CLINICAL STUDY PROTOCOL

A multi-center, open-label trial to assess the long-term safety and efficacy of brexpiprazole as adjunctive therapy in patients with major depressive disorder

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole

CLINICAL PROTOCOL

A multi-center, open-label trial to assess the long-term safety and efficacy of brexpiprazole as adjunctive therapy in patients with major depressive disorder

Protocol No. 331-102-00059

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-102-00059
Protocol Title:	A multi-center, open-label trial to assess the long-term safety and efficacy of brexpiprazole as adjunctive therapy in patients with major depressive disorder
Clinical Phase/ Type of Trial:	Phase 3 Long-term trial
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:	To assess the safety and efficacy of the long-term use of brexpiprazole as adjunctive therapy in combination with a commercially available antidepressant (selective serotonin reuptake inhibitor [SSRI] or serotonin-noradrenaline reuptake inhibitor [SNRI] for rollover subjects and SSRI, SNRI, or mirtazapine for new subjects) in subjects with major depressive disorder who continue receiving the treatment from the double-blind trial (331-102-00058) and in newly enrolled patients 65 years or older with major depressive disorder.
Trial Design:	A multi-center, open-label trial
Subject Population:	Target subjects will be those continuing on from the double-blind trial (331-102-00058) and newly recruited patients 65 years of age or older whose condition corresponds to major depressive disorder. The target number of subjects to complete 52 weeks of administration was set at 100 subjects and the sample size needed to assess the safety of brexpiprazole in the elderly was set as 30 subjects receiving IMP administration.
Inclusion/Exclusion Criteria:	Inclusion criteria Rollover subjects 1) Outpatients 2) Subjects who have completed the double-blind period (Phase B) of the double-blind trial (331-102-00058) and can commence the treatment period of this trial within 28 days from Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) 3) Subjects 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) Subjects with a DSM-5 classification-based diagnosis of

"major depressive disorder, single episode" or "major depressive disorder, recurrent episode"

New subjects

5) Outpatients
6) Male and female patients ≥ 65 years of age (at the time of informed consent)
7) Subjects 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
8) Patients with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" whose current episode has persisted for at least 8 weeks
9) 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.
10) Patients undergoing treatment with SSRI, SNRI, or mirtazapine at the time of informed consent

Exclusion criteria

Rollover subjects

1) Female subjects who are pregnant or breastfeeding or who have positive pregnancy test (urine) results at baseline
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) Subjects who experience a change to the manic state in the antidepressant treatment period (Phase A) of the double-blind trial (331-102-00058)
4) Subjects who are discovered to not meet the inclusion criteria or to fall under any of the exclusion criteria in the double-blind trial (331-102-00058)
5) Subjects who showed marked noncompliance with the IMP treatment in the double-blind trial (331-102-00058) (subjects whose IMP compliance rates are < 65% between prescribed visits)
6) Subjects receiving treatment with antipsychotics and psychostimulants for current major depressive episode (excluding the use of IMP in the double-blind trial [331-102-00058] and use of sulpiride for depression/depressive state or gastric/duodenal ulcer)
7) Subjects receiving treatment with monoamine oxidase inhibitors (MAO inhibitors) within 2 weeks before baseline
8) Subjects using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before baseline
9) Subjects hospitalized for the current major depressive episode after the antidepressant treatment period (Phase A) of the double-blind trial (331-102-00058)
10) Subjects with a history of electroconvulsive therapy
11) Subjects 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
12) Subjects with a diagnosis of any personality disorders (borderline personality disorder, antisocial personality disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, histrionic

personality disorder) according to DSM-5

13) Subjects experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current major depressive episode

14) Subjects with a Montgomery Åsberg Depression Rating Scale (MADRS) score of ≥ 5 for Item 10. Suicide, a Hamilton Rating Scale for Depression (HAM-D) score for suicide (No. 11) of ≥ 3, those answering "Yes" to question 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at baseline, 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

15) Subjects with clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders; subjects can be enrolled if the conditions are mild or well controlled and will not hamper assessment of safety and efficacy.

16) 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 baseline
- Patients meeting either of the following criteria for poor blood glucose control at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058)
  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

17) Subjects 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.

18) Subjects 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), or abnormal thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) (assessed based on results from the central laboratory)

19) Subjects meeting any of the following criteria or showing symptoms at baseline
    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
20) Subjects with a complication of ischemic heart diseases, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), or subjects with a history of angioplasty, stent placement, or coronary artery bypass
21) Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome
22) Subjects with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
23) Subjects with a history of hypersensitivity to antidepressants
24) Subjects with the following clinical laboratory test values or electrocardiogram (ECG) parameters at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) (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
25) Subjects with a history or complication of allergy to more than one medication
26) The following subjects falling under the contraindications in the package insert for brexpiprazole tablet

a) Subjects in a coma
b) Subjects under the strong influence of central nervous system depressants including barbiturate analogs/anesthetics
c) Subjects receiving adrenaline
d) Subjects with a history of hypersensitivity to components of brexpiprazole tablet

27) Subjects who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator

New subjects

28) Sexually active male subjects 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.
29) 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
30) 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)
31) Patients receiving treatment with MAO inhibitors within 2 weeks before baseline
32) Patients using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before baseline
33) Patients with a treatment history showing that all antidepressants (also including those not used for the current major depressive episode) cannot be tolerated
34) Patients with a history of electroconvulsive therapy
35) 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

36) 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

37) Patients experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current major depressive episode

38) Patients receiving a new psychotherapy within 6 weeks prior to informed consent

39) Patients who have previously taken brexpiprazole

40) Patients who have participated in other clinical trials within 60 days prior to informed consent

41) Patients answering "Yes" to question 4 or 5 of C-SSRS at screening or baseline, 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

42) 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.

43) 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) HbA1c of ≥ 8.0% according to the global standard value [NGSP value]
  b) Fasting blood glucose level of ≥ 126 mg/dL or non-fasting blood glucose level of ≥ 200 mg/dL

44) 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

45) 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 since acquisition of informed consent), or abnormal TSH and FT4 levels at screening (assessed based on results from the central laboratory)

46) Patients meeting any of the following criteria or showing symptoms at screening or baseline
   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
47) Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), or patients with a history of angioplasty, stent placement, or coronary artery bypass
48) Patients with a history of neuroleptic malignant syndrome or serotonin syndrome
49) Patients with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
50) 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) AST: > 2 times the upper limit of the reference range
   e) ALT: > 2 times the upper limit of the reference range
   f) CPK: > 3 times the upper limit of the reference range
   g) Creatinine: ≥ 2 mg/dL
   h) QTcF: ≥ 450 msec
51) Patients with a history of hypersensitivity to antidepressants
52) Patients with a history or complication of allergy to more than one medication
53) 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 54) Patients 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:	Treatment period 1) Drugs, doses, and regimens: • Commercially available antidepressant For rollover subjects, an antidepressant (SSRI or SNRI) used in the double-blind trial (331-102-00058) will continue to be used throughout the treatment period, with no changes from the final dose and regimen. For new subjects, an antidepressant (SSRI, SNRI, or mirtazapine) being used at the time of informed consent will continue to be used throughout the treatment period, with no changes from the dose and regimen at the time of informed consent. During the treatment period, dose adjustment within the approved dose range is allowed according to the judgement of the investigator or subinvestigator, but the dose may not be altered at the time of dose escalation of brexpiprazole at Week 1. • Brexpiprazole Administration of brexpiprazole will commence at 1 mg/day and subjects will continue to receive a single brexpiprazole 1 mg tablet once daily by the oral route until the observations, examinations, and evaluations at Week 1. Following the observations, examinations, and evaluations performed at Week 1, subjects will be administered a single brexpiprazole 2 mg tablet once daily by the oral route. Subjects who cannot tolerate doses of 2 mg/day will be withdrawn from the trial. 2) Treatment period: 52 weeks
Trial Assessments:	Efficacy: MADRS, Clinical Global Impression — Improvement CGI-I, Clinical Global Impression — Severity of Illness (CGI-S), HAM-D, Sheehan Disability Scale (SDS) Other: EuroQol-5 Dimension 5-level (EQ-5D-5L) questionnaire Safety:

