Table of Contents

Protocol 331-201-00079

Otsuka Pharmaceutical Development & Commercialization, Inc.
Investigational Medicinal Product

Brexpiprazole (OPC-34712)
REVISED CLINICAL PROTOCOL

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole as Adjunctive Therapy in the Maintenance Treatment of Adults With Major Depressive Disorder.

Protocol No. 331-201-00079
IND No. 103,958
EudraCT No. 2018-000601-22

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Sponsor Representatives: Director Global Clinical Development	[redacted]
Director, Clinical Management	[redacted]
Senior Manager, Clinical Management	[redacted]
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety Fax: 877-464-7787 Email: incdrugsafety@incresearch.com
Issue Date: Date of Amendment 1: Date of Amendment 2:	23 Feb 2018 15 Jun 2018 08 Jul 2020

Protocol 331-201-00079

Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it related to COVID-19. If any protocol specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol 331-201-00079

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-201-00079 IND No.: 103,958 EudraCT No.: 2018-000601-22
Protocol Title:	A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of brexpiprazole as adjunctive therapy in the maintenance treatment of adults with major depressive disorder.
Clinical Phase/Trial Type:	3, Therapeutic confirmatory
Treatment Indication:	Major depressive disorder
Objectives:	Primary: To compare the efficacy of brexpiprazole (2 to 3 mg/day) to placebo as adjunctive therapy to antidepressant therapy (ADT) for the maintenance treatment in adults with major depressive disorder (MDD). Secondary: To evaluate the safety and tolerability of brexpiprazole (2 to 3 mg/day) as adjunctive therapy to ADT in the proposed subject population with MDD.
Trial Design:	This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety, efficacy, and tolerability of brexpiprazole (2 to 3 mg/day) as adjunctive therapy to protocol-specified open-label ADT in subjects with a diagnosis of a current major depressive episode of at least 8 weeks in duration with an inadequate response to 1 or 2 adequate ADTs. The trial will be organized as follows: • *Screening Period*: The screening period will range from a minimum of 3 days to a maximum of 6 weeks and will begin when informed consent is signed. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to allow subjects to continue their current ADT for an adequate duration, if needed. • *Acute Treatment Phase (Phase A)*: Subjects will be enrolled into a 6- to 8-week single-blind Acute Treatment Phase (Phase A) if they meet the entrance criteria. The purpose of this phase is to identify subjects who respond to

	adjunctive brexpiprazole + protocol-specified ADT. Treatment will consist of single-blind brexpiprazole plus continuation of the ADT taken during the screening period. The investigator should titrate to the dose of brexpiprazole that optimizes efficacy with the protocol-specified ADT with minimum tolerability issues. Subjects will attend weekly visits during the Acute Treatment Phase and will be evaluated at Weeks 6 to 8 to determine whether they meet response criteria as defined in the blinded addendum to the protocol. Subjects not meeting response criteria by the Week 8 visit will be discontinued from the trial. • *Stabilization Phase (Phase B)*: Subjects who meet response criteria at the end of the Phase A will continue to a 12-week Stabilization Phase (Phase B). The purpose of this phase is to ensure subjects are able to maintain stability of depression symptoms at the dose of brexpiprazole optimized during Phase A. To proceed to the Double-blind Randomized Withdrawal Phase (Phase C), subjects must meet the stability criteria as defined in the blinded addendum to the protocol. Subjects not meeting stability criteria will be discontinued from the trial. • *Double-blind Randomized Withdrawal Phase (Phase C)*: Subjects eligible for the Double-blind Randomized Withdrawal Phase will be randomized 1:1 to double-blind treatment with brexpiprazole + ADT or placebo + ADT for up to 26 weeks. Transition from the Stabilization Phase to the Double-blind Randomized Withdrawal Phase should not be made evident to the subject. During the Double-blind Randomized Withdrawal Phase, subjects will be evaluated in the clinic at biweekly visits for the first 2 visits and at monthly visits thereafter. Subjects meeting the criteria for relapse will be withdrawn due to lack of efficacy. • *Follow-up*: Subjects who are discontinued, withdrawn, or complete the trial will be followed up for safety 21 (+2) days after the last dose of investigational medicinal product (IMP) by telephone contact or clinic visit at the investigator's discretion. Subjects should be prescribed appropriate depression treatment as per the investigator or the subject's psychiatrist or primary care physician.
Subject Population:	Male and female outpatients between 18 and 65 years, inclusive, with a diagnosis of recurrent MDD and a current major depressive episode of at least 8 weeks in duration with an inadequate response to 1 or 2 adequate ADTs, and currently taking protocol-mandated ADTs at an adequate dose.

Protocol 331-201-00079

	Adequate treatment is defined as an ADT taken for at least 6 weeks in duration at a minimum dose (or higher) as specified in the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ). Inadequate response is defined as < 50% reduction in depressive symptom severity, as assessed by the ATRQ.

Inclusion/Exclusion Criteria:	Key inclusion criteria include the following:
	• Subjects with both a diagnosis of recurrent MDD, and in a current major depressive episode of ≥ 8 weeks in duration, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by both the MINI and an adequate clinical psychiatric evaluation.
	• Subjects must have reported a history for the current major depressive episode of an inadequate response to 1 or 2 adequate antidepressant treatments, and subjects must currently be taking a protocol-mandated antidepressant treatment at an adequate dose and duration, and must not have reported ≥ 50% improvement (as defined by the ATRQ). For subjects who are currently on an adequate dose of a protocol mandated ADT but for an inadequate duration, the screening period may be used to achieve adequate duration. At Phase A baseline, all subjects must have either 2 or 3 documented inadequate responses to antidepressant treatment for the current episode as defined by the ATRQ.
	• Subjects with a 17-item Hamilton Depression Rating Scale (HAM-D17) total score ≥ 18 at the screening and Phase A baseline visits.
	
	Key exclusion criteria include the following:
	• Subjects with a primary DSM-5 diagnosis of:
	  • Schizophrenia Spectrum and Other Psychotic Disorders
	  • Bipolar and Related Disorders
	  • Obsessive compulsive disorder
	  • Feeding and Eating Disorders (including anorexia nervosa or bulimia)
	  • Neurocognitive disorders (including but not limited to: Delirium, Major or Mild Neurocognitive Disorder due to: Alzheimer's, Parkinson's, Traumatic Brain Injury)
	  • Panic disorder
	  • Post-traumatic stress disorder

Protocol 331-201-00079

	• Subjects with a current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal or histrionic personality disorder or intellectual disability Please see the complete list of inclusion and exclusion criteria.
Trial Sites:	It is anticipated that approximately 2100 subjects will be screened from approximately 75 sites to enroll approximately 1450 subjects into Phase A in order to enroll approximately 700 in Phase B and randomize 450 subjects in Phase C.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Treatment will consist of oral brexpiprazole plus 1 of 7 protocol-specified oral ADTs: citalopram hydrobromide (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules. Subjects will be on an adequate treatment as specified in the ATRQ. Brexpiprazole doses will be 2 to 3 mg/day depending on tolerability assessed during dose titration in Phase A. Doses of each ADT are listed in the protocol.
Trial Assessments:	Efficacy: Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression - Severity of Illness Scale (CGI-S), and Sheehan Disability Scale (SDS) Pharmacokinetic, Pharmacogenomics, [redacted] plasma concentrations of brexpiprazole, cytochrome P450 (CYP) 2D6 metabolizer activity, [redacted] Safety: Adverse event (AE) reporting, clinical laboratory tests, 12-lead electrocardiogram, vital signs, physical examination, Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Columbia-Suicide Severity Rating Scale (C-SSRS) Screening/Other: HAM-D17, Mini International Neuropsychiatric Interview (MINI), ATRQ, medical and medication history, psychiatric history, urine drug screening, urine pregnancy test
Criteria for Evaluation:	Primary Endpoint: The primary endpoint is time-to-relapse by any criteria as defined in the blinded addendum to this protocol.

Protocol 331-201-00079

	Key Secondary Endpoints: • Change from randomization in the SDS mean total score at Week 46 (last observation carried forward) • Time-to-functional relapse based on SDS criteria
Statistical Methods:	The objective of the primary analysis is to compare the efficacy of brexpiprazole (2 to 3 mg/day) + ADT with that of placebo + ADT with regard to time-to-relapse. The statistical comparison will be performed by the log-rank test comparing the 2 treatment groups (brexpiprazole + ADT versus placebo + ADT) at an overall nominal significance level of 0.05 (2-sided) using the Double-blind Randomized Withdrawal (Phase C) Efficacy Sample. Assuming that each subject will be followed for up to 26 weeks after randomization (Week 20) or until relapse, and allowing for a 20% loss to follow-up, the projected total number of subjects to be randomized into the trial (Phase C) is 450. Using a 1:1 randomization ratio, the number of subjects to be randomized into each treatment group is 225. Assuming approximately 68% of subjects will progress from Stabilization Phase to Double-blind Randomized Withdrawal Phase, it is expected that approximately 700 subjects will be enrolled into Stabilization Phase of the trial to allow 450 subjects to be randomized. Assuming approximately 55% subjects will progress from the Acute Treatment Phase to the Stabilization Phase, it is expected that approximately 1450 subjects will be enrolled into the Acute Treatment Phase. However, only the number of relapse events (ie, 104 events) is the hard sample size in this protocol. The other estimates, such as number of randomized subjects and number of subjects entering the Acute Treatment Phase and the Stabilization Phase, are only based on projections using assumptions that may or may not hold in this trial. Therefore, the actual number of subjects enrolled into the Acute Treatment Phase, the Stabilization Phase, or Double-blind Randomized Withdrawal Phase may vary from the projected values.
Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 39 months, of which approximately 22 months are allotted for recruitment of subjects. Individual participation for subjects who complete the trial without early withdrawal will range from 47 to 55 weeks, consisting of a 3-day up to 6-week screening period, a 6- to 8-week single-blind Acute Treatment Phase, a 12-week single-blind Stabilization Phase, and up to 26-week

Protocol 331-201-00079

	Double-Blind Randomized Withdrawal Phase, and a 21 (+ 2)-day follow-up.

Protocol 331-201-00079

Table of Contents

Protocol 331-201-00079

Protocol 331-201-00079

Protocol 331-201-00079

Protocol 331-201-00079

List of In-text Tables

Protocol 331-201-00079

List of In-text Figures

Protocol 331-201-00079

List of Appendices

Protocol 331-201-00079

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin, 5-hydroxytryptamine
ADHD	Attention deficit/hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	activated prothromplastin time
AST	Aspartate aminotransferase
ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
BARS	Barnes Akathisia Rating Scale
BUN	Blood urea nitrogen
CGI-S	Clinical Global Impression - Severity of Illness
CR	Controlled release
CRA	Clinical research associate
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CST	Clinical Surveillance Team
CYP	Cytochrome P450
D	Dopamine
DBP	Diastolic blood pressure
DILI	Drug Induced Liver Injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
ET	Early termination
EudraCT	European Clinical Trial Data Base
[redacted]	[redacted]
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
HAM-D17	Hamilton Depression Rating Scale 17-Item
HbA1c	Glycosylated hemoglobin
HIV	Human immunodeficiency virus
IARC	Interim Analysis Review Committee
IB	Investigator's Brochure
ICF, eICF	Informed consent form, electronic informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent ethics committee

IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
K_i	Inhibition constant
LDH	Lactic dehydrogenase
LOCF	Last observation carried forward
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
OC	Observed case
OPC	Otsuka Pharmaceutical Co.
OTC	Over-the-counter
PE	Physical examination
PK	Pharmacokinetic
PQC	Product quality complaint
PT	Prothrombin time
PTSD	Post-traumatic stress disorder
QTcF	QT interval ,corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SDS	Sheehan Disability Scale
SIGH-D	Structured Interview Guide for the Hamilton Depression Rating Scale
T_4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
US	United States
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
XR	Extended release

1 Introduction

Major depressive disorder (MDD) is a serious medical illness associated with significant suicide risk and marked disability. Despite the availability of numerous treatments (eg, pharmacotherapy, cognitive behavioral psychotherapy, electroconvulsive therapy), achievement of consistent and favorable long-term outcomes remains challenging. Although there are different classes of antidepressants, most patients with MDD do not achieve adequate response or remission. Most patients with MDD will experience relapses and recurrences, and the risk of recurrence increases with every successive major depressive episode.[1,2]

In the STAR*D trial, 51.4% and 71.5% of patients did not respond adequately to first- and second-line treatment, respectively, with 83.7% still not achieving response after 4 courses of treatment. One-third of patients did not achieve remission after as many as 4 different treatment strategies.[3,4,5,6] Patients who fail to achieve a full remission have a more recurrent and chronic course, increased medical and psychiatric comorbidities, and greater functional burden.[7]

Practice guidelines emphasize the importance of adequate treatment for MDD, including continuation of pharmacotherapy after an initial response is achieved to prevent relapse and maintenance treatment in individuals at risk of recurrence.[2] Second-generation antipsychotics such as aripiprazole and quetiapine have been shown to be associated with significant clinical improvements in patients who had not experienced an adequate response to prior antidepressant medications[8,9,10,11]; however, the side effect profiles of currently approved products may be unacceptable to many patients, subsequently limiting their use in clinical practice.[12] Consequently, there has been an ongoing medical need to identify adjunctive strategies that offer the efficacy of second-generation antipsychotics, while reducing the frequency and burden of side effects.

Brexpiprazole (OPC-34712 and Lu AF41156) is a novel atypical antipsychotic synthesized by Otsuka that is being codeveloped by Otsuka and Lundbeck. Brexpiprazole is currently approved in the United States (US), Canada, and Australia as monotherapy for the treatment of schizophrenia and in the US for use as an adjunctive therapy to antidepressants for the treatment of MDD. Brexpiprazole is a serotonin (5-hydroxytryptamine [5-HT]) –dopamine (D) activity modulator which is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors, and an antagonist at serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all with subnanomolar potencies.

Protocol 331-201-00079

1.1 Nonclinical Data

Efficacy and safety pharmacology of brexpiprazole are summarized in Section 1.1.1 and Section 1.1.2. A complete description of the available data from nonclinical studies, including pharmacokinetic and toxicology studies in different animal species can be found in the Investigator's Brochure (IB).[13]

1.1.1 Efficacy Pharmacology

While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (inhibition constant [K_i]: 0.1 - 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ with affinity in the same subnanomolar K_i range (K_i: 0.2 - 0.6 nM). The 5 HT_{1A}/D_2 receptor partial agonist activity in combination with 5 HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy. These mechanisms of actions have previously shown activity in preclinical models for MDD.

Please refer to the IB[13] for more detailed information.

1.1.2 Safety Pharmacology

Please refer to the IB[13] for information.

1.2 Clinical Data

As of 17 Apr 2017, the brexpiprazole clinical development program consisted of a total of 68 clinical trials conducted in North America, Latin America, Europe, and Asia (60 completed and 8 ongoing). This total includes 61 trials conducted under United States (US) Investigational New Drug Applications (INDs) (54 completed and 7 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of attention-deficit/hyperactivity disorder (ADHD), agitation associated with dementia of the Alzheimer's type, or post-traumatic stress disorder (PTSD); and 7 non-US IND trials (6 completed and 1 ongoing in either South Korea or Japan) conducted in healthy subjects and subjects with schizophrenia.

Please refer to the IB[13] for more detailed information.

Protocol 331-201-00079

1.2.1 Pharmacokinetics/Pharmacodynamics

The pharmacokinetics (PK) of single and multiple doses of brexpiprazole was studied in healthy subjects and in subjects with MDD, ADHD, and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, brexpiprazole and 1 metabolite, DM-3411, were identified as the major analytes that are present in human plasma. In vitro, the activity of DM-3411 is 17 times lower than that of brexpiprazole and thus is considered a minimally active metabolite. Both brexpiprazole and DM-3411 pharmacokinetics were linear in healthy subjects following single oral doses of brexpiprazole 0.2 to 6.0 mg. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Steady state PK was linear following multiple daily doses of brexpiprazole in the range of 0.5 to 2.0 mg to healthy subjects. The accumulation factor based on maximum (peak) plasma concentration (C_{max}) and area under the concentration time curve calculated to the last observable concentration at time t (AUC_t) was approximately 4 times. After multiple dose administration of brexpiprazole (1.0 to 12.0 mg/day) to subjects with schizophrenia or schizoaffective disorder, brexpiprazole and DM-3411 mean terminal elimination half-life at steady state was 95.4 and 89.3 hours, respectively; median t_{max} was 3.0 and 8.0 hours, respectively.

