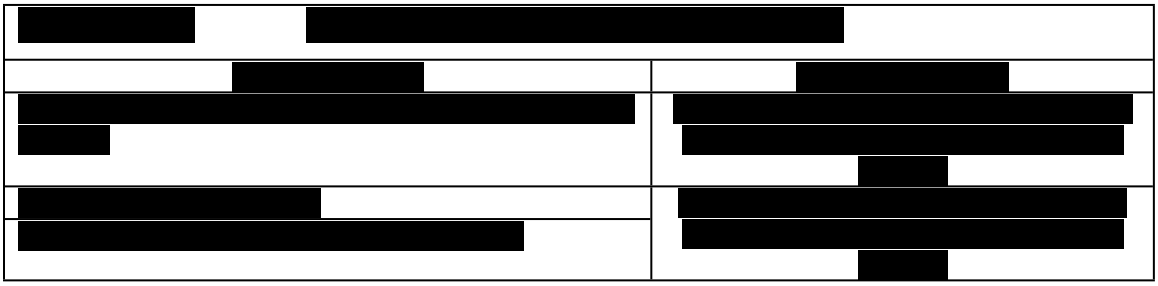
The following lifestyle considerations apply for the trial:

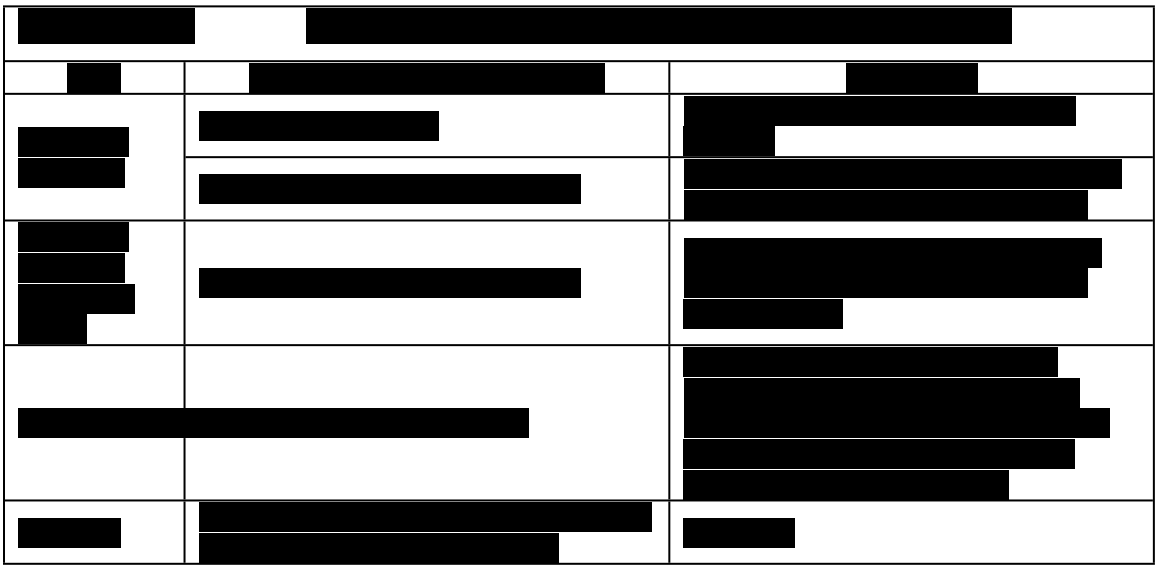
- Meals and diets
- Alcohol
- Activity

5.3.1 Meals and Dietary Restrictions

[redacted]

[redacted]





[redacted]

[redacted]

5.3.2 Alcohol

[redacted]

5.3.3 Activity

[redacted]

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not randomized. All AEs must be reported after subject informed consent has been obtained, including screening failures due to AEs, irrespective of administration of drugs used in the clinical trial.

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

- Date of informed consent
- Date of screening examination
- Demographics (date of investigation, date of birth, sex at birth, race, ethnicity, country [Japan])
- Result of eligibility assessment
- Administration status of predosing product
- Screen failure date
- Reason for screen failure
- AEs

Subjects excluded for positive drug/alcohol screen or for CYP2D6 PM or Unknown phenotype are not eligible to be rescreened. However, subjects excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. If a reexamination can be performed within the acceptable window of the screening period, it will not be necessary to obtain reconsent and only the tests relevant to changed characteristic will be performed. If a reexamination cannot be performed within the acceptable window of the screening period, new written consent must be obtained and a new subject ID assigned prior to screening examination.

6 Trial Treatments

6.1 Investigational Medicinal Product Administration and Predosing

The drugs used in the clinical trial are indicated below. Please refer to the most current version of the brexpiprazole IB for further information.

Drugs used in the clinical trial other than the IMP (predosing products): Brexpiprazole conventional tablet (1 mg) or OD tablet (0.5 mg or 1 mg)

IMP: brexpiprazole QW formulation 24 mg tablet

6.1.1 Predosing Product

The predosing method is indicated below.

Screening period

Only brexpiprazole-naive subjects will be administered the following to verify that they have no acute hypersensitivity to brexpiprazole. Regarding the status of predosing, whether or not predosing is performed, the type of brexpiprazole tablet (conventional

tablet or OD tablet), the start and end dates of predosing, and the dose per day (mg) will be recorded in the source documents and eCRF.

1) Predosing products: Brexpiprazole conventional tablet (1 mg) or OD tablet (0.5 mg or 1 mg)
2) Dose and regimen

   Brexpiprazole-naive subjects will undergo and complete oral administration of brexpiprazole conventional tablet 1 mg (1 mg × 1 tablet) or OD tablet 1 mg (1 mg × 1 tablet or 0.5 mg × 2 tablets) for 2 consecutive days no later than 20 days prior to commencement of brexpiprazole QW formulation administration in Period 1.

