CLINICAL STUDY PROTOCOL

A multi-center, randomized, double-blind, placebo-controlled, parallel group-comparison trial to assess the efficacy and safety of brexpiprazole as adjunctive therapy in patients with major depressive disorder

NCT Number: NCT03697603
PRT NO.: 331-102-00058
Version Date: 23 Jan 2020 (Version 3.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole

CLINICAL PROTOCOL

A multi-center, randomized, double-blind, placebo-controlled, parallel group-comparison trial to assess the efficacy and safety of brexpiprazole as adjunctive therapy in patients with major depressive disorder

Protocol No. 331-102-00058

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	2/3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	[redacted]

Issue Date:	23 May 2018
Amendment 1:	23 Oct 2018
Amendment 2:	23 Jan 2020
Version No.:	3.0

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-102-00058
Protocol Title:	A multi-center, randomized, double-blind, placebo-controlled, parallel group-comparison trial to assess the efficacy and safety of brexpiprazole as adjunctive therapy in patients with major depressive disorder
Clinical Phase/ Type of Trial:	Phase 2/3 Confirmatory study
Treatment Indication:	Patients with major depressive disorder ("major depressive disorder, single episode" or "major depressive disorder, recurrent episode") according to the classification criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5®)
Objectives:	Primary endpoint: To assess the dosage and efficacy of brexpiprazole as adjunctive therapy vs placebo in combination with antidepressants (selective serotonin reuptake inhibitor [SSRI] or serotonin-noradrenaline reuptake inhibitor [SNRI]) in patients with major depressive disorder whose response to single-antidepressant therapy (SSRI or SNRI) was inadequate Secondary endpoint: To assess the safety of brexpiprazole as adjunctive therapy vs placebo in combination with antidepressants (SSRI or SNRI) in patients with major depressive disorder whose response to single-antidepressant therapy (SSRI or SNRI) was inadequate
Trial Design:	A multi-center, randomized, double-blind, placebo-controlled, parallel group-comparison trial
Subject Population:	The double-blind period (Phase B) of this trial will be conducted in patients ≥ 20 to < 65 years of age with major depressive disorder who showed inadequate response to commercially available antidepressant (SSRI or SNRI) in an 8-week evaluation performed in the antidepressant treatment period (Phase A). The planned number of subjects proceeding to the double-blind period (Phase B) is set as follows: brexpiprazole 1 mg/day group: 240; brexpiprazole 2 mg/day group: 240; placebo group: 240; total: 720.
Inclusion/Exclusion Criteria:	Inclusion criteria At screening 1) Outpatients, or inpatients at the time of informed consent whose treatment status can be successfully shifted to outpatient status before enrollment in the antidepressant treatment period (Phase A) 2) Male and female patients ≥ 20 to < 65 years of age (at the

time of informed consent)

3) Patients who have a level of comprehension sufficient to allow them to give written informed consent to all of the observation/examination/evaluation items specified in the protocol, and who can understand the contents of the trial
4) Patients with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode," and whose current episode has persisted for at least 8 weeks
5) Patients who have received 1 to 3 adequate antidepressant drug treatments for the current major depressive episode and whose response to all of the treatments has been inadequate.
   Adequate antidepressant drug treatment:
   Treatment with an antidepressant at an approved dose for at least 6 weeks (for combination therapy, treatment for at least 3 weeks)
   Inadequate response:
   With complete recovery from depressive symptoms and not the slightest improvement considered as 100% and 0%, respectively, patients carry out self-evaluations for improvement by antidepressant drug treatments used to date, from among 4 grades (< 25% Improvement, 25% to 49% Improvement, 50% to < 75% Improvement, and ≥ 75% Improvement), with the evaluations corresponding to < 25% Improvement or 25% to 49% Improvement classified as inadequate response.
   Patients who, among 1 to 3 adequate antidepressant drug treatments, have received treatment for ≥ 6 weeks at least once (receiving only combination therapies for ≥ 3 weeks does not qualify) are eligible for selection.
6) Patients with a total score of ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D), based on the evaluation conducted at screening

At the initiation of the antidepressant treatment period (Phase A)

7) Outpatients
8) Subjects with a HAM-D 17-item total score of ≥ 18 based on the evaluation at the initiation of the antidepressant treatment period (Phase A)

At the initiation of the double-blind period (Phase B) (criteria for proceeding)

9) Outpatients
10) Subjects with a HAM-D 17-item total score of ≥ 14 at Week 8 of the antidepressant treatment period (Phase A)
11) Subjects in whom the reduction rate for HAM-D 17-item total

scores is < 50% at Week 8 of the antidepressant treatment period (Phase A), as compared with at the initiation of the antidepressant treatment period (Phase A).

12) Subjects in whom Clinical Global Impression – Improvement (CGI-I) scores have been consistently 3 (minimally improved) to 7 (very much worse) throughout the antidepressant treatment period (Phase A)

Exclusion criteria

At screening

1) Women who are pregnant or breastfeeding or who have positive pregnancy test (urine) results at screening
2) Sexually active male subjects or sexually active female subjects of childbearing potential, who will not agree to practice 2 different methods of birth control or to remain abstinent during the trial and for 30 days after the final investigational medicinal product (IMP) administration. For birth control, 2 of the following methods must be used: vasectomy, tubal ligation, vaginal diaphragm, intra-uterine contraceptive device (IUD), oral contraceptives, or condom with spermicide.
3) Patients who have received at least 4 appropriate antidepressant drug treatments for the current major depressive episode but whose response was inadequate to all treatments
4) Patients receiving treatment with antipsychotics and psychostimulants for the current major depressive episode (excluding the use of sulpiride for depression/depressive state or gastric/duodenal ulcer)
5) Patients with a treatment history showing that all antidepressants (including those not used for the current major depressive episode) cannot be tolerated
6) Patients with a history of electroconvulsive therapy
7) Patients with a diagnosis of any of the following diseases according to DSM-5
    a) Neurocognitive disorders
    b) Schizophrenia spectrum and other psychotic disorders
    c) Bipolar and related disorders
    d) Feeding and eating disorders
    e) Obsessive-compulsive disorder
    f) Panic disorder
    g) Posttraumatic stress disorder
8) Patients with a diagnosis of any personality disorders (borderline personality disorder, antisocial personality

disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, and histrionic personality disorder) according to DSM-5

9) Patients experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current major depressive episode
10) Patients receiving a new psychotherapy within 6 weeks prior to informed consent
11) Patients who have previously taken brexpiprazole
12) Patients who have participated in other clinical trials within 60 days prior to informed consent
13) Patients with a HAM-D score for suicide (No. 11) of ≥ 3 at screening, those answering "Yes" to question 4 or 5 of Columbia-Suicide Severity Rating Scale (C-SSRS), or those who are, based on current psychiatric symptoms or past medical history, at high risk of suicide during the trial in the opinion of the investigator or subinvestigator
14) Patients with clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders; patients can be enrolled if the conditions are mild or well controlled and will not hamper assessment of safety and efficacy.
15) 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 (assessed based on results from the central laboratory)
  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

16) Patients with substance abuse or substance dependence, including alcohol and benzodiazepines, based on DSM-5 diagnostic criteria within 180 days prior to informed consent; caffeine and nicotine are not included
17) Patients with a complication of hypothyroidism or hyperthyroidism at informed consent (excluding those in a

stable condition due to medications for the previous 90 days or longer at acquisition of informed consent), or abnormal thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels at screening (assessed based on results from the central laboratory)

18) Patients meeting any of the following criteria or showing symptoms at screening
    a) Poorly controlled hypertension (diastolic blood pressure of > 95 mmHg)
    b) Hypotension with symptoms
    c) Orthostatic hypotension in which blood pressure after 3 minutes of standing is ≥ 30 mmHg lower for systolic blood pressure or ≥ 20 mmHg lower for diastolic blood pressure, compared with pressures in the supine position before standing
19) Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), and patients with a history of angioplasty, stent placement, or coronary artery bypass
20) Patients with a history of neuroleptic malignant syndrome or serotonin syndrome
21) Patients with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
22) Patients with the following clinical laboratory test values or electrocardiogram (ECG) parameters at screening (assessed based on results from the central laboratory and central ECG measurement facility)
    a) Platelet count: ≤ 75,000 /mm^3
    b) Hemoglobin: ≤ 9 g/dL
    c) Absolute neutrophil count: ≤ 1000 /mm^3
    d) Aspartate aminotransferase (AST): > 2 times the upper limit of the reference range
    e) Alanine aminotransferase (ALT): > 2 times the upper limit of the reference range
    f) Creatine phosphokinase (CPK): > 3 times the upper limit of the reference range
    g) Creatinine: ≥ 2 mg/dL
    h) QT interval as corrected by Fridericia's formula (QTcF): ≥ 450 msec
23) Patients with a history of hypersensitivity to antidepressants

24) Patients with a history or complication of allergy to more than one medication

25) The following patients falling under the contraindications in the package insert for brexpiprazole tablet

a) Patients in a coma

b) Patients under the strong influence of central nervous system depressants including barbiturate analogs/anesthetics

c) Patient receiving adrenaline

d) Patient with a history of hypersensitivity to components of brexpiprazole tablet

26) Patients who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator

At the initiation of the antidepressant treatment period (Phase A)

27) Pregnant or breastfeeding female subjects, or those with positive pregnancy test (urine) results at the initiation of the antidepressant treatment period (Phase A)

28) Subjects newly requiring hospitalization for the current major depressive episode during the screening period

29) Patients with a HAM-D score for suicide (No. 11) of ≥ 3 at the initiation of the antidepressant treatment period (Phase A), those answering "Yes" to question 4 or 5 of C-SSRS, or those who are, based on current psychiatric symptoms or past medical history, at high risk of suicide during the trial in the opinion of the investigator or subinvestigator

30) Patients meeting any of the following criteria or showing symptoms at the initiation of the antidepressant treatment period (Phase A)

a) Poorly controlled hypertension (diastolic blood pressure of > 95 mmHg)

b) Hypotension with symptoms

c) Orthostatic hypotension in which blood pressure after 3 minutes of standing is ≥ 30 mmHg lower for systolic blood pressure or ≥ 20 mmHg lower for diastolic blood pressure, compared with pressures in the supine position before standing

31) Subjects receiving treatment with monoamine oxidase (MAO) inhibitors within 2 weeks before the initiation of the antidepressant treatment period (Phase A)

32) Subjects using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before the initiation of the antidepressant treatment period (Phase A)

33) Subjects with urinary retention, if receiving milnacipran

	34) Subjects with poorly controlled angle closure glaucoma, if receiving duloxetine 35) Subjects who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator
Trial Sites:	170 sites within Japan
Investigational Medicinal Products, Dose, Dosage Regimen, Treatment Period, Formulation, Mode of Administration:	**Antidepressant Treatment period (Phase A)** 1) Drugs: Among commercially available SSRIs (fluvoxamine maleate, paroxetine hydrochloride hydrate, sertraline hydrochloride, and escitalopram oxalate) and SNRIs (milnacipran hydrochloride, duloxetine hydrochloride, and venlafaxine hydrochloride), one antidepressant different from the prior medications of antidepressant*, plus the placebo tablet *Antidepressant that meets the definition for "adequate antidepressant drug treatment" and has been taken at the time of informed consent. 2) Dose and regimen: In the antidepressant treatment period (Phase A), subjects will orally receive an antidepressant (SSRI or SNRI), which is different from the antidepressant prior medications, plus a placebo tablet once daily in a single-blind manner. The antidepressant (SSRI or SNRI) will be administered at the dose and regimen specified in the package insert, and the dose of the antidepressant will be progressively increased, within the approved dose range, to the maximum dose, as far as possible, in accordance with subject status; for the last 2 weeks of the 8-week period, dose and regimen will be fixed. When an antidepressant cannot be administered at a fixed dose and regimen for the last 2 weeks of the 8-week antidepressant treatment period (Phase A) for tolerability-related reasons, the subject will be withdrawn from the trial. 3) Treatment period: 8 weeks **Double-blind period (Phase B)** Subjects who meet the criteria for proceeding to the double-blind period (Phase B) based on the assessment at Week 8 of the antidepressant treatment period (Phase A) will proceed to the double-blind period (Phase B). 1) Drugs: • One commercially available antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) • IMP: – 1 mg/day group: Brexpiprazole 1 mg tablet – 2 mg/day group: Brexpiprazole 1 mg tablet (until the

observations, examinations, and evaluations performed at Week 1) and brexpiprazole 2 mg tablet (following the observations, examinations, and evaluations performed at Week 1)

- Placebo group: Placebo tablet

2) Dose and regimen:

- Commercially available antidepressant (SSRI or SNRI):
  An antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) will be continued with no changes from the final dose and regimen; no changes in dose, regimen, or drug will be allowed.
- IMP:
  - 1 mg/day group: One brexpiprazole 1 mg tablet will be orally administered once daily.
  - 2 mg/day group: Treatment will be started at 1 mg of brexpiprazole per day and one brexpiprazole 1 mg tablet will be orally administered once daily until the observations, examinations, and evaluations performed at Week 1. Following the observations, examinations, and evaluations performed at Week 1, one brexpiprazole 2 mg tablet will be orally administered once daily.
  - Placebo group: One placebo tablet will be orally administered once daily.

3) Treatment period: 6 weeks

Antidepressant-responder Treatment-continuation Period (Phase A+)

Antidepressant responders who do not meet the criteria for proceeding to the double-blind period (Phase B) based on the assessment at Week 8 of the antidepressant treatment period (Phase A) will proceed to the antidepressant-responder treatment-continuation period (Phase A+).

1) Drugs:
   The antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) plus a placebo tablet
2) Dose and regimen:
   Subjects will receive an antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) with no changes from the final dose and regimen, plus oral placebo (1 tablet) once daily in a single-blind manner.
3) Treatment period: 6 weeks

Trial Assessments:	**Efficacy:** Montgomery Åsberg Depression Rating Scale (MADRS), CGI-I, Clinical Global Impression − Severity of Illness (CGI-S), HAM-D, the Montgomery Åsberg Depression Rating Scale Self-assessment (MADRS-S), Sheehan Disability Scale (SDS) **Safety:** Adverse events, laboratory tests, vital signs (body temperature, diastolic blood pressure and systolic blood pressure, and pulse rate [supine, sitting, and standing positions]), physical examinations, waist circumference, body weight, 12-lead ECG, pregnancy test, C-SSRS, Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) **Screening:** Subject demographics, height **Pharmacokinetic and Pharmacogenomic Assessments and** [redacted] Plasma brexpiprazole concentrations, CYP2D6 genetic testing [redacted]
Criteria for Evaluation	**Primary Endpoints:** Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS total scores at Week 6 of the double-blind period (Phase B) **Secondary Endpoints:** • MADRS response rate at Week 6 of the double-blind period (Phase B) The proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline (Week 8 of the antidepressant treatment period [Phase A]) • MADRS remission rate at Week 6 of the double-blind period (Phase B) The proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline (Week 8 of the antidepressant treatment period [Phase A]), with their MADRS total scores, at Week 6 of the double-blind period (Phase B), being ≤ 10 • CGI-I improvement rate at Week 6 of the double-blind period (Phase B) The proportion of subjects who score 1 or 2 on the CGI-I scale at Week 6 of the double-blind period (Phase B)

	• Mean changes in CGI-S at Week 6 of the double-blind period (Phase B) Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in CGI-S at Week 6 of the double-blind period (Phase B) • Mean changes in HAM-D 17-item total scores at Week 6 of the double-blind period (Phase B) Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in HAM-D 17-item total scores at Week 6 of the double-blind period (Phase B) • Mean changes in mean SDS scores at Week 6 of the double-blind period (Phase B) Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in mean SDS scores at Week 6 of the double-blind period (Phase B) • Mean changes in MADRS-S total scores at Week 6 of the double-blind period (Phase B) Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS-S total scores at Week 6 of the double-blind period (Phase B) **Safety Endpoints:** Adverse events, laboratory tests, vital signs (body temperature, diastolic blood pressure and systolic blood pressure, and pulse rate [supine, sitting, and standing positions]), physical examinations, waist circumference, body weight, body mass index, 12-lead ECG, C-SSRS, DIEPSS, AIMS, BARS **Pharmacokinetic and Pharmacogenomic Endpoints:** Plasma brexpiprazole concentrations, CYP2D6 genetic testing
Statistical Methods:	**Statistical Methods for Primary Endpoints:** The primary endpoint is mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS total scores at Week 6 of the double-blind period (Phase B). For the primary analysis, Mixed-model Repeated Measure (MMRM) analysis will be performed using the observed cases data set in full analysis set. The statistical hypotheses will be tested, based on differences in least square means between each brexpiprazole group and the placebo group, which are calculated by MMRM. To adjust for multiplicity of tests, due to there being 2 comparisons with the placebo group, a fixed-sequence approach will be used to control overall type 1 error rates. Comparison between the brexpiprazole 2 mg/day group and placebo group will be performed first; only when significance is observed at a two-sided significance level of 5%, will comparison between the brexpiprazole 1 mg/day group and placebo group be

	performed at a two-sided significance level of 5%. The MMRM will include treatment group (brexpiprazole 1 mg/day group, brexpiprazole 2 mg/day group, and placebo group), time point (double-blind period [Phase B] Weeks 1, 2, 3, 4, 5, and 6), and interaction between treatment group and time point as factors, and baseline and interaction between baseline and time point as covariates. Unstructured error variance-covariance structure will be assumed. For a degree-of-freedom approximation, the Kenward-Roger method will be used. For each time point, least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% confidence intervals (CIs) will be determined. **Rationale for target number of subjects:** In phase 3, double-blind, placebo-controlled trials of fixed doses of brexpiprazole (331-10-227, 331-10-228, and 331-13-214) conducted outside Japan, changes from baseline in MADRS total scores at Week 6 of the double-blind period (Phase B) have been analyzed by the MMRM method (for 331-10-227 and 331-10-228 trials, based on the results for efficacy from an analysis of subgroups meeting the inclusion criteria that had been revised in the middle of the trials), which demonstrated that the differences between the brexpiprazole groups (the 3 mg group in 331-10-227 trial, and the 2 mg group in 331-10-228 and 331-13-214 trials) and the placebo group were −1.9, −3.2, and −2.3, respectively, and that the standard deviations obtained from standard errors and numbers of subjects at Week 6 of the double-blind period (Phase B) were 7.2, 7.7, and 8.2, respectively. On the assumption that the difference in changes from baseline in MADRS total scores at Week 6 of the double-blind period (Phase B) is −2.4 for the brexpiprazole group compared with the placebo group with a standard deviation of 7.7, this trial will require 218 subjects per group to ensure a power of 90% in a two-sided test with a significance level of 0.05. We have decided that the planned number of subjects for randomization will be 240 per group, assuming that 7% of subjects will discontinue the trial during the double-blind period (Phase B) and some subjects will be excluded from analysis.
Trial Duration:	01 Jun 2018 to 31 Jul 2022 (planned)

Table of Contents

List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	5-Hydroxytryptamine, serotonin
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CK	Creatine kinase
CPK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D_2 receptor	Dopamine D_2 receptor
DIEPSS	Drug Induced Extra-Pyramidal Symptoms Scale
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and statistical manual of mental disorders fifth edition
EDTA	Ethylenediaminetetraacetic acid
EM	Extensive metabolizer
FAS	Full analysis set
FT4	Free thyroxine
GCP	Good Clinical Practice
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HAM-D	Hamilton Rating Scale for Depression
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IRE	Immediately reportable event
IM	Intermediate metabolizer
IRB	Institutional review board
IWRS	Interactive web response system
JSMD	Japanese Society of Mood Disorders
LDH	Lactate (lactic acid) dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LSMD	Least square mean difference
MADRS	Montgomery Åsberg Depression Rating Scale
MADRS-S	The Montgomery Åsberg Depression Rating Scale Self-assessment

Abbreviation	Definition
MAO inhibitor	Monoamine oxidase inhibitor
MOR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MMRM	Mixed-model repeated measures
MNOR	Missing not at random
NGSP	The National Glycohemoglobin Standardization Program
OC	Observed Cases
PANSS	Positive and Negative Syndrome Scale
PM	Poor metabolizer
PQC	Product quality complaint
PT	Prothrombin time
PT (INR)	Prothrombin time (international normalized ratio)
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate by Bazett's formula
QTcF	QT corrected for heart rate by Fridericia's formula
QTcN	QT corrected for heart rate by FDA Neuropharmacological Division formula
SDS	Sheehan Disability Scale
SIGH-D	Structured Interview Guide for HAM-D
SIGMA	Structured Interview Guide for MADRS
SNRI	Serotonin-noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
T3/T4	Triiodothyronine/levothyroxine
TEAE	Treatment-emergent adverse event; adverse event occurring after initiation of IMP administration in the double-blind period (Phase B)
TSH	Thyroid-stimulating hormone
γ-GTP	γ-glutamyl transpeptidase

1 Introduction

Depression is a condition that often takes a chronic course, causing significant suffering and imposing a burden on the patient. The disease interferes with the daily activities and social life of patients, who continue to suffer from decreased social functioning unless the disease remits.[1] Moreover, depression is one of the major risk factors for suicide and, according to a psychological autopsy study, 60% to 70% of those who committed suicide had been diagnosed with depression.[2] The number of suicides in Japan, even though a downward trend has been noted since 2012, was 21897 in 2016,[3] which is still high compared with other developed countries. According to a published report by the Ministry of Health, Labour and Welfare (MHLW), the economic loss from depression resulting in leaves of absence from work, loss of employment, or suicide, etc, is estimated to be approximately 2.7 trillion yen in 2009.[4] Decreased social functioning and increased suicide rate attributable to depression have become serious social problems. Under this circumstance, treatment of depression plays an important role in society.

