CLINICAL STUDY PROTOCOL

A multi-center, open-label clinical pharmacology trial to investigate the pharmacokinetics, tolerability, and safety of brexpiprazole once-weekly (QW) formulation administered as single and multiple oral doses in patients with schizophrenia

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

CLINICAL PROTOCOL

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Protocol No. 331-102-00150

CONFIDENTIAL – PROPRIETARY INFORMATION

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Sponsor:	Otsuka Pharmaceutical Co., Ltd.
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-102-00150
Protocol Title:	A multi-center, open-label clinical pharmacology trial to investigate the pharmacokinetics, tolerability, and safety of brexpiprazole once-weekly (QW) formulation administered as single and multiple oral doses in patients with schizophrenia
Clinical Phase/ Trial Type:	Phase 1 Clinical pharmacology trial
Treatment Indication:	Schizophrenia
Objectives:	To evaluate the pharmacokinetics (PK), tolerability, and safety of brexpiprazole QW formulation administered as single and multiple doses in patients with schizophrenia.
Trial Design:	A multi-center, open-label clinical pharmacology trial to investigate the PK, tolerability, and safety of brexpiprazole QW formulation administered as single and multiple doses. The trial comprises the single administration period (Cohort 1) and the repeated administration period (Cohort 2). The dose used in the repeated administration period (Cohort 2) will be determined based on plasma drug concentrations obtained in the single administration period (Cohort 1). The single administration period (Cohort 1) comprises Period 1, in which the conventional tablet will be administered, and Periods 2 and 3, in which the QW formulation will be administered. If the single administration period (Cohort 1) fails to produce sufficient plasma drug concentrations, another single administration period (Cohort 1') will be added during which the QW formulation will be administered at higher single doses. The repeated administration period (Cohort 2) comprises Period 1, in which subjects will receive a single administration of the conventional tablet, and Period 2, in which subjects will receive 5 administrations of the QW formulation. In the single administration period (Cohort 1), subjects will receive a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, the QW formulation at 24 mg on Day 1 of Period 2, and the QW formulation at 48 mg on Day 1 of Period 3, all as single administrations in a fasted state. In the single administration period (Cohort 1'), subjects will receive a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, the QW formulation at 30 mg on Day 1 of Period 2, and the QW formulation at 60 or 54 mg on Day 1 of Period 3, all as single administrations in a fasted state.

	In the repeated administration period (Cohort 2), subjects will receive a single administration of a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, and repeated administration of the QW formulation on Days 1, 8, 15, 22, and 29 of Period 2. The doses of the QW formulation will be determined based on the results of the single administration period (Cohort 1 and, as necessary, Cohort 1').
Subject Population:	Patients with schizophrenia from 18 years of age to under 65 years of age Single administration period (Cohort 1): 20 subjects Single administration period (Cohort 1'): 20 subjects (as necessary) Repeated administration period (Cohort 2): 20 subjects
Inclusion/Exclusion Criteria:	**[For all cohorts]** **Inclusion criteria** 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 the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5®) 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) Persons who provide written informed consent before commencement of any trial-related procedures and whom the investigator or subinvestigator judges to be capable of following all the conditions of this trial 6) Patients who, in the judgement of the investigator or subinvestigator, have stable psychotic symptoms maintained by administration of an antipsychotic (other than clozapine) within the dosing range indicated below, before commencement of investigational medicinal product (IMP) administration • Antipsychotic medication comprising no more than two active components • A daily dose equivalent to no more than 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 Appendix 5.

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.

Exclusion criteria

1) Patients with a diagnosis of a concurrent mental disorder besides schizophrenia (schizoaffective disorder, major depressive disorder, bipolar I disorder, bipolar II disorder, general anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, dementia or mild neurocognitive disorder, personality disorder, etc) based on the DSM-5® diagnostic criteria. However, this exclusion does not apply to caffeine- or tobacco-related disorders.
2) Patients who fail to meet the specified requisite washout periods for the prohibited concomitant drugs and foods indicated below before commencement of IMP administration, or patients who are anticipated to take any of the drugs or foods in the following table during the study period

Drugs and Foods	Washout Period
Adrenaline	28 days
Rexulti tablets	21 days
Clozapine	Starting from informed consent
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers listed in Appendix 3 (Except topical agents listed in Appendix 4 for which use with the IMP is permitted)	14 days
Other investigational drugs under development	60 days
Foods and beverages containing St. John's Wort, Ginkgo biloba, goldenseal, or echinacea (Echinacea purpurea)	14 days
Foods and beverages containing grapefruit, Seville orange, or star fruit	7 days

3) Patients who have previously undergone gastrointestinal surgery that could affect PK evaluations
4) Patients who are using clozapine at the time of informed consent

5) Patients who have received electroconvulsive therapy within 60 days before commencement of IMP administration

6) Patients with clinically problematic disorders of the nervous system, liver, kidneys, metabolic system, blood system, immune system, cardiovascular system, respiratory system, or digestive system (However, such patients may be included if the condition is mild or well-controlled and is considered to not affect safety or PK evaluations.)

7) Patients who fall under any of the following criteria at screening

- Inadequately controlled hypertension (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

8) Patients with any of the following laboratory or electrocardiogram (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	AST: > 2 × upper limit of normal
ALT: > 2 × upper limit of normal	CPK: > 3 × upper limit of normal
Creatinine: ≥ 2 mg/dL	QTcF > 450 msec

9) 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
  a) Glycosylated hemoglobin (HbA1c) of ≥ 7.0% according to the global standard value [NGSP value]

b) Fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL

10) 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

11) 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

12) Patients with a positive drug test at screening (However, such patients may be included if their condition is not diagnosed as substance-related or addictive disorder, according to the DSM-5® diagnostic criteria.)

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 complication of hypothyroidism or hyperthyroidism (except in cases where the condition has been kept stable for at least 90 days through drug therapy) or patients who show abnormal values for thyroid-stimulating hormone (TSH) and free thyroxin (FT_4) in the screening examination

16) 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

17) 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

18) Patients who before commencement of IMP administration are judged to have a significant risk of committing suicide based on medical history or diagnosis, who have shown suicidal behavior within the past 2 years, or who have answered “yes” to Question 4 or 5 in the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past 24 months

19) Female patients who are nursing or have a positive pregnancy test result before administration of the IMP

20) Sexually active male patients and sexually active female patients of child-bearing potential who do not agree to practice 2 methods of birth control or remain abstinent during this trial and for 30 days after the final administration of IMP. If practicing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, or condom (all methods approved or certified in Japan)

21) Patients with a history of allergy to more than one medication

22) Patients with a history of hypersensitivity or allergy to brexpiprazole

23) Patients who have participated in another clinical trial within 60 days before commencement of IMP administration

24) Patients who have been compulsorily hospitalized under the Mental Health and Welfare Law of Japan

25) Patients judged by the investigator or subinvestigator to be unsuitable for participation in the trial

Trial Site(s):	Approximately 20 sites within Japan
Investigational Medicinal Products, Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	[Brexpiprazole QW formulation] • Cohort 1 (single administration period) On Day 1 of each of Periods 2 and 3 in Cohort 1 (single administration period), subjects will receive a single oral administration of the QW formulation at the dose specified in the following table together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the QW formulation until 2 hours after administration, except for the water taken at the time of administration.

	Dose					
Treatment period	Period 2			Period 3		
Regimen	Dose	Tablet	No. of tablets	Dose	Tablet	No. of tablets
1	24 mg	24 mg tablet	1 tablet	48 mg	24 mg tablet	2 tablets

- Cohort 1' (as necessary) (single administration period)
  On Day 1 of each of Periods 2 and 3 in Cohort 1' (single administration period), subjects will receive a single oral administration of the QW formulation together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the QW formulation until 2 hours after administration, except for the water taken at the time of administration. The doses of the QW formulation used in Cohort 1' (as necessary) (single administration period) will be determined according to the protocol-defined criteria for progression to the repeated administration period (Cohort 2) from the single administration period (Cohort 1 and Cohort 1' [as necessary]), and the QW formulation will be administered as per regimen 1 or 2 shown in the following table.

	Dose					
Treatment period	Period 2			Period 3		
Regimen	Dose	Tablet	No. of tablets	Dose	Tablet	No. of tablets
1	30 mg	30 mg tablet	1 tablet	54 mg	24 mg tablet 30 mg tablet	1 tablet each
2	30 mg	30 mg tablet	1 tablet	60 mg	30 mg tablet	2 tablets

- Cohort 2 (repeated administration period)
  Subjects will be orally administered the QW formulation together with approximately 150 mL of water in the morning after at least 10 hours of fasting, as per one of regimens 1 to 5 shown in the following table based on the results of the single administration period (Cohort 1 and Cohort 1' [as necessary]). Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the QW formulation until 2 hours after administration, except for the water taken at the time of administration.

	Dose					
Treatment period	Period 2					
Day	1			8, 15, 22, and 29		
Regimen	Dose	Tablet	No. of tablets	Dose	Tablet	No. of tablets
1	24 mg	24 mg tablet	1 tablet	48 mg	24 mg tablet	2 tablets

	2	18 mg	18 mg tablet	1 tablet	36 mg	18 mg tablet	2 tablets
	3	24 mg	24 mg tablet	1 tablet	42 mg	18 mg tablet 24 mg tablet	1 tablet each
	4	30 mg	30 mg tablet	1 tablet	54 mg	24 mg tablet 30 mg tablet	1 tablet each
	5	30 mg	30 mg tablet	1 tablet	60 mg	30 mg tablet	2 tablets
	[Other IMPs: Brexpiprazole 2 mg conventional tablet] On Day 1 of Period 1 in each cohort, subjects will receive a single oral administration of a brexpiprazole 2 mg conventional tablet together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the conventional tablet until 2 hours after administration, except for the water taken at the time of administration.						
Trial Assessments:	[For all cohorts] PK: plasma drug concentrations Safety: adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), weight, 12-lead ECG, C-SSRS, Drug-induced Extrapyramidal Symptoms Scale (DIEPSS), concomitant medications and therapies Screening/Other: demographics, pregnancy test, urine drug screening, CYP2D6 genotyping, Clinical Global Impression - Severity of illness (CGI-S), Clinical Global Impression - Improvement (CGI-I), blood sampling for DNA storage						
Criteria for Evaluation:	**PK endpoints:** Plasma concentrations and PK parameters of brexpiprazole after single and repeated administration of QW formulation **Safety (For all cohorts):** Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), weight, 12-lead ECG, DIEPSS, C-SSRS **Pharmacogenomics:** CYP2D6 genotyping **Other:** CGI-S, CGI-I						
Statistical Methods:	**Statistical methods for PK endpoints** The PK parameters of brexpiprazole for the QW formulation and conventional tablet at each dose will be determined through noncompartmental PK analysis. Descriptive statistics of the following variables will be produced:						

[Brexpiprazole QW formulation]

1) Period 2 of the single administration period (Cohort 1 and Cohort 1' [as necessary])
   a) Plasma concentration of brexpiprazole after a single administration of the QW formulation
   b) PK parameters of brexpiprazole after a single administration of the QW formulation
      C_{max}, t_{max}, t_{last}, C_{max}/D
   c) Relative C_{max} of brexpiprazole for the QW formulation as compared with a conventional tablet
      Relative C_{max} (%)
      = (C_{max} of QW formulation/dose of QW formulation)/(C_{max} of conventional tablet/dose of conventional tablet) × 100
2) Period 3 of the single administration period (Cohort 1 and Cohort 1' [as necessary])
   a) Plasma concentration of brexpiprazole after a single administration of the QW formulation
   b) PK parameters of brexpiprazole after a single administration of the QW formulation
      C_{max}, AUC_{∞}, AUC_t, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{∞}/D, AUC_t/D
   c) Relative bioavailability of brexpiprazole for the QW formulation as compared with a conventional tablet
      Relative bioavailability (%)
      = (AUC_{∞} of QW formulation/dose of QW formulation) /(AUC_{∞} of conventional tablet/dose of conventional tablet) × 100
   d) Relative C_{max} of brexpiprazole for the QW formulation as compared with a conventional tablet
      Relative C_{max} (%)
      = (C_{max} of QW formulation/dose of QW formulation)/(C_{max} of conventional tablet/dose of conventional tablet) × 100
3) Period 2 of the repeated administration period (Cohort 2)
   a) Plasma concentration of brexpiprazole after the fifth administration of the QW formulation

	b) PK parameters of brexpiprazole after the fifth administration of the QW formulation C_{max}, AUC_{168h}, t_{max}, λ_z, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{168h}/D c) Plasma trough concentrations of brexpiprazole from the first administration of the QW formulation to after the fifth administration (C_{168h}) d) Accumulation of brexpiprazole after the fifth administration of the QW formulation as compared with that after the first administration [R5,ac(C_{168h})] [Brexpiprazole conventional tablet] (for all cohorts, Period 1) 1) Plasma concentration of brexpiprazole after a single administration of a conventional tablet 2) PK parameters of brexpiprazole after a single administration of a conventional tablet C_{max}, AUC_{∞}, AUC_t, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{∞}/D, AUC_t/D **Rationale for target number of subjects:** The target number of subjects is not based on a statistical hypothesis test. A simulation was performed with the PK model created based on PK data of the conventional tablet and QW-A formulation used in the QW-A formulation group in Trial 331-102-00021 conducted in Japan, and the probability that the mean plasma concentration of brexpiprazole after repeated administration of the QW-A formulation would be within the target range of concentration was determined. On the basis of this probability, the sample size was determined to be 20 subjects each for the single administration period (Cohort 1) and the repeated administration period (Cohort 2). Likewise, the sample size for an additional single administration period (Cohort 1') with a new dose was also determined to be 20 subjects.
Trial Duration:	October 2019 to May 2021 The duration of trial participation for each subject will be a maximum of 105 days for the single administration period (Cohort 1 and, as necessary, Cohort 1') and a maximum of 108 days for the repeated administration period (Cohort 2) (each period including a washout period). Each period is indicated below. In cases where subjects withdrawn from the single administration period (Cohort 1) at the discretion

	of the sponsor subsequently take part in the trial again, the duration of their trial participation will be a maximum of 85 days if they resume participation in the trial from Period 2 and a maximum of 58 days if they resume participation in the trial from Period 3. • Screening All cohorts: Between 28 days and 1 day before the first administration of the IMP • Period 1 All cohorts: Day 1 of IMP administration to Day 20 (including a washout period of 20 days [+ 8 days max]) • Period 2 Cohort 1 and Cohort 1' (as necessary) (single administration period): Day 1 of IMP administration to Day 27 (including a washout period of 27 days [+ 8 days max]) Cohort 2 (repeated administration period): Day 1 of IMP administration to Day 42 • Period 3 Cohort 1 and Cohort 1' (as necessary) (single administration period): Day 1 of IMP administration to Day 14 • Follow-up Cohort 1 and Cohort 1' (as necessary) (single administration period): Day 28 of IMP administration to Day 30 in Period 3 Cohort 2 (repeated administration period): Day 56 of IMP administration to Day 60 in Period 2

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Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BE	Bioequivalence
BMI	Body mass index
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity of Illness
CIOMS	Council for International Organizations of Medical Science
CPK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic data capture
EM	Extensive metabolizer
GCP	Good Clinical Practice
γ-GTP	Gamma glutamyl transpeptidase
HbA1c	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IM	Intermediate metabolizer
IRB	Institutional review board
IRE	Immediately reportable event
LDH	Lactic dehydrogenase
LSMD	Least square mean difference
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
OROS	Osmotic-controlled release oral delivery system
PANSS	Positive and Negative Syndrome Scale
PCS	Potentially Clinically Significant
PK	Pharmacokinetic
PM	Poor metabolizer
PQC	Product quality complaint
QTc	QT corrected for heart rate
QTcF	QT interval as corrected by Fridericia's formula
QW	Quaque (Once) Weekly
TEAE	Treatment-emergent adverse event
WOCBP	Women of child-bearing potential
AUC	Area under the concentration time curve
AUC_{∞}	Area under the concentration time curve from time zero to infinity
AUC_{∞}/D	Area under the concentration time curve per dose
AUC_%Extrap	Ratio of area under the concentration-time curve from t_{last} to infinity versus AUC_{∞}

Abbreviation	Definition
AUC_t	Area under the concentration time curve calculated to the last observable concentration at time t
AUC_t/D	AUC_t per dose
CL/F	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	Apparent clearance of drug from plasma after extravascular administration per body weight
C_{max}	Maximum (peak) plasma concentration of the drug
$C_{max/D}$	C_{max} per dose
λ_z	Terminal elimination rate constant
$t_{1/2,z}$	Terminal phase elimination half life
t_{last}	Time of the last measurable concentration
t_{max}	Time to maximum (peak) plasma concentration

1 Introduction

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,[1,2] and approximately 713,000 people are affected with the disease in Japan (based on the 2011 Patient Survey by the Ministry of Health, Labour and Welfare).[3] 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 flare/relapse of symptoms, maintain the alleviated condition, and improve cognitive function or at least not impair cognitive function in the course of treatment. In either treatment phase, continuous treatment for an appropriate period is considered to contribute to the alleviation of symptoms as well as to good outcomes by preventing flare/relapse from occurring.[4] 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.

As a measure to improve patient adherence to medication, long-acting drugs have been introduced into clinical practice. In Japan, multiple injections are commercially available including long-acting injections of haloperidol decanoate and fluphenazine decanoate as typical antipsychotics, and long-acting injectable suspensions of risperidone and paliperidone palmitate and long-acting injections of aripiprazole hydrate as atypical antipsychotics.

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[5] and serotonin 1A (5-HT1A) receptors [6,7] and antagonist activity at serotonin 2A (5-HT2A) receptors.[5]

Brexpiprazole was studied in clinical trials in the 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 (MDD). 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 approval in Japan in January 2018. The drug is currently undergoing further development for other psychiatric conditions in Japan as well.

The currently 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. This situation indicates that there is an unmet medical need for more easy-to-use long-acting antipsychotics.

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.

In order to find the most appropriate QW formulation, Otsuka conducted a clinical pharmacology trial (Japan 331-102-00021) in Japan for comparative investigation of the pharmacokinetics (PK), tolerability, and safety of 3 types of the brexpiprazole QW formulation administered as single oral doses in patients with schizophrenia. Otsuka then performed a simulation at the steady state using a model created based on the PK results from Trial 331-102-00021. The results suggested that the QW-A formulation, using brexpiprazole fumarate as the bulk form and the osmotic-controlled release oral delivery system (OROS) as the release control system, has a favorable PK profile.

Prompted by these findings, development of a brexpiprazole QW formulation is currently being carried out based on the QW-A formulation.

1.1 Nonclinical Data

As the QW formulation to be administered in this trial contains brexpiprazole fumarate as the active pharmaceutical ingredient, repeated-dose oral toxicity studies in rats and monkeys and in vitro and in vivo genotoxicity studies have been conducted.

A 4-week repeated-dose oral toxicity study of brexpiprazole fumarate was conducted in rats. Changes in general condition attributable to the pharmacological action of the drug included abnormal posture in males and females at doses of 30 mg/kg/day and higher, lacrimation in females at 30 and 100 mg/kg/day, hypothermia, tremor, and lacrimation in males at 100 and 300 mg/kg/day, and incomplete eyelid closure in females at doses of 10 mg/kg/day and higher. Suppressed body weight gain associated with decreased food consumption was observed in males at doses of 30 mg/kg/day and higher and in females at 100 mg/kg/day. Decreased body temperature was observed in both sexes at doses of 30 mg/kg/day and higher. Lobular hyperplasia and milk secretion in the mammary glands in females at doses of 3 mg/kg/day and higher and feminization of the mammary glands in males at doses of 30 mg/kg/day and higher were considered to be due to D_2

antagonism and the resulting increase in serum prolactin levels.[8] In addition, mucification of the vagina at 3 mg/kg/day and higher and of the uterine cervix at 10 mg/kg/day and higher were considered to be due to activation of luteal function triggered by the increase in serum prolactin. Brain lesions observed in males at 300 mg/kg/day and in females at 100 mg/kg/day were associated with a marked decrease in body temperature, as seen in previous toxicity studies of brexpiprazole. In males, histopathological lesions in the testis, epididymis, and seminal vesicles were observed at 100 and 300 mg/kg/day. In conclusion, the no observed adverse effect level (NOAEL) was determined to be 30 mg/kg/day for males and 10 mg/kg/day for females under the conditions of the study.

A 4-week repeated-dose oral toxicity study of brexpiprazole fumarate was conducted in monkeys. Clinical signs included tremors in males and females at 3 and 10 mg/kg/day. Drowsiness, crouching, and eyelid closure were observed in males and females at 10 mg/kg/day, and drowsiness was also observed in males at 3 mg/kg/day. Decreased mean blood pressure was observed in both sexes at doses of 3 mg/kg/day and higher and decreased body temperature was observed in both sexes at 10 mg/kg/day. QT corrected for heart rate (QTc) was prolonged in males at 10 mg/kg/day, but only on Day 1. The NOAEL was considered to be 1 mg/kg/day for both males and females under the conditions of the study.