	Adverse events, clinical 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 Symptom Scale (DIEPSS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) Screening: Subject demographics, height Pharmacokinetic and Pharmacogenomic Assessments: DNA storage (optional)
Criteria for Evaluation	Safety Endpoints: Adverse events, clinical laboratory tests, vital signs (body temperature, diastolic blood pressure and systolic blood pressure and pulse rate [supine, sitting, and standing positions]), physical examination, waist circumference, 12-lead ECG, body weight, body mass index, C-SSRS, DIEPSS, AIMS, BARS Efficacy Endpoints: • Mean changes from baseline in MADRS total scores • MADRS response rate The proportion of subjects in whom MADRS total scores have been reduced by at least 50% from baseline • MADRS remission rate The proportion of subjects in whom MADRS total scores have been reduced by at least 50% from baseline, with their resultant MADRS total scores being ≤ 10 • CGI-I improvement rate The proportion of subjects who score 1 or 2 on the CGI-I scale • Mean changes from baseline in CGI-S • Mean changes from baseline in HAM-D 17-item total score • Mean changes from baseline in mean SDS score Other Endpoints: EQ-5D-5L
Statistical Methods:	Safety analysis Incidences of treatment-emergent adverse events will be determined. Descriptive statistics of actual measurements at each assessment time point and the last assessment time point (Week 52 LOCF) as well as changes from baseline will be determined. Efficacy analysis

	Descriptive statistics of actual measurements at each assessment time point and the last assessment time point (Week 52 LOCF) as well as changes from baseline will be determined. Rationale for target number of subjects To verify the safety of long-term administration, the target number of subjects to complete 52 weeks of administration was set at around 100 subjects. Due to the availability of data on safety in elderly subjects from foreign clinical trials, the sample size needed to assess the safety of brexpiprazole in the elderly was set as 30 new subjects (elderly subjects of age 65 and above) receiving IMP administration.
Trial Duration:	01 Jun 2018 to 31 Jul 2022

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	5-Hydroxytryptamine
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
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
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
MAO inhibitor	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
NGSP	The National Glycohemoglobin Standardization Program
PANSS	Positive and Negative Syndrome Scale
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

Abbreviation	Definition
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
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.

In conclusion, since brexpiprazole adjunctive therapy may also benefit Japanese patients with inadequate response to antidepressants, a placebo-controlled efficacy trial (331-102-00058) has been planned. Considering that major depressive disorder requires long-term treatment including pharmacotherapy, we have decided to conduct this trial to evaluate the long-term safety and efficacy of brexpiprazole.

1.1 Nonclinical Data

Brexpiprazole has been investigated in a number of pharmacological studies for its efficacy as a potential treatment for schizophrenia, major depressive disorder, cognitive impairments, and other psychiatric disorders.

In predictive animal models for antipsychotic-like efficacy, brexpiprazole inhibited apomorphine-induced hyperlocomotion and stereotyped behavior, and conditioned avoidance response in rats, and these effects were more potent than those of aripiprazole. Furthermore, brexpiprazole showed dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitch response in rats, suggesting 5-HT_{2A} receptor antagonism, and the effect was stronger than that of aripiprazole. Moreover, despite it having a lower intrinsic activity for D_2 receptors and higher antipsychotic potency than aripiprazole, the liability for catalepsy of brexpiprazole was comparable with that of aripiprazole, but less than that for haloperidol, olanzapine, and risperidone, suggesting brexpiprazole has a low potential to induce extrapyramidal symptoms. In other in vivo studies, it was demonstrated that brexpiprazole is a D_2 receptor partial agonist in rats consistent with findings in the in vitro functional assays.

Behavioral studies were also conducted to evaluate brexpiprazole as adjunct treatment to antidepressants in rodent models of depression-like (forced swim test and chronic mild stress model) and anxiety-like (marble burying) activity. In the forced swim test (behavioral despair), the administration of brexpiprazole either intraperitoneally (IP) at a very low dose (0.001 or 0.003 mg/kg) in mice or orally at a dose of (3 mg/kg) in rats, significantly reduced immobility time in adjunct treatment with SSRI (paroxetine: $p < 0.05$; sertraline: $p < 0.001$; fluoxetine: $p < 0.001$; escitalopram: $p < 0.05$; fluvoxamine: $p < 0.01$) or SNRI (duloxetine: $p < 0.05$; venlafaxine: $p < 0.05$; desvenlafaxine: $p < 0.001$; milnacipran: $p < 0.05$), whereas each compound alone was ineffective at the dose used in this test. In a chronic mild stress model in mice, adjunct administration of brexpiprazole (0.03 and 0.1 mg/kg, oral, twice daily) further enhanced the effect of fluoxetine alone (10 mg/kg, IP) on coat state score, and significantly improved the nest building during 5 hours while fluoxetine alone was not effective on this behavior. In the marble burying test, co-administration of brexpiprazole (0.1 mg/kg, oral) with paroxetine, sertraline, fluoxetine, or fluvoxamine (10 or 15 mg/kg, oral), enhanced the reduction in marble-burying (anxiolytic-like activity) seen with each SSRI alone. These studies strongly suggested that brexpiprazole has good potential as adjunct treatment for anti-depressant therapy.

These results suggest that, in addition to schizophrenia, brexpiprazole also has excellent therapeutic effect against major depressive disorder.

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) scores, remained stable until Week 52.

1.2.2 Clinical Data From Non-Japanese Trial 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.

1.2.2.4 Long-term Trial in Subjects With Major Depressive Disorder (331-10-238)

This overseas long-term open-label trial evaluated the long-term safety, tolerability, and efficacy of brexpiprazole in subjects with major depressive disorder who had participated in one of the previous phase 3 double-blind brexpiprazole trials (331-10-227, 331-10-228, and 331-12-282) and who remained on medication.

The incidence of AEs was 72.3%.

AEs with an incidence of ≥ 5% were fatigue (6.1%), viral upper respiratory tract infection (5.4%), weight increased (17.7%), increased appetite (6.3%), akathisia (6.7%), headache (7.2%), somnolence (8.0%), anxiety (5.2%), and insomnia (6.3%).

Most AEs were mild or moderate in severity. Four deaths (0.1%) were reported. One death (completed suicide) was considered potentially related to the IMP and the 3 other deaths (gastric ulcer perforation and peritonitis, completed suicide, pulmonary embolism) were considered unrelated to the IMP. The incidence of SAEs was 2.4%, with depression (0.3%) being the most frequently reported SAE. The incidence of AEs leading to discontinuation was 8.6%, with weight increased (2.0%) being the most frequently reported AE leading to discontinuation. No clinically relevant changes were noted in laboratory test values except for prolactin, vital signs, or ECG.

Improvement in all efficacy endpoints, including CGI-S score, was sustained.

1.2.2.5 Long-term Trial in Elderly Subjects With Major Depressive Disorder (16160A)

This overseas long-term open-label trial evaluated the long-term safety, tolerability, and efficacy of flexibly-dosed brexpiprazole in elderly subjects with major depressive disorder who had an inadequate response to antidepressant therapy.

The incidence of AEs was 77.3%. AEs with an incidence of ≥ 5% were fatigue (15.2%), restlessness (12.9%), increased appetite (9.8%), akathisia (8.3%), weight increased (8.3%), anxiety (7.6%), dizziness (7.6%), tremor (6.8%), insomnia (6.1%), nasopharyngitis (6.1%), back pain (5.3%), and headache (5.3%). Most AEs were mild or moderate in severity. One death was reported. AEs with an outcome of death were acute myocardial infarction and myocardial rupture. Both events were considered unrelated to the IMP. The incidence of SAEs was 4.5% and all these SAEs occurred in only 1 subject

each. The incidence of AEs leading to discontinuation was 18.9%, with fatigue (3.0%) being the most frequently reported AE leading to discontinuation. No clinically relevant changes were noted in laboratory test values, vital signs, or ECG.

Improvement in all efficacy endpoints, including CGI-S score, was observed.

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%. Mirtazapine, another first-line drug for major depressive disorder, is an antagonist to alpha 2 presynaptic autoreceptors and heteroreceptors, thereby increasing neurotransmission of serotonin and noradrenaline in the central nervous system, but it has no direct pharmacological effect on the dopaminergic system. 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 SSRI, SNRI, or mirtazapine 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. Furthermore, in an overseas long-term trial in patients with major depressive disorder, 52-week brexpiprazole treatment revealed no significant safety concerns, and its long-term sustained effectiveness was also confirmed. It is expected that the long-term use of brexpiprazole as adjunctive therapy will also be well tolerated in Japanese patients with major depressive disorder, and that the effectiveness will be sustained for a longer period. Based on the above, we have decided to conduct this trial to assess the safety and efficacy of long-term brexpiprazole treatment.