The lifetime and 12-month prevalence of major depressive disorder in Japan were 6.2% and 2.1%, respectively, according to "Study on Mental Health Epidemiological Survey," a study supported by the Health and Labour Sciences Research Grants from fiscal year 2004 to 2006.[5] The Treatment Guidelines issued by the Japanese Society of Mood Disorders (JSMD) (hereinafter referred to as JSMD Treatment Guidelines)[6] list pharmacotherapy with antidepressants as the mainstay in the treatment of major depressive disorder. As first-line agents, the guidelines recommend the following novel antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and mirtazapine, a noradrenergic and specific serotonergic antidepressant. However, remission rates in patients treated with these antidepressants are as low as 30% to 40%.[7] This difficulty in improving or achieving remission of major depressive disorder symptoms interferes with social functioning, causing various issues including loss of employment, withdrawal from education, and divorce.

In the JSMD Treatment Guidelines,[6] the following therapeutic methods are recommended for patients who fail to respond to the initial treatment with first-line agents such as SSRIs, SNRIs, and mirtazapine: Increase the dose to a sufficient level within the range in which adverse reactions are not clinically problematic; treat at the sufficiently increased dose for approximately 4 weeks; and then either change the drug if the patient does not respond to the treatment, or perform augmentation therapy if improvement is noted only in some of the symptoms of depression. Agents used for augmentation therapy include lithium, triiodothyronine/levothyroxine combination

(T3/T4), lamotrigine, valproic acid, carbamazepine, and atypical antipsychotics. While augmentation therapy with lithium has been reported to potentiate the antidepressant effects of drugs in many placebo-controlled studies,[8] most of the drugs investigated in such studies were tricyclic antidepressants. Therefore, little data are available on augmentation of SSRIs or SNRIs at present. As a result of a meta-analysis on lithium toxicity profile,[9] renal impairment, hypothyroidism, increased blood calcium level, and hyperparathyroidism were reported as adverse effects of particular concern. Special attention should be paid to the occurrence of these adverse effects during treatment with lithium. Concerning augmentation therapy with T3/T4, most of the available data are also from studies on tricyclic antidepressants. Furthermore, the efficacy of augmentation therapy with lamotrigine, valproic acid, or carbamazepine has not been sufficiently investigated. In addition, augmentation therapy with lithium, T3/T4, lamotrigine, valproic acid, or carbamazepine has not been approved for the indication of depression.

Meanwhile, concerning augmentation therapy with atypical antipsychotics mediated by the dopaminergic system, aripiprazole is the only antipsychotic agent that has been approved in Japan for use as an adjunctive therapy for the treatment of major depressive disorder. The efficacy of aripiprazole was confirmed in a Japanese double-blind, placebo-controlled trial (031-08-001)[10] and 3 overseas double-blind trials of aripiprazole.[11,12,13] However, the results of these clinical trials suggest that a certain percentage of patients cannot tolerate long-term use of aripiprazole as adjunctive therapy due to adverse events (AEs) such as akathisia and insomnia. This drawback of aripiprazole as an adjunctive therapy remains a therapeutic issue.

Brexpiprazole is a new chemical entity discovered by Otsuka Pharmaceutical Co., Ltd. Unlike aripiprazole, brexpiprazole, even at a low level of < 1 nM, exhibits serotonin (5-HT)$_{1A}$ receptor partial agonist activity, 5-HT$_{2A}$ receptor antagonist activity, and dopamine D_2 receptor (D_2 receptor) partial agonist activity with optimal intrinsic activity. The pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It modulates the serotonergic and dopaminergic systems with its partial agonist activity or antagonist activity. In addition, for adrenergic $\alpha_{1B/2C}$ receptors, it also has similar subnanomolar binding affinity and antagonist activity. These 5-HT$_{1A}$/D_2 receptor partial agonist activities and 5-HT$_{2A}$ and $\alpha_{1B/2C}$ receptor antagonist activities of brexpiprazole are thought to contribute to the antipsychotic, antidepressant, and impulse-control effects. Having the optimal intrinsic activity for D_2 receptors and potent effects on the serotonergic system compared with aripiprazole, brexpiprazole is expected to contribute

to a reduction in the incidence and severity of adverse reactions, such as akathisia and insomnia, which are issues associated with treatment using aripiprazole.

In Japan, brexpiprazole was investigated in a double-blind, placebo-controlled trial in patients with an acute relapse of schizophrenia (331-10-002)[14] and in a long-term trial in outpatients with schizophrenia (331-10-003).[15] Based on the results of these trials as well as overseas clinical trials, an application was filed for marketing authorization of brexpiprazole for the indication of schizophrenia, which was approved in January 2018.[16]

Outside Japan, double-blind, placebo-controlled trials in patients with an acute relapse of schizophrenia (331-10-230 and 331-10-231) were performed, and the results confirmed the efficacy of brexpiprazole and demonstrated its safety.[17,18] In addition, double-blind, placebo-controlled trials in patients with major depressive disorder who had insufficient responses to SSRIs or SNRIs (331-10-227 and 331-10-228) were performed, and the results confirmed the efficacy of brexpiprazole as adjunctive treatment and demonstrated its safety in this patient population.[19,20] Based on the results of the above clinical trials, brexpiprazole was approved in the US not only for the indication of schizophrenia but also received approval as adjunctive treatment of major depressive disorder.[21]

As shown above, outside Japan, the efficacy of brexpiprazole was demonstrated not only in treating schizophrenia but also as adjunctive treatment for major depressive disorder. Therefore, brexpiprazole as adjunctive therapy is also likely to be effective in Japanese patients with inadequate response to antidepressants. The results of overseas clinical trials show that there are no safety-related concerns associated with brexpiprazole as adjunctive therapy. Therefore, use of brexpiprazole as adjunctive therapy is expected to reduce the incidence of adverse reactions such as akathisia and insomnia, which are issues associated with augmentation therapy using aripiprazole, and to enhance treatment adherence.

Based on the above, considering that it would be useful for the treatment of patients with major depressive disorder to investigate the efficacy and safety of brexpiprazole as adjunctive therapy in Japanese patients with inadequate response to antidepressants, we have planned to conduct this clinical trial.

1.1 Nonclinical Data

[redacted]

[redacted]

1.2 Clinical Data

1.2.1 Clinical Data From Japanese Trials in Subjects With Schizophrenia

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

A double-blind, placebo-controlled trial was conducted in Japan to assess the efficacy and safety of fixed-dose brexpiprazole in adult subjects with an acute relapse of schizophrenia. This trial had a total of 4 groups consisting of a placebo group and 3 fixed-dose groups of brexpiprazole (1, 2, and 4 mg/day). The change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score, the primary endpoint, showed significant improvement in the 2-mg group compared with the placebo group (least square 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 the PANSS total score was numerically greater in the 4-mg group than in the placebo group (LSMD: −3.86, p = 0.1959). There was no significant difference between the 1-mg group and the placebo group (LSMD = −0.63).

The efficacy of brexpiprazole at a dose of 2 mg was demonstrated in subjects with an acute relapse of schizophrenia.

The incidence of AEs 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. Most AEs reported in brexpiprazole groups were mild or moderate in severity. One subject in the 4-mg group died. The AE resulting in death was asphyxia. This event was considered unrelated to the investigational medicinal product (IMP). The incidence of serious adverse events (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 any treatment group, 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 in any treatment group. No marked changes were noted in laboratory test values, vital signs, body weight, or electrocardiogram (ECG) in brexpiprazole groups.

1.2.1.2 Long-term Trial in Subjects With Schizophrenia (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.

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. 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 body weight from baseline to the final assessment 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 findings 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.

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

1.2.2 Clinical Data From Overseas Trials in Subjects With Major Depressive Disorder

1.2.2.1 Confirmatory Trial in Subjects With Major Depressive Disorder (331-10-227)

A double-blind, placebo-controlled trial was conducted outside Japan to evaluate the efficacy, safety, and tolerability of fixed doses of brexpiprazole in subjects with major depressive disorder who had an insufficient response to antidepressant therapy. All eligible subjects who passed the screening test entered an 8-week antidepressant treatment period (Phase A) in which SSRI/SNRI and placebo were administered in a single-blind manner. Subjects who responded to SSRI/SNRI and placebo in Phase A

entered a 6-week antidepressant-responder treatment-continuation period (Phase A+) in which SSRI/SNRI and placebo continued to be concomitantly administered for another 6 weeks. Subjects who had an insufficient response to SSRI/SNRI and placebo in Phase A entered a double-blind period (Phase B) in which brexpiprazole or placebo was administered concomitantly with SSRI/SNRI for 6 weeks in a double-blind manner. This trial had a total of 3 treatment groups consisting of a placebo group and 2 fixed-dose groups of brexpiprazole (1 and 3 mg/day). The change from baseline to Week 6 in the Montgomery Åsberg Depression Rating Scale (MADRS) total score, the primary endpoint, showed numerical improvement in the 3-mg group compared with the placebo group (LSMD: −1.52, p = 0.0327). Improvement in the MADRS total score was numerically greater in the 1-mg group than in the placebo group (LSMD: −1.19, p = 0.0925). In the efficacy data from a subgroup meeting the inclusion criteria revised during the trial, the change from baseline to Week 6 in the MADRS total score showed improvement in the 3-mg group compared with the placebo group (LSMD: −1.95, p = 0.0079). Meanwhile, the change from baseline in the 1-mg group was −1.30 (p = 0.0737).

The incidence of AEs was 54.9% in the brexpiprazole 1-mg group, 63.3% in the 3-mg group, and 46.8% in the placebo group. The AEs reported in the brexpiprazole 3-mg group at an incidence of ≥ 5% and at more than double the incidence in the placebo group were akathisia (13.5% in the 3-mg group and 2.3% in the placebo group; hereinafter, the same order shall apply), somnolence (5.7%, 0.5%), and weight increased (5.7%, 0.9%). The AEs reported in the brexpiprazole 1-mg group at an incidence of ≥ 5% and at more than double the incidence in the placebo group were weight increased (6.6% in the 1-mg group and 0.9% in the placebo group; hereinafter, the same order shall apply) and nasopharyngitis (6.6%, 1.8%). Most AEs in either of the brexpiprazole groups were mild or moderate in severity. The incidence of SAEs was 0.4% in the 1-mg group, 0.4% in the 3-mg group, and 0.0% in the placebo group. The incidence of AEs leading to discontinuation was 1.3% in the 1-mg group, 3.5% in the 3-mg group, and 1.4% in the placebo group. The incidences of both SAEs and AEs leading to discontinuation were low in the brexpiprazole groups as in the placebo group. No marked changes were noted in laboratory test values, vital signs, or ECGs in either of the brexpiprazole groups.

1.2.2.2 Confirmatory Trial in Subjects With Major Depressive Disorder (331-10-228)

A double-blind, placebo-controlled trial was conducted outside Japan to evaluate the efficacy, safety, and tolerability of a fixed dose of brexpiprazole in subjects with major depressive disorder who had an insufficient response to antidepressant therapy. The trial

was designed similarly to Trial 331-10-227 and had 2 treatment groups consisting of a placebo group and a brexpiprazole 2-mg group. The change from baseline to Week 6 in the MADRS total score, the primary endpoint, showed significant improvement in the 2-mg group compared with the placebo group (LSMD: −3.12, p = 0.0001). In the efficacy data from a subgroup meeting the inclusion criteria revised during the trial, the change from baseline to Week 6 in the MADRS total score showed improvement in the 2-mg group compared with the placebo group (LSMD: −3.21, p = 0.0002).

The incidence of AEs was 59.0% in the brexpiprazole 2-mg group and 46.6% in the placebo group. The AEs reported in the brexpiprazole 2-mg group at an incidence of ≥ 5% and at more than double the incidence in the placebo group were weight increased (8.0% in the 2-mg group and 3.1% in the placebo group; hereinafter, the same order shall apply) and akathisia (7.4%, 1.0%). Most AEs in the brexpiprazole group or the placebo group were mild or moderate in severity. The incidence of SAEs was 1.1% in the 2-mg group and 1.0% in the placebo group. The incidence of AEs leading to discontinuation was 3.2% in the 2-mg group and 0.0% in the placebo group. The incidences of both SAEs and AEs leading to discontinuation were low in the brexpiprazole group as in the placebo group. No marked changes were noted in laboratory test values, vital signs, or ECGs in the brexpiprazole group.

1.2.2.3 Confirmatory Trial in Subjects With Major Depressive Disorder (331-13-214)

A double-blind, placebo-controlled trial was conducted outside Japan to evaluate the efficacy, safety, and tolerability of a fixed dose of brexpiprazole in subjects with major depressive disorder who had an inadequate response to antidepressant therapy. The trial was designed similarly to Trials 331-10-227 and 331-10-228 and had 2 treatment groups consisting of a placebo group and a brexpiprazole 2-mg group. The change from baseline to Week 6 in the MADRS total score, the primary endpoint, showed significant improvement in the 2-mg group compared with the placebo group (LSMD: −2.30, p = 0.0074).

The incidence of AEs was 59.9% in the brexpiprazole 2-mg group and 49.5% in the placebo group. The AEs reported in the brexpiprazole 2-mg group at an incidence of ≥ 5% and at more than double the incidence in the placebo group were restlessness (8.3% in the 2-mg group and 2.0% in the placebo group; hereinafter, the same order shall apply) and weight increased (5.2%, 0.5%). The AEs reported in the 2-mg group at an incidence of ≥ 5% and at a higher incidence than that in the placebo group were only akathisia (8.3%, 5.0%) and upper respiratory tract infection (5.2%, 5.0%). Most AEs in the brexpiprazole group were mild or moderate in severity. The incidence of SAEs was 0.5%

in the 2-mg group and 0.0% in the placebo group. The incidence of AEs leading to discontinuation was 2.1% in the 2-mg group and 0.5% in the placebo group. The incidences of both SAEs and AEs leading to discontinuation were low in the brexpiprazole group as in the placebo group. No marked changes were noted in laboratory test values, vital signs, or ECGs in the brexpiprazole group.

1.3 Known and Potential Risks and Benefits

Extrapyramidal symptoms, seizures, suicidality, and dyslipidemia have been assessed as important risks associated with the administration of brexpiprazole. The potential mechanism of antipsychotics causing seizures is a class effect thought to be due to a reduction of the seizure threshold in susceptible individuals. The occurrence of suicidal behavior is inherent in psychotic illnesses and mood disorders. In the schizophrenia and major depressive disorder populations, short-term and long-term administration of brexpiprazole was associated with moderate weight gain; however, weight gain did not contribute significantly to IMP discontinuation, and only a few subjects with marked weight gain demonstrated metabolic syndrome. Although not clinically significant, an increase in triglycerides was observed in some trials. Due to this observation and considerations on potential clinical consequences related to weight gain, dyslipidemia is considered to be an important potential risk.

With lower intrinsic activity at the D_2 receptors and more potent effects on the serotonergic system, which is suggested to be involved in the improvement of depressive symptoms, extrapyramidal symptoms, and cognitive function, compared with aripiprazole, evidence suggests that brexpiprazole can reduce the incidence of AEs such as akathisia and other extrapyramidal symptoms, nausea, vomiting, excitement, and irritability, and also improve symptoms of depression. In clinical trials conducted overseas, the incidence of AEs, such as akathisia, which are considered risk factors for low adherence to treatment, was confirmed to be low in patients treated with brexpiprazole. Therefore, brexpiprazole is likely to become a useful treatment option for patients with major depressive disorder who need to receive treatment over a long period of time.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Considering the monoamine hypothesis, one of the assumptions of the underlying pathophysiologic bases of depression, use of drugs that act on the serotonergic, noradrenergic, or dopaminergic system is regarded as the most rational approach to the

treatment of major depressive disorder. SSRIs and SNRIs, which are commonly used to treat major depressive disorder, activate the serotonergic and noradrenergic systems. However, these drugs poorly activate the dopaminergic system with a response rate of 50% to 60%. Aripiprazole is the only antipsychotic agent that has been approved in Japan as augmentation therapy acting directly on the dopaminergic system. However, the drug does have some therapeutic issues that need to be addressed, such as akathisia and insomnia caused by its high intrinsic activity at the D_2 receptor. Unlike aripiprazole, brexpiprazole, even at a low level of < 1 nM, acts on 5-HT_{1A} receptors and 5-HT_{2A} receptors, and acts as an agonist at D_2 receptors with optimal intrinsic activity. Adjunct administration of brexpiprazole with optimal intrinsic activity to SSRIs or SNRIs is likely to act on not only the serotonergic and noradrenergic systems but also the dopaminergic system. Therefore, this treatment is expected to be more effective in treating major depressive disorder patients with a safety profile that is superior to monotherapy with an antidepressant and thereby improve adherence to treatment.

Phase 3, double-blind, placebo-controlled trials of fixed doses of brexpiprazole (331-10-227, 331-10-228, and 331-13-214) conducted outside Japan demonstrated the efficacy of brexpiprazole as adjunctive therapy to SSRIs or SNRIs in patients with major depressive disorder and found no significant safety concerns. It is expected that brexpiprazole as adjunctive therapy will also be effective in Japanese patients with major depressive disorder.