In 4-week repeated-dose oral toxicity studies in rats and monkeys, the effects of brexpiprazole fumarate were similar to those seen in clinical studies of brexpiprazole. No new or unexpected systemic toxicities were observed with brexpiprazole fumarate compared to brexpiprazole.[9,10,11,12,13,14,15] There was also no apparent difference in the toxicokinetic profile between brexpiprazole and brexpiprazole fumarate in both rats and monkeys.

Brexpiprazole fumarate was not genotoxic in a bacterial reverse mutation test, a bone-marrow micronucleus test in rats, or an unscheduled DNA synthesis test in rats.

All relevant data from nonclinical studies in animals (including PK and toxicity studies) are presented in the Investigator's Brochure (IB).

1.2 Clinical Data

1.2.1 Clinical Pharmacology Trial for Comparative Investigation of the Pharmacokinetics, Tolerability, and Safety of Three Types of QW Formulation Administered as Single Oral Doses in Patients With Schizophrenia (Japan 331-102-00021)

A multi-center, open-label, clinical pharmacology trial for comparative investigation of the PK, tolerability, and safety following single oral administration of one of three types

of brexpiprazole QW formulation (Table 1.2-1) in patients with a diagnosis of schizophrenia (295.90) based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5®).

Subjects received one brexpiprazole 2 mg conventional tablet and, after a washout period, received a single administration of one of three QW formulations (12 mg of brexpiprazole).

Table 1.2-1 Three QW Formulations Used in Trial 331-102-00021

Candidate Formulation	No. of Subjects	Bulk Form	Release Control System
QW-A formulation	6	Fumarate	OROS
QW-B formulation	6	Fumarate	HG matrix tablet
QW-C formulation	8	Amorphous solid dispersion	HG matrix tablet

The incidence of adverse events (AEs) at 12 mg of brexpiprazole was 33.3% (2/6) in the QW-A formulation group, 33.3% (2/6) in the QW-B formulation group, and 12.5% (1/8) in the QW-C formulation group. No AEs occurred in more than 1 subject in any formulation group. In addition, no serious adverse events (SAEs), severe AEs, or AEs leading to trial discontinuation were reported in any formulation group.

All QW formulations were associated with extended median t_{max} as compared with the conventional tablet, indicating controlled release of the drug from all QW formulations. The mean $t_{1/2,z}$ after dosing of each QW formulation was similar to that after dosing of the conventional tablet. The main PK parameters of each QW formulation are shown in Table 1.2-2.

Table 1.2-2 Main Pharmacokinetic Parameters of Each QW Formulation in Trial 331-102-00021

Candidate Formulation (mg)	No. of Subjects	C_{max} (ng/mL)	AUC_{∞} (h·ng/mL)	t_{max}[a] (h)	$t_{1/2,z}$ (h)
QW-A formulation (12 mg)	6	61.11 (39.75)	6840 (5360)	30.13 (23.25 - 49.57)	71.5 (18.2)
QW-B formulation (12 mg)	6	46.67 (16.75)	4210 (1260)	24.60 (23.30 - 25.58)	68.4 (26.3)
QW-C formulation (12 mg)	8	63.56 (23.26)	7780 (6170)	18.09 (8.60 - 48.00)	90.2 (53.9)

Mean (standard deviation)

[a]Median (minimum - maximum)

1.2.2 Clinical Data of Conventional Tablet of Brexpiprazole

Among clinical trials of the conventional tablet, the results of trials that confirmed safety and tolerability at the maximum dose of 12 mg and the results of trials in Japanese patients with schizophrenia are summarized below. Refer to the IB for further information.

1.2.2.1 Phase 1 Multiple-dose Trial in Subjects With Schizophrenia or Schizoaffective Disorder (US 331-08-205)

A total of 48 subjects with schizophrenia or schizoaffective disorder received multiple doses of oral brexpiprazole at 2, 4, 6, 8, 10, or 12 mg (6 subjects per dose group plus 2 subjects per group given brexpiprazole 1 mg as a reference group) for 14 days.

The C_{max} and $AUC_{0\text{-}24h}$ increased dose-dependently after multiple-dose administration of brexpiprazole (1 to 12 mg). The $t_{1/2,z}$ of brexpiprazole at steady state ranged from 81.14 to 106.83 hours.

The incidence of adverse events (AEs) in subjects receiving the investigational medicinal product (IMP) (including subjects in the 1-mg reference group) was 89.6% (43/48). Adverse events reported in more than 1 subject included anxiety (31.3%, 15/48), insomnia (22.9%, 11/48), constipation, headache (14.6%, 7/48 each), stomach discomfort, pain in extremity (10.4%, 5/48 each), dyspepsia, agitation, nasal congestion (8.3%, 4/48 each), back pain, sedation, oropharyngeal pain (6.3%, 3/48 each), tachycardia, tongue disorder, upper respiratory tract infection, blood pressure decreased, arthralgia, akathisia, dizziness, and hypotension (4.2%, 2/48 each). Of those, AEs reported in more than 1 subject and considered to be related to the IMP were anxiety (16.7%, 8/48), insomnia, constipation, stomach discomfort (8.3%, 4/48 each), sedation (6.3%, 3/48), tongue disorder, blood pressure decreased, akathisia, and headache (4.2%, 2/48 each). Serious adverse events (SAEs) reported in the 12-mg group were drug hypersensitivity and anxiety in 1 subject each and both events resolved on the day after onset. In addition, no AEs in the 12-mg group led to discontinuation, demonstrating good tolerability of brexpiprazole at up to 12 mg.

1.2.2.2 QT/QTc Trial in Subjects With Schizophrenia or Schizoaffective Disorder (US 331-10-242)

A total of 205 subjects with schizophrenia or schizoaffective disorder received multiple doses of brexpiprazole at 4 mg or 12 mg or placebo for 11 days or moxifloxacin once daily for one day. The 12-mg group included 67 subjects.

The primary endpoint was the time-matched QTcI change from baseline corrected for placebo on Day 11 of brexpiprazole treatment. The results demonstrated that there was no QTcI prolongation after brexpiprazole treatment at either 4 or 12 mg.

The incidence of AEs in subjects receiving 12 mg of brexpiprazole was 71.6% (48/67). Adverse events reported in more than 1 subject included dizziness (8 subjects, 11.9%), akathisia, extrapyramidal disorder, restlessness, headache, nausea (5 subjects each, 7.5%), constipation, somnolence, insomnia (4 subjects each, 6.0%), orthostatic hypotension, vomiting, sedation (3 subjects each, 4.5%), stomach discomfort, nasopharyngitis, muscle rigidity, drooling, application site pruritus, vision blurred, salivary hypersecretion, anaemia, and diarrhoea (2 subjects each, 3.0%). Of those, AEs reported in more than 1 subject and considered to be related to the IMP were dizziness (10.4%, 7/67), extrapyramidal disorder (7.5%, 5/67), akathisia, headache (6.0%, 4/67 each), nausea, sedation, somnolence (4.5%, 3/67 each), constipation, salivary hypersecretion, vomiting, muscle rigidity, drooling, and orthostatic hypotension (3.0%, 2/67 each). No SAEs were reported in the 12-mg group. Adverse events leading to discontinuation in the 12-mg group were dizziness, extrapyramidal disorder (3.0%, 2/67 each), akathisia, psychotic disorder, and joint stiffness (1.5%, 1/67 each). The trial results demonstrated good tolerability of brexpiprazole at 12 mg.

1.2.2.3 Phase 1 Multiple-dose Trial in Subjects With Schizophrenia (Japan 331-10-001)

A total of 21 subjects with schizophrenia received multiple doses of brexpiprazole at 1, 4, or 6 mg once daily for 14 days.

Overall, 90.5% of subjects (19/21) experienced AEs. The incidence of AEs by treatment group was 71.4% (5/7) in the 1-mg group, 100.0% (8/8) in the 4-mg group, and 100.0% (6/6) in the 6-mg group. The most frequently reported AEs (incidence ≥ 5% of all subjects) were blood prolactin increased (38.1%, 8/21), blood creatine phosphokinase increased (14.3%, 3/21), nausea, nasopharyngitis, blood pressure increased, blood prolactin decreased, insomnia, and schizophrenia (9.5%, 2/21 each). The majority of events, including blood prolactin increased, were considered potentially related to the IMP. Serious adverse events of schizophrenia were reported in 2 subjects (1 each in the 1-mg and 4-mg groups), both of which led to discontinuation.

The trial results demonstrated the safety and tolerability of brexpiprazole at up to 6 mg in Japanese subjects with schizophrenia.

1.2.2.4 Dose-finding Trial in Subjects With Schizophrenia (Japan 331-10-002)

A double-blind, placebo-controlled trial was conducted to determine the efficacy, safety, and tolerability of fixed-dose brexpiprazole in adult subjects with an acute relapse of schizophrenia. This trial had 4 groups: a placebo group and 3 fixed doses of brexpiprazole (1, 2, and 4 mg/day). The primary endpoint was change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total score. The primary endpoint of change in PANSS total score from baseline at Week 6 showed significant improvement in the 2-mg group compared with the placebo group (least squares mean difference [LSMD]: −7.32, p = 0.0124). Although there was no significant difference between the 4-mg group and the placebo group, improvement in PANSS total score was numerically greater in the 4-mg group than in the placebo group (LSMD: −3.86, p = 0.1959). Efficacy was observed for brexpiprazole in subjects with an acute relapse of schizophrenia.

The incidence of AEs by treatment group was 70.4% in the 1-mg group, 69.3% in the 2 mg group, 65.5% in the 4-mg group, and 76.7% in the placebo group. Adverse events reported in any of the brexpiprazole groups at an incidence of ≥ 5% and at more than double the incidence in the placebo group were vomiting, blood prolactin increased, diarrhoea, nausea, and dental caries. There was no evident relationship between the dose of brexpiprazole and the incidence of AEs. The majority of AEs reported in brexpiprazole groups and placebo group were mild or moderate in severity. A 52-year-old female subject in the 4-mg group died of asphyxia. This event was considered to be unrelated to the IMP. The incidence of SAEs including death was 7.0% in the 1-mg group, 4.4% in the 2-mg group, 4.4% in the 4-mg group, and 4.3% in the placebo group. In all treatment groups, schizophrenia was the only SAE that occurred in more than 1 subject. The incidence of AEs leading to discontinuation was 16.5% in the 1-mg group, 10.5% in the 2-mg group, 15.0% in the 4-mg group, and 17.2% in the placebo group. The most frequently reported AE leading to discontinuation was schizophrenia for all treatment groups. No marked changes were noted in laboratory test values, vital signs, weight, or electrocardiogram (ECG) in brexpiprazole groups.

1.2.2.5 Long-term Trial in Subjects With Schizophrenia (Japan 331-10-003)

This long-term trial conducted in Japan was an open-label trial to evaluate the safety and efficacy of long-term administration of brexpiprazole in subjects with schizophrenia, either continuing treatment from the dose-finding trial 331-10-002 (rollover subjects) or newly enrolled in this trial.

All efficacy endpoints, including PANSS total score and Clinical Global Impression-Severity of Illness (CGI-S) score, remained stable until Week 52.

The incidence of AEs was 85.2% in newly enrolled subjects, 80.6% in rollover subjects, and 83.6% in all subjects. The most frequently reported AE was nasopharyngitis (25.1%) in newly enrolled subjects, schizophrenia (26.5%) in rollover subjects, and nasopharyngitis (23.1%) in all subjects. Most AEs were mild or moderate in severity. No deaths were reported in this trial. The incidence of SAEs was 10.4% in newly enrolled subjects, 18.4% in rollover subjects, and 13.2% in all subjects. Serious adverse events reported in more than 1 subject were schizophrenia in newly enrolled and rollover subjects and dehydration, akathisia, and schizophrenia in all subjects. The incidence of AEs leading to discontinuation was 10.9% in newly enrolled subjects, 23.5% in rollover subjects, and 15.3% in all subjects. The most frequently reported AE leading to discontinuation was schizophrenia in newly enrolled subjects, rollover subjects, and all subjects. No clinically meaningful changes were noted in laboratory test values, vital signs, or ECGs in newly enrolled subjects, rollover subjects, or all subjects. The mean change in weight from Period 2 baseline to the final assessment (last observation carried forward [LOCF]) was 0.34 kg in newly enrolled subjects, 2.02 kg in rollover subjects, and 0.93 kg in all subjects. There was no marked difference in safety results between newly enrolled subjects and rollover subjects, indicating that switchover to brexpiprazole monotherapy from prior treatment with existing antipsychotic drugs has no significant impact on safety.

1.3 Pharmacokinetics

A simulation was performed using plasma brexpiprazole concentrations observed after dosing of the QW-A formulation at 12 mg in Japanese Trial 331-102-00021 to estimate steady-state plasma brexpiprazole concentrations for the QW-A formulation at 24 and 48 mg. The estimated PK parameters are shown in Table 1.3-1.

Results from Japanese and non-Japanese clinical trials showing PK parameters of repeated administration of brexpiprazole at the clinically recommended doses (Japan: 2 mg; US: 2 and 4 mg) and the maximum dose of 12 mg at which safety and tolerability has been confirmed are summarized in Table 1.3-2.

The PK of brexpiprazole was similar between Japanese and non-Japanese in healthy adults receiving a single dose of brexpiprazole at 0.2 to 6 mg (US 331-07-201 and Japan 331-07-002) and in subjects with schizophrenia receiving multiple doses of brexpiprazole at 1, 4, and 6 mg (US 331-08-205 and Japan 331-10-001). A non-Japanese population PK analysis (Trial 331-12-208) did not identify race as a variation factor for the PK of brexpiprazole.

Table 1.3-1	**Estimated Pharmacokinetic Parameters of Brexpiprazole QW Formulation at Steady State Based on Simulation**		
Summary	**PK Parameter**	**24 mg**	**48 mg**
A simulation was performed with a PK model created based on PK data on the QW-A formulation (n = 6) from Trial 331-102-00021 (Japan).	$C_{ss,max}$ (ng/mL)	88 (69.3)	176 (139)
	$C_{ss,min}$ (ng/mL)	27.6 (27.8)	55.1 (55.6)
	AUC_{168h} (ng·h/mL)	9450 (7890)	18900 (15800)

$C_{ss,max}$ = Maximum plasma concentration at steady state

$C_{ss,min}$ = Minimum plasma concentration at steady state
Mean (standard deviation)

Table 1.3-2	**Pharmacokinetic Parameters of Brexpiprazole at Steady State**			
Trial No. No. of Subjects	**PK Parameter**	**2 mg**	**4 mg**	**12 mg**
331-10-001 (Japan) 4 mg (N = 7)	C_{max} (ng/mL)	ND	164.63 (101.96)	ND
	AUC_{24h} (ng·h/mL)	ND	3238 (2184)	ND
	$AUC_{24h} \times 7$ [a] (ng·h/mL)	ND	22666	ND
331-08-205 (US) 2 mg (N = 6) 4 mg (N = 5) 12 mg (N = 4)	$C_{ss,max}$ (ng/mL)	81.2 (28.3)	199 (134)	382 (30.3)
	$C_{ss,min}$ (ng/mL)	56.8 (23.0)	112 (75.3)	205 (51.7)
	AUC_{24h} (ng·h/mL)	1620 (594)	3950 (2860)	6950 (797)
	$AUC_{24h} \times 7$ [a] (ng·h/mL)	11340	27650	48650
331-10-242 (US) 4 mg (N = 64) 12 mg (N = 53)	C_{max} (ng/mL)	ND	170 (69.8)	462 (249)
	$C_{ss,min}$ (ng/mL)	ND	102 (55.2)	305 (192)
	AUC_{τ} (ng·h/mL)	ND	3100 (1400)	8880 (5110)
	$AUC_{\tau} \times 7$ [a] (ng·h/mL)	ND	21700	61260

$C_{ss,max}$ = Maximum plasma concentration at steady state

$C_{ss,min}$ = Minimum plasma concentration at steady state
Mean (standard deviation)
ND = No data

[a] 7-day data of AUC (7 times the mean AUC_{24h} for each dosing interval)

1.4 Known and Potential Risks and Benefits

Data from overseas phase 1 trials of the conventional tablet of brexpiprazole demonstrate safety and good tolerability in healthy adults exposed to single doses of 0.2 to 6 mg and multiple doses of 2 mg/day.[16,17,18] Data from completed US multiple-dose trials show favorable tolerability in patients with schizophrenia or schizoaffective disorder exposed to multiple doses of up to 12 mg/day of brexpiprazole,[19] in patients with MDD exposed to 4 mg/day of brexpiprazole with commercially available antidepressants,[20,21] and in patients with attention deficit hyperactivity disorder (ADHD) exposed to up to 4 mg/day of brexpiprazole with commercially available stimulants. Furthermore, data from Japanese phase 1 trials indicate favorable tolerability in healthy adults exposed to single doses of up to 4 mg/day[22] and in patients with schizophrenia exposed to multiple doses of up to 6 mg/day.[23] In a Japanese dose-finding trial (331-10-002) in subjects with schizophrenia, the primary endpoint of change from baseline at Week 6 in PANSS total score in the 2 mg brexpiprazole group was significantly different from that in the placebo group. The change observed in the 4 mg group was numerically larger than that in the placebo group, though the difference was not significant. Brexpiprazole was well tolerated in subjects at doses of 1, 2, and 4 mg/day.[24]

Data from completed clinical trials at present indicate that the maximum tolerated dose (MTD) of brexpiprazole for healthy adults is 6 mg as single-dose administration and 2 mg as once-daily, multiple-dose administration (14 days). The MTD of brexpiprazole in patients with schizophrenia, MDD, agitation associated with Alzheimer-type dementia, and ADHD has not been established. Data from completed phase 1 multiple-dose trials indicate tolerability of brexpiprazole at multiple oral doses up to 12 mg/day in patients with schizophrenia or schizoaffective disorder, up to 4 mg/day when administered as an adjunctive therapy in adult patients with MDD or ADHD, and up to 3 mg/day when administered as an adjunctive therapy in elderly patients (70 to 85 years of age) with MDD.

See the IB for further information on brexpiprazole and adverse drug reactions.

2 Trial Rationale and Objectives

2.1 Trial Rationale

As described in Section 1 Introduction, maintenance of drug compliance is thought to be instrumental in alleviating symptoms and achieving favorable outcomes in the treatment

of schizophrenia; 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.

Brexpiprazole, 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. Otsuka is now developing a 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.

In order to find the most appropriate QW formulation, we conducted a clinical pharmacology trial (Japan 331-102-00021) in Japan for comparative investigation of the PK, tolerability, and safety of 3 types of brexpiprazole QW formulation administered as single oral doses in patients with schizophrenia.

Given that the approved clinical dose of brexpiprazole for schizophrenia in Japan is 2 mg and that the dose found to be safe in Japanese subjects in a dose-finding trial (Japan 331-10-002) and a long-term trial (Japan 331-10-003) is 4 mg, the target PK profile of the QW formulation in repeated administration should ideally be as follows: the trough concentration should not fall below that for the brexpiprazole 2 mg conventional tablet and the peak concentration should not significantly exceed that for the brexpiprazole 4 mg conventional tablet.

Data from single 12-mg doses of each QW formulation in Trial 331-102-00021 (Japan) were used to estimate plasma brexpiprazole concentrations following repeated administration. The results indicate that only the QW-A formulation is likely to attain the target PK profile.

Furthermore, a simulation was performed, using a model created based on the PK results for the 12 mg QW-A formulation, to find the dose of the QW formulation that would achieve the target PK profile at the steady state. The results suggest that plasma brexpiprazole concentrations after administration of the QW formulation at 48 mg will generally remain within the target PK profile and will not significantly exceed the peak concentration at the steady state observed after administration of the conventional tablet at 4 mg.

With the above taken into consideration, in this trial, we have decided to use the QW-A formulation with OROS to evaluate the PK, tolerability, and safety of the brexpiprazole QW formulation following single and repeated oral administration in patients with schizophrenia.

2.2 Rationale for CYP2D6 Genotyping and DNA Storage

Cytochrome P450 (CYP) 3A4 and CYP2D6 are involved in the in vitro metabolism of brexpiprazole, and CYP2D6 is known to have multiple genotypes with different enzyme activities. It has also been shown that CYP2D6 genotypes are involved in the PK variability of brexpiprazole. We have decided to investigate CYP2D6 genotypes to evaluate their effects on the PK and safety of brexpiprazole.

We have also decided to store DNA samples to allow for future genomic/genetic analyses in those cases where further explanation is required in addition to the results of CYP2D6 genotyping performed in this trial for the PK of brexpiprazole, new information on genes and PK becomes available, and/or genomic/genetic analyses pertaining to responses to brexpiprazole (efficacy or safety) and the disease are considered useful. DNA storage will be conducted only at the trial sites which have agreed to collect DNA samples for storage, and only subjects who have provided written informed consent for DNA storage (if the subject is a minor or is hospitalized for reasons of medical protection, his or her legally acceptable representative must also give informed consent) will participate in DNA storage. With regard to collecting and storing DNA samples during a clinical trial, the Ministry of Health, Labour and Welfare (MHLW) states, in Q&A 1 in "Regarding Clinical Studies Utilizing Pharmacogenomics (PFSB/ELD Notification No. 0930007 dated 30 Sep 2008),"[25] that it is possible to collect samples from subjects for genomic/genetic analyses relevant to evaluation (PK, efficacy, safety, etc) of an IMP in a clinical trial, provided (1) the target and time of genomic/genetic analyses have been determined at the time of the trial or (2) the target and time of genomic/genetic analyses have yet to be determined at the time of the trial but such analyses related to IMP evaluation may be considered in the future. The International Council for Harmonisation (ICH) also states, in Section 1.4 General Principles in the Guideline on Genomic Sampling and Management of Genomic Data E18[26] as follows: “With advances in science and increased awareness of the impact of genomics, there is a need and an opportunity to maximize the value of the collected samples and the data generated from them. Therefore, genomic sample acquisition is strongly encouraged in all phases and studies of clinical development.”

