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- **Document title:** A Long-term, Phase 3, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Oral OPC-34712 as Adjunctive Therapy in Adults with Major Depressive Disorder, the Orion Trial.
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Long-term, Phase 3, Multicenter, **O**pen-label T**r**ial to Evaluate the Safety and Tolerab**i**lity of **O**ral OPC-34712 as Adju**n**ctive Therapy in Adults with Major Depressive Disorder, the Orion Trial

Protocol No. 331-10-238
IND No. 103,958
EudraCT No. 2011-001351-37

CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	3
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Protocol Synopsis

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: Brexpiprazole (OPC-34712)	Protocol #331-10-238 IND #103,958 EudraCT #2011-001351-37
Protocol Title:	A Long-term, Phase 3, Multicenter, **O**pen-label T**r**ial to Evaluate the Safety and Tolerab**i**lity of **O**ral OPC-34712 as Adju**n**ctive Therapy in Adults with Major Depressive Disorder, the Orion Trial
Clinical Phase:	3
Treatment Indication:	Major Depressive Disorder (MDD)
Objective(s):	Primary: To assess the long-term safety and tolerability of oral OPC-34712 (hereafter referred to by the generic name "brexpiprazole") as adjunctive therapy in the treatment of adults with MDD. Secondary: To assess the long-term efficacy of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD.
Trial Design:	This is a multicenter, 26-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed the last scheduled visit of a double-blind, phase 3 brexpiprazole MDD trial and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD. The original 52 week open-label trial design has been modified in this Amendment 3 to shorten the duration of the trial to 26 weeks; ongoing subjects who have not reached their Week 26 visit will be re-consented and will follow Amendment 3 schedule of assessments. Ongoing subjects who have already completed their Week 26 visit at the time of Amendment 3 will follow Amendment 3 week 26/ET schedule of assessments at their next scheduled visit. The trial will be organized as follows: *Screening/Baseline:* Subjects will be screened for eligibility at the last scheduled visit of the prior double-blind phase 3 trial. Subjects will sign a separate informed consent form for participation in Trial 331-10-238 before any procedures

	specific to the open-label trial are performed. The assessments from the last scheduled visit of the prior double-blind phase 3 trial will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary. *Treatment Phase:* Eligible subjects will receive daily treatment with open-label brexpiprazole and ADT as described in the Investigational Medicinal Product, Dose, Formulation, Mode of Administration section. Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20, and 26. All subjects will receive up to 26 weeks of open-label treatment in Trial 331-10-238. *Follow-up:* Subjects will be followed for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.
Subject Population:	The subject population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD according to the following criteria: • Subjects who participated in Trial 331-10-227, Trial 331-10-228 or 331-13-214 will be eligible for the 331-10-238 trial if they meet one of the following conditions: • Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of Phase B) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214 or • Subjects who continued into Phase A+ (were not randomized into Phase B) at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214, BUT DID NOT meet criteria for remission (defined as a Montgomery Asberg Depression Rating Scale Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214. • Subjects who participated in another double-blind phase 3 brexpiprazole MDD trial will be eligible for 331-10-238 Trial if they have completed the last scheduled visit of the prior double-blind phase 3 trial. • Subjects must qualify for Trial 331-10-238 at the last scheduled visit of the prior double-blind phase 3 trial and

	must be able to continue therapy without interruption between the double-blind and open label trials. Based on the projected enrollment estimates for the prior double-blind phase 3 brexpiprazole MDD trials, up to approximately 3,000 subjects may enroll into Trial 331-10-238.
Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	Trial medication (ie, investigational medicinal product [IMP]) will be provided to the investigator(s) by the sponsor (or designated agent) and will consist of open-label brexpiprazole and open-label ADTs. *Brexpiprazole:* Open-label brexpiprazole will be supplied as 0.5, 1, 2, and 3-mg tablets packaged in weekly blister cards, each containing sufficient tablets for 7 (+ 2 days). Blister cards will be dispensed at each scheduled visit and at unscheduled visits if the dose of brexpiprazole is changed. All doses of brexpiprazole should be taken orally once daily and can be administered without regard to meals. For convenience, brexpiprazole may be taken with the first daily dose of ADT. All subjects will be dosed as follows: • The first dose of open-label brexpiprazole will be taken one day after the last dose is taken for the prior double-blind, phase 3 brexpiprazole MDD trial so that adjunctive treatment will continue without interruption. It is anticipated that the last dose of the double-blind, phase 3 brexpiprazole MDD trial will be taken the day of the last scheduled visit, ie, the day of the Screening/Baseline visit for the open-label trial. Subjects will initiate open-label dosing with brexpiprazole 0.5 mg/day for 1 week. Subjects unable to tolerate brexpiprazole 0.5 mg/day must be withdrawn from the trial. • The dose of brexpiprazole will be increased to 1 mg/day at the Week 1 visit. Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit. • Investigators may further increase the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments is recommended for dose decreases; however, the dose of brexpiprazole can be decreased at the investigator's discretion in a step-wise manner at any time after the

Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

- Subjects who tolerate a reduced dose of brexpiprazole 0.5 mg/day should be rechallenged with brexpiprazole 1 mg/day at least once during the trial. In addition, the dose of brexpiprazole can be re-escalated as necessary following any dose decrease if, in the investigator's judgment, rechallenge with a higher dose is warranted in order to identify an optimum dose for the subject. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

ADT: During the Treatment Phase of Trial 331-10-238, subjects will remain on the same assigned open-label ADT from the prior double-blind, phase 3 brexpiprazole MDD trial. The initial dose of ADT will be the same as the ADT dose taken on the last scheduled visit of the prior double-blind phase 3 trial. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). *After the Week 4 visit*, the dose of ADT can be modified if necessary to achieve optimum efficacy and tolerability for the treatment regimen using the following rules: 1) at least 5 days must elapse between dose increases (either brexpiprazole or ADT), 2) an interval of at least 5 days between dose adjustments (either brexpiprazole or ADT) is recommended for dose decreases; however, the ADT dose can be decreased at the investigator's discretion at any time as needed for tolerability, and 3) subjects must return to the clinic for unscheduled visits if changes to the ADT dose are required between scheduled visits.

ADTs for open-label treatment will be provided in commercial packaging (eg, bottles), with additional labeling for use in this trial, as necessary to fulfill regulatory requirements. Numbered ADT bottles to be dispensed to the subject will be assigned by the IVRS or IWRS. The ADTs to be used in this trial, including allowable doses within the therapeutic range, are as follows:

<u>Selective Serotonin Reuptake Inhibitors:</u>

	Escitalopram (Lexapro®) tablets, 10 and 20 mg/day Fluoxetine (Prozac®) capsules, 20 and 40 mg/day Paroxetine CR (Paxil CR®) controlled-release (CR) tablets, 37.5 and 50 mg/day Sertraline (Zoloft®) tablets, 100, 150, and 200 mg/day Serotonin-norepinephrine Reuptake Inhibitors: Duloxetine (Cymbalta®) delayed-release capsules, 40 and 60 mg/day Venlafaxine XR (Effexor XR®) extended-release (XR) capsules, 75, 150, and 225 mg/day All doses of ADT will be administered orally once daily except for duloxetine 40 mg/day that can be administered once daily or as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily. All ADTs can be given without regard to meals, except for venlafaxine XR which should be taken with food. Subjects should be instructed to take the ADT at approximately the same time each day, if possible.
Criteria for Evaluation:	Primary Outcome Variable: The primary outcome variable is the safety and tolerability of brexpiprazole which will be assessed by examining the frequency and severity of adverse events (AEs). Secondary Outcome Variables: Efficacy: Efficacy variables will be as follows: • Change from baseline in Clinical Global Impression - Severity of Illness scale score; • Mean Clinical Global Impression - Improvement scale score; • Change from baseline in Sheehan Disability Scale score. • Change from baseline in the Inventory of Depressive Symptomatology (Self-Report) Total Score Safety: In addition to AEs, safety variables to be examined in this trial will include physical examinations, vital signs, body weight, waist circumference, clinical laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy tests), and electrocardiograms (ECGs). In general, descriptive

	statistics of changes from baseline will be provided for safety variables based on all available data. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Change from baseline in body mass index (derived programmatically from body weight and height measurements) will be summarized. In addition to the analysis of standard safety variables, other safety variables including the Simpson Angus Scale, the Abnormal Involuntary Movement Scale, the Barnes Akathisia Rating Scale, the Columbia-Suicide Severity Rating Scale, and the Massachusetts General Hospital Sexual Functioning Questionnaire will also be evaluated. Other Outcomes: Responses to the Resource Utilization Form (RUF) will be summarized appropriately to explore the impact of treatment on health care resources.
Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 57 months, of which approximately 51 months are allotted for rollover of subjects from the prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 30 weeks (26 weeks of treatment and 30-day follow-up).

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADHD	Attention-deficit/hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine transaminase
APO	Apomorphine
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate transaminase
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity of Illness scale
C_{max}	Maximum (peak) plasma concentration of the drug
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Controlled-release
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D2	Dopamine type 2 receptor
D3	Dopamine type 3 receptor
DBP	Diastolic blood pressure
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
ET	Early termination
EudraCT	European Clinical Trial Data Base
FDA	Food and Drug Administration
5-HT	Serotonin
5-HT1A	Serotonin type 1A receptor
5-HT2A	Serotonin type 2A receptor
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAM-D17	17-item Hamilton Depression Rating Scale

HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
HEENT	Head, eyes, ears, nose, and throat
hERG	Human ether-a-go-go
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification
IDDM	Insulin-dependent diabetes mellitus
IDS-SR	Inventory of Depressive Symptomatology (Self-Report)
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional review board
IRE	Immediately reportable event
IUD	Intrauterine device
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last-observation-carried-forward
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MSFQ	Massachusetts General Hospital Sexual Functioning Questionnaire
NMS	Neuroleptic malignant syndrome
OC	Observed cases
OPC	Otsuka Pharmaceutical Co.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
OTC	Over-the-counter
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Prothrombin time
QTc	Corrected QT interval
QTcB	QT interval as corrected by Bazett's formula
QTcF	QT interval as corrected by Fridericia's formula
QTcN	QT interval as corrected by the FDA Neuropharm Division formula
RBC	Red blood cell
RUF	Resource Utilization Form
SAE	Serious adverse event
SAS	Simpson Angus Scale
SBP	Systolic blood pressure

SDS	Sheehan Disability Scale
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
T_4	Thyroxine
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
XR	Extended-release

Term	**Definition**
Investigational medicinal product (IMP)	For the purposes of this protocol, IMP refers to all trial medication supplied to the sites by the sponsor (or designated agent) and includes bottles of protocol-specified ADTs and blister cards containing brexpiprazole.
Remission	Montgomery Asberg Depression Rating Scale Total Score ≤ 10.

1 Introduction

Major depressive disorder (MDD) is a debilitating and chronic illness characterized by a broad spectrum of emotional and physical symptoms. Despite the availability of numerous treatments (eg, pharmacotherapy, cognitive behavioral psychotherapy, electroconvulsive therapy [ECT], etc.), achievement of consistent and favorable long-term outcomes still represents an unmet medical need. For patients who experience an initial major depressive episode, the probability of experiencing another episode at some point in the future can be as high as 85%.[1] In addition, 15% of patients may endure chronic symptoms after the first episode, while 35% may experience recurrent episodes.[2] Remission rates are low for initial antidepressant monotherapy treatment (less than 30%) and partial response is common.3 Incomplete response to treatment for MDD is associated with an increased risk of relapse, [4,5] impaired social and occupational functioning,6 and consequently, an increased economic burden.[7, 8] 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.[9] Augmentation of ADT with agents such as lithium, thyroid hormone, anticonvulsants, or psychostimulants has also been explored as a possible means of achieving a more robust response to treatment.

Antipsychotics have been used in combination with antidepressants for treatment of psychotic or delusional forms of depression. However, the use of antipsychotics as adjunctive therapy for non-psychotic depression has been limited due to safety concerns, specifically, the potential for extrapyramidal symptoms (EPS), hyperprolactinemia, weight gain, and excessive sedation. The introduction of atypical antipsychotics has created a renewed interest in adjunctive therapy for MDD, particularly for treatment-resistant MDD. Although initial studies produced mixed results, several atypical antipsychotics have been shown to enhance the response to ADT.[10,11,12,13,14]

OPC-34712 (hereafter referred to by the generic name “brexpiprazole”) is an organic compound synthesized by Otsuka Pharmaceutical Co, Ltd, that is a [redacted] at [redacted], [redacted], and [redacted], an [redacted], and has a [redacted] for [redacted] and [redacted]. Details of the receptor affinity profile of brexpiprazole are summarized in Section 1.1.1. Activity at dopamine and serotonin receptors has been shown to be useful in the treatment of psychiatric disorders, eg,

schizophrenia and bipolar mania. Hence, brexpiprazole is expected to be a promising antipsychotic agent. As the relative activity at these and other receptors appears to be related to the side effect profiles of antipsychotic drugs,[15,16,17,18] brexpiprazole may have the potential to exhibit improved safety compared to other agents. The more potent antagonism at 5-HT2A receptors for brexpiprazole relative to aripiprazole may afford a more favorable profile with respect to sleep quality; whereas, the low binding affinities for histamine and muscarinic receptors suggest that brexpiprazole may have less potential to cause H1-receptor-related weight gain than olanzapine. Preclinical data also suggest that brexpiprazole will have lower potential for hyperprolactinemia than risperidone. Results from initial phase 2 trials showed brexpiprazole to be well tolerated by subjects with MDD and schizophrenia (see Section 1.3).

1.1 Nonclinical Studies

Efficacy and safety pharmacology 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 Brochure.[19]

1.1.1 Efficacy Pharmacology

Brexpiprazole functions as a partial agonist at the D2 receptor. In in vitro assay systems based on forskolin-induced cyclic AMP accumulation and calcium (Ca^{2+}) mobilization in human dopamine D2L receptor-expressing cells, its intrinsic activity at the D2 receptor was slightly lower than that of aripiprazole, another D2 receptor partial agonist. Brexpiprazole inhibited apomorphine (APO)-induced hyperlocomotion, APO-induced stereotyped behavior, and conditioned avoidance response in rats, which are predictive animal models for antipsychotic-like efficacy. The inhibitory effects of brexpiprazole were more potent than those of aripiprazole. Moreover, in contrast to the D2 receptor antagonist risperidone, brexpiprazole did not increase plasma prolactin levels in reserpine-treated rats, thus demonstrating a D2 receptor partial agonistic profile in vivo. Despite its lower intrinsic activity at the D2 receptor, the in vivo catalepsy liability of brexpiprazole, an index of EPS, was similar to that of aripiprazole, but still lower than that of the typical antipsychotic haloperidol. Furthermore, brexpiprazole showed high binding affinity for the 5-HT2A receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT2A receptor antagonistic activity; the effect of brexpiprazole was more potent than that of aripiprazole. In addition, brexpiprazole exhibited high

binding affinities for the D3 and 5-HT1A receptors, acting as a partial agonist at these receptors.

1.1.2 Safety Pharmacology

In safety pharmacology studies in rats at an oral dose of 30 mg/kg or higher, brexpiprazole induced pharmacologically mediated clinical signs considered to be due to depression of the central nervous system (CNS) and dose-dependent decreases in body temperature. When orally administered at up to 30 mg/kg in conscious male beagle dogs, brexpiprazole showed no effect on respiratory parameters or heart rate at any dose tested. Brexpiprazole decreased blood pressure at doses of 3 mg/kg or higher and prolonged both QT interval and corrected QT interval (QTc, by Van de Water's formula) at 30 mg/kg. Brexpiprazole inhibited human *ether-a-go-go* related gene (hERG) current in Chinese hamster ovary cells (CHO-K1) at concentrations of 10^{-8} mol/L or higher, with a 50% inhibitory concentration of 1.17×10^{-7} mol/L. The mechanism for the blood pressure decreasing effect of brexpiprazole was suggested to result from a blockade of the α_1-adrenoceptor in peripheral blood vessels, which is a part of the compound's pharmacological profile. Proarrhythmic risk was also evaluated by examining the effects of brexpiprazole on monophasic action potential parameters in halothane-anesthetized dogs. Brexpiprazole did not affect the terminal repolarization period even at an intravenous dose of 3 mg/kg, suggesting a low potential for proarrhythmic effects. In general, the changes in the CNS, respiratory, and cardiovascular systems observed with brexpiprazole occurred at doses or exposure levels higher than those at which efficacy was confirmed in rats (3 mg/kg), and similar changes were shown to occur after administration of risperidone at similar or lower doses.

1.2 Clinical Studies

1.2.1 Pharmacokinetics/Pharmacodynamics

The pharmacokinetics of single and multiple doses of brexpiprazole was studied in healthy subjects and in subjects with MDD, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, brexpiprazole (OPC-34712) and one 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 as an inactive metabolite. Both brexpiprazole and DM-3411 pharmacokinetics were linear following single oral doses of brexpiprazole 0.2 to 8 mg to healthy subjects. The

terminal phase elimination half-life of brexpiprazole and DM-3411 was 48.3 to 80.8 hours and 48.6 to 77.5 hours, respectively. The median time to maximum (peak) plasma concentration (t_{max}) occurred at approximately 2 to 6 hours postdose for brexpiprazole and at approximately 10 to 24 hours postdose for DM-3411. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Steady state pharmacokinetics also appeared to be linear following multiple daily doses of brexpiprazole in the range of 0.5 to 2 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 to 12 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 CYP3A4 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, or duloxetine (MDD medications coadministered in this trial) may potentially increase brexpiprazole plasma concentrations by up to 2-fold.

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 (PET). The mean D2/D3 receptor occupancies at 4 and 24 hours postdose after 0.25, 0.5, 1, 2, 4, 5, and 6 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 D2/D3 receptor occupancy data and steady-state pharmacokinetic/pharmacodynamic modeling, it was predicted that the

D2/D3 receptor occupancy after multiple daily dose administration of 1 to 2 mg and higher doses of brexpiprazole will result in at least 80% to 90% D2/D3 receptor occupancy.

Additional information on the pharmacokinetics/pharmacodynamics of brexpiprazole and its metabolites in humans can be found in the Investigator Brochure.[19]

1.2.2 Major Depressive Disorder

The efficacy of brexpiprazole as adjunctive therapy for the treatment of MDD has been studied in one completed placebo-controlled trial (Trial 331-08-211). An additional placebo-controlled efficacy trial (Trial 331-09-222) and one long-term open-label safety trial (Trial 331-08-212) are ongoing. Trial 331-08-211 was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of brexpiprazole (0.15 to 2 mg daily) as adjunctive treatment to an assigned open-label ADT in subjects with MDD who have demonstrated an incomplete response to prospective treatment with the same ADT. Subjects with an incomplete response after 8 weeks of treatment with single-blind placebo plus open-label ADT were randomized to 6 weeks of double-blind treatment with either brexpiprazole-plus-ADT or placebo-plus-ADT. Responders continued to receive placebo-plus-ADT for an additional 6 weeks. Randomized subjects received brexpiprazole 0.15 mg/day, 0.50 ± 0.25 mg/day, 1.5 ± 0.50 mg/day, or matching placebo. Subjects randomized to the brexpiprazole 0.50 ± 0.25 mg/day and brexpiprazole 1.5 ± 0.50 mg/day arms were titrated to the target doses (0.50 and 1.5 mg, respectively) over a 2-week period. Dose adjustments were permitted after the subjects received 1 week of treatment at the target dose. Subjects who could not tolerate the lowest dose (brexpiprazole 0.15, 0.25, or 1.0 mg/day or matching placebo, respectively) were to be discontinued from the trial. In this trial, adjunctive brexpiprazole dosed at 1.5 ± 0.50 mg/day was superior to adjunctive placebo with respect to the primary endpoint (change from Week 8 to Week 14 in Montgomery Asberg Depression Rating Scale [MADRS] Total Score) and several secondary efficacy endpoints.[20] Ongoing Trial 331-09-222 is of similar design to Trial 331-08-211, but is exploring an expanded dose range (brexpiprazole 1 to 3 mg/day).