In drug interaction trials in healthy subjects, brexpiprazole was shown to be metabolized by cytochrome P450 (CYP) 3A4 and CYP2D6 isozymes and was not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein. Coadministration of potent CYP3A4 or CYP2D6 inhibitors with brexpiprazole resulted in about a 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half-life of brexpiprazole. Of note, administration of brexpiprazole with fluoxetine, paroxetine, and duloxetine (medications for treatment of MDD coadministered in this trial) may potentially increase brexpiprazole plasma concentrations by up to 2-fold. Pharmacokinetic interactions with ADTs that are strong inhibitors of CYP2D6 are described in Section 2.2.

In a single-dose trial in healthy subjects, approximately 46.0% and 24.6% of administered radioactivity following an oral dose of ^{14}C-brexpiprazole was excreted in feces and urine, respectively. In this same trial, brexpiprazole did not preferentially bind to red blood cells. Brexpiprazole showed high protein binding in human serum (≥ 99.8%) in vitro.

The binding of brexpiprazole to dopamine receptors was assessed using positron emission tomography. The mean D_2/D_3 receptor occupancies at 4 and 24 hours postdose after 0.25, 0.5, 1.0, 2.0, 4.0, 5.0, and 6.0 mg single-dose administration of brexpiprazole

to healthy subjects were 11.4% to 17.4%, 36.5% to 46.3%, 45.6% to 60.2%, 52.7% to 68.6%, 67.9% to 79.5%, 71.9% to 88.2%, and 69.5% to 92.6%, respectively (Trial 331-07-202). Based on the single-dose D_2/D_3 receptor occupancy data and steady-state PK/pharmacodynamic (PD) modeling, it was predicted that the D_2/D_3 receptor occupancy after multiple daily dose administration of 1.0 to 2.0 mg and higher doses of brexpiprazole will result in at least 80% to 90% D_2/D_3 receptor occupancy.

Population PK analysis of phase 1 through phase 3 trials demonstrated no differences in the PK of brexpiprazole between healthy subjects, subjects with MDD, and subjects with either schizophrenia or schizoaffective disorder (in phase 1 trials).

Please refer to the IB for more detailed information.[13]

1.2.2 Major Depressive Disorder

The data derived from 6 adequate and well-controlled short-term trials provides evidence that brexpiprazole 2 mg/day and 3 mg/day is efficacious as adjunctive treatment in adults with MDD who had a persistent inadequate response to antidepressant therapy (ADT).

Please refer to the IB[13] for more detailed information.

1.3 Known and Potential Risks and Benefits

Phase 1 data indicated that brexpiprazole demonstrated good safety and tolerability when administered to healthy volunteers at single doses of 0.2 to 6 mg and at a repeated dose of 2 mg/day. Data from completed repeated dosing trials in the US indicate that brexpiprazole demonstrated good tolerability when administered to subjects with schizophrenia or schizoaffective disorder at doses of up to 12 mg/day; when administered to subjects with MDD at doses of up to 4 mg/day in combination with a marketed antidepressant; up to 3 mg/day as adjunctive therapy in elderly subjects (70 - 85 years of age) with MDD; and when administered to subjects with ADHD at doses of up to 4 mg/day in combination with a marketed stimulant.

Please refer to the current IB[13] for a summary of available nonclinical and clinical safety data.

2 Trial Rationale and Objectives

2.1 Trial Rationale

This trial is a phase 3, double-blind, placebo-controlled, randomized withdrawal maintenance trial of brexpiprazole in subjects who require adjunctive treatment of MDD designed to fulfill a post-marketing commitment to the US Food and Drug

Administration (FDA). There is a paucity of data on long-term use of the combination of ADT and an antipsychotic drug; only 2 studies have been published.[14,15] The trial will assess long-term benefit of continuation of adjunctive therapy in subjects who achieve a level of clinical stabilization. The design is similar to that used in other trials for the evaluation of antipsychotic drugs in long-term management of MDD.[14]

Efficacy and safety of brexpiprazole 2 mg/day and 3 mg/day have been demonstrated in subjects with MDD who had an inadequate response to ADT in four phase 3, short-term fixed- and flexible-dose clinical trials with a 6-week double-blind placebo-controlled treatment phase. A single long-term trial with a 24-week double-blind, placebo-controlled treatment phase was conducted in inadequate responders and failed to demonstrate efficacy in terms of full remission with adjunctive brexpiprazole at flexible doses of 1 to 3 mg/day; however, safety and tolerability were seen over this long-term period.

2.2 Dosing Rationale

The dosing paradigm of brexpiprazole to be used in this trial is based on the current approved dosing for MDD (2 mg/day to 3 mg/day) in product labeling. Subjects will receive [redacted] a target dosage of 2 mg/day up to the maximum recommended daily dosage of 3 mg/day.

The ADTs and dosages approved for use in this trial, are listed in Section 3.2.1. Dose adjustments will be made for those ADTs that are strong inhibitors of CYP2D6 (ie, duloxetine, fluoxetine, and paroxetine). Brexpriprazole labeling states that there is a 2-fold increase in exposure to brexpiprazole in the typical patient when strong CYP2D6 inhibitors are administered. In order to limit the potential higher exposure of brexpiprazole when coadministered with such inhibitors, the upper limit of the therapeutic ADT dose is set at 60 mg for duloxetine, 40 mg for fluoxetine, and 50 mg for paroxetine controlled-release (CR) in the current trial (see Section 3.2.1).

2.3 Trial Objectives

Primary: To compare the efficacy of brexpiprazole (2 to 3 mg/day) to placebo as adjunctive therapy to ADT for the maintenance treatment in adults with MDD.

Secondary: To evaluate the safety and tolerability of brexpiprazole (2 to 3 mg/day) as adjunctive therapy to ADT in the proposed subject population with MDD.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the efficacy, safety, and tolerability of brexpiprazole as adjunctive therapy to a protocol-specified single-blind ADT in the maintenance treatment of adult subjects with a diagnosis of recurrent MDD. This trial consists of a screening period of up to 6 weeks, a 6- to 8-week open-label Acute Treatment Phase, a 12-week Stabilization Phase, an up to 26-week Double-Blind Randomized Withdrawal Phase, and a 21-day safety follow-up.

The trial phases are described below:

Screening Phase: The screening period will range from a minimum of 3 days up to 6 weeks and will begin when informed consent is signed. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments), and to allow subjects to continue their current ADT for an adequate duration as needed.

Acute Treatment Phase (Phase A): At Phase A baseline, all subjects must have either 2 or 3 documented inadequate responses to ADT in total for the current episode as defined by the ATRQ. Subjects will be enrolled into the 6- to 8-week, single-blind, Acute Treatment Phase (Phase A) if they meet the entrance criteria. The purpose of the Acute Treatment Phase is to identify subjects who respond to adjunctive brexpiprazole + protocol-specified ADT. Treatment will consist of single-blind brexpiprazole plus continuation of the ADT taken during the screening period (Section 3.2.1). The investigator should titrate to the dose of brexpiprazole that optimizes efficacy with the protocol-specified ADT with minimum tolerability issues. Subjects will attend weekly visits during the Acute Treatment Phase and will be evaluated at Weeks 6 to 8 to determine whether they meet response criteria as defined in the blinded addendum to the protocol. Subjects not meeting response criteria by the Week 8 visit will be discontinued from the trial.

Stabilization Phase (Phase B): Subjects who meet response criteria at the end of the Acute Treatment Phase will continue to a 12-week Stabilization Phase (Phase B). The purpose of the Stabilization Phase is to ensure subjects are able to maintain stability of depression symptoms at the dose of brexpiprazole optimized during Phase A. To proceed to the Double-blind Randomized Withdrawal Phase (Phase C), subjects must meet the stability criteria as defined in the blinded addendum to the protocol. Subjects not meeting stability criteria will be discontinued from the trial.

Double-blind Randomized Withdrawal Phase (Phase C): Subjects eligible for the Double-blind Randomized Withdrawal Phase will be randomized 1:1 to double-blind treatment with brexpiprazole + ADT or placebo + ADT for up to 26 weeks. Transition from the Stabilization Phase to the Double-blind Randomized Withdrawal Phase should not be made evident to the subject. During the Double-blind Randomized Withdrawal Phase, subjects will be evaluated in the clinic at biweekly visits for the first 2 visits and monthly visits thereafter. Subjects meeting the criteria for relapse as defined in the blinded addendum to the protocol will be withdrawn due to lack of efficacy.

Follow-up: Subjects who are discontinued, withdrawn, or complete the trial will be followed up for safety 21 (+2) days after the last dose of investigational medicinal product (IMP) by telephone contact or clinic visit at the investigator's discretion. Subjects should be prescribed appropriate depression treatment as per the investigator or the subject's psychiatrist or primary care physician.

Protocol 331-201-00079

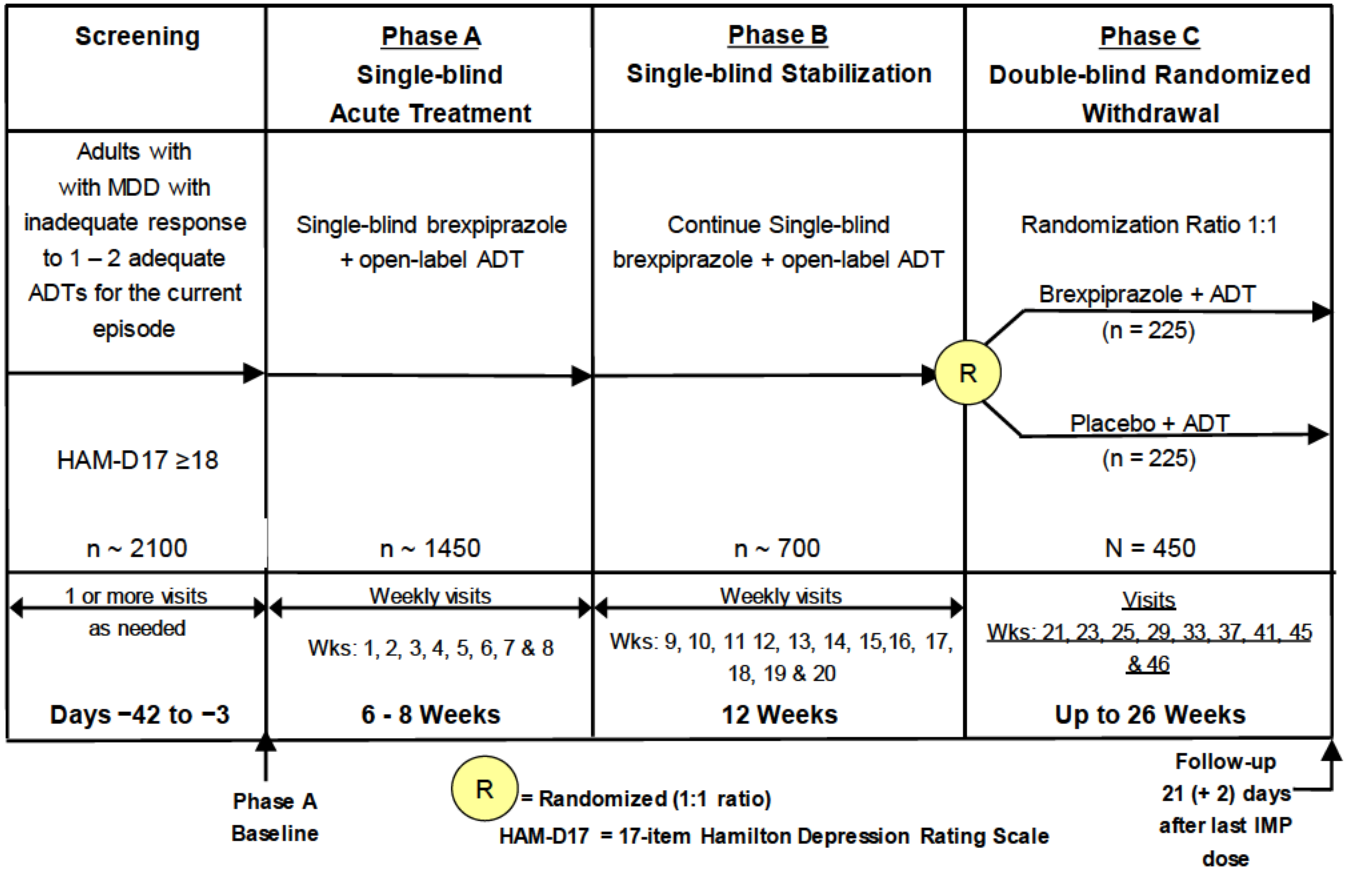


Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

Treatment will consist of single-blind brexpiprazole plus an open-label, protocol-specified ADT (Section 3.2.1). Investigational medicinal product will be provided to the investigator(s) by the sponsor (or designated agent) and will consist of active brexpiprazole tablets, matching placebo tablets, and open-label ADTs. A list of ADTs to be used in this trial, including dosages, is provided in Section 3.2.1.

All doses of IMP should be taken orally at the same time each day. All doses of IMP can be taken without regard to meals. If tolerability issues arise, the timing of administration of the IMP may be adjusted at the investigator's discretion in order to achieve optimum tolerability and compliance.

3.2.1 Protocol-specified Antidepressant Therapy

At screening, subjects must be taking 1 of the 7 ADTs at one of the approved doses listed below for their current major depressive episode. At the Phase A baseline visit, subjects will be allowed to switch from their current/pre-trial generic ADT to the matching trial-provided branded ADT. Subjects will not be permitted to switch to another ADT during the trial. If it is determined that a subject must switch to a different ADT during the course of the trial, the subject must be discontinued.

- Selective Serotonin Reuptake Inhibitors
  - Citalopram hydrobromide (Celexa®), tablets, 20 or 40 mg/day
  - Escitalopram (Lexapro®) tablets, 10 or 20 mg/day
  - Fluoxetine (Prozac®) capsules, 20 or 40 mg/day
  - Paroxetine (Paxil CR®) controlled-release tablets, 37.5 or 50 mg/day
  - Sertraline (Zoloft®) tablets, 100, 150 or 200 mg/day

Note: Fluoxetine 20 mg is dosed once daily. Fluoxetine 40 mg can be dosed once daily or in divided doses twice daily. All doses should be taken at the same time each day. All other treatments are dosed once daily at the same time each day.

- Serotonin-norepinephrine Reuptake Inhibitors
  - Duloxetine (Cymbalta®) delayed-release capsules, 40 or 60 mg/day
  - Venlafaxine XR (Effexor XR®) extended-release (XR) capsules, 75, 150 or 225 mg/day

The sponsor may limit and/or discontinue assignment to any single ADT based on the overall distribution of antidepressants in the trial.

Protocol 331-201-00079

3.2.2 Brexpiprazole + Antidepressant Treatment Dosing Regimen

Acute Treatment Phase (Phase A): Subjects will receive single-blind brexpiprazole + open-label ADT for 6 to 8 weeks. Subjects will be titrated to a target dose of brexpiprazole over a 2- to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication can have their dose increased up to 3 mg. Dose decreases can occur at scheduled or unscheduled visits once a dose of 3 mg is achieved. Subjects not able to tolerate the minimum specified target dose of 2 mg/day will be discontinued. The intention of this dosing paradigm is to have subjects treated at a maximum tolerated dose of brexpiprazole during the Acute Treatment Phase to optimize an efficacious response.

No adjustments to ADT doses are allowed in Phase A without approval from the medical monitor and changes may not be made within 5 days of a change in brexpiprazole dose.

The Acute Treatment Phase dosing schedule for brexpiprazole (flexible dosing with lead-in titration) is presented in Table 3.2.2-1.

[redacted]

Stabilization Phase (Phase B): Eligible subjects who have completed Phase A and enroll in the Stabilization Phase will receive single-blind brexpiprazole + open-label ADT for 12 weeks. Brexpiprazole dose decreases can occur at scheduled or unscheduled visits, but dose increases can occur only at scheduled visits. The dose of brexpiprazole must be stable for the last 4 weeks of the Stabilization Phase. Subjects not meeting stability criteria will be discontinued from the trial.

No adjustments to ADT doses are allowed in Phase B without approval from the medical monitor and changes may not be made within 5 days of a change in brexpiprazole dose.

No dose adjustments to the ADT are allowed in the last 4 weeks of Phase B.

Double-blind Randomized Withdrawal Phase (Phase C): Eligible subjects who have completed the Stabilization Phase will be randomized into the Double-blind Randomized Withdrawal Phase to brexpiprazole or placebo + open-label ADT in a 1:1 ratio for up to 26 weeks. Subjects randomized to brexpiprazole +ADT should maintain the doses of brexpiprazole that they were receiving at Week 20 of the Stabilization Phase. A one-time

change (ie, increase or decrease) in the dose of brexpiprazole or placebo may be permitted after discussion with the medical monitor. If a dose modification for brexpiprazole is implemented during Phase C, a one-time return to the original dose from the start of Phase C is permitted with approval from the medical monitor.