Moreover, this trial has been designed so that sampling for DNA storage can be carried out at the same time as scheduled blood sampling to minimize the discomfort to subjects. Optional collection and storage of DNA samples is thus justified.

2.3 Dosing Rationale

2.3.1 Regimen

The objective of this trial is to evaluate the PK, tolerability, and safety of the brexpiprazole QW formulation administered as single and repeated administration in patients with schizophrenia. The trial design comprises the single administration period (Cohort 1 and, as necessary, Cohort 1') and the repeated administration period (Cohort 2). All cohorts include Period 1 in which subjects will receive the brexpiprazole conventional tablet as a single administration. In each cohort, following a single administration of the conventional tablet, the same subject will undergo a washout period and then receive the QW formulation. The purpose of administering the conventional tablet is set to reduce the effect of interindividual variability on evaluation of the PK profile of the QW formulation.

In the repeated administration period, subjects will receive the brexpiprazole QW formulation once weekly for 5 weeks (a total of 5 administrations). In general, patients on antipsychotic medication could experience AEs soon after therapy is initiated. With this taken into consideration, treatment will begin with a low dose to confirm the safety and tolerability before increasing the dose to the predetermined level. Specifically, a low dose will be used only for the first administration and the predetermined dose will be used for the subsequent 4 administrations in this trial. Four administrations at the predetermined dose is based on the results of a simulation for the QW formulation indicating that 4 once-weekly administrations of the QW formulation are needed for brexpiprazole concentration to reach the steady state.

2.3.2 Dose

2.3.2.1 Single Administration Period (Cohort 1 and Cohort 1' [as Necessary])

2.3.2.1.1 Cohort 1

In the single administration period (Cohort 1) of the trial, the same subject will receive a single administration of the brexpiprazole 2 mg conventional tablet, undergo the washout period, and next receive a single administration of the QW formulation at 24 mg, undergo the washout period, and finally receive a single administration of the QW formulation at 48 mg.

A clinical pharmacology trial for comparative investigation of the PK, tolerability, and safety of 3 types of brexpiprazole QW formulation administered as single oral doses in patients with schizophrenia (Japan 331-102-00021) has demonstrated the safety and tolerability of a single 12-mg dose of the QW formulation. The results of a simulation of repeated administration of the QW formulation at 48 mg based on the PK results of Trial 331-102-00021 indicate that plasma brexpiprazole concentrations after repeated administration of the QW formulation at 48 mg will remain roughly between the trough concentration after administration of the brexpiprazole 2 mg conventional tablet and the peak concentration after administration of the 4 mg conventional tablet, thus suggesting that plasma brexpiprazole concentrations after repeated administration of the QW formulation at 48 mg will not greatly exceed the steady-state peak concentration of the 4 mg conventional tablet, the dose at which safety has been confirmed in Japanese patients. Furthermore, the mean steady-state C_{max} at the maximum dose of 12 mg at which safety and tolerability was confirmed in an overseas repeated administration trial (331-08-205) and an overseas QT/QTc trial (331-10-242) of brexpiprazole conventional tablets in subjects with schizophrenia and schizoaffective disorder was 382 and 462 ng/mL, respectively, and the estimated mean steady-state C_{max} after repeated administration of brexpiprazole QW formulation at 48 mg (176 ng/mL) was lower than either of these results. In view of these findings, the dose was set at 48 mg for the QW formulation to be used in the single administration period (Cohort 1). However, since there is no clinical experience of administering either the brexpiprazole QW formulation or the conventional tablet at doses higher than 12 mg, subjects will be first given the QW formulation at a dose of 24 mg and only subjects for whom safety and tolerability has been confirmed will then receive the drug at 48 mg. For the conventional tablet, the dose was set at 2 mg, the recommended dose for schizophrenia.

2.3.2.1.2 Cohort 1’ (as Necessary)

Prior to the commencement of the repeated administration period (Cohort 2), a simulation of repeated administration of the 2 mg conventional tablet and the QW formulation at 48 mg will be performed using data on plasma brexpiprazole concentrations of the conventional tablet and QW formulation from the single administration period (Cohort 1). Then, on the basis of the PK and safety results, the appropriateness of a 48 mg dose of the QW formulation used in the repeated administration period (Cohort 2) will be assessed. The decision on whether or not to implement Cohort 1’ will be made based on comprehensive assessment of the above.

If the comprehensive assessment indicates that the trough concentration for repeated administration of the QW formulation at 48 mg is likely to fall below that for the 2 mg

conventional tablet, another single administration period will be added as Cohort 1'. The doses used in Cohort 1' will be either of the following based on the results of a simulation.

- A single administration of the QW formulation at 30 mg followed by a single administration of the QW formulation at 54 mg
  or
- A single administration of the QW formulation at 30 mg followed by a single administration of the QW formulation at 60 mg

2.3.2.2 Repeated Administration Period (Cohort 2)

In the repeated administration period (Cohort 2) of the trial, the same subject will receive a single administration of the brexpiprazole 2 mg conventional tablet, undergo the washout period, and next receive a single administration of the QW formulation at 24 mg and, subsequently, 4 administrations of the QW formulation at 48 mg once weekly. The rationale for selecting 48 mg for the QW formulation and 2 mg for the conventional tablet is presented in Section 2.3.2.1 Single Administration Period (Cohort 1 and Cohort 1' [as Necessary]). In general, patients on antipsychotic medication could experience AEs soon after therapy is initiated. With this taken into consideration, treatment will begin with a low dose to confirm the safety and tolerability before increasing the dose to the predetermined level; 24 mg is therefore selected for the first administration of the QW formulation. The repeated administration period (Cohort 2) will use one of the following regimens depending on the results of the single administration period (Cohort 1 and Cohort 1' [as necessary]) (Section 3.8.1 Criteria for Progression to Cohort 2:

- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 30 mg → 4 administrations of the QW formulation at 60 mg
- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 30 mg → 4 administrations of the QW formulation at 54 mg
- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 24 mg → 4 administrations of the QW formulation at 42 mg
- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 18 mg → 4 administrations of the QW formulation at 36 mg

2.4 Trial Objectives

The objective of the clinical trial is to evaluate the PK, tolerability, and safety of brexpiprazole QW formulation administered as single and repeated administration in patients with schizophrenia.

3 Trial Design

3.1 Type/Design of Trial

This is a multi-center, open-label, clinical pharmacology trial to investigate the PK, tolerability, and safety of brexpiprazole QW formulation administered as single and repeated administration in patients with a diagnosis of schizophrenia (295.90) based on the DSM-5®. The trial comprises the single administration period (Cohort 1) and the repeated administration period (Cohort 2). The dose used in the repeated administration period (Cohort 2) will be determined based on plasma drug concentrations obtained in the single administration period (Cohort 1). The single administration period (Cohort 1) comprises Period 1, in which the conventional tablet will be administered, and Periods 2 and 3, in which the QW formulation will be administered. If the single administration period (Cohort 1) fails to produce sufficient plasma drug concentrations, another single administration period (Cohort 1') will be added during which the QW formulation will be administered at higher single doses. Only if progression to the repeated administration period (Cohort 2) is judged to be appropriate based on the results of the single administration period (Cohort 1 and Cohort 1' [as necessary]), will the repeated administration period (Cohort 2) be implemented (see Figure 3.1-1). The repeated administration period (Cohort 2) comprises Period 1, in which subjects will receive a single administration of the conventional tablet, and Period 2, in which subjects will receive 5 administrations of the QW formulation.

In the single administration period (Cohort 1), subjects will receive a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, the QW formulation at 24 mg on Day 1 of Period 2, and the QW formulation at 48 mg on Day 1 of Period 3, all as single administrations in a fasted state.

In the single administration period (Cohort 1'), subjects will receive a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, the QW formulation at 30 mg on Day 1 of Period 2, and the QW formulation at 60 or 54 mg on Day 1 of Period 3, all as single administrations in a fasted state.

In the repeated administration period (Cohort 2), subjects will receive a single administration of a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, and

repeated administration of the QW formulation on Days 1, 8, 15, 22, and 29 of Period 2. The doses of the QW formulation will be determined based on the results of the single administration period (Cohort 1 and Cohort 1' [as necessary]).

In the single administration period (Cohort 1 and Cohort 1' [as necessary]), subjects will be required to be hospitalized at the trial site from the day of IMP administration (Day 1) through the eighth day following IMP administration (Day 8) in Period 1 (conventional tablet) and Periods 2 and 3 (QW formulation). For the other parts of the single administration period, they may remain in the trial site or make trial visits on an outpatient basis. In Period 1 (conventional tablet) of the repeated administration period (Cohort 2), subjects will be required to be hospitalized at the trial site from the day of IMP administration (Day 1) through the eighth day following IMP administration (Day 8). For the other parts of Period 1, they may remain in the trial site or make trial visits on an outpatient basis. In Period 2 (QW formulation) of the repeated administration period (Cohort 2), subjects will be required to be hospitalized at the trial site from the day of the first IMP administration (Day 1) through Day 16, from Day 22 through Day 23, and from Day 29 through Day 36. For the other parts of Period 2, they may remain in the trial site or make visits on an outpatient basis.

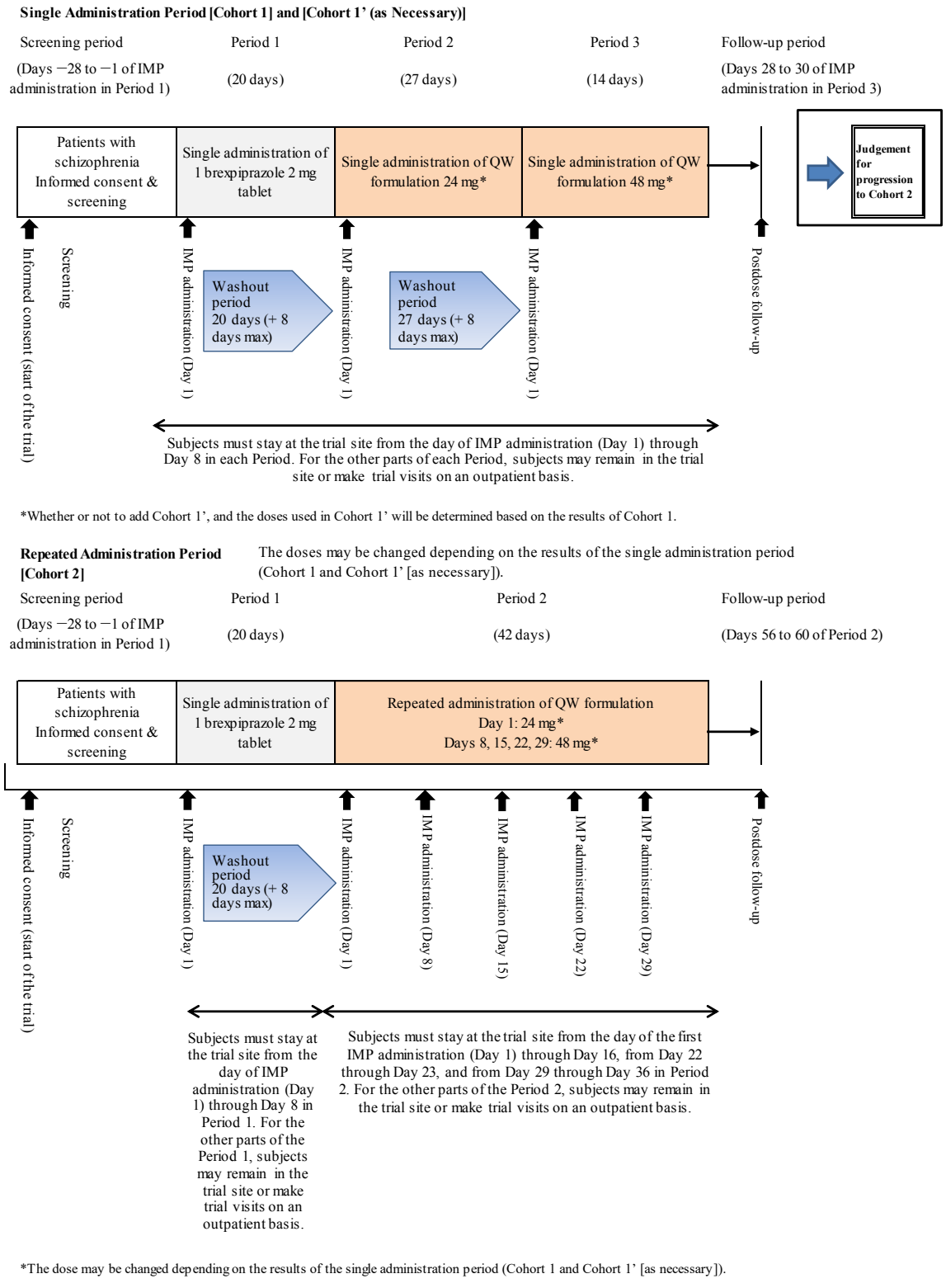

Figure 3.1-1 Trial Design

3.1.1 Cohort 1 (Single Administration Period)

Subjects judged eligible at screening will receive one brexpiprazole 2 mg conventional tablet on Day 1 of Period 1, one 24 mg tablet of the QW formulation on Day 1 of Period 2, and two 24 mg tablets of the QW formulation on Day 1 of Period 3, all as a single oral administration in a fasted state. The trial includes a washout period of 20 days (+ 8 days max) between IMP administration in Period 1 and IMP administration in Period 2 and a washout period of 27 days (+ 8 days max) between IMP administration in Period 2 and IMP administration in Period 3. Brexpiprazole-naïve subjects should be monitored after conventional tablet administration in Period 1 to check if they are free from allergic or hypersensitive reactions. Following administration of the QW formulation in Period 2, safety must be carefully evaluated. Subjects who meet any of the criteria for withdrawal before dose increase as specified in Section 3.9.3.2 Criteria for Withdrawal Before Dose Increase of the QW Formulation must be withdrawn from the trial and not advance to Period 3. If a subject withdrawn from the trial at the discretion of the sponsor after receiving a brexpiprazole 2 mg conventional tablet in Period 1 and undergoing the examinations scheduled for up to Day 14 of Period 1 subsequently takes part in the trial again, the subject will be allowed to resume participation in the trial from Period 2. If a subject withdrawn from the trial at the discretion of the sponsor after receiving a 24 mg tablet of the QW formulation in Period 2 and undergoing the examinations scheduled for up to Day 14 of Period 2 subsequently takes part in the trial again, the subject will be allowed to resume participation in the trial from Period 3.

3.1.2 Cohort 1’ (Additional Single Administration Period, as Necessary)

A simulation of repeated administration will be performed based on the results of Cohort 1 (single administration period). If steady-state plasma brexpiprazole concentrations of the QW formulation are estimated to fall far below the steady-state trough concentration for the 2 mg conventional tablet, Cohort 1’ will be added.

The design described in Section 3.1.1 Cohort 1 (Single Administration Period) applies to Cohort 1’ as well.

The doses of the QW formulation to be used in Cohort 1’ (as necessary) (single administration period) will be determined according to Section 3.8 Procedure for Progression to the Repeated Administration Period (Cohort 2) From the Single Administration Period (Cohort 1 and Cohort 1’ [as Necessary]), and the QW formulation will be administered in a fasted state as per regimen 1 or 2 shown in Table 3.2.1.2.2-1. Brexpiprazole-naïve subjects should be monitored after conventional tablet administration in Period 1 to check if they are free from allergic or hypersensitive

reactions. Following administration of the QW formulation in Period 2, safety must be carefully evaluated. Subjects who meet any of the criteria for withdrawal before dose increase as specified in Section 3.9.3.2 Criteria for Withdrawal Before Dose Increase of the QW Formulation must be withdrawn from the trial and not advance to Period 3.

3.1.3 Cohort 2 (Repeated Administration Period)

Subjects judged eligible at screening will receive a single administration of a brexpiprazole 2 mg conventional tablet on Day 1 of Period 1 in a fasted state. The trial includes a washout period of 20 days (+ 8 days max) between IMP administration in Period 1 and IMP administration in Period 2. Subjects will then receive repeated administration of the QW formulation in a fasted state as per one of the regimens 1 to 5 shown in Table 3.2.1.3.2-1 on Days 1, 8, 15, 22, and 29 of Period 2. Brexpiprazole-naïve subjects should be monitored after conventional tablet administration in Period 1 to check if they are free from allergic or hypersensitive reactions. Following administration of the QW formulation in Period 2, safety must be carefully evaluated. Subjects who meet any of the criteria for withdrawal before dose increase as specified in Section 3.9.3.2 Criteria for Withdrawal Before Dose Increase of the QW Formulation after IMP administration on Day 1 must be withdrawn from the trial without dose increase.

3.2 Trial Treatments

3.2.1 Dose, Regimen and Treatment Period

3.2.1.1 Cohort 1 (Single Administration Period)

3.2.1.1.1 Administration of Brexpiprazole Conventional Tablet

On Day 1 of Period 1, subjects will receive a single oral administration of a brexpiprazole 2 mg conventional tablet together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the conventional tablet until 2 hours after administration, except for the water taken at the time of administration.

3.2.1.1.2 Administration of Brexpiprazole QW Formulation

On Day 1 of each of Periods 2 and 3 in Cohort 1 (single administration period), subjects will receive a single oral administration of the QW formulation at the dose specified in Table 3.2.1.1.2-1 together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of

the QW formulation until 2 hours after administration, except for the water taken at the time of administration.

Table 3.2.1.1.2-1 Doses (Cohort 1) (Single Administration Period)

	Dose					
Treatment period	Period 2			Period 3		
Regimen	Dose	Tablet	No. of Tablets	Dose	Tablet	No. of Tablets
1	24 mg	24 mg tablet	1 tablet	48 mg	24 mg tablet	2 tablets

3.2.1.2 Cohort 1' (as Necessary) (Single Administration Period)

3.2.1.2.1 Administration of Brexpiprazole Conventional Tablet

On Day 1 of Period 1, subjects will receive a single oral administration of a brexpiprazole 2 mg conventional tablet together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the conventional tablet until 2 hours after administration, except for the water taken at the time of administration.

3.2.1.2.2 Administration of Brexpiprazole QW Formulation

On Day 1 of each of Periods 2 and 3 in Cohort 1' (as necessary) (single administration period), subjects will receive a single oral administration of the QW formulation together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the QW formulation until 2 hours after administration, except for the water taken at the time of administration. The doses of the QW formulation to be used in Cohort 1' (as necessary) (single administration period) will be determined according to Section 3.8 Procedure for Progression to the Repeated Administration Period (Cohort 2) From the Single Administration Period (Cohort 1 and Cohort 1' [as Necessary]), and the QW formulation will be administered in a fasted state as per regimen 1 or 2 shown in Table 3.2.1.2.2-1.

Table 3.2.1.2.2-1 Doses (Cohort 1' [as Necessary] [Single Administration Period])

	Dose					
Treatment period	Period 2			Period 3		
Regimen	Dose	Tablet	No. of Tablets	Dose	Tablet	No. of Tablets
1	30 mg	30 mg tablet	1 tablet	54 mg	24 mg tablet 30 mg tablet	1 tablet each
2	30 mg	30 mg tablet	1 tablet	60 mg	30 mg tablet	2 tablets

3.2.1.3 Cohort 2 (Repeated Administration Period)

3.2.1.3.1 Administration of Brexpiprazole Conventional Tablet

On Day 1 of Period 1, subjects will receive a single oral administration of a brexpiprazole 2 mg conventional tablet together with approximately 150 mL of water in the morning after at least 10 hours of fasting. Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the conventional tablet until 2 hours after administration, except for the water taken at the time of administration.

3.2.1.3.2 Administration of Brexpiprazole QW Formulation

In Period 2, subjects will be orally administered the QW formulation together with approximately 150 mL of water in the morning after at least 10 hours of fasting, as per one of regimens 1 to 5 shown in Table 3.2.1.3.2-1 based on the results of the single administration period (Cohort 1 and Cohort 1' [as necessary]). Subjects are not to take any food until 4 hours after administration. Subjects are not to take any fluids from 1 hour before administration of the QW formulation until 2 hours after administration, except for the water taken at the time of administration.