This trial will assess the long-term safety and efficacy of brexpiprazole as adjunctive therapy, primarily in rollover subjects from a Japanese double-blind trial (331-102-00058). Therefore, brexpiprazole 2 mg/day, which is the dose established for the double-blind trial (331-102-00058) and is a dose at which efficacy has been verified in multiple overseas clinical trials, was selected as a maintenance dose in this trial. A starting dose was set at brexpiprazole 1 mg/day, the same starting dose as in the double-blind trial (331-102-00058). The same safety and efficacy endpoints as those employed in the double-blind trial (331-102-00058) will also be used. In this trial, an antidepressant (any

one of SSRIs or SNRIs) used in the double-blind trial (331-102-00058) will be administered with no changes in the final dose and regimen, and brexpiprazole will be used at a dose of 2 mg/day (starting dose: 1 mg/day) in combination with the antidepressant. Duration of the treatment was set at 52 weeks, based on "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (PAB/PCD Notification No. 592 dated 24 May 1995).

As prevalence of major depressive disorder is also high in the elderly, it is probable that the drug will also be used for elderly patients aged 65 years or older after approval is obtained for its use as adjunctive therapy in major depressive disorder. Therefore, new subjects 65 years or older will also be involved, in view of the necessity to assess the long-term safety and efficacy of brexpiprazole as adjunctive therapy in elderly patients with major depressive disorder and based on the recommendations in "Studies in Support of Special Populations: Geriatrics" (PAB/NDD Notification No. 104 dated 02 Dec 1993). In newly enrolled subjects, an antidepressant will be used, which will be a drug that the subject is using at the time of informed consent, either an SSRI, SNRI, or mirtazapine. An overseas long-term clinical trial in patients with major depressive disorder aged 65 years or older also demonstrated the excellent tolerability of brexpiprazole in elderly patients.

The US package insert of brexpiprazole[21] contains warnings regarding antidepressant-related suicidal ideation or suicidal behavior, and also in the Japanese package insert of brexpiprazole, 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 conclude that assessment of the long-term safety and efficacy of brexpiprazole as adjunctive therapy in conjunction with commercially available antidepressants (SSRIs or SNRIs for rollover subjects and SSRIs, SNRIs, or mirtazapine for newly enrolled subjects) in Japanese patients with major depressive disorder is scientifically and ethically justified.

2.2 Rationale for DNA Storage

This trial will involve the optional storage of DNA samples from newly enrolled subjects. Samples for DNA storage will be collected only from subjects who have provided written consent to DNA storage and only at trial sites which have agreed to sampling for DNA

storage. Concerning collecting DNA samples during the trial period and storing them, MHLW states as follows in Q&A 1 in "Regarding Clinical Studies Utilizing Pharmacogenomics (PFSB/ELD Notification No. 0930007 dated 30 Sep 2008)": It is permissible to obtain samples from subjects for genomic/genetic analysis in association with the evaluation of the IMP (eg, pharmacokinetics, efficacy, safety) if either of the following 2 circumstances apply: 1) The target and time of genomic/genetic analysis are specified at the time of implementation of a trial; or 2) Genomic/genetic analysis in association with the IMP evaluation is planned to be performed in the future although the target or time of the analysis is not specified at the time of implementation of a trial. In Q&A 2, MHLW also states that it is permissible to obtain samples from subjects for genomic/genetic analysis which is not associated with the evaluation of the IMP.

Based on the above, we concluded that DNA storage conducted to enable future exploratory investigation regarding the relationships between DNA mutations (eg, gene polymorphism) and therapeutic responses to brexpiprazole and/or relationships between DNA mutations and the onset, severity, or progression of the disease is justified.

In this trial, rollover subjects from the double-blind trial (331-102-00058) will be excluded from DNA storage, because they are already the target of DNA storage in the previous trial.

2.3 Rationale for Dosing and Regimen

2.3.1 Rationale 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.

2.3.2 Rationale for Dose

2.3.2.1 Rationale for Maintenance Dose

Based on the efficacy of brexpiprazole at 2 mg/day confirmed in overseas clinical trials in patients with major depressive disorder and the similarity in the pharmacokinetics of brexpiprazole observed in Japanese and non-Japanese populations, a dose of 2 mg/day is likely to be effective in Japanese patients with major depressive disorder. A maintenance dose of 2 mg/day was selected for this trial to evaluate the long-term safety and efficacy of 2 mg/day of brexpiprazole.

2.3.2.2 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.

2.4 Trial Objectives

The objective of the trial is to assess the safety and efficacy of the long-term use of brexpiprazole as adjunctive therapy in concomitant use with a commercially available antidepressant (SSRI or SNRI for rollover subjects and SSRI, SNRI, or mirtazapine for new subjects) in subjects with major depressive disorder who continue receiving the treatment from the double-blind trial (331-102-00058) and in newly enrolled patients 65 years or older with major depressive disorder.

3 Trial Design

3.1 Type/Design of Trial

The trial is a multi-center, open-label trial to assess the safety and efficacy of the long-term use of brexpiprazole as adjunctive therapy in conjunction with a commercially available antidepressant (SSRI or SNRI for rollover subjects and SSRI, SNRI, or mirtazapine for new subjects) at a dose and regimen specified in the package insert. Subjects of the trial are those who have completed the double-blind period (Phase B) of the double-blind trial (331-102-00058), and newly enrolled patients 65 years or older with major depressive disorder who have received 1 to 3 adequate antidepressant drug treatments[a] for major depressive episodes and have shown an inadequate response[b] to all of these treatments.

The trial design is shown in Figure 3.1-1. The trial comprises a screening period, treatment period, 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.