6.1.2 Investigational Medicinal Product

The IMP administration method is indicated below. Please refer to Section 4.1 for the administration method and treatment duration for each period and each treatment group. Regarding the status of trial treatment, the date and time of IMP administration and the dose (the number of tablets taken) will be recorded in the source documents and eCRF. The status of meal consumption will also be recorded in the source documents and eCRF (see Section 5.3.1).

1) IMP: brexpiprazole QW formulation 24 mg tablet
2) Dose and regimen

Period 1 and Period 2

Subjects who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be randomized at a 1:1 ratio to either the fasting-state-administration-first group or the fed-state-administration-first group on the day before administration of the IMP in Period 1 (or on the day of IMP administration if preparation of the high-fat meal is completed in time) and will receive the IMP in Period 1 and Period 2 as follows. To the extent possible, the IMP will be administered at approximately the same time of day in both Period 1 and Period 2. [redacted] For administration in the fed state in Period 1 or Period 2, if the high-fat meal cannot be eaten completely during the period specified in Section 5.3.1, the date of IMP administration may be postponed once only, after consultation with the subject.

1) Fasting-state-administration-first group

   In Period 1, a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately

150 mL of water following at least 10 hours of fasting. In Period 2, following at least 10 hours of fasting, the subject will consume a high-fat meal within 20 minutes, after which a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water within 10 minutes of finishing the meal.

2) Fed-state-administration-first group

In Period 1, following at least 10 hours of fasting, the subject will consume a high-fat meal within 20 minutes, after which a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water within 10 minutes of finishing the meal. In Period 2, a single oral dose of two 24 mg tablets of brexpiprazole QW formulation (48 mg as brexpiprazole) will be administered with approximately 150 mL of water following at least 10 hours of fasting.

6.1.3 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the brexpiprazole IB and separate manual. The predosing products (brexpiprazole conventional tablets 1 mg or OD tablets 0.5 mg or 1 mg) stored at the trial site will be used for predosing. They will not be provided by the sponsor for the purpose of predosing.

6.2.1 Packaging and Labeling

The IMP will be provided by the sponsor or designated agent to the IMP manager. [redacted]

6.2.2 Storage

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

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

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

6.2.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, and returned. The IMP manager may not provide IMP to any subject not participating in this trial.

The drugs used in the clinical trial other than the IMP that are not supplied by the sponsor and that are used from those stored at the trial site should be managed according to the site-specific procedures for handling, storage, and dispensing.

6.2.4 Returns and Destruction

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

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Medical Device or Medicinal Product or a falsified, tampered, or diverted product after it is released for distribution to a clinical trial.

Examples include, but are not limited to, communications involving:

- Failure/malfunction of a medicinal product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor’s designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or

designee must notify the sponsor or sponsor's designee of the information indicated in Section 6.2.5.2 by e-mail (address: [redacted]) immediately after becoming aware of any PQC.

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

6.2.5.2 Information Required for Reporting Product Quality Complaints

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

6.2.5.3 Return Process When Any Product Quality Complaint Is Received

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

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

6.2.5.4 Assessment/Evaluation

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

6.2.6 Investigational Medicinal Product Reserve Sample Requirements

Not applicable.

6.3 Measures to Minimize/Avoid Bias

Since the primary endpoint in this trial is based on plasma drug concentrations, bias does not arise from not implementing blinding.

This trial will be conducted in a randomized, open-label, 2-arm, 2-period crossover fashion. Subjects who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be randomized at a 1:1 ratio to either the fasting-state-administration-first group or the fed-state-administration-first group on the day before

administration of the IMP in Period 1 (or on the day of IMP administration if preparation of the high-fat meal is completed in time).

6.4 Subject Compliance

Subjects will be placed under the supervision of the investigator. The investigator will instruct subjects to:

1) Comply with the specified dose and regimen when taking the predosing product and IMP,
2) Adhere to the specified schedule during the trial,
3) Observe the lifestyle restrictions during the trial (see Section 5.3),
4) Cooperate in bowel-movement investigation from 3 days before IMP administration (Day −3) until 7 days postdose (Day 8) in Period 1 and Period 2,
5) Not take any prohibited concomitant medications (see Section 6.5.1),
6) Not receive any prohibited concomitant therapies (see Section 6.5.1), and
7) Not disclose any information obtained through participation in the trial to any third party.

For subjects who meet the criteria specified in Section 7, the required measures must be taken.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (prescription medications, over-the-counter medications, herbal remedies, etc) and therapies taken by the subject from 30 days prior to signing of informed consent through the last scheduled contact in the source documents and eCRF. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the source documents and eCRF.

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

6.5.1 Prohibited Concomitant Medications or Therapies

The use of the following medications is prohibited from the specified date and time through the last scheduled contact:

[redacted]

[redacted]

The use of the following medications is prohibited from the specified date and time until completion of Day 14 examination in Period 2 or withdrawal examination:

[redacted]

The use of the following non-drug therapy is prohibited from the day of informed consent until completion of Day 14 examination or withdrawal examination in Period 2:

[redacted]

6.5.2 Restricted Concomitant Medications or Therapies

The use of the following medications is restricted from the day of IMP administration in Period 1 until completion of Day 14 examination in Period 2 or withdrawal examination, except for prohibited concomitant medications:

- Antipsychotics other than brexpiprazole
  The use of other antipsychotics at a steady dose and regimen is permitted. The dose or frequency may be reduced at the discretion of the investigator in response to symptom improvement or maintenance or from a safety perspective. As-needed use is not allowed.
  The upper limit of dose and regimen of antipsychotics are as follows:
  - Antipsychotic medication comprising no more than 2 active components, and
  - A daily dose equivalent to ≤ 600 mg/day of chlorpromazine
    - If multiple antipsychotics are taken in the same day, this is to be the combined equivalent dose.
    - Chlorpromazine equivalent doses are based on Equivalent Conversion Table for Antipsychotics, as specified separately.