This trial has been designed to assess the doses and efficacy of brexpiprazole as adjunctive therapy in Japanese patients with major depressive disorder who have an inadequate response to antidepressants, and to confirm the drug's safety. As was the case in the overseas trials, this trial has an antidepressant treatment period (Phase A), in which commercially available antidepressants and placebo will be administered in a single-blind manner, and a double-blind period (Phase B) in subjects with an inadequate response to antidepressants, in which brexpiprazole administered adjunctively with antidepressants will be compared with placebo. The antidepressant treatment period (Phase A) was set at 8 weeks, which is considered sufficient based on the JSMD Treatment Guidelines.[6] The antidepressant agent to be used will be an SSRI or SNRI, as in the overseas trials. The duration of the double-blind period (Phase B) for comparison with the placebo group was set at 6 weeks, the same duration used in the overseas trials.

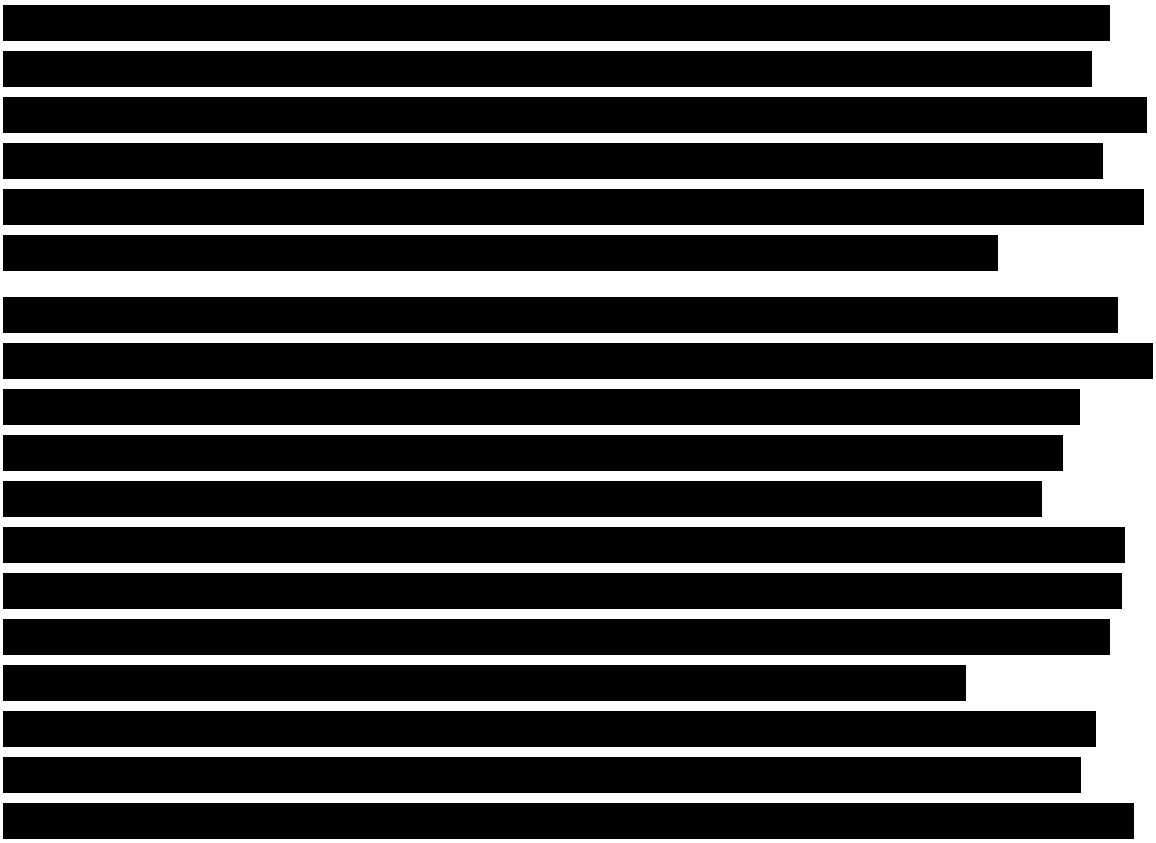
As in the overseas trials, the primary endpoint is the mean change in MADRS, which is used worldwide as a depression assessment scale. In order to assess the efficacy and doses of brexpiprazole, this trial will have a total of 3 treatment groups consisting of the brexpiprazole 1 mg/day group and 2 mg/day group and the placebo group.

The US package insert of brexpiprazole tablets[21] contains warnings regarding antidepressant-related suicidal ideation or suicidal behavior, and also in the Japanese package insert of the drug for the indication of schizophrenia, patients with a history of suicidal ideation or suicide attempt come under Careful Administration. Considering the above, criteria that require the exclusion or discontinuation of patients at high risk of suicide have been established as exclusion or discontinuation criteria to minimize the risk of suicide during the trial and thereby to ensure the safety of subjects.

Based on the above, we concluded that assessment of the efficacy and safety of brexpiprazole as adjunctive therapy in Japanese major depressive disorder patients receiving brexpiprazole or placebo once daily for 6 weeks in combination with an antidepressant (SSRI or SNRI) is scientifically and ethically justified.

2.2 Rationale for CYP2D6 Genetic Testing and DNA Storage

The metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 based on *in vitro* metabolism studies, and CYP2D6 is known to have multiple genotypes with different enzyme activities. Therefore, in this trial, examination will be performed on CYP2D6 genotypes that affect the pharmacokinetics of brexpiprazole.



[redacted]

2.3 [redacted]

[redacted]

2.4 Rationale for Dosing and Regimen

2.4.1 Rational for Regimen

All clinical trials of brexpiprazole in patients with major depressive disorder conducted outside Japan have employed once daily oral administration. This trial will likewise employ once daily oral administration of brexpiprazole, as the drug is approved in the US with this regimen and because it has been confirmed that there are no major differences in the pharmacokinetics of brexpiprazole between Japanese and non-Japanese populations.

2.4.2 Rationale for Dosage

2.4.2.1 Rationale for Treatment Groups

Given that brexpiprazole was approved in the US at a dose of 2 mg/day as the recommended dose based on the results of overseas clinical trials, in which the efficacy of 2 mg/day of the drug was demonstrated in patients with major depressive disorder, and that the pharmacokinetics of the drug is similar between Japanese and non-Japanese populations, a dose level of 2 mg/day was considered to also be effective in Japanese patients with major depressive disorder and was selected for this trial. In a double-blind

trial conducted outside Japan (331-10-227), the brexpiprazole 1-mg group exhibited greater improvement compared with the placebo group ($p < 0.05$) at any time point during Weeks 1 through 5, and there were no marked differences between the 1-mg group and the 3-mg group in MADRS response rate (≥ 50% decrease in the MADRS total score from baseline) or MADRS remission rate (MADRS total score ≤ 10 and ≥ 50% reduction in the MADRS total score from baseline) at Week 6. Although the efficacy of 1 mg/day of brexpiprazole was not confirmed in clinical trials conducted outside Japan in patients with major depressive disorder, the dose level of 1 mg/day was also selected in this trial to ascertain if this dose would be the minimal effective dose in Japanese patients.

2.4.2.2 Rationale for a Starting Dose of 1 mg/day

Overseas clinical trials of brexpiprazole involving patients with major depressive disorder employed a starting dose of 0.5 or 1 mg/day, with no great differences in safety noted during the dose-escalation period at either of the starting doses; therefore, a starting dose of 1 mg/day was selected in order to attain an effective dose swiftly.

2.5 Trial Objectives

The objective of the trial is to assess the dosage and efficacy of brexpiprazole as adjunctive therapy vs placebo in combination with antidepressants (SSRI or SNRI), in patients with major depressive disorder, and whose response to single-antidepressant therapy (SSRI or SNRI) was inadequate. The primary endpoint is mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS total scores at Week 6 of the double-blind period (Phase B), and the mean changes will be compared between antidepressant treatments and brexpiprazole as adjunctive therapy.

The secondary endpoints are as follows: MADRS response rate: the proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline (Week 8 of the antidepressant treatment period [Phase A]); MADRS remission rate: the proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline, with their MADRS total scores at Week 6 of the double-blind period (Phase B), being ≤ 10; Clinical Global Impression – Improvement (CGI-I) improvement rate: the proportion of subjects who score 1 or 2 on the CGI-I scale at Week 6 of the double-blind period (Phase B); mean changes from baseline in CGI-S scale at Week 6 of the double-blind period (Phase B); mean changes from baseline in Hamilton Rating Scale for Depression (HAM-D) 17-item total scores at Week 6 of the double-blind period (Phase B); mean changes from baseline in mean Sheehan Disability Scale (SDS) scores at

Week 6 of the double-blind period (Phase B); and mean changes from baseline in MADRS Self-assessment (MADRS-S) total scores at Week 6 of the double-blind period (Phase B). The dosage and efficacy of brexpiprazole as adjunctive therapy in combination with antidepressants (SSRI or SNRI) will be assessed in relation to these endpoints.

The safety of brexpiprazole as adjunctive therapy vs placebo in combination with antidepressants (SSRI or SNRI) in patients with major depressive disorder whose response to single-antidepressant therapy (SSRI or SNRI) was inadequate will also be assessed.

3 Trial Design

3.1 Type/Design of Trial

The trial is a multi-center, randomized, double-blind, placebo-controlled, parallel group-comparison trial to assess the efficacy and safety of brexpiprazole as adjunctive therapy in patients with major depressive disorder, who have received 1 to 3 adequate antidepressant drug treatments[a] for the current major depressive episode and have shown an inadequate response[b] to all of these treatments, and whose response during the antidepressant treatment period (Phase A) has also been inadequate.

The trial design is shown in Figure 3.1-1. The trial comprises a screening period, antidepressant treatment period (Phase A), double-blind period (Phase B) or antidepressant-responder treatment-continuation period (Phase A+), and post-treatment observation period.

[a] Definition of "adequate antidepressant drug treatment" is provided below.

Treatment with an antidepressant at an approved dose for at least 6 weeks (for combination therapy, treatment for at least 3 weeks)

[b] Definition of "inadequate response" is provided below.

With complete recovery from depressive symptoms and not the slightest improvement considered as 100% and 0%, respectively, patients carry out self-evaluations for improvement by antidepressant drug treatments used to date, from among 4 grades (< 25% Improvement, 25% to 49% Improvement, 50% to < 75% Improvement, and ≥ 75% Improvement), with the evaluations corresponding to < 25% Improvement or 25% to 49% Improvement classified as inadequate response.
Patients who, among 1 to 3 adequate antidepressant drug treatments, have received

treatment for ≥ 6 weeks at least once (receiving only combination therapies for ≥ 3 weeks does not qualify) are eligible for selection.

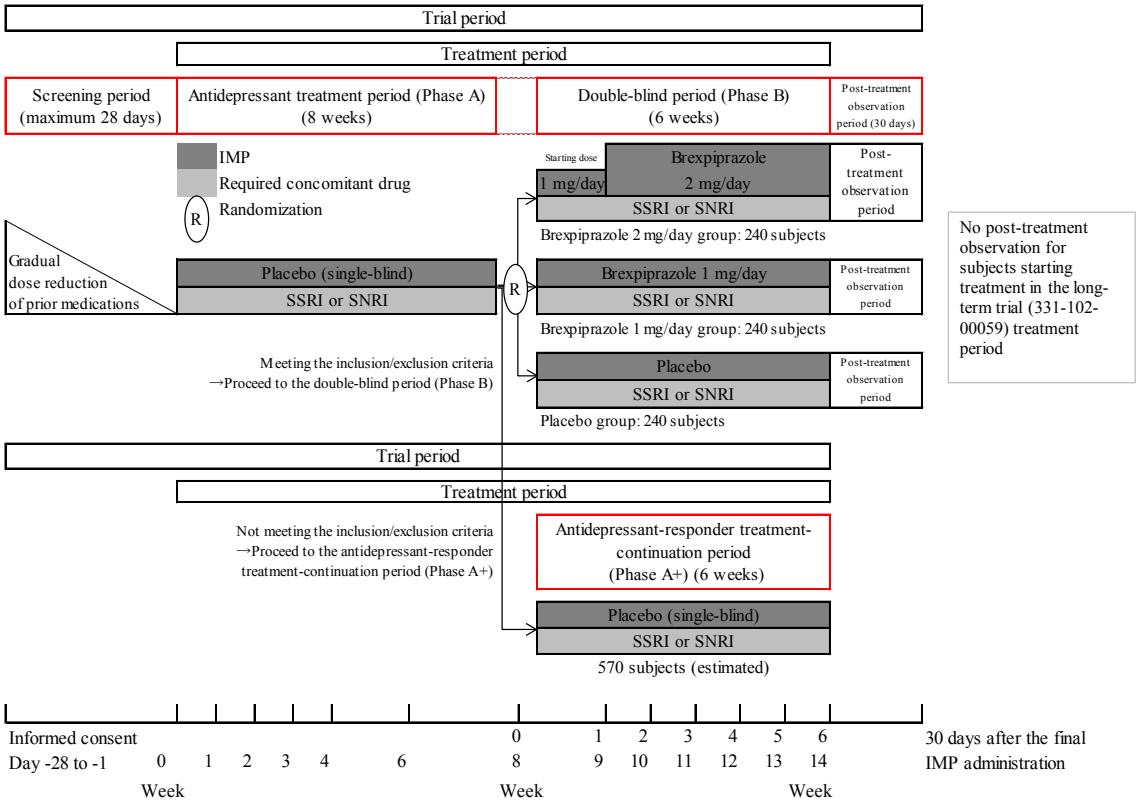


Figure 3.1-1 Trial Design

3.2 Trial Treatments

3.2.1 Antidepressant Treatment Period (Phase A)

(1) Drugs

Among commercially available SSRIs (fluvoxamine maleate, paroxetine hydrochloride hydrate, sertraline hydrochloride, and escitalopram oxalate) and SNRIs (milnacipran hydrochloride, duloxetine hydrochloride, and venlafaxine hydrochloride), one antidepressant that is different from the prior medications of antidepressant*, plus the placebo tablet

* Antidepressant that meets the definition for "adequate antidepressant drug treatment" and has been taken at the time of informed consent.

(2) Dose and regimen

In the antidepressant treatment period (Phase A), subjects will orally receive an antidepressant (SSRI or SNRI), which is different from the antidepressant prior medications, plus a placebo tablet once daily in a single-blind manner. The antidepressant (SSRI or SNRI) will be administered at the dose and regimen specified in the package insert, and the dose of the antidepressant will be progressively increased, within the approved dose range, to the maximum dose, as far as possible, in accordance with subject status; for the last 2 weeks of the 8-week period, dose and regimen will be fixed. A placebo tablet will be orally administered once daily. When an antidepressant cannot be administered at a fixed dose and regimen for the last 2 weeks of the 8-week antidepressant treatment period (Phase A) for tolerability-related reasons, the subject will be withdrawn from the trial.

(3) Treatment period

8 weeks

[Rationale for Treatment Period]

The JSMD Treatment Guidelines[6] state that it is often difficult to determine whether the patient has responded to first-line drug after treatment for 3 to 4 weeks and that it often takes 4 to 6 weeks or even 8 weeks for the drug to show any antidepressant effect. Based on the above statement in the JSMD Treatment Guidelines, a duration of 8 weeks will be employed to assess the effects of SSRI or SNRI.

3.2.2 Double-blind Period (Phase B)

At Week 8 of the antidepressant treatment period (Phase A), subjects who meet the criteria for proceeding to the double-blind period (Phase B) will proceed to the double-blind period (Phase B).

(1) Drugs

- One commercially available antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A)
- IMP:
  - 1 mg/day group: brexpiprazole 1 mg tablet
  - 2 mg/day group: brexpiprazole 1 mg tablet (until observations, examinations, and assessments at Week 1) and brexpiprazole 2 mg tablet (after observations, examinations, and assessments at Week 1)
  - Placebo group: placebo tablet

(2) Dose and regimen

- Commercially available antidepressant (SSRI or SNRI):
  An antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) will be continued with no changes from the final dose and regimen; no changes in dose, regimen, or drug will be allowed.
- IMP:
  - 1 mg/day group: One brexpiprazole 1 mg tablet will be orally administered once daily.
  - 2 mg/day group: Treatment will be started with brexpiprazole at 1 mg/day. One brexpiprazole 1 mg tablet will be orally administered once daily until observations, examinations, and assessments at Week 1. After the observations, examinations, and assessments at Week 1, one brexpiprazole 2 mg tablet will be orally administered once daily.
  - Placebo group: One placebo tablet will be orally administered once daily.

(3) Treatment period

6 weeks

[Rationale for Treatment Period]

Phase 3, double-blind, placebo-controlled trials conducted outside Japan in patients with major depressive disorder (331-10-227, 331-10-228, and 331-13-214) employed a duration of 6 weeks as the double-blind period and demonstrated the efficacy of brexpiprazole as adjunctive therapy vs placebo. Meanwhile, it has been confirmed that there are no major differences in the pharmacokinetics of brexpiprazole between Japanese and non-Japanese populations. Therefore, a duration of 6 weeks will also be employed in this trial, because the same treatment period as that in overseas phase 3, double-blind, placebo-controlled trials (331-10-227, 331-10-228, and 331-13-214) was considered necessary to assess the efficacy of adjunctive therapy.

3.2.3 Antidepressant-responder Treatment-continuation Period (Phase A+)

Antidepressant responders who do not meet the criteria for proceeding to the double-blind period (Phase B) based on the assessment at Week 8 of the antidepressant treatment period (Phase A) will proceed to the antidepressant-responder treatment-continuation period (Phase A+).

(1) Drugs

A commercially available antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) plus the placebo tablet

(2) Dose and regimen

Subjects will receive an antidepressant (SSRI or SNRI) used in the antidepressant treatment period (Phase A) with no changes from the final dose and regimen, plus oral placebo (1 tablet) once daily in a single-blind manner.

(3) Treatment period

6 weeks

[Rationale for Treatment Period]

To maintain single-blinding, it is necessary to set the duration to be the same as that of the double-blind period (Phase B).

3.3 Trial Population

Adult patients with “major depressive disorder, single episode” or “major depressive disorder, recurrent episode” according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

3.3.1 Number of Subjects and Trial Population

The trial will be conducted in patients 20 to < 65 years of age who have major depressive disorder (major depressive disorder, single episode; major depressive disorder, recurrent episode) according to the DSM-5 classification. After provision of informed consent, subjects considered eligible at the screening examination and at the examination performed at the initiation of the antidepressant treatment period (Phase A) will commence the antidepressant treatment period (Phase A) in which they will receive antidepressants different from their prior antidepressant medications (SSRI or SNRI) and placebo tablets for 8 weeks in a single-blind manner. Subjects showing no response to the antidepressants during the antidepressant treatment period (Phase A) who meet the criteria for proceeding will proceed to the double-blind period (Phase B) to receive the IMP (brexpiprazole at 1 or 2 mg/day, or placebo) for 6 weeks in combination with the antidepressants used in the antidepressant treatment period (Phase A). The planned number of subjects proceeding to the double-blind period (Phase B) is set as follows: brexpiprazole 1 mg/day group: 240; brexpiprazole 2 mg/day group: 240; placebo group: 240; total: 720.