No doses adjustments to the ADT are allowed in Phase C.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population will include male and female outpatients between 18 and 65 years of age at the time of consent, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of recurrent MDD and a current major depressive episode confirmed by both the Mini International Neuropsychiatric Interview (MINI) and an adequate clinical psychiatric evaluation. The current episode must be at least 8 weeks in duration.

Subjects must meet all eligibility criteria specified in Section 3.4.2 (inclusion criteria) and Section 3.4.3 (exclusion criteria).

The sponsor reserves the right to utilize external quality oversight methods to ensure the validity of diagnosis, severity of illness, and other factors determining appropriateness of subject selection.

It is anticipated that approximately 1450 subjects will be enrolled into Phase A in order to enroll approximately 700 in Phase B and randomize 450 subjects in Phase C.

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject identification (ID) number upon completion of the consent process.

3.4 Eligibility Criteria

3.4.1 Informed Consent

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

Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline 11 and local regulatory requirements. The investigator will ensure that the sponsor or its designee reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB/IEC.

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

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

Prospective trial participants will be provided with controlled access to the electronic informed consent application by site staff. When the site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign the electronic ICF (eICF) application and an electronic date and time stamp will be applied to the signature. The eICF utilizes the IRB approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations does not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

All reference to ICF throughout this document will be inclusive of both consent modalities to ensure all circumstances are covered.

The participant will be given a printed, signed copy of the eICF. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

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

[redacted]

3.4.2 Inclusion Criteria

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

Table 3.4.2-1 Inclusion Criteria

1.	Informed consent prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed consent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent procedures must be in accordance with the trial site's IRB/IEC and local regulatory requirements.
2.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medications, to read and understand the written word in order to complete subject-reported outcomes measures, and to be reliably rated on assessment scales.
3.	Male and female outpatient subjects 18 to 65 years of age, inclusive, at the time of informed consent.
4.	Subjects with both a diagnosis of recurrent MDD, and in a current major depressive episode of ≥ 8 weeks in duration, as defined by DSM-5 criteria and confirmed by both the MINI and an adequate clinical psychiatric evaluation.
5.	Subjects must have reported a history for the current major depressive episode of an inadequate response to 1 or 2 adequate ADTs (as defined by the ATRQ). In addition, subjects must currently be taking a protocol-mandated antidepressant treatment at a dose defined in Section 3.2.1 and adequate duration (as defined by the ATRQ), and must not have reported ≥ 50% improvement (as defined by the ATRQ). For subjects who are currently on an adequate dose of a protocol-mandated ADT but for an inadequate duration, the screening period may be used to achieve adequate duration. At Phase A baseline, all subjects must have either 2 or 3 documented inadequate responses to ADT in total for the current episode as defined by the ATRQ.
6.	Subjects with a HAM-D17 total score ≥ 18 at the screening and Phase A baseline visits.
7.	Subjects willing to discontinue all prohibited psychotropic medications to meet protocol-required washouts prior to and during the trial period.

ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; HAM-D17 = 17-item Hamilton Depression Rating Scale.

NOTE: An inadequate response is defined as < 50% reduction in depressive symptom severity, as assessed by the ATRQ. Adequate treatment is defined as an antidepressant treatment for at least 6 weeks in duration at a minimum dose (or higher) as specified in the ATRQ.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria

Sex and Reproductive Status	
1.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
2.	Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.

Protocol 331-201-00079

Table 3.4.3-1 Exclusion Criteria	
Target disease	
3.	Subjects who report treatment with adjunctive antipsychotic medication with an antidepressant for a minimum of 3 weeks during the current major depressive episode.
4.	Subjects who report allergies or an intolerability (lifetime treatment history) to trial-provided ADTs that have not been prescribed to the subject during the current major depressive episode.
5.	Subjects who have received ECT for the current major depressive episode.
6.	Subjects who have had an inadequate response to ECT at any time in the past or who have had a vagus nerve stimulation or deep brain stimulation device implanted at any time for the management of treatment-resistant depression. Subjects who have had transcranial magnetic stimulation during the current major depressive episode.
7.	Subjects with a current need for involuntary commitment or who have been hospitalized within 4 weeks of screening for the current major depressive episode.
8.	Subjects with a primary DSM-5 diagnosis of: • Schizophrenia Spectrum and Other Psychotic Disorders • Bipolar and Related Disorders • Obsessive compulsive disorder • Feeding and Eating Disorders (including anorexia nervosa or bulimia) • Neurocognitive disorders (including but not limited to: Delirium, Major or Mild Neurocognitive Disorder due to: Alzheimer's, Parkinson's, Traumatic Brain Injury) • Panic disorder • PTSD
9.	Subjects with a current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal or histrionic personality disorder or intellectual disability
10.	Subjects experiencing hallucinations, delusions, or any psychotic symptomatology in the current major depressive episode
11.	Subjects receiving new onset psychotherapy (individual, group, marriage, or family therapy) within 42 days of screening or at any time during participation in the trial.
Medical History and Concurrent diseases	
12.	Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months, OR Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months OR Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, OR Subjects who, in the opinion of the investigator, present a serious risk of suicide.
13.	Subjects who have met DSM-5 criteria for substance use disorder (moderate or severe) within the past 60 days; including alcohol and benzodiazepines, but excluding nicotine.
14.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) and/or an abnormal result for free T_4 at screening, unless discussed with and approved by the medical monitor.

Protocol 331-201-00079

Table 3.4.3-1 Exclusion Criteria	
15.	Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C. Medical conditions that are minor or well controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a corresponding high body mass index, need to be reviewed and discussed with the medical monitor.
16.	Subjects with diabetes mellitus (IDDM and non-IDDM) are ineligible for the trial unless their condition is stable and well-controlled as determined by satisfying **ALL** of the following criteria at screening and Phase A baseline: • Screening HbA1c < 7.0%, **AND** • Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, **AND** • Subject has not had any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes. Subjects with non-IDDM (ie, any subjects not using insulin) must also satisfy the following criterion: • Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening. Subjects with newly diagnosed diabetes during screening will be excluded.
17.	Subjects with uncontrolled hypertension (DBP > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms. NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above.
18.	Subjects with known ischemic heart disease or history of myocardial infarction- or congestive heart failure (whether controlled or uncontrolled).
19.	Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile seizure, post traumatic, or alcohol withdrawal.
Physical and Laboratory Results	
20.	Subjects with a positive drug screen for cocaine or other drugs of abuse (excluding known prescription stimulants and other prescribed medications and marijuana). Detectable levels of alcohol, marijuana, barbiturates, or opiates in the drug screen are not exclusionary if, in the investigator's documented opinion, the subject does not meet DSM-5 criteria for moderate to severe substance use disorder and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, and participation is agreed to by the medical monitor prior to treatment.

Protocol 331-201-00079

Table 3.4.3-1 Exclusion Criteria	
21.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) WBC count ≤ 2800/mm^3 5) AST > 2 × ULN 6) ALT > 2 × ULN 7) Creatinine ≥ 2 mg/dL 8) HbA1c ≥ 7.0% 9) Abnormal free T_4, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if result for TSH is abnormal.) 10) CPK > 3 × ULN, unless discussed with and approved by the medical monitor 11) QTcF ≥ 450 msec for males and ≥ 470 for females NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and would impact the safety of the subject or the interpretation of the trial results. Criteria are provided to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters or vital signs should be repeated 1 time to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Based on the QTcF corrections reported by the central service, a subject will be excluded if the correction equals or exceeds 450 msec for males and 470 msec for females for 2 or more of the 3 time points of the ECGs conducted. If only 1 ECG time point has a corrected QTc of equal to or greater than 450 msec for males or 470 msec for females for either correction factor and it is not reproduced at either of the other 2 time points, the subject meets the inclusion criteria.
Prohibited Therapies or Medications	
22.	Treatment with a MAOI (eg, Nardi® [phenelzine] or EMSAM® [selegiline]) within the 14 days prior to the first dose of IMP in Phase A.
23.	Use of benzodiazepines and/or hypnotics (including non-benzodiazepine sleep aids) within 7 days prior to the first dose of IMP in Phase A.
24.	Use of varenicline within 5 days prior to the first dose of IMP in Phase A.
25.	Use of oral (or immediate release intramuscular) neuroleptics within 7 days prior or long-acting approved neuroleptics ≤ 1 full cycle plus 1/2 cycle (length of 1 cycle based on the prescribing label) prior to the first dose of IMP in Phase A.
26.	Subjects who would be likely to require prohibited concomitant therapy during the trial.
27.	Subjects who have been exposed to brexpiprazole in any prior clinical trial or have received commercial brexpiprazole (Rexulti).
Allergies and Adverse Drug Reactions	
28.	Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome.
29.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.
Other	
30.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
31.	Inability to tolerate oral medication or swallow tablets.
32.	Subjects who participated in any clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
33.	Any subject who, in the opinion of the investigator, should not participate in the trial.
Exclusion Criteria Assessed at the Week 6 through 8 Visits	
34.	Subjects who do not meet predetermined blinded criteria for response.

Protocol 331-201-00079

Table 3.4.3-1 Exclusion Criteria	
35.	Subjects with a positive result for cocaine or other illicit drugs at any scheduled visit during Phase A. Subjects with a positive urine drug screen due to marijuana, prescription or OTC medications or products and/or a positive blood alcohol result may continue to Phase B only after consultation and approval by the medical monitor.
36.	Subjects who, in the opinion of the principal investigator or medical monitor, developed any clinically significant safety concerns during participation in Phase A (eg, laboratory values, ECG findings, or medical conditions).
Exclusion Criteria Assessed at the Week 20 Visit	
37.	Subjects who do not meet predetermined blinded stabilization criteria.
38.	Subjects with a positive result for cocaine or other illicit drugs at any scheduled visit during Phase B. Subjects with a positive urine drug screen due to marijuana, prescription or OTC medications or products and/or a positive blood alcohol result may continue to Phase C only after consultation and approval by the medical monitor.
39.	Subjects who, in the opinion of the principal investigator or medical monitor, developed any clinically significant safety concerns during participation in Phase B (eg, laboratory values, ECG findings, or medical conditions).
40.	Subjects who, in the opinion of the investigator, medical monitor or clinical surveillance team, are not suitable for randomization for other reasons.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = Creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; ECG = electrocardiogram; ECT = electroconvulsive therapy; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; IRT = interactive response technology; MAOI = monoamine oxidase inhibitor; QTcF = QT interval as corrected for heart rate by Fridericia's formula; SBP = systolic blood pressure; T_4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cells; WOCBP = women of childbearing potential.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects must agree to restrictions to medications as described in Section 4.

During screening, subjects with a positive blood alcohol screen should be reassessed for alcohol abuse and dependence before consultation with medical monitor about approval for inclusion. Subjects with a positive drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results should be excluded from the trial. Subjects with a positive drug screen for cocaine or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of marijuana, opiates, barbiturates, prescription or over-the-counter (OTC) medications, or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, or the subject does not

meet DSM-5 criteria for substance abuse or dependence, may continue evaluation for the trial following consultation and approval by the medical monitor.

Screen failures previously excluded for a positive blood alcohol test or a positive urine drug screen due to use of marijuana, opiates, barbiturates, prescription or OTC medications or products may be retested or rescreened for participation in the trial with consent of the medical monitor. Screen failures excluded for any other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that a screen failure is rescreened after the screening period expires, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the time-to-relapse by any criteria as defined in the blinded addendum to this protocol.

3.5.2 Secondary Endpoints

The key secondary endpoints are:

- Change from randomization in SDS mean total score at Week 46 (last observation carried forward[LOCF])
- Time-to-functional relapse based on Sheehan Disability Scale (SDS) criteria.

Other secondary endpoints are:

- Percentage of subjects who relapse
- Percentage of subjects maintaining remission
- Mean change from randomization in MADRS total score (LOCF)
- Mean change from randomization in CGI-S score (LOCF)
- Mean change from randomization in each of the SDS individual item scores (LOCF)

[redacted]

[redacted]

3.6 Measures to Minimize/Avoid Bias

During the entire trial, treatment with ADT will be open-label. The investigator and the subject will have knowledge of the ADT treatment.

During the Acute Treatment Phase (Phase A) and the Stabilization Phase (Phase B), treatment will be single-blind, meaning that the investigator, but not the subject, will have knowledge of brexpiprazole administration. Both the investigator and subject will be blinded to response and stabilization/randomization criteria. The investigator, but not subject, will be informed if a subject meets response criteria between Weeks 6 and 8 in Phase A and if the subject meets stabilization/randomization criteria in Phase B. Subjects will not know when they transition between phases.

During the Double-Blind Randomized Withdrawal Phase (Phase C), IMP other than ADT will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (ie, placebo or brexpiprazole). Subjects will be randomly assigned by the interactive response technology (IRT) to receive brexpiprazole + ADT or matching placebo + ADT. The randomization will be stratified by trial centers. Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc (OPDC) Biometrics Department. Sponsor and Clinical Research Organization (CRO) personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the IRT, and reporting serious adverse events (SAEs) to regulatory agencies.

3.6.1 Randomization

Personnel at the trial sites will be blinded to the details of the randomization criteria. The scale scores will be entered into the eSource system at Weeks 6, 7, and 8 during the Acute Treatment Phase. The investigator will be informed by eSource if the subject meets score-based criteria for response (ie, whether a subject is a “Phase A Responder” or a “Phase A Inadequate Responder”). The score-based criteria for response are identified in a blinded addendum to this protocol. At the end of the Stabilization Phase (Week 20), the investigator will be informed by eSource if the subject meets randomization criteria.

3.7 Trial Procedures

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 39 months, of which approximately 22 months are allotted for recruitment of subjects. Individual participation for subjects who complete the trial without early withdrawal will range from 47 to 55 weeks, consisting of a 3-day to 6-week screening period, a 6- to 8-week single-blind acute treatment phase, a 12-week single-blind stabilization phase, an up to a 26-week double-blind treatment phase, and a 21 (+ 2)-day follow-up.

External quality oversight methods will be used by the Clinical Surveillance Team (CST) at Syneos Health to promote appropriate subject enrollment and randomization. Such methods will require sites to communicate certain aspects of subject data (collected in the course of the protocol and per the Schedule of Assessments) to the CST. Subjects cannot be enrolled until the CST review process has been completed and the site has received the final notification from the Medical Director or Clinical Scientist. Sites can expect that CST review and feedback to site on screening data will occur within 2 business days of receipt of full data set. Decisions regarding inclusion of subjects at time of enrollment and assessment of subject safety throughout the trial primarily remain at the discretion of the investigator; however, the medical monitor may recommend exclusion or discontinuation of a subject based on individual subject data.

Trial assessment time points are summarized in Table 3.7-1 (Screening and Phase A), Table 3.7-2 (Phase B), and Table 3.7-3 (Phase C).

Table 3.7-1 Schedule of Assessments - Screening and Acute Treatment Phase (Phase A)

Assessment	Screening	Acute Treatment Phase								
	Day −42 to −3	Phase A Base-line	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	Week 7 (± 2 days)	Week 8/ End-of Phase A or ET[a] (± 2 days)
Entrance criteria and subject history										
Informed Consent	X									
Inclusion/exclusion criteria	X	X								
Demography	X									
Medical history	X									
Psychiatric history	X									
MINI	X									
HAM-D17	X	X								
Antidepressant history (ATRQ)	X									
Prior medication washout[b]	X									
HIV, HBsAg, and anti-HCV[c]	X									
Efficacy										
MADRS		X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X
SDS		X						X		
Safety										
Physical examination[d]	X									X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X								X
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[c]	X	X								X
Prolactin[c]		X								X
HbA1c[c]	X	X								

Table 3.7-1 Schedule of Assessments - Screening and Acute Treatment Phase (Phase A)

Assessment	Screening	Acute Treatment Phase								
	Day −42 to −3	Phase A Base-line	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	Week 7 (± 2 days)	Week 8/ End-of Phase A or ET[a] (± 2 days)
TSH, with reflex to T_4 if TSH is abnormal	X									
Coagulation parameters (PT, aPTT, INR)	X									
Blood alcohol[g]	X					X				X
Urine drug screen[g,h]	X					X				X
Urine pregnancy test (WOCBP only)[i]	X	X	X			X				X
SAS		X						X		
AIMS		X						X		
BARS		X						X		
C-SSRS[j]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications[k]	X	X	X	X	X	X	X	X	X	X
Other										
IMP dispensing		X	X	X	X	X	X	X	X	X
IMP accountability			X	X	X	X	X	X	X	X
[redacted]		X								
[redacted]	[redacted]									
[redacted]	[redacted]	[redacted]								

anti-HCV = hepatitis C antibodies; aPTT = activated prothrombplastin time; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; HBsAg = Hepatitis B Surface Antigen; INR = International Normalized Ratio; PT = prothrombin time; SAS = Simpson Angus Scale.