1.2.3 Schizophrenia

A dose-ranging, placebo-controlled trial for the monotherapy treatment of adults with schizophrenia has been performed in subjects experiencing an acute exacerbation of schizophrenia (Trial 331-07-203). The outcome of this trial suggests an active dose range

of brexpiprazole 1 to 6 mg/day for the treatment of schizophrenia.[21] In addition to the double-blind, placebo-controlled trial, a long-term open-label safety trial (Trial 331-08-210) is ongoing.

1.2.4 Other Indications

Brexpiprazole is being investigated in a proof-of-concept trial in adult ADHD (Trial 331-08-213). This is a multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial in which adults with ADHD who have an incomplete/partial response to stimulant therapy in a prospective treatment phase are randomized to double-blind treatment with either brexpiprazole-plus-stimulant or placebo-plus-stimulant. This trial is ongoing; therefore, results are not available.

1.3 Known and Potential Risks and Benefits

As of 31 Dec 2010, 14 clinical trials involving brexpiprazole have been completed worldwide, including 10 in the United States (US), 1 in multiple countries (including the US), 2 in Japan, and 1 in Korea. An additional 4 trials are currently ongoing (3 in the US and 1 in multiple countries [including the US]). The collective trials can be classified as follows: four phase 1 pharmacokinetic (PK) trials in healthy subjects, 2 drug interaction trials in healthy subjects, one phase 1 PET trial in healthy subjects, one phase 1b polysomnography trial in subjects with schizophrenia, five phase 1 PK trials in specific patient populations, and six phase 2 efficacy and/or safety trials. Brexpiprazole has been well tolerated by healthy volunteers at single doses up to 6 mg and at multiple doses up to 2 mg/day. In patient trials, brexpiprazole has been well tolerated at multiple doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder, up to 4 mg/day in subjects with MDD who received concomitant ADT, and up to 4 mg/day in adults with ADHD who received concomitant stimulant therapy.

In the 11 completed phase 1 and 2 clinical trials performed under the US IND (two phase 2 trials, one phase 1b trial, and eight phase 1 trials), 673/973 (69.2%) subjects who received brexpiprazole either alone or coadministered with another marketed medication reported at least one treatment-emergent adverse event (TEAE) compared to 158/253 (62.5%) subjects who received placebo either alone or coadministered with another marketed medication. The most common TEAEs reported for brexpiprazole in the completed trials (≥ 5% in the total brexpiprazole group and more than the total placebo group) were headache (10.6%), dizziness (8.0%), anxiety (7.1%), akathisia (7.0%), and nausea (5.5%). In the total placebo group, TEAEs that occurred in ≥ 5% of subjects were headache (9.9%), insomnia (9.1%), and constipation (5.5%).

One death was reported in the completed phase 2 trial in adults with acute schizophrenia (Trial 331-07-203). The subject was not on any investigational medicinal product (IMP) at the time of death, and the death was not considered by the investigator to be related to IMP. The incidence of serious TEAEs (fatal and non-fatal) that were reported during treatment with brexpiprazole administered either alone or coadministered with another medication (19/973 subjects, 2.0%) was comparable to placebo administered either alone or coadministered with another medication (4/253 subjects, 1.6%). Furthermore, treatment with brexpiprazole does not appear to promote suicidal behavior in subjects with MDD or schizophrenia.

Brexpiprazole did not result in any consistent, clinically relevant changes in laboratory values, vital signs (blood pressure or heart rate), or electrocardiogram (ECG) parameters in the completed phase 1 and 2 clinical trials in subjects with MDD or schizophrenia. Statistically significant increases in weight were observed with brexpiprazole relative to placebo in both sample populations. Brexpiprazole exhibited a favorable profile with respect to movement disorders in subjects with MDD at doses up to 3 mg/day (Trial 331-09-221) and in subjects with schizophrenia at doses up to 12 mg/day (Trial 331-08-205). In the dose-ranging trial that enrolled subjects who were experiencing an acute exacerbation of schizophrenia (Trial 331-07-203), an increase in the incidence of EPS was observed at the highest dose (ie, brexpiprazole 5.0 ± 1.0 mg/day).

Please refer to the current Investigator Brochure for a summary of available nonclinical and clinical safety data.[19]

Risks associated with use of the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) used in Trial 331-10-238 can be found in the prescribing information for the open-label ADTs.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Investigations of the interactions between serotonin and norepinephrine following sustained treatment with SSRIs provide a pharmacological basis for use of atypical antipsychotics as an augmentation strategy in treatment-resistant MDD. At the cellular level, increased serotonergic activity from prolonged reuptake inhibition appears to attenuate the firing of noradrenergic neurons indirectly through increased activation of

5-HT2A receptors.[22] The resulting decrease in noradrenergic tone may contribute to the suboptimal therapeutic response observed clinically with long-term administration of SSRIs.[23] As brexpiprazole demonstrated antagonism at 5-HT2A receptors, the attenuated response to SSRIs may be reversed with coadministration of brexpiprazole and SSRIs, thus enhancing clinical outcomes.

Because the management of MDD may require prolonged administration of ADT(s) with or without an augmenting agent, safety monitoring for longer than the period required to achieve initial response is warranted. In the brexpiprazole clinical development program for MDD, phase 2 and phase 3 trials examined the 6-week safety and efficacy of brexpiprazole augmentation of ADTs. For phase 2, subjects who completed either of the trials had the option to enroll into an open-label rollover trial in which they received brexpiprazole for up to 52 weeks (Trial 331-08-212). The current trial (Trial 331-10-238) provides an open-label rollover option for double-blind phase 3 brexpiprazole MDD trials and will expand on the knowledge gained in these trials by assessing the long-term safety, tolerability, and efficacy of brexpiprazole when administered concomitantly with antidepressant medications.

2.2 Dosing Rationale

A dose range of brexpiprazole 0.5 to 3 mg/day was selected for the current open-label trial to encompass the dose range of the double-blind efficacy trials (ie, brexpiprazole 1 to 3 mg/day) and to include an option for a reduced dose for tolerability (ie, 0.5 mg/day) in order to maximize subject retention in the long-term trial. Therapeutic dose ranges of ADT are based on product labels and clinical practice. Data from phase 1 drug interaction trials (Trial 331-08-207 and Trial 331-08-208) indicated that coadministration of CYP2D6 inhibitors (eg, paroxetine, fluoxetine, and duloxetine) with brexpiprazole could cause potentially higher plasma concentrations of brexpiprazole (up to 2-fold). 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 in the current trial.

2.3 Trial Objectives

Primary: To assess the long-term safety and tolerability of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD.

Secondary: To assess the long-term efficacy of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, 26-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent ADT. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed the last scheduled visit of a double-blind phase 3 brexpiprazole MDD trial and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD. A schematic of the trial design is presented in Figure 3.1-1.

The trial will be organized as follows:

Screening/Baseline: Subjects will be screened for eligibility at the last scheduled visit of the prior double-blind phase 3 trial. Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-10-238 before any procedures specific to the open-label trial are performed. The assessments from the last scheduled visit of the prior double-blind phase 3 trial will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

Treatment Phase: Eligible subjects will receive daily treatment with open-label brexpiprazole and ADT as described in Section 3.2. Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20, and 26. All subjects will receive up to 26 weeks of open-label treatment in Trial 331-10-238 and follow the schedule of assessments described in Table 3.6-1.

Follow-up: Subjects will be followed for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.

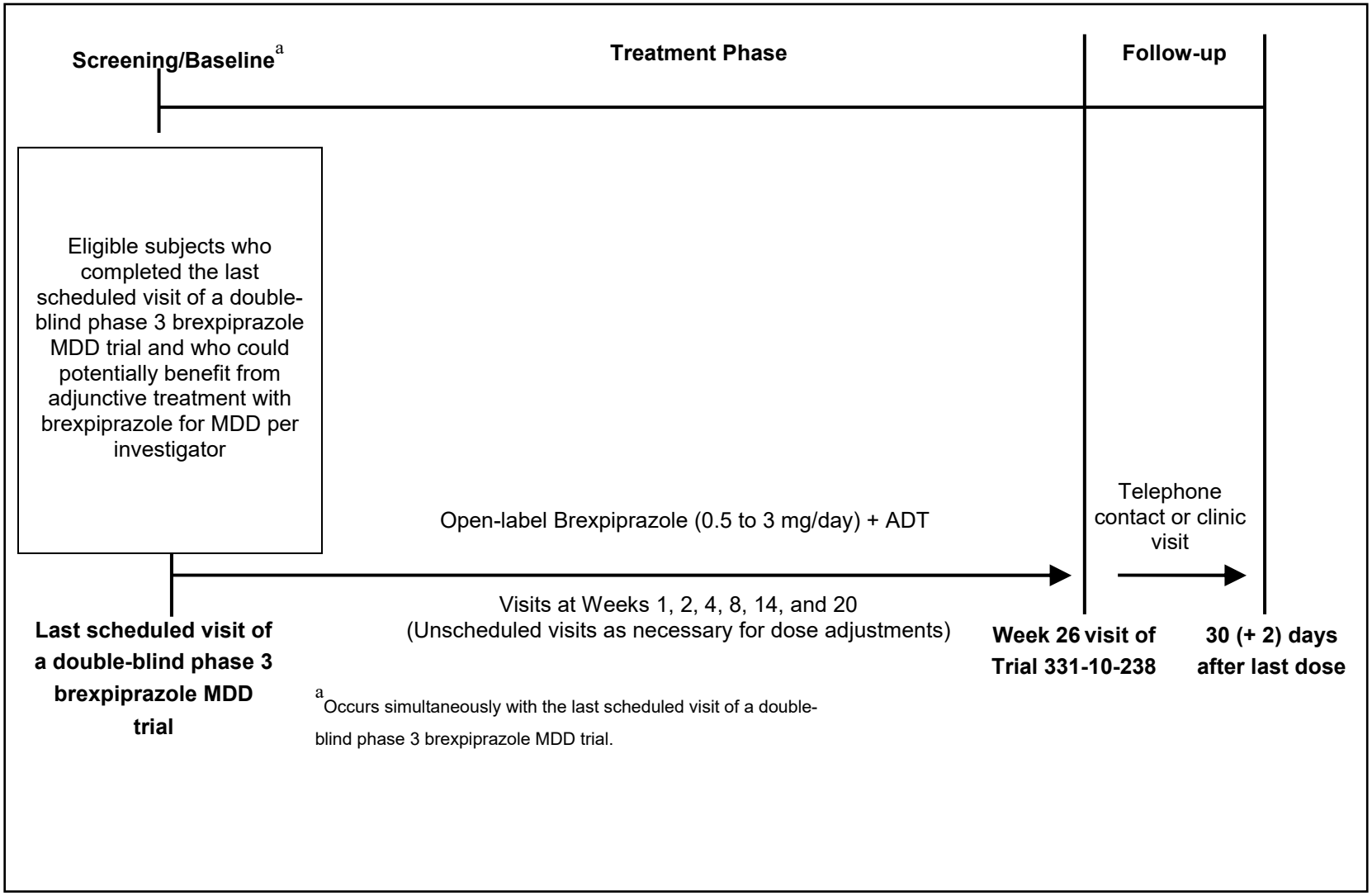

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

3.2.1 Treatment Administration

3.2.1.1 Brexpiprazole

The first dose of open-label brexpiprazole will be taken one day after the last dose is taken for the prior double-blind, phase 3 efficacy trial so that adjunctive treatment will continue without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the last scheduled visit ie, the day of the Screening/Baseline visit for the open-label trial. Subjects will initiate open-label dosing with brexpiprazole 0.5 mg/day for 1 week. Subjects unable to tolerate brexpiprazole 0.5 mg/day must be withdrawn from the trial. The dose of brexpiprazole will be increased to 1 mg/day at the Week 1 visit. Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit.

Investigators may further increase the dose to brexpiprazole 2 mg/day and then to brexpiprazole 3 mg/day, with an interval of at least 5 days between dose increases. An interval of at least 5 days between dose adjustments is recommended for dose decreases; however, the dose of brexpiprazole can be decreased at the investigator's discretion in a step-wise manner at any time after the Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits. The dosing schedule is summarized in Table 3.2.1.1-1. Additional information on dose adjustments is provided in Section 3.2.2.1.

All doses of brexpiprazole should be taken orally once daily and can be administered without regard to meals. For convenience, brexpiprazole may be taken with the first daily dose of ADT.

Table 3.2.1.1-1 Dosing Schedule for Brexpiprazole

IMP	Trial Visit				
	Screening/ Baseline	**Week 1**[a]	**Week 2**[b]	**Week 4**[b]	**Visits at Weeks 8, 14, and 20**[b]
Brexpiprazole (mg/day)[c]	0.5	1	0.5, 1 or 2	0.5, 1, 2 or 3	0.5, 1, 2, or 3
ADT[d]	Final dose from double-blind trial	No change[e]	No change[e]	No change[e]	Change to ADT dose is permitted as described in Section 3.2.2.2.

[a]Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit.

[b]Step-wise increases in the dose of brexpiprazole must be separated by at least 5 days. Although step-wise decreases in the brexpiprazole dose are permitted at any time after the Week 1 visit to a minimum of 0.5 mg/day, an interval of at least 5 days between dose adjustments is recommended. See Section 3.2.2.1 for additional information on dose adjustments. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

[c]Subjects unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial.

[d]Throughout Trial 331-10-238, the subject must remain on the same ADT that was assigned in the prior double-blind phase 3 trial.

[e]It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized.

3.2.1.2 ADT

During the Treatment Phase of Trial 331-10-238, subjects will remain on the same assigned open-label ADT from the prior double-blind, phase 3 efficacy trial. Numbered ADT bottles to be dispensed to the subject will be assigned by the IVRS or IWRS. The initial dose of ADT for the open-label trial will be the same as the ADT dose taken on the last scheduled visit of the prior double-blind phase 3 trial. The ADTs to be used in Trial 331-10-238, including allowable doses within the therapeutic range, are listed in Table 3.2.1.2-1. Adjustments to the ADT dose are permitted as described in Section 3.2.2.2. If in the clinical judgment of the investigator a subject should permanently discontinue their assigned ADT or change to a different ADT, the subject must be withdrawn from the trial. All doses of ADT will be administered orally once daily except for duloxetine 40 mg/day that can be administered once daily or as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily. All ADTs can be given without regard to meals, except for venlafaxine XR, which should be taken with food. Subjects should be instructed to take the ADT at approximately the same time each day, if possible.

Table 3.2.1.2-1 Open-label Antidepressant Therapy (ADT) Allowable Doses Within Therapeutic Dose Ranges for MDD			
Generic Name	**Brand Name**	**Dosage Form**	**Allowable Doses Within Therapeutic Dose Range (mg/day)[a]**
SSRIs			
Escitalopram	Lexapro®	Tablet	10 and 20
Fluoxetine	Prozac®	Capsule	20 and 40
Paroxetine CR	Paxil CR®	Controlled-release Tablet	37.5 and 50
Sertraline	Zoloft®	Tablet	100, 150, and 200
SNRIs			
Duloxetine	Cymbalta®	Delayed-release capsule	40 and 60
Venlafaxine XR	Effexor XR®	Extended-release capsule	75, 150, and 225

CR = controlled release; XR = extended release.

[a] All doses are to be administered orally once daily except for duloxetine 40 mg/day that can be administered once daily or as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily. All doses should be taken at approximately the same time each day, if possible.

3.2.2 Dose Adjustments

Dose modifications to both brexpiprazole and ADT will be permitted to optimize therapeutic benefit according to the rules described below for each treatment. However, the dose of brexpiprazole and the dose of ADT should not both be changed at the same visit.

3.2.2.1 Brexpiprazole

Allowable dose modifications to the daily dose of brexpiprazole are summarized in Table 3.2.2.1-1. At least 5 days must elapse between dose increases for brexpiprazole. An interval of at least 5 days between dose adjustments is recommended for dose decreases; however, the dose of brexpiprazole can be decreased at the investigator's discretion in a step-wise manner at any time after the Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

Subjects who are unable to tolerate the 0.5 mg/day dose of brexpiprazole must be withdrawn from the trial. However, subjects whose brexpiprazole dose is decreased to

0.5 mg/day and who demonstrate adequate tolerability at this dose should be rechallenged with a 1 mg/day dose within approximately 6 to 8 weeks after the dose is decreased to 0.5 mg/day. If tolerability issues arise following the rechallenge, the dose may be decreased again to 0.5 mg/day. Further rechallenge at 1 mg/day may be performed at the investigator's discretion. The dose of brexpiprazole can be increased as necessary following a dose decrease at any other dose if, in the investigator's judgment, rechallenge with a higher dose is warranted in order to identify an optimum dose for the subject. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

Table 3.2.2.1-1 Dose Modifications for Brexpiprazole

Dose Increases[a,b]		
Current Dose of Brexpiprazole	Incremental Increase	Adjusted Brexpiprazole dose
0.5 mg	0.5 mg	1 mg
1 mg	1 mg	2 mg
2 mg	1 mg	3 mg
Dose Decreases[b,c]		
Current Dose of Brexpiprazole	Incremental Decrease	Adjusted Brexpiprazole dose
0.5 mg	Not permitted[d]	0.5 mg[d]
1 mg	0.5 mg	0.5 mg
2 mg	1 mg	1 mg
3 mg	1 mg	2 mg

[a] At least 5 days must elapse between dose increases.

[b] Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

[c] An interval of at least 5 days between dose adjustments is recommended for dose decreases; however, the investigator may decrease the dose of brexpiprazole at any time after the Week 1 visit for tolerability.

[d] Subjects unable to tolerate 0.5 mg/day of brexpiprazole must be withdrawn from the trial.

3.2.2.2 ADT

It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). *After the Week 4 visit*, the dose of ADT can be modified if necessary to achieve optimum efficacy and tolerability for the treatment regimen using the following rules: 1) at least 5 days must elapse between dose increases (either brexpiprazole or ADT), 2) an interval of at least 5 days between dose adjustments (either brexpiprazole or ADT) is recommended for dose decreases; however, the ADT dose can be decreased at the investigator's discretion at any time as needed for tolerability, and 3) subjects must return to the clinic for unscheduled visits if changes to the ADT dose are required between scheduled visits.

The Sponsor reserves the right to use a generic equivalent should any marketed antidepressant become unavailable during the course of the trial.