Subjects responding to antidepressants during the antidepressant treatment period (Phase A) and not meeting the criteria for proceeding to the double-blind period (Phase B) will not proceed to the double-blind period (Phase B) and will instead proceed to the antidepressant-responder treatment-continuation period (Phase A+), to receive 6-week

treatment with placebo tablets in addition to the antidepressants (SSRI or SNRI) used in the antidepressant treatment period (Phase A), in a single-blind manner.

3.3.2 Subject Number Assignment

[redacted]

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be obtained from all subjects on their voluntary decision. Consent will be documented on a written informed consent form (ICF) with the subject's signature. The ICF will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[22] and regulatory requirements.

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

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

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

Subjects may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

For CYP2D6 genetic testing, [redacted], a separate ICF will be used for explanation and written informed consent will be obtained from subjects on their voluntary decision in a similar manner. CYP2D6 genetic testing is mandatory,

and subjects who do not consent to CYP2D6 genetic testing cannot participate in the trial.

[redacted]

3.4.2 Inclusion Criteria

Subjects must meet the inclusion criteria described in Table 3.4.2-1.

Subjects who meet all of the following inclusion criteria at the initiation of the screening period, antidepressant treatment period (Phase A), and double-blind period (Phase B), are eligible for selection.

Table 3.4.2-1 Inclusion Criteria

At screening	
1	Outpatients, or inpatients at the time of informed consent whose treatment status can be successfully shifted to outpatient status before enrollment in the antidepressant treatment period (Phase A)
2	Male and female patients ≥ 20 to < 65 years of age (at the time of informed consent)
3	Patients who have a level of comprehension sufficient to allow them to give written informed consent to all of the observation/examination/evaluation items specified in the protocol, and who can understand the contents of the trial
4	Patients with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" and whose current episode has persisted for at least 8 weeks
5	Patients who have received 1 to 3 adequate antidepressant drug treatments for the current major depressive episode and whose response to all of the treatments has been inadequate. Definitions of "adequate antidepressant drug treatments" and "inadequate response" are provided below. Adequate antidepressant drug treatment Treatment with an antidepressant at an approved dose for at least 6 weeks (for combination therapy, treatment for at least 3 weeks) Inadequate response With complete recovery from depressive symptoms and not the slightest improvement considered as 100% and 0%, respectively, patients carry out self-evaluations for improvement by antidepressant drug treatments used to date, from among 4 grades (< 25% Improvement, 25% to 49% Improvement, 50% to < 75% Improvement, and ≥ 75% Improvement), with the evaluations corresponding to < 25% Improvement or 25% to 49% Improvement classified as inadequate response. Patients who, among 1 to 3 adequate antidepressant drug treatments, have received treatment for ≥ 6 weeks at least once (receiving only combination therapies for ≥ 3 weeks does not qualify) are eligible for selection.
6	Patients with a HAM-D 17-item total score of ≥ 18 based on the evaluation conducted at screening
At the initiation of the antidepressant treatment period (Phase A)	
7	Outpatients
8	Subjects with a HAM-D 17-item total score of ≥ 18 based on the evaluation at the initiation of the antidepressant treatment period (Phase A)
At the initiation of the double-blind period (Phase B) (criteria for proceeding)	
9	Outpatients
10	Subjects with a HAM-D 17-item total score of ≥ 14 at Week 8 of the antidepressant treatment period (Phase A)
11	Subjects in whom the reduction rate for HAM-D 17-item total scores is < 50% at Week 8 of the antidepressant treatment period (Phase A), as compared with at the initiation of the antidepressant treatment period (Phase A).

Table 3.4.2-1 Inclusion Criteria	
12	Subjects in whom CGI-I scores have been consistently 3 (minimally improved) to 7 (very much worse) throughout the antidepressant treatment period (Phase A)

[Rationale for inclusion criteria]
Screening period
1. This criterion is specified in view of subject safety, as treatment should be prioritized in subjects whose condition requires hospitalization.
2. Patients younger than 65 years will be selected for appropriate assessment of safety of the drug, because the package insert of brexpiprazole tablet specifies, in Precautions, careful administration in the elderly, and because the elderly generally have decreased physiological functions. Furthermore, the lower age limit was determined to be 20 years for ethical considerations.
3. This criterion is specified for ethical considerations.

4 to 6. These criteria are specified for appropriate assessment of efficacy.

At the initiation of the antidepressant treatment period (Phase A)
7. This criterion is specified in view of subject safety, as treatment should be prioritized in subjects whose condition requires hospitalization.
8. This criterion is specified for appropriate assessment of efficacy.

At the initiation of the double-blind period (Phase B)
9. This criterion is specified in view of subject safety, as treatment should be prioritized in subjects whose condition requires hospitalization.

10 to 12. These criteria are specified for appropriate assessment of efficacy.

3.4.3 Exclusion Criteria

Patients will be excluded if they fall under any of the exclusion criteria described in Table 3.4.3-1 during the screening period or at the initiation of the antidepressant treatment period (Phase A).

Table 3.4.3-1 Exclusion Criteria	
At screening	
1	Women who are pregnant or breastfeeding or who have positive pregnancy test (urine) results at screening
2	Sexually active male subjects or sexually active female subjects of childbearing potential, who will not agree to practice 2 different methods of birth control or to remain abstinent during the trial and for 30 days after the final IMP administration. For birth control, 2 of the following methods must be used: vasectomy, tubal ligation, vaginal diaphragm, intra-uterine contraceptive device (IUD), oral contraceptives, or condom with spermicide.
3	Patients who have received at least 4 appropriate antidepressant drug treatments for the current major depressive episode but whose response was inadequate to all treatments
4	Patients receiving treatment with antipsychotics and psychostimulants for the current major depressive episode (excluding the use of sulpiride for depression/depressive state or gastric/duodenal ulcer)
5	Patients with a treatment history showing that all antidepressants (including those not used for the current major depressive episode) cannot be tolerated
6	Patients with a history of electroconvulsive therapy

Table 3.4.3-1 Exclusion Criteria	
7	Patients with a diagnosis of any of the following diseases according to DSM-5 a) Neurocognitive disorders b) Schizophrenia spectrum and other psychotic disorders c) Bipolar and related disorders d) Feeding and eating disorders e) Obsessive-compulsive disorder f) Panic disorder g) Posttraumatic stress disorder
8	Patients with a diagnosis of any personality disorders (borderline personality disorder, antisocial personality disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, and histrionic personality disorder) according to DSM-5
9	Patients experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current major depressive episode
10	Patients receiving a new psychotherapy within 6 weeks prior to informed consent
11	Patients who have previously taken brexpiprazole
12	Patients who have participated in other clinical trials within 60 days prior to informed consent
13	Patients with a HAM-D score for suicide (No. 11) of ≥ 3 at screening, those answering "Yes" to question 4 or 5 of Columbia-Suicide Severity Rating Scale (C-SSRS), or those who are, based on current psychiatric symptoms or past medical history, at high risk of suicide during the trial in the opinion of the investigator or subinvestigator
14	Patients with clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders; patients can be enrolled if the conditions are mild or well controlled and will not hamper assessment of safety and efficacy.
15	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 (assessed based on results from the central laboratory) 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
16	Patients with substance abuse or substance dependence, including alcohol and benzodiazepines, based on DSM-5 diagnostic criteria within 180 days prior to informed consent; caffeine and nicotine are not included
17	Patients with a complication of hypothyroidism or hyperthyroidism at informed consent (excluding those in a stable condition due to medications for the previous 90 days or longer at acquisition of informed consent), or abnormal thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels at screening (assessed based on results from the central laboratory)
18	Patients meeting any of the following criteria or showing symptoms at screening a) Poorly controlled hypertension (diastolic blood pressure of > 95 mmHg) b) Hypotension with symptoms c) Orthostatic hypotension in which blood pressure after 3 minutes of standing is ≥ 30 mmHg lower for systolic blood pressure or ≥ 20 mmHg lower for diastolic blood pressure, compared with pressures in the supine position before standing

Table 3.4.3-1 Exclusion Criteria	
19	Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), and patients with a history of angioplasty, stent placement, or coronary artery bypass
20	Patients with a history of neuroleptic malignant syndrome or serotonin syndrome
21	Patients with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
22	Patients with the following clinical laboratory test values or ECG parameters at screening (assessed based on results from the central laboratory and central ECG measurement facility) a) Platelet count: ≤ 75,000/mm^3 b) Hemoglobin: ≤ 9 g/dL c) Absolute neutrophil count: ≤ 1000/mm^3 d) Aspartate aminotransferase (AST): > 2 times the upper limit of the reference range e) Alanine aminotransferase (ALT): > 2 times the upper limit of the reference range f) Creatine phosphokinase (CPK): > 3 times the upper limit of the reference range g) Creatinine: ≥ 2 mg/dL h) QT interval as corrected by Fridericia's formula (QTcF): ≥ 450 msec
23	Patients with a history of hypersensitivity to antidepressants
24	Patients with a history or complication of allergy to more than one medication
25	The following patients falling under the contraindications in the package insert for brexpiprazole tablet a) Patients in a coma b) Patients under the strong influence of central nervous system depressants including barbiturate analogs/anesthetics c) Patients receiving adrenaline d) Patients with a history of hypersensitivity to components of brexpiprazole tablet
26	Patients who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator
At the initiation of the antidepressant treatment period (Phase A)	
27	Pregnant or breastfeeding female subjects, or those with positive pregnancy test (urine) results at the initiation of the antidepressant treatment period (Phase A)
28	Subjects newly requiring hospitalization for the current major depressive episode during the screening period
29	Patients with a HAM-D score for suicide (No. 11) of ≥ 3 at the initiation of the antidepressant treatment period (Phase A), those answering "Yes" to question 4 or 5 of C-SSRS, or those who are, based on current psychiatric symptoms or past medical history, at high risk of suicide during the trial in the opinion of the investigator or subinvestigator
30	Patients meeting any of the following criteria or showing symptoms at the initiation of the antidepressant treatment period (Phase A) a) Poorly controlled hypertension (diastolic blood pressure of > 95 mmHg) b) Hypotension with symptoms c) Orthostatic hypotension in which blood pressure after 3 minutes of standing is ≥ 30 mmHg lower for systolic blood pressure or ≥ 20 mmHg lower for diastolic blood pressure, compared with pressures in the supine position before standing
31	Subjects receiving treatment with monoamine oxidase (MAO) inhibitors within 2 weeks before the initiation of the antidepressant treatment period (Phase A)
32	Subjects using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before the initiation of the antidepressant treatment period (Phase A)
33	Subjects with urinary retention, if receiving milnacipran

Table 3.4.3-1 Exclusion Criteria	
34	Subjects with poorly controlled angle closure glaucoma, if receiving duloxetine
35	Subjects who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator

[Rationale for exclusion criteria]
Screening period
1, 2. These criteria are specified in view of safety, as safety of treatment with the drug is yet to be established in pregnant and breastfeeding women.
3, 4. These criteria are specified for appropriate assessment of efficacy.
5. This criterion is specified in view of safety.
6. This criterion is specified in view of safety, as a combination of antidepressants and electroconvulsive therapy is likely to lower the convulsive threshold.
7 to 10. These criteria are specified for appropriate assessment of efficacy.
11. This criterion is specified because of the potential impact on blinding.
12. This criterion is specified in view of safety.
13. This criterion is specified to minimize the risk of suicide during the trial.
14 to 16. These criteria are specified in view of safety.
17. This criterion is specified for appropriate assessment of efficacy, as patients with thyroid disorders may have depressive symptoms.
18 to 20. These criteria are specified in view of safety.
21. This criterion is specified in view of safety, as the drug may lower the convulsive threshold.
22 to 26. These criteria are specified in view of safety.

At the initiation of the antidepressant treatment period (Phase A)
27. This criterion is specified in view of safety, as safety of treatment with the drug is yet to be established in pregnant and breastfeeding women.
28 to 30. These criteria are specified in view of safety.
31. This criterion is specified in view of safety, as package inserts for antidepressants indicate that for patients receiving MAO inhibitors, the antidepressants should be administered after an interval of at least 2 weeks from discontinuation of MAO inhibitors.
32. This criterion is specified for appropriate assessment of efficacy.
33 to 35. These criteria are specified in view of safety.

3.5 Endpoints

3.5.1 Primary Endpoint(s)

Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS total scores at Week 6 of the double-blind period (Phase B)

[Rationale]

MADRS, used worldwide as a depression assessment scale, was created primarily to assess psychiatric symptoms of depression and exclude somatic symptoms; therefore, the scale is generally used in clinical trials that involve patients with major depressive disorder. As all placebo-controlled trials of fixed doses of brexpiprazole conducted outside Japan in patients with major depressive disorder have employed mean changes in MADRS scores as the primary endpoint, the same primary endpoint will be employed in

this trial also. As the high inter-rater reliability of MADRS has been confirmed by using the Structured Interview Guide for MADRS (SIGMA), SIGMA will be used in this trial also.

3.5.2 Secondary Endpoint(s)

- MADRS response rate at Week 6 of the double-blind period (Phase B)
  The proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline (Week 8 of the antidepressant treatment period [Phase A])
- MADRS remission rate at Week 6 of the double-blind period (Phase B)
  The proportion of subjects in whom MADRS total scores at Week 6 of the double-blind period (Phase B) have been reduced by at least 50% from baseline (Week 8 of the antidepressant treatment period [Phase A]), with their MADRS total scores, at Week 6 of the double-blind period (Phase B), being ≤ 10
- CGI-I improvement rate at Week 6 of the double-blind period (Phase B)
  The proportion of subjects who score 1 or 2 on the CGI-I scale at Week 6 of the double-blind period (Phase B)
- Mean changes in CGI-S at Week 6 of the double-blind period (Phase B)
  Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in CGI-S at Week 6 of the double-blind period (Phase B)
- Mean changes in HAM-D 17-item total scores at Week 6 of the double-blind period (Phase B)
  Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in HAM-D 17-item total scores at Week 6 of the double-blind period (Phase B)
- Mean changes in mean SDS scores at Week 6 of the double-blind period (Phase B)
  Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in mean SDS scores at Week 6 of the double-blind period (Phase B)
- Mean changes in MADRS-S total scores at Week 6 of the double-blind period (Phase B)
  Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS-S total scores at Week 6 of the double-blind period (Phase B)

[Rationale]

The MADRS response rate and MADRS remission rate were selected because they are useful for assessing the effects of antidepressants and are used in many clinical trials.

CGI-I and CGI-S were selected because they are an overall assessment that enables comprehensive assessment of the subject's clinical symptoms and are used in many clinical trials.

HAM-D was selected because it is useful for assessing a wide range of depressive symptoms including somatic and psychiatric symptoms and is used in many clinical trials.

SDS was selected because it is a functional impairment assessment scale composed of 3 daily living function-related items (work/school, social life, and communication and role within in family), and enables functional assessment through self-assessment.

MADRS-S was created by modifying 9 subjective report-based assessment items among the 10 MADRS assessment items (excluding the objective assessment item, namely, "apparent sadness") to allow self-assessment; it was selected to assess improvement in depressive symptoms based on the subject's self-assessment.

3.5.3 Safety Endpoints

Adverse events, laboratory tests, vital signs (body temperature, diastolic blood pressure and systolic blood pressure, and pulse rate [supine, sitting, and standing positions]), physical examinations, waist circumference, body weight, 12-lead ECG, pregnancy test, Columbia-Suicide Severity Rating Scale (C-SSRS), Drug-Induced Extrapyramidal Symptom Scale (DIEPSS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS)

3.5.4 Pharmacokinetic Endpoint

Plasma brexpiprazole concentrations

3.5.5 Pharmacogenomic Endpoint

CYP2D6 genetic testing

3.6 Measures to Minimize/Avoid Bias

This trial has a double-blind design. In the double-blind period (Phase B), subjects will be randomly assigned to the brexpiprazole 1 mg/day group, the brexpiprazole 2 mg/day group, or placebo group at a 1:1:1 ratio. Details of the randomization method are provided in separately documented procedures. The treatment assignment code will be revealed to neither the subject nor the investigator. The sponsor's staff involved in the trial, including contract research organizations (excluding the bioanalytical laboratory and the genetic analysis laboratory), will also remain blind to treatment assignment codes for the duration of the trial.

Prior to the start of the trial, those who are involved in packaging the IMP and the sponsor will confirm that the IMP is not identifiable.

Documents providing treatment assignment codes will be strictly retained until unblinding is performed after finalization of all the case report forms (CRFs) and database.

The emergency code break information will be managed by the interactive web response system (IWRS) until completion of the trial. In the event that a subject has a medical emergency and knowledge of the treatment assignment code is necessary for treatment, the blind will be broken in accordance with the instructions provided in Section 5.6, Procedure for Breaking the Blind.

The results of plasma drug concentration measurements and CYP2D6 genetic testing should not be disclosed until unblinding after the end of the trial. These measurements should be performed respectively at the designated bioanalysis laboratory and genetic analysis laboratory, but not at laboratories of trial sites.

3.7 Trial Procedures

Schedules of all examinations and assessment/observations in the screening period, antidepressant treatment period (Phase A), double-blind period (Phase B), antidepressant-responder treatment-continuation period (Phase A+), and post-treatment observation period are provided in Table 3.7-1, Table 3.7-2, and Table 3.7-3, respectively.

The investigator or subinvestigator should conduct observations, examinations, and evaluations in accordance with the schedules. For items that can be performed by a clinical trial associate, such as examination of subject demographics and laboratory tests, a clinical trial associate can perform them under the supervision of the investigator.

Table 3.7-1 Schedule of Assessments (Screening Period and Antidepressant Treatment Period [Phase A])

Test Period (Acceptable Window) / Items	Screening Period	Antidepressant Treatment Period (Phase A)							
	At screening (Day −28 to −1)	At initiation (Day 1)	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 2 days)	Week 8 (± 2 days)	At discontin-uation
Acquisition of informed consent	●								
Eligibility judgement	●	●							
Subject demographics	●								
MADRS		●		●		●	●	●	●
CGI-I			●	●	●	●	●	●	●
CGI-S	●	●	●	●	●	●	●	●	●
HAM-D	●	●						●	●
SDS		●						●	●
MADRS-S questionnaire		●		●		●	●	●	●
Laboratory tests	●							●[d]	●
Vital signs	●	●	●			●		●	●
Physical examinations	●	●	●	●	●	●	●	●	●
Waist circumference		●						●	●
Height	●								
Body weight	●							●	●
12-lead ECG	●							●	●
Pregnancy test	●[b]	●[b]						●[b]	●[b]
C-SSRS	●	●	●	●	●	●	●	●	●
DIEPSS								●	
AIMS								●	
BARS								●	
[redacted]	[redacted]								
[redacted]	[redacted]								
Adverse events	←----------								----------→
IMP and requisite concomitant medication[a]			●	●	●	●	●	●	●
Concomitant drugs/ therapies	←----------								----------→

[a] Treatment compliance regarding IMP and requisite concomitant medication will be recorded.

[b] Pregnancy tests will be performed only in female subjects of childbearing potential.

[redacted]

[d] For this item, subjects will be asked to visit the trial site in a fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at Week 8 of the antidepressant treatment period (Phase A), and in a fasting state to the extent possible at other times, including at the discontinuation examination.