However, this does not include administration of antipsychotic medication at doses equivalent to less than 100 mg/day of chlorpromazine, which are not expected to have any antipsychotic effect.

- Antiparkinsonian drugs and valbenazine
  The use of these medications is permitted only when extrapyramidal symptoms are present and such use is necessary in the opinion of the investigator. The dose and regimen must comply with the instructions in the package insert, and dosing within 12 hours before Drug Induced Extrapyramidal Symptoms Scale (DIEPSS) assessment must be avoided. Prophylactic use is not allowed. Therefore, in subjects who are using antiparkinsonian drugs or valbenazine at the time of informed consent, even if they are without a history of extrapyramidal symptoms related to the concomitant medications, use of these medications must be suspended by the day of IMP administration.

  Before new use or dose increase of such medications, extrapyramidal symptoms will be assessed by DIEPSS.
- Beta-blockers
  The use of β-blockers will be permitted only for the treatment of nonpsychiatric complications (eg, cardiovascular disorders) and only if the dose and regimen remain unchanged from before participation in the trial.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention after the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

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

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC/EC if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The head of the trial site will notify the sponsor promptly if the investigator or the IRB/IEC/EC at the site discontinues participation in the trial.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

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

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may discontinue the IMP for the reasons listed below. Only one reason for discontinuation (the main reason) and the date of discontinuation will be recorded in the source documents and eCRF. Any AE related to treatment discontinuation must always be regarded as the reason for the discontinuation.

- Adverse event
  - Death
  - Continuing IMP places the subject at undue risk as determined by the investigator
    - Safety concern that is possibly, probably, or likely related to IMP
    - SAE
    - Exacerbation or progression of the underlying disease
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Subject vomits within 12 hours after IMP administration
  - Subject shows allergic reaction or hypersensitivity to brexpiprazole
  - Other potentially IMP-related safety concerns or AEs
- Occurrence of major protocol deviation
  - Failure to meet the inclusion/exclusion criteria (however, treatment discontinuation based on assessment of the results of clinical laboratory tests and central ECG assessment in Period 1 baseline examination is not considered a protocol deviation)
  - Randomized by mistake

  - Subject uses, or it is considered that the subject needs to use, any prohibited concomitant medication or therapy
  - Noncompliance with IMP administration
    - Failure to take the specified number of IMP tablets on the day of IMP administration
- Protocol-specific withdrawal criterion met
  - Prior to IMP administration in Period 1 and Period 2, the subject is unable to finish the prescribed high-fat meal within 30 minutes after starting to eat and also fails to complete IMP administration after finishing eating within 30 minutes after starting to eat (however, the date of IMP administration may be postponed once only, after consultation with the subject)
  - Subjects with a positive drug screen for cocaine, or subjects with a positive drug screen for any other drug who are dependent on the drug or are unlikely to overcome their drug dependency in the opinion of the investigator
  - Subjects with a positive alcohol breath test who are dependent on alcohol or are unlikely to overcome their alcohol dependency in the opinion of the investigator
- Lost to follow-up
- Investigator's decision (other than AE)
- Pregnancy (see Section 10.3)
- Trial site terminated by sponsor
- Trial terminated by sponsor
- Request by the subject's parent/legal guardian to discontinue treatment (including consent withdrawal by the subject's parent/legal guardian)
- Request by the subject to discontinue treatment (including consent withdrawal by the subject)
- Other

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

7.3.4 Withdrawal of Consent or Assent

Each subject has the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely

withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

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

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

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

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

7.3.5 Procedures to Encourage Continued Trial Participation

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

understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Definition of Subjects Lost to Follow-up

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

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

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

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Table 1.3-1.

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

Blood samples for plasma drug concentration measurement will be collected at the time points described in the schedule of assessments (Table 1.3-1).

8.2.1 Pharmacokinetic Plasma Samples

1) Time Points for Blood Sampling

Blood samples for drug concentration measurement will be collected at the time points described in the schedule of assessments (Table 1.3-1). The acceptable window for blood sampling time points should follow Table 1.3-2. Whether or not a blood

sample is collected and the date and time of blood sampling will be recorded in the source documents and the eCRF.

2) Blood Sampling and Measurement Methods

Blood samples (2 mL) will be collected in vacutainers containing heparin and processed into plasma to determine the concentrations of brexpiprazole and metabolite [redacted] by validated high performance liquid chromatography-tandem mass spectrometry. Metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, blood samples for drug concentration measurement may be used for the investigation of a bioanalytical method, if needed.

All plasma samples will be shipped to the bioanalytical laboratory. The bioanalytical laboratory will submit an electronic file containing the final data to the sponsor. Therefore, there is no need to record the results of measurements in the source documents and the eCRF.

Details of the sample collection, handling, and shipping methods are provided in separately prepared procedures.

3) Rationale for Time Points for Blood Sampling

[redacted]

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Cytochrome P450 2D6 genetic testing is mandatory.

[Rationale for pharmacogenomic assessment]

Cytochrome P450 3A4 and CYP2D6 are involved in the metabolism of brexpiprazole, and CYP2D6 is known to have multiple genotypes with different enzyme activities.

Therefore, in this trial it has been decided to investigate CYP2D6 genotypes which are involved in the PK variability of brexpiprazole. Cytochrome P450 2D6 genetic testing will be performed as part of screening to exclude from the trial subjects with reduced or unknown CYP2D6 activity (see Section 4.3.1).

8.4.1 Pharmacogenomic Samples

Blood samples for CYP2D6 genetic testing will be collected at the time points described in the schedule of assessments (Table 1.3-1). Whether or not sample collection is performed and the date of blood sampling will be recorded in the source documents and the eCRF.