3.3 Trial Population

The trial population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD according to the following criteria:

- Subjects who participated in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214 will be eligible for Trial 331-10-238 if they meet one of the following conditions:
  - Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of phase B) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214 or
  - Subjects who continued into Phase A+ (were not randomized into Phase B) at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214, **BUT DID NOT** meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214.
- Subjects who participated in a double-blind phase 3 brexpiprazole MDD trial will be eligible for the 331-10-238 trial if they have completed the last scheduled visit of the double-blind phase 3 trial.
- Subjects must qualify for Trial 331-10-238 at the last scheduled visit of the prior double-blind phase 3 trial and must be able to continue therapy without interruption between the double-blind and open-label trials. Based on the projected enrollment estimates for the prior double-blind phase 3 brexpiprazole MDD trials, up to approximately 3,000 subjects may enroll into Trial 331-10-238.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legal representative, as applicable for local laws). Consent will be documented on a written ICF. The ICF will be approved by the same Institutional Review Board/Independent Ethics Committee (IRB/IEC) that approves this protocol. Each ICF will comply with the FDA regulations in 21 Code of Federal Regulations (CFR) Part 50, International Conference on Harmonization Good Clinical Practice (ICH GCP), and local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF used in the trial, prior to 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 prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s). The ICF for the open-label trial may be provided to potential candidates for review and discussion toward completion of the prior double-blind phase 3 trial, but the form must not be signed until the day of the Screening/Baseline visit for Trial 331-10-238 (ie, the last scheduled visit of the prior double-blind phase 3 trial).

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

In addition to the English version of the ICF, the document may also be translated by the central translation vendor into local languages for use in this trial. Translation with back-translation for confirmation will be utilized to ensure accuracy.

3.4.2 Inclusion Criteria

Subjects are required to meet the following inclusion criteria:

Table 3.4.2-1 Inclusion Criteria

	All Subjects
1.	Subjects who are able to provide written informed consent and/or consent obtained from a legally acceptable representative (as required by IRB/IEC) prior to the initiation of any protocol-required procedures.
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/capsule ingestion, and discontinuation of prohibited concomitant medication; 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 outpatients 18 to 65 years of age, inclusive, at the time of informed consent for Trial 331-10-238.
4	Subjects willing to discontinue all prohibited psychotropic medications starting from the time of signing the ICF and during the trial period (refer to Section 4).

Table 3.4.2-1 Inclusion Criteria	
	331-10-227, 331-10-228 and 331-13-214 Subjects Only
5.	Subjects who, in the opinion of the investigator, could potentially benefit from administration of brexpiprazole as adjunctive therapy to their antidepressant therapy and who meet one of the following criteria: a) Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of Phase B) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214 or b) Subjects who continued into Phase A+ (were not randomized into Phase B) at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214, **BUT DID NOT** meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227, Trial 331-10-228 or Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214...
	Eligible Subjects From Other Double-Blind Phase 3 Brexipiprazole MDD Trials
6.	Subjects who completed the last scheduled visit of the prior double-blind phase 3 trial, and who in the opinion of the investigator, could potentially benefit from administration of brexpiprazole as adjunctive therapy to their antidepressant therapy.

3.4.3 Exclusion Criteria

Subjects entering the open-label trial at the last scheduled visit of the prior double-blind phase 3 trial will be excluded from Trial 331-10-238 if they meet any of the following exclusion criteria.

Table 3.4.3-1 Exclusion Criteria	
Sex and Reproductive Status	
1.	Sexually active females of childbearing potential (see Section 5.5) and male subjects who are not practicing two different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who will not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use two of the following precautions: vasectomy, tubal ligation (subject or partner), vaginal diaphragm, IUD, birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide.
2.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving open-label brexpiprazole in Trial 331-10-238.
Administrative	
3.	Subjects with a major protocol violation during the course of their participation in the prior double-blind phase 3 trial. Minor violations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-10-238; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the prior double-blind phase 3 trial would be considered a major violation that would result in exclusion from Trial 331-10-238. **The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.**
Target Disease	
4.	Subjects who have received ECT for the current depressive episode.
5.	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 management of treatment-resistant depression. Subjects who have had Transcranial Magnetic Stimulation during the current major depressive episode.
6.	Subjects with a current need for involuntary commitment or who have been hospitalized during the prior double-blind phase 3 trial for the current major depressive episode.

Table 3.4.3-1 Exclusion Criteria	
7.	Subjects with a current Axis I (DSM-IV-TR) diagnosis of: • Delirium, dementia, amnestic or other cognitive disorder • Schizophrenia, schizoaffective disorder, or other psychotic disorder • Bipolar I or II disorder • Eating disorder (including anorexia nervosa or bulimia) • Obsessive compulsive disorder • Panic disorder • Post-traumatic stress disorder
8.	Subjects with a current Axis II (DSM-IV-TR) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal or histrionic personality disorder.
9.	Subjects experiencing hallucinations, delusions or any psychotic symptomatology in the current depressive episode.
10.	Subjects receiving new onset psychotherapy (individual, group, marriage, or family therapy) during the prior double-blind phase 3 trial.
Medical History and Concurrent Diseases	
11.	Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) at entry, **OR** Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) at entry, **OR** Subjects with a response of "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) at entry, **OR** Subjects who, in the opinion of the investigator (including consideration of responses on the C-SSRS throughout the prior double-blind phase 3 trial), present a serious risk of suicide. Note: "Entry" is defined as the last scheduled visit of the prior double-blind phase 3 trial.
12.	Subjects who have met DSM-IV-TR criteria for substance abuse or dependence within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
13.	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 T4 at screening/baseline. Eligibility of subjects excluded based on an abnormal free T4 result can be discussed with the medical monitor if, in the investigator's judgment, the subject is a suitable candidate for the trial.
14.	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 adverse event 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.
15.	Subjects with IDDM (ie, any subjects using insulin) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying **ALL** of the following criteria: • Screening/baseline HbA1c < 7.0%, **AND** • Screening/baseline fasting glucose must be ≤ 125 mg/dL, **AND** • Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) or diabetes has been well-controlled by diet during the prior double-blind phase 3 trial, **AND** • Subject has not had any hospitalizations due to diabetes or complications related to diabetes during the prior double-blind phase 3 trial, **AND** • Subject's diabetes is not newly diagnosed during screening/baseline for Trial 331-10-238. Continuation of subjects excluded based on abnormal laboratory test results from the

Table 3.4.3-1 Exclusion Criteria	
	screening/baseline visit should be discussed with the medical monitor, if in the investigator's judgement the subject is a suitable candidate for the trial.
16.	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.
17.	Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery.
18.	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	
19.	Subjects with a positive drug screen for cocaine, marijuana, or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or 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 may continue evaluation for the trial following consultation and approval by the medical monitor.
20.	The following Screening/baseline laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75,000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) AST > 2 × ULN 5) ALT > 2 × ULN 6) CPK > 3 × ULN, unless discussed with and approved by the medical monitor 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) QTcF ≥ 450 msec 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 are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in Appendix 3, Appendix 4, and Appendix 5 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Eligibility should be based on the Screening/baseline laboratory test and ECG results. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility. Continuation of subjects excluded based on abnormal laboratory test and ECG results should be discussed with the medical monitor, if in the investigator's judgement, the subject is a suitable candidate for the trial.
Prohibited Therapies or Medications	
21.	Subjects who would be likely to require prohibited concomitant therapy during the trial (see Table 4.1-1)[a].
Allergies and Adverse Drug Reactions	
22.	Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome.
23.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.

Table 3.4.3-1 Exclusion Criteria	
Other	
24.	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.
25.	Any subject who, in the opinion of the investigator, should not participate in the trial.

ALT = alanine transaminase; AST = aspartate transaminase; CPK = creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; IUD = intrauterine device; NMS = neuroleptic malignant syndrome; OTC = over-the-counter; 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.

[a] Use of CYP2D6 inhibitors or CYP3A4 inhibitors and inducers is prohibited during the trial. 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.

Subjects who do not qualify for the open-label trial at the Screening/Baseline visit may not be rescreened at a later date. If results of clinical laboratory tests from the last scheduled visit of the prior double-blind phase 3 trial are not available to assess eligibility, the assessment for the affected criteria should be based on the last available measurement during the respective double-blind trial. Results from the last visit of the double-blind trial should be reviewed when they become available and action should be taken as described in Section 3.6.2.1 if there are any clinically significant and/or exclusionary values.

3.5 Primary and Secondary Outcome Variables

3.5.1 Primary Outcome Variable

The primary outcome variable is the safety and tolerability of brexpiprazole, which will be assessed by examining the frequency and severity of adverse events (AEs).

3.5.2 Secondary Outcome Variables

3.5.2.1 Efficacy Variables

Efficacy variables will be as follows:

- Change from baseline in Clinical Global Impression - Severity of Illness scale (CGI-S) score;
- Mean Clinical Global Impression - Improvement scale (CGI-I) score;
- Change from baseline in Sheehan Disability Scale (SDS) score.

- Change from baseline in the Inventory of Depressive Symptomatology (Self-Report) (IDS-SR) Total Score

3.5.2.2 Safety Variables

In addition to AEs, safety variables to be examined in this trial will include physical examinations, vital signs, body weight, waist circumference, clinical laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy tests), ECGs, the Simpson Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ).

Mean change from baseline and the incidence of potentially clinically relevant abnormal values will be calculated for vital signs, body weight, routine laboratory tests (including prolactin), and ECG parameters. Mean change from baseline will be calculated for coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], and International Normalized Ratio [INR]), glycosylated hemoglobin (HbA1c), thyroid-stimulating hormone (TSH), waist circumference, and body mass index (BMI; derived programmatically from body weight and height measurements). A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. EPS will be evaluated by calculating mean change from baseline on the SAS, AIMS, and BARS. Sexual dysfunction will be evaluated as change from baseline in MSFQ score. The C-SSRS will be used to assess and classify reported suicidal behavior. By-patient listings of physical examination findings will be reviewed as a further assessment of safety.

3.5.2.3 Other Outcome Variables

Responses to the Resource Utilization Form (RUF) will be summarized appropriately to explore the impact of treatment on health care resources.

3.6 Trial Procedures

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 57 months, of which approximately 51 months are allotted for rollover of subjects from prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 30 weeks (26 weeks of treatment and 30-day follow-up). Trial assessment time points are summarized in Table 3.6-1.

Table 3.6-1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)							Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26/ET[b]	
ENTRANCE CRITERIA									
Informed consent[d]	X								
Inclusion/exclusion criteria	X								
Medical history	X[e]								
EFFICACY									
CGI-S	X	X	X	X	X	X	X	X	
CGI-I[f]	X					X		X	
SDS	X					X		X	
IDS-SR	X					X		X	
SAFETY									
Physical examination	X							X	
Waist circumference	X					X		X	
Vital signs[g]	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X					X		X	
Clinical laboratory tests[i]	X[j]					X[k]		X[k]	
HbA1c	X[j]					X[k]		X[k]	
Drug screen/blood alcohol[l]	X	X		X	X	X		X	
Urine pregnancy test (WOCBP only)[m]	X	X	X	X	X	X	X	X	
SAS	X	X	X	X	X	X	X	X	
AIMS	X					X		X	
BARS	X	X	X	X	X	X	X	X	
C-SSRS[n]	X	X	X	X	X	X	X	X	
MSFQ	X							X	
Adverse events	X[o]	X	X	X	X	X	X	X	X

Table 3.6-1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)							Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26/ET[b]	
Concomitant medications[p]	X	X	X	X	X	X	X	X	X
OTHER									
Dose adjustments[q]		X	X	X	X	X	X		
RUF[r]	X							X	
Register visit in IVRS/IWRS[s]	X	X	X	X	X	X	X	X	
IMP dispensing	X	X	X	X	X	X	X		
IMP accountability		X	X	X	X	X	X	X	

IVRS = interactive voice response system; IWRS = interactive web response system; WOCBP = women of childbearing potential.

[a]Screening for Trial 331-10-238 occurs simultaneously with Baseline at the last scheduled visit of the prior double-blind phase 3 trial. All assessments listed under screening need to be performed at Screening/Baseline of Trial 331-10-238; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.

[b]If a subject discontinues prematurely before Week 26, procedures noted for Week 26 must be completed at the early termination (ET) visit. Subjects who have completed 26 weeks or more, will have the Week 26/ET procedures at their next scheduled visit.

[c]Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety and applies to all subjects (completers and early withdrawals).

[d]Informed consent for Trial 331-10-238 will occur at Screening/Baseline and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e]Update, if necessary.

[f]Improvement should be based on the subject's status at the last scheduled visit of the prior double-blind phase 3 trial.

[g]Vital signs include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (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.

[h]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Subjects will be enrolled in Trial 331-10-238 based on the screening/baseline ECG results from the trial site. If the screening/baseline ECG results from the central reader (ie, the last scheduled visit of the prior double-blind phase 3 trial), when available, indicate a QTcF

≥ 450 msec at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[i] Includes hematology (including PT, aPTT, and INR), serum chemistry (including prolactin and TSH, with reflex to free thyroxine [T_4] if the result for TSH is abnormal), and urinalysis.

[j] Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline laboratory assessments (ie, the last scheduled visit of the prior double-blind phase 3 trial).

[k] Clinical laboratory tests should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 26/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

[l] 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.

[m] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at Screening/Baseline must not be enrolled in Trial 331-10-238 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.

[n] "Since Last Visit" C-SSRS form.

[o] AE recording will begin with the signing of the ICF for Trial 331-10-238.

[p] 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.

[q] Adjustments to the dose of brexpiprazole or ADT are permitted to optimize efficacy and tolerability as described in Section 3.2. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). At least 5 days must elapse between dose increases for brexpiprazole and ADT. An interval of at least 5 days between dose adjustments is also recommended for dose decreases; however, the investigator may decrease the dose of brexpiprazole or ADT as needed for tolerability according to the rules described in Section 3.2.2. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole or ADT (increases or decreases) are required between scheduled visits. All eligible subjects entering from prior double-blind phase 3 brexpiprazole MDD trials must be able to continue therapy without interruption between the double-blind and open label trials.

[r] Baseline RUF is completed at Screening/Baseline for all subjects. The Follow-up RUF (as well as hospitalization questions) is completed at Week 26/ET visit.

[s] The IVRS/IWRS will be accessed at unscheduled visits if new blister cards are dispensed for dose adjustment of brexpiprazole.

3.6.1 Schedule of Assessments

3.6.1.1 Screening/Baseline

Subjects entering Trial 331-10-238 must sign the ICF for the open-label trial before any procedures specific to Trial 331-10-238 can be performed. Subjects will retain the same subject identification (Subject ID) number assigned in the prior double-blind phase 3 trial. The following procedures need to be performed at Screening/Baseline of Trial 331-10-238; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.

- Inclusion/exclusion criteria for Trial 331-10-238 will be reviewed to assure the subject's eligibility.
- Medical history will be updated, if necessary, using information from the prior double-blind phase 3 trial.
- Subjects will submit to a physical examination and assessments of waist circumference, vital signs, and ECG.
- The investigator (or qualified designee) will administer the CGI-S and CGI-I.
- Subjects will complete any Baseline instrument (ie, SDS, IDS-SR, and MSFQ).
- An adequately trained and experienced clinician will administer any EPS scale (ie, SAS, AIMS, and BARS).
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- Concomitant medications will be reviewed to assure that the subject is not receiving any prohibited medications.
- Subjects will complete the Baseline RUF.
- For subjects entering Trial 331-10-238 after completing the last scheduled visit of the prior double-blind phase 3 trial, a fasting blood sample will be drawn for analysis of any clinical laboratory parameter (ie, the clinical laboratory parameters specified in Table 3.6.2.1-1) that was not drawn at the last scheduled visit of the prior double-blind phase 3 trial.
- AE recording will begin with the signing of the ICF for Trial 331-10-238.
- Trial personnel will call the interactive voice response system (IVRS) or access the interactive web response system (IWRS) to register the visit and to obtain blister card and ADT bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed. Treatment will begin with brexpiprazole 0.5 mg/day for 1 week. The ADT will be the same as the one taken during the prior double-blind phase 3 trial. The dose of ADT should not be changed at this time.

3.6.1.2 Week 1

All subjects will attend a visit at Week 1 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- 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.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected for urine screen(s) for drugs of abuse.
- Women of childbearing potential (WOCBP) will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The dose of brexpiprazole will be increased to 1 mg/day. Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.
- AEs and concomitant medications will be recorded.

3.6.1.3 Week 2

All subjects will attend a visit at Week 2 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.

- 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.
- WOCBP will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The investigator will adjust the dose of brexpiprazole as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized. Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.
- AEs and concomitant medications will be recorded.

3.6.1.4 Week 4

All subjects will attend a visit at Week 4 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- 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.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected for urine screen(s) for drugs of abuse.
- WOCBP will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The investigator will adjust the dose of brexpiprazole as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. If necessary, the dose of

ADT can be changed after the Week 4 visit, but not at the same visit as a change to the dose of brexpiprazole (see Section 3.2.2.2). Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.

- AEs and concomitant medications will be recorded.

3.6.1.5 Week 8

All subjects will attend a visit at Week 8 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- 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.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected for urine screen(s) for drugs of abuse.
- WOCBP will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.
- AEs and concomitant medications will be recorded.

3.6.1.6 Week 14

All subjects will attend a visit at Week 14 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S and CGI-I.
- Waist circumference will be measured.
- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- The subject will complete the IDS-SR and SDS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- 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 is drawn.
- A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, and TSH, with reflex to free T4 if the result for TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected.
- Samples will be obtained for blood alcohol testing. Additional blood alcohol testing may be performed at any other time at the discretion of the investigator.
- Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. Additional urine drug screens may be performed at any other time at the discretion of the investigator.
- WOCBP will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.
- AEs and concomitant medications will be recorded.

3.6.1.7 Week 20

All subjects will attend a visit at Week 20 (± 2 days) where the following evaluations will be performed:

- The investigator (or qualified designee) will administer the CGI-S.
- An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- 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.
- WOCBP will be given a urine pregnancy test. 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.
- Drug accountability will be performed for brexpiprazole and ADT.
- The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject.
- AEs and concomitant medications will be recorded.

3.6.1.8 End of Treatment (Week 26/ET)

The Week 26 visit signifies the end of treatment. Therefore, all subjects will undergo a complete evaluation at Week 26 (± 2 days). In addition, Week 26 evaluations are to be completed, if possible, for any subject withdrawn from the trial prematurely. Since the original 52 week open-label trial design has been modified as a part of Amendment 3 to shorten the duration of the trial to 26 weeks, ongoing subjects who have not reached their Week 26 visit will be re-consented and will follow Amendment 3 schedule of assessments. Ongoing subjects who have already completed their Week 26 visit at the time Amendment 3 is approved will follow Amendment 3 week 26/ET schedule of assessments at their next scheduled visit. The following activities and assessments will occur at Week 26 (or at the ET visit, if applicable):

- The investigator (or qualified designee) will administer the CGI-S and CGI-I.

- An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The subject will complete the MSFQ, SDS, IDS-SR, and the Follow-up RUF.
- 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 is drawn.
- A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, and TSH, with reflex to free T_4 if TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected for urinalysis and urine screen(s) for drugs of abuse.
- WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test.
- Final drug accountability will be performed.
- Trial personnel will call the IVRS or access the IWRS to register completion or discontinuation from the trial.
- AEs and concomitant medications will be recorded.

3.6.1.9 Follow-up

Follow-up safety information (AEs and concomitant medications) will be collected 30 (+ 2) days after the last dose of open-label medication for all subjects (completers and early withdrawals). Follow-up information can be obtained via telephone contact or clinic visit at the investigator's discretion.

3.6.2 Safety Assessments

3.6.2.1 Clinical Laboratory Tests

As it is unlikely that the final laboratory test results from the last scheduled visit of the prior double-blind phase 3 trial will be available at the time of enrollment in Trial 331-10-238, the investigator is to review the subject's most recent laboratory test results from the prior double-blind phase 3 trial for compliance with the exclusion criteria

and the presence of abnormal laboratory test results that, in the investigator's judgment, are medically significant and would impact the safety of the subject or the interpretation of the trial results. Subjects meeting any of these criteria will be excluded from Trial 331-10-238. Appendix 4 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. If one or more results from the screening/baseline sample are clinically significant and/or exclusionary when the results from the last scheduled visit of the prior double-blind phase 3 trial become available, the test(s) should be repeated. The subject may continue to receive trial medication pending results of the repeat laboratory tests at the investigator's discretion. If the abnormality remains upon retest, the medical monitor should be contacted to discuss the subject's eligibility for continued participation in Trial 331-10-238.