Table 3.2.1.3.2-1 Doses (Cohort 2 [Repeated Administration Period])

	Dose					
Treatment period	**Period 2**					
Day	1			8, 15, 22, and 29		
Regimen	Dose	Tablet	No. of Tablets	Dose	Tablet	No. of Tablets
1	24 mg	24 mg tablet	1 tablet	48 mg	24 mg tablet	2 tablets
2	18 mg	18 mg tablet	1 tablet	36 mg	18 mg tablet	2 tablets
3	24 mg	24 mg tablet	1 tablet	42 mg	18 mg tablet 24 mg tablet	1 tablet each
4	30 mg	30 mg tablet	1 tablet	54 mg	24 mg tablet 30 mg tablet	1 tablet each
5	30 mg	30 mg tablet	1 tablet	60 mg	30 mg tablet	2 tablets

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

3.3.1.1 Number of Subjects

The target number of subjects is 40 in total: 20 subjects completing assessment on Day 14 of Period 3 in the single administration period (Cohort 1) and 20 subjects completing assessment on Day 42 of Period 2 in the repeated administration period (Cohort 2). If another single administration period (Cohort 1') with new doses is added, the target

number of subjects for Cohort 1' (as necessary) is also 20 subjects completing assessment on Day 14 of Period 3 of this cohort (in that case, making a total of 60 subjects) (see Section 7.1 Determination of Sample Size).

3.3.1.2 Trial Population

Patients from 18 years of age to under 65 years of age with a diagnosis of schizophrenia (295.90) based on DSM-5®

3.3.2 Subject Numbering

Each subject who provided written consent to participate in the trial will be assigned a unique subject identifier (site number [3 digits] + subject number [S + 5 digits]). The site number will be designated by the sponsor. A subject number is a serial in-site number starting with S00001, which is given to each subject in chronological order of provision of consent. Each subject who takes part in the trial again following withdrawal from the trial at the discretion of the sponsor will be assigned the same subject identifier that was assigned to them at the time when they first participated in the trial.

3.4 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, either by the investigator, subinvestigator, or by the medical monitor.

3.4.1 Informed Consent

Informed consent will be obtained from all subjects (and the subjects' legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision. Consent will be documented on a written informed consent form (ICF). The ICF will be approved by the same institutional review board (IRB) that approves this protocol. In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again, informed consent will also be obtained from all such subjects (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[2], and local regulatory requirements.

Investigators or subinvestigators may discuss the possibility for entry with a potential subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are

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

Potential subjects (and the subjects' legal representatives if they are minors or are hospitalized for reasons of medical protection) 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 plain language to the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) by the investigator or subinvestigator, the IRB approved written ICF will be signed and dated by both the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) and the person obtaining consent (investigator or subinvestigator). If a study collaborator has provided a supplemental explanation, the IRB approved written ICF will also be signed and dated by the study collaborator. The subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects (and the subjects' legal representatives if they are minors or are hospitalized for reasons of medical protection) 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 an informed and voluntary decision as to whether or not they wish to continue their participation in the trial.

For CYP2D6 genetic testing and DNA storage, separately from the main trial, written informed consent will be obtained from subjects (and the subjects' legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision in a similar manner. CYP2D6 genetic testing is mandatory and those subjects (and the subjects' legal representatives if they are minors or are hospitalized for reasons of medical protection) who do not consent to CYP2D6 genetic testing cannot participate in the trial. On the other hand, DNA storage is optional and refusal to allow DNA storage will not affect trial participation. In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again, written informed consent will be obtained from them (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision, if they have yet to complete CYP2D6 genetic testing.

3.4.2 Inclusion Criteria

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

Subjects withdrawn from the trial at the discretion of the sponsor will have to be reevaluated to ensure they still meet the inclusion criteria in Table 3.4.2-1 if they are to take part in the trial again.

Table 3.4.2-1 Inclusion Criteria (for All Cohorts)

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®
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	Persons who provide written informed consent before commencement of any trial-related procedures and whom the investigator or subinvestigator judges to be capable of following all the conditions of this trial
6	Patients who, in the judgement of the investigator or subinvestigator, have stable psychotic symptoms maintained by administration of an antipsychotic (other than clozapine) within the dosing range indicated below, before commencement of IMP administration • Antipsychotic medication comprising no more than two active components • A daily dose equivalent to no more than 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 Appendix 5. 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.

[Rationale for inclusion criteria]

1. This criterion is based on epidemiological data on age at onset and prevalence of schizophrenia. An age of 18 years was set as the lower limit because individuals of this age, a high age in adolescence, are old enough to take responsibility for their own health and drug therapy, 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 subject safety and possible effects on PK evaluation.
4. This criterion was set to reduce possible interindividual variations in PK due to obesity. Considering that the subjects in this trial are patients, the upper limit for obesity or adiposity was set as a BMI of less than 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.

3.4.3 Exclusion Criteria

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

Subjects withdrawn from the trial at the discretion of the sponsor cannot take part in the trial again if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria (for All Cohorts)

1	Patients with a diagnosis of a concurrent mental disorder besides schizophrenia (schizoaffective disorder, major depressive disorder, bipolar I disorder, bipolar II disorder, general anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, dementia or mild neurocognitive disorder, personality disorder, etc) based on DSM-5® (However, this exclusion does not apply to caffeine- or tobacco-related disorders)
2	Patients who fail to meet the specified requisite washout periods for the prohibited concomitant drugs and foods indicated below before commencement of IMP administration, or patients who are anticipated to take any of the drugs or foods in the following table during the study period

Drugs and Foods	Washout Period
Adrenaline	28 days
Rexulti tablets (planned)	21 days
Clozapine	Starting from informed consent
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers listed in Appendix 3 (Except topical agents listed in Appendix 4 for which use with the IMP is permitted)	14 days
Other investigational drugs under development	60 days
Foods and beverages containing St. John's Wort, Ginkgo biloba, goldenseal, or echinacea (Echinacea purpurea)	14 days
Foods and beverages containing grapefruit, Seville orange, or star fruit	7 days

3	Patients who have previously undergone gastrointestinal surgery that could affect PK evaluations
4	Patients who are using clozapine at the time of informed consent
5	Patients who have received electroconvulsive therapy within 60 days before commencement of IMP administration

Table 3.4.3-1 Exclusion Criteria (for All Cohorts)	
6	Patients with clinically problematic disorders of the nervous system, liver, kidneys, metabolic system, blood system, immune system, cardiovascular system, respiratory system, or digestive system (However, such patients may be included if the condition is mild or well-controlled and is considered to not affect safety or PK evaluations.)
7	Patients who fall under any of the following criteria at screening • Inadequately controlled hypertension (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
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 AST: > 2 × upper limit of normal ALT: > 2 × upper limit of normal CPK: > 3 × upper limit of normal Creatinine: ≥ 2 mg/dL QTcF > 450 msec
9	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 a) Glycosylated hemoglobin (HbA1c) of ≥ 7.0% according to the global standard value [NGSP value] b) Fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL
10	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
11	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

Table 3.4.3-1	Exclusion Criteria (for All Cohorts)
12	Patients with a positive drug test at screening (However, such patients may be included if their condition is not diagnosed as substance-related or addictive disorder, according to the DSM-5® diagnostic criteria.)
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 complication of hypothyroidism or hyperthyroidism (except in cases where the condition has been kept stable for at least 90 days through drug therapy) or patients who show abnormal values for thyroid-stimulating hormone (TSH) and free thyroxin (FT_4) in the screening examination
16	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
17	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
18	Patients who before commencement of IMP administration are judged to have a significant risk of committing suicide based on medical history or diagnosis, who have shown suicidal behavior within the past 2 years, or who have answered "yes" to Questions 4 or 5 in the Columbia-Suicide Severity Rating Scale (C-SSRS) within the last 24 months.
19	Female patients who are nursing or have a positive pregnancy test result before administration of the IMP
20	Sexually active male patients and sexually active female patients of child-bearing potential who do not agree to practice 2 methods of birth control or remain abstinent during this trial and for 30 days after the final administration of IMP. If practicing birth control, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, or condom (all methods approved or certified in Japan)
21	Patients with a history of allergy to more than one medication
22	Patients with a history of hypersensitivity or allergy to brexpiprazole
23	Patients who have participated in another clinical trial within 60 days before commencement of IMP administration
24	Patients who have been compulsorily hospitalized under the Mental Health and Welfare Law of Japan
25	Patients judged by the investigator or subinvestigator to be unsuitable for participation in the trial

Subjects excluded for positive drug test are not eligible to be rescreened for participation in the trial. However, subjects excluded for other reasons may be rescreened if the exclusion characteristic has changed. In the event that the subject is rescreened, a new

ICF must be signed, a new subject number assigned, and all screening procedures repeated.

[Rationale for Exclusion Criteria]	
1, 25.	These criteria are specified to exclude patients considered to be inappropriate for inclusion in this trial.
2, 6.	These criteria are specified in consideration of safety and PK.
3.	This criterion is specified in consideration of PK.
5.	This criterion is specified in consideration of safety, as concomitant use of electroconvulsive therapy is likely to lower the convulsive threshold.
4, 7 to 17, 20 to 24.	These criteria were set based on safety consideration.
18.	This criterion is specified to minimize the risk of suicide during the trial period.
19.	This criterion is specified in consideration on safety, as the safety of brexpiprazole during pregnancy or while breastfeeding has not yet been established.

3.5 Endpoints

3.5.1 Pharmacokinetic Endpoints

Plasma concentrations and PK parameters of brexpiprazole after single and repeated administration of QW formulation

3.5.2 Safety (for All Cohorts)

Adverse events, clinical laboratory tests, physical examination, vital signs (blood pressure, pulse rate, and body temperature), weight, 12-lead ECG, Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), Columbia-Suicide Severity Rating Scale (C-SSRS)

3.5.3 Pharmacogenomics

CYP2D6 genotyping

3.5.4 Other

CGI-S, Clinical Global Impression-Improvement (CGI-I)

3.6 Measures to Minimize/Avoid Bias

This trial has an open-label design.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1 and Table 3.7-2. Acceptable windows for observations, tests, and assessments are shown in Table 3.7-3 to Table 3.7-6.

Table 3.7-1 Schedule of Assessments (Cohort 1 and Cohort 1' [as Necessary]; Single Administration Period)

Treatment Period	Screening	Period 1 (2 mg Conventional Tablet)														Washout period[d]	Period 2 (24 mg QW Formulation)										Washout period[d]	Period 3 (48 mg QW Formulation)												Early Termination[b]	Follow-up
Day	-28 to -1	1							2	3	4	6	8	11	14		1				2	3	4	6	8	14		1				2	3	4	6	8	11	14		
Hours postdose		Predose	0	2	4	6	8	12	24	48	72	120	168	240	312		Predose	0	3	9	24	36	48	72	120	168	312		Predose	0	3	9	24	36	48	72	120	168	240	312		Days 28-30
Informed consent	X																																							
Informed consent to CYP2D6 genotyping	X																																							
Informed consent to blood sampling for DNA storage (optional)	X																																							
Inclusion/exclusion criteria	X																																							
Demographics (including height)	X																																							
Urine drug screening	X																X[f]											X[f]													
Pregnancy test (women of childbearing potential only)	X	X[f]													X		X[f]									X		X[f]											X	X	
Blood sampling for CYP2D6 genotyping		X																																						
Blood sampling for DNA storage (optional)		X																																						
Subject enrollment	X	X															X											X													
IMP administration			X															X											X												
Blood sampling for plasma drug concentration measurement		X[g]		X	X	X	X	X	X	X	X	X	X	X	X		X[g]		X	X	X	X	X			X		X[g]		X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[d]	X														X							X			X							X				X		X	X	
Physical examination	X	X[g]							X				X		X		X[g]		X	X	X	X	X	X	X	X	X		X[g]		X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse rate, body temperature)	X	X[g]							X				X		X		X[g]			X	X		X	X		X	X		X[g]			X	X		X	X		X	X	X	
Weight	X	X[f]													X		X[f]									X	X		X[f]									X	X	X	
12-lead ECG[e]	X	X[a,f]							X						X					X	X			X		X	X					X	X			X		X	X	X	
DIEPSS		X[f]											X		X		X[f]							X		X	X		X[f]							X		X	X	X	X
C-SSRS	X	X[f]							X				X		X		X[f]				X		X	X	X	X	X		X[f]			X		X	X	X	X	X	X	X	
CGI-S		X[f]											X		X		X[f]									X	X		X[f]									X	X	X	
CGI-I													X		X											X	X											X	X	X	
Adverse events	←																																							→
Concomitant medications and therapies	←																																							→
Hospitalization period	Outpatient visits permitted	Hospitalization												Outpatient visits permitted			Hospitalization									Outpatient visits permitted		Hospitalization										Outpatient visits permitted			

Note 1: This table shows time points for assessments and should be used together with Section 3.7.3 Schedule of Assessments, which summarizes the timing of assessments and activities by trial period/trial day.

Note 2: If Cohort 1' (as necessary) (single administration period) is added, the doses of the QW formulation used in Periods 2 and 3 may be changed (Section 3.2 Trial Treatments).

[a] If IMP administration takes place within 14 days after the same test was performed during screening, a repeat test is not required.

[b]If the subject refuses an early termination (ET) assessment or if the investigator or subinvestigator finds it impossible to perform an ET assessment in emergencies or for other reasons, only feasible observation/tests will be performed.

[c]A washout period of 20 days (+ 8 days max) will be placed between IMP administration in Period 1 and IMP administration in Period 2 and a washout period of 27 days (+ 8 days max) will be placed between IMP administration in Period 2 and IMP administration in Period 3.

[d]A thyroid function test will be performed only at 1 time point: screening.

[e]Must be performed prior to blood sampling for plasma drug concentration measurement and clinical laboratory tests.

[f]Must be performed within 1 day predose.

[g]Must be performed within 2 hours predose.

Table 3.7-2 Schedule of Assessments (Cohort 2; Repeated Administration Period)

Treatment Period	Screening	Period 1 (2 mg Conventional Tablet)														Washout period[c]
Day / Days postdose (1 day postdose defined as the day of most immediate administration)	-28 to -1	1							2	3	4	6	8	11	14	
Hours postdose		Predose	0	2	4	6	8	12	24	48	72	120	168	240	312	
Informed consent	X															
Informed consent to CYP2D6 genotyping	X															
Informed consent to blood sampling for DNA storage (optional)	X															
Inclusion/exclusion criteria	X															
Demographics (including height)	X															
Urine drug screening	X															
Pregnancy test (women of childbearing potential only)	X	X[f]													X	
Blood sampling for CYP2D6 genotyping		X														
Blood sampling for DNA storage (optional)		X														
Subject enrollment	X	X														
IMP administration			X													
Blood sampling for plasma drug concentration measurement		X[g]		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[d]	X														X	
Physical examination	X	X[g]							X				X		X	
Vital signs (blood pressure, pulse rate, body temperature)	X	X[g]							X				X		X	
Weight	X	X[f]													X	
12-lead ECG[e]	X	X[a,f]							X						X	
DIEPSS		X[f]											X		X	
C-SSRS	X	X[f]							X				X		X	
CGI-S		X[f]											X		X	
CGI-I													X		X	
Adverse events	←															
Concomitant medications and therapies	←															
Hospitalization period	Outpatient visits permitted	Hospitalization												Outpatient visits permitted		

Treatment Period	Period 2																																		Follow-up
	24 mg QW Formulation							48 mg QW Formulation																										Early termination[b]	
Day	1			2	3	4	6	8			9	10	11	13	15		16	18	22		23	25	29				30		31	32	34	36	39	42		
Days postdose (1 day postdose defined as the day of most immediate administration)	1			2	3	4	6	1			2	3	4	6	1		2	4	1		2	4	1				2		3	4	6	8	11	14		Days 56-60
Hours postdose	Predose	Administration (1)	9					Predose	Administration (2)[h]	9					Predose	Administration (3)[h]			Predose	Administration (4)[h]			Predose	Administration (5)[i]	3	9	24	36	48	72	120	168	240	312		
Informed consent																																				
Informed consent to CYP2D6 genotyping																																				
Informed consent to blood sampling for DNA storage (optional)																																				
Inclusion/exclusion criteria																																				
Demographics (including height)																																				
Urine drug screening	X[f]																																			
Pregnancy test (women of childbearing potential only)	X[f]																																	X	X	
Blood sampling for CYP2D6 genotyping																																				
Blood sampling for DNA storage (optional)																																				
Subject enrollment	X																																			
IMP administration		X							X							X				X				X												
Blood sampling for plasma drug concentration measurement	X[g]							X[g]							X[g]				X[g]				X[g]		X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests[d]					X			X[f]				X			X[f]				X[f]				X[f]											X	X	
Physical examination	X[g]		X	X	X	X	X	X[g]		X	X	X	X	X	X[g]		X	X	X[g]		X	X	X[g]		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse rate, body temperature)	X[g]		X	X	X	X		X[g]		X	X	X	X		X[g]		X	X	X[g]		X	X	X[g]				X		X	X		X		X	X	
Weight	X[f]							X[f]							X[f]				X[f]				X[f]											X	X	
12-lead ECG[e]			X	X		X		X[f]		X	X		X		X[f]		X	X	X[f]		X	X	X[f]				X			X		X		X	X	
DIEPSS	X[f]					X		X[f]					X		X[f]				X[f]				X[f]									X		X	X	X
C-SSRS	X[f]			X	X	X	X	X[f]			X	X	X	X	X[f]		X	X	X[f]		X	X	X[f]				X		X	X	X	X	X	X	X	
CGI-S	X[f]							X[f]							X[f]				X[f]				X[f]									X		X	X	
CGI-I								X[f]							X[f]				X[f]				X[f]									X		X	X	
Adverse events																																				→
Concomitant medications and therapies																																			→	
Hospitalization period	Hospitalization																	Outpatient visits permitted	Hospitalization			Outpatient visits permitted	Hospitalization										Outpatient visits permitted			

Note 1: This table shows time points for assessments and should be used together with Section 3.7.3 Schedule of Assessments, which summarizes the timing of assessments and activities by trial period/trial day.

Note 2: The doses of the QW formulation may be changed depending on the results of Cohort 1 and Cohort 1' (as necessary) (single administration period) (Section 3.2 Trial Treatments).

[a]If IMP administration takes place within 14 days after the same test was performed during screening, a repeat test is not required.

[b]If the subject refuses an early termination (ET) assessment or if the investigator or subinvestigator finds it impossible to perform an ET assessment in emergencies or for other reasons, only feasible observation/tests will be performed.

[c]A washout period of 20 days (+ 8 days max) will be placed between IMP administration in Period 1 and IMP administration in Period 2.

[d]A thyroid function test will be performed only at 1 time point: screening.

[e]Must be performed prior to blood sampling for plasma drug concentration measurement and clinical laboratory tests.

[f]Must be performed within 1 day predose.

[g]Must be performed within 2 hours predose.

[h]With Day 1 defined as the day of the first administration, administration on Days 8, 15, and 22 must take place within ± 24 hours of the clock time when the first administration occurred.

[i]With Day 1 defined as the day of the first administration, administration on Day 29 must take place within ± 5 hours of the clock time when the first administration occurred.

Table 3.7-3	**Acceptable Windows for Observations, Tests, and Assessments Following a Single Administration of Conventional Tablet (Period 1 of Cohort 1 and Cohort 1' [as Necessary] [Single Administration Period] and Period 1 of Cohort 2 [Repeated Administration Period])**
Time Point	**Acceptable Window for All Observations, Tests, and Assessments (Including Blood Sampling for Plasma Drug Concentration Measurement)**
Predose	Blood sampling for plasma drug concentration measurement, physical examination, vital signs: within 2 hours predose Other: within 1 day predose
2, 4, 6, 8, 12 hours postdose	± 30 minutes
24, 48, 72 hours postdose	± 2 hours
120 hours postdose	−2 to + 4 hours
168 hours postdose	± 4 hours
240, 312 hours postdose	± 24 hours

In cases of withdrawal, only feasible observations/tests/assessments will be performed.

Table 3.7-4	**Acceptable Windows for Observations, Tests, and Assessments Following a Single Administration of QW Formulation (Period 2 of Cohort 1 and Cohort 1' [as Necessary] [Single Administration Period])**
Time Point	**Acceptable Window for All Observations, Tests, and Assessments (Including Blood Sampling for Plasma Drug Concentration Measurement)**
Predose	Blood sampling for plasma drug concentration measurement, physical examination, vital signs: within 2 hours predose Other: within 1 day predose
3 hours postdose	± 30 minutes
9 hours postdose	± 30 minutes Only 12-lead ECG: ± 60 minutes
24, 36, 48, 72 hours postdose	± 2 hours
120 hours postdose	−2 to + 4 hours
168 hours postdose	± 4 hours
312 hours postdose	± 24 hours

In cases of withdrawal, only feasible observations/tests/assessments will be performed.

Table 3.7-5	**Acceptable Windows for Observations, Tests, and Assessments Following a Single Administration of QW Formulation (Period 3 of Cohort 1 and Cohort 1' [as Necessary] [Single Administration Period])**
Time Point	**Acceptable Window for All Observations, Tests, and Assessments (Including Blood Sampling for Plasma Drug Concentration Measurement)**
Predose	Blood sampling for plasma drug concentration measurement, physical examination, vital signs: within 2 hours predose Other: within 1 day predose
3 hours postdose	± 30 minutes
9 hours postdose	± 30 minutes Only 12-lead ECG: ± 60 minutes
24, 36, 48, 72 hours postdose	± 2 hours
120 hours postdose	−2 to + 4 hours
168 hours postdose	± 4 hours
240, 312 hours postdose	± 24 hours

In cases of withdrawal, only feasible observations/tests/assessments will be performed.