Table 3.7-2 Schedule of Assessments (Double-blind Period [Phase B])

Items \ Test Period (Acceptable Window)	Double-blind Period (Phase B)[b]							Post-treatment Observation Period
	Week 1 (± 1 day)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	At discontinuation	After 30 days[g] (± 5 days)
MADRS	●	●	●	●	●	●	●	
CGI-I	●	●	●	●	●	●	●	
CGI-S	●	●	●	●	●	●	●	
HAM-D						●	●	
SDS			●			●	●	
MADRS-S questionnaire	●	●	●	●	●	●	●	
Laboratory tests			●			●[d]	●	
Vital signs	●	●	●	●	●	●	●	
Physical examinations	●	●	●	●	●	●	●	●
Waist circumference						●	●	
Body weight						●	●	
12-lead ECG						●	●	
Pregnancy test						●[e]	●[e]	
C-SSRS	●	●	●	●	●	●	●	●
DIEPSS	●	●	●	●	●	●	●	
AIMS						●	●	
BARS						●	●	
[redacted]	[redacted]							
Blood sampling for CYP2D6 genetic testing						●	●	
[redacted]	[redacted]							
Adverse events	←----------						----------→	←---→
IMP and requisite concomitant medication[a]	●	●	●	●	●	●	●	
Concomitant drugs/ therapies	←----------						----------→	←---→

PK = pharmacokinetics

[a] Treatment compliance regarding IMP and requisite concomitant medication will be recorded.

[b] The starting point of the double-blind period (Phase B) is the day of assessment at Week 8 of the antidepressant treatment period (Phase A).

[redacted]

[d] For this item, subjects will be asked to visit the trial site in a fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at Week 6 of the double-blind period (Phase B), and in a fasting state to the extent possible at other times, including at the discontinuation examination.

[e] Pregnancy tests will be performed only in female subjects of childbearing potential.

[redacted]

[g] The starting point of the post-treatment observation period is the day of the final IMP administration. These items do not need to be performed for subjects who have commenced the treatment period of the long-term trial (331-102-00059).

Table 3.7-3 Schedule of Assessments (Antidepressant-responder Treatment-continuation Period [Phase A+])

Test Period (Acceptable Window) / Items	Antidepressant-responder Treatment-continuation Period (Phase A+)[b]						
	Week 1 (± 1 day)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	At discontin-uation
MADRS						●	●
CGI-I						●	●
CGI-S						●	●
HAM-D						●	●
SDS						●	●
MADRS-S questionnaire						●	●
Laboratory tests						●[c]	●
Vital signs	●	●	●	●	●	●	●
Physical examinations	●	●	●	●	●	●	●
Waist circumference						●	●
Body weight						●	●
12-lead ECG						●	●
Pregnancy test						●[d]	●[d]
C-SSRS	●	●	●	●	●	●	●
DIEPSS						●	●
AIMS						●	●
BARS						●	●
[redacted]	[redacted]						
Adverse events	←----------						----------→
IMP and requisite concomitant medication[a]	●	●	●	●	●	●	●
Concomitant drugs/ therapies	←----------						----------→

[a] Treatment compliance regarding IMP and requisite concomitant medication will be recorded.

[b] The starting point of the antidepressant-responder treatment-continuation period (Phase A+) is the day of assessment at Week 8 of the antidepressant treatment period (Phase A).

[c] For this item, subjects will be asked to visit the trial site in a fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at Week 6 of the antidepressant-responder treatment-continuation period (Phase A+), and in a fasting state to the extent possible at the discontinuation examination.

[d] Pregnancy tests will be performed only in female subjects of childbearing potential.

[redacted]

3.7.1 Schedule of Assessments

The investigator or subinvestigator will conduct the trial in accordance with the schedules shown in Table 3.7-1 to Table 3.7-3. The methods of observation, examination, and

evaluation are prescribed in Section 3.7.2, Efficacy Assessments, to Section 3.7.3, Safety Assessments.

3.7.1.1 Informed Consent

Before all screening examinations, written informed consent is to be obtained from subjects. After acquisition of informed consent followed by IWRS registration, a subject ID will be assigned to the subject and recorded. Management of IWRS after the first registration is separately specified in written procedures, as a management system particularly for subject enrollment status and IMP. The investigator or subinvestigator will record the subject ID and date on which signed inform consent was obtained in the subject screening log. The subject ID and date on which signed inform consent was obtained will also be recorded in the source documents and the CRF.

3.7.1.2 Screening

After acquisition of informed consent and within 28 days before commencement of the antidepressant treatment period (Period A), the investigator or subinvestigator will perform the observations/examinations for the screening period, as specified in Table 3.7-1 Schedule of Assessments (Screening Period and Antidepressant Treatment Period [Phase A]) and record the results in the source documents and the CRF. After subjects are judged eligible to participate in this trial, the dose of the antidepressant prior medication will be reduced gradually to a dose level that enables safe substitution. The investigator or subinvestigator will then record enrollment status, date of enrollment, and reasons for any failed enrollment in the subject screening log.

The investigator or subinvestigator will examine the following subject demographics and record the results in the source documents and the CRF. Regarding the treatment history for the current major depressive episode, all antidepressant prior medications and their effectiveness, as well as psychotherapies/somatic therapies up until 6 weeks before informed consent, will be examined. To determine their effectiveness, the results of evaluation will be classified as < 25% Improvement, 25% to 49% Improvement, 50% to < 75% Improvement, and ≥ 75% Improvement (complete recovery from depressive symptoms and not the slightest improvement considered as 100% and 0%, respectively), based on the patient's self-evaluations.

- Date of visit
- Subject demographics
  - Date of investigation
  - Date of birth
  - Sex

- For female subjects: whether the subject is a woman of childbearing potential[a] (If not, the reason is to be recorded.)
  [a]Women of childbearing 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).
- Race
- Ethnicity
- Country where trial is performed
- DSM-5-based diagnostic name and severity as well as specific terms (with anxious distress, with mixed features, with melancholic features, with atypical features, with mood-congruent psychotic features, with mood-incongruent psychotic features, with catatonia, with peripartum onset, and with seasonal pattern)
- Date of first onset of major depressive disorder
- Frequency of major depressive episodes
- Date of onset of the current depressive episode
- Prior medication used to treat the current major depressive episode (all antidepressants)
- Prior therapy used to treat the current major depressive episode (psychotherapies/somatic therapies up until 6 weeks before informed consent)
- Frequency of appropriate antidepressant drug treatments of the current major depressive episode (treatment for at least 6 weeks at the approved dose for the antidepressant, or treatment for at least 3 weeks with combination therapy)
- All prior medications and therapies used within 30 days before acquisition of informed consent
- Medical history (within 2 years before acquisition of informed consent, although matters pertaining to the inclusion or exclusion criteria are not limited to 2 years) and complications

- Results of eligibility criteria assessment

3.7.1.3 Observations/Examinations at the Initiation of the Antidepressant Treatment Period (Phase A)

After gradual dose reduction of prior medications, the investigator or subinvestigator will perform observations/examinations at the initiation of the antidepressant treatment period (Phase A), as specified in Table 3.7-1 Schedule of Assessments (Screening Period and Antidepressant Treatment Period [Phase A]), and record the results and findings as well as the date of visit in the source documents and the CRF. Subject eligibility will be assessed, and the results of the assessment will be registered in the IWRS and recorded in

the source documents and the CRF. For subjects assessed as eligible, date of enrollment in the antidepressant treatment period (Phase A) will be recorded in the source documents and the CRF.

3.7.1.4 Observations/Examinations During the Antidepressant Treatment Period (Phase A)

Subjects meeting the eligibility criteria based on observations/examinations at the initiation of the antidepressant treatment period (Phase A) will proceed to the 8-week antidepressant treatment period (Phase A) to receive an antidepressant (SSRI or SNRI), which is different from the antidepressants they had been taking previously, and placebo tablets in a single-blind manner. After proceeding to the antidepressant treatment period (Phase A), the investigator or subinvestigator will perform the observations/examinations required in the antidepressant treatment period (Phase A) as specified in Table 3.7-1 Schedule of Assessments (Screening Period and Antidepressant Treatment Period [Phase A]) and record the results and findings as well as the date of visit in the source documents and the CRF. Furthermore, whether or not subjects can proceed to the double-blind period (Phase B) will be determined based on the results of observations/examinations at Week 8 of the antidepressant treatment period (Phase A), and the results of assessment will be registered in the IWRS and recorded in the source documents and the CRF. Based on an assessment at Week 8 of the antidepressant treatment period (Phase A), if the investigator or subinvestigator confirms that the subject is eligible to proceed, the subject will proceed to the double-blind period (Phase B); and if the investigator or subinvestigator determines that the subject is not eligible to proceed, the subject will be entered in the antidepressant-responder treatment-continuation period (Phase A+). Subjects meeting the criteria for proceeding to Phase B based on an assessment at Week 8 of the antidepressant treatment period (Phase A) will be randomly assigned to the brexpiprazole 1 mg/day group, the brexpiprazole 2 mg/day group, or the placebo group at a 1:1:1 ratio. Date of assignment and assignment number will be recorded in the source documents and the CRF. For subjects who do not meet the criteria for proceeding to Phase B, date of enrollment in the antidepressant-responder treatment-continuation period (Phase A+) will be recorded in the source documents and the CRF.

3.7.1.5 Observations/Examinations During the Double-blind Period (Phase B)

Subjects meeting the criteria for proceeding to Phase B based on an assessment at Week 8 of the antidepressant treatment period (Phase A) will continue to receive the same antidepressant (SSRI or SNRI) as in the antidepressant treatment period (Phase A) with no changes in the dose and regimen, and will receive the IMP (brexpiprazole 1 mg/day,

brexpiprazole 2 mg/day [1 mg/day until observations/examinations/assessments at Week 1], or placebo) for 6 weeks. After proceeding to the double-blind period (Phase B), the investigator or subinvestigator will perform the observations/examinations required in the double-blind period (Phase B) as specified in Table 3.7-2 Schedule of Assessments (Double-blind Period [Phase B]) and record the results and findings as well as the date of visit in the source documents and the CRF.

The investigator or subinvestigator will register the required items in the IWRS after each subject has completed the 6-week treatment.

3.7.1.6 Observations/Examinations During the Antidepressant-responder Treatment-continuation Period (Phase A+)

Subjects not meeting the criteria for proceeding to Phase B based on an assessment at Week 8 of the antidepressant treatment period (Phase A) will continue to receive the same antidepressant (SSRI or SNRI) as in the antidepressant treatment period (Phase A) with no changes in the dose and regimen, and will receive placebo for 6 weeks in a single-blind manner. The investigator or subinvestigator will perform the observations/examinations specified in Table 3.7-3 Schedule of Assessments (Antidepressant-responder Treatment-continuation Period [Phase A+]) and record the results and findings as well as the date of visit in the source documents and the CRF.

The investigator or subinvestigator will register the required items in the IWRS after each subject has completed the 6-week treatment.

3.7.1.7 Observations/Examinations in the Post-treatment Observation Period

In all subjects who proceed to the double-blind period (Phase B) but not to the long-term trial (331-102-00059), the investigator or subinvestigator will perform the observations/examinations specified in Table 3.7-2 Schedule of Assessments (Double-blind Period [Phase B]) at a site visit made 30 days (± 5 days) after final IMP administration and record the results and findings as well as the date of visit in the source documents and the CRF. The investigator or subinvestigator will register the required items in the IWRS after each subject has completed the post-treatment observation period.

3.7.1.8 Examinations at Discontinuation

If a subject is withdrawn from the trial during the antidepressant treatment period (Phase A), the double-blind period (Phase B), or the antidepressant-responder treatment-continuation period (Phase A+), the investigator or subinvestigator will perform the required examinations at discontinuation, as specified in Table 3.7-1 Schedule of Assessments (Screening Period and Antidepressant Treatment Period [Phase A]), Table

3.7-2 Schedule of Assessments (Double-blind Period [Phase B]), and Table 3.7-3 Schedule of Assessments (Antidepressant-responder Treatment-continuation Period [Phase A+]), and record the results along with the date of visit in the source documents and the CRF.

The investigator or subinvestigator will register the required items in IWRS at the time of each subject's withdrawal.

3.7.1.9 Acceptable Window for Testing

Observations/examinations and other procedures are to be performed within an acceptable window for testing, as specified in Table 3.7.1.9-1, with consideration of the availability of each subject for site visits, etc.

Table 3.7.1.9-1 Acceptable Window for Examinations/Assessment Period

The starting point of the antidepressant treatment period (Phase A) is the day of assessment at the initiation of the antidepressant treatment period (Phase A).

Examination Point	Reference Day	Acceptable Window (From the Reference Day)
At screening	Day of assessment at the initiation of the antidepressant treatment period (Phase A)	Day −28 to −1
Day of assessment at the initiation of the antidepressant treatment period (Phase A)	Day 1	−
Week 1 of the antidepressant treatment period (Phase A)	Day 8	± 2 days
Week 2 of the antidepressant treatment period (Phase A)	Day 15	± 2 days
Week 3 of the antidepressant treatment period (Phase A)	Day 22	± 2 days
Week 4 of the antidepressant treatment period (Phase A)	Day 29	± 2 days
Week 6 of the antidepressant treatment period (Phase A)	Day 43	± 2 days
Week 8 of the antidepressant treatment period (Phase A)	Day 57	± 2 days
At discontinuation	−	−

At discontinuation: Performed within a possible window at a feasible time point.

Table 3.7.1.9-1 Acceptable Window for Examinations/Assessment Period

The starting point of the double-blind period (Phase B) is the day of assessment at Week 8 of the antidepressant treatment period (Phase A).

Examination Point	Reference Day	Acceptable Window (From the Reference Day)
Day of assessment at Week 8 of the antidepressant treatment period (Phase A)	Day 1	–
Week 1 of the double-blind period (Phase B)	Day 8	± 1 day
Week 2 of the double-blind period (Phase B)	Day 15	± 2 days
Week 3 of the double-blind period (Phase B)	Day 22	± 2 days
Week 4 of the double-blind period (Phase B)	Day 29	± 2 days
Week 5 of the double-blind period (Phase B)	Day 36	± 2 days
Week 6 of the double-blind period (Phase B)	Day 43	± 2 days
At discontinuation	–	–

At discontinuation: Performed within a possible window at a feasible time point.

The starting point of the antidepressant-responder treatment-continuation period (Phase A+) is the day of assessment at Week 8 of the antidepressant treatment period (Phase A).

Examination Point	Reference Day	Acceptable Window (From the Reference Day)
Day of assessment at Week 8 of the antidepressant treatment period (Phase A)	Day 1	–
Week 1 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 8	± 1 day
Week 2 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 15	± 2 days
Week 3 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 22	± 2 days
Week 4 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 29	± 2 days
Week 5 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 36	± 2 days
Week 6 of the antidepressant-responder treatment-continuation period (Phase A+)	Day 43	± 2 days
At discontinuation	–	–

At discontinuation: Performed within a possible window at a feasible time point.

The starting point of the post-treatment observation period is the day of the final IMP administration.

Period	Reference Day	Acceptable Window (From the Reference Day)
Day of final IMP administration	Day 1	–
Post-treatment observation period	Day 31	± 5 days

3.7.2 Efficacy Assessments

3.7.2.1 Montgomery Åsberg Depression Rating Scale

(1) Time points

At the initiation and Weeks 2, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

A trained and qualified investigator or subinvestigator will assess the following 10 symptoms of depression in the subject on a 7-point scale (0 to 6) using SIGMA at the specified assessment time points, and record the date, time, and results of assessment in the source documents and the CRF.

1. Apparent sadness	2. Reported sadness	3. Inner tension	4. Reduced sleep
5. Reduced appetite	6. Concentration difficulties	7. Lassitude	8. Inability to feel
9. Pessimistic thoughts	10. Suicidal thoughts		

3.7.2.2 Clinical Global Impression – Improvement

(1) Time points

At Weeks 1, 2, 3, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

The investigator or subinvestigator will assess the improvement of depressive symptoms in the subject on the following 8-point scale using CGI-I at the specified assessment time points. Improvement relative to the subject's condition at the initiation of the antidepressant treatment period (Phase A) will be assessed during the antidepressant treatment period (Phase A), and the improvement relative to the subject's condition at Week 8 of the antidepressant treatment period (Phase A) will be assessed during the double-blind period (Phase B) and the antidepressant-responder treatment-continuation period (Phase A+). The date, time, and results of assessment will be recorded in the source documents and the CRF.

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

3.7.2.3 Clinical Global Impression - Severity of Illness

(1) Time points

At screening, the initiation and Weeks 1, 2, 3, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

The investigator or subinvestigator will assess the severity of the subject's depressive symptoms on the following 8-point scale using CGI-S at the specified assessment time points, and record the date, time, and results of assessment in the source documents and the CRF.

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			

3.7.2.4 Hamilton Rating Scale for Depression

(1) Time points

At screening, the initiation and Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

A trained and qualified investigator or subinvestigator will assess the following 21 symptoms of depression in the subject on a 5-point scale (0 to 4) for Items No. 1, 2, 10 to 14, 16 to17, and 19, on a 4-point scale (0 to 3) for Items No. 5 and 20, and on a 3-point scale (0 to 2) for Items No. 3, 4, 6 to 9, 15, 18, and 21 using the Structured Interview Guide for HAM-D (SIGH-D) at the specified assessment time points, and calculate the total score for Items No. 1 to 17, and record the date, time, and results of assessment in the source documents and the CRF.

1. Depressed mood	2. Work and activities	3. Genital symptoms	
4. Somatic symptoms gastrointestinal		5. Loss of weight	6. Early (initial) insomnia
7. Middle insomnia	8. Late (terminal) insomnia	9. Somatic symptoms general	
10. Feelings of guilt	11. Suicide	12. Anxiety psychic	13. Anxiety somatic
14. Hypochondriasis	15. Insight	16. Retardation	17. Agitation
18. Diurnal variation	19. Depersonalization and derealization		20. Paranoid symptoms
21. Obsessional and compulsive symptoms			

3.7.2.5 Sheehan Disability Scale

(1) Time Points

At the initiation and Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 3 and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

The investigator or subinvestigator will use SDS at the specified assessment time points and ask subjects to self-rate the degree of impairment for each of 3 items ("work/school," "social life," and "family life/home responsibilities") on an 11-point scale ranging from 0 (not at all) to 10 (extremely) and the number of "days lost" and "days unproductive" caused by symptoms in the past week. The investigator or subinvestigator will record the date, time, and results of assessment in the source documents and the CRF.

3.7.2.6 Montgomery Åsberg Depression Rating Scale Self-assessment

(1) Time points

At the initiation and Weeks 2, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

All subjects will self-assess each of the following 10 MADRS-S items, selecting the applicable level on a scale from 0 to 3 at the specified assessment time points. The investigator or subinvestigator will record the date, time, and results of assessment in the source documents and the CRF.

Staying power	1. Mood	2. Feelings of unease	3. Sleep	4. Appetite
5. Ability to concentrate	6. Initiative	7. Emotional involvement	8. Pessimism	9. Zest for life

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

(1) Time Points

At screening (in the fasting state to the extent possible), Week 8 (in the fasting state) or at discontinuation (in the fasting state to the extent possible) of the antidepressant treatment period (Phase A), Week 3 (in the fasting state to the extent possible) and Week 6 (in the fasting state) or at discontinuation (preferably in the fasting state) of the double-blind period (Phase B), and Week 6 (in the fasting state) or at discontinuation (in the fasting state to the extent possible) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

Subjects will be asked to visit the trial site in the fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at Week 8 of the antidepressant treatment period (Phase A) and Week 6 of the double-blind period (Phase B) or the antidepressant-responder treatment-continuation period (Phase A+) and in the fasting state to the extent possible at other time points including examinations at discontinuation.