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 labs, 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. Urine will be collected and blood will be drawn from subjects at the scheduled visits designated in Table 3.6-1. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Screening/baseline laboratory assessments will be performed after a minimum 8-hour fast per the protocol instructions for the double-blind phase 3 trials. All subjects must be fasting for a minimum of 8 hours prior to the blood draw at Week 26/ET and should be fasting for a minimum of 8 hours prior to all other blood draws during the Treatment Phase, if possible. If a subject is not fasting at a visit other than Week 26/ ET, the blood draw should still be performed and the status documented as nonfasting on the laboratory requisition sheet. The Week 26/ET blood draw must be rescheduled to accommodate the fasting requirement. 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.

Table 3.6.2.1-1 Safety Clinical Laboratory Tests

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis: pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (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 or SGPT AST or SGOT BUN CPK Creatinine LDH Total bilirubin Triglycerides Cholesterol (total, LDL, and HDL) Calcium Chloride Glucose Insulin Magnesium Bicarbonate Inorganic phosphorous Sodium Potassium Total protein Uric acid GGT Prolactin Albumin Additional Tests: Urine pregnancy (WOCBP)[a] TSH, with reflex to free T_4 if TSH is abnormal PT, aPTT, and INR HbA1c

ALP = alkaline phosphatase; ALT or SGPT = alanine transaminase; AST or SGOT = aspartate transaminase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; HbA1c = glycosylated hemglobin; HDL = high density lipoprotein; LDH = lactic dehydrogenase; LDL = low density lipoprotein; RBC = red blood cell.

[a] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at Screening/Baseline 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.

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. Follow-up unscheduled labs should be performed on clinically significant abnormalities. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care.

To be eligible for Trial 331-10-238, subjects are not permitted to have laboratory values within the following exclusionary ranges:

1) Platelets ≤ 75,000/mm^3
2) Hemoglobin ≤ 9 g/dL
3) Neutrophils, absolute ≤ 1000/mm^3
4) Aspartate transaminase (AST) > 2 × upper limit of normal (ULN)
5) Alanine transaminase (ALT) > 2 × ULN
6) Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
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.)

3.6.2.2 Physical Examination and Vital Sign Assessments

3.6.2.2.1 Physical Examination

The complete physical examination at the last scheduled visit of the prior double-blind phase 3 trial will serve as the screening/baseline physical examination for the current protocol. A complete physical examination will consist of a review of the following body systems: HEENT, thorax, abdomen, urogenital, extremities, neurological, and skin and mucosae. Repeat measurement of height is not required during Trial 331-10-238 if a Screening/Baseline value is available from the prior double-blind phase 3 trial. Waist circumference will be measured at Screening/Baseline, Week 14, and Week 26/ET. 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.
- 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.[24]

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 screening/baseline examination should be documented as an AE and followed to a satisfactory conclusion.

3.6.2.2.2 Vital Signs

Vital sign measurements 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, and finally standing. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

Subjects with uncontrolled hypertension (Screening/Baseline DBP > 95 mmHg) 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/Baseline 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/baseline 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 3 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.

3.6.2.3 ECG Assessments

Twelve-lead ECGs will be recorded at the visits specified in Table 3.6-1. 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 early termination. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site 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.

As the results from the central reader will not be available at the Screening/Baseline visit, the subject will be enrolled into Trial 331-10-238 based on the local ECG results. A screening/baseline ECG finding of QTc corrected for heart rate by Fridericia's formula (QTcF) ≥ 450 msec is exclusionary (see Table 3.4.3-1). In addition, subjects should be excluded if they have any other abnormal ECG finding at Screening/Baseline 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 screening/baseline 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. Appendix 5 is provided as a guide for determining potentially clinically relevant ECG abnormalities. If the results from the central reader, when available, indicate a screening/baseline QTcF ≥ 450 msec, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial.

3.6.2.4 Other Safety Assessments

It is required that a trained and experienced clinician administer the safety assessments, including the EPS scales (SAS, AIMS, and BARS) and C-SSRS. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training and materials for rating will be provided by Bracket.

3.6.2.4.1 Simpson Angus Scale (SAS)

The SAS[25] (Appendix 10) 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 (see Section 4). Investigators are encouraged to delay scale administration until 12 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 electronic case report form (eCRF).

3.6.2.4.2 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[26] assessment (Appendix 11) 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 two 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 (see Section 4). Investigators are encouraged to delay scale administration until 12 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 eCRF.

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).

3.6.2.4.3 Barnes Akathisia Rating Scale (BARS)

The BARS[27] (Appendix 12) 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 (see Section 4). Investigators are encouraged to delay scale administration until 12 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 eCRF.

The BARS Global Score is defined as the global clinical assessment of akathisia.

3.6.2.4.4 Suicidality

Suicidality will be monitored during the trial using the C-SSRS. Subjects completed the "Baseline/Screening" C-SSRS form at the beginning of the prior double-blind phase 3 trial; therefore, only the "Since Last Visit" C-SSRS form will be used in Trial 331-10-238. A copy of the "Since Last Visit" C-SSRS form is provided in Appendix 13.

3.6.2.4.5 Sexual Function

The MSFQ[28] is a measure of a subject's self-reported sexual functioning. It consists of 5 items that are each rated as one of six defined grades of functioning (Appendix 14). The investigator or designated trial personnel should ensure that a subject completes this instrument completely and legibly.

3.6.3 Efficacy Assessments

It is required that appropriately trained and qualified individuals administer the CGI-S and CGI-I. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training and materials for rating will be provided by Bracket.

3.6.3.1 Clinical Global Impression - Severity of Illness Scale (CGI-S)

The severity of illness for each subject will be rated using the CGI-S.[26] 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: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. A sample of the CGI-S is provided in Appendix 6.

3.6.3.2 Clinical Global Impression - Improvement Scale (CGI-I)

The efficacy of trial treatment will be rated for each subject using the CGI-I.[26] The rater or investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared to the subject's condition at Screening/Baseline (ie, last scheduled visit of the prior double-blind phase 3 trial). Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. A sample of the CGI-I is provided in Appendix 7.

3.6.3.3 Subject Assessment Recording

3.6.3.3.1 Sheehan Disability Scale (SDS)

The SDS[29,30] is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities (Appendix 8). The SDS is a visual analogue scale that uses spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess disability across the three 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 two questions related to productivity losses due to the psychiatric symptoms and impairment.

3.6.3.3.2 Inventory of Depressive Symptomatology (Self-Report)

The IDS-SR[31] is a 30-item self-report measure used to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of MDD (Appendix 9). The investigator or designated trial personnel should ensure that a subject completes this instrument completely and legibly.

3.6.3.3.3 Resource Utilization Form (RUF)

The RUF is a self-report tool designed to collect information regarding the extent of medical care sought by subjects while participating in the trial (Appendix 15). The number of hospitalizations and days of hospitalization within the past 12 months will be collected on the Baseline Form at Screening/Baseline, including any hospitalizations that may have occurred during the subject's participation in the prior double-blind phase 3 trial. The number of visits to various practitioners for mental health and other reasons within the 3 months prior to Screening/Baseline (excluding any visits from the prior double-blind phase 3 trial) will be collected on the Baseline Form and the number of such visits occurring during the trial (excluding visits related to the trial) will be collected on the Follow-up Form at Week 26/ET.

3.6.4 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 eCRF page for the last subject completing or withdrawing from the trial.

3.7 Stopping Rules, Withdrawal Criteria and Procedures

3.7.1 Entire Trial or Treatment Arm(s)

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

3.7.2 Individual Center

A particular center may be terminated from the trial at the discretion of the investigator, sponsor, or IRB, eg, for non-enrollment of subjects or noncompliance with the protocol. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/EC at the site.

3.7.3 Individual Subject

If a subject discontinues from the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and the eCRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal. All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if

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

a) 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;

b) treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;

c) subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.11, Subject Compliance);

d) at the request of the subject, investigator, sponsor or designee, or regulatory authority;

e) subject becomes pregnant;

f) subject cannot tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day), the minimum protocol-defined therapeutic dose of ADT (see Table 3.2.1.2-1), or requires a different ADT; or

g) subject is lost to follow-up.

The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 26 must complete the Week 26/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+ 2) days after the last dose of IMP for evaluation of safety. This assessment can be accomplished via telephone contact or clinic visit at the investigator's discretion. Withdrawn subjects will not be replaced.

3.8 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment, whether through randomization or open assignment. For the purposes of Trial 331-10-238, treatment begins with the first dose of open-label brexpiprazole in the Treatment Phase. Subjects who do not qualify for Trial 331-10-238 at the last scheduled visit of the prior double-blind phase 3 trial may not be rescreened.

3.9 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 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 the Week 26 visit will be defined as completers. Protocol-specified post-treatment follow-up contacts will not qualify as the "last scheduled visit." Subjects who are not completers are defined as those who "discontinued the trial."

3.10 Definition of Lost to Follow-up

Subjects who cannot be contacted on or before the Week 26 visit during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as "lost to follow-up" as the reason for discontinuation. The site will make three 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.

3.11 Subject Compliance

Responsible trial personnel will dispense the IMP (ie, brexpiprazole and ADTs). 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.

3.12 Protocol Deviations

This trial is intended to be conducted as described in this protocol. 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, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor's designee (medical monitor) at the earliest possible time by telephone. Investigator and sponsor (or sponsor's designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the designated medical monitor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

Concomitant medications taken by subjects who are rolling over into Trial 331-10-238 from a prior double-blind phase 3 trials should be reviewed for the prohibited medications listed in Table 4.1-1. Any subject taking a prohibited concomitant medication should not be enrolled in Trial 331-10-238.

Table 4.1-1 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 the ADTs listed in Table 3.2.1.2-1 d) Mood stabilizers (ie, lithium) e) Benzodiazepines, except when used to manage treatment emergent AEs such as agitation and anxiety[a] f) Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage treatment-emergent AEs related to insomnia[b] 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 CNS effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements, etc)
2.	Investigational agents
3.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. Selected CYP2D6 inhibitors[c] are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, clomipramine, pyrilamine, diphenhydramine, quinidine, terbinafine, halofantrine, tripelennamine. Selected CYP3A4 inhibitors are: amiodarone, fluvoxamine, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone. The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial.
4.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.

GABA = gamma-aminobutyric acid.

[a] Administration of specific oral benzodiazepines is permitted for the short-term management of treatment emergent AEs such as anxiety and agitation up to a maximum of 6 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. 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. 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. 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 eCRF.

[b] Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize one 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 eCRF.

[c] 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 (see Section 4.2.1).

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

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.[32]
- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan), linezolid, and methylene blue since there have been rare post-marketing 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 SNRIs and these drugs.[33,34,35]

Electroconvulsive therapy was prohibited during the prior double-blind phase 3 trials and is also prohibited for the duration of Trial 331-10-238. Transcranial magnetic stimulation is also prohibited. In addition, subjects may not undergo implantation of a device for vagus nerve stimulation or deep brain stimulation during the trial.

Use of intramuscular benzodiazepines and continual use of oral benzodiazepines are prohibited throughout the trial. However, administration of specific oral benzodiazepines is permitted for the short-term management of treatment emergent AEs such as anxiety and agitation up to a maximum of 6 mg/day lorazepam (or equivalent) in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. 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. 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.

Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize one 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.

Anticholinergics are permitted for the treatment of EPS up to a maximum of 4 mg/day benztropine or its equivalent and propranolol is permitted for akathisia or tremor up to a maximum of 20 mg three times daily (total of 60 mg/day). Sites should only utilize medications that are approved for these indications in their respective countries.

Benzodiazepines, non-benzodiazepine sleep aids, anticholinergics, and propranolol 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 medication documented, including a notation of the drug name, dose, and time of administration on the eCRF.

Fluoxetine, paroxetine, and duloxetine are protocol-defined ADTs in this trial; however, they are also CYP2D6 inhibitors. Data from Trial 331-08-207 and Trial 331-08-208 indicate that coadministration of CYP2D6 inhibitors with brexpiprazole can cause potentially higher plasma concentrations of brexpiprazole (up to 2-fold). 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. The investigator should consider the potential for higher brexpiprazole plasma concentrations when adjusting the dose of brexpiprazole for subjects who are receiving fluoxetine, paroxetine CR, or duloxetine as the assigned ADT.

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

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they initiated the therapy at least 42 days before enrollment in the prior double-blind phase 3 trial, participated in the therapy regularly during the prior double-blind phase 3 trial, and commit to maintain their participation during the course of Trial 331-10-238, or unless permission is obtained from the medical monitor.

Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to dosing and during the trial is prohibited. Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- death
- life-threatening, ie, the subject was, in the opinion of the investigator or the sponsor, 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 or substantial disruption of the ability to conduct normal life functions.
- requires in-patient hospitalization or prolongs an existing hospitalization
  NOTE: A pre-scheduled hospitalization is not considered an SAE; however, SAE forms must be completed for all other hospitalizations, including hospitalization for psychiatric reasons. Psychosocial hospitalizations (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) should not be reported as 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.

Non-serious adverse events are all AEs that do not meet the criteria for a "serious" AE.

If a subject is experiencing an extrapyramidal symptom, the specific extrapyramidal symptom must be indicated on the AE page of the eCRF. Examples of AEs that are considered extrapyramidal symptoms include, but are not limited to: generalized rigidity,

hyperkinesia, dyskinesia, bradykinesia, akinesia, dystonia, hypertonia, akathisia, tremor, flexed posture, involuntary muscle contractions, athetosis, and chorea. If a subject is experiencing two or more of these symptoms, whether or not treatment with an anticholinergic is required, this is considered as extrapyramidal syndrome and must be entered as "extrapyramidal syndrome" on the AE page of the eCRF instead of the individual symptoms. Permitted treatments for EPS are described in Section 4.2.1.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE that necessitates discontinuation of IMP.
- Potential Hy's Law cases (any increase of AST or ALT ≥ 3 times the upper normal limit with an increase in total bilirubin ≥ 2 times the upper normal limit).
- 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 INC Research. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

Clinical Laboratory 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 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 determined by the investigator to be an abnormal change from baseline for that subject, this is considered an AE.

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

Possibly related: There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear.

Unlikely related: There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and the AE.

Not Related: There is no temporal or reasonable relationship to the IMP administration.

Investigators will assess IMP causality based on brexpiprazole.

5.2 Eliciting and Reporting Adverse Events

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

Note: Normal pregnancy is not an AE and should not be recorded on the eCRFs; guidelines outlined in Section 5.5 should be followed for pregnancy reporting.

In addition, INC Research (Appendix 2) must be notified immediately by telephone or fax of any immediately reportable events 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 (IRE)

The investigator must immediately (ie, within 24 hours) report any serious adverse event, potential Hy's law cases, or confirmed pregnancy by telephone or by fax to INC Research as outlined in Appendix 2 after either the investigator or site personnel become aware of the event. An Immediately Reportable Event (IRE) form must be completed and transmitted per the instructions in the Operations Manual. (Please note that the IRE form is NOT the AE eCRF.)

Non-serious events that require discontinuation of IMP (including laboratory abnormalities) should be reported to INC Research within 3 working days. The IRE form must be completed and sent by fax or overnight courier to INC Research.

Subjects experiencing SAEs should be followed clinically until their health has returned to 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.

5.4 Potential Hy's Law Cases

For a subject that experiences an elevation in AST or ALT that is ≥ 3 times the upper normal limit, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the upper normal limit, confirmatory repeat laboratory samples should be drawn within 48 to 72 hours of the initial draw. If these values are confirmed, trial personnel will complete an IRE form with all values listed and also report the event as an AE on the eCRFs. Please note: If the subject was enrolled into the trial with non-exclusionary elevated transaminase levels at baseline, please discuss any potential drug-induced liver injury events with the Medical Monitor.

5.5 Pregnancy

WOCBP and men who are sexually active must use an effective method of birth control during the course of the trial and for at least 30 days after the last dose in a manner such that risk of failure is minimized. Unless the subject is sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remains abstinent, two of the following precautions must be used: vasectomy or tubal ligation (subject and partner), vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about trial participation for WOCBP. The topics should generally include:

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

Prior to 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 ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

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

If a subject or investigator suspects that the subject may be pregnant prior to IMP administration, 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 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 withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Drug Safety and Pharmacovigilance Department of INC Research (see Appendix 2 for contact information).

The investigator must immediately notify INC Research of any pregnancy associated with IMP exposure, including at least 30 days after the last dose for female subjects and the female partner(s) of a male subject and record the event on the IRE form and forward it to INC Research. INC Research 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 INC Research, 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 six months.

5.6 Follow-up of Adverse Events

For this trial, information on AEs will be followed for up to 30 (+ 2) days after the last dose of IMP has been administered.

5.6.1 Follow-up of Non-serious Adverse Events

Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE eCRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the eCRF.

5.6.2 Follow-up of Post Trial Serious Adverse Events

Serious adverse events that are **identified on the last scheduled contact** must be recorded on the AE eCRF page and reported to INC Research according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported** SAEs, or **new SAEs.** The investigator will follow SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or 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 INC Research up to the point the event has been resolved.

This trial requires that subjects be actively monitored for SAEs up to 30 (+ 2) days after discharge from the trial.

5.6.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

Any new SAEs reported by the subject to the investigator that 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 INC Research. This may include SAEs that are captured on follow-up visit or telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow related SAEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to INC Research up to the point the event has been resolved.

6 Pharmacokinetic Analysis

Not Applicable

7 Statistical Analysis

7.1 Primary and Secondary Outcome Variable Analysis

7.1.1 Data Sets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: comprises all subjects who sign an ICF for the trial.

Safety Sample: comprises those subjects who receive at least one dose of open-label brexpiprazole as adjunctive therapy to one of the allowed ADTs.

Efficacy Sample: comprises those subjects in the Safety Sample who have at least one postbaseline efficacy evaluation of CGI-S.

The Safety Sample will be used for all baseline and safety summaries.

The Efficacy Sample will be used for the CGI-S summaries.

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

The last-observation-carried-forward (LOCF) data set will include data recorded at a given visit in the Treatment Phase or, if no observation is recorded at that visit, data carried forward from the previous visit in the Treatment Phase. Data collected prior to or on the first day of Treatment Phase dosing will not be carried forward or averaged with Treatment Phase data to impute missing values for the LOCF data set.

7.1.2 Handling of Missing Data

In order to assess sensitivity of results due to missing data, two types of analyses will be performed for analyses by visit: LOCF and OC. The LOCF and OC data sets are defined in Section 7.1.1. The OC data set will be used for analyses at each visit and the LOCF data set will be used for the last visit analyses.

7.1.3 Primary Outcome Analysis

The primary safety analysis is the frequency and severity of AEs (see Section 7.4.1).

7.1.4 Secondary Outcome Analysis

Secondary efficacy endpoints are as follows:

1) Change from baseline in CGI-S score, by trial week and at the last visit;
2) Mean CGI-I score, by trial week and at the last visit;
3) Change from baseline in SDS score, by trial week and at the last visit;
4) Change from baseline in IDS-SR Total Score, by trial week and at the last visit.