[a]The End of Phase A visit will also be the ET visit for subjects who do not meet the response criteria. The investigator or site staff will provide relevant information for a blinded assessment of score-based response criteria for each subject. Whether or not a subject is an inadequate responder in Phase A will

be confirmed by eSource based on the score-based criteria defined in the blinded addendum to this protocol. The site will be notified of the subject's response status during the Weeks 6, 7, or 8 visits. Any subject who does not meet the criteria for adequate response will be discontinued from the trial. If a subject meets response criteria at Week 6 or 7 they will complete the Week 8 procedures and any remaining visits in Phase A will not be completed.

[b]Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods in Table 4.1-1 Prohibited and restricted medications requiring a washout of at least 24 hours before the first dose of protocol-specified ADT in Phase A are listed in Table 4.1-2 and Table 4.1-4.

[c]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at the baseline visit and should be drawn after a minimum 8-hour fast at all other visits. If fasting blood samples are not feasible at visits other than the baseline visit, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[d]To include measurement of height and waist circumference at screening and waist circumference at all other time points.

[e]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[f]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. A QTcF ≥ 450 msec for males and ≥ 470 msec for females at screening is exclusionary. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. Subjects will continue in the trial based on Week 8 ECG results from the trial site. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[g]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

[h]Eligibility for continuation in the trial beyond the Week 8 visit is based in part on the Week 4 urine drug screen and blood alcohol results. Subjects whose Week 4 urine drug screen is positive for cocaine or other illicit drugs must be withdrawn from the trial. Subjects with a positive urine drug screen at Week 4 due to prescription or OTC medications or products may continue evaluation in the trial only after consultation and approval by the medical monitor.

[i]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[j]The "baseline/screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the baseline visit to assure that the subject continues to qualify for the trial. Any subject with suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after the baseline visit.

[k]All medications taken within 30 days of informed consent will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in Section 4.1.

Protocol 331-201-00079

Table 3.7-2 Schedule of Assessment - Stabilization Phase (Phase B)

Assessment	Week 9 (± 2 days)	Week 10 (± 2 days)	Week 11 (± 2 days)	Week 12 (± 2 days)	Week 13 (± 2 days)	Week 14 (± 2 days)	Week 15 (± 2 days)	Week 16 (± 2 days)	Week 17 (± 2 days)	Week 18 (± 2 days)	Week 19 (± 2 days)	Week 20/ Random-ization/ ET[a,b] (± 2 days)
Efficacy												
MADRS	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X
SDS	X					X						X
Safety												
Physical examination[c]												X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]								X				
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[f]												X
Prolactin[f]												X
HbA1c[f]												X
Urine drug screen[g]								X				
Urine pregnancy test (WOCBP only)[h]				X				X				X
SAS				X								X
AIMS				X								X
BARS				X								X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Other												
Randomization												X
IMP dispensing	X	X	X	X	X	X	X	X	X	X	X	X

Table 3.7-2 Schedule of Assessment - Stabilization Phase (Phase B)

Assessment	Week 9 (± 2 days)	Week 10 (± 2 days)	Week 11 (± 2 days)	Week 12 (± 2 days)	Week 13 (± 2 days)	Week 14 (± 2 days)	Week 15 (± 2 days)	Week 16 (± 2 days)	Week 17 (± 2 days)	Week 18 (± 2 days)	Week 19 (± 2 days)	Week 20/ Randomization/ ET[a,b] (± 2 days)
IMP accountability	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic samples								X				X
Pharmacogenomic sample												X[i]
[redacted]												
[redacted]												

[a]For subjects who meet stability criteria, the Week 20 visit, Randomization, will be the baseline visit for all subsequent Phase C visits; for subjects who do not meet the stability criteria, the Week 20 visit will be the ET visit. Stability criteria are defined in the blinded addendum to this protocol.

[b]If a subject discontinues prematurely, procedures noted for Week 20 must be completed at the ET visit.

[c]Includes waist circumference.

[d]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[e]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. ECG results will be evaluated at the investigational site to monitor safety. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. The ECG is to be completed before any blood sample is collected.

[f]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at the Week 20/Randomization visit and should be drawn after a minimum 8-hour fast at all other visits. If fasting blood samples are not feasible at visits other than the Week 20/Randomization visit, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[g]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

[h]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

Protocol 331-201-00079

[i]Pharmacogenomic sample is only to be collected during randomization. If a subject early terminates at Week 20, no sample will be collected.

[redacted]

Table 3.7-3 Double-blind Randomized Withdrawal Phase (Phase C)

Assessments	Week 21 (± 2 days)	Week 23 (± 2 days)	Week 25 (± 2 days)	Week 29 (± 2 days)	Week 33 (± 2 days)	Week 37 (± 2 days)	Week 41 (± 2 days)	Week 45 (± 2 days)	Week 46/ ET[a]/ End of Phase C or MDD Relapse (± 2 days)	Follow-up Safety visit (21 + 2 days)
Efficacy										
MADRS	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	
SDS	X	X	X	X	X	X	X	X	X	
Safety										
Physical examination[b]									X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	
12-lead ECG[d]				X					X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[e]									X	
Prolactin[e]									X	
Blood alcohol[f]									X	
Urine drug screen[f]					X				X	
Urine pregnancy test (WOCBP only)[g]					X				X	
SAS			X		X		X		X	
AIMS			X		X		X		X	
BARS			X		X		X		X	
C-SSRS	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Table 3.7-3 Double-blind Randomized Withdrawal Phase (Phase C)

Assessments	Week 21 (± 2 days)	Week 23 (± 2 days)	Week 25 (± 2 days)	Week 29 (± 2 days)	Week 33 (± 2 days)	Week 37 (± 2 days)	Week 41 (± 2 days)	Week 45 (± 2 days)	Week 46/ ET[a]/ End of Phase C or MDD Relapse (± 2 days)	Follow-up Safety visit (21 + 2 days)
Other										
IMP dispensing	X	X	X	X	X	X	X	X		
IMP accountability	X	X	X	X	X	X	X	X	X	
Pharmacokinetic samples						X			X	
[redacted]										
[redacted]										

[a]For subjects who discontinue early, attempts should be made to complete ALL evaluations, particularly efficacy assessments (ie, MADRS, CGI-S, and SDS), for the Week 46/ET visit prior to the administration of any new antidepressant medications. However, if the subject receives a new antidepressant prior to ET procedures, no efficacy assessments should be done.

[b]Includes waist circumference.

[c]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[d]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. ECG results will be evaluated at the investigational site to monitor safety. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. The ECG is to be completed before any blood sample is collected.

[e]Blood samples for clinical laboratory tests should be drawn after the subject has been fasting for at least 8 hours, if possible. If fasting blood samples are not feasible, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[f]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

Protocol 331-201-00079

[g]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[redacted]

3.7.1 Schedule of Assessments

3.7.1.1 Screening (Day −42 to Day −3)

The screening period begins after consent has been obtained. Although the screening period takes place between Day −42 and Day −3, subjects will participate in screening activities for 3 days. After the subject has provided consent, a subject number will be assigned. Screening evaluations will include the following:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial. Subjects cannot be enrolled until the CST review process has been completed and the site has received the final notification from the Medical Director or Clinical Scientist. Sites can expect that CST review and feedback to site on screening data will occur within 2 business days of receipt of full data set.
- Demographic data will be recorded.
- A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years which is considered to be clinically relevant per the investigator's judgment.
- Psychiatric history will be recorded, including the DSM-5 diagnosis of MDD that will be made by an adequately trained and experienced clinician and will be confirmed by the administration of the MINI (Section 3.7.2.4.1).
- Antidepressant history will be assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ; Section 3.7.2.4.3). If the subject is on their current antidepressant for an inadequate duration at the time of the administration of the ATRQ, the subject may be contacted via telephone to collect their response to the current ADT once the subject is on this treatment for an adequate duration.
- Medications (including those that were taken within 30 days of screening) will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited/restricted medications are provided in Table 4.1-1, Table 4.1-2, and Table 4.1-4.
- Washout from prohibited concomitant medications, if applicable (Table 4.1-1).
- The investigator (or qualified designee) who is adequately trained will complete the 17-item Hamilton Depression Rating Scale (HAM-D17) (Table 3.4.2-1; Section 3.7.2.4.2).
- The investigator (or qualified designee) who is adequately trained will complete the "Baseline/Screening" Columbia-Suicide Severity Rating Scale (C-SSRS) form to exclude subjects with a significant risk of suicidal behavior (Table 3.4.3-1; Section 3.7.3.5.4).
- A complete physical examination (including height and waist circumference) will be performed.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the

following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3-1 for exclusions based on outcome of screening vital sign measurements. Vital signs will be completed before any blood is collected.

- A standard 12-lead electrocardiogram (ECG) will be performed after the subject has been supine and at rest for at least 5 minutes. See Table 3.4.3-1 for exclusions based on ECG results. The ECG is to be completed before any blood sample is collected.
- Blood samples will be drawn for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including glycosylated hemoglobin [HbA1c], and thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T_4] if the result for TSH is abnormal and for infectious diseases) after a minimum 8-hour fast at screening. If fasting blood samples are not feasible, nonfasting blood samples may be collected. See Table 3.4.3-1 for exclusions based on outcome of screening clinical laboratory tests.
- Samples will be obtained for blood alcohol testing. See Section 3.4.3 for details regarding subjects with a positive blood alcohol test.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Section 3.4.3 for exclusions based on outcome of screening urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all women of childbearing potential (WOCBP). All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- Adverse events will be recorded beginning with the completion of the consent process.
- [redacted]
- [redacted]

3.7.1.2 Acute Treatment Phase

3.7.1.2.1 Baseline (Day 1)

If the subject continues to be eligible for the trial after the screening period, the following procedures will be performed:

- Inclusion/exclusion criteria will be verified.
- A qualified and certified rater will administer MADRS and HAM-D17.
- The investigator (or qualified designee) will administer the CGI-S.
- The subject will complete the SDS.
- Vital sign measurements (body temperature, blood pressure, and heart rate) and body weight will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes.

- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood sample is collected.
- Blood samples for clinical laboratory tests (hematology and serum chemistry), including HbA1c and prolactin, must be drawn after a minimum 8-hour fast.
- A urine sample will be collected for urinalysis.
- If the subject has signed a separate consent form, blood may be drawn for FBR (or at any other visit).
- A urine pregnancy test will be performed for all WOCBP. All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- An adequately trained and experienced clinician will administer the Simpson Angus Scale (SAS; Section 3.7.3.5.1), Abnormal Involuntary Movement Scale (AIMS; Section 3.7.3.5.2), and Barnes Akathisia Rating Scale (BARS; Section 3.7.3.5.3) to assess extrapyramidal symptoms (EPS).
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS (Section 3.7.3.5.4) form.
- Adverse events and concomitant medications will be recorded.
- IMP will be dispensed to the subject.

3.7.1.2.2 Weeks 1 through 7 (Phase A)

The following evaluations will be performed at the designated visits in Phase A:

- A qualified and certified rater will administer MADRS *at Weeks 1 through 7*.
- The investigator (or qualified designee) will administer the CGI-S *at Weeks 1 through 7*.
- The subject will complete the SDS *only at Week 6*.
- Criteria will be assessed for the Stabilization Phase (Phase B) by a qualified rater *at Weeks 4 through 7*.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes, at *Weeks 1 through 7*. Vital signs are to be completed before any blood is drawn.
- Blood alcohol will be tested and a urine drug screen performed *at Week 4*.
- A urinary pregnancy test (WOCBP only) will be performed *at Weeks 1, and 4*. Any positive result must be confirmed by a serum pregnancy test. WOCBP with a positive serum pregnancy test result must discontinue the IMP and be withdrawn from the trial.
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS *only* at *Week 6*.

- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form at *Weeks 1 through 7*.
- Adverse events and concomitant medications will be recorded *at Weeks 1 through 7*.
- IMP will be dispensed to the subject *at Weeks 1 through 7*.
- Any need for dose modification will be assessed *at Weeks 1 through 4*.
- Drug accountability will be performed *at Weeks 1 through 7*.

3.7.1.2.3 End of Phase A (Weeks 6, 7, or 8) or Early Termination

Subjects who meet the response criteria, as defined in the blinded addendum to this protocol, either at Week 6, Week 7, or Week 8 will have the following assessments performed. For subjects who meet these criteria at Week 6 or Week 7, these assessments will replace the Week 6 and Week 7 assessments described in Section 3.7.1.2.2. For subjects who do not meet response criteria at Visit 8, this will be an ET visit and the following procedures will be performed.

- A qualified and certified rater will administer the MADRS.
- The investigator (or qualified designee) will administer the CGI-S.
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
- A complete physical examination (including waist circumference) will be performed.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood sample is collected.
- Blood alcohol will be tested and a urine drug screen performed.
- A blood draw will be collected for clinical laboratory tests and urine will be collected for urinalysis. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A urinary pregnancy test (WOCBP only) will be performed. Any positive result must be confirmed by a serum pregnancy test. WOCBP with a positive serum pregnancy test result must discontinue the IMP and be withdrawn from the trial.
- Adverse events and concomitant medications will be recorded.
- IMP will be dispensed to the subject.
- Drug accountability will be performed.

3.7.1.3 Stabilization Phase, Week 9 through Week 20/Randomization (Phase B)

The following assessments will occur during the Stabilization Phase:

- A qualified and certified rater will administer the MADRS *at Weeks 9 through 20*.
- The investigator (or qualified designee) will administer the CGI-S *at Weeks 9 through 20.*
- The subject will complete the SDS *at Weeks 9, 14, and 20*.
- A complete physical examination (including waist circumference) will be performed *at Week 20 only.*
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded *at Weeks 9 through 20*. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes *at Week 16*. The ECG is to be completed before any blood sample is collected.
- A fasting blood draw must be collected for clinical laboratory tests (hematology and serum chemistry) and urine will be collected for urinalysis *at Week 20*. The laboratory tests will include prolactin. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Blood samples will be drawn for PK analysis *at Weeks 16 and 20*.
- A urine drug screen will be performed *at Week 16*.
- A urinary pregnancy test (WOCBP only) will be performed *at Weeks 12, 16, and 20*. Any positive result must be confirmed by a serum pregnancy test. WOCBP with a positive serum pregnancy test result must discontinue the IMP and be withdrawn from the trial.
- A qualified and certified rater will administer the SAS, AIMS, and BARS *at Weeks 12 and 20*.
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form *at Weeks 9 through 20.*
- Adverse events and concomitant medications will be recorded *at Weeks 9 through 20*.
- IMP will be dispensed to the subject *at Weeks 9 through 20*.
- Drug accountability will be performed *at Weeks 9 through 20*.
- Subjects will be randomized at the *Week 20*/*Randomization visit*.
- [redacted]
- Blood sample will be drawn for pharmacogenomic analysis at the *Week 20*/*Randomization visit*. If a subject early terminates at Week 20, no sample will be collected.

3.7.1.4 Double-blind Randomized Withdrawal Phase (Week 21 through Week 46/End of Phase C/Relapse) (Phase C)

The following assessments will occur during the Double-blind Randomized Withdrawal Phase:

- A qualified and certified rater will administer the MADRS *at Weeks 21 through 46*.
- The investigator (or qualified designee) will administer the CGI-S *at Weeks 21 through 46.*
- The subject will complete the SDS *at Weeks 21 through 46*.
- For subjects who discontinue early, attempts should be made to complete ALL evaluations, particularly efficacy assessments (ie, MADRS, CGI-S, and SDS), for the *Week 46/ET* visit prior to the administration of any new antidepressant medications. However, if the subject receives a new antidepressant prior to ET procedures, no efficacy assessments should be done.
- A complete physical examination (including waist circumference) will be performed *at Week 46 only.*
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded *at Weeks 21 through 46*. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes *at Weeks 29 and 46*. The ECG is to be completed before any blood sample is collected.
- A fasting blood draw should be collected for clinical laboratory tests (hematology and serum chemistry) and urine will be collected for urinalysis *at Week 46*. If fasting blood samples are not feasible, nonfasting blood samples may be collected. The laboratory tests will also include prolactin *at Week 46.* Vital sign and ECG assessments should be completed before any blood samples are collected.
- Blood alcohol will be tested *at Week 46*.
- Blood samples will be drawn for PK analysis *at Weeks 37 and 46*.
- A urine drug screen will be performed *at Weeks 33 and 46*.
- A urinary pregnancy test (WOCBP only) will be performed *at Weeks 33 and 46*. Any positive result must be confirmed by a serum pregnancy test. WOCBP with a positive serum pregnancy test result must discontinue the IMP and be withdrawn from the trial.
- A qualified and certified rater will administer the SAS, AIMS, and BARS, *at Weeks 25, 33, 41, and 46*. The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form *at Weeks 21 through 46.*
- Adverse events and concomitant medications will be recorded *at Weeks 21 through 46*.
- IMP will be dispensed to the subject *at Weeks 21 through 45*.