Blood and urine samples will be collected from each subject at the time of clinical laboratory tests as specified in the assessment schedules shown in Table 3.7-1 through Table 3.7-3, and the date and time of blood sampling and the date of urine sampling as well as the fasting or fed state during blood sampling will be recorded in the source documents and the CRF. In this trial, the central laboratory selected by the sponsor will be used. Clinical laboratory test values determined at the central laboratory will be used for eligibility assessment. For appropriate procedures for the collection, handling, and shipment of samples, separately documented procedures will be prepared and provided prior to the start of the trial. The central laboratory will report the results of tests to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of tests and date and sign the clinical laboratory test report to make it an official document. The results of laboratory tests, which will be reported directly from the central

laboratory to the sponsor as an electronic file, do not need to be recorded in the source documents or the CRF.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Red Blood Cell count White blood cell count Differential count of white blood cells (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count Hemoglobin Hematocrit Urinalysis: pH Protein Glucose Occult blood Urobilinogen Specific gravity Ketone body	Serum chemistry: AST (Glutamic oxaloacetic transaminase [GOT]) ALT (Glutamic pyruvic transaminase [GPT]) Alkaline Phosphatase (ALP) Lactic Dehydrogenase (LDH) Gamma-glutamyl transpeptidase (γ-GTP) Total protein Albumin Total bilirubin Cholesterol (total cholesterol, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol) Triglycerides Blood urea nitrogen (BUN) Creatinine Uric acid Creatine kinase (CK) (CPK) Serum electrolytes (Na, K, Cl, Ca, Mg, P, bicarbonate) Blood glucose HbA1c (NGSP value) Prothrombin time (PT) Activated partial thromboplastin time (APTT) PT (international normalized ratio [INR]) Endocrinology: Serum prolactin Insulin FT4 TSH

To be performed in subjects in the fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at Week 8 of the antidepressant treatment period (Phase A) and Week 6 of the double-blind period (Phase B) or the antidepressant-responder treatment-continuation period (Phase A+) and in the fasting state to the extent possible at other time points including examinations at discontinuation

3.7.3.3 Vital Signs and Physical Examination

(1) Vital signs

(a) Time points

At screening, the initiation and Weeks 1, 4, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(b) Methods

After keeping the subject in a relaxed state, body temperature will be measured and then blood pressure (systolic and diastolic) and pulse rate will be measured in the supine, sitting, and standing positions in accordance with the measurement methods specified by the trial site. For body temperature, the date and result of measurement will be recorded in the source documents and the CRF. Blood pressure and pulse rate will be measured in the supine, sitting, and standing positions, in this order, after maintaining each position for at least 3 minutes. The date, time, positions, and results of measurement will be recorded in the source documents and the CRF.

(2) Physical examination

(a) Time points

At screening, the initiation and Weeks 1, 2, 3, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), post-treatment observation period, and Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(b) Methods

The investigator or subinvestigator will perform a physical examination that includes the assessment items shown below through subject interview and other relevant methods and record the physical findings in the source documents. The date and results of examinations at screening and only the dates of examinations after the initiation of the antidepressant treatment period (Phase A) will be recorded in the source documents and the CRF. Any clinically significant physical findings compared with findings at screening are to be recorded as AEs.
Assessment items: HEENT (head, eyes, ears, nose, and throat), chest, abdomen, urogenital organs, limbs, nerves, and skin mucosa

(3) Waist circumference

(a) Time points

At the initiation and Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(b) Methods

Measurement will be performed while the subject is minimally clothed (lightly clothed, removing heavy outer garments). The top of the hip bone and the upper edge of the right iliac crest will be located, and then a measuring tape will be placed horizontally all the way around the abdomen at the height of the iliac crest. Prior to measurement, the person engaged in measurement should ensure that the measuring tape is snug without indenting the subject's skin and is parallel to the floor. At the end of a normal expiration, waist circumference will be measured in centimeters (rounded off to the nearest whole number) and the date and result of measurement will be recorded in the source documents and the CRF.

(4) Height and body weight

(a) Time points

At screening, Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

However, height will be measured only at screening.

(b) Methods

Body weight and height will be measured at the specified time points, and the date and results of measurement will be recorded in the source documents and the CRF (body weight in increments of 0.1 kg, height in increments of 0.1 cm). Body weight will be measured by the standard measurement method (fully clothed but without shoes) using a reliable, calibrated scale (the same scale should always be used to measure a particular subject).

3.7.3.4 12-lead Electrocardiography

(1) Time points

At screening, Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

The investigator or subinvestigator will record the subject's ECG using a 12-lead electrocardiograph supplied by the central ECG laboratory, assess whether the ECG

result is normal or abnormal, and record the date and time of ECG, normal/abnormal judgement, and abnormal findings in the source documents and the CRF. The original of the 12-lead ECG chart will be kept in the medical record or the investigator's file. The central ECG laboratory will collect 12-lead ECG data and measure heart rate, PR interval, RR interval, QRS interval, QT interval, and QT corrected for heart rate (QTc) [QTcB = QT interval/(RR interval)$^{1/2}$, QTcF = QT interval/(RR interval)$^{1/3}$, QTcN = QT interval/(RR interval)$^{0.37}$], and the physician of the central ECG laboratory will assess the data. The central ECG laboratory will report the results of analysis to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of analysis and date and sign the analysis result report to make it an official document. The investigator or subinvestigator will reconfirm the normal/abnormal judgement with reference to the analysis result report sent from the central ECG laboratory. The results of analysis, which will be reported directly from the central ECG laboratory to the sponsor as an electronic file, do not need to be recorded in the source documents or the CRF.

3.7.3.5 Pregnancy Test

(1) Time points

At screening, the initiation and Week 8 (or discontinuation) of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

A urine pregnancy test will be performed in women of childbearing potential[a] and the date of urine sampling and the result of the test will be recorded in the source documents and the CRF. If the urine test is positive, another pregnancy test will be performed using serum [excluding the time of screening and the initiation of the antidepressant treatment period (Phase A)] and the date of blood sampling will be recorded in the source documents and the CRF. A serum pregnancy test will be performed by the central laboratory selected by the sponsor. For appropriate procedures for the collection, handling, and shipment of samples, separately documented procedures will be prepared and provided prior to the start of the trial. The central laboratory will report the results of tests to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of tests and date and sign the clinical laboratory test report to make it an official document. The results of serum tests, which will be reported directly from the central laboratory to the sponsor as an electronic file, do not need to be recorded in the source documents or the CRF.

[a:] Women of childbearing 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).

3.7.3.6 Columbia-Suicide Severity Rating Scale

(1) Time points

At screening, the initiation and Weeks 1, 2, 3, 4, 6, and 8 (or discontinuation) of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), post-treatment observation period, and Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

This scale consists of the "Baseline Version," which assesses the lifetime history of suicide-related events and suicidal ideation and the "Since Last Visit Version," which focuses on suicidality since the last assessment in the trial. The "Baseline Version" will be used at screening and the "Since Last Visit Version" will be used at subsequent time points for C-SSRS assessment. The date, time, and results of assessment will be recorded in the source documents and the CRF.

The presence of suicidal ideation 1 or 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 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 injury is 0, “potential lethality” will be rated on a 3-point scale.

Suicidal ideation: 1. Wish to be dead 2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent
Suicidal behavior: Actual attempt Non-suicidal self-injurious behavior
Interrupted attempt Aborted attempt Preparatory acts or behavior Suicidal behavior
Suicide (only for "Since Last Visit Version")

3.7.3.7 Drug Induced Extra-Pyramidal Symptoms Scale

(1) Time points

At Week 8 of the antidepressant treatment period (Phase A), Weeks 1, 2, 3, 4, 5, and 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

The investigator or subinvestigator will assess the following 9 items related to extra-pyramidal symptoms on a 5-point scale ranging from 0 (none, normal) to 4 (severe) using DIEPSS at specified time points. The date, time, and results of assessment will be recorded in the source documents and the CRF.

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

3.7.3.8 Abnormal Involuntary Movement Scale

(1) Time points

At Week 8 of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

Using AIMS, the investigator or subinvestigator will assess the severity of abnormal involuntary movement at 7 sites (“muscles of facial expression,” “lips and perioral area,” “jaw,” “tongue,” “upper extremities [arms, wrists, hands, and fingers],” “lower extremities [legs, knees, ankles, and toes],” and “neck, shoulders, and hips”) and 3 global judgment items on a 5-point scale ranging from 0 (none) to 4 (severe) and assess the dental status items “current problems with teeth and/or dentures” and “Dose patient usually wear dentures” as either “yes” or “no,” at the specified time points. The date, time, and results of assessment will be recorded in the source documents and the CRF.

3.7.3.9 Barnes Akathisia Rating Scale

(1) Time points

At Week 8 of the antidepressant treatment period (Phase A), Week 6 (or discontinuation) of the double-blind period (Phase B), and Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+)

(2) Methods

Using BARS, the investigator or subinvestigator will assess "objective," "subjective—awareness of restlessness," and "subjective—distress related to restlessness" for akathisia on a 4-point scale and a "global clinical assessment of akathisia" on a 6-point scale at the specified time points. The date, time, and results of assessment will be recorded in the source documents and the CRF.

3.7.4 Prior and Concomitant Medications and Therapies

The investigator or subinvestigator will examine the use of the following prior and concomitant medications and therapies. For prior and concomitant medications, the name of the drug, purpose of use (excluding prior medications used to treat the current major depressive episode), dose, frequency, route of administration, start and end dates of treatment, and treatment response (for prior medications used to treat the current major depressive episode) will be examined and recorded in the source documents and the CRF. For prior and concomitant therapies, the name of the therapy, purpose of use (excluding prior therapies used to treat the current major depressive episode), and the start and end dates of treatment will be examined and recorded in the source documents and the CRF.

- Prior medications and therapies
  - Prior medications used to treat the current major depressive episode (all antidepressants)
  - Prior therapies used to treat the current major depressive episode (psychotherapies/somatic therapies up until 6 weeks before informed consent)
  - All prior medications and therapies used within 30 days before acquisition of informed consent
- Concomitant medications and therapies
  - Concomitant medications and therapies used during the trial period (including treatments for AEs)

3.7.5 Investigational Medicinal Product

(1) Treatment compliance

The investigator or subinvestigator will confirm the subject's IMP compliance during the interval between 2 consecutive scheduled visits after proceeding to the antidepressant treatment period (Phase A) and record the consumed daily dose and the start and end dates of IMP administration in the source documents and the CRF.

(2) Compliance rate

$$\text{Compliance rate (\%)} = \frac{\text{Doses consumed between 2 consecutive scheduled visits (number of tablets)}}{\text{“Number of prescribed days between 2 consecutive scheduled visits” (number of days)} \times \text{1 tablet}} \times 100$$

(3) Compliance instruction

The investigator, subinvestigator, or IMP manager will provide subjects with compliance instructions with particular attention to the following points:

- The subject should take the IMP once daily, removing only the prescribed daily amount of the IMP from the sheet.
- The subject must bring any missed/unused doses (IMP tablets) to the trial site at the next visit.
- Contact information for any questions about taking the IMP
- The subject must not discard any empty IMP sheets but should bring them to the trial site at the next visit.
- The subject should be withdrawn from the trial if the subject’s IMP compliance during an interval between 2 consecutive scheduled visits is less than 65%.

3.7.6 Requisite Concomitant Medication

The investigator or subinvestigator will confirm the subject’s compliance with the requisite concomitant medication, a commercially available antidepressant (SSRI or SNRI), during the interval between 2 consecutive scheduled visits after proceeding to the antidepressant treatment period (Phase A) and record the name of the drug, prescribed daily dose, consumed daily dose, and start and end dates of administration in the source documents and the CRF.

3.7.7 Pharmacokinetic Assessment, Pharmacogenomic Assessment, and [redacted]

3.7.7.1 Pharmacokinetic Assessment

Plasma brexpiprazole concentrations will be measured by validated high performance liquid chromatography/tandem mass spectrometry. Metabolites that are not presented in the protocol may be measured based on newly obtained information.

The bioanalytical laboratory will measure drug concentrations only for samples collected from subjects in the brexpiprazole 1 mg/day group or the brexpiprazole 2 mg/day group after recording the use of the documents providing treatment assignment codes. Access to the documents containing treatment assignment codes will be strictly controlled and not

disclosed to anyone other than those who need them to carry out trial-related activities in the opinion of the person responsible for drug concentration measurements. The bioanalytical laboratory will hold the results of drug concentration measurements in strict confidence and submit an electronic file containing these results to the sponsor after unblinding.

3.7.7.1.1 Blood Sampling Time Point

[redacted]

3.7.7.1.2 Plasma Samples for Pharmacokinetic Assessment

All plasma samples will be shipped to the bioanalytical laboratory. The date and time of IMP administration immediately before blood sampling and the date and time of blood sampling will be recorded in the source documents and the CRF. The results of measurements, which will be reported directly from the bioanalytical laboratory to the sponsor as an electronic file after unblinding, do not need to be recorded in the source documents or the CRF. Detailed handling and shipping methods of samples are provided in Appendix 1.

3.7.7.2 Pharmacogenomic Assessment

3.7.7.2.1 CYP2D6 Genetic Testing

CYP2D6 genotypes and phenotypes will be analyzed. CYP2D6 genetic testing is mandatory. [redacted]
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 be disclosed to subjects.

The genetic analysis laboratory will select blood samples collected from subjects in the brexpiprazole 1 mg/day group and the brexpiprazole 2 mg/day group and extract DNA after recording the use of the documents providing treatment assignment codes. Blood samples collected from subjects in the placebo group will be discarded in accordance with the procedure specified by the genetic analysis laboratory. Access to the documents containing treatment assignment codes will be strictly controlled and not be disclosed to anyone except for those who need them to carry out trial-related activities in the opinion of the person responsible for genetic testing. The genetic analysis laboratory will hold the

results of CYP2D6 genetic testing in strict confidence and submit an electronic file containing these results to the sponsor after unblinding.

3.7.7.2.1.1 Blood Sampling Time Point

Blood sampling will be performed at Week 6 of the double-blind period (Phase B) or at discontinuation. If resampling of blood is necessary, it will be performed by the end of the trial date.

3.7.7.2.1.2 Samples for CYP2D6 Genetic Testing

All blood samples will be shipped to the genetic analysis laboratory. The date and time of blood sampling will be recorded in the source documents and the CRF. The results of measurements, which will be reported directly from the genetic analysis laboratory to the sponsor as an electronic file after unblinding, do not need to be recorded in the source documents or the CRF. Detailed handling and shipping methods of samples are provided in Appendix 1.

3.7.7.2.2 [redacted]

3.7.7.2.2.1 [redacted]

[redacted]

3.7.7.2.2.2 [redacted]

[redacted]

3.7.7.2.2.3 Timing of Blood Sampling

[redacted]

3.7.7.2.2.4 Handling of Samples

[redacted]

[redacted]

3.7.7.2.2.5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.7.7.2.2.6 [redacted]

[redacted]

[redacted]

[redacted]

3.7.7.2.2.7 [redacted]

[redacted]

3.7.7.3 [redacted]

3.7.7.3.1 Objective

[redacted]

3.7.7.3.2 Target Population

[redacted]

3.7.7.3.3 Blood Collection Time Points

[redacted]

3.7.7.3.4 Handling of Samples

[redacted]

[redacted]

3.7.7.3.5 [redacted]

[redacted]

3.7.7.3.6 [redacted]

[redacted]

3.7.7.3.7 [redacted]

[redacted]

[redacted]

3.7.8 End of Trial

The end of trial date is defined as the date of completion or discontinuation of the trial as recorded on the trial completion page or the date of last visit or contact or date of final contact attempt as recorded on the follow-up page of the CRF prepared for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 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.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB 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.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After commencement of the treatment period, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is no satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. However, for subjects who have undergone randomization, each investigator or subinvestigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4 Procedures to Encourage Continued Trial Participation.

3.8.3.2 Documenting Reasons for Discontinuation

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

one reason for discontinuation (the main reason) can be recorded in the source documents and CRF, along with the date of discontinuation.

1) Adverse event:
   a) Death
   b) Subjects experiences exacerbation of symptoms of the underlying disease, and the investigator or subinvestigator judges that continued participation in the trial is inappropriate
   c) Subject experiences a change to the manic state
   d) Based on clinical symptoms, subject is considered to be at high risk of suicide in the opinion of the investigator or subinvestigator or has an MADRS score for Suicidal Thought (No. 10) of ≥ 5 or HAM-D suicide score (No. 11) of ≥ 3, or those answering "Yes" to question 4 or 5 of C-SSRS.
   e) Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
   f) Continuation of IMP would place the subject at undue risk as determined by the investigator or subinvestigator (eg, there is a safety concern possibly, probably, or likely related to IMP)
      i) SAE
      ii) Other safety concern or AE possibly, probably, or likely related to IMP
2) Subject's withdrawal of informed consent
   a) Reasons unrelated to medical condition (issues regarding subject's convenience, such as a change of residence or other commitments: provide detail and review AE history with subject)
   b) Withdrawal of informed consent (complete written withdrawal of consent form)
3) Marked noncompliance with the IMP regimen
   a) Compliance rate of < 65% during the interval between 2 consecutive scheduled visits
4) Protocol deviation
   a) Subject is discovered to have not been in accord with inclusion/exclusion criteria
   b) Subject has received any prohibited concomitant drugs or therapies, or is judged to be in need of such
   c) Dose of antidepressant (SSRI or SNRI) cannot be fixed from Week 7 of the antidepressant treatment period [Phase A])
5) Lost to follow-up
6) Pregnancy (see Section 5.5 Pregnancy)
7) Termination of all or part of the trial by the sponsor
8) Discontinuation of the trial site by the sponsor
9) Lack of efficacy

10) Impossibility of protocol compliance or judgement by the investigator or subinvestigator that discontinuation is necessary for any reason other than the above

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. Follow-up procedures in Section 3.8.3.1 Treatment Discontinuation must be followed.

3.8.3.3 Withdrawal of Consent

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

Complete withdrawal of consent requires refusal by a subject 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 documents 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 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 may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section

3.8.3.1 Treatment Discontinuation). A subject 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 3.8.3.2 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 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.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal for subjects who have undergone randomization, investigators or subinvestigators will be given instructions to meet and discuss with the subject 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 wishes to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject has signed an ICF), but who is not enrolled in the antidepressant treatment period (Phase A). For screen failures, the following information will be recorded in the source documents and the CRF:

- Date of visit
- Date of informed consent
- Subject demographics
  - Date of investigation
  - Date of birth
  - Sex
  - Race
  - Ethnicity
  - Country where trial is performed
- Results of eligibility criteria assessment
- Date of assessment as screen failure
- Reason for screening failure

Subjects who participate in this trial but who are categorized as screening failures are permitted to be rescreened. Prior to rescreening, if performed, informed consent must be newly obtained and a new subject ID must be assigned.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for safety and efficacy irrespective of whether the subject actually receives all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For the purposes of this trial, subjects who are evaluated at Week 6 of the double-blind period (Phase B) or antidepressant-responder treatment-continuation period (Phase A+) will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the examinations at Week 6 of the double-blind period (Phase B) or antidepressant-responder treatment-continuation period (Phase A+) during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Subjects who did not commence the treatment period of the long-term trial (331-102-00059) and did not undergo post-treatment observation after completing the examinations at Week 6 of the double-blind period (Phase B) will also be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The 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, and will make a record of the inability to contact the subject, recording the dates of the 3 attempts at contact and the method(s) of contact in the source documents and the date and method of the last attempt at contact in the CRF.