Descriptive statistics will be provided for each endpoint. The analysis will be carried out on the Efficacy Sample. Descriptive statistics will be summarized at each trial visit using the OC data set and at the last visit using the LOCF data set.

7.2 Sample Size

The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects from the prior double-blind phase 3 brexpiprazole MDD

trials. Therefore, the number of eligible subjects will be limited by the number of subjects enrolled into these protocols. Based on the projected enrollment estimates for the prior double-blind phase 3 trials, up to approximately 3,000 subjects may enroll into Trial 331-10-238.

7.3 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

7.4 Safety Analyses

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and BMI. In addition, data from the following safety scales will be evaluated: SAS, AIMS, BARS, C-SSRS, and MSFQ. Analyses regarding safety and tolerability will be conducted based on the Safety Sample, which is defined in Section 7.1.1. In general, baseline measurements of safety variables are defined as their last measurements prior to the first dose of open-label brexpiprazole.

7.4.1 Adverse Events

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

a) TEAEs by severity
b) Potentially drug-related TEAEs
c) TEAEs with an outcome of death
d) Serious TEAEs
e) Discontinuations due to TEAEs

7.4.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, prolactin concentrations, coagulation parameters (PT, aPTT, and INR), HbA1c, and TSH will be provided. In addition, potentially clinically significant results in laboratory tests identified using prospectively defined criteria will be summarized.

7.4.3 Physical Examination and Vital Signs Data

By-patient listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs will be provided. Potentially clinically significant results in vital signs will also be summarized.

7.4.4 ECG Data

Mean change from baseline and incidence of clinically significant changes will be calculated for ECG parameters.

For the analysis of QT and QTc, data from three consecutive complexes (representing three consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB=QT/(RR)^{0.5}$
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

7.4.5 Other Safety Data

Descriptive statistics will be provided for the SAS, AIMS, BARS, and MSFQ scales. Change from baseline in body weight will be summarized by descriptive statistics, as well as incidence of clinically significant changes in body weight. Descriptive statistics will also be provided for change from baseline in waist circumference and BMI. Descriptive statistics will be summarized at each visit using the OC data set and at the last visit using the LOCF data set.

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.

7.5 Other Outcomes

The percentage of subjects hospitalized for exacerbation of symptoms (including emergency department visits) will be tabulated as a measure of healthcare resource

utilization. The frequency of outpatient visits to various healthcare providers (eg, primary care physician, psychiatrists, other mental health practitioners, etc.) not required per the protocol will also be examined.

8 Trial Drug Management

8.1 Packaging and Labeling

Trial drugs will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will consist of open-label brexpiprazole and open-label ADTs. Open-label brexpiprazole will be supplied as 0.5, 1, 2, and 3-mg tablets packaged in weekly blister cards, each containing sufficient tablets for 7 (+ 2 days). Blister cards will contain single tablet strengths (ie, brexpiprazole 0.5, 1, 2, or 3 mg/day) and subjects will take 1 tablet daily. When accessed by the site, the IVRS or IWRS will assign a specific blister card number to be dispensed to a subject. New weekly blister cards will be dispensed at each scheduled visit and at unscheduled visits if the dose of brexpiprazole is changed.

Each blister card used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, Subject ID (to be filled in by the site staff/investigator), subject's initials or other unique identifier, name of the investigator (to be filled in by the site staff/investigator), site number (to be filled in by the site staff/investigator), subject's initials (to be filled in by the site staff/investigator), date dispensed (to be filled in by the site staff/investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements. Once a blister card has been assigned to a subject via the IVRS or IWRS, it cannot be dispensed to another subject.

ADTs 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. Once an ADT bottle has been assigned to a subject via the IVRS or IWRS, it cannot be dispensed to another subject. 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. Subjects must remain on the same ADT for the duration

of the trial (ie, Screening/Baseline through Week 26/ET). Any subject who cannot tolerate the minimum protocol-defined therapeutic dose of ADT (see Table 3.2.1.2-1) or who is required to change from one ADT to another must be withdrawn from the trial.

8.2 Storage

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

Brexpiprazole should be stored according to the storage conditions indicated on the clinical label. The open-label ADTs should be stored as per the individual manufacturers' label recommendations on the package insert or the ADT clinical label. The clinical site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator, or designee, must maintain an inventory record of trial drugs (including brexpiprazole and ADTs) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP (including brexpiprazole and ADTs) must be returned to Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) (or a designated contractor).

All IMP returned to OPDC (or the designated contractor) must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number. Returned supplies should be in the original containers (eg, blister cards and ADT commercial packaging). The assigned trial monitor will facilitate the return of unused and/or partially used IMP.

8.5 Reporting of Product Quality Complaints

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

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

- Online – Send information required for reporting purposes (listed below) to [redacted]
- Phone - [redacted] Call Center at [redacted].

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 OAPI-EQC.

It should be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to OAPI-EQC for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of Product Quality complaints will be handled by OAPI EQC-QM group.

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.

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;
- The date of the visit and the corresponding Visit in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, and duration of any AEs and the investigator's assessment of relationship to the IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of all clinicians 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. Any changes to information in the trial progress notes or other source documents will be initialed and dated on the day the change is made by a site trial staff member authorized to make the change. Changes will be made by striking a single line through erroneous 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.

Information from the trial progress notes and other source documents will be data entered by investigative site personnel directly onto eCRFs in the sponsor's electronic data capture system.

9.3 File Management at the Trial Site

The investigator will ensure that the trial center file is maintained in accordance with Section 8 of the ICH GCP 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

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following three periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

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 the sponsor or designated agent 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 the eCRF data on the CD-ROM and any data clarification forms received from the sponsor (or sponsor's

designee). Such documentation is subject to inspection by the sponsor, sponsor's designee, and relevant regulatory agencies. 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 (or designee) in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, FDA regulations 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 or designee will visit the site during the trial, as well as communicate frequently via telephone and written communications.

10.2 Auditing

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

Regulatory authorities may inspect the investigator 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, the ICH GCP Guideline, and all other applicable local laws and regulatory requirements. Each trial site will seek approval by an IRB or EC according to regional requirements. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator, subinvestigator, 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.

12 Confidentiality

All information generated in this trial will be considered highly confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. 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 initials and unique subject numbers in eCRFs. Per country regulations, if subject initials cannot be collected, another unique identifier will be used. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

13 Amendment Policy

The investigator will not make any changes to this protocol without prior written consent from the sponsor (or sponsor's designee) and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it be 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. Except for non-substantial (ie, administrative) amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety or physical or mental integrity of subjects, the conduct or management of the trial, the scientific value of the trial or the quality or safety of IMP(s) used in the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor (or sponsor's designee) will submit protocol amendments to the FDA or other regulatory agencies.

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 of the new ICF by the IRB/IEC, repeat informed consent will be obtained from subjects in a timely manner before expecting continued participation in the trial.

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Appendix 1 Names of Sponsor Personnel

Primary Medical Contact:
[redacted]
Phone [redacted]
Mobile [redacted]

Backup Medical Contact:
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Phone [redacted]
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E-mail [redacted]

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Primary Clinical Contact:
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email: [redacted]

Backup Clinical Contacts:
[redacted]
Phone [redacted]

Fax [redacted]

[redacted]

Phone
Fax [redacted]

Appendix 2 Institutions Concerned With the Trial

Clinical Research Organization
INC Research
3201 Beechleaf Court, Suite 600
Raleigh, NC 27604-1547
USA

Safety Reporting
Please report SAEs, AEs requiring discontinuation of drug product, and pregnancies to INC Research Pharmacovigilance & Drug Safety as follows:

Country	Safety Fax Line
United States	[redacted]
Canada	[redacted]
France	[redacted]
Germany	[redacted]
Hungary	[redacted]
Poland	[redacted]
Romania	[redacted]
Russia	[redacted]
Slovakia	[redacted]
Ukraine	[redacted]
All other countries	[redacted]

Medical Monitors

North America:
Primary:
[redacted]
Phone: [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

Backup:
[redacted]
Phone: [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

EU:
[redacted]
Phone: [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

Clinical Lab - ECG Central Reader
eResearch Technology
1818 Market Street, Suite 1000
Philadelphia, PA 19103-3638
USA

Central Laboratory
Covance Laboratories
8211 SciCor Drive
Indianapolis, IN 46214
USA

Subject Recruitment/Retention
INC Research
3201 Beechleaf Court, Suite 600
Raleigh, NC 27604-1547
USA

Materials for Subject Recruitment/Retention
Southport Graphics
210 James Jackson Avenue
Cary, NC, 27513
USA
Phone: (919) 650-3822

Electronic Data Capture
Medidata Solutions
79 5th Avenue, 8th floor
New York, NY 10003
USA

Rater Training
Bracket
575 East Swedesford Road, Suite 200
Wayne, PA 19087
USA

IVRS/IWRS
S-Clinica
6, chaussée de Boondael
B-1050 Brussels, Belgium

Translation Agency
Global Language Solutions, Inc.
25 Enterprise, Suite 500
Aliso Viejo, CA 92656
USA

Central IRB
Schulman Associates IRB
4445 Lake Forest Drive
Suite 300
Cincinnati, OH 45242
USA

Appendix 3 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).

Appendix 4 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

Appendix 5 Criteria for Identifying ECG 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.

Appendix 6 Clinical Global Impression - Severity of Illness Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

Appendix 7 Clinical Global Impression - Improvement Scale (CGI-I)

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at the last scheduled visit of the prior double-blind phase 3 trial (ie, prior to enrollment into Trial 331-10-238), how much has patient changed?

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

Appendix 8 Sheehan Disability Scale (SDS)

Instructions to the investigator:

The Sheehan Disability Scale is a measurement of functional disability and impairment due to psychiatric symptoms. It consists of 3 functional impairment items and 2 items related to productivity losses due to the symptoms and impairment.

The Sheehan Disability Scale is a self rated questionnaire and should be administered to the patient to be completed on his/her own without the presence or influence of study investigator/nurse or other individuals.

You should instruct the patient to report the disability and impairment experienced during the **past week** due to his/her **symptoms**. Emphasize that you will not interfere with the completion or have any comments to the patient's responses.

Please note that a questionnaire that has been completed by the patient is considered as source data and cannot be amended by the investigator or any other individual.

Reference:
Sheehan DV. The Anxiety Disease. New York. Charles Scribner and Sons, 1983
Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. International Clinical Psychopharmacology 1996;11:89-95.

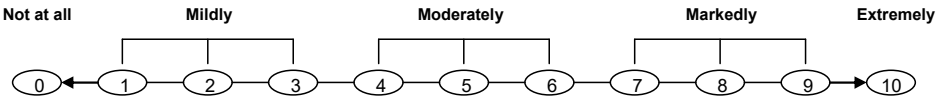
SHEEHAN DISABILITY SCALE

A BRIEF, PATIENT RATED, MEASURE OF DISABILITY AND IMPAIRMENT

Please mark ONE circle for each scale.

WORK* / SCHOOL

The symptoms have disrupted your work / school work:

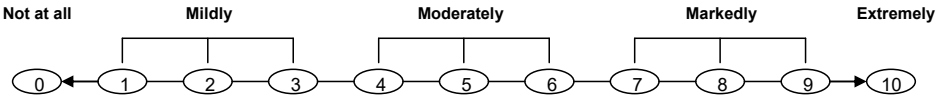


☐ I have not worked / studied at all during the past week for reasons unrelated to disorder.

* Work includes paid, unpaid volunteer work or training

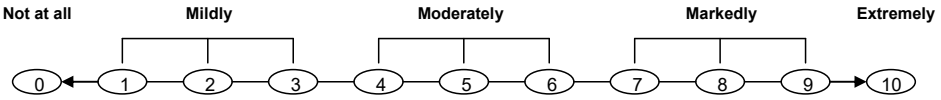
SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:



DAYS LOST

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities?_____

DAYS UNDERPRODUCTIVE

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced?_____

Appendix 9 Inventory of Depressive Symptomatology (Self-Report) (IDS-SR)

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:

   0 I never take longer than 30 minutes to fall asleep.
   1 I take at least 30 minutes to fall asleep, less than half the time.
   2 I take at least 30 minutes to fall asleep, more than half the time.
   3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:

   0 I do not wake up at night.
   1 I have a restless, light sleep with a few brief awakenings each night.
   2 I wake up at least once a night, but I go back to sleep easily.
   3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

   0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   1 More than half the time, I awaken more than 30 minutes before I need to get up.
   2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

   0 I sleep no longer than 7-8 hours/night, without napping during the day.
   1 I sleep no longer than 10 hours in a 24-hour period including naps.
   2 I sleep no longer than 12 hours in a 24-hour period including naps.
   3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:

   0 I do not feel sad.
   1 I feel sad less than half the time.
   2 I feel sad more than half the time.
   3 I feel sad nearly all of the time.

6. Feeling Irritable:

   0 I do not feel irritable.
   1 I feel irritable less than half the time.
   2 I feel irritable more than half the time.
   3 I feel extremely irritable nearly all of the time.

7. Feeling Anxious or Tense:

   0 I do not feel anxious or tense.
   1 I feel anxious (tense) less than half the time.
   2 I feel anxious (tense) more than half the time.
   3 I feel extremely anxious (tense) nearly all of the time.

8. Response of Your Mood to Good or Desired Events:

   0 My mood brightens to a normal level which lasts for several hours when good events occur.
   1 My mood brightens but I do not feel like my normal self when good events occur.
   2 My mood brightens only somewhat to a rather limited range of desired events.
   3 My mood does not brighten at all, even when very good or desired events occur in my life.

9. Mood in Relation to the Time of Day:

   0 There is no regular relationship between my mood and the time of day.
   1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).
   2 In general, my mood is more related to the time of day than to environmental events.
   3 My mood is clearly and predictably better or worse at a particular time each day.

   9A. Is your mood typically worse in the morning, afternoon or night? (circle one)

   9B. Is your mood variation attributed to the environment? (yes or no) (circle one)

10. The Quality of Your Mood:

    0 The mood (internal feelings) that I experience is very much a normal mood.
    1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.
    2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.
    3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.

Please complete either 11 or 12 (not both)

11. Decreased Appetite:

    0 There is no change in my usual appetite.
    1 I eat somewhat less often or lesser amounts of food than usual.
    2 I eat much less than usual and only with personal effort.
    3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

12. Increased Appetite:

    0 There is no change from my usual appetite.
    1 I feel a need to eat more frequently than usual.
    2 I regularly eat more often and/or greater amounts of food than usual.
    3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

13. Decreased Weight (Within the Last Two Weeks):

    0 I have not had a change in my weight.
    1 I feel as if I've had a slight weight loss.
    2 I have lost 2 pounds or more.
    3 I have lost 5 pounds or more.

14. Increased Weight (Within the Last Two Weeks):

    0 I have not had a change in my weight.
    1 I feel as if I've had a slight weight gain.
    2 I have gained 2 pounds or more.
    3 I have gained 5 pounds or more.

15. Concentration/Decision Making:

    0 There is no change in my usual capacity to concentrate or make decisions.
    1 I occasionally feel indecisive or find that my attention wanders.
    2 Most of the time, I struggle to focus my attention or to make decisions.
    3 I cannot concentrate well enough to read or cannot make even minor decisions.

16. View of Myself:

    0 I see myself as equally worthwhile and deserving as other people.
    1 I am more self-blaming than usual.
    2 I largely believe that I cause problems for others.
    3 I think almost constantly about major and minor defects in myself.

17. View of My Future:

    0 I have an optimistic view of my future.
    1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
    2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
    3 I see no hope of anything good happening to me anytime in the future.

18. Thoughts of Death or Suicide:

    0 I do not think of suicide or death.
    1 I feel that life is empty or wonder if it's worth living.
    2 I think of suicide or death several times a week for several minutes.
    3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

19. General Interest:

    0 There is no change from usual in how interested I am in other people or activities.
    1 I notice that I am less interested in people or activities.
    2 I find I have interest in only one or two of my formerly pursued activities.
    3 I have virtually no interest in formerly pursued activities.

20. Energy Level:

    0 There is no change in my usual level of energy.
    1 I get tired more easily than usual.
    2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
    3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

21. Capacity for Pleasure or Enjoyment (excluding sex):

    0 I enjoy pleasurable activities as much as usual.
    1 I do not feel my usual sense of enjoyment from pleasurable activities.
    2 I rarely get a feeling of pleasure from any activity.
    3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

    0 I'm just as interested in sex as usual.
    1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
    2 I have little desire for or rarely derive pleasure from sex.
    3 I have absolutely no interest in or derive no pleasure from sex.

23. Feeling slowed down:

    0 I think, speak, and move at my usual rate of speed.
    1 I find that my thinking is slowed down or my voice sounds dull or flat.
    2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
    3 I am often unable to respond to questions without extreme effort.

24. Feeling restless:

    0 I do not feel restless.
    1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
    2 I have impulses to move about and am quite restless.
    3 At times, I am unable to stay seated and need to pace around.

25. Aches and pains:

    0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
    1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
    2 I have these sorts of pains most of the time.
    3 These pains are so bad they force me to stop what I am doing.

26. Other bodily symptoms:

    0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
    1 I have some of these symptoms but they are mild and are present only sometimes.
    2 I have several of these symptoms and they bother me quite a bit.
    3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

27. Panic/Phobic symptoms:

    0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
    1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
    2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
    3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

28. Constipation/diarrhea:

    0 There is no change in my usual bowel habits.
    1 I have intermittent constipation or diarrhea which is mild.
    2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
    3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

29. Interpersonal Sensitivity:

    0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
    1 I have occasionally felt rejected, slighted, criticized or hurt by others.
    2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
    3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

30. Leaden Paralysis/Physical Energy:

    0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
    1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without negative effect on work, school, or activity level.
    2 I feel physically weighted down (without physical energy) more than half the time.
    3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

Which 3 items (questions) were the easiest to understand? _____

Thank you

Range 0-84 Score: _____

Appendix 10 Simpson Angus Scale (SAS)

Circle the appropriate score for each item:	
1.	**GAIT** The patient is examined as he walks into the examining room; his gait, the swing of arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:
0	Normal
1	Mild diminution in swing while the patient is walking
2	Obvious diminution in swing suggesting shoulder rigidity
3	Stiff gait with little or no arm swing noticeable
4	Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion.
2.	**ARM DROPPING** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides, in a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly.
0	Normal, free fall with loud slap and rebound
1	Fall slowed slightly with less audible contact and little rebound
2	Fall slowed, no rebound
3	Marked slowing, no slap at all
4	Arms fall as though against resistance; as though through glue
3.	**SHOULDER SHAKING** The subject's arms are bent at a right angle at the elbow and taken one at a time by the examiner who grabs one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
4.	**ELBOW RIGIDITY** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to the procedure is rated. (The presence of cogwheel rigidity is noted separately.)
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

5.	**WRIST RIGIDITY** The wrist is held in one hand and then the fingers held by the examiner's other hand with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
6.	**HEAD ROTATION** The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patient's head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.
0	Loose, no resistance
1	Slight resistance to movement although the time to rotate may be normal
2	Resistance is apparent and time of rotation is slowed
3	Resistance is obvious and rotation is slowed
4	Head appears stiff and rotation is difficult to carry out
7.	**GLABELLA TAP** Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
0	0-5 blinks
1	6-10 blinks
2	11-15 blinks
3	16-20 blinks
4	21 and more blinks
8.	**TREMOR** Patient is observed walking into examining room and then is examined for this item:
0	Normal
1	Mild finger tremor, obvious to sight and touch
2	Tremor of hand or arm occurring spasmodically
3	Persistent tremor of one or more limbs
4	Whole body tremor
9.	**SALIVATION** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
0	Normal
1	Excess salivation so that pooling takes place if the mouth is open and the tongue raised
2	Excess salivation is present and might occasionally result in difficulty in speaking
3	Speaking with difficulty because of excess salivation
4	Frank drooling

10.	**AKATHISIA** Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient report can help make the assessment.
0	No restlessness reported or observed
1	Mild restlessness observed
2	Moderate restlessness observed
3	Restlessness is frequently observed
4	Restlessness persistently observed

Adapted and used with permission by Simpson GN and Angus JWS, “A Rating Scale for Extrapyramidal Side Effects,” *Acta Psychiatr Scand*, 1970, 212 (Suppl 44):11-9.