Protocol 331-201-00079

- Drug accountability will be performed *at Weeks 21 through 46*.
- [redacted]

3.7.1.5 Post-treatment Follow-up Safety Visit (21 + 2 days)

Adverse events and concomitant medications will be recorded at this Visit 21 (+2) days after the last dose of IMP via telephone contact or clinic visit at the investigator's discretion.

3.7.2 Efficacy Assessments

It is required that trained and experienced clinicians administer the MADRS and CGI-S. In addition, the raters must be certified for this trial to administer the MADRS. The number of raters within each trial center should be kept to a minimum. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by Bracket (Wayne, PA).

3.7.2.1 Montgomery Asberg Depression Rating Scale

The MADRS[16] will be utilized as the primary efficacy assessment of a subject's level of depressive symptoms and must be administered using a structured interview guide.

Detailed instructions for administration of the structured interview will be provided. This scale consists of 10 items each with 7 defined grades of severity.

3.7.2.2 Clinical Global Impression - Severity of Illness Scale

The severity of illness for each subject will be rated using the CGI-S[17]. To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

3.7.2.3 Sheehan Disability Scale

The SDS[18,19] is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. The SDS is a visual analogue scale that uses spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess disability across the 3 domains. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0 = not at all, to 10 = extremely. Scores of 5 and above are associated with significant functional impairment. In addition to the visual scale, the SDS includes

2 questions related to productivity losses due to the psychiatric symptoms and impairment.

3.7.2.4 Subject Assessment Recording

3.7.2.4.1 Mini International Neuropsychiatric Interview

The MINI[20] will be conducted at the screening visit to confirm the subject's diagnosis of MDD and to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided.

3.7.2.4.2 Hamilton Depression Rating Scale 17-Item Version

The HAM-D17[21,22] will be utilized at screening as a secondary assessment of a subject's level of depression and to determine eligibility, and must be administered utilizing the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D). Detailed instructions for administration of this structured interview will be provided in the SIGH-D. It is required that trained and experienced clinicians administer the HAM-D17.

3.7.2.4.3 Antidepressant Treatment Response Questionnaire

The ATRQ[23] will be used to collect a subject's history of pharmacologic treatment for their current major depressive episode, will be administered during screening as part of the collection of a subject's psychiatric history and will be utilized to determine eligibility for entry into the trial. If the subject is on their current antidepressant for an inadequate duration at the time of the administration of the ATRQ, the subject may be contacted via telephone to collect their response to the current ADT once the subject is on this treatment for an adequate duration to complete the ATRQ.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially

for determining eligibility for the trial. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP.

Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically. A list of clinical laboratory assessments is provided in Table 3.7.3.2-1.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis: pH Specific Gravity Protein Ketones Glucose Blood Microscopic analysis (performed only if any part of the urinalysis is not negative) Urine Drug Screens: Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Opiates Phencyclidine Propoxyphene Other: Blood Alcohol	Serum Chemistry: ALP ALT Albumin AST Bicarbonate Bilirubin, total BUN CPK Calcium Chloride Cholesterol (total, low density lipoprotein, and high density lipoprotein) Creatinine GGT Glucose Inorganic phosphorus Insulin LDH Magnesium Potassium Protein, total Sodium TSH T_4 (if needed) Uric acid Triglycerides Additional Tests: Urine or serum pregnancy for WOCBP PT aPTT INR HbA1c Prolactin Additional Tests (screening only); HIV HbsAg anti-HCV

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; LDH =lactic dehydrogenase; RBC = red blood cells.

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 1 for criteria for identifying laboratory values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets $\leq 75000/mm^3$
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute $\leq 1000/mm^3$
- WBC count $\leq 2800/mm^3$
- Aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2 × ULN
- Creatinine ≥ 2 mg/dL
- HbA1c ≥ 7.0%
- Abnormal free T_4, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if result for TSH is abnormal.)
- CPK > 3 × ULN, unless discussed with and approved by the medical monitor
- QTcF ≥ 450 msec for males and ≥ 470 for females

The total volume of blood to be collected during the trial per subject is expected to be approximately 150 mL.

A pregnancy test will be conducted in WOCBP prior to trial intervention; results must be available prior to the administration of the IMP. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

3.7.3.3 Physical Examination and Vital Signs

A complete physical examination will consist of measurement of height and waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae.

Height will be measured with a stadiometer, measuring stick, or tape. Waist circumference will be measured with each physical examination. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- The waist circumference measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.

The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the Phase A baseline examination should be documented as an AE and followed to a satisfactory conclusion.

The measurement of vital signs will include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. The following guidelines will aid in the standardization of body weight measurements:

- The same scale should be used to weigh a given subject each time, if possible.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit.

Blood pressure and heart rate measurements will be made in the supine, sitting, and standing positions after the subject has been in each position for at least 3 minutes. The supine measurements will be performed first followed by sitting.

Subjects with uncontrolled hypertension (screening DBP > 95 mmHg in any position) or symptomatic hypotension are excluded from the trial as are subjects with orthostatic hypotension defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of

≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure OR development of symptoms (see Table 3.4.3-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Appendix 2 is included to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.7.3.4 Electrocardiogram Assessments

All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an electroconvulsive therapy (ECT). Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

If, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject and/or the interpretation of the trial results) or meets an exclusion criterion (see Table 3.4.3-1), the subject should be excluded from the trial. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each time point). The central ECG service will provide the corrections for the 3 ECGs performed. Based on the QT interval corrected for heart rate by Fridericia's formula (QTcF) reported by the central service, a subject will be excluded if the corrections are ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of ≥ 450 msec in men and ≥ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.

Refer to Appendix 3 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical

significance postrandomization. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. Please consult the medical monitor in case of questions.

3.7.3.5 Other Safety Assessments

3.7.3.5.1 Simpson Angus Scale

The SAS[24] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (Table 4.1-2 and Table 4.1-3). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible.

However, if delaying administration of the scale is not feasible, the SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

3.7.3.5.2 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[17,25,26] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress).

For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (Table 4.1-2 and Table 4.1-3). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

3.7.3.5.3 Barnes Akathisia Rating Scale (BARS)

The BARS[26,27] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (Table 4.1-2 and Table 4.1-3). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

3.7.3.5.4 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS[27]. This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject with active suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary or secondary

objectives) on the eSource. Details of prohibited and restricted medications are provided in Section 4.1. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eSource.

3.7.5 Pharmacokinetic/Pharmacogenomic Assessments

[redacted] At the Week 20/Randomization visit, a blood sample will be collected for assessments of CYP 2D6 metabolizer activity for subjects randomized in to Phase C. Blood sampling for plasma concentrations of brexpiprazole will be collected in the Stabilization Phase (Phase B) during the Week 16 and Week 20 visits and in the Double-blind Randomized Withdrawal Phase (Phase C) during the Week 37 and Week 46/ET visits.

All blood samples for PK assessments will be shipped to the testing facility for analysis. All blood samples for pharmacogenomic assessments will be shipped to the pharmacogenomics laboratory. Detailed handling and shipping instructions are provided in Appendix 4.

3.7.6 End of Trial

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

3.7.7 Interim Analysis Review Committee

This trial is planned to be monitored for efficacy under the supervision of an independent Interim Analysis Review Committee (IARC). In particular, for assessment of efficacy, 2 interim analyses are planned to be performed, with the second interim analysis performed only if the first is not positive (see Section 7.4.4). The details of the IARC structure and its roles and responsibilities will be documented in an IARC charter.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

Two interim analyses are planned so that the trial can be terminated once the primary objective of the trial is met in order to minimize exposure of subjects to placebo in Phase C. The first interim analysis will be performed after 50% of events have been

achieved. If the result of this interim analysis is positive, the trial will be terminated and investigators will be notified. If the interim analysis is negative, a second interim analysis will be performed after 75% of events have been achieved.

3.8.2 Individual Site

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

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

No treatment interruptions are permitted in this trial.

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.5.

3.8.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAEs
    - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up

- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

In addition, subjects meeting the following criteria must be withdrawn from the trial:

- Occurrence of any AE, intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (Section 3.12)
- At the request of the subject, investigator, OPDC or designee, or regulatory authority;
- Subject becomes pregnant
- Subject cannot tolerate the minimum dose of brexpiprazole (ie, 2 mg/day or matching placebo)
- Subject does not fulfill the response criteria by Week 8 of Phase A.
- Subject does not fulfill stability criteria by Week 12 of Phase B. In addition, subjects who have more than 3 excursions (ie, do not meet stability criteria at a scheduled visit) during Phase B and subjects with 3 consecutive excursions or an excursion on the last visit of the Phase B are to be withdrawn. A missed visit during Phase B will be considered an excursion.
- Subjects that do not maintain a stable dose of IMP or ADT for the last 4 weeks of Phase B
- Subject meets criteria for relapse in Phase C
- Subject is lost to follow-up

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow up procedures in Section 3.8.3.2 must be followed.

3.8.3.4 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 can also discontinue a subject’s participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject’s verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

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

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject completes the consent process), but who is not randomized or assigned trial treatment.

Screen failures due to exclusionary criteria may be rescreened at any time if the exclusion characteristic has changed.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed 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 purposes of this trial, subjects who complete Visit 46 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Visit 46 during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also noncompliant and should be considered for

discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

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

4 Restrictions

4.1 Prohibited Medications

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP in Phase A.

Table 4.1-1 List of Medications Prohibited Before the Trial

	Medication	Required Duration of Washout
1.	Antipsychotics (depot or long-acting injectable)	One full cycle plus 1/2 cycle
2.	Monoamine oxidase inhibitors	14 days
3.	Antipsychotics (oral)	7 days
4.	Benzodiazepines	7 days
5..	Hypnotics, including non-benzodiazepine sleep aids	7 days

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

Table 4.1-2 List of Medications Prohibited During the Trial

1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants c) Antidepressants other than those prescribed as IMP d) Mood stabilizers (ie, lithium) e) Benzodiazepines, except when used to manage treatment-emergent AEs such as agitation and anxiety (See Table 4.1-3) f) Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage treatment-emergent AEs related to insomnia[a] g) Stimulants h) Opioid analgesics, unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc)
2.	Investigational agents
3.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial. See Table 4.1-4 below provides a select list of CYP2D6 inhibitors and CYP3A4 inhibitors and inducers which are prohibited within 14 days prior to the first dose of brexpiprazole in Phase A or Phase B (as appropriate to the subject's point of entry into the trial) and for the duration of the trial.
4.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.
5.	Varenicline

[a]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia for up to 7 days total in Phase A, up to 7 days total in Phase B, and up to 7 days total in Phase C, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eSource.

Table 4.1-3 presents the protocol-specified oral benzodiazepines that can be used as rescue medication in this trial. Oral lorazepam and oral oxazepam are to be used, if available. In countries or at investigative sites where lorazepam and oxazepam are not

available, use of oral diazepam or oral clonazepam may be acceptable if prior authorization is obtained from the medical monitor.

Table 4.1-3 Oral Benzodiazepine Rescue Therapy During the Trial

Oral Benzodiazepine[a]	Maximum Allowable Weekly Dose (mg/week)		
	Phase A	Phase B	Phase C
Lorazepam[b]	12	10	6
Oxazepam[b]	180	150	90
Diazepam[b,c]	60	50	30
Clonazepam[b,c]	6	5	3

[a]Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eSource.

[b]The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. Short-acting benzodiazepines are to be used whenever possible. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects.

[c]In countries or institutions where no short-acting benzodiazepines are commercially available, use of oral diazepam or oral clonazepam may be acceptable if prior authorization is obtained from the medical monitor.

Table 4.1-4 below provides a select list of CYP2D6 inhibitors and CYP3A4 inhibitors and inducers which are prohibited within 14 days prior to the first dose of brexpiprazole in Phase A or Phase B and for the duration of the trial.

Protocol 331-201-00079

Table 4.1-4 List of Medications Prohibited During the Trial: CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers

Selected CYP2D6 inhibitors[a]	Selected CYP3A4 inhibitors	Selected CYP3A4 inducers
celecoxib	amiodarone	carbamazepine
hydroxyzine	fluvoxamine	oxcarbazepine
chloroquine	amprenavir	phenytoin
methadone	indinavir	dexamethasone
chlorpheniramine	aprepitant	primidone
moclobemide	itraconazole	efavirenz
clemastine	chloramphenicol	rifampin
clomipramine	ketoconazole	nevirapine
pyrilamine	cimetidine	St. John's Wort
diphenhydramine	nefazodone	phenobarbitol
quinidine	clarithromycin	troglitazone
terbinafine	nelfinavir	
halofantrine	clotrimazole (if used orally)	
tripelennamine	quinupristin/dalfopristin	
	delavirdine	
	ritonavir	
	diltiazem	
	saquinavir	
	erythromycin	
	troleandomycin	
	fluconazole	
	verapamil	

[a]Fluoxetine, paroxetine, and duloxetine are protocol-defined ADTs that are also CYP2D6 inhibitors. In order to limit the potential higher exposure of brexpiprazole when coadministered with such inhibitors, the upper limit of the therapeutic ADT dose is limited to 40 mg for fluoxetine, 50 mg for paroxetine CR, and 60 mg for duloxetine.

4.2 Other Restrictions

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. In particular, the investigator should caution the subject about concomitant use of the following during the trial:

- Non-steroidal anti-inflammatory drugs, aspirin, or other drugs that interfere with coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of upper gastrointestinal bleeding.
- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan), linezolid, and methylene blue since there have been rare postmarketing reports of serotonin syndrome or serotonin syndrome-like reactions

(eg, mental status changes, hyperreflexia, autonomic effects, lack of coordination, and diarrhea) following the concomitant use of SSRIs or serotonin-norepinephrine reuptake inhibitors and these drugs.

All trial personnel should be familiar with the content of the IB for brexpiprazole in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

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 medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient 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 non-medical 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 adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE)

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity case (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 documented on the AE eSource if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from Phase A 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 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 (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

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

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

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

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and on the eSource provided by the sponsor. Serious AE 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.

A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the source documents and on the eSource provided by the sponsor.

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

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource).

Subjects experiencing SAEs should be followed clinically until their health has returned to Phase A baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

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

5.5 Pregnancy

Women of child-bearing 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 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, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge 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 must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- ICF
- 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 eICF stating that the above-mentioned risk factors and the consequences were discussed with her.

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

During the trial, all WOCBP should be instructed to contact the investigator 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 serum 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 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. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department (see the cover page of this protocol for contact information).

The investigator 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 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

The investigator is encouraged to contact the sponsor/CRO medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

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

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 21 (± 2) days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource page, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the Phase A baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

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

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

6 Pharmacokinetic/Pharmacogenomic Analysis

Collected blood samples in the Stabilization Phase (Phase B) during the Week 16 and Week 20 visits and in Double Blind Randomized Withdrawal Phase (Phase C) during the Week 37 and Week 46/ET visit will be analyzed for plasma concentrations of brexpiprazole. The samples will be collected at the same time of collection of clinical laboratory samples and the time of the last 3 doses prior to the PK sampling will also be collected at the time of PK sample collection.

A sample to assess the CYP2D6 metabolizing status and other enzymes will be collected at the Week 20/Randomization visit. [redacted]

7 Statistical Analysis

Complete details of the planned statistical analysis will be presented in the statistical analysis plan (SAP).

7.1 Sample Size

The primary objective of this trial is to show superiority of brexpiprazole (2 to 3 mg/day) + ADT over placebo + ADT in time to relapse of MDD signs and/or symptoms. Time-to-relapse criteria are defined in the blinded addendum to this protocol. The 2-sided log-rank test will be used to test for statistical significance of the differences between the 2 survival curves.