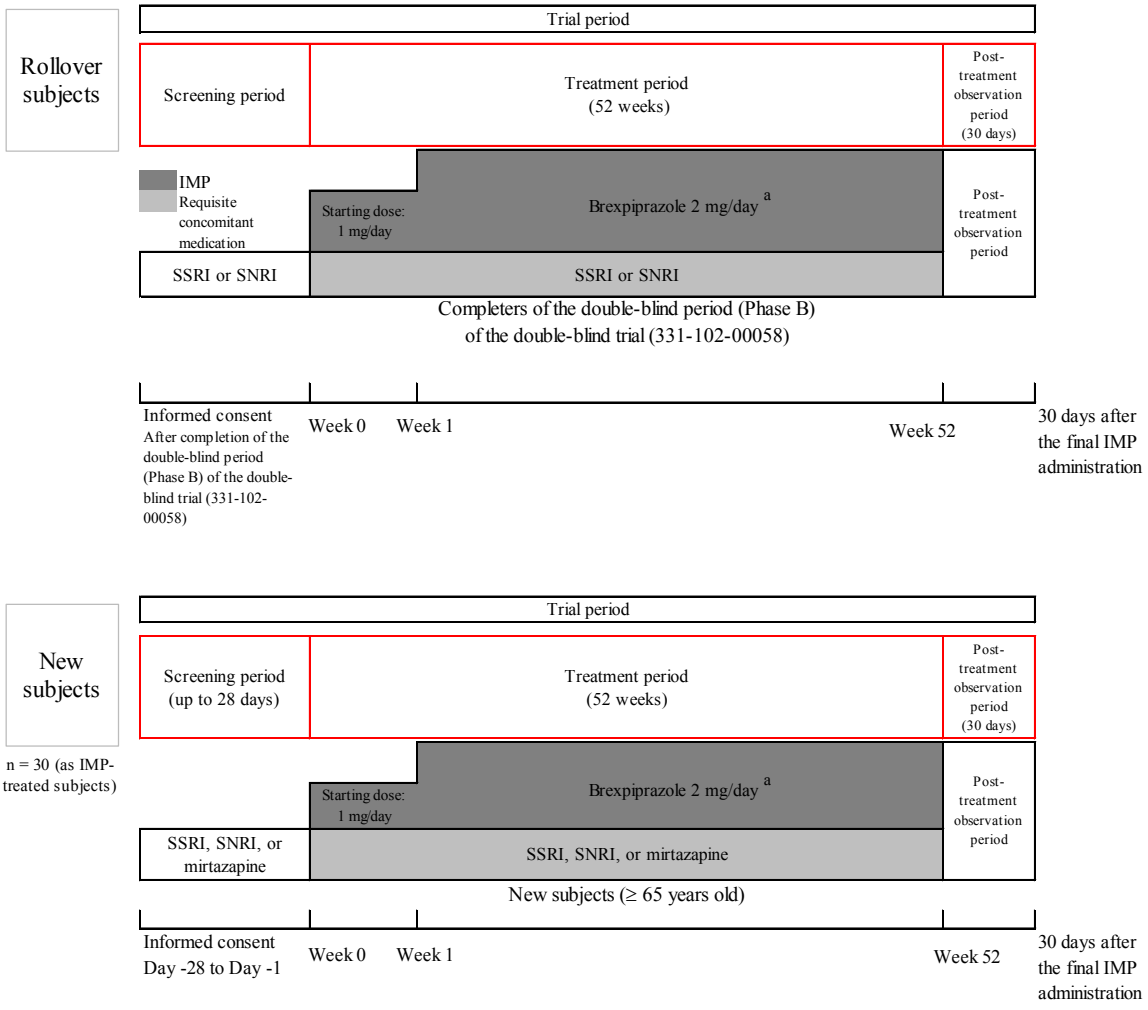

Figure 3.1-1 Trial Design

[a] Administration of brexpiprazole will commence at 1 mg/day and the dose will be increased to 2 mg/day after observations, examinations, and assessments at Week 1. Subjects who cannot tolerate doses of 2 mg/day will be withdrawn from the trial.

3.2 Trial Treatments

(1) Drugs, dose, and regimen

- Commercially available antidepressant
  For rollover subjects, an antidepressant (SSRI or SNRI) used in the double-blind trial (331-102-00058) will continue to be used throughout the treatment period, with no changes from the final dose and regimen. For new subjects, an antidepressant (SSRI, SNRI, or mirtazapine) being used at the time of informed consent will continue to be used throughout the treatment period, with no changes from the dose and regimen used at informed consent.
  During the treatment period, dose adjustment within the approved dose range is allowed according to the judgement of the investigator or subinvestigator, but the dose may not be altered at the time of dose escalation of brexpiprazole at Week 1.
- Brexpiprazole
  Administration of brexpiprazole will commence at 1 mg/day and subjects will continue to receive a single brexpiprazole 1 mg tablet once daily by the oral route until the observations, examinations, and evaluations at Week 1. Following the observations, examinations, and evaluations at Week 1, subjects will be administered a single brexpiprazole 2 mg tablet once daily by the oral route. Subjects who cannot tolerate doses of 2 mg/day will be withdrawn from the trial.

(2) Treatment period

52 weeks

[Rationale for treatment period]

Treatment duration was set at 52 weeks with reference to "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (PAB/PCD Notification No. 592 dated 24 May 1995).

3.3 Trial Population

Adult and elderly patients with "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)

3.3.1 Number of Subjects and Trial Population

The trial will be conducted in patients who have major depressive disorder (major depressive disorder, single episode; major depressive disorder, recurrent episode) according to the DSM-5 classification. Concerning rollover subjects from the double-blind trial (331-102-00058), their eligibility for proceeding to the long-term trial will be

assessed, after acquisition of informed consent to the long-term trial, based on the results of examinations and assessments at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) and at baseline. The eligibility of new subjects will be judged after acquisition of informed consent from elderly patients 65 years or older, based on the results of examinations and assessments at screening and baseline. As the sample size needed to assess the safety and efficacy of brexpiprazole in the elderly, the number of subjects receiving the treatment was set at 30.

3.3.2 Subject Number Assignment

Following the provision of written informed consent to participate in this trial, each rollover subject will continue to use the subject identifier (ID) assigned in the previous double-blind trial (331-102-00058), and each new subject will be assigned a unique subject ID (site number [3 digits] + subject number [S + 5 digits]). The site number will be designated by the sponsor. A subject number is a serial in-site number starting with S20001, , which is given to each subject in the order of provision of consent.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be obtained from all subjects on their voluntary decision. Rollover subjects will provide written informed consent after completion of observations, examinations, and assessments at Week 6 in the double-blind period (Phase B) of the previous double-blind trial (331-102-00058). 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 DNA storage, 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. DNA storage is optional and refusal to allow DNA storage will not affect trial participation.

3.4.2 Inclusion Criteria

Subjects must meet the inclusion criteria described in Table 3.4.2-1. For both rollover subjects from the double-blind trial (331-102-00058) and new subjects, those meeting all the inclusion criteria below at screening (for new subjects only) and baseline are eligible for selection.

Table 3.4.2-1 Inclusion Criteria

Rollover Subjects	
1	Outpatients
2	Subjects completing the double-blind period (Phase B) of the double-blind trial (331-102-00058) who are able to commence treatment within 28 days from Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058)
3	Subjects 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	Subjects with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode"
New Subjects	
5	Outpatients
6	Male and female patients ≥ 65 years of age (at the time of informed consent)
7	Subjects 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
8	Patients with a DSM-5 classification-based diagnosis of "major depressive disorder, single episode" or "major depressive disorder, recurrent episode" whose current episode has persisted for at least 8 weeks

Table 3.4.2-1 Inclusion Criteria	
9	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.
10	Patients undergoing treatment with SSRI, SNRI, or mirtazapine at the time of informed consent

[Rationale for inclusion criteria]
Rollover subjects
1. This criterion is specified in view of subject safety, as treatment should be prioritized in subjects whose condition requires hospitalization.
2. This criterion is specified to select subjects who will adhere to the protocol and in whom the long-term treatment will be possible.
3. This criterion is specified for ethical considerations.
4. This criterion is specified for appropriate assessment of safety and efficacy.

New subjects
5. This criterion is specified in view of subject safety, as treatment should be prioritized in subjects whose condition requires hospitalization.
6. Patients 65 years or older will be involved, based on the specifications in "Studies in Support of Special Populations: Geriatrics" (PAB/NDD Notification No. 104 in 02 Dec 1993).
7. This criterion is specified for ethical considerations.

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

3.4.3 Exclusion Criteria

For both rollover subjects from the double-blind trial (331-102-00058) and new subjects, subjects or patients will be excluded from the trial if they meet any of the exclusion criteria, provided in Table 3.4.3-1 at screening (only for new subjects) and baseline.

Table 3.4.3-1 Exclusion Criteria	
Rollover subjects	
1	Female subjects who are pregnant or breastfeeding or who have positive pregnancy test (urine) results at baseline
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	Subjects who experience a change to the manic state in the antidepressant treatment period (Phase A) of the double-blind trial (331-102-00058)
4	Subjects who are discovered to not meet the inclusion criteria or to fall under any of the exclusion criteria in the double-blind trial (331-102-00058)
5	Subjects who showed marked noncompliance with the IMP treatment in the double-blind trial (331-102-00058) (subjects whose IMP compliance rates are < 65% between prescribed visits)
6	Subjects receiving treatment with antipsychotics and psychostimulants for current major depressive episode (excluding the use of IMP in the double-blind trial [331-102-00058] and use of sulpiride for depression/depressive state or gastric/duodenal ulcer)
7	Subjects receiving treatment with monoamine oxidase inhibitors (MAO inhibitors) within 2 weeks before baseline
8	Subjects using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before baseline
9	Subjects hospitalized for the current major depressive episode after the antidepressant treatment period (Phase A) of the double-blind trial (331-102-00058)
10	Subjects with a history of electroconvulsive therapy
11	Subjects 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
12	Subjects 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
13	Subjects experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current depressive episode
14	Subjects with a MADRS score of ≥ 5 for Item 10. Suicide, a Hamilton Rating Scale for Depression (HAM-D) score for suicide (No. 11) of ≥ 3, those answering "Yes" to question 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline, 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
15	Subjects with clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders; subjects can be enrolled if the conditions are mild or well controlled and will not hamper assessment of safety and efficacy.