Table 3.7-6 Acceptable Windows for Observations, Tests, and Assessments Following Repeated Administration of QW Formulation (Period 2 of Cohort 2 [Repeated Administration Period])

Day of QW Formulation Administration (Day 1 is defined as the day of the first administration)	Time Point (0 hour [1 day postdose] is defined as the time and day of the most immediate administration)	Plasma Drug Concentration Measurement	Other Observations, Tests, Assessments
Day 1 Day 8[a]	Predose	Within 2 hours predose	Physical examination, vital signs: within 2 hours predose Other: within 1 day predose
	9 hours postdose	NA	± 4 hours
	2, 3, 4, 6 days	NA	Within the same day
Day 15[a] Day 22[a]	Predose	Within 2 hours predose	Physical examination, vital signs: within 2 hours predose Other: within 1 day predose
	2 days	NA	Within the same day
	4 days	NA	± 1 day
Day 29 (last)[b]	Predose	Within 2 hours predose	Physical examination, vital signs: within 2 hours predose Other: within 1 day predose
	3 hours postdose	± 30 minutes	± 30 minutes
	9 hours postdose	± 30 minutes	± 30 minutes
	24, 36, 48, 72 hours postdose	± 2 hours	± 2 hours
	120 hours postdose	−2 to + 4 hours	−2 to + 4 hours
	168 hours postdose	± 4 hours	± 4 hours
	240 hours postdose 312 hours postdose	± 24 hours	± 24 hours

In cases of withdrawal, only feasible observations/tests/assessments will be performed.

[a]With Day 1 defined as the day of the first administration, administration on Days 8, 15, and 22 must take place within ± 24 hours of the clock time when the first administration occurred.

[b]With Day 1 defined as the day of the first administration, administration on Day 29 must take place within ± 5 hours of the clock time when the first administration occurred.

3.7.1 General Inpatient Procedures

Subjects will remain either in a seated or semi recumbent position for the first 4 hours following IMP administration except during brief periods where protocol related procedures need to be performed.

3.7.2 Dietary Requirements

See Section 3.2 Trial Treatments.

3.7.3 Schedule of Assessments

3.7.3.1 Screening (for All Cohorts)

Prior to initiation of any protocol-related procedures, the procedures and characteristics of the trial will be explained to the subject and written informed consent will be obtained from the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection). The following subject information will be recorded on source documents and the electronic case report form (eCRF).

- Date of informed consent
- Subject identifier
- Previous subject identifier, if the subject was rescreened
- Date of informed consent for CYP2D6 genetic testing*
- Date of informed consent for DNA storage (optional)*

* Informed consent will be obtained before blood sampling for CYP2D6 genetic testing and blood sampling for DNA storage (optional).

In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again and resume participation in the same cohort, the procedures and characteristics of the trial will be explained to them and written informed consent will be obtained from them (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) prior to initiation of any protocol-related procedures. The following subject information will be recorded on the source documents and the eCRF.

- Date on which informed consent was obtained again
- Subject identifier
- Date of informed consent for CYP2D6 genetic testing**
- Date of informed consent for DNA storage (optional)**

** Informed consent will be obtained before blood sampling for CYP2D6 genetic testing and blood sampling for DNA storage (optional). However, if blood samples had already been collected before the subject was withdrawn from the trial, it will not be necessary to obtain consent again.

After informed consent is obtained, the following observations, tests, and assessments will be performed as screening procedures within 28 days before IMP administration in Period 1 (Days −28 to −1), and the subject's eligibility to participate in the trial will be assessed.

[Items]

- Inclusion/exclusion criteria
- Demographics (date of birth, sex, country [Japan], race, ethnicity, complications, medical history)
- Height, weight, and body mass index (BMI): Height will be measured in increments of 0.1 cm. For a height measured to the second or further decimal place, the number will be rounded off to the first decimal place. BMI will be determined based on height and weight measurements at screening, using the following formula: BMI = weight (kg) / height $(m)^2$.
- Urine drug screening
- Urine pregnancy test (women of childbearing potential only)
- Clinical laboratory tests (blood and urine samplings)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature): Blood pressure and pulse rate 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 (performed prior to blood sampling for clinical laboratory tests)
- C-SSRS (the "Baseline/Screening Version" will be used)
- AEs
- Concomitant medications and therapies

In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again and resume participation in the same cohort, the following observations, tests, and assessments will be performed as screening procedures, after informed consent is obtained, within 28 days (Days −28 to −1) before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial, and their eligibility to participate in the trial will be assessed.

[Items]

- Inclusion/exclusion criteria
- Height,* weight, and BMI*: Height will be measured in increments of 0.1 cm. For a height measured to the second or further decimal place, the number will be rounded off to the first decimal place. BMI will be determined based on height and weight measurements at screening, using the following formula: BMI = weight (kg) / height $(m)^2$.

* The height measurement obtained at screening when the subject first participated in the trial may be used. In that case, the height measurement obtained at screening when the subject first participated in the trial should be used in calculation of BMI.

- Urine drug screening

- Urine pregnancy test (women of childbearing potential only)
- Clinical laboratory tests (blood and urine sampling)
- Physical examination
- Vital signs (blood pressure, pulse rate, and body temperature): Blood pressure and pulse rate 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 (performed prior to blood sampling for clinical laboratory tests)
- C-SSRS (the "Since Last Visit" will be used)
- AEs
- Concomitant medications and therapies

3.7.3.2 Administration of Brexpiprazole Conventional Tablet (Period 1) (for All Cohorts)

3.7.3.2.1 Day 1 of Period 1

3.7.3.2.1.1 Enrollment of Subjects

On Day 1 of Period 1, one brexpiprazole conventional tablet will be administered to eligible subjects.

3.7.3.2.1.2 Within 1 Day Predose

The following will be performed.

- Pregnancy test
- Blood sampling for CYP2D6 genetic testing (including blood sampling for DNA storage [optional])
- Blood sampling for plasma drug concentration measurement (within 2 hours predose)
- Physical examination (within 2 hours predose)
- Vital signs (blood pressure, pulse rate, and body temperature) (within 2 hours predose)
- Weight
- 12-Lead ECG
- DIEPSS
- C-SSRS (The "Since Last Visit" will be used)
- CGI-S
- AEs
- Concomitant medications and therapies

12-Lead ECG may be omitted if IMP administration takes place within 14 days after the same test was performed during screening.

3.7.3.2.1.3 Postdose

The investigator or subinvestigator will perform the observations, tests, and assessments indicated in Table 3.7-1 and Table 3.7-2 and record their dates and results.

3.7.3.3 QW Formulation Single Administration Periods (Periods 2 and 3 of Cohort 1 and Cohort 1' [as Necessary])

The investigator or subinvestigator will enroll subjects who he/she thinks can safely receive IMP administration in Periods 2 and 3, perform the observations, tests, and assessments indicated in Table 3.7-1, and record their dates and results. Subjects withdrawn from the trial at the discretion of the sponsor will only be enrolled again to resume participation in the trial from Period 2 or 3 if they are confirmed to be eligible.

3.7.3.4 QW Formulation Repeated Administration Period (Period 2 of Cohort 2)

The investigator or subinvestigator will enroll subjects who he/she thinks can safely receive IMP administration in Period 2, perform the observations, tests, and assessments indicated in Table 3.7-2, and record their dates and results.

3.7.3.5 Follow-up After IMP Administration (for All Cohorts)

The following observations, tests, and assessments will be performed between Day 28 and Day 30 of Period 3 of Cohort 1 and Cohort 1' (as necessary) (single administration period) and between Day 56 and Day 60 of Period 2 of Cohort 2 (repeated administration period).

[Items]

- Physical examination
- DIEPSS
- AEs

3.7.4 Prior and Concomitant Medications

The investigator or subinvestigator will record on the source documents and eCRF all medications (name of drug, purpose of use, dose, frequency, route of administration, start and end dates of treatment) and therapies (name of therapy, purpose of use, start and end dates of treatment) taken by the subject from 30 days prior to signing of informed consent through the end of assessment on Day 14 of Period 3 or the end of early termination (ET) assessment in Cohort 1 and Cohort 1' (as necessary) (single administration period) and

from 30 days prior to signing of informed consent through the end of assessment on Day 42 of Period 2 or the ET assessment in Cohort 2. The investigator or subinvestigator will record all medications (name of drug, purpose of use, dose, frequency, route of administration, start and end dates of treatment) and therapies (name of therapy, purpose of use, start and end dates of treatment) 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) on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, medications and therapies will be recorded in the same manner after participation in the trial is resumed. Medications and therapies that were introduced after withdrawal from the trial at the discretion of the sponsor and terminated up to 30 days before the date on which the subject provided his/her signature for re-consent will be recorded as far as possible.

3.7.5 Safety Assessments

3.7.5.1 Adverse Events

Refer to Section 5 Reporting of Adverse Events for the methods and timing for assessing, recording, and analyzing AEs.

3.7.5.2 Clinical Laboratory Assessments

Data on laboratory test items shown in Table 3.7.5.2-1 will be collected at scheduled time points using measuring kits supplied by the central laboratory. The investigator or subinvestigator will review, sign, and date the laboratory assessment report submitted by the central laboratory and record the dates on which blood and urine samples are taken on the source documents and eCRF.

A pregnancy test (human chorionic gonadotropin [hCG] in urine) will be conducted in women of child-bearing potential (WOCBP) prior to trial intervention; results must be available prior to the administration of the IMP.

Table 3.7.5.2-1 Clinical Laboratory Assessments	
Hematology Hemoglobin Hematocrit Red blood cell (RBC) count White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Platelet count Urinalysis Occult blood Glucose Microscopic analysis of RBC/WBC count (per high powered field) pH Protein Ketones Specific gravity	Serum Chemistry Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Albumin Bilirubin, total Blood urea nitrogen (BUN) Uric acid Cholesterol, total Creatinine Gamma glutamyl transpeptidase (γ-GTP) Glucose Lactic dehydrogenase (LDH) Serum electrolytes (Na, K, Cl, Ca, Mg, P, HCO_3) Protein, total Triglycerides Creatine phosphokinase (CPK) Prolactin Glycosylated hemoglobin (HbA1c) Insulin Thyroid function test[a] Thyroid-stimulating hormone (TSH), free thyroxine (FT_4)

[a]Will be performed at only 1 time point: screening.

3.7.5.3 Urine Drug Screening

Data on the following items will be collected at scheduled time points using measuring kits supplied by the central laboratory. The investigator or subinvestigator will record the dates on which urine samples are taken on the eCRF.

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Cocaine
- Marijuana
- Opiates
- Phencyclidine

3.7.5.4 Physical Examination and Vital Sign Assessments

A physical examination will be performed at scheduled time points. The physical examination includes the head, ears, eyes, nose, throat, chest, abdomen, urogenital system, limbs, nerves, skin, and mucosa.

At screening, all physical findings observed after informed consent will be recorded, together with the date of examination, on the source documents and eCRF. Thereafter, whether a physical examination is performed or not and, if performed, the date of examination will be recorded on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and subsequently take part in the trial again, whether a physical examination is performed or not at screening and subsequent time points and, if performed, the date of examination will be recorded on the source documents and eCRF.

It is preferable to have the same physician perform all physical examinations for any individual subject throughout the course of the trial wherever possible. Any new, clinically relevant, postscreening physical findings obtained from the start of the trial to the physical examination before IMP administration on Day 1 of Period 2 and any new, clinically relevant physical findings obtained after the start of IMP administration in Period 2 in comparison with those obtained before IMP administration on Day 1 of Period 2 will be recorded as AEs on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2, any new, clinically relevant physical findings obtained during the screening period in comparison with those obtained at the first screening before withdrawal and any new, clinically relevant physical findings obtained during Periods 2 and 3 in comparison with those obtained before IMP administration in Period 2 will be recorded as AEs on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 3, any new, clinically relevant physical findings obtained during the screening period and Period 3 in comparison with those obtained before IMP administration in Period 2 before withdrawal will be recorded as AEs on the source documents and eCRF.

Vital signs will be measured at scheduled time points. Body temperature (axillary) will be measured in increments of 0.1°C and the date and result of measurement will be recorded on the source documents and eCRF. Blood pressure (systolic and diastolic) and pulse rate will be measured in a sitting position following at least 3 minutes' rest and the date and result of measurement will be recorded on the source documents and eCRF. At screening only, blood pressure and pulse rate will also be measured in the supine and standing positions.

3.7.5.5 Weight

Weight will be measured at scheduled time points. Weight should be measured in 0.1 kg increments using the same scale and the standard measurement method (the subject should wear his/her usual clothes but without shoes) throughout the course of the trial. The date and result of measurement will be recorded on the source documents and eCRF.

3.7.5.6 Electrocardiogram Assessments

Electrocardiography will be performed at scheduled time points using a 12-lead electrocardiograph supplied by the central ECG laboratory.

An ECG will be taken after the subject has remained at rest for at least 5 minutes in a supine position. The heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT interval (QTcF) will be measured. The central ECG laboratory will analyze the measurements and submit an ECG analysis report to the sponsor and the investigator or subinvestigator.

The investigator or subinvestigator will review, sign, and date each ECG reading by referring to the ECG analysis report and record the date of ECG, whether the ECG is normal/abnormal, and findings on the source documents and eCRF. The ECG should be performed prior to any blood sampling (if applicable) at scheduled time points.

3.7.5.7 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale will be performed at 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. The date and result of assessment will be recorded on the source documents and eCRF.

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")

3.7.5.8 Drug-induced Extrapyramidal Symptoms Scale

The investigator or subinvestigator will use DIEPSS at scheduled time points to assess the following 9 items on a 5-point scale from 0 (none, normal) to 4 (severe). The date and result of assessment will be recorded on the source documents and eCRF.

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

3.7.6 Pharmacokinetic Assessments

Plasma concentrations of brexpiprazole will be analyzed using validated high-performance liquid chromatography-tandem mass spectrometry. Additional metabolites that are not identified in the protocol may also be analyzed if new information becomes available. If the need arises, plasma may be used in the study of analysis methods.

The bioanalytical laboratory will submit the results of drug concentration measurement in the form of an electronic file to the sponsor. It is therefore not necessary to record the measurement results on the source documents and eCRF.

3.7.6.1 Time Points for Blood Sampling

3.7.6.1.1 Brexpiprazole Conventional Tablet

In Period 1 of both the single administration period (Cohort 1 and Cohort 1' [as necessary]) and the repeated administration period (Cohort 2), blood samples after dosing of a conventional tablet will be collected at the time points shown in Table 3.7-1 and Table 3.7-2 or at withdrawal. Acceptable windows for blood sampling after dosing of a conventional tablet are shown in Table 3.7-3.

3.7.6.1.2 Brexpiprazole QW Formulation

In Periods 2 and 3 of the single administration period (Cohort 1 and Cohort 1' [as necessary]) and Period 2 of the repeated administration period (Cohort 2), blood samples after dosing of the QW formulation will be collected at the time points shown in Table 3.7-1 and Table 3.7-2 or at withdrawal. Acceptable windows for blood sampling after dosing of the QW formulation are shown in Table 3.7-4 to Table 3.7-6.

[Rationale for time points for blood sampling]

Time points for blood sampling for the conventional tablet were determined based on the following: A single oral dose trial (331-07-002), a multiple oral dose trial (331-10-001), a bioequivalence trial of oral solution (331-10-005), and a bioavailability trial of orally disintegrating tablets (331-102-00019) were conducted in Japan. After conventional tablets 2 mg and 4 mg were administered as a single dose, the median t_{max} for the unchanged drug was 6 hours, and the mean elimination half-life, which was determined at 3 to 8 time points between 36 to 312 hours postdose, was 52.9 to 72.7 hours. A total of 13 time points, namely, predose and 2, 4, 6, 8, 12, 24, 48, 72, 120, 168, 240, and 312 hours postdose, were set for blood sampling in Period 1 of both the single administration period (Cohort 1 and Cohort 1' [as necessary]) and the repeated administration period (Cohort 2) to cover the PK process from absorption to elimination, with reference to the results of the above 4 trials as well as "Partial Amendments to Guideline for Bioequivalence Studies of Generic Products (PFSB/ELD Notification No.0229-10 dated 29 Feb 2012)" (hereinafter referred to as "BE Guideline"), Section 3 Test, A. II. 1. 5) Measurement of biological samples, b. Sampling schedule.

Time points for blood sampling for the QW formulation were determined with reference to the PK data on the OROS formulation from a clinical pharmacology trial (Japan 331-102-00021) for comparative investigation of the PK, tolerability, and safety of 3 types of brexpiprazole QW formulation administered as single oral doses in patients with schizophrenia and with reference to the BE Guideline. A total of 11 time points, namely, predose and 3, 9, 24, 36, 48, 72, 120, 168, 240, and 312 hours postdose, were set for

blood sampling in Period 3 of the single administration period (Cohort 1 and Cohort 1' [as necessary]) and for the fifth administration in Period 2 of the repeated administration period (Cohort 2) to cover the PK process from absorption to elimination. For each of the first to fourth administrations of the QW formulation, 168 hours postdose, the time point of trough concentration, was set for blood sampling to ascertain if the plasma brexpiprazole concentration has reached the steady state. In addition, a total of 7 time points, namely, predose and 3, 9, 24, 36, 48, and 168 hours postdose, were set for blood sampling in Period 2 of the single administration period (Cohort 1 and Cohort 1' [as necessary] to obtain samples for use in estimation of parameters with a population PK analysis model.

3.7.6.2 Pharmacokinetic Plasma Samples

All plasma samples will be shipped to the bioanalytical laboratory. Detailed handling and shipping instructions are provided in Appendix 1.

3.7.7 CYP2D6 Genetic Testing

CYP2D6 genotype and phenotype will be analyzed. CYP2D6*1, *2, *4, *5, *10, *14, *18, *21, and *41 alleles will be analyzed. The CYP2D6 genotype will be determined for each subject based on the CYP2D6 genotyping table (Appendix 2). In addition, based on the CYP2D6 genotype, the phenotype will be classified into the following 4 types: extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM), and unknown. The results of CYP2D6 genetic testing will not, in principle, be disclosed to subjects

The genetic test laboratory will submit the results of CYP2D6 genetic testing in the form of an electronic file to the sponsor. It is therefore not necessary to record the test results on the source documents and eCRF.

3.7.7.1 Deoxyribonucleic Acid Blood Samples for CYP2D6 Genetic Testing

All blood samples will be shipped to the genetic test laboratory. Detailed handling and shipping instructions are provided in Appendix 1.

3.7.8 Future Biospecimen Research Samples

3.7.8.1 DNA Storage

3.7.8.1.1 Objective of DNA Storage

DNA storage will be conducted to enable future exploratory investigation regarding specific DNA mutations related to individual differences in responses to brexpiprazole

(efficacy, safety, or PK) and/or specific DNA mutations related to disease onset, severity, progression, etc.

3.7.8.1.2 Target Subjects of DNA Storage

Blood samples for DNA storage will be collected at the trial sites where DNA storage has been approved by the IRB. Only subjects from whom written informed consent for DNA storage has been obtained on a voluntary basis will be included (if the subject is a minor or hospitalized for reasons of medical protection, written consent must also be obtained from the subject's legal representative).

3.7.8.1.3 Blood Samples for DNA Storage

All blood samples will be shipped to the DNA storage facility. Detailed handling and shipping instructions are provided in Appendix 1. DNA samples will be stored until the earliest of the following time points: 1) when genomic/genetic analysis is judged to be unnecessary, 2) when 15 years have passed since receipt of informed consent for the first DNA storage, 3) when the subject withdraws consent to participate in DNA storage.

3.7.8.1.4 Genomic/Genetic Analysis

Genomic/genetic analysis will be performed only when considered useful for the purpose described in Section 3.7.8.1.1 Objective of DNA Storage.

If it is decided to perform genomic/genetic analysis, a pharmacogenomic research protocol will be prepared and the analysis will be carried out in compliance with the applicable local regulations to be followed when conducting analysis, after obtaining approval from the sponsor's IRB. The results will not be included in the clinical study report. A separate study report will be produced instead.

Target genes for genomic/genetic analysis have yet to be identified and a genomewide association analysis using DNA chips, microarrays, next-generation sequencers, etc, may also be performed; however, the results will still only be used for the purpose specified in Section 3.7.8.1.1 Objective of DNA Storage.

DNA samples for genomic/genetic analysis will be double-coded at the DNA storage facility and then shipped to the genomic/genetic analysis facility (yet to be determined), where genomic/genetic analysis will be performed under a double-coded condition.

3.7.8.1.5 Informed Consent for DNA Storage

Information for Subjects and ICF for DNA storage and genomic/genetic analysis using stored DNA will be prepared and written informed consent will be obtained from each subject consenting to participate in DNA storage. The date of consent will be recorded on the source documents and eCRF.

If the subject withdraws consent to participate in DNA storage during the DNA storage period, the sponsor will instruct the DNA storage facility to dispose of the subject's DNA sample. The DNA storage facility will then dispose of the DNA sample while maintaining subject anonymity. However, if the subject's sample has become unidentifiable, for example, if information (eg, a code table) that links a DNA sample with subject information has been discarded, the disposal of the DNA sample of the subject who has withdrawn consent may become impossible. However, withdrawal from the trial will not be considered withdrawal of consent for DNA storage. Even if they request their sample(s) to be destroyed, subjects will not lose any benefits, medical treatment, or legal rights which they are allowed. Any results of genomic/genetic analysis obtained prior to the withdrawal of consent will not be disposed of.