Blood samples (2 mL) will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA will be extracted from a whole blood sample and used to determine genotypes and related phenotypes for CYP2D6. The method used to determine these genotypes may also generate genotype data for additional genes related to absorption, distribution, metabolism, and excretion. Phenotyping of these additional genes is not currently planned but may be considered in the future. If so, the phenotyping data may be included in a PK analysis to be reported separately.

All pharmacogenomic (PGx) samples will be shipped to the PGx laboratory. The PGx laboratory will perform PGx analyses and submit the results of phenotype determination to the sponsor and investigator. After dating and signing the clinical laboratory test report, the investigator will record the results of phenotype determination in the source documents and eCRF. The analysis results will be disclosed to subjects by the investigator only at their request.

The PGx laboratory will submit an electronic file containing the final data to the sponsor.

Details of the sample collection, handling, and shipping methods are provided in separately prepared procedures.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

[redacted].

[redacted]

[redacted]

[redacted]

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8. Each safety assessment will be performed at the time points described in the schedule of assessments (Table 1.3-1).

8.7.1 Clinical Laboratory Assessments

8.7.1.1 Hematology, Blood chemistry, Urinalysis, and Thyroid Function Test

Clinical laboratory samples will be collected to perform the clinical laboratory assessments described in Section 10.2. The total volume of blood to be collected during the trial will be documented in the ICF.

Refer to Section 8.7.6 for urine drug screening and alcohol breath test.

1) Timing

Refer to Table 1.3-1.

Blood sampling should be performed after at least 8 hours of fasting, to the extent possible.

2) Test Items

Refer to Section 10.2.

3) Methods

Clinical laboratory tests for the items listed in the table in Section 10.2 will be performed at specified time points using test kits supplied by the central laboratory. The central laboratory will analyze the samples and report the analysis results as needed to the investigator for review. The investigator will then date and sign the clinical laboratory test report to make it an official document. Whether or not blood and urine samples are collected, the date and time of blood sampling and the date and time of urine sampling, and whether or not the subject has fasted for at least 8 hours will be recorded in the source documents and the eCRF. As the results of clinical laboratory tests are reported directly from the central laboratory to the sponsor as an electronic file, they do not need to be recorded in the source documents or the eCRF. For the procedures for the collection, handling, and shipment of samples, the separately prepared procedures should be followed.

8.7.1.2 Pregnancy Test (For Females of Child-bearing Potential)

1) Timing

Refer to Table 1.3-1.

2) Test Items

Pregnancy test (human chorionic gonadotropin [hCG] in urine)

3) Methods

A urine pregnancy test will be performed at the specified time points on FOCBPs (all women excluding sterile and postmenopausal women). If a urine test is positive, then a serum test will be performed. Whether or not a urine sample is collected for urine pregnancy test, the date and time of urine sampling and the test result, and if a serum pregnancy test is performed, whether or not a blood sample is collected and the date and time of blood sampling will be recorded in the source documents and the eCRF. A serum pregnancy test will be performed by the central laboratory selected by the sponsor. For the correct procedures for the collection, handling, and shipment of samples, separate procedures will be prepared and provided prior to the start of the

trial. The central laboratory will report the results of tests to the investigator, who will review the results of tests and date and sign the clinical laboratory test report to make it an official document. As the results of serum tests will be reported directly from the central laboratory to the sponsor as an electronic file, they do not need to be recorded in the source documents or the eCRF.

For FOCBPs, a pregnancy test will be performed before initiation of any trial procedure and the test result must be obtained before the first dose of IMP.

A sterile woman is defined as a woman who successfully underwent a reproductive sterilization procedure (hysterectomy and bilateral ovariectomy). A postmenopausal woman is defined as a woman who has been amenorrheic for at least 12 months without any medical cause.

8.7.2 Physical Examination

1) Timing

Refer to Table 1.3-1.

2) Test Items

Head, eye, ear, nose, and throat, chest, abdomen, limb, nerves, and skin mucosa

3) Methods

The investigator will perform a physical examination of the subject and record findings in the source documents. At screening, whether or not examination is performed and the date, time, and results of examination will be recorded in the eCRF. Thereafter, whether or not examination is performed and the date and time of examination will be recorded in the eCRF. As far as possible, the same assessor will perform assessment of the same subject throughout the trial period.

8.7.3 Vital Signs

Subjects should be monitored for potentially clinically significant vital signs values.

1) Timing

Refer to Table 1.3-1.

Measurement immediately after blood collection should be avoided (measurement prior to blood collection if at all possible)

2) Test Items

Body temperature, systolic and diastolic blood pressure (in supine, sitting, and standing positions), and pulse rate (in supine, sitting, and standing positions)

3) Methods

Body temperature will be measured in increments of 0.1°C, and whether or not measurement is performed, the date and time of measurement, and the measurement results will be recorded in the source documents and eCRF.

Blood pressure and pulse rate measurement at screening will be performed in the supine position followed by the sitting and standing positions. Measurement in each position will be performed after that position has been maintained for at least 3 minutes and whether or not measurement is performed, posture at measurement, the date and time of measurement, and the measurement results will be recorded in the source documents and eCRF. At time points other than screening, vital signs will be measured only in the sitting position after that position has been maintained for at least 3 minutes, and whether or not vital signs are measured, posture at measurement, the date and time of measurement, and the measurement results will be recorded in the source documents and the eCRF. In the event that the subject complains of symptoms suggestive of orthostatic hypotension before assessment at any time point after the Period 1 baseline examination, vital signs will also be measured in the supine and standing positions, in the order of supine, sitting, and standing positions, as done at screening, wherever possible.