Table 3.4.3-1 Exclusion Criteria	
16	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 baseline • Patients meeting either of the following criteria for poor blood glucose control at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) (assessed based on results from the central laboratory) a) HbA1c of ≥ 7.0% according to the global standard value [NGSP value] b) Fasting blood glucose level of ≥ 126 mg/dL or non-fasting blood glucose level of ≥ 200 mg/dL
17	Subjects 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.
18	Subjects 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), or abnormal thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) (assessed based on results from the central laboratory)
19	Subjects meeting any of the following criteria or showing symptoms at baseline 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
20	Subjects with a complication of ischemic heart diseases, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), or subjects with a history of angioplasty, stent placement, or coronary artery bypass
21	Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome
22	Subjects with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
23	Subjects with a history of hypersensitivity to antidepressants
24	Subjects with the following clinical laboratory test values or ECG parameters at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) (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
25	Subjects with a history or complication of allergy to more than one medication

Table 3.4.3-1 Exclusion Criteria	
26	The following subjects falling under the contraindications in the package insert for brexpiprazole tablet a) Subjects in a coma b) Subjects under the strong influence of central nervous system depressants including barbiturate analogs/anesthetics c) Subjects receiving adrenaline d) Subjects with a history of hypersensitivity to components of brexpiprazole tablet
27	Subjects who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator
New Subjects	
28	Sexually active male subjects 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.
29	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
30	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)
31	Patients receiving treatment with MAO inhibitors within 2 weeks before baseline
32	Patients using benzodiazepines (excluding ultrashort-acting sleep inducers) within 1 week before baseline
33	Patients with a treatment history showing that all antidepressants (also including those not used for the current major depressive episode) cannot be tolerated
34	Patients with a history of electroconvulsive therapy
35	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
36	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
37	Patients experiencing hallucinations or delusions, or showing mood-incongruent psychotic features, in the current major depressive episode
38	Patients receiving a new psychotherapy within 6 weeks prior to informed consent
39	Patients who have previously taken brexpiprazole
40	Patients who have participated in other clinical trials within 60 days prior to informed consent
41	Patients answering "Yes" to question 4 or 5 of C-SSRS at screening or baseline, 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
42	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.

Table 3.4.3-1 Exclusion Criteria	
43	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) HbA1c of ≥ 8.0% according to the global standard value [NGSP value] b) Fasting blood glucose level of ≥ 126 mg/dL or non-fasting blood glucose level of ≥ 200 mg/dL
44	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
45	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 since acquisition of informed consent), or abnormal TSH and FT4 levels at screening (assessed based on results from the central laboratory)
46	Patients meeting any of the following criteria or showing symptoms at screening or baseline 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
47	Patients with a complication of ischemic heart disease, myocardial infarction, or congestive heart failure (irrespective of well or poorly controlled), or patients with a history of angioplasty, stent placement, or coronary artery bypass
48	Patients with a history of neuroleptic malignant syndrome or serotonin syndrome
49	Patients with a history or complication of epilepsy or epileptic seizures, excluding pediatric febrile seizures, post-traumatic seizures, alcohol withdrawal seizures, and other seizures
50	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) AST: > 2 times the upper limit of the reference range e) ALT: > 2 times the upper limit of the reference range f) CPK: > 3 times the upper limit of the reference range g) Creatinine: ≥ 2 mg/dL h) QTcF: ≥ 450 msec
51	Patients with a history of hypersensitivity to antidepressants
52	Patients with a history or complication of allergy to more than one medication

Table 3.4.3-1 Exclusion Criteria	
53	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
54	Patients who otherwise should not participate in the trial in the opinion of the investigator or subinvestigator

[Rationale for exclusion criteria]
Rollover subjects
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. This criterion is specified for appropriate assessment of efficacy.
4. This criterion is specified in view of safety
5, 6. These criteria are specified for appropriate assessment of efficacy.
7. This criterion is specified in view of safety, as package inserts for antidepressants indicate that for subjects receiving MAO inhibitors, the antidepressants should be administered after an interval of at least 2 weeks from discontinuation of MAO inhibitors.
8. This criterion is specified for appropriate assessment of efficacy.
9. This criterion is specified in view of safety.
10. This criterion is specified in view of safety, as a combination of antidepressants and electroconvulsive therapy is likely to lower the convulsive threshold.
11 to 13. These criteria are specified for appropriate assessment of efficacy.
14. This criterion is specified to minimize the risk of suicide during the trial.
15 to 17. These criteria are specified in view of safety.
18. This criterion is specified for appropriate assessment of efficacy, as subjects with thyroid disorders may have depressive symptoms.
19 to 21. These criteria are specified in view of safety.
22. This criterion is specified in view of safety, as the drug may lower the convulsive threshold.
23 to 27. These criteria are specified in view of safety.

New subjects
28. This criterion is specified in view of safety.
29,30 These criteria are specified for appropriate assessment of efficacy.
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. This criterion is specified in view of safety.
34. This criterion is specified in view of safety, as a combination of antidepressants and electroconvulsive therapy is likely to lower the convulsive threshold.
35 to 40. These criteria are specified for appropriate assessment of efficacy.
41. This criterion is specified to minimize the risk of suicide during the trial.
42 to 44. These criteria are specified in view of safety.
45. This criterion is specified for appropriate assessment of efficacy, as patients with thyroid disorders may have depressive symptoms.
46 to 48. These criteria are specified in view of safety.
49. This criterion is specified in view of safety, as the drug may lower the convulsive threshold.
50 to 54. These criteria are specified in view of safety.

3.5 Endpoints

3.5.1 Safety Endpoints

- Adverse events
- Physical examination
- Clinical laboratory tests
- Vital signs (body temperature, diastolic blood pressure, systolic blood pressure, and pulse rate [supine, sitting, and standing positions])
- Waist circumference
- 12-lead ECG
- Body weight
- Body mass index (BMI)
- Drug induced Extra-pyramidal Symptom Scale (DIEPSS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Columbia Suicide Severity Rating Scale (C-SSRS)

3.5.2 Efficacy Endpoints

- Mean changes from baseline in MADRS total scores
- MADRS response rate
  The proportion of subjects in whom MADRS total scores have been reduced by at least 50% from baseline
- MADRS remission rate
  The proportion of subjects in whom MADRS total scores have been reduced by at least 50% from baseline, with their resultant MADRS total scores being ≤ 10
- Clinical Global Impression — Improvement (CGI-I) improvement rate
  The proportion of subjects who score 1 or 2 on the CGI-I scale
- Mean changes from baseline in CGI-S
- Mean changes from baseline in Hamilton Rating Scale for Depression (HAM-D) 17-item total score
- Mean changes from baseline in mean Sheehan Disability Scale (SDS) score

[Rationale]

MADRS is used worldwide as a depression assessment scale, was created primarily to assess psychiatric symptoms of depression and exclude somatic symptoms, and is generally used in clinical trials that involve patients with major depressive disorder; therefore, the same endpoint will be employed in this trial also.

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 utilizing MADRS.

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.

3.5.3 Other Endpoints

- EuroQol-5 Dimension 5-level (EQ-5D-5L) questionnaire

3.6 Measures to Minimize/Avoid Bias

This is an uncontrolled trial.

3.7 Trial Procedures

The schedule of all examinations and assessments/observations in the screening period, treatment period, and post-treatment observation period is provided in Table 3.7-1.

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 clinical laboratory tests, a clinical trial associate can perform them under the supervision of the investigator.