3.7.8.1.6 Disclosure of Genomic/Genetic Analysis Results to Subjects

Even if genomic/genetic analysis provides some information, such findings would only be exploratory or at an early stage of research, and therefore their scientific reliability and accuracy would not have been fully confirmed. Since disclosure of information the reliability of which has not been scientifically established would be of no benefit to the subjects, the sponsor will not, in principle, disclose the results of genomic/genetic analysis to the subjects.

3.7.9 Other Evaluations

3.7.9.1 Clinical Global Impression - Severity of Illness

The investigator or subinvestigator will assess the severity of schizophrenia on the following 8-point scale using the CGI-S at scheduled time points. The date and result of assessment will be recorded on the source documents and eCRF.

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

3.7.9.2 Clinical Global Impression - Improvement

The investigator or subinvestigator will assess the improvement of schizophrenia on the following 8-point scale using the CGI-I at scheduled time points. In Period 1, the current condition of the subject at the start of Period 1 will be assessed and in Period 2 and Period 3 (Cohort 1 and Cohort 1' [as necessary] [single administration period] only), improvement from the start of Period 2 will be assessed. The date and results of assessment will be recorded on the source documents and eCRF.

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

3.7.10 End of Trial

The end of trial date is defined as the end date of follow-up of the last subject completing the trial, or if the subject is lost to follow-up, the date of the last contact attempt.

3.8 Procedure for Progression to the Repeated Administration Period (Cohort 2) From the Single Administration Period (Cohort 1 and Cohort 1' [as Necessary])

3.8.1 Criteria for Progression to Cohort 2

The sponsor will determine through discussions, and consultation with the medical expert as necessary, whether or not to progress to the repeated administration period (Cohort 2) based on the results of the PK, safety, and CYP2D6 genotype profiles in the single administration period (Cohort 1 and Cohort 1' [as necessary]).

1) PK criteria and procedure for progression to Cohort 2
   Using plasma brexpiprazole concentration data on the conventional tablet and QW formulation from Cohort 1 (single administration period), repeated administration of the 2 mg conventional tablet and the QW formulation at 48 mg will be simulated to ascertain if the dose of 48 mg is appropriate for the QW formulation to be used in Cohort 2 (repeated administration period). If the results of the simulation predict that the QW formulation at 48 mg will produce plasma concentrations far below the trough concentration after repeated dosing of the conventional tablet at 2 mg, then Cohort 1' (single administration period) will be added with the QW formulation at a dose of 54 or 60 mg to assess the safety and tolerability and the doses to be used in Cohort 2 (repeated administration period) will be reassessed. If Cohort 1' (single administration period) is added, a simulation will be performed, and its results will be reviewed in the same manner as in Cohort 1 to ascertain if the selected dose is appropriate for the QW formulation to be used in Cohort 2 (repeated administration period). Conversely, if the results of the simulation predict that the QW formulation at 48 mg will produce plasma concentrations far exceeding the peak concentration after repeated dosing of the conventional tablet at 4 mg, an appropriate dose for repeated administration of the QW formulation will be estimated (36 or 42 mg) based on the results of the simulation and a decision will be made on whether or not to progress to Cohort 2 (repeated administration period).
   In the event that the sponsor finds it impossible to come to a decision alone, the sponsor will consult the medical expert as necessary and determine through discussions whether or not to progress to Cohort 2 (repeated administration period). The contents of the discussions will also be recorded.
2) Safety criteria and procedure for progression to Cohort 2
   If the safety results of the QW formulation in Cohort 1 or Cohort 1' (as necessary) (single administration period) meet any of the following criteria, the sponsor will

consult the medical expert and determine through discussions whether or not to progress to the repeated administration period (Cohort 2). The contents of the discussions will also be recorded.
Between dosing of the QW formulation in Period 2 and 14 days after dosing of the QW formulation in Period 3,

a) At least 1 subject experienced an IMP-related SAE or at least 2 subjects experienced a severe IMP-related AE. Adverse events associated with exacerbation of the underlying disease will be comprehensively assessed through discussions between the medical expert and the sponsor to determine the feasibility of progression to Cohort 2 (repeated administration period).
b) At least 1 subject experienced IMP-related abnormal blood pressure (systolic blood pressure of < 80 mmHg).
c) At least 1 subject experienced any of the following IMP-related abnormal ECGs:
    i) QTc interval (QTcF) of > 500 ms (results at the central ECG laboratory)
    ii) Prolongation in QTc interval (QTcF) by > 60 ms from baseline (predose in Period 2) (results at the central ECG laboratory)

3.8.2 Doses of Brexpiprazole QW Formulation in the Repeated Administration Period (Cohort 2)

The doses of the QW formulation in Cohort 2 (repeated administration period) may be any of the following depending on the PK results in Cohort 1 and Cohort 1' (as necessary) (single administration period):

1) If the results of Cohort 1 (single administration period) with the QW formulation at 48 mg indicate that progression to the repeated administration period (Cohort 2) is appropriate:

- The same subject will receive a single administration of a 2 mg conventional tablet, undergo the washout period, and next receive the first administration of the QW formulation at 24 mg and, subsequently, 4 administrations of the QW formulation at 48 mg.

2) If the results of Cohort 1 (single administration period) indicate that the doses need to be changed (based on the results of Cohort 1' [single administration period]):

- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 30 mg → 4 administrations of the QW formulation at 60 mg
- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 30 mg → 4 administrations of the QW formulation at 54 mg

3) If the results of Cohort 1 (single administration period) indicate that the doses need to be changed (based on the results of a simulation):

- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 24 mg → 4 administrations of the QW formulation at 42 mg
- A single administration of a 2 mg conventional tablet → washout → the first administration of the QW formulation at 18 mg → 4 administrations of the QW formulation at 36 mg

In the event that CYP2D6 genotype-related dose adjustment of the QW formulation is considered necessary on the basis of the results of Cohort 1 and Cohort 1' (as necessary) (single administration period), the sponsor will determine the doses in the repeated administration period (Cohort 2) after discussions with the medical expert as necessary. The contents/results of the discussions will be recorded.

3.9 Stopping Rules, Withdrawal Criteria, and Procedures

3.9.1 Entire Trial

In the event of sponsor termination or suspension of the trial for any reason, prompt notification will be given to the heads of the trial sites and regulatory authorities in accordance with regulatory requirements.

3.9.2 Individual Site

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

3.9.3 Individual Subject Discontinuation

3.9.3.1 Treatment Discontinuation

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

3.9.3.2 Criteria for Withdrawal Before Dose Increase of the QW Formulation

Subjects who meet any of the following criteria after a single administration of the QW formulation in Period 2 of Cohort 1 and Cohort 1' (as necessary) (single administration period) or after the first administration of the QW formulation in Period 2 of Cohort 2 (repeated administration period) will be withdrawn from the trial without dose increase or further administration of the QW formulation.

If, by 2 weeks after a single administration of the QW formulation in Period 2 of Cohort 1 and Cohort 1' (as necessary) (single administration period) or by 1 week after the first administration of the QW formulation in Period 2 of Cohort 2 (repeated administration period):

1) Subject experiences either of the following AEs:
- An IMP-related SAE
- A severe IMP-related AE
  If the event is associated with exacerbation of the underlying disease, the subject can remain in the trial at the discretion of the investigator.

2) Subject experiences IMP-related abnormal blood pressure (systolic blood pressure of < 80 mmHg)
3) Subject experiences any of the following IMP-related abnormal ECGs:
- QTc interval (QTcF) of > 500 ms
- Prolongation in QTc interval (QTcF) by > 60 ms from baseline (predose in Period 2)

4) Subject shows hypersensitivity or allergic reaction to brexpiprazole
5) The investigator or subinvestigator judges the subject to be unsuitable for dose increase of the brexpiprazole QW formulation.

3.9.3.3 Documenting Reasons for Discontinuation

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

- Adverse event:
  - Continuation of IMP would place the subject at undue risk as determined by the investigator or subinvestigator
    - Safety concern possibly, probably, or likely related to IMP
    - SAE
    - Exacerbation or progression of the underlying disease

    - Meeting the criteria for withdrawal before dose increase
  - 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
- Withdrawal of informed consent by the legal representative of the subject
- Withdrawal of informed consent by the subject
- Lost to follow-up
- Pregnancy (see Section 5.5 Pregnancy)
- Investigator's or subinvestigator's decision (other than AE)
- Major protocol deviation
- Termination of all or part of the trial by the sponsor
- Other (record details)

If the subject discontinues IMP due to an AE, the investigator, subinvestigator, or other trial personnel, will make every effort to follow the event until the event is resolved or stabilized, or the subject is lost to follow-up or has died. The procedures in Section 5.7 Follow-up of Adverse Events must be followed.

3.9.3.4 Withdrawal of Consent

All subjects (and subjects' legal representatives if subjects are minors or are hospitalized for reasons of medical protection) have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects (and subjects' legal representatives if subjects are minors or are hospitalized for reasons of medical protection) cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) provides their written withdrawal of consent or there is other written documentation by the investigator or subinvestigator confirming the verbal intent of the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires refusal by a subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) of ALL of the following methods of follow-up (these methods of follow-up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and 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 of a subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) for an 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 (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.9.3.1 Treatment Discontinuation). A subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 3.9.3.3 Documenting Reasons for Discontinuation 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 (and subjects' legal representatives if subjects are minors or are hospitalized for reasons of medical protection) who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.9.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be given instructions to meet and discuss with the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) their options of continuing in the trial, preferably on therapy. The

investigator or subinvestigator should ensure understanding and documentation of the reasons why the subject (and the subject's legal representative if the subject is a minor or is hospitalized for reasons of medical protection) wishes to withdraw consent.

3.10 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject signs an ICF), but who is not enrolled in the trial prior to IMP administration on Day 1 of Period 1 in each cohort.

It is permissible for subjects who sign an ICF but who are not enrolled in the trial prior to IMP administration on Day 1 of Period 1 to be rescreened. In the event that rescreening is not completed within the original screening period, consent must be newly obtained and a new subject identifier must be assigned. However, for those subjects who were withdrawn from the trial at the discretion of the sponsor and who agree to take part in the trial again and sign the ICF again, but who are not enrolled in the trial prior to IMP administration on Day 1 of their scheduled treatment period (Period 2 or 3), the same subject identifier as the original will also be used for the repeated rescreening.

For screen failures, the following information will be recorded on the source documents and screen failure-specific eCRF:

Subject identifier, date of visit, date of obtaining informed consent, date of birth, sex, date of screen failure determination, reason for screen failure, country (Japan), race, and ethnicity.

3.11 Definition of Completed Subjects

The trial period is defined as the time period during which subjects are evaluated in regard to the primary objectives of the trial irrespective of whether the subject actually receives all doses of the IMP. Subjects who complete the last scheduled sampling for PK assessments for the PK trial will be defined as trial completers. For the purposes of this trial, subjects who complete assessment on Day 14 of Period 3 in Cohort 1 or Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) will be defined as trial completers.

3.12 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted during or before the treatment period and those who do not have a known reason for discontinuation (eg, withdrawal of consent or AE, etc.) will be defined as subjects lost to follow-up.

The investigator, subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the 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 a subject becomes lost to follow-up, the results of the investigation (whether or not the subject was contacted, occurrence or non-occurrence of AEs, date of contact, method of contact) will be recorded in the source data and the eCRF.

3.13 Subject Compliance

The time of administration and the dose of each IMP will be recorded on the source documents and eCRF. Information on missed doses and whether the IMP was taken in an inappropriate manner will also be recorded on the source documents and eCRF. An oral check will be performed immediately after IMP administration to ensure that the subject has swallowed the IMP.

3.14 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 therapy criteria), the investigator, subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator and sponsor 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 or subinvestigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

The use of the following drugs between each specified date and the completion of assessment on Day 14 of Period 3 in Cohort 1 or Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) or the completion of ET assessment is prohibited:

- CYP2D6 inhibitors and CYP3A4 inhibitors and inducers listed in Appendix 3 (from 14 days prior to IMP administration in Period 1*), excluding the topical agents listed in Appendix 4 for which concomitant use with the IMP is permitted.
- Rexulti tablets (from 21 days prior to IMP administration in Period 1*)
- Clozapine (from informed consent)
- Adrenaline (from 28 days prior to IMP administration in Period 1*)

- Other investigational medicinal products under development (unapproved drugs) (from 60 days prior to IMP administration in Period 1*)

* For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the drugs is prohibited from 14, 21, 28, and 60 days, respectively, before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.

4.2 Prohibited Therapies

The use of the following therapy between 60 days prior to IMP administration in Period 1* of each cohort and the completion of assessment on Day 14 of Period 3 in Cohort 1 or, Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) or the completion of ET assessment is prohibited:

- Electroconvulsive therapy

* For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the therapy is prohibited from 60 days before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.

4.3 Restricted Medications

The use of the following drugs between Day 1 of Period 1* of each cohort and the completion of assessment on Day 14 of Period 3 in Cohort 1 or Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) or the completion of ET assessment is restricted:

* For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the drugs is restricted from Day 1 of IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.

- Other antipsychotic drugs
  The use of other antipsychotic drugs at a steady dose and regimen will be permitted within the dosing range indicated below. The dose or frequency may be reduced at the discretion of the investigator or subinvestigator in response to symptom improvement or maintenance or from a safety perspective.
  Upper limit of dose and regimen
  - Antipsychotic medication comprising no more than two active components
  - A daily dose equivalent to no more than 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 the conversion values listed in Appendix 5.

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
  The use of antiparkinsonian drugs will be permitted only when the subject has extrapyramidal symptoms and the investigator or subinvestigator concludes that these drugs should be used. In that case, the dose and regimen should comply with the package insert. However, preventive use will be prohibited. Therefore, subjects who have no extrapyramidal symptoms but are taking antiparkinsonian drugs at the time of informed consent must temporarily discontinue the medication. Extrapyramidal symptoms should be assessed using DIEPSS prior to new use or dose increase of an antiparkinsonian drug. It is not permitted for any antiparkinsonian drug to be administered within 12 hours prior to DIEPSS assessment.
- β-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.

4.4 Other Restrictions

- The consumption of foods and beverages containing grapefruit, Seville orange, or star fruit between 7 days prior to IMP administration in Period 1* of each cohort and the completion of assessment on Day 14 of Period 3 in Cohort 1 or Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) or the completion of ET assessment is prohibited.
- The consumption of foods and beverages containing St. John's Wort, Ginkgo biloba, goldenseal, or echinacea (Echinacea purpurea) between 14 days prior to IMP administration in Period 1* of each cohort and the completion of assessment on Day 14 of Period 3 in Cohort 1 or Cohort 1' (as necessary) (single administration period) or on Day 42 of Period 2 in Cohort 2 (repeated administration period) or the completion of ET assessment is prohibited.

* For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the consumption of these foods and beverages is prohibited from 7 and 14 days, respectively, before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as complications at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse drug reaction is any untoward and unintended response to an IMP related to any dose administered.

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

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

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

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

Immediately Reportable Event (IRE):

- Any SAE
- Any AE related to occupational exposure.

- Potential serious hepatotoxicity (see Section 5.4 Potential Serious Hepatotoxicity)
- 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 to the sponsor. Pregnancy will only be recorded on the AE eCRF if there is a complication or abnormality in the newborn.

Clinical Laboratory Assessment Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator needs to verify whether this is an abnormal (ie, clinically relevant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically relevant by the investigator or subinvestigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation or meets the criteria for an SAE, this is considered an AE.

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

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not related: There is no temporal or causal relationship between the IMP and the AE.

Date of Onset and Recovery (for diarrhea and vomiting, date and time of onset and date and time of recovery):

Date of onset: The date of onset of an AE or date of confirmation of an AE. If the severity or seriousness of the reported event changes, the date of exacerbation will be taken as the "date of onset of AE."

Date of recovery: The date of recovery of an AE or date of confirmation of recovery of an AE. For clinical laboratory items, this shall be the date of blood or urine sampling. In the case of death, this shall be the date of death.

Outcome:

The outcome of an AE will be selected from the following 6 categories (one only). If the subject died, the date of death will be recorded; if the subject's condition was ameliorated (recovering), unrecovered, or unknown, the date of outcome confirmation will be recorded.

- Recovered
- Ameliorated (recovering)
- Unrecovered
- Recovered but with sequelae
- Death
- Unknown (for some reason, a follow-up investigation could not be performed even once)

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will periodically 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 eCRFs provided by the sponsor. The name of an AE, date of onset, date of recovery, seriousness, severity, causal relationship to the IMP, and outcome will be recorded on the source documents and eCRF.

Adverse event and SAE collection is to begin after a subject has signed the ICF and continue until the end of trial date. Adverse events occurring in the screening period and Period 1 will be assessed in comparison with the subject's condition at the time of consent/screening, and AEs occurring in Period 2 and Period 3 (Cohort 1 and Cohort 1' (as necessary) [single administration period] only) will be assessed in comparison with the subject's condition at the start of Period 2. For subjects who were withdrawn from the

trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, AEs and SAEs will be collected from the time participation in the trial resumes until the end of the trial. However, AEs that occur after withdrawal from the trial at the discretion of the sponsor and resolve before the date on which the subject provided his/her signature for re-consent will also be collected as far as possible. Adverse events will be assessed based on the following:

- Subjects who resume participation in the trial from Period 2: Adverse events occurring in the screening period will be assessed in comparison with their condition at the time of consent/screening when they first participated in the trial, and AEs occurring in Period 2 and Period 3 will be assessed in comparison with their condition prior to IMP administration in Period 2.
- Subjects who resume participation in the trial from Period 3: Adverse events occurring in the screening period and Period 3 will be assessed in comparison with their condition at the start of Period 2 when they first participated in the trial.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

A reported AE that undergoes a change in severity or seriousness must be reported as a new AE on the eCRF.

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

5.3 Immediately Reportable Events

The investigator or subinvestigator must report any SAEs, AEs related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy immediately after the investigator, subinvestigator, or designee becomes aware of the event. The IRE form and so on should be completed and sent by e-mail to the sponsor, using the contact information on the title page of this protocol. (Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE eCRF.) Due consideration must be given to the subject's privacy when an IRE form is sent by e-mail, etc.

Subjects experiencing SAEs or IREs should be followed clinically as described in Section 5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events. It is expected that the investigator or subinvestigator will provide or arrange appropriate

supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

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

5.5 Pregnancy

Women of child-bearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject or their partner is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, intrauterine device, or condom (all methods approved or certified in Japan). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators or subinvestigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

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

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

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of the pregnancy test are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the serum pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and so on, and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy. This procedure also applies to the case where the partner of a subject becomes pregnant.

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

5.6 Procedure for Breaking the Blind

Not applicable.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the end of trial date (final day of

observation) will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). The follow-up information after the end of trial date (final day of observation) will be recorded in the subject's medical record.

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

This trial requires that subjects be actively monitored for SAEs and IREs up to the end of trial date (final day of observation).

Serious AEs and IREs that are identified or ongoing at the end of trial date must be recorded on the AE eCRF page. Between the end of trial date for the individual subject and the end of trial date for the last subject, if any new information regarding an SAE or IRE becomes available (eg, the event is resolved), this must be reported to the sponsor using the IRE form and so on, and the information must be recorded on the AE eCRF page.

The investigator or subinvestigator will follow SAEs and IREs, and will continue to report any significant information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died, using the IRE form and so on.

Resolved means that the subject has returned to the baseline state of health, and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring After the End of Trial Date (Final Day of Observation)

Any new SAEs or IREs reported to the investigator or subinvestigator, which occur after the end of trial date (final day of observation) and are determined by the investigator or subinvestigator to be associated with the use of the IMP, should be reported to the sponsor. This includes SAEs and IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator or subinvestigator will follow SAEs and IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died, using the IRE form and so on.

6 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic Analysis

6.1 Pharmacokinetic Methods

The PK parameters of brexpiprazole for the QW formulation and conventional tablet at each dose will be determined through noncompartmental PK analysis. Descriptive statistics of the following variables will be produced.