8.7.4 Electrocardiogram

Subjects should be monitored for potentially clinically significant ECG results.

1) Timing

Refer to Table 1.3-1.

Measurement immediately after blood collection should be avoided (measurement prior to blood collection if at all possible)

2) Methods

ECG will be recorded with the subject in a supine position and having been at rest for at least 5 minutes. The 12-lead electrocardiograph provided by the central ECG laboratory will be used to record ECGs. Measurement results for heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval (QTcF) will be analyzed at the central ECG laboratory. The investigator will confirm the results of analysis reported by the central ECG laboratory and date and sign the analysis result report to make it an official document. The investigator will make a judgment by referring to the analysis result report sent from the central ECG laboratory and record whether or not measurement is performed and the date and time of measurement,

normal/abnormal judgment, and any abnormal findings in the source documents and eCRF.

ECG results for this trial will be analyzed at the central ECG laboratory. As the results of analysis are reported directly from the central ECG laboratory to the sponsor as an electronic file, they do not need to be recorded in the source documents or the eCRF.

8.7.5 Columbia-Suicide Severity Rating Scale

1) Timing

Refer to Table 1.3-1.

2) Methods

The investigator or designated person will perform the C-SSRS assessment at the scheduled time points. The C-SSRS assesses the occurrence, severity, and frequency of suicidal ideation/behavior during the assessment period. This assessment consists of the "Baseline/Screening Version," which assesses the history of suicide-related events and suicidal ideation in the lifetime and within the last 24 months, and the "Since Last Visit Version," which focuses on suicidality since the last assessment in the trial. The "Baseline/Screening Version" will be used at screening and the "Since Last Visit" will be used at subsequent time points for C-SSRS assessment. Whether or not assessment is performed and the date and time of assessment, and the assessment results will be recorded in the source documents and the eCRF. As far as possible, the same assessor will perform assessment of the same subject throughout the trial period.

The presence of suicidal ideation 1 to 2 will be assessed with "yes" or "no," and if the answer to 2 is "yes," suicidal ideation 3 to 5 will be assessed. If the answer to suicidal ideation 1 or 2 is "yes," the intensity of ideation will also be rated. Intensity of ideation will be rated on a 5-point scale for frequency and duration and a 6-point scale for controllability, deterrents, and reasons for ideation.

The following suicidal behavior will also be assessed with "yes" or "no," and if the answer is "yes," details will be assessed, and the total numbers of each suicide attempt will be recorded.

If there is an actual attempt, actual lethality/physical damage will be rated on a 6-point scale, and if actual lethality/physical damage is 0, potential lethality will be rated on a 3-point scale.

Suicidal ideation:

1. Wish to be dead

2. Non-specific active suicidal thoughts

3. Active suicidal ideation with any methods (not plan) without intent to act

4. Active suicidal ideation with some intent to act, without specific plan

5. Active suicidal ideation with specific plan and intent

Suicidal behavior:

Actual attempt, non-suicidal self-injurious behavior, interrupted attempt

Aborted attempt, preparatory acts or behavior, suicidal behavior, suicide (only for "Since Last Visit Version")

8.7.6 Other Safety Variables

8.7.6.1 Body Weight

1) Timing

Refer to Table 1.3-1.

Before eating if at all possible, and preferably at approximately the same time of day each time.

2) Methods

Body weight should be measured using the same scales and the standard measurement method (the subject should wear his/her usual clothes but without shoes) throughout the course of the trial. Weight will be measured in 0.1 kg increments. For a weight measured to the second or further decimal place, the number will be rounded off to the first decimal place. Whether or not measurement is performed and the date and time of measurement, and the measurement results will be recorded in the source documents and the eCRF.

8.7.6.2 Drug-Induced Extrapyramidal Symptoms Scale

1) Timing

Refer to Table 1.3-1.

2) Methods

The investigator will use DIEPSS to assess the following 9 items related to extrapyramidal symptoms on a 5-point scale (0: none, normal, 1: minimal, questionable, 2: mild, 3: moderate, 4: severe). Whether or not assessment is performed and the date and time of assessment, and the assessment results will be

recorded in the source documents and the eCRF. As far as possible, the same assessor will perform assessment of the same subject throughout the trial period.

1. Gait	2. Bradykinesia	3. Sialorrhea	4. Muscle rigidity	5. Tremor
6. Akathisia	7. Dystonia	8. Dyskinesia	9. Overall severity	

8.7.6.3 Alcohol Breath Test

1) Timing

Refer to Table 1.3-1.

An alcohol breath test will be performed before any other examinations scheduled for the visit. If the test result is positive, then whether the trial can be continued without any problems will be determined, and only after a repeat alcohol breath test is negative will the other examinations be performed.

2) Methods

An alcohol breath test will be performed using a device provided by the sponsor. Whether or not examination is performed, the date and time of assessment, and assessment result will be recorded in the source documents and the eCRF.

If the test result is positive, then whether the trial can be continued without any problems will be determined, and only after a repeat alcohol breath test is negative will the other examinations be performed. For subjects with a positive alcohol breath test who are dependent on alcohol or are unlikely to overcome their alcohol dependency in the opinion of the investigator, trial treatment will be discontinued.

8.7.6.4 Urine Drug Screening

1) Timing

Refer to Table 1.3-1.

2) Methods

Drug screening data for the following items will be collected using the test kits provided by the central laboratory. Whether or not urine sampling is performed, the date and time of urine sampling, and result of assessment will be recorded in the source documents and the eCRF. For subjects with a positive drug screen for cocaine, or subjects with a positive drug screen for any other drug who are dependent on the drug or are unlikely to overcome their drug dependency in the opinion of the investigator, trial treatment will be discontinued.