Table 3.7-1 Schedule of Assessments

Test Period (Acceptable Window) / Items		Treatment Period																	Post-treatment observation period [j] 30 days after final dose (± 5 days)
	At screening (new subjects) [b]	At baseline (rollover subjects)	At baseline (new subjects)	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 16 (± 7 days)	Week 20 (± 7 days)	Week 24 (± 7 days)	Week 28 (± 7 days)	Week 32 (± 7 days)	Week 36 (± 7 days)	Week 40 (± 7 days)	Week 44 (± 7 days)	Week 48 (± 7 days)	Week 52 (± 7 days)	At discontinuation	
Acquisition of informed consent	•	•[d]																		
Eligibility judgement	•	•	•																	
Subject demographics	•	•[e]																		
MADRS		•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CGI-I				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CGI-S		•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
HAM-D		•[f]	•								•							•	•	
SDS		•[f]	•								•							•	•	
EQ-5D-5L questionnaire		•	•				•				•			•				•	•	
Laboratory tests	•[c]	•[c, f]				•	•		•		•		•		•			•[c]	•	
Vital signs	•	•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Physical examination	•	•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Waist circumference		•[f]	•			•	•		•		•		•		•			•	•	
Height	•	•[g]																		
Body weight	•	•[f]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	
12-lead ECG	•	•[f]	•			•	•		•		•		•		•			•	•	
Pregnancy test		•[f, h]					•[h]				•[h]				•[h]			•[h]	•[h]	
C-SSRS	•	•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
DIEPSS		•[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
AIMS		•[f]	•				•				•							•	•	
BARS		•[f]	•				•				•							•	•	
Blood sampling for DNA storage						•[i]													•[i]	

Table 3.7-1 Schedule of Assessments

Test Period (Acceptable Window) / Items	At screening (new subjects)[b]	Treatment Period: At baseline (rollover subjects)	At baseline (new subjects)	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 16 (± 7 days)	Week 20 (± 7 days)	Week 24 (± 7 days)	Week 28 (± 7 days)	Week 32 (± 7 days)	Week 36 (± 7 days)	Week 40 (± 7 days)	Week 44 (± 7 days)	Week 48 (± 7 days)	Week 52 (± 7 days)	At discontinuation	Post-treatment observation period[j] 30 days after final dose (± 5 days)
Adverse events	←----------																			----------→
IMP and requisite concomitant medication[a]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant drugs/ therapies	←----------																			----------→

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

[b] Clinical laboratory test values and body weight values at screening will be used as baseline values.

[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 screening, baseline, and Week 52, and in a fasting state to the extent possible at other times, including at the discontinuation examination.

[d] Informed consent will be obtained after the observations, examinations, and assessments at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) and before the baseline assessments for this trial.

[e] Data taken at screening for the double-blind trial (331-102-00058) will be used as the subject demographic data for rollover subjects (date of birth, sex, childbearing potential, race, ethnicity, country where trial is performed, history of major depressive disorder, medical history, complications). Medical history and complications will be reinvestigated.

[f] For rollover subjects, if the examinations and assessments at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) have been performed within a period of 7 days prior to the day of baseline assessment (Day −7 to Day 0), the data will be used as baseline data for this trial.

[g] For rollover subjects, data obtained at screening in the double-blind trial (331-102-00058) will be used.

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

[i] Blood sampling for DNA storage will be performed once only for new subjects who have provided written consent. Blood sampling will be performed at discontinuation only for subjects who discontinue before the Week 4 visit.

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

3.7.1 Schedule of Assessments

3.7.1.1 Informed Consent

Before all examinations, written informed consent is to be obtained from subjects. Rollover subjects will provide written informed consent after completion of the observations, examinations, and assessments at Week 6 of the preceding double-blind trial (331-102-00058). The procedures for progressing from the double-blind trial (331-102-00058) are separately specified in written procedures. After acquisition of informed consent, subjects will be registered in the interactive web response system (IWRS). For rollover subjects, the same subject ID will be used as in the double-blind trial (331-102-00058) and for new subjects a new subject ID will be assigned. 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 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 case report form (CRF).

3.7.1.2 Screening (New Subjects Only)

After acquisition of informed consent and within 28 days before commencement of the treatment period, the investigator or subinvestigator will perform the examinations and assessments at the screening (Table 3.7-1) and record the results in the source documents and CRF, and will also judge subject eligibility for trial participation. 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
  - 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 in the Treatment Period (52 Weeks)

The investigator or subinvestigator will judge eligibility of rollover subjects from the double-blind trial (331-102-00058), based on the results of examinations and assessments at baseline and clinical laboratory values and 12-lead ECG at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058). The treatment period will commence within 28 days from Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058). If the examinations and assessments at Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) have been performed within a period of 7 days prior to the day of baseline assessment (Day −7 to Day 0), the data will be used as baseline data for this trial. The eligibility of new subjects will be judged based on the results of examinations and assessments at screening and baseline. The result of the eligibility judgement will be registered in the IWRS and

recorded in the source documents and CRF. If subjects are judged to be eligible, the date of enrollment in the treatment period will be recorded in the source documents and CRF.

Eligible subjects will start receiving brexpiprazole at a starting dose of 1 mg/day, in an open-label manner.

The investigator or subinvestigator will perform examinations/assessments in the treatment period, as specified in the schedule of examinations/assessments (Table 3.7-1) and record the result along with the visit date 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 completion of IMP administration in Week 52.

3.7.1.4 Observations/Examinations in the Post-treatment Observation Period

For all subjects receiving the IMP, the investigator or subinvestigator will perform the assessments scheduled for the post-treatment observation period, as specified in the schedule of examinations/assessments (Table 3.7-1), 30 days (± 5 days) after final IMP administration and record the results along with the visit date 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 conclusion of the post-treatment observation period.

3.7.1.5 Examinations at Discontinuation

If a subject is withdrawn from the trial during the treatment period, the investigator or subinvestigator will perform the required examinations at discontinuation, as specified in the schedule of examinations/assessments (Table 3.7-1) and record the results along with the visit date 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.

3.7.1.6 Acceptable Window for Testing

Observations/examinations and other procedures are to be performed within an acceptable window for testing, as specified in Table 3.7.1.6-1, with consideration of the availability of each subject for site visits, etc.

Table 3.7.1.6-1 Acceptable Window for Examinations/Assessment Period		
Examination Point	**Reference Day**	**Acceptable Window (From the Reference Day)**
At screening (new subjects only)	**Day of baseline assessment**	**−28 to −1 days**
Day of baseline assessment	Day 1	–
Week 1 of the treatment period	Day 8	± 2 days
Week 2 of the treatment period	Day 15	± 2 days
Week 4 of the treatment period	Day 29	± 2 days
Week 8 of the treatment period	Day 57	± 7 days
Week 12 of the treatment period	Day 85	± 7 days
Week 16 of the treatment period	Day 113	± 7 days
Week 20 of the treatment period	Day 141	± 7 days
Week 24 of the treatment period	Day 169	± 7 days
Week 28 of the treatment period	Day 197	± 7 days
Week 32 of the treatment period	Day 225	± 7 days
Week 36 of the treatment period	Day 253	± 7 days
Week 40 of the treatment period	Day 281	± 7 days
Week 44 of the treatment period	Day 309	± 7 days
Week 48 of the treatment period	Day 337	± 7 days
Week 52 of the treatment period	Day 365	± 7 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 the final IMP administration	Day 1	–
The 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 baseline and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

(2) Method

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 the Structured Interview Guide for the MADRS (SIGMA) at 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, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

(2) Method

The investigator or subinvestigator will assess the improvement of depressive symptoms in the subject on the following 8-point scale using CGI-I at specified assessment time points, and record the date, time, and results of assessment 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 baseline and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

(2) Method

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 baseline and Weeks 24 and 52 (or discontinuation)

(2) Method

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 the HAM-D (SIGH-D) at specified assessment time points, and calculate the total score for Items No. 1 to 17, and record the date, time, and results of the 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 baseline and Weeks 24 and 52 (or discontinuation)

(2) Method

The investigator or subinvestigator will use the SDS at 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.

3.7.3 Other Assessments

3.7.3.1 EuroQol-5 Dimension

(1) Time points

At baseline and Weeks 8, 24, 36, and 52 (or discontinuation)

(2) Method

The investigator will use the EQ-5D-5L questionnaire at specified assessment time points and allow the subject self-assess their general health on the day of assessment, and record the date, time, and results of assessment in the source documents and the CRF. The EQ-5D-5L questionnaire consists of 2 parts: In Part 1, the subject will self-assess 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a scale of 1 to 5 (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = extreme problems); In Part 2, the subject will self-rate their health on a visual analog scale (0 = the worst health you can imagine, 100 = the best health you can imagine).