Appendix 11 Abnormal Involuntary Movement Scale (AIMS)

Movement ratings: rate highest severity observed. Rate movements that occur upon activation one **less** than those observed spontaneously.		**Code for items 1-7:** **0** = None **1** = Minimal, may be extreme normal **2** = Mild **3** = Moderate **4** = Severe
		(Circle One)
FACIAL AND ORAL MOVEMENTS:	**1.** **MUSCLES OF FACIAL EXPRESSION** e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	**0 1 2 3 4**
	2. **LIPS AND PERIORAL AREA** e.g. puckering, pouting, smacking.	**0 1 2 3 4**
	3. **JAW** e.g. biting, clenching, chewing, mouth opening, lateral movement.	**0 1 2 3 4**
	4. **TONGUE** Rate only increase in movement both in and out of mouth, not inability to sustain movement.	**0 1 2 3 4**
EXTREMITY MOVEMENTS:	**5.** **UPPER (ARMS, WRISTS, HANDS, FINGERS)** include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do not include tremor (i.e. repetitive, regular, rhythmic).	**0 1 2 3 4**
	6. **LOWER (LEGS, KNEES, ANKLES, TOES)** e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	**0 1 2 3 4**
TRUNK MOVEMENTS:	**7.** **NECK, SHOULDERS, HIPS** e.g. rocking, twisting, squirming, pelvic gyrations	**0 1 2 3 4**
GLOBAL JUDGMENTS:	**8.** Severity of abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**
	9. Incapacitation due to abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**
	10. Patient's awareness of abnormal movements Rate only subject's report.	No awareness **0** Aware, no distress **1** Aware, mild distress **2** Aware, moderate distress **3** Aware, severe distress **4**
DENTAL STATUS:	**11.** Any current problems with teeth and/or dentures?	No **0** Yes **1**
	12. Does patient usually wear dentures?	No **0** Yes **1**

Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976

Appendix 12 Barnes Akathisia Rating Scale (BARS)

Rating scale for drug-induced akathisia (Barnes Akathisia Rating Scale)

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time and/or reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global clinical assessment of akathisia

0 *Absent*. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable*. Non-specific inner tension and fidgety movements

2 Mild akathisia. Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia*. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia*. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia*. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: A rating scale for drug-induced akathisia. T.R.E. Barnes, *British Journal of Psychiatry* (1989), **154**, 672-676.

Appendix 13 Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted]*; inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 14 Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ)

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you (consider "normal" the time in your life prior to the past month when you were most satisfied with your sexual functioning).

a) How has your interest in sex been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

b) How has your ability to get sexually aroused or excited been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

c) How has your ability to achieve orgasm been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

d) (for men only) How has your ability to get and maintain an erection been over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

e) How would you rate your overall sexual satisfaction over the past month?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

Appendix 15 Resource Utilization Form (RUF)

BASELINE

We are interested in how often you have sought medical care or were hospitalized for any type of condition. (Note: **Do not include** any research visits.) Please refer to your personal calendar. Enter 0 if there were no visits (Question 1) or no hospitalizations (Questions 2 to 5).

1. In the past 3 months, how many visits did you make to any of the following?

	Number of visits
a. A primary care doctor	☐☐ visits
b. Psychiatrist	☐☐ visits
c. Counselor, psychologist or other mental health professional	☐☐ visits
d. Physicians other than your primary care doctor or mental health professional	☐☐ visits
e. An emergency room or urgent care facility for the treatment of your emotions, nerves, or mental health	☐☐ visits
f. An emergency room or urgent care facility <u>for any other reason</u>?	☐☐ visits

2. In the past <u>12 months</u>, how many times were you hospitalized for the treatment of your emotions, nerves, or mental health?

   (Enter 0 if there were no hospitalizations.) ☐☐ number of times hospitalized

3. In the past <u>12 months</u>, how many times were you hospitalized <u>for any other reason</u>?

   (Enter 0 if there were no hospitalizations.) ☐☐ number of times hospitalized

4. IF YOU WERE HOSPITALIZED in the past <u>12 months</u>, for how many days were you in the hospital for your emotions, nerves, or mental health? ☐☐ days hospitalized

5. IF YOU WERE HOSPITALIZED in the past <u>12 months</u>, for how many days were you hospitalized <u>for any other reasons</u>? ☐☐ days hospitalized

FOLLOW-UP

We are interested in how often you have sought medical care for any type of condition since you started the study. (Note: **Do not include** any research visits.) Please refer to your personal calendar. Enter 0 if no visits were made.

1. Since you started the study, how many visits did you make to any of the following?

	Number of visits
a. A primary care doctor	☐☐ visits
b. Psychiatrist	☐☐ visits
c. Counselor, psychologist or other mental health professional	☐☐ visits
d. Physicians other than your primary care doctor or mental health professional	☐☐ visits
e. An emergency room or urgent care facility for the treatment of your emotions, nerves or mental health	☐☐ visits
f. An emergency room or urgent care facility for any other reason?	☐☐ visits

Appendix 16 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 23 November 2011

PURPOSE:

The sponsor has determined the need for a formal amendment to the original protocol approved on 11 May 2011 to add additional clarity to trial procedures and to make several administrative changes.

BACKGROUND:

1. Clarification of trial procedures

1) Clarify dosing schedule of duloxetine 40 mg/day (once daily or 20 mg twice daily).
2) Clarify interval between dose adjustments by changing description from "at least one week" to "at least 5 days" and revise wording regarding rechallenge after dose is decreased to 0.5 mg/day.
3) Clarify that the serum pregnancy test is the definitive test for determining pregnancy, irrespective of urine pregnancy test result.
4) Clarify that subjects who are sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) are not required to use two different methods of birth control.
5) Per recent posting from FDA, add linezolid and methylene blue to list of drugs that may result in serotonin syndrome if coadministered with SSRIs or SNRIs.

2. Administrative changes and correction of typographical errors

- 1) Replace OPC-34712 with approved generic name (ie, brexpiprazole)
- 2) Add EudraCT number
- 3) Update primary medical contact for OPDC personnel
- 4) Change name of United BioSource Corporation to Bracket
- 5) Update address of Schulman Associates IRB.

MODIFICATIONS TO PROTOCOL:

- **<u>Bold and underlined text:</u>** Changed text
- ~~**Bold and strikethrough text:**~~ Deleted text

- ***Bold and italicized text:*** Added text

TITLE PAGE

Brexpiprazole (OPC-34712***)***

Protocol No. 331-10-238
IND No. 103,958
EudraCT No. 2011-001351-37

Sponsor Representatives:

[redacted]

~~**Phone**~~
~~**Fax**~~
~~**E-mail**~~

[redacted]

Phone
Fax
E-mail

Issue Date: 11 May 2011
Date of Amendment 1: ***23 November 2011***

Entire protocol, Footnote

~~**27 May 2011**~~

23 November 2011

SYNOPSIS, Name of Product:

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: ***Brexpiprazole (***OPC-34712***)***	Protocol #331-10-238 ***IND #103,958*** ***EudraCT #2011-001351-37***

SYNOPSIS, Objective(s):

Primary: To assess the long-term safety and tolerability of oral OPC-34712 ***(hereafter referred to by the generic name "brexpiprazole")*** as adjunctive therapy in the treatment of adults with MDD.

Secondary: To assess the long-term efficacy of oral ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy in the treatment of adults with MDD.

SYNOPSIS, Trial Design, Paragraph 1, Sentences 1 and 3:

This is a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive ~~**OPC-34712**~~ **brexpiprazole** in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed one of the double-blind, phase 3 efficacy trials (ie, Trial 331-10-227 or Trial 331-10-228) and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral ~~**OPC-34712**~~ **brexpiprazole** for MDD.

SYNOPSIS, Trial Design, Paragraph 3, *Treatment Phase*, Sentence 1:

Eligible subjects will receive daily treatment with open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT as described in the Investigational Medicinal Product, Dose, Formulation, Mode of Administration section.

SYNOPSIS, Subject Population, Paragraph 1, Sentence 1:

The subject population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with ~~**OPC-34712**~~ **brexpiprazole** for MDD and who meet one of the following conditions:

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, Paragraph 1:

Trial medication (ie, investigational medicinal product [IMP]) will be provided to the investigator(s) by the sponsor (or designated agent) and will consist of open-label ~~**OPC-34712**~~ **brexpiprazole** and open-label ADTs.

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, *OPC-34712*, Paragraph 1 and bulleted list:

~~***OPC-34712***~~ ***Brexpiprazole***: Open-label ~~**OPC-34712**~~ **brexpiprazole** will be supplied as 0.5, 1, 2, and 3-mg tablets packaged in weekly blister cards, each containing sufficient tablets for 7 (+ 2 days). Blister cards will be dispensed at each scheduled visit and at unscheduled visits if the dose of ~~**OPC-34712**~~ **brexpiprazole** is changed. All doses of ~~**OPC-34712**~~ **brexpiprazole** should be taken orally once daily and can be administered without regard to meals. For convenience, ~~**OPC-34712**~~ **brexpiprazole** may be taken with the first daily dose of ADT.

All subjects will be dosed as follows:

- The first dose of open-label ~~**OPC-34712**~~ **brexpiprazole** will be taken one day after the last dose is taken for the double-blind, phase 3 efficacy trial so that adjunctive treatment will continue without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Week 14 visit of Trial

331-10-227 or Trial 331-10-228 (ie, the day of the Screening/Baseline visit for the open-label trial). Subjects will initiate open-label dosing with **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ for 1 week. Subjects unable to tolerate **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ must be withdrawn from the trial.

- The dose of **brexpiprazole** ~~**OPC-34712**~~ will be increased to 1 mg/day at the Week 1 visit. Subjects unable to tolerate **brexpiprazole** 1 mg/day ~~**OPC-34712**~~ may decrease to 0.5 mg/day at any time after the Week 1 visit.
- Investigators may further increase the dose to **brexpiprazole** 2 mg/day ~~**OPC-34712**~~ and then to **brexpiprazole** 3 mg/day ~~**OPC-34712**~~, with an interval of at least ~~**one week**~~ **5 days** between dose increases. An interval of at least ~~**one week**~~ **5 days** between dose adjustments is recommended for dose decreases; however, the dose of **brexpiprazole** ~~**OPC-34712**~~ can be decreased at the investigator's discretion in a step-wise manner at any time after the Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.
- Subjects who tolerate a reduced dose of **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ should be rechallenged with **brexpiprazole** 1 mg/day ~~**OPC-34712**~~ at least once during the trial. In addition, the dose of **brexpiprazole** ~~**OPC-34712**~~ can be re-escalated as necessary following any dose decrease if, in the investigator's judgment, rechallenge with a higher dose is warranted in order to identify an optimum dose for the subject. Subjects must return to the clinic for unscheduled visits if changes to the dose of **brexpiprazole** ~~**OPC-34712**~~ (increases or decreases) are required between scheduled visits.

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, *ADT*, Paragraph 1, Sentences 3 and 4:

It is recommended that the dose of ADT not be changed while the dose of **brexpiprazole** ~~**OPC-34712**~~ is being optimized (ie, no change to ADT up to and including the Week 4 visit). *After the Week 4 visit*, the dose of ADT can be modified if necessary to achieve optimum efficacy and tolerability for the treatment regimen using the following rules: 1) at least ~~**one week**~~ **5 days** must elapse between dose increases (either **brexpiprazole** ~~**OPC-34712**~~ or ADT), 2) an interval of at least ~~**one week**~~ **5 days** between dose adjustments (either **brexpiprazole** ~~**OPC-34712**~~ or ADT) is recommended for dose decreases; however, the ADT dose can be decreased at the investigator's discretion at any time as needed for tolerability, and 3) subjects must return to the clinic for unscheduled visits if changes to the ADT dose are required between scheduled visits.

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, *ADT*, Paragraph 3:

All doses of ADT will be administered orally once daily except for duloxetine 40 mg/day that ~~is~~ **can be** administered ***once daily or*** as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily.

SYNOPSIS, Criteria for Evaluation, Primary Outcome Variable:

The primary outcome variable is the safety and tolerability of **brexpiprazole** ~~**OPC-34712**~~ which will be assessed by examining the frequency and severity of adverse events (AEs).

List of Abbreviations and Definitions of Terms:

EudraCT	***European Clinical Trial Data Base***
Investigational medicinal product (IMP)	For the purposes of this protocol, IMP refers to all trial medication supplied to the sites by the sponsor (or designated agent) and includes bottles of protocol-specified ADTs and blister cards containing **brexpiprazole** ~~**OPC-34712**~~.

Section 1, Introduction, Paragraph 3:

OPC-34712 ***(hereafter referred to by the generic name "brexpiprazole")*** is an organic compound synthesized by Otsuka Pharmaceutical Co, Ltd, that is a [redacted] at [redacted], [redacted], [redacted], [redacted], and [redacted], an antagonist at [redacted], and has a [redacted] for [redacted] and [redacted] Details of the receptor affinity profile of ~~**OPC-34712**~~ **brexpiprazole** are summarized in Section 1.1.1. Activity at dopamine and serotonin receptors has been shown to be useful in the treatment of psychiatric disorders, eg, schizophrenia and bipolar mania. Hence, ~~**OPC-34712**~~ **brexpiprazole** is expected to be a promising antipsychotic agent. As the relative activity at these and other receptors appears to be related to the side effect profiles of antipsychotic drugs,15,16,17,18 ~~**OPC-34712**~~ **brexpiprazole** may have the potential to exhibit improved safety compared to other agents. The more potent antagonism at 5-HT2A receptors for ~~**OPC-34712**~~ **brexpiprazole** relative to aripiprazole may afford a more favorable profile with respect to sleep quality; whereas, the low binding affinities for histamine and muscarinic receptors suggest that ~~**OPC-34712**~~ **brexpiprazole** may have less potential to cause H1-receptor-related weight gain than olanzapine. Preclinical data also suggest that ~~**OPC-34712**~~ **brexpiprazole** will have lower potential for hyperprolactinemia than risperidone.

Results from initial phase 2 trials showed ~~OPC-34712~~ **brexpiprazole** to be well tolerated by subjects with MDD and schizophrenia (see Section 1.3).

Section 1.1.1, Efficacy Pharmacology:

~~OPC-34712~~ **Brexpiprazole** functions as a partial agonist at the D2 receptor. In in vitro assay systems based on forskolin-induced cyclic AMP accumulation and calcium (Ca^{2+}) mobilization in human dopamine D2L receptor-expressing cells, its intrinsic activity at the D2 receptor was slightly lower than that of aripiprazole, another D2 receptor partial agonist. ~~OPC-34712~~ **Brexpiprazole** inhibited apomorphine (APO)-induced hyperlocomotion, APO-induced stereotyped behavior, and conditioned avoidance response in rats, which are predictive animal models for antipsychotic-like efficacy. The inhibitory effects of ~~OPC-34712~~ **brexpiprazole** were more potent than those of aripiprazole. Moreover, in contrast to the D2 receptor antagonist risperidone, ~~OPC-34712~~ **brexpiprazole** did not increase plasma prolactin levels in reserpine-treated rats, thus demonstrating a D2 receptor partial agonistic profile in vivo. Despite its lower intrinsic activity at the D2 receptor, the in vivo catalepsy liability of ~~OPC-34712~~ **brexpiprazole**, an index of EPS, was similar to that of aripiprazole, but still lower than that of the typical antipsychotic haloperidol. Furthermore, ~~OPC-34712~~ **brexpiprazole** showed high binding affinity for the 5-HT2A receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT2A receptor antagonistic activity; the effect of ~~OPC-34712~~ **brexpiprazole** was more potent than that of aripiprazole. In addition, ~~OPC-34712~~ **brexpiprazole** exhibited high binding affinities for the D3 and 5-HT1A receptors, acting as a partial agonist at these receptors.

Section 1.1.2, Safety Pharmacology:

In safety pharmacology studies in rats at an oral dose of 30 mg/kg or higher, ~~OPC-34712~~ **brexpiprazole** induced pharmacologically mediated clinical signs considered to be due to depression of the central nervous system (CNS) and dose-dependent decreases in body temperature. When orally administered at up to 30 mg/kg in conscious male beagle dogs, ~~OPC-34712~~ **brexpiprazole** showed no effect on respiratory parameters or heart rate at any dose tested. ~~OPC-34712~~ **Brexpiprazole** decreased blood pressure at doses of 3 mg/kg or higher and prolonged both QT interval and corrected QT interval (QTc, by Van de Water's formula) at 30 mg/kg. ~~OPC-34712~~ **Brexpiprazole** inhibited human *ether-a-go-go* related gene (hERG) current in Chinese hamster ovary cells (CHO-K1) at concentrations of 10^{-8} mol/L or higher, with a 50% inhibitory concentration of 1.17 ×

10^{-7} mol/L. The mechanism for the blood pressure decreasing effect of ~~**OPC-34712**~~ **brexpiprazole** was suggested to result from a blockade of the α_1-adrenoceptor in peripheral blood vessels, which is a part of the compound's pharmacological profile. Proarrhythmic risk was also evaluated by examining the effects of ~~**OPC-34712**~~ **brexpiprazole** on monophasic action potential parameters in halothane-anesthetized dogs. ~~**OPC-34712**~~ **Brexpiprazole** did not affect the terminal repolarization period even at an intravenous dose of 3 mg/kg, suggesting a low potential for proarrhythmic effects. In general, the changes in the CNS, respiratory, and cardiovascular systems observed with ~~**OPC-34712**~~ **brexpiprazole** occurred at doses or exposure levels higher than those at which efficacy was confirmed in rats (3 mg/kg), and similar changes were shown to occur after administration of risperidone at similar or lower doses.

Section 1.2.1, Pharmacokinetics/pharmacodynamics:

The pharmacokinetics of single and multiple doses of ~~**OPC-34712**~~ **brexpiprazole** was studied in healthy subjects and in subjects with MDD, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, ***brexpiprazole (***OPC-34712***)*** and one 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 ~~**OPC-34712**~~ **brexpiprazole** and thus is considered as an inactive metabolite. Both ~~**OPC-34712**~~ **brexpiprazole** and DM-3411 pharmacokinetics were linear following single oral doses of **brexpiprazole** 0.2 to 8 mg ~~**OPC-34712**~~ to healthy subjects. The terminal phase elimination half-life of ~~**OPC-34712**~~ **brexpiprazole** and DM-3411 was 48.3 to 80.8 hours and 48.6 to 77.5 hours, respectively. The median time to maximum (peak) plasma concentration (t_{max}) occurred at approximately 2 to 6 hours postdose for ~~**OPC-34712**~~ **brexpiprazole** and at approximately 10 to 24 hours postdose for DM-3411. In healthy subjects, administration of single-dose ~~**OPC-34712**~~ **brexpiprazole** with a high-fat meal did not affect its rate and extent of absorption.