- Amphetamines
- Barbiturates
- Benzodiazepines

- Cannabinoids
- Cocaine
- Marijuana
- Opiates
- Phencyclidine

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a drug used in the clinical trial and which does not necessarily have a causal relationship with this treatment. In this trial, any untoward medical occurrence in a subject not administered a drug used in the clinical trial is also deemed as an AE. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to a drug used in the clinical trial, related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug used in the clinical trial caused the AE.

There are adverse reactions to drugs used in the clinical trial specified in the GCP and adverse reactions to the IMP as an endpoint in this trial. This section describes the definition of the former.

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

For the purposes of this trial, AEs in the screening period will be assessed by comparing against the subject's condition at the time of informed consent, AEs in Period 1 will be assessed by comparing against the subject's condition at the start of IMP administration in Period 1, and AEs in Period 2 will be assessed by comparing against the subject's condition at the start of IMP administration in Period 2.

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

- Death

- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported. Note that hospitalization is an outcome of some event, and, therefore, the reason for the hospitalization should be reported whenever possible. In the event the reason is not known, the event of hospitalization should still be reported as an SAE.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs). No AESIs have been identified for the IMP to be administered during this trial.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure (eg, an investigator getting a skin rash after exposure to a medication). Non-subject AEs would not be recorded on the eCRF form but must be reported on an IRE form, etc, and submitted to the sponsor.
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the subject or the partner of the subject. Pregnancy will only be documented on the

AE eCRF if the pregnancy occurs in a female subject and there is an abnormality or complication (see Section 10.3).

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

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

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

Causality to IMP or other drugs used in the clinical trial: Assessment of causal relationship of an AE to the use of the IMP or other drugs used in the clinical trial is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP or other drugs used in the clinical trial and the AE.

Not Related: There is no temporal or causal relationship between the IMP or other drugs used in the clinical trial and the AE.

8.8.2 Eliciting and Reporting Adverse Events

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

including screening failures due to AEs, irrespective of administration of drugs used in the clinical trial.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Medical or surgical procedures (eg, endoscopy, appendectomy) should not be reported as AEs; however, the condition that led to the procedure may be reported as an AE.

If a reported AE worsens in its severity or seriousness, it should be reported as a new AE in the source documents and eCRF.

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

The AE, start date and time, end date (end date and time for diarrhea, vomiting, and constipation), seriousness, severity, relationship to trial treatment (causality), action taken with trial treatment, and outcome will be recorded in the source documents and the eCRF. Causality and measures taken regarding drug administration will be assessed and recorded for all drugs used in the clinical trial. When SAEs are reported using an IRE form, etc, causality and action taken regarding drug administration will be assessed for drugs used in the clinical trial other than the IMP as done for the IMP and will be recorded in the source documents.

For subjects who are suspected to have COVID-19 during the trial, the investigator will check their antigen test results and take appropriate measures (eg, trial discontinuation) as necessary in consideration of their safety. If a positive COVID-19 test is confirmed, this will be reported as an AE in the source documents and eCRF.

8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, etc, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy), by e-mail in principle to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any

other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.8.2.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

8.8.6 Potential Serious Hepatotoxicity

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

8.8.7 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.8.8 Follow-up of Adverse Events

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the source documents and AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the source documents and eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs until the last scheduled contact.

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

trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

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

- the events are resolved,
- the events have stabilized,
- the subject is lost to follow-up, or
- the subject has died.

Resolution means that the subject has returned to the state of health observed at the start of IMP administration and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

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

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

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

8.9 Treatment of Overdose

For treatment of overdoses, please refer to the IB section for overdose.

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

8.11.1 Height

1) Timing

Refer to Table 1.3-1.

2) Methods

Height will be measured in increments of 0.1 cm by the standard measurement method (the subject should wear his/her usual clothes but without shoes). For a height measured to the second or further decimal place, the number will be rounded off to the first decimal place. Whether or not measurement is performed and the date and results of measurements will be recorded in the source documents and the eCRF.

8.11.2 Clinical Global Impression - Severity of Illness

1) Timing

Refer to Table 1.3-1.

2) Methods

The investigator will assess the severity of schizophrenia on the following 8-point scale using the Clinical Global Impression-Severity of Illness (CGI-S). Whether or not assessment is performed and the date and time of assessment, and the assessment results will be recorded in the source documents and the eCRF.

0. Not assessed 1. Normal, not ill at all 2. Borderline mentally ill 3. Mildly ill
4. Moderately ill 5. Markedly ill 6. Severely ill
7. Among the most extremely ill patients

8.11.3 Clinical Global Impression - Global Improvement

1) Timing

Refer to Table 1.3-1.

2) Methods

The investigator will assess the improvement of schizophrenia on the following 8-point scale using the Clinical Global Impression - Global Improvement (CGI-I). Within each period, improvement will be assessed by comparing the subject's condition after IMP administration or at withdrawal with that at the start of that period. Whether or not assessment is performed and the date and time of assessment, and the assessment results will be recorded in the source documents and the eCRF.

0. Not assessed 1. Very much improved 2. Much improved
3. Minimally improved 4. No change 5. Minimally worse
6. Much worse 7. Very much worse

8.11.4 Bowel-movement Investigation

1) Timing

Refer to Table 1.3-1.

2) Methods

From Day −3 through Day 8 of Period 1 and Period 2, subjects will keep a record of the date and time of bowel movements (with multiple entries if there are multiple bowel movements) and the condition of the stool (hard, normal, soft, muddy to watery). With the subject's records used as the source documents, the date and time of bowel movement and the condition of the stool will be recorded in the eCRF.

9 Statistical Considerations

9.1 Sample Size

[redacted]

[redacted]

9.2 Datasets for Analysis

9.2.1 Food Effect Analysis Set

The food effect analysis set includes all subjects for whom C_{max}, AUC_{∞} or AUC_t could be calculated throughout Period 1 and Period 2.