3.12 Subject Compliance

The investigator or subinvestigator will give subjects the following instructions to ensure compliance with the protocol:

1) Site visits are to be made on the scheduled visit days as specified in the protocol (see Section 3.7.1.9).
2) No prohibited concomitant drugs are to be taken during the period from informed consent to Week 6 (or discontinuation) of the double-blind period (Phase B) or to

Week 6 (or discontinuation) of the antidepressant-responder treatment-continuation period (Phase A+).

3) No commercially available brexpiprazole is to be taken during the period from Week 6 (or discontinuation) of the double-blind period (Phase B) to the post-treatment observation period.
4) The requirements regarding the method, duration, and frequency of administration of a commercially available antidepressant and the IMP are to be complied with (see Section 3.2). If IMP compliance during the interval between 2 consecutive scheduled visits is less than 65%, the subject will be withdrawn from the trial (see Section 3.8.3).
5) Subjects must take appropriate contraceptive methods as instructed (see Section 5.5).

3.13 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. For major deviations, the date on which the deviation occurred and the details of the deviation will be recorded in the source documents and the CRF.

4 Restrictions

The use of the following drugs, etc., and therapies will be prohibited or restricted.

4.1 Prohibited Concomitant Medications

For appropriate assessment of the efficacy and safety of brexpiprazole, use of the drugs shown below will be prohibited. Discontinuation of these drugs following gradual dose reduction in the screening period but before the start of the prohibition period shown below may be allowed, if deemed necessary by the investigator or subinvestigator.

- One week prior to the initiation of the antidepressant treatment period (Phase A) to the treatment period (the antidepressant treatment period [Phase A], and the double-blind period [Phase B] or the antidepressant-responder treatment-continuation period [Phase A+])
  - Benzodiazepines (excluding ultrashort-acting sedative-hypnotic drugs)
    *Necessary washout period: 7 days

- Two weeks prior to the initiation of the antidepressant treatment period (Phase A) to the treatment period (the antidepressant treatment period [Phase A], and the double-blind period [Phase B] or the antidepressant-responder treatment-continuation period [Phase A+])
  - MAO inhibitors
    *Necessary washout period: 14 days
- Twenty-four hours before the initiation of the antidepressant treatment period (Phase A) to the treatment period (the antidepressant treatment period [Phase A], and the double-blind period [Phase B] or the antidepressant-responder treatment-continuation period [Phase A+])
  - Central nervous system drugs (excluding ultrashort-acting sedative-hypnotic drugs, anticholinergic drugs for Parkinson's disease, antipyretic analgesic anti-inflammatory drugs, and general cold drugs)
    Note: Concomitant use of CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers specified in this section is prohibited (eg, chlorpheniramine, diphenhydramine, clemastine, and celecoxib).
  - Chinese medicine (drugs indicated for neurosis, anxiety neurosis, neurasthenia, insomnia, and other disorders)
  - Over-the-counter drugs used as hypnotics
  - Supplements used for improvement of depressive symptoms (St. John's wort, S-adenosylmethionine [SAM-e], ω-3 fatty acids, Kava extracts, and gamma-aminobutyric acid [GABA])
  - Varenicline
  - Adrenaline
  - CYP2D6 inhibitors (excluding topical agents in the dosage forms permitted for concomitant use as specified in Appendix 3):

Drug category	Nonproprietary name
Antihistamines	clemastine, chlorpheniramine, diphenhydramine
Antiallergic minor tranquilizers	hydroxyzine
Antiinflammatory agents	celecoxib
Analgesics	methadone
Antifungal agents	terbinafine
Antiarrhythmic agents	quinidine
Acid suppressants	cimetidine
Overactive bladder treatments	mirabegron
Antidepressants	clomipramine
Hyperthyroidism treatments	cinacalcet
Erythematosus treatments	hydroxychloroquine

- CYP3A4 inhibitors (excluding topical agents in the dosage forms permitted for concomitant use as specified in Appendix 3):

Drug category	Nonproprietary name
Antibiotics	erythromycin, quinupristin/dalfopristin (injection), clarithromycin, chloramphenicol, ciprofloxacin
Antifungal agents	itraconazole, clotrimazole, fluconazole, voriconazole
Calcium antagonists	diltiazem, verapamil
Antiarrhythmic agents	amiodarone
Acid suppressants	cimetidine
Antiemetics	aprepitant
Antineoplastic agents	imatinib, crizotinib
Immunosuppressants	ciclosporin
Anti-HIV agents	atazanavir, indinavir, cobicistat (combination), saquinavir, nelfinavir, fosamprenavir, ritonavir, lopinavir/ritonavir (combination)
Hepatitis C treatments	telaprevir, ombitasvir/paritaprevir/ritonavir (combination)

- CYP3A4 inducers (excluding topical agents in the dosage forms permitted for concomitant use as specified in Appendix 3):

Drug category	Nonproprietary name
Corticosteroids	cortisone, dexamethasone, triamcinolone, hydrocortisone, fludrocortisone, prednisolone, betamethasone, methylprednisolone
Antihormones	enzalutamide, mitotane
Cervical ripening agents	prasterone
Central nervous system stimulants	modafinil
Antiepileptics	oxcarbazepine, carbamazepine, phenytoin, fosphenytoin, phenobarbital, primidone
Pulmonary hypertension treatments	bosentan
Antituberculous agents	rifampicin (rifampin)
Anti-HIV agents	etravirine, efavirenz, nevirapine

- Drugs not approved in Japan
- Foods: Food products containing St. John's wort, and grapefruit, starfruit, Seville orange, and their juice and other processed products

- Post-treatment observation period
  - Commercially available brexpiprazole

4.2 Prohibited Concomitant Therapies

For appropriate assessment of the efficacy and safety of brexpiprazole, the following therapies are prohibited during the treatment period (antidepressant treatment period [Phase A], and double-blind period [Phase B] or antidepressant-responder treatment-continuation period [Phase A+]).

- Somatic therapy (electroconvulsive therapy, high-intensity phototherapy, sleep deprivation, transcranial magnetic stimulation)
- Psychotherapy (excluding supportive psychotherapies used in general clinical practice)

4.3 Restricted Concomitant Drugs

- Ultrashort-acting sedative-hypnotic drugs
  Ultrashort-acting sedative-hypnotic drugs that can be used in this trial are restricted to zolpidem, zopiclone, eszopiclone, and triazolam. During the treatment period (antidepressant treatment period [Phase A], and double-blind period [Phase B] or antidepressant-responder treatment-continuation period [Phase A+]), the concomitant use of only one of the aforementioned drugs is allowed; 2 or more drugs are not to be coadministered simultaneously. Change in the types of the aforementioned drugs is allowed. Regarding ultrashort-acting sedative-hypnotic drugs, the concomitant use in the double-blind period (Phase B) or the antidepressant-responder treatment-continuation period (Phase A+) is allowed but only when the drugs have been used concomitantly in the antidepressant treatment period (Phase A).
- Anticholinergic drugs for Parkinson's disease
  Concomitant use of anticholinergic drugs for Parkinson's disease is allowed only in the double-blind period (Phase B). Anticholinergic drugs for Parkinson's disease, for which concomitant use is allowed, are biperiden, trihexyphenidyl, profenamine, piroheptine, and mazaticol. In the case where extrapyramidal symptoms occur and use is necessary in the opinion of the investigator or subinvestigator, only one drug can be coadministered with no prophylactic use allowed. Change in the types of the aforementioned drugs is allowed.
- Antipyretic analgesic anti-inflammatory drugs, antihistamines
  The concomitant use during the treatment period (antidepressant treatment period [Phase A], and double-blind period [Phase B] or the antidepressant-responder treatment-continuation period [Phase A+]) is allowed if the drugs were being used to treat complications at the time of informed consent; however, no changes in dose and regimen are allowed unless AEs occur or the use of these drugs is considered unnecessary because of remission of symptoms. Furthermore, short-term concomitant use, including use such as a medication for colds, is also allowed. The topical external use of these drugs is allowed.
  Note: Concomitant use of CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers specified in Section 4.1 Prohibited Concomitant Medications is prohibited

(eg, chlorpheniramine, diphenhydramine, clemastine, and celecoxib). "Short-term" is defined as 1 week in principle. If antipyretic analgesic anti-inflammatory drugs or antihistamines that were not in use at the time of informed consent have been used for more than 2 weeks or if the use of these drugs for more than 2 weeks is judged to be necessary, the subject will be withdrawn from the trial under the reason for discontinuation "Subject has received any prohibited concomitant drugs or therapies, or is judged to be in need of such."

- β-Blockers
  During the treatment period (antidepressant treatment period [Phase A], and double-blind period [Phase B] or the antidepressant-responder treatment-continuation period [Phase A+]), use is allowed only for treatment of cardiovascular diseases, with no changes in the dose and regimen employed at the time of informed consent. The topical external use of these drugs is allowed.

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 drug-induced liver injury (DILI) (see Section 5.4).
- 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 in the source documents and the AE section of the CRF if there is an abnormality or complication. This applies both to pregnancies of subjects and pregnancies of subjects' partners.

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 medically relevant by the investigator or subinvestigator (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. 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 between an AE and the IMP:

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

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

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will 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?" For all AEs (serious and nonserious) reported by the subject, the event name, start and stop dates, severity, seriousness, relationship to IMP, actions taken regarding IMP administration, and outcome thereof must be recorded in the source documents and CRFs provided by the sponsor. Adverse event and SAE collection is to begin after a subject has signed the ICF. In this trial, AEs occurring during the screening period and the antidepressant treatment period (Phase A) will be assessed in comparison to the subject's condition at screening, and AEs occurring during the double-blind period (Phase B) and the antidepressant-responder treatment-continuation period (Phase A+) will be assessed in comparison to the subject's condition at Week 8 of the antidepressant treatment period (Phase A).

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

In addition, the sponsor must be notified immediately by e-mail, in principle, 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 SAE, potential DILI, or confirmed pregnancy to the sponsor by e-mail (using the contact information on the title page of this protocol) immediately after either the investigator, subinvestigator, or designee becomes aware of the event. The IRE form and so on should be completed and sent by e-mail, in

principle, to the sponsor. Please note that the IRE form is NOT the AE section of the CRF. Due consideration must be given to privacy when the IRE form and so on is sent by mail or other means of communication.

For subjects experiencing SAEs or IREs, such AEs should be followed until the events are resolved or stabilized, or the subject is lost to follow-up or has died. *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. 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 Drug-induced Liver Injury

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 level 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 in the source documents and CRF.

5.5 Pregnancy

Women of childbearing potential (WOCBP) 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, vaginal diaphragm, intrauterine device, oral contraceptives, or condom with spermicide. 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.

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 pregnancy tests 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 forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator 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

In an emergency situation, such as when a subject experiences an SAE, if breaking the treatment assignment code is considered necessary by the investigator or subinvestigator to ensure the subject's safety, the investigator or subinvestigator will be able to obtain the emergency code break information through IWRS in accordance with the separately specified procedures. The investigator or subinvestigator must contact the sponsor within 24 hours of opening the code, and prepare a document containing the reason and process of opening the code and submit it to the sponsor. If the blind is broken, the Department of Pharmacovigilance must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, the IMP may not be reinitiated for that subject.

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 in the source documents and the AE section of the CRF, with the current status (ongoing or resolved/recovered) noted. All nonserious events (other than immediately reportable events) that are ongoing at the end of trial date (final day of observation) will be recorded as ongoing in the source documents and CRF. For any AE having been identified throughout the trial, during data analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). The follow-up information after the 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 30 days (±5 days) after the final day of IMP administration (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 in the source documents and the AE section of the CRF. 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 in the source documents and the AE section of the CRF. 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.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable 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/Pharmacogenomic/ [redacted] Analysis

6.1 Pharmacokinetic Analysis Methods

Descriptive statistics of plasma brexpiprazole concentrations will be determined for each treatment group.

6.2 Pharmacogenomic Analysis Methods

A list of data obtained from CYP2D6 genetic assessment will be provided without summarization. [redacted]

6.3 [redacted]

[redacted]

7 Statistical Analysis

For the double-blind period (Phase B), the definitions of the datasets for analysis and the analysis methods for the specified endpoints are described below.

The detailed statistical analysis plan for the double-blind period (Phase B) and the analysis plans for the antidepressant treatment period (Phase A) and the antidepressant-responder treatment-continuation period (Phase A+) are described in a separate Statistical Analysis Plan. The Statistical Analysis Plan will be finalized prior to data lock.

7.1 Determination of Sample Size

In phase 3, double-blind, placebo-controlled, fixed dose trials of brexpiprazole (331-10-227, 331-10-228, and 331-13-214) conducted outside Japan, changes from baseline in MADRS total scores at Week 6 of the double-blind period (Phase B) have been analyzed by the Mixed-model Repeated Measure (MMRM) method (for 331-10-227 and 331-10-228, based on the results for efficacy from an analysis of subgroups meeting the inclusion criteria that had been revised in the middle of the trials), which demonstrated that the differences between the brexpiprazole groups (the 3 mg group in 331-10-227, and the 2 mg group in 331-10-228 and 331-13-214) and the placebo group were −1.9, −3.2, and −2.3, respectively, and that the standard deviations obtained from standard errors and numbers of subjects at Week 6 of the double-blind period (Phase B) were 7.2, 7.7 and 8.2, respectively. On the assumption that the difference in changes from baseline in MADRS total scores at Week 6 of the double-blind period (Phase B) is −2.4 for the brexpiprazole group compared with the placebo group with a standard deviation of 7.7, this trial will require 218 subjects per group to ensure a power of 90% in a two-sided test with a significance level of 0.05. We have decided that the planned number of subjects for randomization will be 240 per group, assuming that 7% of subjects will discontinue the trial during the double-blind period (Phase B) and some subjects will be excluded from analysis.

7.2 Datasets for Analysis

7.2.1 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will comprise subjects who have been treated with brexpiprazole and for whom plasma drug concentration data have been obtained.

7.2.2 Full Analysis Set

The full analysis set (FAS) will comprise subjects who, after randomization, have received at least 1 dose of the IMP in the double-blind period (Phase B), and from whom MADRS total scores have been obtained at baseline and at least 1 time point after initiation of the treatment.

7.2.3 Safety Analysis Set

The safety analysis set will comprise subjects who, after randomization, have received at least 1 dose of the IMP in the double-blind period (Phase B).

7.3 Handling of Missing Data

The primary analysis of the primary endpoint will be performed in the observed cases (OC) dataset by MMRM without data imputation for missing data under the missing at random (MAR) assumption. As a sensitivity analysis for the handling of missing data, placebo multiple imputation and tipping point analysis will be performed under the missing not at random (MNAR) assumption. Details are described in the statistical analysis plan.

For efficacy and safety analyses, the last observation carried forward (LOCF) method (in which missing post-dose data are imputed by the last observed data after initiation of IMP treatment) will be used as needed.

For pharmacokinetic analysis, no imputation will be performed for missing data.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analyses

The primary endpoint is mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS total scores at Week 6 of the double-blind period (Phase B).

For the primary analysis, MMRM analysis will be performed using the OC data set in the FAS. The statistical hypotheses will be tested, based on differences in least square means between each brexpiprazole group and the placebo group, which are calculated by MMRM. To adjust for multiplicity of tests, due to there being 2 comparisons with the placebo group for each of the brexpiprazole groups, a fixed-sequence approach will be used to control overall type 1 error rates. Comparison between the brexpiprazole 2 mg/day group and placebo group will be performed first; only when significance is observed at a two-sided significance level of 5%, will comparison between the brexpiprazole 1 mg/day group and placebo group be performed at a two-sided significance level of 5%.

The MMRM will include treatment group (brexpiprazole 1 mg/day group, brexpiprazole 2 mg/day group, and placebo group), time point (double-blind period [Phase B] Weeks 1, 2, 3, 4, 5, and 6), and interaction between treatment group and time point as factors, and baseline and interaction between baseline and time point as covariates. Unstructured error

variance-covariance structure will be assumed. For a degree-of-freedom approximation, the Kenward-Roger method will be used. If any problems in convergence status arise in the estimation of variance components, heterogeneous Toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry, which are error variance-covariance structures, will be applied in this order, and the first structure that achieves convergence will be used in the primary analysis. If anything other than an unstructured variance-covariance structure is selected, a sandwich estimator for standard errors will be used.

For each time point, least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% confidence intervals (CIs) will be determined.

7.4.2 Secondary Endpoint Analyses

- MADRS response rate at Week 6 of the double-blind period (Phase B)
- MADRS remission rate at Week 6 of the double-blind period (Phase B)
- CGI-I improvement rate at Week 6 of the double-blind period (Phase B)

For the MADRS response rate, a χ^2 test will be performed for between-treatment-group comparison using the LOCF data set. Differences in the response rates between each of the brexpiprazole groups and the placebo group, and the two-sided 95% CIs will be determined. For MADRS remission rate and CGI-I improvement rate, the same analysis employed for the MADRS response rate will be used.

- Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in HAM-D 17-item total scores at Week 6 of the double-blind period (Phase B)

Using the LOCF data set, analysis will be performed by ANCOVA model with treatment group as a factor and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

- Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in CGI-S at Week 6 of the double-blind period (Phase B)
- Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in mean SDS scores at Week 6 of the double-blind period (Phase B)
- Mean changes from baseline (Week 8 of the antidepressant treatment period [Phase A]) in MADRS-S total scores at Week 6 of the double-blind period (Phase B)

As performed for the primary endpoint, MMRM analysis will be performed.

7.4.3 Interim Analysis

No interim analyses are planned.

7.5 Analysis of Demographic and Baseline Characteristics

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

7.6 Safety Analysis

Safety analysis for the double-blind period (Phase B) will be performed using the safety analysis set. Baseline is defined as Week 8 of the antidepressant treatment period (Phase A).

7.6.1 Adverse Events

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

- Adverse events occurring after initiation of IMP administration in the double-blind period (Phase B) (treatment-emergent adverse events [TEAEs])
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

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

7.6.2 Clinical Laboratory Data

For each quantitative laboratory parameter, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.

For each laboratory parameter (excluding qualitative parameters), actual 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 treatment group and for the overall brexpiprazole group.

For each qualitative laboratory parameter, a shift table from baseline will be produced for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with potentially clinically significant laboratory test values will be determined for each treatment group and for the overall brexpiprazole group.

7.6.3 Physical Examination and Vital Signs Data

Physical examination data will be provided in a listing.

For each vital sign parameter, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with potentially clinically significant vital signs will be determined for each treatment group and for the overall brexpiprazole group.

7.6.4 Electrocardiogram Data

For heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.

A shift table from baseline for normal/abnormal 12-lead ECG will be produced for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with actual measurements of corrected QT interval (QTcF, QTcB, QTcN) at each time point of > 450 msec, > 480 msec, and > 500 msec will be determined for each treatment group and for the overall brexpiprazole group. Numbers and proportions of subjects with changes from baseline of > 30 msec and > 60 msec will be determined for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with ECG results meeting the criteria for potentially clinically significant ECG data will be determined for each treatment group and for the overall brexpiprazole group.