6.1.1 Brexpiprazole QW Formulation

6.1.1.1 Period 2 of the Single Administration Period (Cohort 1 and Cohort 1' [as Necessary])

1) Plasma concentration of brexpiprazole after a single administration of the QW formulation
2) PK parameters of brexpiprazole after a single administration of the QW formulation
   C_{max}, t_{max}, t_{last}, C_{max}/D
3) Relative C_{max} of brexpiprazole for the QW formulation as compared with a conventional tablet
   Relative C_{max} (%)
   = (C_{max} of QW formulation/dose of QW formulation)/(C_{max} of conventional tablet/dose of conventional tablet) × 100

6.1.1.2 Period 3 of the Single Administration Period (Cohort 1 and Cohort 1' [as Necessary])

1) Plasma concentration of brexpiprazole after a single administration of the QW formulation
2) PK parameters of brexpiprazole after a single administration of the QW formulation
   C_{max}, AUC_{∞}, AUC_t, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{∞}/D, AUC_t/D
3) Relative bioavailability of brexpiprazole for the QW formulation as compared with a conventional tablet
   Relative bioavailability (%)
   = (AUC_{∞} of QW formulation/dose of QW formulation)/(AUC_{∞} of conventional tablet/dose of conventional tablet) × 100
4) Relative C_{max} of brexpiprazole for the QW formulation as compared with a conventional tablet
   Relative C_{max} (%)

= (C_{max} of QW formulation/dose of QW formulation)/(C_{max} of conventional tablet/dose of conventional tablet) × 100

6.1.1.3 Period 2 of the Repeated Administration Period (Cohort 2)

1) Plasma concentration of brexpiprazole after the fifth administration of the QW formulation
2) PK parameters of brexpiprazole after the fifth administration of the QW formulation
   C_{max}, AUC_{168h}, t_{max}, λ_z, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{168h}/D
3) Plasma trough concentrations of brexpiprazole from the first administration of the QW formulation to after the fifth administration of the QW formulation (C_{168h})
4) Accumulation of brexpiprazole after the fifth administration of the QW formulation as compared with that after the first administration [R5,ac(C_{168h})]

6.1.2 Brexpiprazole Conventional Tablet (for All Cohorts, Period 1)

1) Plasma concentration of brexpiprazole after a single administration of a conventional tablet
2) PK parameters of brexpiprazole after a single administration of a conventional tablet
   C_{max}, AUC_{∞}, AUC_t, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D, AUC_{∞}/D, AUC_t/D

6.2 Pharmacodynamic Methods

No pharmacodynamic (PD) analysis is planned.

6.3 Pharmacokinetic/Pharmacodynamic Methods

No PK/PD analysis is planned.

6.4 Pharmacogenomic Methods

A list of data obtained from CYP2D6 genetic assessment will be provided without summarization. See Section 3.7.8.1.4 Genomic/Genetic Analysis for genomic/genetic analysis.

7 Statistical Analysis

This section defines datasets for analysis and describes the methods for analyzing endpoints. A detailed statistical analysis plan is provided in a separate Statistical Analysis Plan. The Statistical Analysis Plan will be finalized prior to data lock.

7.1 Determination of Sample Size

The target number of subjects is not based on a statistical hypothesis test. A simulation was performed with the PK model created based on PK data on the conventional tablet and QW-A formulation used in the QW-A formulation group in Trial 331-102-00021 conducted in Japan, and the probability that the mean plasma concentration of brexpiprazole after repeated administration of the QW-A formulation would be within the target range of concentration was determined. On the basis of this probability, the sample size was determined to be 20 subjects each for the single administration period (Cohort 1) and the repeated administration period (Cohort 2). Likewise, the sample size for an additional single administration period (Cohort 1') with a new dose was also determined to be 20 subjects.

7.2 Datasets for Analysis

7.2.1 Pharmacokinetic Analysis Set

The PK analysis set will consist of subjects who received the QW formulation and had plasma drug concentration measurements. The following subjects will be excluded from the PK analysis set:

- Subjects who vomited within 12 hours postdose

7.2.2 Safety Analysis Set

The safety analysis set will consist of all subjects who received any QW formulation.

7.3 Handling of Missing Data

Data imputation will not be performed for missing data.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analyses

See Section 6.1 Pharmacokinetic Methods.

7.4.2 Secondary Endpoint Analyses

See Section 6.1 Pharmacokinetic Methods.

7.5 Analysis of Demographic and Other Baseline Characteristics

Depending on data characteristics, frequency distribution or descriptive statistics of demographic and other baseline characteristics will be produced for the single

administration period (Cohort 1 and Cohort 1’ [as necessary]) and the repeated administration period (Cohort 2) based on PK and safety analysis sets.

7.6 Safety Analysis

Each safety endpoint will be summarized for each dose (Periods 2 and 3) of the QW formulation in the single administration period (Cohort 1 and Cohort 1’ [as necessary]) and for the repeated administration period (Cohort 2) based on safety analysis set.

The baseline for statistical analysis is defined as data measured immediately prior to IMP administration in Period 2.

7.6.1 Adverse Events

All AEs will be coded by system organ class and the ICH Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized:

- AEs occurring after administration of the QW formulation (treatment-emergent adverse events [TEAEs])
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the trial

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

Descriptive statistics of actual measurements and changes from baseline of laboratory test parameters (excluding qualitative urinalysis) at each time point will be produced.

For each laboratory parameter (excluding qualitative parameters), measurements 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 range 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 percentage of subjects with abnormal changes that are potentially clinically significant (PCS) will be determined. The number and percentage of subjects with abnormal changes in liver function (Hy's Law cases) will be determined.

7.6.3 Physical Examination Data

A list of physical findings will be provided.

7.6.4 Vital Signs Data

Descriptive statistics of actual measurements and changes from baseline of each parameter at each time point will be produced. The number and percentage of subjects with PCS in vital signs and weight will be determined.

7.6.5 Electrocardiogram Data

A shift table from baseline for normal/abnormal finding of 12-lead ECG will be produced.

Descriptive statistics of actual measurements and changes from baseline at each time point will be produced.

The number and percentage of subjects with actual measurements of corrected QT interval (QTcF) at each time point in each period being > 450 msec, > 480 msec, and > 500 msec will be determined. The number and percentage of subjects with changes from baseline being > 30 msec and > 60 msec will be determined.

7.6.6 Other Safety Data

7.6.6.1 Drug-Induced Extrapyramidal Symptoms Scale

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

7.6.6.2 Columbia-Suicide Severity Rating Scale

The number and percentage 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.

7.7 Pharmacodynamic Analysis

No PD analysis is planned.

7.8 Analyses of Other Endpoints

7.8.1 Clinical Global Impression - Severity of Illness and Clinical Global Impression - Improvement

A list of subjects whose CGI-S or CGI-I has worsened will be provided.

8 Management of Investigational Medicinal Product

Refer to the investigator's brochure on brexpiprazole for details regarding IMP management.

8.1 Packaging and Labeling

The IMP will be provided to the IMP manager by the sponsor or designated agent. The IMP will be supplied as packages. Each package used in the dosing period will be labeled to clearly disclose "the IMP is intended only for clinical research," the protocol number, IMP name, number of tablets, lot number, expiry date, storage conditions, sponsor's name and address, and precautions for use.

8.2 Storage

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

The IMP must be stored according to the storage conditions indicated on the clinical label.

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

8.3 Accountability

The IMP manager must maintain an inventory record of IMP (including the investigational product and active control) received, dispensed, administered, or returned.

8.4 Returns and Destruction

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

All IMP returned to the sponsor must be accompanied by appropriate documentation and be 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 unused and/or partially used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate, or other third party that alleges

deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

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

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, 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, subinvestigator, or designee must notify the sponsor via e-mail immediately after becoming aware of the PQC according to the procedure outlined in Section 8.5.2 Information Required for Reporting Product Quality Complaints.

- PQC_331-102-00150@otsuka.jp

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

8.5.2 Information Required for Reporting Product Quality Complaints

The following information is required for reporting purposes:

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

8.5.3 Return Process for Product Quality Complaints

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

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, medical records, electronic data, screening logs, and recorded data from automated instruments.

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

Investigator(s)/trial site(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. Information on drug concentration measurements, CYP2D6 genetic testing, and DNA storage (eg, master copies of reports, measurement data) will be stored at the bioanalytical laboratory, genetic test laboratory, and DNA storage facility, respectively. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the trial site, an investigator or subinvestigator will document all significant observations and findings in the medical records. At a minimum, these records will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the

investigator's or subinvestigator's assessment of relationship to IMP must also be recorded;

- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of all investigators or subinvestigators (or designees) who made an entry in the medical records.

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. Any changes to information in the medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or subinvestigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the medical records and other source documents will be entered by trial site personnel directly onto eCRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail.

9.3 File Management at the Trial Site

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

9.4 Record Retention at the Trial Site

The trial site will retain all the trial-related documents and records for 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.

- Until the date 2 years after manufacturing and marketing approval date; 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, until the date 3 years after receipt of such notification.
- Until the date 3 years after termination or completion of the trial.
- Until the date on which it is decided to end DNA storage

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

10 Quality Control and Quality Assurance

10.1 Monitoring

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

10.2 Auditing

The sponsor's (or designee's) Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

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

10.3 Protocol Deviations

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

- Subjects who were enrolled in the trial even though they did not satisfy the entry criteria

- Subjects who fell under the withdrawal criteria during the trial but were not withdrawn from the trial
- Subjects who received the wrong treatment or dose
- Subjects who received a prohibited concomitant therapy

The FDA defines a protocol deviation/violation as an unplanned excursion from the protocol that is not implemented or intended as a systematic change.

Otsuka categorizes clinical protocol deviations as major versus minor. A major deviation is an intentional or accidental action or omission in a trial conduct that could potentially have a negative impact on the integrity of the trial's primary scientific objectives or has a significant potential to have a negative impact on the safety or efficacy assessments of any trial subject. Major deviations are those that might significantly affect the completeness, accuracy, or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

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

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

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

Investigators or subinvestigators are expected to document potential protocol deviations as well as their medical assessment regarding continuation of the subject(s) due to the protocol deviation. Of the protocol deviations, only major deviations will be recorded in eCRFs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. The trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, IRE forms, etc, the investigator or subinvestigator and their staff will take measures to ensure adequate care in protecting

subject privacy. To this end, a subject number or subject identifier will be used to identify each subject.

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

12 Confidentiality

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

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

13 Amendment Policy

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

When the IRB, investigators, or the sponsor conclude that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent

will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

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

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

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

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

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Appendix 1 Handling and Shipping of Bioanalytical Samples

1) Information to be written on the label and recording

Write on the label affixed to each storage tube the required information such as protocol number, subject identifier, date of sampling, time point of sampling, description of sample, laboratory parameters, aliquot number (only for samples for drug concentration measurement; eg, aliquot 1, aliquot 2).

Be sure to enter the actual date of sampling (the actual date and time of sampling for drug concentration measurement), not the scheduled date and time, on the source documents and CRF.

2) Handling and shipping of samples for drug concentration measurement

Collect a blood sample into a 2 mL vacuum blood collection tube containing sodium heparin using a venipuncture technique or an indwelling catheter. If an indwelling catheter is used, the catheter may be flushed with normal saline or heparin. Following sampling, slowly invert the tube a few times to mix well. Within 45 minutes of the sample being taken, perform refrigerated centrifugation at approximately 4°C (approximately 3,000 rpm [approximately 1,710 × G] for approximately 10 minutes). Transfer plasma aliquots into 2 appropriately labeled storage tubes (in the case of a small sample, transfer 0.3 mL of the sample into one storage tube and the remaining sample into the other). Within 90 minutes of the sample being taken, place the 2 plasma samples in a freezer at a temperature no higher than –20°C. Within 3 business days of sampling, ship plasma samples to the central laboratory, which will in turn send them to the bioanalytical laboratory. When shipping, place samples together with plenty of dry ice in a well-insulated container. The samples will be stored in a freezer at a temperature no higher than –70°C at the bioanalytical laboratory.

Unused plasma samples are to be stored at the bioanalytical laboratory and will be disposed of after the clinical study report is completed.

3) Handling and shipping of samples for CYP2D6 genetic testing

Collect a blood sample into a 2 mL vacuum blood collection tube containing EDTA dipotassium using a venipuncture technique or an indwelling catheter. If an indwelling catheter is used, the catheter may be flushed with normal saline. Following sampling, slowly invert the tube 8 to 10 times to mix well, and transfer the blood sample into an appropriately labeled storage tube. Within 60 minutes of the sample being taken, place the sample in a freezer at a temperature no higher than –20°C. Within 3 business days of sampling, ship blood samples to the central laboratory, which will in turn send them to the genetic test laboratory. When shipping, place samples together with plenty of dry ice in a well-insulated container. The samples will be stored in a freezer at a temperature no

higher than –70°C at the genetic test laboratory. The genetic test laboratory will extract DNA from blood samples and store DNA samples in a freezer at a temperature no higher than –70°C.

Unused DNA samples are to be stored at the genetic test laboratory and will be disposed of with subject anonymity being maintained following the institutional procedure after the clinical study report is completed.

4) Handling and shipping of samples for DNA storage

Collect a blood sample into a 2 mL vacuum blood collection tube containing EDTA dipotassium using a venipuncture technique or an indwelling catheter. If an indwelling catheter is used, the catheter may be flushed with normal saline. Following sampling, slowly invert the tube 8 to 10 times to mix well, and transfer the blood sample into an appropriately labeled storage tube. Within 60 minutes of the sample being taken, place the sample in a freezer at a temperature no higher than –20°C. Within 3 business days of sampling, ship blood samples to the central laboratory, which will in turn send them to the DNA storage facility. When shipping, place samples together with plenty of dry ice in a well-insulated container. The samples will be stored in a freezer at a temperature no higher than –70°C at the DNA storage facility. The DNA storage facility will double-code samples by assigning a personal code to each sample, extract DNA from blood samples, and store DNA samples in a freezer at a temperature no higher than −70°C. Upon the sponsor's request, the DNA storage facility will dispose of DNA samples while maintaining subject anonymity following the institutional procedure.

Appendix 2 CYP2D6 Genotyping Table

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

E = EM, I = IM, P = PM

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

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

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

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

If the genotype cannot be determined, the genotype will be classified as "not determinable (ND)."

If the genotype cannot be determined or if the phenotype cannot be singled out, the phenotype will be classified as "unknown."

Appendix 3 List of CYP Inhibitors/Inducers

CYP3A4 inhibitors

Mechanism of Action	Generic Name	Remarks
Dyslipidemia drug	Atorvastatin	
Dyslipidemia drug	Lomitapide	
Immunosuppressant	Ciclosporin	
Immunosuppressant	Tacrolimus	
Antiemetic	Aprepitant	
Antiemetic	Fosaprepitant	
Anti-arrhythmia drug	Amiodarone	
Anti-arrhythmia drug	Quinidine	
Anti-arrhythmia drug	Verapamil	
Antihypertensive	Amlodipine	
Antihypertensive	Felodipine	
Vasodilator	Diltiazem	
Anxiolytic	Alprazolam	
Anxiolytic	Tofisopam	
Antidepressant	Fluvoxamine	
Antiparkinsonian drug	Istradefylline	
Antimicrobial drug	Azithromycin	
Antimicrobial drug	Erythromycin	
Antimicrobial drug	Clarithromycin	
Antimicrobial drug	Ciprofloxacin	
Antifungal drug	Itraconazole	
Antifungal drug	Clotrimazole	
Antifungal drug	Ketoconazole	
Antifungal drug	Fluconazole	
Antifungal drug	Voriconazole	
Antifungal drug	Miconazole	
Antiplatelet drug	Cilostazol	
Antiplatelet drug	Ticagrelor	
Antituberculosis drug	Isoniazid	
Antitumor drug	Imatinib	
Antitumor drug	Crizotinib	
Antitumor drug	Nilotinib	
Antitumor drug	Pazopanib	
Antitumor drug	Bicalutamide	
Antitumor drug	Lapatinib	
Anti-HIV drug	Atazanavir	
Anti-HIV drug	Indinavir	
Anti-HIV drug	Indinavir/ritonavir	
Anti-HIV drug	Elvitegravir/ritonavir	
Anti-HIV drug	Cobicistat	
Anti-HIV drug	Saquinavir	
Anti-HIV drug	Saquinavir/ritonavir	

Mechanism of Action	Generic Name	Remarks
Anti-HIV drug	Danoprevir/ritonavir	
Anti-HIV drug	Darunavir/ritonavir	
Anti-HIV drug	Tipranavir/ritonavir	
Anti-HIV drug	Nelfinavir	
Anti-HIV drug	Paritaprevir/ritonavir/(ombitasvir and/or dasabuvir)	
Anti-HIV drug	Fosamprenavir	
Anti-HIV drug	Ritonavir	
Anti-HIV drug	Lopinavir/ritonavir	
Oral contraceptive drugs	Oral contraceptive drugs	
Muscle relaxant	Chlorzoxazone	
Gastric acid suppressant	Cimetidine	
Gastric acid suppressant	Ranitidine	
Hepatitis C drug	Telaprevir	
Food with functional claims	Gingko biloba	
Supplement	Goldenseal (yellow puccoon)	

CYP3A4 inducers

Mechanism of Action	Generic Name	Remarks
Adrenocortical hormone preparations	Adrenocortical hormone preparations	Including the following drugs cortisone, hydrocortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, fludrocortisone, prasterone
Pulmonary hypertension drug	Bosentan	
Diabetes mellitus drug	Pioglitazone	
Central stimulant	Modafinil	
Antiemetic	Aprepitant	
Antihormone drug	Enzalutamide	
Antihormone drug	Mitotane	
Antiepileptic	Carbamazepine	
Antiepileptic	Clobazam	
Antiepileptic	Phenytoin	
Antiepileptic	Fosphenytoin	
Antiepileptic	Phenobarbital	*Includes the following phenobarbital derivatives phenobarbital, amobarbital, pentobarbital, barbital, secobarbital, primidone
Antiepileptic	Rufinamide	
Antituberculosis drug	Rifampicin	
Antitumor drug	Vemurafenib	
Anti-HIV drug	Etravirine	
Anti-HIV drug	Efavirenz	
Anti-HIV drug	Rifabutin	
Supplement	Echinacea (Echinacea purpurea)	
Supplement	St. John's wort	

CYP2D6 inhibitors

Mechanism of Action	Generic Name	Remarks
Hyperuricemia drug	Febuxostat	
Antihypertensive drug	Labetalol	
Antihypertensive drug	Hydralazine	
Antihypertensive drug	Diltiazem	
Anti-arrhythmia drug	Verapamil	
Anti-arrhythmia drug	Propafenone	
Anti-arrhythmia drug	Quinidine	
Anti-arrhythmia drug	Amiodarone	
Oral contraceptive drug	Ethinylestradiol	
Oral contraceptive drug	Levonorgestrel	
Oral contraceptive drug	Norethisterone	
Oral contraceptive drug	Desogestrel	
Gastric acid suppressant	Ranitidine	
Gastric acid suppressant	Cimetidine	
Analgesic	Methadone	
Anti-inflammatory analgesic	Celecoxib	
Antihistamine	Diphenhydramine	
Antiepileptic	Clobazam	
Antifungal drug	Terbinafine	
Hyperthyroidism drug	Cinacalcet	
Antidepressant	Venlafaxine	
Antidepressant	Paroxetine	
Antidepressant	Fluvoxamine	
Antidepressant	Duloxetine	
Antidepressant	Sertraline	
Antidepressant	Escitalopram	
Antitumor drug	Vemurafenib	
Antitumor drug	Pazopanib	
Antitumor drug	Gefitinib	
Antitumor drug	Imatinib	
Antitumor drug	Abiraterone	
Anti-HIV drug	Ritonavir	
Anti-HIV drug	Cobicistat	
Overactive bladder drug	Mirabegron	
Lupus erythematosus drug	Hydroxychloroquine	
Supplement	Echinacea (Echinacea purpurea)	

Appendix 4 Criteria for Allowing Concomitant Use of Topical CYP2D6 Inhibitors, CYP3A4 Inhibitors, and CYP3A4 Inducers

Section 4.1 Prohibited Medications in this protocol lists CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers as prohibited concomitant medications in view of pharmacokinetic interactions. This appendix provides a definition of "topical" CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers.

1. Conditions Pertaining to Topical Agents in This Document

In view of possible drug-drug interactions between the IMP and concomitant medications, the use of drugs that have a systemic effect and are absorbed from the gastrointestinal tract or mucosa and predominantly transferred into the systemic circulation should be avoided. However, concomitant use of "topical" CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers is permitted under the condition that they are unlikely to enter the systemic circulation as defined below.

Topical agents that may possibly enter the systemic circulation based on their route of administration or dosage form, even if they meet both of the following conditions, should be reviewed individually with reference to Section 2. Other Remarks About Topical Agents in this appendix, and any questions or concerns should be communicated to the sponsor.

[Conditions under which a topical agent can be used concomitantly with the IMP]

A topical agent is defined as a drug that:

1) Is intended to have a local effect, AND
2) Does not reach the gastrointestinal tract.
   2) In consideration of possible absorption from the gastrointestinal tract and possible impact on metabolic enzymes present in the gastrointestinal epithelium.

2. Other Remarks About Topical Agents

Criteria for permitting/prohibiting concomitant use for each dosage form are indicated below. Classification of dosage form is based on the Japanese Pharmacopoeia Seventeenth Edition, General Rules for Preparations, [3] Official Monographs, excerpted below (see Section 3. Dosage Forms That May Fall Under Common Topical Agents (Excerpt From the Japanese Pharmacopoeia Seventeenth Edition, General Rules for Preparations, [3] Official Monographs) for the excerpt table).

- "Preparations for inhalation" and "preparations for nasal application" are not included as topical agents and must not be used concomitantly with the IMP because they are likely to enter the systemic circulation.

- "Preparations for vaginal application" and "preparations for rectal application" are not included as topical agents and must not be used concomitantly with the IMP because they are likely to enter the systemic circulation.
- "Preparations for oro-mucosal application," except "preparations for gargles," are not included as topical agents and must not be used concomitantly with the IMP because some preparations are intended to have a systemic effect or can reach the gastrointestinal tract.
- "Preparations for ophthalmic application" and "preparations for otic application" are included as topical agents and can be used concomitantly with the IMP.
- "Preparations for cutaneous application," except "patches" intended to have a systemic effect, are included as topical agents and can be used concomitantly with the IMP.