9.2.2 Safety Analysis Set

The safety analysis set includes all subjects who were administered at least one dose of IMP.

9.3 Handling of Missing Data for Primary Endpoint Analysis

No imputation procedures will be applied for missing data.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Not applicable.

9.4.2 Safety Analysis

The safety analysis set will be used for analysis by meal condition. The baseline value will be the last measurement prior to IMP administration in each period.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized. A TEAE in each period is defined as a TEAE that occurs after IMP administration in each period up to before IMP administration in the next period (if the IMP is to be administered in the next period).

- TEAEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs

Similarly, IMP-related TEAEs will also be summarized.

9.4.2.2 Clinical Laboratory Data

For each quantitative laboratory parameter, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated.

For each quantitative laboratory parameter, measured values will be classified as “lower than the lower limit of the reference range,” “within the reference range,” and “higher than the upper limit of the reference range” using the reference ranges specified by the central laboratory, and a shift table from baseline will be produced. For each qualitative laboratory parameter, a shift table from baseline will be produced.

The number and proportion of subjects in whom any measurement after IMP administration in each period up to before IMP administration in the next period (if the IMP is to be administered in the next period) meets the criteria for potentially clinically significant laboratory test values will be determined.

9.4.2.3 Physical Examination and Vital Signs

Listings of physical examination findings will be provided.

For each vital sign parameter, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated.

The number and proportion of subjects in whom any measurement after IMP administration in each period up to before IMP administration in the next period (if the IMP is to be administered in the next period) meets the criteria for potentially clinically significant vital signs will be determined.

9.4.2.4 Electrocardiogram Data

For each ECG parameter, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated.

A shift table from baseline for normal/abnormal judgment on ECG in each period will be produced.

The numbers and proportions of subjects with actual measurements of QTcF interval of > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds after IMP administration in each period up to before IMP administration in the next period (if the IMP is to be administered in the next period) will be determined. The numbers and proportions of subjects with changes from baseline of > 30 milliseconds and > 60 milliseconds will be determined.

The number and proportion of subjects in whom any measurement after IMP administration in each period up to before IMP administration in the next period (if the

IMP is to be administered in the next period) meets the criteria for potentially clinically significant ECG values will be determined.

9.4.2.5 Columbia-Suicide Severity Rating Scale

The number and proportion of subjects with each C-SSRS item (suicidality, suicidal ideation, suicidal behavior, completed suicide, emergence of suicidal ideation, emergence of serious suicidal ideation, worsening of suicidal ideation, and emergence of suicidal behavior) at each time point will be determined.

9.4.2.6 Other Safety Data

9.4.2.6.1 Body Weight and Body Mass Index

For body weight and BMI, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated.

The number and proportion of subjects in whom any measurement after IMP administration in each period up to before IMP administration in the next period (if the IMP is to be administered in the next period) meets the criteria for potentially clinically significant body weight will be determined.

9.4.2.6.2 Drug Induced Extrapyramidal Symptoms Scale

For the DIEPSS total score (total of scores for items 1 through 8) and a score for each DIEPSS item, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics or the frequency distribution of demographic and other baseline characteristics will be determined overall and for each group in each analysis set.

9.4.3.2 Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated in subjects who received at least one dose of the brexpiprazole QW formulation and had at least one plasma drug concentration measurement. The analyses described in Section 9.4.3.2.1 2) and Section 9.4.3.2.2 2) will be performed on the food effect analysis set.

9.4.3.2.1 Analysis of Primary Efficacy Endpoint

1) Endpoint

Geometric mean ratio and two-sided 90% confidence interval of C_{max}, AUC_{∞}, and AUC_t of brexpiprazole in plasma after administration in a fed state versus administration in a fasting state

2) Statistical Methods

The natural log-transformed C_{max}, AUC_{∞}, and AUC_t of brexpiprazole in plasma will be analyzed using a linear mixed-effects model with group (fasting-state-administration-first group or fed-state-administration-first group), meal condition (fasting or fed), and period (Period 1, Period 2) as fixed effects, and within-group subjects as a random effect, and the differences in means of natural log-transformed values between meal conditions (fed-state administration − fasting-state administration) and their two-sided 90% confidence intervals will be calculated. The differences in the mean natural log-transformed values (fed-state administration − fasting-state administration) and their two-sided 90% confidence intervals will be inverse-transformed to calculate the ratio of geometric mean values (fed-state administration/fasting-state administration) and two-sided 90% confidence interval.

9.4.3.2.2 Analyses of Secondary Pharmacokinetic Endpoints

1) Endpoints

a) Plasma concentrations of brexpiprazole and metabolite [redacted]

b) C_{max}, AUC_{∞}, AUC_t, t_{max}, $t_{1/2,z}$, CL/F,[a] CL/F/BW,[a] t_{last}, AUC_%Extrap, and λ_z of brexpiprazole and metabolite [redacted] in plasma

[a]For brexpiprazole only

c) Ratios of the AUC (AUC_{∞} and AUC_t) of metabolite [redacted] to that of brexpiprazole

2) Statistical Methods

Descriptive statistics will be calculated as described below. However, if more than half of the subjects in an analysis set are excluded from summarization due to missing values, not calculable, or rejected data, descriptive statistics to be calculated for that parameter will include only the number of subjects in the analysis set and the number of subjects tabulated.

a) Plasma drug concentration

- For 1) a), descriptive statistics will be calculated at each blood sampling time point excluding the withdrawal time point by meal condition and compound.