3.7.4 Safety Assessments

3.7.4.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.4.2 Clinical Laboratory Assessments

(1) Time points

At screening (new subjects only, in the fasting state), baseline (rollover subjects only, in the fasting state), Weeks 4, 8, 16, 24, 32, and 40 (in the fasting state to the extent possible), and Week 52 (in the fasting state) or discontinuation (in the fasting state to the extent possible)

(2) Method

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 screening (new subjects only), baseline (rollover subjects only), and Week 52, and in a fasting state to the extent possible at other time points including examination 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, 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 3.7.4.2-1 Clinical Laboratory Assessments

Hematology: Red Blood Cell count White blood cell count Differential count of white blood cells (neutrophils, eosinophils, basophils, monocytes, 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 a fasting state (a fast for at least 8 hours [including drinks containing sugar, such as juice]) at screening (new subjects only), baseline (rollover subjects only), and Week 52, and in a fasting state to the extent possible at other time points including examination at discontinuation

3.7.4.3 Vital Signs and Physical Examination

(1) Vital signs

(a) Time points

At screening (new subjects only), baseline, and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

(b) Method

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 (new subjects only), baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (discontinuation), and post-treatment observation

(b) Method

The investigator or subinvestigator will perform a physical examination that includes assessment items shown below through a medical interview and other relevant methods and record physical findings in the source documents. At screening (new subjects) and baseline (rollover subjects), the date and results of examination will be recorded, and at baseline (new subjects) and from Week 1 (rollover subjects) onward, only the date of examination will be recorded in the source documents and the CRF. Any clinically significant physical findings compared with findings at screening (new subjects) or baseline (rollover subjects) are to be recorded as AEs.
Assessment items: HEENT (head, eyes, ears, nose, and throat), chest, abdomen, urogenital system, limbs, nerves, skin, and mucosa.

(3) Waist circumference

(a) Time points

At baseline and Weeks 4, 8, 16, 24, 32, 40, and 52 (or discontinuation)

(b) Method

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 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 on the source documents and the CRF.

(4) Height and body weight

(a) Time points

At screening (new subjects only), baseline (rollover subjects only), and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

However, height will be measured only at screening (new subjects only).

(b) Method

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).

3.7.4.4 12-Lead Electrocardiography

(1) Time points

At screening (for new subjects only), baseline, and Weeks 4, 8, 16, 24, 32, 40, and 52 (or discontinuation)

(2) Method

The investigator or subinvestigator will perform electrocardiography 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 judgment, and abnormal findings in the source documents and the CRF. The original of the 12-lead ECG chart will be kept in the medical records 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/$(\text{RR interval})^{1/2}$, QTcF = QT interval/$(\text{RR interval})^{1/3}$, QTcN = QT interval/$(\text{RR interval})^{0.37}$], 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.

3.7.4.5 Pregnancy Test

(1) Time points

At baseline and Weeks 8, 24, 40, and 52 (or discontinuation)

(2) Method

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 (except for test at baseline), another pregnancy test will be performed using serum 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).

3.7.4.6 Columbia-Suicide Severity Rating Scale

(1) Time points

At screening (new subjects only), baseline, and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation), and post-treatment observation

(2) Method

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 damage is 0, “potential lethality” will be rated on a 3-point scale.

Suicidal ideation: 1. Wish to be dead 2. Non-specific active suicidal thoughts

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

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

5. Active suicidal ideation with specific plan and intent

Suicidal behavior: Actual attempt Non-suicidal self-injurious behavior

Interrupted attempt Aborted attempt Preparatory acts or behavior Suicidal behavior

Suicide (only for "Since Last Visit Version")

3.7.4.7 Drug-induced Extrapyramidal Symptoms Scale

(1) Time points

At baseline and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or discontinuation)

(2) Method

The investigator or subinvestigator will assess the following 9 items related to extra-pyramidal symptoms on a 5-point scale ranging from 0 (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	

3.7.4.8 Abnormal Involuntary Movement Scale

(1) Time points

At baseline and Weeks 8, 24, and 52 (or discontinuation)

(2) Method

Using AIMS, the investigator or subinvestigator will assess the severity of abnormal involuntary movements 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.

3.7.4.9 Barnes Akathisia Rating Scale

(1) Time points

At baseline and Weeks 8, 24, and 52 (or discontinuation)

(2) Method

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 "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.

3.7.5 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 (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 CRF.

- Prior medications and therapies (new subjects)
  - 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
- Prior medications and therapies (rollover subjects)
  - All prior medications and therapies used after Week 6 of the double-blind period (Phase B) in the double-blind trial (331-102-00058)
- Concomitant medications and therapies
  - Concomitant medications and therapies used during the trial (including treatments for AEs)

3.7.6 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 commencement of the treatment period and record the consumed daily dose and start and end dates of treatment 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%.

3.7.7 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 for rollover subjects and SSRI, SNRI, or mirtazapine for new subjects), during the interval between 2 consecutive scheduled visits after commencement of the treatment period and record the name of drug, prescribed daily dose, consumed daily dose, and start and end dates of treatment in the source documents and the CRF.

3.7.8 Pharmacogenomic Assessments

3.7.8.1 DNA Storage (for New Subjects Only)

3.7.8.1.1 Objective of DNA Storage

DNA storage will be conducted to enable future exploratory investigation regarding the relationships between specific DNA mutations and individual differences in the efficacy, safety, or pharmacokinetics of brexpiprazole, and/or the relationships between specific DNA mutations and disease onset, severity, progression, etc.

3.7.8.1.2 Target Subjects of DNA Storage

New subjects from whom written informed consent for DNA storage has been obtained will be included. Consent to DNA storage is voluntary. DNA storage will be conducted only if approved by the trial site’s IRB, etc. Informed consent for DNA storage must be obtained prior to blood sampling for DNA storage.

3.7.8.1.3 Timing of Blood Sampling

Blood sampling will be performed at Week 4 of the treatment period (or at discontinuation if a subject withdraws before the Week 4 visit). If resampling of blood, if necessary, it will be performed during the trial period.

3.7.8.1.4 Handling of Samples

All blood samples will be shipped to the DNA storage facility. The timing of blood sampling will be recorded in the source documents and CRF. Details regarding handling and shipment of samples are described in Appendix 1. DNA samples will be stored until the earliest of the following time points: 1) when genomic/genetic analysis is judged to be unnecessary, 2) when 15 years have passed since receipt of informed consent from the first subject, 3) when the subject withdraws consent to DNA storage.

3.7.8.1.5 Genomic/Genetic Analysis

Genomic/genetic analysis will be performed only when exploratory investigation regarding the relationships between specific DNA mutations and individual differences in

the efficacy, safety, or pharmacokinetics of brexpiprazole and/or the relationships between specific DNA mutations and disease onset, severity, progression, etc is considered to be useful.

If it is decided to perform genomic/genetic analysis, a pharmacogenomic research protocol will be prepared and, after approval has been obtained from the sponsor's IRB, the analysis will be carried out in compliance with the regulations of each country regarding analysis plans.

Genes that may be targeted in genomic/genetic analysis include genes considered to be possibly related to individual differences in the efficacy, safety, or pharmacokinetics of brexpiprazole and genes considered to be possibly related to diseases; however, at present those genes have not yet been identified.

A genomewide association analysis using DNA chips, microarrays, next-generation sequencers, etc, may also be performed for genomic/genetic analysis; however, the results will still only be used for the purpose of identifying genes possibly related to individual differences in the efficacy, safety, or pharmacokinetics of brexpiprazole and/or the relationships between specific DNA mutations and disease onset, severity, progression, etc. The results of genomic/genetic analysis will be reported to the sponsor by the genomic/genetic analysis facility while the samples are still double-coded.

3.7.8.1.6 Informed Consent for DNA Storage

An ICF for DNA storage and genomic/genetic analysis using stored DNA will be prepared separately from the ICF for the trial, and written informed consent to DNA storage will be obtained from each subject in person. The date of informed consent will be recorded in the source documents and CRF.

If the subject withdraws consent to participate in DNA storage during the DNA storage period, the sponsor will instruct the DNA storage facility to dispose of the subject's DNA. However, withdrawal from the trial will not be considered withdrawal of consent for DNA storage. Upon receipt of a notification for disposal from the sponsor, the DNA storage facility will dispose of the DNA sample without anyone being aware of whose sample it is. Any results of genomic/genetic analysis obtained prior to the withdrawal of consent will not be disposed of.

3.7.8.1.7 Disclosure of Genomic/Genetic Analysis Results to Subjects

In this trial, genomic/genetic analysis will be performed for genes considered to be possibly related to individual differences in the efficacy, safety, or pharmacokinetics of brexpiprazole, and/or genes considered to be possibly related to diseases; however, even if the analysis results show some relationship, such a relationship would only be

exploratory or at an early stage of research, and therefore its scientific reliability and accuracy would not have been fully confirmed. Since disclosure of information for which scientific evaluation has not yet been verified would be of no benefit to the subjects, the sponsor will not disclose the results of genomic/genetic analysis to the subjects.