3. Dosage Forms That May Fall Under Common Topical Agents (Excerpt From the Japanese Pharmacopoeia Seventeenth Edition, General Rules for Preparations, [3] Official Monographs)

Topical agents are broadly classified primarily by the route of administration and application site, and subclassified by the configuration, function, and characteristics of the drug formulation.

Table 1 Definition of Topical CYP2D6 Inhibitors, CYP3A4 Inhibitors, and CYP3A4 Inducers

Route of Administration/ Application Site	Configuration/Function/Characteristics of the Drug Formulation		Concomitant Use as a Topical Agent[a]
2. Preparations for oro-mucosal application	2.1. Tablets for oro-mucosal application	2.1.1. Troches/lozenges	Not permitted
		2.1.2. Sublingual tablets	Not permitted
		2.1.3. Buccal tablets	Not permitted
		2.1.4. Mucoadhesive tablets	Not permitted
		2.1.5. Medicated chewing gums	Not permitted
	2.2. Liquids and solutions for oro-mucosal application	2.2.1. Preparations for gargles	Permitted
	2.3. Sprays for oro-mucosal application		Not permitted
	2.4. Semi-solid preparations for oro-mucosal application		Not permitted
5. Preparations for inhalation	5.1. Inhalations	5.1.1. Dry powder inhalers	Not permitted
		5.1.2. Inhalation liquids and solutions	Not permitted
		5.1.3. Metered-dose inhalers	Not permitted
6. Preparations for ophthalmic application	6.1. Ophthalmic liquids and solutions		Permitted
	6.2. Ophthalmic ointments		Permitted
7. Preparations for otic application	7.1. Ear preparations		Permitted

Table 1	**Definition of Topical CYP2D6 Inhibitors, CYP3A4 Inhibitors, and CYP3A4 Inducers**		
Route of Administration/ Application Site	**Configuration/Function/Characteristics of the Drug Formulation**		**Concomitant Use as a Topical Agent[a]**
8. Preparations for nasal application	8.1. Nasal preparations	8.1.1. Nasal dry powder inhalers	Not permitted
		8.1.2. Nasal liquids and solutions	Not permitted
9. Preparations for rectal application	9.1. Suppositories for rectal application		Not permitted
	9.2. Semi-solid preparations for rectal application		Not permitted
	9.3. Enemas for rectal application		Not permitted
10. Preparations for vaginal application	10.1. Tablets for vaginal use		Not permitted
	10.2. Suppositories for vaginal use		Not permitted
11. Preparations for cutaneous application	11.1. Solid dosage forms for cutaneous application	11.1.1. Powders for cutaneous application	Permitted
	11.2. Liquids and solutions for cutaneous application	11.2.1. Liniments	Permitted
		11.2.2. Lotions	Permitted
	11.3. Sprays for cutaneous application	11.3.1. Aerosols for cutaneous application	Permitted
		11.3.2. Pump sprays for cutaneous application	Permitted
	11.4. Ointments		Permitted
	11.5. Creams		Permitted
	11.6. Gels		Permitted
	11.7. Patches	11.7.1. Tapes	Not permitted[b]
		11.7.2. Cataplasms/ gel patches	Not permitted[b]

[a]Classified based on Sections 1 and 2 above.

[b]Concomitant use of agents intended to have a local effect is permitted.

Appendix 5 Equivalent Conversion of Antipsychotics

The daily chlorpromazine (CP) equivalent dose will be calculated by the following formula, using the equivalence conversion values of antipsychotics (Table 1).

Daily CP equivalent dose = Daily dose of antipsychotic (mg) / equivalent conversion value of antipsychotic × 100

Table 1 Equivalent Conversion Table for Antipsychotics (by Route of Administration)

Drug Name	Route of Administration	Equivalent Conversion Value Used for Calculation	Article Providing Evidence
Oral drugs			
Aripiprazole	Oral	4	1-d
Asenapine	Oral	2.5	1-e
Oxypertine	Oral	80	1-d
Olanzapine	Oral	2.5	1-d
Quetiapine	Oral	66	1-d
Clocapramine	Oral	40	1-d
Chlorpromazine	Oral	100	1-d
Spiperone	Oral	1	1-d
Sultopride	Oral	200	1-d
Sulpiride	Oral	200	1-d
Zotepine	Oral	66	1-d
Tiapride	Oral	100	1-d
Timiperone	Oral	1.3	1-d
Trifluoperazine	Oral	5	1-d
Nemonapride	Oral	4.5	1-d
Paliperidone	Oral	1.5	1-d
Haloperidol	Oral	2	1-d
Pipamperone	Oral	200	1-d
Pimozide	Oral	4	1-d
Fluphenazine	Oral	2	1-d
Prochlorperazine	Oral	15	1-d
Blonanserin	Oral	4	1-d
Propericiazine	Oral	20	1-d
Bromperidol	Oral	2	1-d
Perphenazine	Oral	10	1-d
Perospirone	Oral	8	1-d
Mosapramine	Oral	33	1-d
Moperone	Oral	12.5	1-d
Risperidone	Oral	1	1-d
Reserpine	Oral	0.15	1-d
Levomepromazine	Oral	100	1-d

Table 1 Equivalent Conversion Table for Antipsychotics (by Route of Administration)

Drug Name	Route of Administration	Equivalent Conversion Value Used for Calculation	Article Providing Evidence
Prolonged action drugs for injection			
Aripiprazole	Prolonged action drug for injection	100 mg/4 weeks	1-f
Paliperidone palmitate	Prolonged action drug for injection	18.75 mg/4 weeks	1-f
Haloperidol decanoate	Prolonged action drug for injection	30 mg/4 weeks	1-b
Fluphenazine decanoate	Prolonged action drug for injection	15 mg/4 weeks	1-f
Risperidone	Prolonged action drug for injection	10 mg/2 weeks	1-c
Injected formulations			
Haloperidol	Intramuscular/intravenous administration	1	1-d
Chlorpromazine	Intramuscular administration	33	1-b
Levomepromazine	Intramuscular administration	25	1-b
Sulpiride	Intramuscular administration	50	1-b
Perphenazine	Intramuscular administration	2	1-b
Prochlorperazine	Intramuscular administration	2.1	1-b
Timiperone	Intramuscular administration	0.19	1-b

1-a: Inagaki A, Inada T. No. 18: 2006 Psychotropic Dose Equivalence. Japanese Journal of Clinical Psychopharmacology. 2006;9:1443-7.

1-b: Inagaki A, Inada T. No. 20: Dose Equivalence of Antipsychotics for Injection. Japanese Journal of Clinical Psychopharmacology. 2007;10:2373-7.

1-c: Inagaki A, Inada T. No. 22: Dose Equivalence of Prolonged Action Antipsychotics (3): Risperidone Long Acting Formulation for Injection. Japanese Journal of Clinical Psychopharmacology. 2010;13:1349-53.

1-d: Inagaki A, Inada T. No. 23: Dose Equivalence of New Antipsychotics (6): Paliperidone Sustained Release Formulation. Japanese Journal of Clinical Psychopharmacology. 2012;15:397-404.

1-e: Inagaki A, Inada T. No. 26: Dose Equivalence of New Antipsychotics (7): Asenapine. Japanese Journal of Clinical Psychopharmacology. 2017;20:88-97.

1-f : Inagaki A, Inada T. No. 25: Dose Equivalence of Prolonged Action Antipsychotics (4): Aripiprazole Prolonged Action Water Suspension Formulation for Intramuscular Injection. Japanese Journal of Clinical Psychopharmacology. 2015;18:1475-1480.

Appendix 6 Protocol Amendments/Administrative Changes

Amendment: Number: 1

Issue Date: 09 Sep 2019

PURPOSE:

Reconsideration/modification of the trial duration and clarification of descriptions

BACKGROUND:

The trial duration was reconsidered and modified. Ambiguous descriptions were clarified.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
Protocol Synopsis Trial Duration:	November 2019 to March 2021	October 2019 to March 2021
Section 5.3 Immediately Reportable Events	… (Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE eCRF.)	… (Please note that the IRE form is a specific form provided by the sponsor and is NOT the AE eCRF.) Due consideration must be given to the subject's privacy when an IRE form is sent by e-mail, etc.
Chapter 11 Ethics and Responsibility	Further, in preparing and handling eCRFs, the investigator or subinvestigator and their staff …	Further, in preparing and handling eCRFs, IRE forms, etc, the investigator or subinvestigator and their staff …

ADDITIONAL RISK TO THE SUBJECT

There is no additional risk to the subjects.

Amendment: Number: 2

Issue Date: 28 Jan 2020

PURPOSE:

Acceptance of re-enrollment of subjects who were withdrawn from the trial at the discretion of the sponsor, clarification of the relevant procedures, reconsideration/modification of prohibited medications, modification of the trial duration in association with withdrawal from the trial at the discretion of the sponsor, and correction of clerical errors

BACKGROUND:

Some subjects were withdrawn from the trial at the discretion of the sponsor. The sponsor has decided to allow re-enrollment of these subjects in the trial. The trial duration was reconsidered and modified in association with withdrawal from the trial at the discretion of the sponsor, prohibited medications were reconsidered and modified, and clerical errors were corrected.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
Protocol Synopsis Trial Duration:	October 2019 to March 2021	October 2019 to May 2021
Protocol Synopsis Trial Duration:	… Each period is indicated below.	… Each period is indicated below. In cases where subjects withdrawn from the single administration period (Cohort 1) at the discretion of the sponsor subsequently take part in the trial again, the duration of their trial participation will be a maximum of 85 days if they resume participation in the trial from Period 2 and a maximum of 58 days if they resume participation the trial from Period 3.
Section 3.1.1 Cohort 1 (Single Administration Period)	Following administration of the QW formulation in Period 2, …must be withdrawn from the trial and not advance to Period 3.	Following administration of the QW formulation in Period 2, …must be withdrawn from the trial and not advance to Period 3. If a subject withdrawn from the trial at the

Location	Before Change	After Change
		discretion of the sponsor after receiving a brexpiprazole 2 mg conventional tablet in Period 1 and undergoing the examinations scheduled for up to Day 14 of Period 1 subsequently takes part in the trial again, the subject will be allowed to resume participation in the trial from Period 2. If a subject withdrawn from the trial at the discretion of the sponsor after receiving a 24 mg tablet of the QW formulation in Period 2 and undergoing the examinations scheduled for up to Day 14 of Period 2 subsequently takes part in the trial again, the subject will be allowed to resume participation in the trial from Period 3.
Section 3.3.2 Subject Numbering	… which is given to each subject in chronological order of provision of consent.	… which is given to each subject in chronological order of provision of consent. Each subject who takes part in the trial again following withdrawal from the trial at the discretion of the sponsor will be assigned the same subject identifier that was assigned to them at the time when they first participated in the trial.
Section 3.4.1 Informed Consent	The ICF will be approved by the same institutional review board (IRB) that approves this protocol.	The ICF will be approved by the same institutional review board (IRB) that approves this protocol. In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again, informed consent will also be obtained from all such subjects (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision.
Section 3.4.1 Informed Consent	On the other hand, DNA storage is optional … will not affect trial participation.	On the other hand, DNA storage is optional … will not affect trial participation. In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again, written informed consent will be obtained from them (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) on their voluntary decision, if they have yet to complete CYP2D6 genetic testing.

Location	Before Change	After Change
Section 3.4.2 Inclusion Criteria	Subjects are required to meet the inclusion criteria in Table 3.4.2-1.	Subjects are required to meet the inclusion criteria in Table 3.4.2-1. Subjects withdrawn from the trial at the discretion of the sponsor will have to be reevaluated to ensure they still meet the inclusion criteria in Table 3.4.2-1 if they are to take part in the trial again.
Section 3.4.3 Exclusion Criteria	Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.	Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1. Subjects withdrawn from the trial at the discretion of the sponsor cannot take part in the trial again if they meet any of the exclusion criteria in Table 3.4.3-1.
Section 3.7.3.1 Screening (for All Cohorts)	*Informed consent will be obtained before blood sampling for CYP2D6 genetic testing and blood sampling for DNA storage (optional). After informed consent is obtained, …	*Informed consent will be obtained before blood sampling for CYP2D6 genetic testing and blood sampling for DNA storage (optional). In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again and resume participation in the same cohort, the procedures and characteristics of the trial will be explained to them and written informed consent will be obtained from them (and their legal representatives if they are minors or are hospitalized for reasons of medical protection) prior to initiation of any protocol-related procedures. The following subject information will be recorded on the source documents and the eCRF. • Date on which informed consent was obtained again • Subject identifier • Date of informed consent for CYP2D6 genetic testing** • Date of informed consent for DNA storage (optional)** **Informed consent will be obtained before blood sampling for CYP2D6 genetic testing and blood sampling for DNA storage (optional). However, if blood samples had already been collected before the subject was withdrawn from the trial, it will not be necessary to obtain consent again.

Location	Before Change	After Change
		After informed consent is obtained, …
Section 3.7.3.1 Screening (for All Cohorts)	• Height, …will be determined … BMI = weight (kg) / height $(m)^2$. … • Vital signs … will take place only at screening).	• Height, …will be determined … BMI = weight (kg) / height $(m)^2$. … • Vital signs … will take place only at screening). Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.
Section 3.7.3.1 Screening (for All Cohorts)	… • Concomitant medications and therapies	… • Concomitant medications and therapies In cases where subjects withdrawn from the trial at the discretion of the sponsor subsequently take part in the trial again and resume participation in the same cohort, the following observations, tests, and assessments will be performed as screening procedures, after informed consent is obtained, within 28 days (Days −28 to −1) before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial, and their eligibility to participate in the trial will be assessed. [Items] • Inclusion/exclusion criteria • Height,* weight, and body mass index (BMI)*: Height will be measured in increments of 0.1 cm. For a height measured to the second or further decimal place, the number will be rounded off to the first decimal place. BMI will be determined based on height and weight measurements at screening, using the following formula: BMI = weight (kg) / height $(m)^2$. *The height measurement obtained at screening when the subject first participated in the trial may be used. In that case, the height measurement obtained at screening when the subject first participated in the trial should be used in calculation of BMI. • Urine drug screening

Location	Before Change	After Change
		• Urine pregnancy test (women of childbearing potential only) • Clinical laboratory tests (blood and urine sampling) • Physical examination • Vital signs (blood pressure, pulse rate, and body temperature): Blood pressure and pulse rate 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 (performed prior to blood sampling for clinical laboratory tests) • C-SSRS (the "Since Last Visit" will be used) • AEs • Concomitant medications and therapies
Section 3.7.3.3 QW Formulation Single Administration Periods (Periods 2 and 3 of Cohort 1 and Cohort 1' [as Necessary])	The investigator or subinvestigator will … and record their dates and results.	The investigator or subinvestigator will … and record their dates and results. Subjects withdrawn from the trial at the discretion of the sponsor will only be enrolled again to resume participation in the trial from Period 2 or 3 if they are confirmed to be eligible.
Section 3.7.4 Prior and Concomitant Medications	The investigator or subinvestigator will … on the source documents and eCRF.	The investigator or subinvestigator will … on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, medications and therapies will be recorded in the same manner after participation in the trial is resumed. Medications and therapies that were introduced after withdrawal from the trial at the discretion of the sponsor and terminated up to 30 days before the date on which the subject provided his/her signature for re-consent will be recorded as far as possible.

Location	Before Change	After Change
Section 3.7.5.4 Physical Examination and Vital Sign Assessments	… the date of examination will be recorded on the source documents and eCRF.	… the date of examination will be recorded on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and subsequently take part in the trial again, whether a physical examination is performed or not at screening and subsequent time points and, if performed, the date of examination will be recorded on the source documents and eCRF.
Section 3.7.5.4 Physical Examination and Vital Sign Assessments	It is preferable to have the same physician perform all physical examinations for any individual subject throughout the course of the trial wherever possible. Any new, clinically relevant findings at postscreening physical examinations will be recorded as AEs on the source documents and eCRF.	It is preferable to have the same physician perform all physical examinations for any individual subject throughout the course of the trial wherever possible. Any new, clinically relevant, postscreening physical findings obtained from the start of the trial to the physical examination before IMP administration on Day 1 of Period 2 and any new, clinically relevant physical findings obtained after the start of IMP administration in Period 2 in comparison with those obtained before IMP administration on Day 1 of Period 2 will be recorded as AEs on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2, any new, clinically relevant physical findings obtained during the screening period in comparison with those obtained at the first screening before withdrawal and any new, clinically relevant physical findings obtained during Periods 2 and 3 in comparison with those obtained before IMP administration in Period 2 will be recorded as AEs on the source documents and eCRF. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 3, any new, clinically relevant physical findings obtained during the screening period and Period 3 in comparison with those obtained before IMP administration in Period 2 before withdrawal will be recorded as AEs on the source documents and eCRF.

Location	Before Change	After Change
Section 3.10 Screen Failures	In the event that rescreening is not completed … new subject identifier must be assigned.	In the event that rescreening is not completed …new subject identifier must be assigned. However, for those subjects who were withdrawn from the trial at the discretion of the sponsor, who agree to take part in the trial again and sign the ICF again, but who are not enrolled in the trial prior to IMP administration on Day 1 of their scheduled treatment period (Period 2 or 3), the same subject identifier as the original will also be used for the repeated rescreening.
Section 4.1 Prohibited Medications	No asterisk or footnote	Asterisks were added to each "Period 1" in the itemized list. The following footnote was added: *For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the drugs is prohibited from 14, 21, 28, and 60 days, respectively, before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.
Section 4.2 Prohibited Therapies	No asterisk or footnote	An asterisk was added to "Period 1." The following footnote was added: *For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the therapy is prohibited from 60 days before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.
Section 4.3 Restricted Medications	No asterisk or footnote	An asterisk was added to "Period 1." The following footnote was added: *For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the use of the drugs is restricted from Day 1 of IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.
Section 4.4 Other Restrictions	No asterisk or footnote	Asterisks were added to each "Period 1" in the itemized list. The following footnote was added: *For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, the

Location	Before Change	After Change
		consumption of these foods and beverages is prohibited from 7 and 14 days, respectively, before IMP administration in the treatment period (Period 2 or 3) in which they are to resume participation in the trial.
Section 5.2 Eliciting and Reporting Adverse Events	Adverse event and SAE collection is … the subject's condition at the start of Period 2.	Adverse event and SAE collection is … the subject's condition at the start of Period 2. For subjects who were withdrawn from the trial at the discretion of the sponsor and resume participation in the trial from Period 2 or 3, AEs and SAEs will be collected from the time participation in the trial resumes until the end of the trial. However, AEs that occur after withdrawal from the trial at the discretion of the sponsor and resolve before the date on which the subject provided his/her signature for re-consent will also be collected as far as possible. Adverse events will be assessed based on the following: • Subjects who resume participation in the trial from Period 2: Adverse events occurring in the screening period will be assessed in comparison with their condition at the time of the consent/screening when they first participated in the trial, and AEs occurring in Period 2 and Period 3 will be assessed in comparison with their condition prior to IMP administration in Period 2. • Subjects who resume participation in the trial from Period 3: Adverse events occurring in the screening period and Period 3 will be assessed in comparison with their condition at the start of Period 2 when they first participated in the trial.
Appendix 3 List of CYP Inhibitors/Inducers CYP3A4 inducers	No description	The following was added to CYP3A4 inducers: Mechanism of Action: Antiepileptic Generic Name: Fosphenytoin Remarks: no addition
Appendix 3 List of CYP Inhibitors/Inducers	Remarks: *Includes the following phenobarbital derivatives phenobarbital, amobarbital,	Remarks: *Includes the following phenobarbital derivatives phenobarbital, amobarbital,

Location	Before Change	After Change
CYP3A4 inducers	pentobarbital, barbital, secobarbital, primidone	pentobarbital, barbital, secobarbital, primidone Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.

ADDITIONAL RISK TO THE SUBJECT

There is no additional risk to the subjects.

Amendment: Number: 3

Issue Date: 18 Jun 2020

PURPOSE:

Reconsideration/modification of the assessment schedule in response to the results from Cohort 1 and clarification of descriptions

BACKGROUND:

The assessment schedule was reconsidered and modified in response to the results from Cohort 1. Ambiguous descriptions were clarified.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
Section 3.1.3 Cohort 2 (Repeated Administration Period)		The following was added to the end of the section. Following administration of the QW formulation in Period 2, safety must be carefully evaluated. Subjects who meet any of the criteria for withdrawal before dose increase as specified in Section 3.9.3.2 Criteria for Withdrawal Before Dose Increase of the QW Formulation after IMP administration on Day 1 must be withdrawn from the trial without dose increase.
Section 3.7 Trial Procedures Table 3.7-2 Schedule of Assessments (Cohort 2; Repeated Administration Period)		Clinical laboratory tests were added to Day 10 of Period 2.

ADDITIONAL RISK TO THE SUBJECT

There is no additional risk to the subjects.

Agreement

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

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, brexpiprazole, the 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 brexpiprazole will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

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

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse events in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety

results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____ _____

Principal Investigator's Name Name of Trial Site

_____

Signature Date

The sponsor's signature for this Agreement is provided as an electronic signature. The electronic signature page is attached to this Agreement.