7.6.5 Other Safety Data

- Body weight, body mass index (BMI), and waist circumference
  For body weight, BMI, and waist circumference, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.
  In addition, using the LOCF data set, analysis will be performed by the ANCOVA model with treatment group as a factor and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

Numbers and proportions of subjects with results meeting the criteria for potentially clinically significant body weight gain or loss will be determined for each treatment group and for the overall brexpiprazole group.

- DIEPSS, AIMS, and BARS
  For DIEPSS total score (total of scores for items 1 through 8) and score for each DIEPSS item, AIMS total score (total of scores for items 1 through 7) and score for each of the items 8 through 10, and BARS, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.
  In addition, using the LOCF data set, analysis will be performed by the ANCOVA model with treatment group as a factor and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.
- C-SSRS
  Numbers and proportions of subjects for 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 for each treatment group and for the overall brexpiprazole group.

8 Management of Investigational Medicinal Product

Refer to the investigator's brochure on brexpiprazole and the separately-specified manual for details regarding IMP management.

8.1 Packaging and Labeling

[redacted]

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 is to be stored at room temperature.

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 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. [redacted] 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) regarding the IMP 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)
- Vial defects
- 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 (or sponsor's designee) 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. (E-mail address [redacted])

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

- 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, drug number)
- Clinical protocol reference (protocol 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. In all cases, subject confidentiality must be maintained in accordance with 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 each clinician (or designee) 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 electronic CRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail.

9.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local

regulations. The trial site will take measures to 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 whichever is the longer of the four periods indicated below. 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
- Until the date on which it is decided to end biomarker sample storage

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) 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 the 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 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 Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents,

the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits.

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

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. Each trial site will seek approval/favorable opinion by an IRB according to the requirements of each region, 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 source documents, CRFs, and the IRE form and so on, the investigator or subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject. Financial aspects, subject insurance, and publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

12 Confidentiality

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

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

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s),

must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or 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 concludes that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

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

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

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

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

15 References

1 Lecrubier Y. How do you define remission? Acta Psychiatr Scand 2002;106(Suppl.415):7-11.

2 Takahashi Y. Mood disorder and suicide. Japanese Journal of Clinical Psychiatry. 2000;29:877-84.

3 Office for Policy of Suicide Prevention, Ministry of Health, Labour and Welfare, and Community Safety Planning Division, National Police Agency. 2016 Situation of suicide [Internet]: March 23, 2017 [accessed on 2018 Jan 9]. Available from: http://www.npa.go.jp/safetylife/seianki/jisatsu/H28/H28_jisatunojoukyou_01.pdf

4 Ministry of Health, Labour and Welfare. Economic benefits of prevention of suicide/depression (social loss from suicide/depression). [Internet]: September 7, 2010 [accessed on 2018 Jan 9]. Available from: http://www.mhlw.go.jp/stf/houdou/2r9852000000qvsy.html

5 Kawakami N. Study on mental health epidemiological survey. A research project supported by the FY 2004 to 2006 Health and Labour Sciences Research Grants (Research project for mental health science). Study report for "Study on mental health epidemiological survey." 2007.

6 Committee for Treatment Guidelines of Mood Disorders of the Japanese Society of Mood Disorders. Guidelines for Treatment of Depression. Edition 2. Tokyo: Igaku-Shoin Ltd.; 2017.

7 Inoue T, Kitaichi Y, Honda M, Tanaka T, Suzuki K, Nakagawa S, et al. Research on treatment for depressive patients resistant to SSRIs and SNRIs. Psychiatria et Neurologia Japonica. 2003;105:1318.

8 Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: Two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry. 2007;68(6):935-40.

9 McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379:721–8.

10 Kamijima K, Higuchi T, Ishigooka J, Ohmori T, Ozaki N, Kanba S, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: A randomized, double-blind, placebo-controlled study (ADMIRE study). Journal of Affective Disorders. 2013;151:899-905.

11 Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: A multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68(6):843-53.

12 Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder a second multicenter, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychopharmacology. 2008;28(2):156-65.

13 Berman RM, Fava M, Those ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-

controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009;14(4):197-206.

[14] Otsuka Pharmaceutical Co, Ltd. A dose-finding trial of OPC-34712 in patients with schizophrenia. Clinical Study Report for Protocol 331-10-002, issued 18 Dec 2015.

[15] Otsuka Pharmaceutical Co, Ltd. A long-term trial of OPC-34712 in patients with schizophrenia. Clinical Study Report for Protocol 331-10-003, issued 18 Dec 2015.

[16] Otsuka Pharmaceutical Co, Ltd. Package insert for Rexulti (brexpiprazole). April 2018.

[17] Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophrenia Research. 2015;164:127-35.

[18] Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2015;172(9):870-80.

[19] Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: A phase 3, randomized, double-blind study. J Clin Psychiatry. 2015;76(9):1232-40.

[20] Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, et al. Efficacy and safety adjunctive brexpiprazole 2 mg in major depressive disorder: A phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224-31.

[21] Otsuka Pharmaceutical Co, Ltd. Package insert for Rexulti (brexpiprazole). USA. February 2017.

[22] International Conference on Harmonization (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2014 Dec 5]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

Appendix 1 Handling and Shipping of Bioanalytical Samples

(1) [redacted]

[redacted]

(2) [redacted]

[redacted]

(3) [redacted]

[redacted]

[redacted]

(4) [redacted]

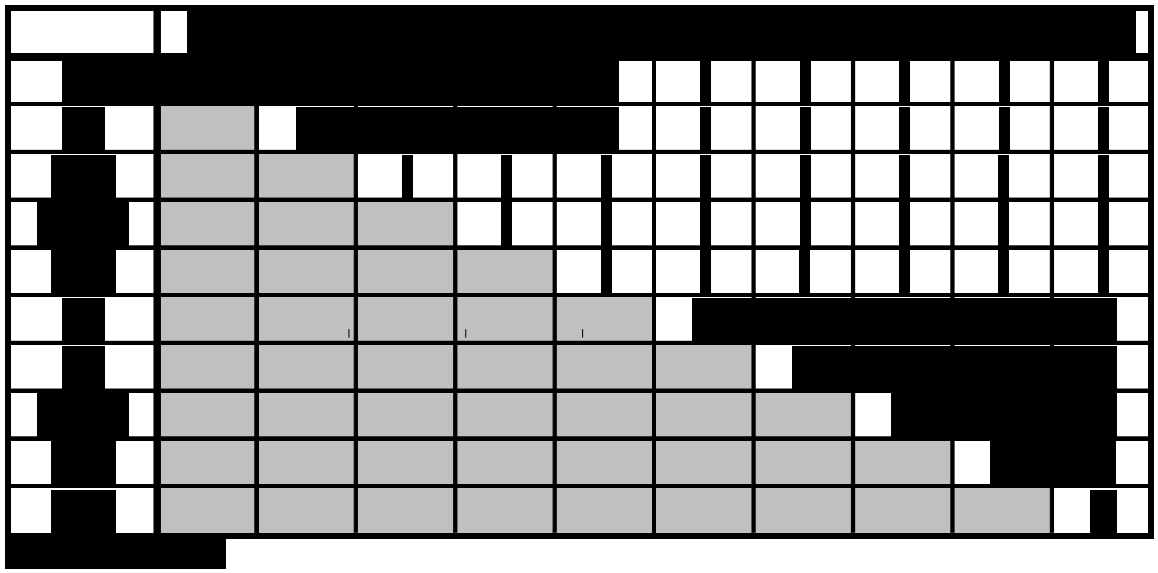
[redacted]rocedure.

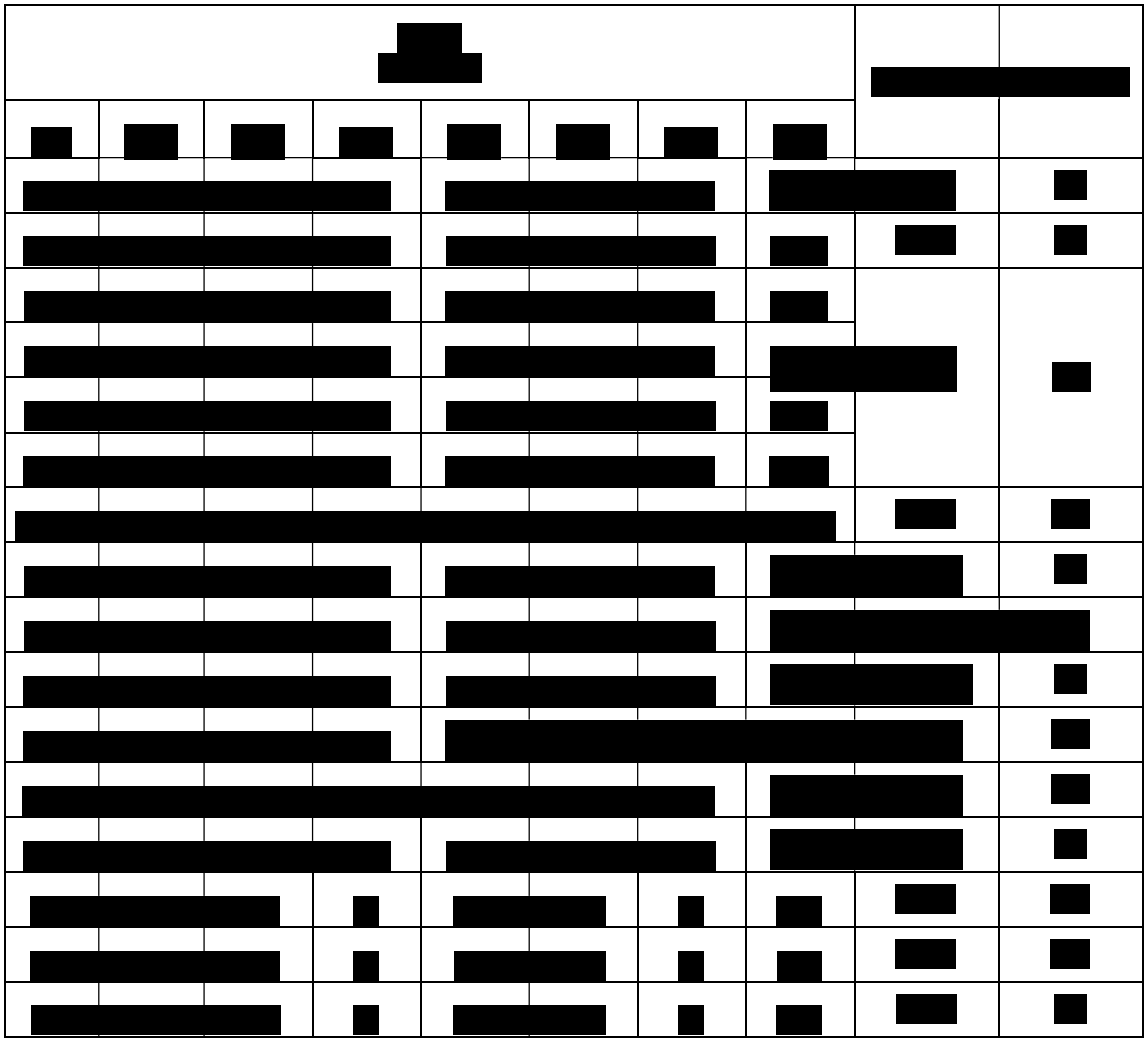
(5) [redacted]

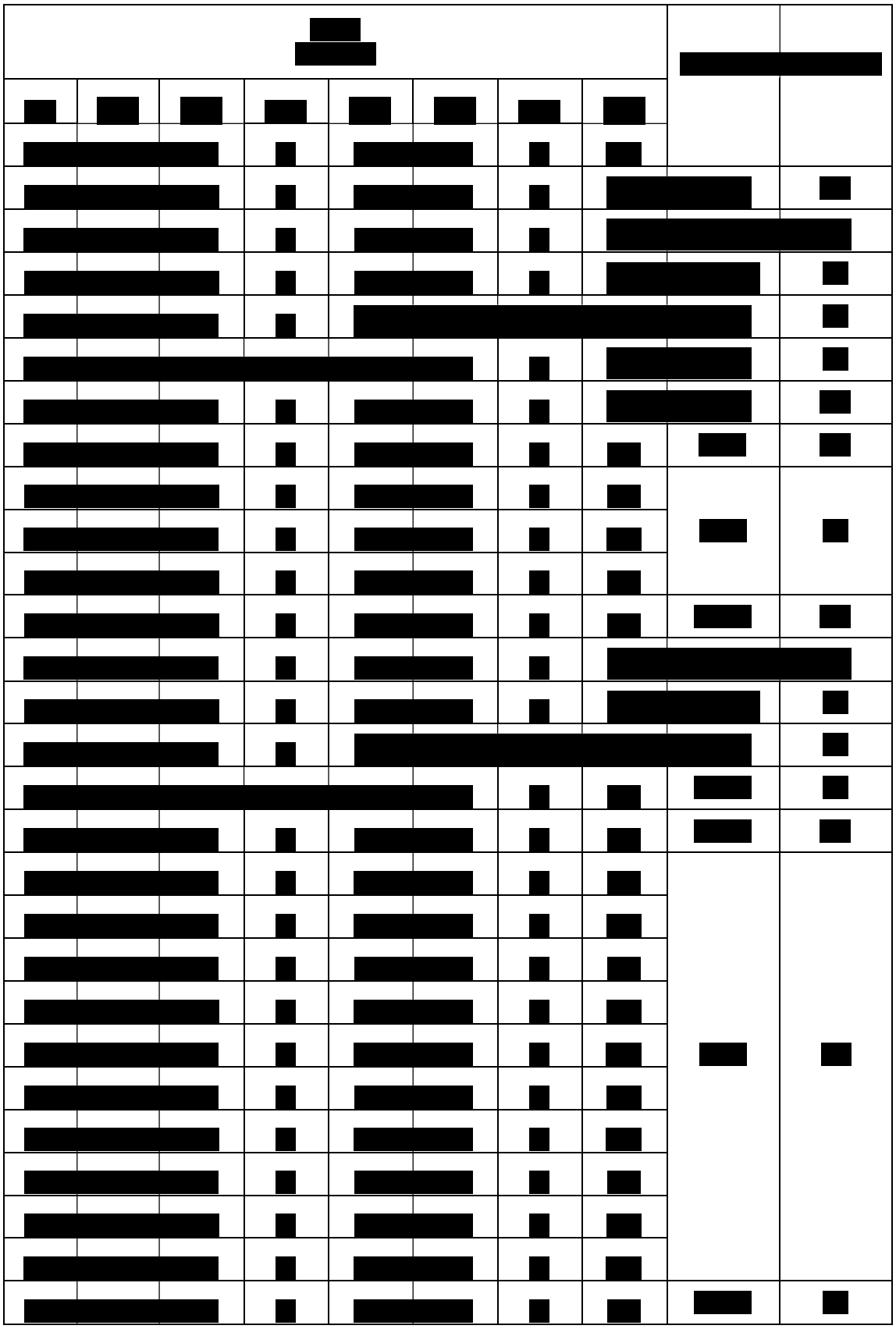
[redacted]

[redacted]

Appendix 2 CYP2D6 Genotyping Table







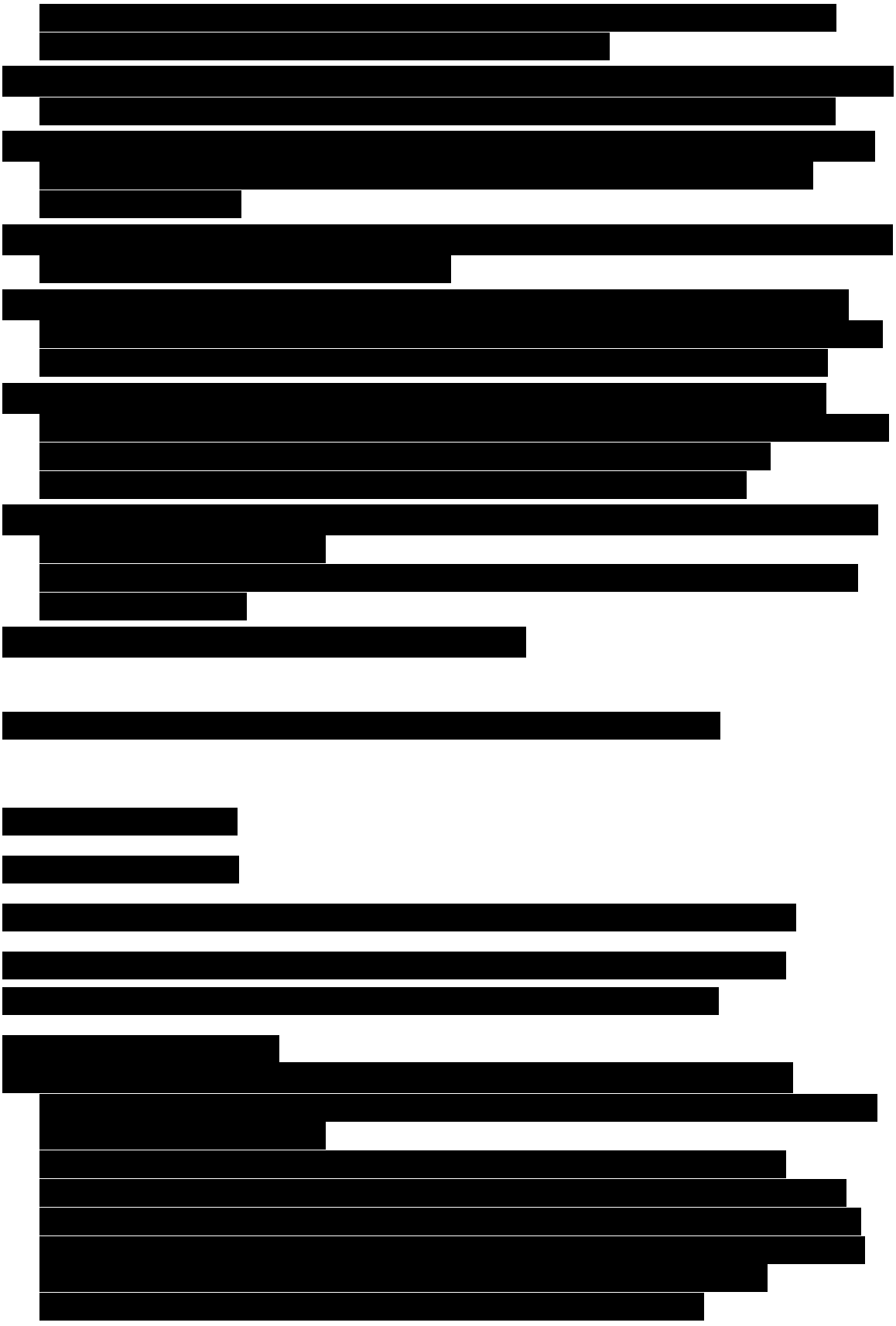
Appendix 3 Criteria for Allowing Concomitant Use of Topical CYP2D6 Inhibitors, CYP3A4 Inhibitors, and CYP3A4 Inducers

[redacted]

[redacted]

Appendix 4 Protocol Amendments/Administrative Changes

[redacted]



[redacted]

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.