Based on the results from a completed randomized withdrawal trial of olanzapine/fluoxetine combination versus fluoxetine monotherapy to assess prevention of relapse in subjects with treatment-resistant depression, it is reasonable to expect that 30% of subjects who receive placebo and 16% of subjects treated with brexpiprazole will relapse in 6 months, a hazard ratio of 0.49 (brexpiprazole + ADT versus placebo + ADT) is derived. Thus, 104 relapse events are needed in this trial to reach 95% power to test the primary hypothesis of the protocol at a 2-sided 0.05 alpha level. The sample size estimates used a 1:1 randomization ratio (brexpiprazole + ADT: placebo + ADT) which allowed 2 interim looks at 50% and 75% of events accrual time points. The O'Brian-Fleming boundaries were used for sample size calculation of the interim analysis so that the first interim analysis will be conducted when 52 relapse events are available and the second interim analysis will be conducted when 78 relapse events are available. The 2-sided alpha levels for these 2 interim analyses are 0.003 and 0.018 respectively, and the alpha left for the final analysis when 104 relapse events are available will be 0.044.

Assuming that each subject will be followed for 6 months after randomization and allowing for a 20% loss to follow-up, the projected total number of subjects to be randomized into the trial is 450. Using a 1:1 randomization ratio, the number of subjects to be randomized into each treatment group is 225. Assuming approximately 68% of subjects will progress from the Stabilization Phase (Phase B) to Double-blind Randomized Withdrawal (Phase C), it is expected that 700 subjects will be enrolled into the Stabilization Phase of the trial to allow 450 subjects to be randomized. Assuming approximately 55% subjects will be progress from the Acute Treatment Phase to the Stabilization Phase, it is expected that approximately 1450 subjects will be enrolled into the Acute Treatment Phase. However, only the number of relapse events (ie, 104 events) is the hard sample size in this protocol. The other estimates, such as number of randomized subjects and number of subjects entering the Acute Treatment Phase and the Stabilization Phase, are only based on projection using assumptions that may or may not hold in this trial. Therefore, the actual number of subjects enrolled into the Acute Treatment Phase, the Stabilization Phase, or Double-blind Randomized Withdrawal Phase may vary from the projected values.

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

- Phase A Safety Sample: Comprises all subjects who took at least 1 dose of brexpiprazole in Phase A.
- Phase B Safety Sample: Comprises all subjects who took at least 1 dose of brexpiprazole in Phase B.
- Phase B Efficacy Sample: All subjects who enter Phase B (ie, receive at least 1 dose of brexpiprazole) and have at least one postbaseline efficacy evaluation in Phase B.
- Phase C Safety Sample: All subjects who are randomized to double-blind treatment and receive at least 1 dose of double-blind IMP in Phase C.
- Phase C Efficacy Sample: Based on the Intent-to-Treat (ITT) principle, the full analysis set of this trial will be composed of all subjects randomized to the double-blind treatment who take at least one dose of IMP in Phase C and who have at least 1 post-randomization efficacy evaluation in Phase C.

For the primary analysis of time to event, all subjects belonging to the Phase C Efficacy Sample will be included in the analysis. Subjects who withdraw early from the trial or who are still in the trial at the end of Week 46 will be considered as providing censored observations.

The observed case (OC) dataset will consist of the actual observations recorded at each visit and will be used to present summaries per trial week.

The LOCF data set will include data recorded at a given Phase C visit or, if no observation is recorded at that visit, data carried forward from the previous Phase C visit. Week 20 data (the last visit of Phase B) will not be carried forward to impute missing values for the LOCF data set.

The LOCF and OC data sets for Phases A and B will be derived in a manner similar to the process described for Phase C.

7.3 Handling of Missing Data

For missing data resulting from early withdrawal from the trial in Phase C, subjects who withdraw early will be censored in the primary efficacy analysis at the time when they withdraw from the trial. In order to assess sensitivity of results due to missing data, two types of analyses will be performed for analyses by visit in Phases B and C: LOCF and OC. The LOCF and OC data sets are defined in the SAP. The OC data set will be used for analyses at each trial visit and the LOCF data set will be used for analyses at the last visit.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary efficacy endpoint of this trial is time-to-relapse by any criteria as defined in the blinded addendum to this protocol, measured from Week 20 (randomization) into the Double-blind, Randomized Withdrawal Treatment Phase). The objective of the primary analysis is to compare the efficacy of brexpiprazole (2 to 3 mg/day) + ADT with that of placebo + ADT with regard to time-to-relapse. The statistical comparison will be performed by the log-rank test comparing the 2 treatment groups (brexpiprazole + ADT versus placebo + ADT) at an overall nominal significance level of 0.05 (2-sided) using the Double-blind Randomized Withdrawal Efficacy Sample. Interim analyses are planned to be performed at approximately 50% and 75% of events accrual time points using the O'Brian-Fleming boundaries for rejection of the null hypothesis. Details of the interim analyses are provided in Section 7.4.4.

Additionally, for the primary endpoint, a 95% confidence interval for the hazard ratio (brexpiprazole + ADT vs placebo + ADT) will be provided using the Cox Proportional Hazard model with term of treatment in the model.

The Phase C Efficacy Sample will be used in the above analysis. Subjects who withdraw early from the trial or who are still in the trial at the end of Week 46 will be considered as providing censored observations. Subjects who stay in the trial but have no relapses in an interim analysis will be censored at the date of data cut-off for the interim analysis.

7.4.2 Secondary Endpoint Analysis

7.4.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints are:

- Change from randomization in the SDS mean total score at Week 46 (LOCF)
- Time to-functional relapse based on SDS criteria.

In order to preserve the overall type I error rate at the 0.05 level, the following testing procedure will be used. If the primary hypothesis of comparing time-to-relapse between brexpiprazole + ADT and placebo + ADT is rejected at an overall nominal alpha level of 0.05, then the hypothesis of comparing first key secondary efficacy endpoint of change from randomization in the SDS mean total score at Week 46 between brexpiprazole + ADT and placebo + ADT will be tested at the 0.05 level. If the hypothesis based on the first key secondary endpoint is rejected at the 0.05 level, then the hypothesis of comparing the other key secondary efficacy endpoint of time-to-functional relapse based on SDS criteria between brexpiprazole + ADT and placebo + ADT will be tested at the 0.05 level.

7.4.2.2 Other Secondary Efficacy Endpoints

Secondary efficacy measures include assessment of rates of relapse and time-to-relapse for individual relapse criteria. Response, stabilization, and remission rates will also be assessed for brexpiprazole administration prior to randomization. Response is defined based on MADRS and CGI-S criteria, and remission is defined based on MADRS criteria.

Other secondary efficacy endpoints evaluated for the Double-blind Randomized Withdrawal Phase will include:

- Percentage of subjects who relapse
- Percentage of subjects maintaining remission
- Mean change from randomization in MADRS score (LOCF)
- Mean change from randomization in CGI-S score (LOCF)
- Mean change from randomization in each of the SDS individual item scores (LOCF)

Baseline for the Double-blind Randomized Withdrawal Phase (Phase C) is Week 20, which is the last visit of the Stabilization Phase prior to the first dose of double-blind IMP in the Double-blind Randomized Withdrawal Phase. Analysis of the change from randomization for other secondary efficacy endpoints will be based on subjects in the

Phase C Efficacy Sample. Analysis of the CGI-S score endpoint will be based on subjects in the Phase C Efficacy Sample who have post-Phase C baseline CGI-S observations.

For the other secondary efficacy parameters in the Double-blind Randomized Withdrawal Phase, time-to-relapse variables will be analyzed by the same log-rank test and Cox Proportional Hazard model described in the primary analysis, percentage of subjects will be analyzed by the CMH tests adjusting for country, and mean change from randomization variables will be analyzed by an ANCOVA approach using LOCF data, with terms of treatment, center, and baseline as a covariate. As exploratory analyses, MMRM approach with terms of treatment, center, visit, treatment visit interaction, and baseline visit interaction using observed data will performed.

Descriptive statistics will be provided for the Acute Treatment Phase and the Stabilization Phase. Details of efficacy analyses will be provided in the SAP.

[redacted]

7.4.4 Interim Analysis

Two interim analyses are planned for assessment of efficacy. These analyses are planned to be performed following a group sequential approach at approximately 50% and 75% of events accrual time points and will include all randomized subjects. The second interim analysis (at 75% of events) will be performed only if the first interim analysis is not positive. Subjects who withdraw early from the trial or who are still in the trial at the end of Week 46 will be considered as providing censored observations. The O'Brian-Fleming boundaries will be used for the interim analysis so that the first interim analysis will be conducted when 52 relapse events are available and the second interim analysis, if needed, will be conducted when 78 relapse events are available (Table 7.4.4-1).[28] The 2-sided alpha levels for these two interim analyses are 0.003051 and 0.018325 respectively, and the alpha left for the final analysis will be 0.044005. Additionally, a 95% confidence interval for the hazard ratio (brexpiprazole + ADT vs placebo + ADT) will be provided

using the Cox Proportional Hazard model with term of treatment in the model. If the null hypothesis is rejected at either interim analysis time point, the trial will be terminated for having achieved the primary endpoint of a significantly lower incidence with brexpiprazole + ADT compared with placebo + ADT. A separate Relapse Event Evaluation Committee will review and track each relapse event identified and documented. An Interim Analysis Plan will be developed to document the details of data flow and other logistical considerations relating to the interim analyses.

Table 7.4.4-1 Boundaries for Rejection of Null Hypothesis for Interim and Final Analyses

Analysis	Number of events	2-sided alpha Level[a]
Interim analysis #1 (~50%)	52	0.003051
Interim analysis #2 (~75%)	78	0.018325
Final analysis (100%)	104	0.044005

[a]Obtained using PASS 14 sample size software.

The interim monitoring of efficacy will be performed by an independent IARC (Section 3.7.7). Should the interim analysis be performed at a different time, different frequency, the spending function approach as originally introduced by Lan and DeMets[29] will be applied to adjust the critical values in order to guarantee an overall 0.05 alpha level. The spending functions corresponding to O'Brien-Fleming boundaries will be formally applied to the time-to-event analysis (using the log-rank test).

7.5 Analysis of Demographic and Baseline Characteristics

Demographic characteristics at Phase C baseline including age, race, ethnicity, gender, weight, height, and body mass index (BMI) for the randomized subjects will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

Disease severity and psychiatric history at Phase C baseline will also be summarized by descriptive statistics for the Safety Sample to identify any potential lack of balance between the treatment groups for the Phase C efficacy sample.

7.6 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (C-SSRS) and EPS (eg, the SAS, AIMS, and BARS). Safety analysis will be conducted based on the Safety Sample defined in Section 7.2. In general, baseline of a safety variable is defined as the last observation of

the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

7.6.1 Adverse Events

7.6.1.1 Phase A

Deaths, serious TEAEs, and AEs leading to discontinuation from trial or trial treatment during Phase A will be listed for the Phase A Safety Sample.

7.6.1.2 Phase B

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:

- Treatment-emergent adverse events (TEAEs)
- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

7.6.1.3 Phase C

The incidence of the following events will be summarized by treatment group (brexpiprazole +ADT versus placebo + ADT):

- TEAEs
- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements and prolactin concentrations will be provided. In addition, the incidence of potentially clinically relevant values identified using criteria prospectively defined in the SAP for laboratory tests will be summarized for Phases B and C. Analyses will be

performed using the Safety Sample appropriate to the trial phase. Results will be presented by treatment group (brexpiprazole +ADT versus placebo + ADT) for Phase C.

7.6.3 Physical Examination and Vital Signs Data

Physical examination findings will be listed by subject. Potentially clinically relevant results in vital signs and body weight will also be summarized.

Summary statistics for change from baseline in vital signs, body weight, and waist circumference will be provided.

7.6.4 Electrocardiogram Data

Mean change from baseline and incidence of clinically significant changes will be calculated for ECG parameters. The data will be provided for each trial phase using the appropriate Safety Sample.

For the analysis of QT and QTc data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: QTcB = QT/(RR)0.5, and
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: QTcF = QT/(RR)0.33

Results will be summarized by visit.

7.6.5 Other Safety Data

Descriptive statistics will be provided for change from baseline to end of phase in SAS, AIMS, and BARS scores for Phases A, B and C, separately. Results will be summarized by visit. In addition, change from end of Phase B to end of Phase C in scores for the SAS, AIMS, and BARS scales will be evaluated using ANCOVA with baseline value as covariate and treatment as factor. The OC data sets will be used in the analyses of these EPS scales.

Suicidality monitored during the trial using the C-SSRS will be summarized as number and percentage of subjects reporting any suicidal behavior, ideation, behavior by type (4 types), ideation by type (5 types), and treatment-emergent suicidal behavior and ideation.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the IB.[13]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) 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 disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

Antidepressant therapies will be supplied as bulk drug in commercial packaging (eg, bottles) with an ancillary trial-specific label that will be positioned such that it will not obscure the original commercial label. The Sponsor reserves the right to use a generic equivalent, should any marketed antidepressant become unavailable during the course of the trial. Each ADT bottle used in the trial will be labeled to clearly disclose the bottle number, subject ID, subject's initials, protocol number, ADT drug name, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements. The amount of open-label ADT dispensed to a subject at each visit will be contingent upon the prescribed daily dose of ADT as well as the duration between trial visits.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored according to the storage conditions indicated on the clinical label(s). The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

All used IMP containers, unused IMP, and partially-used IMP should be destroyed at the trial site(s) or at the site level in accordance with all local and national regulations.

On-site destruction will only occur after drug accountability for the IMP being destroyed has been completed by the CRA (clinical research associate). On-site destruction will be performed by both site personnel and CRA personnel. On-site Destruction Certificates

will be linked to specific drug unit ID number(s) or batch number(s) and quantities of clinical supplies destroyed at the clinical site. The original Destruction Certificates will be retained at clinical sites, and copies will be placed in the trial master file.

8.5 Reporting of Product Quality Complaints

A product quality complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- 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 or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to OAPI-EQCProductComplaints@Otsuka-us.com
- Phone - Rocky Mountain Call Center at 1-800-438-6055.

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

8.5.2 Information Required for Reporting Purposes

- Description of compliant

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

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC 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 local regulatory requirements.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's 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 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 progress notes as described above.

Source documents and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application - rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical

research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper 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 clinician.

Another exception will be safety laboratory data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source record will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered on the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Food and Drug Administration (FDA) regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated

during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

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, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site 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 data on the eSource application with source documents. The investigator agrees to participate with audits.

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

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, 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 or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling the eSource, the investigator, sub-investigator and their staff will take measures to ensure adequate care in

protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

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

12 Confidentiality

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

Subjects will be identified only by unique subject numbers on the eSource. 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/IEC. 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/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC 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 after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such

cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

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

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

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

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

15 References

1 Neirenberg AA, Petersen TJ, Alpert JE. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. J Clin Psychiatry. 2003;64 Suppl 15:13-17.

2 American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. Arlington, VA: American Psychiatric Association; 2010.

3 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006 Nov;163(11):1905-1917.

4 Papakostas GI. Major depressive disorder: Psychosocial impairment and key considerations in functional improvement. Am J Manag Care. 2009;15:S316-321.

5 Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology. 2006;31:1841-1853.

6 Nelson JC. The STAR*D study: a four-course meal that leaves us wanting more. Am J Psychiatry. 2006 Nov;163(11):1864-1866.

7 McIntyre RS, O'Donovan C. The human cost of not achieving full remission in depression. Can J Psychiatry. 2004;49(Suppl 1):S10-16.

8 Trivedi MH, Thase ME, Osuntokun O, Henley DB, Case M, Watson SB, et al. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. J Clin Psychiatry. 2009;70:387-396.

9 Bauer M, El-Khalili N, Datto C, Szamosi J, Eriksson H. A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. J Affect Disord. 2010;127:19-30.

10 Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008;28:156-165.

11 Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68:843-853.

12 Gao K, Kemp DE, Fein E, Wang Z, Fang Y, Ganocy SJ, et al. Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. J Clin Psychiatry. 2011;72:1063-1071.

13 Otsuka Pharmaceutical Co, Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., H. Lundbeck A/S. REXULTI® (brexpiprazole) Investigator's Brochure, Edition 13. Otsuka Report, issued 10 Aug 2017.

[14] Brunner E, Tohen M, Osuntokun O, Landry J, Thase ME. Efficacy and safety of olanzapine/fluoxetine combination vs fluoxetine monotherapy following successful combination therapy of treatment-resistant major depressive disorder. Neuropsychopharmacology. 2014;39(11):2549-2559.