Steady state pharmacokinetics also appeared to be linear following multiple daily doses of ~~**OPC-34712**~~ **brexpiprazole** in the range of 0.5 to 2 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 ~~**OPC-34712**~~ **brexpiprazole** (1 to 12 mg/day) to subjects with schizophrenia or schizoaffective disorder, ~~**OPC-34712**~~ **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, ~~**OPC-34712**~~ **brexpiprazole** was shown to be metabolized by CYP3A4 and CYP2D6 isozymes and was not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein. Coadministration of potent CYP3A4 or CYP2D6 inhibitors with ~~**OPC-34712**~~ **brexpiprazole** resulted in about a 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half life of ~~**OPC-34712**~~ **brexpiprazole**. Of note, administration of ~~**OPC-34712**~~ **brexpiprazole** with fluoxetine, paroxetine, or duloxetine (MDD medications coadministered in this trial) may potentially increase ~~**OPC-34712**~~ **brexpiprazole** plasma concentrations by up to 2-fold.

In a single-dose trial in healthy subjects, approximately 46.0% and 24.6% of administered radioactivity following an oral dose of ^{14}C-~~**OPC-34712**~~ **brexpiprazole** was excreted in feces and urine, respectively. In this same trial, ~~**OPC-34712**~~ **brexpiprazole** did not preferentially bind to red blood cells. ~~**OPC-34712**~~ **Brexpiprazole** showed high protein binding in human serum (≥ 99.8%) in vitro.

The binding of ~~**OPC-34712**~~ **brexpiprazole** to dopamine receptors was assessed using positron emission tomography (PET). The mean D2/D3 receptor occupancies at 4 and 24 hours postdose after 0.25, 0.5, 1, 2, 4, 5, and 6 mg single dose administration of ~~**OPC-34712**~~ **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 D2/D3 receptor occupancy data and steady-state pharmacokinetic/pharmacodynamic (PK/PD) modeling, it was predicted that the D2/D3 receptor occupancy after multiple daily dose administration of 1 to 2 mg and higher doses of ~~**OPC-34712**~~ **brexpiprazole** will result in at least 80% to 90% D2/D3 receptor occupancy.

Additional information on the pharmacokinetics/pharmacodynamics of ~~**OPC-34712**~~ **brexpiprazole** and its metabolites in humans can be found in the Investigator Brochure.[19]

Section 1.2.2, Major Depressive Disorder

The efficacy of ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy for the treatment of MDD has been studied in one completed placebo-controlled trial (Trial 331-08-211). An additional placebo-controlled efficacy trial (Trial 331-09-222) and one long-term open-label safety trial (Trial 331-08-212) are ongoing. Trial 331-08-211 was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and

efficacy of ~~OPC-34712~~ **brexpiprazole** (0.15 to 2 mg daily) as adjunctive treatment to an assigned open-label ADT in subjects with MDD who have demonstrated an incomplete response to prospective treatment with the same ADT. Subjects with an incomplete response after 8 weeks of treatment with single-blind placebo plus open-label ADT were randomized to 6 weeks of double-blind treatment with either ~~OPC-34712~~ **brexpiprazole**-plus-ADT or placebo-plus-ADT. Responders continued to receive placebo-plus-ADT for an additional 6 weeks. Randomized subjects received **brexpiprazole** 0.15 mg/day~~OPC-34712~~, 0.50 ± 0.25 mg/day ~~OPC-34712~~, 1.5 ± 0.50 mg/day ~~OPC-34712~~, or matching placebo. Subjects randomized to the **brexpiprazole** 0.50 ± 0.25 mg/day ~~OPC-34712~~ and **brexpiprazole** 1.5 ± 0.50 mg/day ~~OPC-34712~~ arms were titrated to the target doses (0.50 and 1.5 mg, respectively) over a 2-week period. Dose adjustments were permitted after the subjects received 1 week of treatment at the target dose. Subjects who could not tolerate the lowest dose (**brexpiprazole** 0.15, 0.25, or 1.0 mg/day ~~OPC-34712~~or matching placebo, respectively) were to be discontinued from the trial. In this trial, adjunctive ~~OPC-34712~~ **brexpiprazole** dosed at 1.5 ± 0.50 mg/day was superior to adjunctive placebo with respect to the primary endpoint (change from Week 8 to Week 14 in Montgomery Asberg Depression Rating Scale [MADRS] Total Score) and several secondary efficacy endpoints.[20] Ongoing Trial 331-09-222 is of similar design to Trial 331-08-211, but is exploring an expanded dose range (**brexpiprazole** 1 to 3 mg/day~~OPC-34712~~).

Section 1.2.3, Schizophrenia, Sentence 2:

The outcome of this trial suggests an active dose range of **brexpiprazole** 1 to 6 mg/day ~~OPC-34712~~ for the treatment of schizophrenia.[21]

Section 1.2.4, Other Indications, Sentences 1 and 2:

~~OPC-34712~~ **Brexpiprazole** is being investigated in a proof-of-concept trial in adult ADHD (Trial 331-08-213). This is a multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial in which adults with ADHD who have an incomplete/partial response to stimulant therapy in a prospective treatment phase are randomized to double-blind treatment with either ~~OPC-34712~~ **brexpiprazole**-plus-stimulant or placebo-plus-stimulant.

Section 1.3, Known and Potential Risks and Benefits, Paragraph 1, Sentences 1, 4, and 5:

As of 31 Dec 2010, 14 clinical trials involving ~~**OPC-34712**~~ **brexpiprazole** have been completed worldwide, including 10 in the United States (US), 1 in multiple countries (including the US), 2 in Japan, and 1 in Korea.

~~**OPC-34712**~~ **Brexpiprazole** has been well tolerated by healthy volunteers at single doses up to 6 mg and at multiple doses up to 2 mg/day. In patient trials, ~~**OPC-34712**~~ **brexpiprazole** has been well tolerated at multiple doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder, up to 4 mg/day in subjects with MDD who received concomitant ADT, and up to 4 mg/day in adults with ADHD who received concomitant stimulant therapy.

Section 1.3, Known and Potential Risks and Benefits, Paragraph 2, Sentences 1 and 2:

In the 11 completed phase 1 and 2 clinical trials performed under the US IND (two phase 2 trials, one phase 1b trial, and eight phase 1 trials), 673/973 (69.2%) subjects who received ~~**OPC-34712**~~ **brexpiprazole** either alone or coadministered with another marketed medication reported at least one treatment-emergent adverse event (TEAE) compared to 158/253 (62.5%) subjects who received placebo either alone or coadministered with another marketed medication. The most common TEAEs reported for ~~**OPC-34712**~~ **brexpiprazole** in the completed trials (≥ 5% in the total ~~**OPC-34712**~~ **brexpiprazole** group and more than the total placebo group) were headache (10.6%), dizziness (8.0%), anxiety (7.1%), akathisia (7.0%), and nausea (5.5%).

Section 1.3, Known and Potential Risks and Benefits, Paragraph 3, Sentences 3 and 4:

The incidence of serious TEAEs (fatal and non-fatal) that were reported during treatment with ~~**OPC-34712**~~ **brexpiprazole** administered either alone or coadministered with another medication (19/973 subjects, 2.0%) was comparable to placebo administered either alone or coadministered with another medication (4/253 subjects, 1.6%). Furthermore, treatment with ~~**OPC-34712**~~ **brexpiprazole** does not appear to promote suicidal behavior in subjects with MDD or schizophrenia.

Section 1.3, Known and Potential Risks and Benefits, Paragraph 4:

~~**OPC-34712**~~ **Brexpiprazole** did not result in any consistent, clinically relevant changes in laboratory values, vital signs (blood pressure or heart rate), or electrocardiogram (ECG) parameters in the completed phase 1 and 2 clinical trials in subjects with MDD or schizophrenia. Statistically significant increases in weight were observed with ~~**OPC-34712**~~ **brexpiprazole** relative to placebo in both sample populations. ~~**OPC-34712**~~ **Brexpiprazole** exhibited a favorable profile with respect to movement disorders in subjects with MDD at doses up to 3 mg/day (Trial 331-09-221) and in subjects with

schizophrenia at doses up to 12 mg/day (Trial 331-08-205). In the dose-ranging trial that enrolled subjects who were experiencing an acute exacerbation of schizophrenia (Trial 331-07-203), an increase in the incidence of EPS was observed at the highest dose (ie, **brexpiprazole** 5.0 ± 1.0 mg/day ~~**OPC-34712**~~).

Section 2.1, Trial Rationale, Paragraph 1, Sentence 4:

As ~~**OPC-34712**~~ **brexpiprazole** demonstrated antagonism at 5-HT2A receptors, the attenuated response to SSRIs may be reversed with coadministration of ~~**OPC-34712**~~ **brexpiprazole** and SSRIs, thus enhancing clinical outcomes.

Section 2.1, Trial Rationale, Paragraph 2:

Because the management of MDD may require prolonged administration of ADT(s) with or without an augmenting agent, safety monitoring for longer than the period required to achieve initial response is warranted. In the ~~**OPC-34712**~~ **brexpiprazole** clinical development program for MDD, phase 2 and phase 3 trials examined the 6-week safety and efficacy of ~~**OPC-34712**~~ **brexpiprazole** augmentation of ADTs. For phase 2, subjects who completed either of the trials had the option to enroll into an open-label rollover trial in which they received ~~**OPC-34712**~~ **brexpiprazole** for up to 52 weeks (Trial 331-08-212). The current trial (Trial 331-10-238) provides an open-label rollover option for the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228) and will expand on the knowledge gained in these trials by assessing the long-term safety, tolerability, and efficacy of ~~**OPC-34712**~~ **brexpiprazole** when administered concomitantly with antidepressant medications.

Section 2.2, Dosing Rationale, Paragraph 1:

A dose range of **brexpiprazole** 0.5 to 3 mg/day ~~**OPC-34712**~~ was selected for the current open-label trial to encompass the dose range of the double-blind efficacy trials (ie, **brexpiprazole** 1 to 3 mg/day ~~**OPC-34712**~~) and to include an option for a reduced dose for tolerability (ie, 0.5 mg/day) in order to maximize subject retention in the long-term trial. Therapeutic dose ranges of ADT are based on product labels and clinical practice. Data from phase 1 drug interaction trials (Trial 331-08-207 and Trial 331-08-208) indicated that coadministration of CYP2D6 inhibitors (eg, paroxetine, fluoxetine, and duloxetine) with ~~**OPC-34712**~~ **brexpiprazole** could cause potentially higher plasma concentrations of ~~**OPC-34712**~~ **brexpiprazole** (up to 2-fold). In order to limit the potential higher exposure of ~~**OPC-34712**~~ **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 in the current trial.

Section 2.3, Trial Objectives:

Primary: To assess the long-term safety and tolerability of oral ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy in the treatment of adults with MDD.

Secondary: To assess the long-term efficacy of oral ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy in the treatment of adults with MDD.

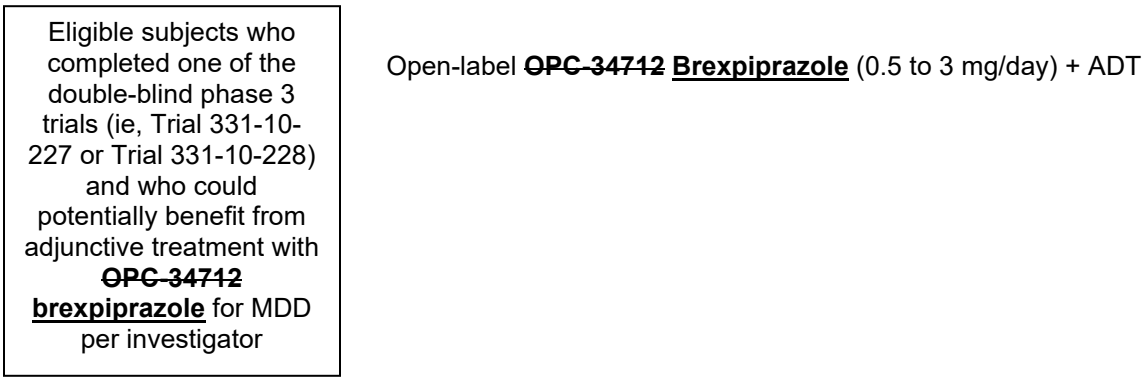
Section 3.1, Type/Design of Trial, Paragraph 1, Sentences 1 and 3:

This is a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive ~~**OPC-34712**~~ **brexpiprazole** in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed one of the double-blind, phase 3 efficacy trials (ie, Trial 331-10-227 or Trial 331-10-228) and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral ~~**OPC-34712**~~ **brexpiprazole** for MDD.

Section 3.1, Type/Design of Trial, Paragraph 3, *Treatment Phase*, Sentence 1:

Eligible subjects will receive daily treatment with open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT as described in Section 3.2.

Figure 3.1-1, Population and treatment group descriptions:



Section 3.2.1.1, ~~**OPC-34712**~~ **Brexpiprazole**:

The first dose of open-label ~~**OPC-34712**~~ **brexpiprazole** will be taken one day after the last dose is taken for the double-blind, phase 3 efficacy trial so that adjunctive treatment will continue without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Week 14 visit of Trial 331-10-227 or

Trial 331-10-228 (ie, the day of the Screening/Baseline visit for the open-label trial). Subjects will initiate open-label dosing with **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ for 1 week. Subjects unable to tolerate **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ must be withdrawn from the trial. The dose of ~~**OPC-34712**~~ **brexpiprazole** will be increased to 1 mg/day at the Week 1 visit. Subjects unable to tolerate **brexpiprazole** 1 mg/day ~~**OPC-34712**~~ may decrease to 0.5 mg/day at any time after the Week 1 visit.

Investigators may further increase the dose to **brexpiprazole** 2 mg/day ~~**OPC-34712**~~ and then to **brexpiprazole** 3 mg/day ~~**OPC-34712**~~, with an interval of at least ~~**one week**~~ **5 days** between dose increases. An interval of at least ~~**one week**~~ **5 days** between dose adjustments is recommended for dose decreases; however, the dose of ~~**OPC-34712**~~ **brexpiprazole** can be decreased at the investigator's discretion in a step-wise manner at any time after the Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response. Subjects must return to the clinic for unscheduled visits if changes to the dose of ~~**OPC-34712**~~ **brexpiprazole** (increases or decreases) are required between scheduled visits. The dosing schedule is summarized in Table 3.2.1.1-1. Additional information on dose adjustments is provided in Section 3.2.2.1.

All doses of ~~**OPC-34712**~~ **brexpiprazole** should be taken orally once daily and can be administered without regard to meals. For convenience, ~~**OPC-34712**~~ **brexpiprazole** may be taken with the first daily dose of ADT.

Table 3.2.1.1-1 Dosing Schedule for ~~OPC-34712~~ Brexpiprazole

IMP	Trial Visit				
	Screening/ Baseline	**Week 1**[a]	**Week 2**[b]	**Week 4**[b]	**Visits at Weeks 8, 14, 20, 26, 32, 38, and 44**[b]
~~**OPC-34712**~~ **Brexpiprazole** (mg/day)[c]	0.5	1	0.5, 1 or 2	0.5, 1, 2 or 3	0.5, 1, 2, or 3
ADT[d]	Final dose from double-blind trial	No change[e]	No change[e]	No change[e]	Change to ADT dose is permitted as described in Section 3.2.2.2.

[a] Subjects unable to tolerate **brexpiprazole** 1 mg/day ~~**OPC-34712**~~ may decrease to 0.5 mg/day at any time after the Week 1 visit.

[b] Step-wise increases in the dose of ~~**OPC-34712**~~ **brexpiprazole** must be separated by at least ~~**one week**~~ **5 days**. Although step-wise decreases in the ~~**OPC-34712**~~ **brexpiprazole** dose are permitted at any time after the Week 1 visit to a minimum of 0.5 mg/day, an interval of at least ~~**one week**~~ **5 days** between dose adjustments is recommended. See Section 3.2.2.1 for additional information on dose adjustments. Subjects must return to the clinic for unscheduled visits if changes to the dose of ~~**OPC-34712**~~ **brexpiprazole** (increases or decreases) are required between scheduled visits.

[c]Subjects unable to tolerate the minimum dose of ~~**OPC-34712**~~ **brexpiprazole** (ie, 0.5 mg/day) must be withdrawn from the trial.

[d]Throughout Trial 331-10-238, the subject must remain on the same ADT that was assigned in the double-blind phase 3 trial (ie, Trial 331-10-227 or Trial 331-10-228).

[e]It is recommended that the dose of ADT not be changed while the dose of ~~**OPC-34712**~~ **brexpiprazole** is being optimized.

Section 3.2.1.2, ADT, Sentence 7:

All doses of ADT will be administered orally once daily except for duloxetine 40 mg/day that ~~**is**~~ **can be** administered ***once daily or*** as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily.

Table 3.2.1.2-1, Footnote a:

[a]All doses are to be administered orally once daily except for duloxetine 40 mg/day that ~~**is**~~ **can be** administered ***once daily or*** as duloxetine 20 mg twice daily, duloxetine 60 mg/day that can be administered once daily or as duloxetine 30 mg twice daily, and fluoxetine 40 mg/day that can be administered once daily or in divided doses twice daily. All doses should be taken at approximately the same time each day, if possible.

Section 3.2.2, Dose Adjustments

Dose modifications to both ~~**OPC-34712**~~ **brexpiprazole** and ADT will be permitted to optimize therapeutic benefit according to the rules described below for each treatment. However, the dose of ~~**OPC-34712**~~ **brexpiprazole** and the dose of ADT should not both be changed at the same visit.

Section 3.2.2.1, ~~**OPC-34712**~~ **Brexpiprazole**

Allowable dose modifications to the daily dose of ~~**OPC-34712**~~ **brexpiprazole** are summarized in Table 3.2.2.1-1. At least ~~**one week**~~ **5 days** must elapse between dose increases for ~~**OPC-34712**~~ **brexpiprazole**. An interval of at least ~~**one week**~~ **5 days** between dose adjustments is recommended for dose decreases; however, the dose of ~~**OPC-34712**~~ **brexpiprazole** can be decreased at the investigator's discretion in a step-wise manner at any time after the Week 1 visit as needed for tolerability to a minimum of 0.5 mg/day. Subjects must return to the clinic for unscheduled visits if changes to the dose of ~~**OPC-34712**~~ **brexpiprazole** (increases or decreases) are required between scheduled visits.

Subjects who are unable to tolerate the 0.5-mg/day dose of ~~**OPC-34712**~~ **brexpiprazole** must be withdrawn from the trial. However, subjects whose ~~**OPC-34712**~~ **brexpiprazole**

dose is decreased to 0.5 mg/day and who demonstrate adequate tolerability at this dose should be rechallenged with a 1-mg/day dose within approximately 6 to 8 weeks after ~~**starting**~~ the **dose is decreased to** 0.5 mg/day ~~**dose**~~. If tolerability issues arise following the rechallenge, the dose may be decreased again to 0.5 mg/day. Further rechallenge at 1 mg/day may be performed at the investigator's discretion. The dose of ~~**OPC-34712**~~ **brexpiprazole** can be re-escalated as necessary following a dose decrease at any other dose if, in the investigator's judgment, rechallenge with a higher dose is warranted in order to identify an optimum dose for the subject. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

Table 3.2.2.1-1 Dose Modifications for ~~OPC-34712~~ Brexpiprazole

Dose Increases[a,b]		
Current Dose of ~~**OPC-34712**~~ **Brexpiprazole**	Incremental Increase	Adjusted ~~**OPC-34712**~~ **Brexpiprazole** dose
0.5 mg	0.5 mg	1 mg
1 mg	1 mg	2 mg
2 mg	1 mg	3 mg
Dose Decreases[b,c]		
Current Dose of ~~**OPC-34712**~~ **Brexpiprazole**	Incremental Decrease	Adjusted ~~**OPC-34712**~~ **Brexpiprazole** dose
0.5 mg	Not permitted[d]	0.5 mg[d]
1 mg	0.5 mg	0.5 mg
2 mg	1 mg	1 mg
3 mg	1 mg	2 mg

[a] At least ~~**one week**~~ **5 days** must elapse between dose increases.