- The descriptive statistics to be calculated will include the number of subjects in the analysis set, the number of subjects tabulated, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

b) Plasma PK parameters (except for λ_z)

- For 1) b), descriptive statistics will be calculated by meal condition and compound.
- For 1) c), descriptive statistics will be calculated by meal condition.
- The descriptive statistics to be calculated will include the number of subjects in the analysis set, the number of subjects tabulated, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum. However, descriptive statistics to be calculated for t_{max} and t_{last} will be the number of subjects in the analysis set, the number of subjects tabulated, minimum, median, and maximum.

9.4.3.3 Pharmacodynamic Analysis

No pharmacodynamic (PD) analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

Listings of data on CYP2D6 phenotypes will be provided. The frequency distribution will be determined as described in Section 9.4.3.1.

9.4.3.6 Exploratory Endpoint Analysis

[redacted]

9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design is applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

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

10.1.1 Ethics and Responsibility

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

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

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol. If a potential subject is under hospitalization for medical care and protection, written informed consent must also be obtained from his or her parent/legal guardian, as specified by local laws.

Each ICF will comply with the ICH GCP Guidelines, and local regulatory requirements.

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

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

Once appropriate essential information has been provided and fully explained in layman’s language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions and have those questions answered, the IRB-approved paper ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee). The subject will

receive a copy of the signed ICF; the original shall be kept on file by the investigator. Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

For PGx assessment, informed consent will be obtained as part of the main trial. Pharmacogenomic assessment is mandatory for trial participation, and subjects who do not consent to PGx assessment cannot participate in the trial.

If blood samples for FBR are to be collected, a similar consent process to that for the main trial is to be followed using a separate ICF. Consent must be obtained before the blood samples can be collected. Blood sampling for FBR is optional, and refusal to provide blood samples for FBR will not affect participation in the main trial.

10.1.3 Confidentiality

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

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

10.1.4 Quality Control and Quality Assurance

The sponsor will implement the trial-related quality management activities in accordance with ICH GCP guidance and standard operating procedures.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP 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 monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel (including those in charge of blood sampling for clinical laboratory tests) will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

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

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

10.1.5 Protocol Deviations

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

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

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as records of the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial (except for those related to drug concentration measurement, PGx assessment, and FBR) will be maintained by the trial sites and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. Documents related to drug concentration measurement, PGx assessment, and FBR (eg, original reports, measurement data, etc) will be retained by the bioanalytical laboratory, PGx laboratory, and biorepository /laboratory related to FBR, respectively. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- Documentation of baseline and demographic characteristics (eg, age, sex, race, ethnicity, etc);
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP or other drugs used in the clinical trial must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and IMP compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical records as described above.

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

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

10.1.6.3 File Management at the Trial Site

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

10.1.6.4 Records Retention at the Trial Site

The trial site will retain all the trial-related documents and records for the longest of the following 3 periods. 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.

- A period of at least 2 years after the date on which approval to market the drug is obtained. 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, a period of at least 3 years after receipt of such notification.
- A period of at least 3 years after discontinuation or completion of the trial.
- A period of FBR sample storage.

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

10.1.6.5 Publication Authorship Requirements

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

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

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

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

10.2 Appendix 2: Clinical Laboratory Tests

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

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Hematocrit RBC count WBC count (absolute and differential) Platelets Urinalysis: Occult blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Ketone body Specific gravity	Blood chemistry: ALP ALT AST Albumin Total bilirubin BUN Uric acid Serum electrolytes (Na, K, Cl, Ca, Mg, P, bicarbonate) Cholesterol (total cholesterol, LDL cholesterol, and HDL cholesterol) Creatinine γ-GTP Glucose LDH Total protein Triglyceride CPK Prolactin HbA1c Insulin Thyroid function test (at screening only): TSH and FT_4 Additional tests: Urine (or serum) pregnancy test for females of childbearing potential Urine drug screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, marijuana, opiates, and phencyclidine) Alcohol breath test

ALP = alkaline phosphatase; BUN = blood urea nitrogen; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; RBC = red blood cell; WBC = white blood cell; γ-GTP = Gamma-glutamyl transpeptidase.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who are postmenopausal). Postmenopausal is defined as being amenorrheic for at least 12 months without any medical cause. Females of non-childbearing potential do not meet the definition of FOCBP.

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 28 days after the last administration of drugs used in the clinical trial. Unless the subject or their partner is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or remains abstinent during the trial and for 28 days after the last administration of drugs used in the clinical trial, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, condom (all of which are approved in Japan). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the source document. Subjects must also agree not to donate sperm or eggs from trial screening through 28 days after the last administration of drugs used in the clinical trial.

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

- General information
- ICF
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

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

A urine or serum pregnancy test for hCG will be performed at screening on all FOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

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

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

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 28 days after the last dose of drugs used in the clinical trial, and record the event on the IRE form, etc, and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

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10.5 Appendix 5: Sample Menus of High-fat Meals

Breakfast served before fed-state IMP administration must meet the requirements specified in Section 5.3.1. Sample high-fat menus are shown in Table 10.5-1.

Table 10.5-1 Sample High-fat Menus

	Meal Components	Amount of Intake
Sample 1	Vacuum-packed white rice	200 g (1 pack)
	Retort pouch curry	1 pouch
	Package of milk	200 mL (1 pack)
	Canned Spam	100 g (approximately half of 1 can)
Sample 2	Vacuum-packed white rice	180 g (1 pack)
	Retort pouch beef stew	1 pouch
	Retort-packed ham	140 g (1 pack)
	Water	150 mL

10.6 Appendix 6: Protocol Amendments

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

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

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

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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 medicinal product, brexpiprazole (OPC-34712), the concurrent 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 OPC-34712 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 eCRF 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 research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, I do not comply with the protocol to avoid an immediate hazard to subjects, I will 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 experiences 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 may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____
Principal Investigator Print Name	Trial Site Print Name
_____	_____
Signature	Date

The sponsor signed this agreement electronically. The page of electronic signature is attached to this agreement.