[15] Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. Neuropsychopharmacol. 2006;31:2505-2513.

[16] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.

[17] Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

[18] Sheehan DV. The Anxiety Disease. New York: Charles Scribner & Sons; 1983.

[19] Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11(Suppl 3):89-95.

[20] Sheehan D, Janavs J, Harnett-Sheehan K, Sheehan M, Gray C, Lecrubier Y, et al. Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies, Version 6.0.0. Copyright 1992-2010 Sheehan DV & Lecrubier Y.

[21] Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278-296.

[22] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.

[23] Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649-659.

[24] Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212(Suppl 44):S11-19.

[25] Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publication No. ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare; 1976.

[26] Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-676.

[27] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

[28] O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometric. 1979;35:549-556.

[29] Lan KKG, DeMets DL, Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-663.

Protocol 331-201-00079

16 Appendices

Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,000/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

Protocol 331-201-00079

Appendix 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic Hypotension	≥ 20 mmHg decrease in systolic blood pressure and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not Applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Protocol 331-201-00079

Appendix 3 Criteria for Identifying Electrocardiogram Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTcF ≥ 450 msec (males and females)	

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

Protocol 331-201-00079

Appendix 4 Handling and Shipment of Bioanalytical Samples

Pharmacokinetic Sample Collection

A sample of 4 mL of blood for PK testing will be collected into 4-mL Vacutainer tubes containing sodium heparin. Each tube should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from the tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. All tubes must be labeled using the central lab's bar-code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the PK sample information. It is important to note the exact date and time of the blood collection, the date and time of the last dose of brexpiprazole/placebo prior to each blood draw, and the time of the meal closest to the last dose.

The sample must be stored at −70°C, if available, or −20°C or below. If only a −20°C freezer is available, samples must be shipped within 30 days of collection and primary and backup samples may be shipped together. If samples are stored in a −70°C freezer, then one tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab. If neither a −70°C nor −20°C freezer is available, the primary and backup PK samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.

Pharmacogenomic Sample Collection

A 4-mL whole blood sample for the pharmacogenomic determination of drug metabolizing enzymes and transporters will be collected by venipuncture into a 4-mL Vacutainer tube containing potassium ethylenediaminetetraacetic acid (K2EDTA). Each tube should be gently inverted 10 times to ensure proper mixing with the anticoagulant. Refrigerate the whole blood samples at 4°C for at least 1 day (but no longer than 4 days), then store upright at −20°C or below. If refrigerating is not possible, samples can be frozen directly from ambient. The tube will be shipped on dry ice to the central laboratory.

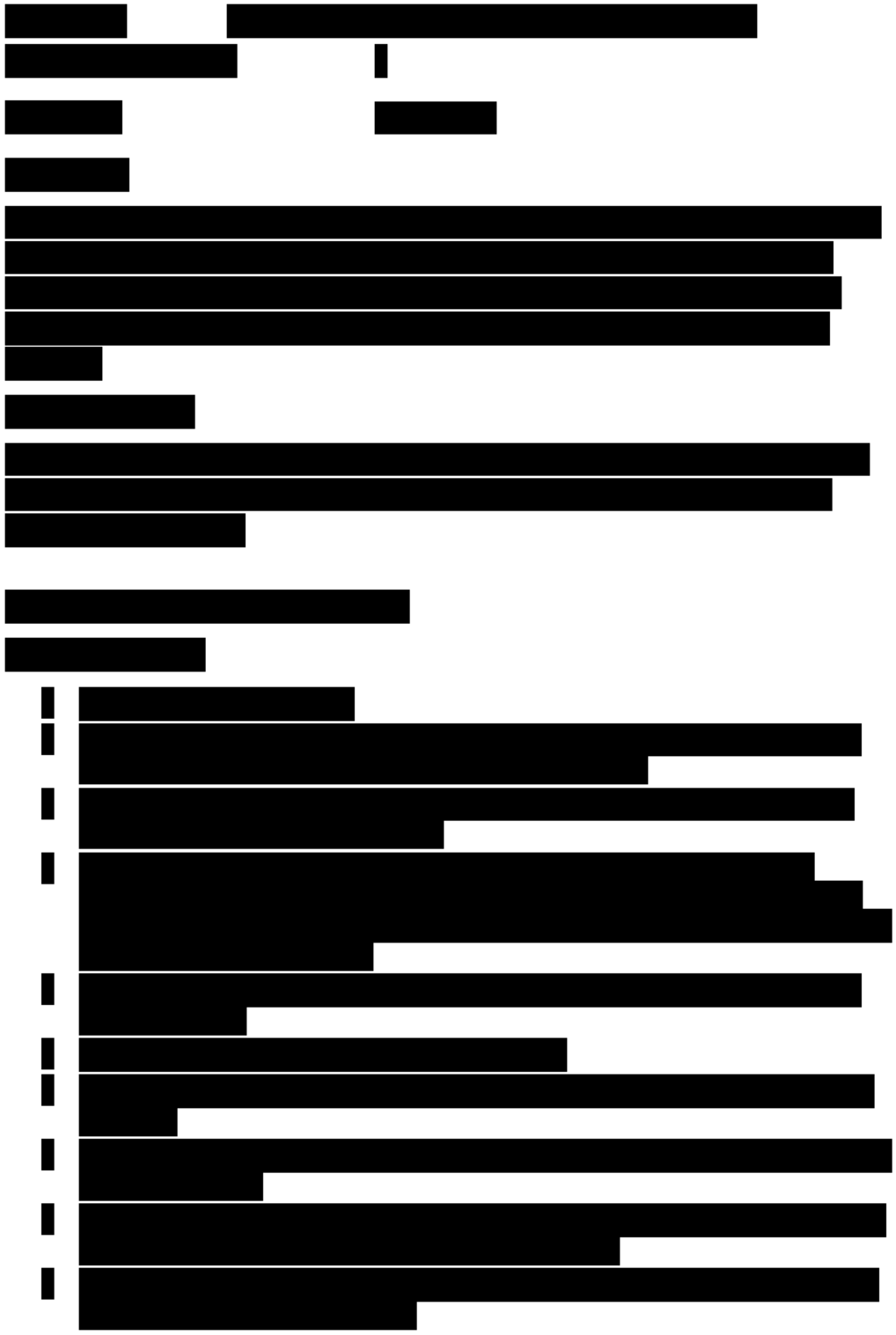
[redacted]

Protocol 331-201-00079

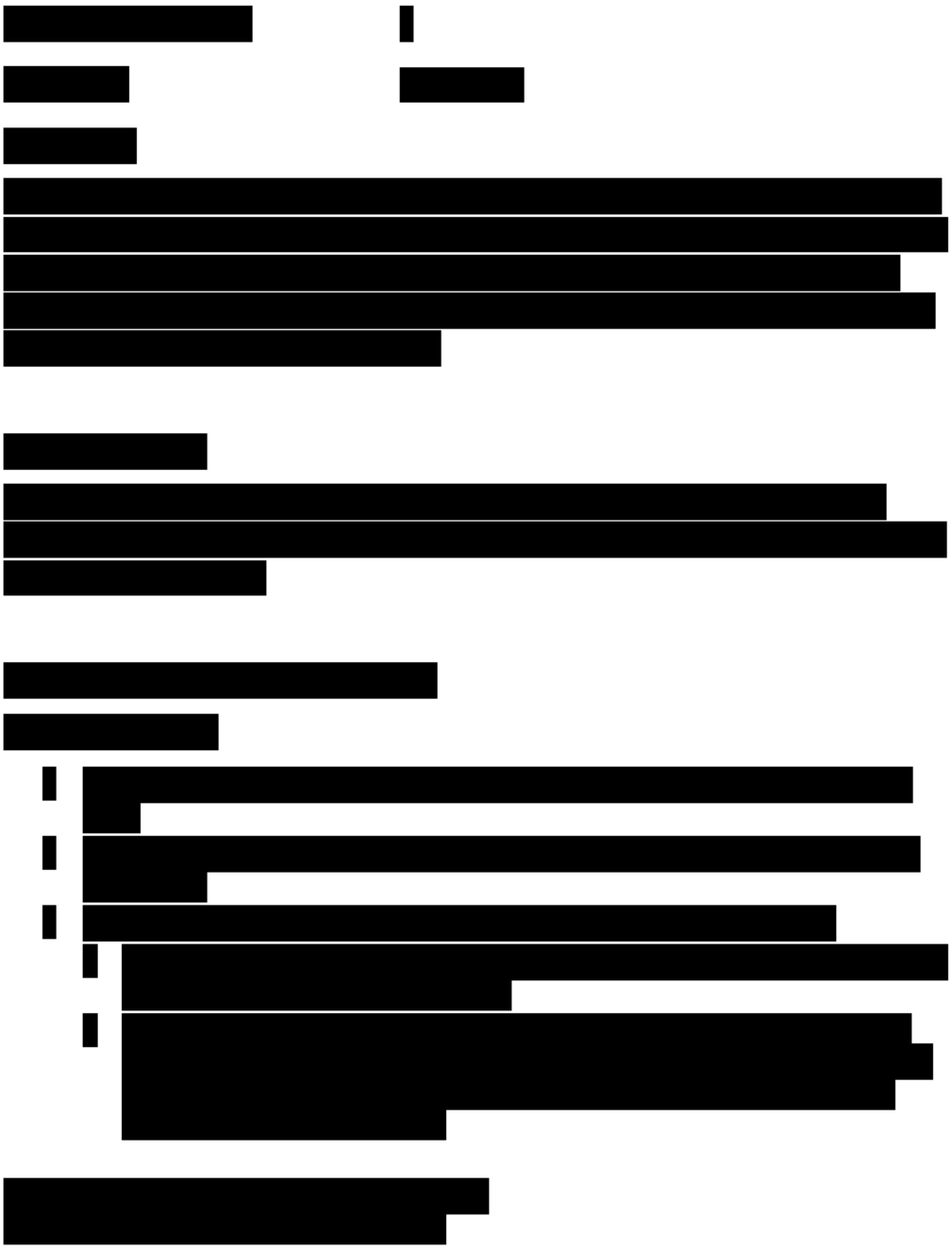
[redacted]

Plasma or whole blood samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container. Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. When possible, samples should be shipped together to reduce the number of shipments.

The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC. Shipments from clinical sites will be via an overnight carrier to the central laboratory.



Protocol 331-201-00079



This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: 331-201-00079 Protocol Amendment 2

Document Number: [redacted]

Document Version: 10.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Approval	08-Jul-2020 13:29:20
[redacted]	Biostatistics Approval	08-Jul-2020 00:31:05
[redacted]	Approved for Clinical Pharmacology and Nonclinical	09-Jul-2020 16:05:01

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 331-201-00079

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole as Adjunctive Therapy in the Maintenance Treatment of Adults With Major Depressive Disorder

Protocol No. 331-201-00079
IND No. 103,958
EudraCT No. 2018-000601-22

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety Fax: (877) 464-7787 E-mail: safetyreporting@syneoshealth.com
Issue Date:	16 Jul 2020

Protocol 331-201-00079

Trial Conduct for COVID-19

All procedures and assessments in the protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, the appropriate measures to be followed will be provided in this document.

Protocol 331-201-00079

Table of Contents

List of In-text Tables

List of In-text Figures

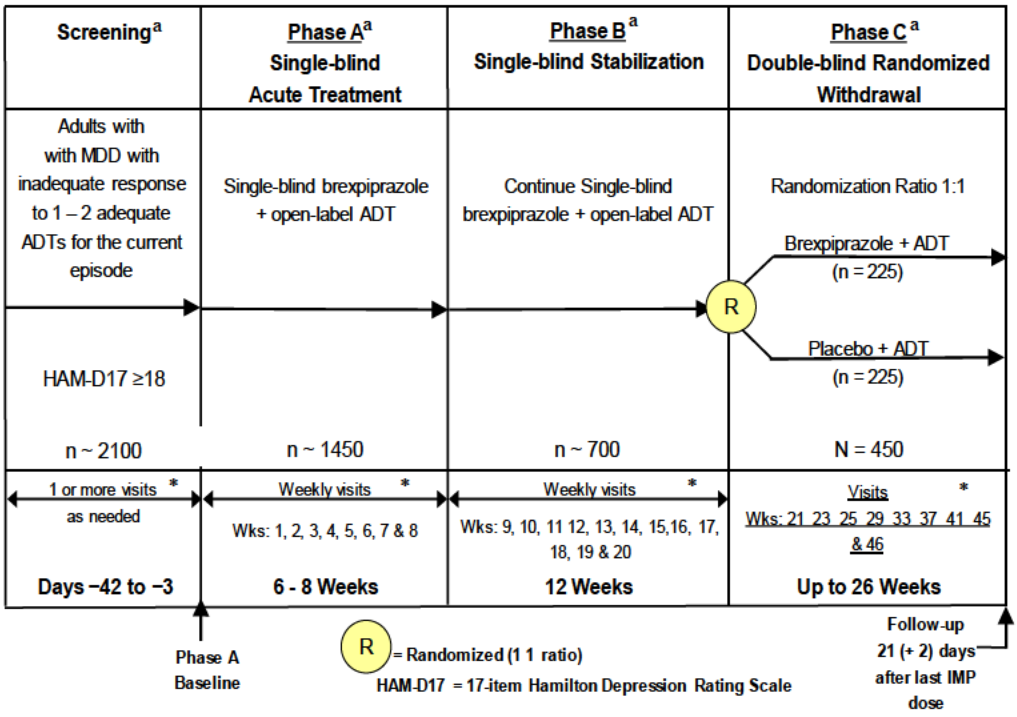
List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
Anti-HCV	Hepatitis C antibodies
aPTT	Activated prothromplastin time
ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
BARS	Barnes Akathisia Rating Scale
CGI-S	Clinical Global Impression - Severity of Illness
C-SSRS	Columbia-Suicide Severity Rating Scale
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
EudraCT	European Clinical Trial Data Base
FOCBP	Females of childbearing potential
HAM-D17	Hamilton Depression Rating Scale
HBsAG	Hepatitis B Surface Antigen
HIV	Human immunodeficiency virus
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional review board
IRE	Immediately reportable event
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
PT	Prothrombin time
SAE	Serious adverse event
SAS	Simpson Angus Scale
SDS	Sheehan Disability Scale
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
US	United States

Protocol 331-201-00079

1 Trial 331-201-00079 COVID-19 Protocol Summary

1.1 Trial Design Schematic



[a]Screening, baseline, and Week 6-8 visits of Phase A; Week 20 of Phase B; and Week 46 of Phase C need to be conducted in clinic

Figure 1.1-1 COVID-19 Impact Trial Design Schematic

1.2 Schedule of Assessments

Table 1.2-1 COVID-19 Impact Schedule of Assessments (Phase A)

Assessment	Screening	Acute Treatment Phase								
	Day −42 to −3	Phase A Base-line	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	Week 7 (± 2 days) (as needed)[a]	Week 8/ End-of Phase A or ET[a] (± 2 days)
	In-person	In-person						In-person	In-person	In-person
Entrance criteria and subject history										
Informed Consent	X									
Inclusion/exclusion criteria	X	X								
Demography	X									
Medical history	X									
Psychiatric history	X									
MINI	X									
HAM-D17	X	X								
Antidepressant history	X									
Prior medication washout[b]	X									
HIV, HBsAg, and anti-HCV[c]	X									
Efficacy										
MADRS[d]		X	Remote	Remote	Remote	Remote	Remote	X	X	X
CGI-S[d]		X	Remote	Remote	Remote	Remote	Remote	X	X	X
SDS		X						X		
Safety										
Physical examination[e]	X									X
Vital signs[f]	X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X	X	X
12-lead ECG[h]	X	X								X

Table 1.2-1 COVID-19 Impact Schedule of Assessments (Phase A)

Assessment	Screening	Acute Treatment Phase								
	Day −42 to −3	Phase A Base-line	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	Week 7 (± 2 days) (as needed)[a]	Week 8/ End-of Phase A or ET[a] (± 2 days)
	In-person	In-person						In-person	In-person	In-person
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[c]	X	X								X
Prolactin[c]		X								X
HbA1c[c]	X	X								
TSH, with reflex to T_4 if TSH is abnormal	X									
Coagulation parameters (PT, aPTT, & INR)	X									
Blood alcohol[i]	X					X[j]				X
Urine drug screen[i,k]	X					X[j]				X
Urine pregnancy test (FOCBP only)[l,m]	X	X	Remote			Remote				X
SAS[n]		X						X		
AIMS		X						X		
BARS		X						X		
C-SSRS[o,p]	X	X	Remote	Remote	Remote	Remote	Remote	X	X	X
Adverse events[o]	X	X	Remote	Remote	Remote	Remote	Remote	X	X	X
Concomitant medications[o,q]	X	X	Remote	Remote	Remote	Remote	Remote	X	X	X
Other										
IMP dispensing[r]		X	Remote	Remote	Remote	Remote	Remote	X	X	X
IMP accountability[r]			Remote	Remote	Remote	Remote	Remote	X	X	X

Table 1.2-1 COVID-19 Impact Schedule of Assessments (Phase A)

Assessment	Screening	Acute Treatment Phase								
	Day −42 to −3	Phase A Base-line	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6 (± 2 days)	Week 7 (± 2 days) (as needed)[a]	Week 8/ End-of Phase A or ET[a] (± 2 days)
	In-person	In-person						In-person	In-person	In-person
[redacted]										
[redacted]										
[redacted]										

anti-HCV = hepatitis C antibodies; aPTT = activated prothrombplastin time; ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-S = Clinical Global Impression - Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; ET = End of trial; HBsAg = Hepatitis B Surface Antigen; IMP = Investigational medicinal product; INR = International Normalized Ratio; MADRS = Montgomery Asberg Depression Rating Scale; MDD = Major depressive disorder; MINI = Mini International Neuropsychiatric Interview; PT = prothrombin time; SAS = Simpson Angus Scale; T_4 = Thyroxine; TSH = Thyroid-stimulating hormone; US = United States.