3.7.9 End of Trial

The end of trial date is defined as the date of last visit or contact or date of final contact attempt as recorded on the post-treatment 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, 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) Subject can no longer be administered antidepressant (SSRI or SNRI for rollover subjects and SSRI, SNRI, or mirtazapine for new subjects)
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, 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 treatment period of the trial. 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 screen failure

New 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 received 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 52 of the treatment period 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 52 of 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 undergo post-treatment observation 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 their compliance with the protocol.

1) Site visits are to be made on the scheduled visit days as specified in the protocol (see Section 3.7.1.6).
2) No prohibited concomitant drugs are to be taken during the period from informed consent to Week 52 of the treatment period (or discontinuation).
3) No commercially available brexpiprazole is to be taken during the period from the assessment at Week 52 of the treatment period (or discontinuation) to the end of 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 the 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 measures 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

4.1 Prohibited Concomitant Medications

For appropriate assessment of the efficacy and safety of brexpiprazole, use of the drugs shown below is prohibited. However, in cases where rollover subjects have been using such drugs after Week 6 of the double-blind period (Phase B) of the double-blind trial (331-102-00058) or new subjects are using them during the screening period of this trial at the discretion of the investigator or subinvestigator, their dose should be gradually reduced and then discontinued by the following prohibition period:

- From 1 week prior to commencement of the treatment period through the end of the treatment period
  - Benzodiazepines (excluding ultrashort-acting sedative-hypnotic drugs)
    *Necessary washout period: 7 days
- From 2 weeks prior to commencement of the treatment period through the end of the treatment period
  - MAO inhibitors
    *Necessary washout period: 14 days
- From24 hours before commencement of the treatment period through the end of the treatment period

  - 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: Caution should be exercised to avoid concomitant use of CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers specified in Section 4.4 Other Restrictions (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
  - Drugs not approved in Japan
- During the 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.

- 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

The use of the following drugs is restricted during the treatment period.

- 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. The concomitant use of only one of the aforementioned drugs is allowed during the treatment period; 2 or more drugs are not to be coadministered simultaneously. Change in the types of the aforementioned drugs is allowed.
- Anticholinergic drugs for Parkinson's disease
  Anticholinergic drugs for Parkinson's disease, for which concomitant use during the treatment period 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

  Concomitant use is allowed if subjects were already using the drugs at the time of informed consent to treat complications; 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 as a medication for colds during the treatment period, is also allowed. The topical external use of these drugs is allowed.
  Note: Caution should be exercised to avoid concomitant use of CYP2D6 inhibitors, CYP3A4 inhibitors, and CYP3A4 inducers specified in Section 4.4 Other Restrictions (eg, chlorpheniramine, diphenhydramine, clemastine, and celecoxib).

- β-Blockers

  During the treatment period, 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.

4.4 Other Restrictions

CYP2D6 inhibitors, CYP3A4 inhibitors and inducers, food products containing St. John's wort, and grapefruit, star fruit, Seville orange, and their juice and other processed products are likely to affect the pharmacokinetics of brexpiprazole and potentiate or reduce its effects. Caution should be exercised to avoid the consumption of these drugs and foods.

– CYP2D6 inhibitors (excluding topical agents in the dosage forms permitted for concomitant use as specified in Appendix 2):

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 2):

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 2):

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

- Foods and beverages: Food products containing St. John's wort, and grapefruit, star fruit, Seville orange, and their juice and other processed products

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 new subjects) or baseline (for rollover subjects) for preplanned procedures for which the underlying condition was known and no worsening occurred. For rollover subjects, AEs that occurred during the double-blind trial (331-102-00058) and persist without recovery or resolution, but have not become exacerbated, will not be counted as AEs occurring in this trial. 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.

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

Not applicable.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded 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 Pharmacogenomic Analysis

6.1 Pharmacogenomic Methods

Refer to Section 3.7.8.1.5 Genomic/Genetic Analysis for genomic/genetic analysis.

7 Statistical Analysis

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

7.1 Sample Size

To verify the safety of long-term administration, the target number of subjects to complete 52 weeks of administration was set at around 100 subjects. Due to the availability of data on safety in elderly subjects from foreign clinical trials, the sample size needed to assess the safety of brexpiprazole in the elderly was set as 30 new subjects (elderly subjects of age 65 and above) receiving IMP administration.

7.2 Datasets for Analysis

7.2.1 Efficacy Analysis Set

The efficacy analysis set will comprise subjects who have received at least 1 dose of the IMP, and from whom MADRS total scores have been obtained at baseline and at least 1 time point after initiation of the treatment.

7.2.2 Safety Analysis Set

The safety analysis set will comprise subjects who have received at least 1 dose of the IMP.

Unless otherwise specified, analysis will be performed for each of the following groups:

- Rollover subjects from the double-blind trial (331-102-00058) who were assigned to the brexpiprazole groups in the double-blind period (Phase B)
- Rollover subjects from the double-blind trial (331-102-00058) who were assigned to the placebo group in the double-blind period (Phase B)
- All rollover subjects from the double-blind trial (331-102-00058)
- New subjects (elderly subjects aged 65 years or older)
- All subjects (rollover and new subjects combined)

7.3 Handling of Missing Data

The analysis of last assessment time point will be performed using the last observation carried forward method (herein after referred to as "LOCF"), by which missing data at Week 52 will be imputed by the last observed data after initiation of IMP treatment.

7.4 Efficacy Endpoint Analysis

Efficacy analysis will be performed using the efficacy analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in the trial.

- MADRS total score
- CGI-S
- HAM-D 17 total score
- Mean SDS score

Descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 52 LOCF) will be determined.

- MADRS response rate
- MADRS remission rate
- CGI-I improvement rate

Numbers and proportions of subjects will be determined at each time point and the last assessment time point (Week 52 LOCF).

7.5 Analysis of Other Endpoints

- EQ-5D-5L
  For each item, descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 52 LOCF) will be determined.

7.6 Analysis of Demographic and Baseline Characteristics

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

7.7 Safety Analysis

Safety analysis will be performed using the safety analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in the trial.

7.7.1 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:

- Adverse events occurring after initiation of IMP administration (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.

7.7.2 Clinical Laboratory Data

For each quantitative laboratory parameter, descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 52 LOCF) will be calculated.

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 qualitative laboratory parameter, a shift table from baseline will be produced.

Numbers and proportions of subjects with potentially clinically significant laboratory test values will be determined.

7.7.3 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 and the last assessment time point (Week 52 LOCF) will be calculated.

Numbers and proportions of subjects with potentially clinically significant vital signs will be determined.

7.7.4 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 and the last assessment time point (Week 52 LOCF) will be calculated.

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

Numbers and proportions of subjects with actual measurements of corrected QT interval (QTcF, QTcB, QTcN) at each time point and the last assessment time point (Week 52

LOCF) of > 450 msec, > 480 msec, and > 500 msec will be determined. Numbers and proportions of subjects with changes from baseline of > 30 msec and > 60 msec will be determined.

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

7.7.5 Other Safety Data

- Body weight, BMI, and waist circumference
  For body weight, BMI, and waist circumference, descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 52 LOCF) will be calculated.
  Numbers and proportions of subjects with results meeting the criteria for potentially clinically significant body weight gain or loss will be determined.
- DIEPSS, AIMS, and BARS
  For DIEPSS total score (total of scores for items 1 through 8) and the score for each DIEPSS item, AIMS total score (total of scores for items 1 through 7) and the score for each of the items 8 through 10, and BARS, descriptive statistics of actual measurements and changes from baseline at each time point and the last assessment time point (Week 52 LOCF) will be calculated.
- 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 and the last assessment time point (Week 52 LOCF) will be determined

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

The IMP will be provided to the IMP manager by the sponsor or designated agent. The IMP will be supplied as blister cards. Each blister card used in the dosing period will be labeled to clearly indicate that the drug is for clinical trial use and to disclose the subject ID, compound ID, the protocol number, sponsor's name and address, route of administration, manufacturing number, expiry date, storage conditions, etc.

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, destroyed, or returned.

8.4 Returns and Destruction

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

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original blister cards. 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: PQC_331-102-00059@otsuka.jp)

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

8.5.2 Information Required for Reporting Product Quality Complaints

- 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 progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the 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 three 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

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.

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