[a]The End of Phase A visit will also be the ET visit for subjects who do not meet the response criteria. The investigator or site staff will provide relevant information for a blinded assessment of score-based response criteria for each subject. Whether or not a subject is an inadequate responder in Phase A will be confirmed by eSource based on the score-based criteria defined in the blinded addendum to this protocol. The site will be notified of the subject's response status during the Weeks 6, 7, or 8 visits. Any subject who does not meet the criteria for adequate response will be discontinued from the trial. If a subject meets response criteria at Week 6 or 7 they will complete the Week 8 procedures and any remaining visits in Phase A will not be completed.

[b]Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods in Table 4.1-1 of protocol. Prohibited and restricted medications requiring a washout of at least 24 hours before the first dose of protocol-specified ADT in Phase A are listed in Table 4.1-2 and Table 4.1-4 of protocol.

[c]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at the baseline visit and should be drawn after a minimum 8-hour fast at all other visits. If fasting blood samples are not feasible at visits other than the baseline visit, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[d]MADRS and CGI-S can be collected remotely by telephone or video.

[e]To include measurement of height and waist circumference at screening and waist circumference at all other time points.

[f]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[g]Vital signs are not required at remote visits; however, vital signs may be collected by the subject at home if appropriate collection devices are available.

[h]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. A QTcF ≥ 450 msec for males and ≥ 470 msec for females at screening is exclusionary. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. Subjects will continue in the trial based on Week 8 ECG results from the trial site. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[i]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

[j]The blood alcohol and urine drug screen assessments can be conducted at a local lab if available.

[k]Eligibility for continuation in the trial beyond the Week 8 visit is based in part on the Week 4 urine drug screen and blood alcohol results. Subjects whose Week 4 urine drug screen is positive for cocaine or other illicit drugs must be withdrawn from the trial. Subjects with a positive urine drug screen at Week 4 due to prescription or OTC medications or products may continue evaluation in the trial only after consultation and approval by the medical monitor.

[l]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[m]Females of child bearing potential (FOCBP) should be sent pregnancy kits for Weeks 4 and 8 visits if possible with IMP dispensation for the week prior (Week 3 visit).

[n]The SAS requires assessment of rigidity and requires physical touch, so it will not be possible to conduct via video remotely and this should be documented accordingly in eSource.

[o]C-SSRS, adverse events, and concomitant medication information can be collected using telephone.

[p]The "baseline/screening" C-SSRS form will be completed for all subjects at screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at the baseline visit to assure that the subject continues to qualify for the trial. Any subject with suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Table 3.4.3-1 of protocol). The "Since Last Visit" C-SSRS form will also be completed at all visits after the baseline visit.

[q]All medications taken within 30 days of informed consent will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in Section 4.1 of the protocol.

[r]IMP should be shipped using courier services. If not using local couriers, other IMP dispensation and accountability is reviewed on a case by case basis.

[redacted]

Table 1.2-2	**COVID-19 Impact Schedule of Assessments (Phase B)**											
Assessment	**Week 9 (± 2 days)**	**Week 10 (± 2 days)**	**Week 11 (± 2 days)**	**Week 12 (± 2 days)**	**Week 13 (± 2 days)**	**Week 14 (± 2 days)**	**Week 15 (± 2 days)**	**Week 16 (± 2 days)**	**Week 17 (± 2 days)**	**Week 18 (± 2 days)**	**Week 19 (± 2 days)**	**Week 20/ Random-ization/ ET[a,b] (± 2 days)**
												In person
Efficacy												
MADRS[c]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
CGI-S[c]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
SDS[c]	Remote					Remote						X
Safety												
Physical examination[d]												X
Vital signs[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
12-lead ECG[g]								X[h]				
Clinical laboratory tests (hematology, serum chemistry, & urinalysis)[i]												X
Prolactin[i]												X
HbA1c[i]												X
Urine drug screen[j]								X[h]				
Urine pregnancy test (FOCBP only)[k,l]				Remote				Remote				X
SAS[m]												X
AIMS[n]				Remote								X

Table 1.2-2 COVID-19 Impact Schedule of Assessments (Phase B)

Assessment	Week 9 (± 2 days)	Week 10 (± 2 days)	Week 11 (± 2 days)	Week 12 (± 2 days)	Week 13 (± 2 days)	Week 14 (± 2 days)	Week 15 (± 2 days)	Week 16 (± 2 days)	Week 17 (± 2 days)	Week 18 (± 2 days)	Week 19 (± 2 days)	Week 20/ Randomization/ ET[a,b] (± 2 days)
												In person
BARS[n]				Remote								X
C-SSRS[o]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
Adverse events[o]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
Concomitant medications[o]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
Other												
Randomization												X
IMP dispensing[p]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
IMP accountability[p]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X
Pharmacokinetic samples[q]												X
Pharmacogenomic sample												X[r]
[redacted]												
[redacted]												

[a]For subjects who meet stability criteria, the Week 20 visit, Randomization, will be the baseline visit for all subsequent Phase C visits; for subjects who do not meet the stability criteria, the Week 20 visit will be the ET visit. Stability criteria are defined in the blinded addendum to this protocol.

[b]If a subject discontinues prematurely, procedures noted for Week 20 must be completed at the ET visit.

[c]MADRS, CGI-S, and SDS can be collected remotely by telephone or video.

[d]Includes waist circumference.

[e]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[f]Vital signs are not required at remote visits; however, vital signs may be collected by the subject at home if appropriate collection devices are available.

[g]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. ECG results will be evaluated at the investigational site to monitor safety. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. The ECG is to be completed before any blood sample is collected.

[h]The ECG and urine drug screen assessments can be conducted at a local lab if available.

[i]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at the Week 20/Randomization visit and should be drawn after a minimum 8-hour fast at all other visits. If fasting blood samples are not feasible at visits other than the Week 20/Randomization visit, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[j]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

[k]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[l]FOCBP should be sent pregnancy kits for Weeks 12, 16, and 20 visits if possible with IMP dispensation for the week prior (Week 3 visit).

[m]The SAS requires assessment of rigidity and requires physical touch, so it will not be possible to conduct via video remotely and this should be documented accordingly in eSource.

[n]AIMS & BARS can be assessed remotely using only video.

[o]C-SSRS, adverse events, and concomitant medication information can be collected using telephone.

[p]IMP should be shipped using courier services. If not using local couriers, other IMP dispensation and accountability is reviewed on a case by case basis.

[q]Pharmacokinetic samples will be collected at the in-clinic visits as per schedule of assessment.

[r]Pharmacogenomic sample is only to be collected during randomization. If a subject early terminates at Week 20, no sample will be collected.

Protocol 331-201-00079

[redacted]

Table 1.2-3 COVID-19 Impact Schedule of Assessments (Phase C)										
Assessments	**Week 21 (± 2 days)**	**Week 23 (± 2 days)**	**Week 25 (± 2 days)**	**Week 29 (± 2 days)**	**Week 33 (± 2 days)**	**Week 37 (± 2 days)**	**Week 41 (± 2 days)**	**Week 45 (± 2 days)**	**Week 46/ ET[a]/ End of Phase C or MDD Relapse (± 2 days)**	**Follow-up Safety visit (21 + 2 days)**
									In person	**In person**
Efficacy										
MADRS[b]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	
CGI-S[b]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	
SDS[b]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	
Safety										
Physical examination[c]									X	
Vital signs[d]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	
12-lead ECG[f]				X[g]					X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[h]									X	
Prolactin[h]									X	
Blood alcohol[i]									X	
Urine drug screen[i]					X[g]				X	
Urine pregnancy test (FOCBP only)[j,k]					Remote				X	
SAS[l]									X	
AIMS[m]			Remote		Remote		Remote		X	

Table 1.2-3 COVID-19 Impact Schedule of Assessments (Phase C)

Assessments	Week 21 (± 2 days)	Week 23 (± 2 days)	Week 25 (± 2 days)	Week 29 (± 2 days)	Week 33 (± 2 days)	Week 37 (± 2 days)	Week 41 (± 2 days)	Week 45 (± 2 days)	Week 46/ ET[a]/ End of Phase C or MDD Relapse (± 2 days)	Follow-up Safety visit (21 + 2 days)
									In person	In person
BARS[m]			Remote		Remote		Remote		X	
C-SSRS[n]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	
Adverse events[n]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	X
Concomitant[n] medications	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	X
IMP dispensing[o]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote		
IMP accountability[o]	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	X	
Pharmacokinetic samples[p]									X	
[redacted]										
[redacted]										

[a]For subjects who discontinue early, attempts should be made to complete ALL evaluations, particularly efficacy assessments (ie, MADRS, CGI-S, and SDS), for the Week 46/ET visit prior to the administration of any new antidepressant medications. However, if the subject receives a new antidepressant prior to ET procedures, no efficacy assessments should be done.

[b]MADRS, CGI-S, and SDS can be collected remotely by telephone or video.

[c]Includes waist circumference.

[d]Vital signs include body weight, body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting, and standing after the subject has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[e]Vital signs are not required at remote visits; however, vital signs may be collected by the subject at home if appropriate collection devices are available.

[f]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. ECG results will be evaluated at the investigational site to monitor safety. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. The ECG is to be completed before any blood sample is collected.

[g]The ECG and urine drug screen assessments can be conducted at a local lab if available.

[h]Blood samples for clinical laboratory tests should be drawn after the subject has been fasting for at least 8 hours, if possible. If fasting blood samples are not feasible, nonfasting blood samples may be collected. Vital sign and ECG assessments should be completed before any blood samples are collected.

[i]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator.

[j]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[k]FOCBP should be sent pregnancy kits for Weeks 33 and 46 visits if possible with IMP dispensation for the week prior (Week 3 visit).

[l]The SAS requires assessment of rigidity and requires physical touch, so it will not be possible to conduct via video remotely and this should be documented accordingly in eSource.

[m]AIMS & BARS can be assessed remotely using only video.

[n]C-SSRS, adverse events, and concomitant medication information can be collected using telephone.

[o]IMP should be shipped using courier services. If not using local couriers, other IMP dispensation and accountability is reviewed on a case by case basis.

[p]Pharmacokinetic samples will be collected at the in-clinic visits as per schedule of assessment.

[redacted]

2 General Considerations

2.1 Reconsent

If there is an immediate need to reconsent subjects during the period of COVID-19 restrictions, a paper reconsent process will be followed and sites are encouraged to contact the contract research organization (CRO) and sponsor with questions. In regions where remote capacity exists to collect remote eConsent, information will be provided by the CRO and sponsor will provide the necessary information.

2.2 Protocol Deviations

Prior to approval of this addendum, protocol deviations that occurred as a direct result of the COVID-19 pandemic were to be recorded in eSource as a protocol deviation for data capture purposes. A “direct result” is defined as being due to actual COVID-19 illness, or as a result of quarantine, social distancing, or site closures. All other deviations will follow the normal deviation process described in the protocol . Following approval of this addendum, the included revised procedures will not longer be classified as protocol deviations and therefore will not be documented within eSource as a protocol deviation for data capture purposes.

2.3 Guidance to Record Adverse Events and Discontinuations Due to COVID-19

If a subject tests positive OR is presumed positive with COVID-19, the subject may continue in the trial with virtual visits only as long as they remain asymptomatic for COVID-19. An adverse event (AE) of “Coronavirus Infection” OR “Coronavirus Positive Test Result” must be recorded on the AE page of the electronic case report form (eCRF). All subjects who are symptomatic for COVID-19 must be reviewed with the medical monitor and approval must be received for the subject to continue in the trial with virtual visits. A positive test result or a presumed positive subject is not automatically a serious adverse event (SAE), unless an SAE criterion is met (eg, hospitalization). If the event meets the criterion for an SAE, then the subject will be discontinued from the trial.

If a subject discontinues due to COVID-19 either because they test positive OR are presumed positive with COVID-19, then the primary reason for discontinuation should be reported as “Adverse Event” and indicate the AE number in the “Specify the reason for

discontinuation" space that corresponds with the AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result." Be sure to remember to enter an AE in the AE form for the "Coronavirus Infection" OR "Coronavirus Positive Test Result."

If a subject discontinues due to COVID-19 other than the subject testing positive OR being presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Other." Be sure to specify the reason as "COVID-19" followed by the reason ensuring that the prefix of the description includes "COVID-19." Do note that the reason "Other" should be selected even if the subject decides to withdraw consent or if the investigator decides to withdraw the subject due to COVID-19 concerns.

2.4 Statistical Analyses

Any impact of COVID-19 on the planned statistical analyses for the trial will be described in the final statistical analysis plan.

2.5 Clinical Outcomes

To decrease variability, sites should attempt to standardize the method of administration for a scale for an individual subject and across all subjects in the trial. Assessments should be administered by the same qualified/trained rater who rated the subject previously; if this is not possible due to staff availability and/or technological limitations, discuss relevant information with previous raters to obtain clinical context (note that per protocol raters must be trained/qualified to conduct assessments in all cases). Raters should conduct all assessments for that visit during the same remote session, where possible.

Please refer to "Virtual Visit Instructions for Sites" for modification of administration methods for remote visits.

3 Trial Population

3.1 Inclusion Criteria

The subject must provide electronic informed consent form (eICF) at screening and must be able to understand that he or she can withdraw from the trial at any time. All eICF procedures must be in accordance with the trial site's IRB/IEC and local regulatory requirements.

3.2 Exclusion Criteria

Subjects will be excluded if experiencing COVID-19 infection or infection symptoms.

4 Trial Procedures

4.1 Safety Assessments

4.1.1 Pregnancy

Pregnancy tests will be performed as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- For planned visits that require a pregnancy test for females of child bearing potential (FOCBP), the site will provide the necessary tests and instructions so the test may be performed at home;
- Applicable subjects will perform a pregnancy test prior to dosing with IMP, ensuring a date and time-stamped picture or video of the result is taken, followed by notification to the site staff of the results via telephone, or other means, on the appropriate visits. Subjects will also provide the site staff with the date- and time-stamped picture/video.
  - If negative, site to inform the subject to proceed with dosing.
  - If positive, the site must instruct the subject to immediately stop taking IMP, and the site will refer to the Pregnancy section of the protocol for appropriate immediately reportable event reporting.
    - Further instruction must be agreed upon in consultation with the sponsor but an option may include the site informing the subject to continue to withhold IMP and to perform a repeat urine pregnancy test in 2 days (> 48 hours from first test). Subjects would again be asked to take a date and time-stamped picture or video of the result, followed by notification to the site staff of the results via telephone, or other means. Subjects would also provide the site staff with the date- and time-stamped picture/video.
      - If the second result is positive, the subject will be discontinued from the trial, and be instructed to contact their healthcare professional and the trial site (if possible) for further instructions.
      - If the second result is negative, the site will contact the CRO and sponsor for guidance and next steps.

4.1.2 Extrapyramidal Symptom Scales

The subjects will be administered extrapyramidal symptom (ESP) assessments (AIMS and BARS) remotely by providing the subject verbal instructions and observing their movements over video. Any ESP assessments unable to be completed due to COVID-19 restrictions should be documented accordingly in eSource.

5 Investigational Medicinal Product

Clinical sites are permitted to ship IMP directly to subjects per agreed study processes due to COVID-19 restrictions.