[b] Subjects must return to the clinic for unscheduled visits if changes to the dose of ~~**OPC-34712**~~ **brexpiprazole** (increases or decreases) are required between scheduled visits.

[c] An interval of at least ~~**one week**~~ **5 days** between dose adjustments is recommended for dose decreases; however, the investigator may decrease the dose of ~~**OPC-34712**~~ **brexpiprazole** at any time after the Week 1 visit for tolerability.

[d] Subjects unable to tolerate 0.5 mg/day of ~~**OPC-34712**~~ **brexpiprazole** must be withdrawn from the trial.

Section 3.2.2.2, ADT:

It is recommended that the dose of ADT not be changed while the dose of ~~**OPC-34712**~~ **brexpiprazole** is being optimized (ie, no change to ADT up to and including the Week 4 visit). *After the Week 4 visit*, the dose of ADT can be modified if necessary to achieve optimum efficacy and tolerability for the treatment regimen using the following rules: 1) at least ~~**one week**~~ **5 days** must elapse between dose increases (either ~~**OPC-34712**~~

brexpiprazole or ADT), 2) an interval of at least ~~**one week**~~ **5 days** between dose adjustments (either ~~**OPC-34712**~~ **brexpiprazole** or ADT) is recommended for dose decreases; however, the ADT dose can be decreased at the investigator's discretion at any time as needed for tolerability, and 3) subjects must return to the clinic for unscheduled visits if changes to the ADT dose are required between scheduled visits.

Section 3.3, Trial Population, Paragraph 1, Sentence 1:

The trial population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with ~~**OPC-34712**~~ **brexpiprazole** for MDD ~~and who meet one of the following conditions~~:

Table 3.4.2-1, Criterion 3:

3.	Subjects who, in the opinion of the investigator, could potentially benefit from administration of ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy to their antidepressant therapy and who meet one of the following criteria: a) Subjects who completed participation in the Double-blind Randomization Phase (ie, Week 14 visit of Phase B) in Trial 331-10-227 or Trial 331-10-228 or b) Subjects who met criteria for a response at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227 or Trial 331-10-228, **BUT DID NOT** meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227 or Trial 331-10-228.

Table 3.4.3-1, Criterion 2 and Footnote a:

2.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving open-label ~~**OPC-34712**~~ **brexpiprazole** in Trial 331-10-238.

[a]Use of CYP2D6 inhibitors or CYP3A4 inhibitors and inducers is prohibited during the trial. Fluoxetine, paroxetine, and duloxetine are protocol-defined ADTs that are also CYP2D6 inhibitors. In order to limit the potential higher exposure of ~~**OPC-34712**~~ **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.

Section 3.5.1, Primary Outcome Variable:

The primary outcome variable is the safety and tolerability of ~~**OPC-34712**~~ **brexpiprazole** which will be assessed by examining the frequency and severity of adverse events (AEs).

Table 3.6-1, Footnotes o, s and u:

[o]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ at Screening/Baseline must not be enrolled in Trial 331-10-238~~.~~ and ~~**S**~~**s**ubjects with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ 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.

[s] Adjustments to the dose of ~~**OPC-34712**~~ **brexpiprazole** or ADT are permitted to optimize efficacy and tolerability as described in Section 3.2. It is recommended that the dose of ADT not be changed while the dose of ~~**OPC-34712**~~ **brexpiprazole** is being optimized (ie, no change to ADT up to and including the Week 4 visit). At least ~~**one week**~~ **5 days** must elapse between dose increases for ~~**OPC-34712**~~ **brexpiprazole** and ADT. An interval of at least ~~**one week**~~ **5 days** between dose adjustments is also recommended for dose decreases; however, the investigator may decrease the dose of ~~**OPC-34712**~~ **brexpiprazole** or ADT as needed for tolerability according to the rules described in Section 3.2.2. Subjects must return to the clinic for unscheduled visits if changes to the dose of ~~**OPC-34712**~~ **brexpiprazole** or ADT (increases or decreases) are required between scheduled visits.

[u] The IVRS/IWRS will be accessed at unscheduled visits if new blister cards are dispensed for dose adjustment of ~~**OPC-34712**~~ **brexpiprazole**.

Section 3.6.1.1, Screening/Baseline, Bullet 7:

- Trial personnel will call the interactive voice response system (IVRS) or access the interactive web response system (IWRS) to register the visit and to obtain blister card and ADT bottle number assignments. The assigned open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT will be dispensed. Treatment will begin with **brexpiprazole** 0.5 mg/day ~~**OPC-34712**~~ for 1 week. The ADT will be the same as the one taken during the double-blind phase 3 trial (ie, Trial 331-10-227 of Trial 331-10-228). The dose of ADT should not be changed at this time.

Section 3.6.1.2, Week 1, Bullets 10, 11, and 12:

- Women of childbearing potential (WOCBP) will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ must discontinue the IMP and be withdrawn from the trial.
- Drug accountability will be performed for ~~**OPC-34712**~~ **brexpiprazole** and ADT.
- The dose of ~~**OPC-34712**~~ **brexpiprazole** will be increased to 1 mg/day. Subjects unable to tolerate **brexpiprazole** 1 mg/day ~~**OPC-34712**~~ may decrease to 0.5 mg/day at any time after the Week 1 visit. It is recommended that the dose of ADT not be changed while the dose of ~~**OPC-34712**~~ **brexpiprazole** is being optimized. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for ~~**OPC-34712**~~ **brexpiprazole** and ADT, and to obtain blister card and bottle number assignments. The assigned open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT will be dispensed to the subject.
-

Section 3.6.1.3, Week 2, Bullets 6, 7 and 8:

- WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ must discontinue the IMP and be withdrawn from the trial.
- Drug accountability will be performed for ~~**OPC-34712**~~ **brexpiprazole** and ADT.

- The investigator will adjust the dose of ~~**OPC-34712**~~ **brexpiprazole** as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. It is recommended that the dose of ADT not be changed while the dose of ~~**OPC-34712**~~ **brexpiprazole** is being optimized. Any subject unable to tolerate the minimum dose of ~~**OPC-34712**~~ **brexpiprazole** (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for ~~**OPC-34712**~~ **brexpiprazole** and ADT, and to obtain blister card and bottle number assignments. The assigned open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT will be dispensed to the subject.
-

Section 3.6.1.4, Week 4, Bullets 9, 10 and 11:

- WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ must discontinue the IMP and be withdrawn from the trial.
- Drug accountability will be performed for ~~**OPC-34712**~~ **brexpiprazole** and ADT.
- The investigator will adjust the dose of ~~**OPC-34712**~~ **brexpiprazole** as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. If necessary, the dose of ADT can be changed after the Week 4 visit, but not at the same visit as a change to the dose of ~~**OPC-34712**~~ **brexpiprazole** (see Section 3.2.2.2). Any subject unable to tolerate the minimum dose of ~~**OPC-34712**~~ **brexpiprazole** (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for ~~**OPC-34712**~~ **brexpiprazole** and ADT, and to obtain blister card and bottle number assignments. The assigned open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT will be dispensed to the subject.
-

Section 3.6.1.5, Week 8, Bullets 11, 12 and 13:

- WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ must discontinue the IMP and be withdrawn from the trial.
- Drug accountability will be performed for ~~**OPC-34712**~~ **brexpiprazole** and ADT.
- The investigator will adjust the dose of ~~**OPC-34712**~~ **brexpiprazole** as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for ~~**OPC-34712**~~ **brexpiprazole** and ADT, and to obtain blister card and bottle number assignments. The assigned open-label ~~**OPC-34712**~~ **brexpiprazole** and ADT will be dispensed to the subject.
-

Section 3.6.1.6, Long-term Treatment Visits (Weeks 14, 20, 26, 32, 38, and 44), Bullets 7, 8 and 9 after Paragraph 1:

- WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ must discontinue the IMP and be withdrawn from the trial.
- Drug accountability will be performed for ~~**OPC-34712**~~ **brexpiprazole** and ADT.
- The investigator will adjust the dose of ~~**OPC-34712**~~ **brexpiprazole** as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for ~~**OPC-34712**~~ **brexpiprazole** and ADT, and to obtain blister card and bottle number assignments. The assigned open-label ~~**OPC34712**~~ **brexpiprazole** and ADT will be dispensed to the subject.
-

Table 3.6.2.1-1, Footnote a:

[a] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ at Screening/Baseline must not be enrolled in Trial 331-10-238~~**.**~~ **and** ~~**S**~~**s**ubjects with **a** positive ~~**urine and**~~ serum pregnancy test result~~**s**~~ during the trial must discontinue treatment and be withdrawn from the trial.

Section 3.6.2.4, Other Safety Assessments, Sentence 5:

Training and materials for rating will be provided by ~~**United BioSource Corporation**~~ **Bracket**.

Section 3.6.3, Efficacy Assessments, Sentence 5:

Training, certification, and materials for rating will be provided by ~~**United BioSource Corporation**~~ **Bracket**.

Section 3.7.3, Individual Subject, Item f:

f) subject cannot tolerate the minimum dose of ~~**OPC-34712**~~ **brexpiprazole** (ie, 0.5 mg/day), the minimum protocol-defined therapeutic dose of ADT (see Table 3.2.1.2-1), or requires a different ADT; or

Section 3.8, Screen Failures, Sentence 2:

For the purposes of Trial 331-10-238, treatment begins with the first dose of open-label ~~**OPC-34712**~~ **brexpiprazole** in the Treatment Phase.

Section 3.11, Subject Compliance, Sentence 1:

Responsible trial personnel will dispense the IMP (ie, ~~**OPC-34712**~~ **brexpiprazole** and ADTs).

Table 4.1-1, Footnote c:

[c] Fluoxetine, paroxetine, and duloxetine are protocol-defined ADTs that are also CYP2D6 inhibitors. In order to limit the potential higher exposure of ~~**OPC-34712**~~ **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 (see Section 4.2.1).

Section 4.2.1, Restricted Therapies and Precautions, Bullet 2 after Paragraph 1:

- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan)***, linezolid, and methylene blue*** since there have been rare post-marketing reports of serotonin syndrome or serotonin syndrome-like reactions (eg, **mental status changes,** ~~**weakness,**~~ hyperreflexia***, autonomic effects,*** ~~**and**~~ lack of coordination***, and diarrhea***) following the concomitant use of SSRIs ***or SNRIs*** and ~~**triptans**~~ **these drugs**.[33,*34,35*]

Section 4.2.1, Restricted Therapies and Precautions, Paragraphs 7 and 8:

Fluoxetine, paroxetine, and duloxetine are protocol-defined ADTs in this trial; however, they are also CYP2D6 inhibitors. Data from Trial 331-08-207 and Trial 331-08-208 indicate that coadministration of CYP2D6 inhibitors with ~~**OPC-34712**~~ **brexpiprazole** can cause potentially higher plasma concentrations of ~~**OPC-34712**~~ **brexpiprazole** (up to 2-fold). In order to limit the potential higher exposure of ~~**OPC-34712**~~ **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. The investigator should consider the potential for higher ~~**OPC-34712**~~ **brexpiprazole** plasma concentrations when adjusting the dose of ~~**OPC-34712**~~ **brexpiprazole** for subjects who are receiving fluoxetine, paroxetine CR, or duloxetine as the assigned ADT.

All trial personnel should be familiar with the content of the Investigator Brochure for ~~**OPC-34712**~~ **brexpiprazole** in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

Section 5.1, Definitions, Last sentence:

Investigators will assess IMP causality based on ~~**OPC-34712**~~ **brexpiprazole**.

Section 5.5, Pregnancy, Paragraph 1, Sentence 2:

Unless the subject ~~**and his/her partner(s) are**~~ **is** sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain**s** abstinent, two 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 or sponge with spermicide.

Section 7.1.1, Data Sets for Analysis, Safety Sample definition:

Safety Sample: comprises those subjects who receive at least one dose of open-label ~~**OPC-34712**~~ **brexpiprazole** as adjunctive therapy to one of the allowed ADTs.

Section 7.4, Safety Analyses, Last sentence:

In general, baseline measurements of safety variables are defined as their last measurements prior to the first dose of open-label ~~**OPC-34712**~~ **brexpiprazole**.

Section 8.1, Packaging and Labeling, Paragraph 1:

Trial drugs will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will consist of open-label ~~**OPC-34712**~~ **brexpiprazole** and open-label ADTs. Open-label ~~**OPC-34712**~~ **brexpiprazole** will be supplied as 0.5, 1, 2, and 3-mg tablets packaged in weekly blister cards, each containing sufficient tablets for 7 (+ 2 days). Blister cards will contain single tablet strengths (ie, **brexpiprazole** 0.5, 1, 2, or 3 mg/day ~~**OPC-34712**~~) and subjects will take 1 tablet daily. When accessed by the site, the IVRS or IWRS will assign a specific blister card number to be dispensed to a subject. New weekly blister cards will be dispensed at each scheduled visit and at unscheduled visits if the dose of ~~**OPC-34712**~~ **brexpiprazole** is changed.

Section 8.2, Storage, Paragraph 2, Sentence 1:

~~**OPC-34712**~~ **Brexpiprazole** should be stored according to the storage conditions indicated on the clinical label.

Section 8.3, Accountability:

The investigator, or designee, must maintain an inventory record of trial drugs (including ~~**OPC-34712**~~ **brexpiprazole** and ADTs) received, dispensed, administered, and returned.

Section 8.4, Returns and Destruction, Paragraph 1:

Upon completion or termination of the trial, all unused and/or partially used IMP (including ~~**OPC-34712**~~ **brexpiprazole** and ADTs) must be returned to Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) (or a designated contractor).

Section 14, References:

[33] US Food and Drug Administration [homepage on the Internet]. Rockville, MD: FDA Public Health Advisory 2006 19 Jul [~~**updated 2006 24 Nov;**~~ cited ~~**4 Nov 2008**~~ **24 Oct 2011**]. Available at [redacted]

[redacted]

34 ***US Food and Drug Administration [homepage on the Internet]. Rockville, MD: FDA Drug Safety Communication 2011 26 Jul [updated 2011 21 Oct; cited 24 Oct 2011]. Available at***
[redacted]

35 ***US Food and Drug Administration [homepage on the Internet]. Rockville, MD: FDA Drug Safety Communication 2011 26 Jul [updated 2011 21 Oct; cited 24 Oct 2011]. Available at***
[redacted]

Appendix 1, Names of Sponsor Personnel, Primary Medical Contact:

[redacted]
Phone
Fax [redacted]

Appendix 2, Institutions Concerned With the Trial

Rater Training
~~**United BioSource Corporation**~~
~~**Specialty Clinical Services**~~
Bracket
575 East Swedesford Road, Suite 200
Wayne, PA 19087
USA

Central IRB
Schulman Associates IRB
~~**4290 Glendale-Mulford Road**~~
4445 Lake Forest Drive
Suite 300
Cincinnati, OH 45242
USA

Add:

Appendix 16 Protocol Amendment(s)/Administrative Change(s)

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects as a result of this protocol amendment.

Amendment Number: 2

Issue Date: 16 November 2012

PURPOSE:

The sponsor has determined the need for a formal amendment to amendment 1 approved on 23 November 2011 to allow enrollment of eligible subjects who completed the last scheduled visit of a double-blind phase 3 brexpiprazole MDD trial, to remove the definitions of incomplete response and response, to match the specifications for potential Hy's Law cases, to clarify that the contraceptive methods of vasectomy and tubal ligation apply to the subject and partner, to update study duration and the estimated number of enrolled subjects, and to make administrative changes.

BACKGROUND:

1. Enrollment of subjects who completed the last scheduled visit of a double-blind phase 3 brexpiprazole MDD trial

1) Add subjects who completed the last scheduled visit of double-blind phase 3 brexpiprazole MDD trials as those eligible for enrollment into Trial 331-10-238
2) Add statement that all assessments listed under screening need to be performed at Screening/Baseline of Trial 331-10-238; and that if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238

2. Definitions of incomplete response and response

- 1) Remove the definitions for incomplete response and response for Trial 331-10-227 and Trial 331-10-228

3. Hy's Law specifications

- 1) Update the specifications for potential Hy's Law cases

4. Contraceptive methods of vasectomy and tubal ligation

1) Clarify that that the contraceptive methods of vasectomy and tubal ligation apply to the subject and partner

5. Study duration and number of enrolled subjects

1) Update the study duration to approximately 63 months, of which approximately 51 months are allotted for rollover of subjects from the prior double-blind phase 3 trials
2) Update number of estimated enrolled subjects to 3,000

6. Administrative changes and correction of typographical errors

1) Update primary and backup medical contact for OPDC personnel
- 2) Remove safety reporting information for Czech Republic and add safety reporting information for "All Other Countries"

MODIFICATIONS TO PROTOCOL:

- **Bold and underlined text:** Changed text
- ~~**Bold and strikethrough text:**~~ Deleted text
- ***Bold and italicized text:*** Added text

TITLE PAGE

Issue Date:	11 May 2011
Date of Amendment 1:	23 November 2011
Date of Amendment 2:	***16 November 2012***

Entire protocol, Footnote

~~**23 November 2011**~~

16 November 2012

SYNOPSIS, Trial Design, Paragraph 1, Sentence 3:

This is a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed ***the last scheduled visit*~~**one**~~ of ~~**the**~~***a*** double-blind, phase 3 ~~efficacy~~ ***brexpiprazole MDD*** trial~~**s (ie, Trial 331-10-227 or Trial 331-10-228)**~~ and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD.

SYNOPSIS, Trial Design, Paragraph 3, *Screening/Baseline*, Sentences 1 and 3:

Subjects will be screened for eligibility at the last ***scheduled*** visit ***of the prior double-blind phase 3 trial*** ~~**of Trial 331-10-227 or Trial 331-10-228 (ie, Week 14)**~~. Subjects will sign a separate informed consent form for participation in Trial 331-10-238 before any procedures specific to the open-label trial are performed. The assessments from the ***last scheduled visit of the prior double-blind phase 3 trial*** ~~**Week 14 visit of Trial 331-10-227 or Trial 331-10-228**~~ will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial.

SYNOPSIS, Trial Design, Paragraph 3, *Follow-up*:

Subjects will be followed ~~**up**~~ for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.

SYNOPSIS, Subject Population:

The subject population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD ***according to the following criteria*** ~~**and who meet one of the following conditions**~~:

- ***Subjects who participated in Trial 331-10-227 or Trial 331-10-228 only will be eligible for the 331-10-238 study if they meet one of the following conditions:***
  - Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of Phase B) in Trial 331-10-227 or Trial 331-10-228 or
  - Subjects who ~~**met criteria for a response**~~ ***continued into Phase A+ (were not randomized into Phase B)*** at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227 or Trial 331-10-228, **BUT DID NOT** meet criteria for remission (defined as a ***Montgomery Asberg Depression Rating Scale*** ~~**MADRS**~~ Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227 or Trial 331-10-228.
- ***Subjects who participated in another double-blind phase 3 brexpiprazole MDD trial will be eligible for the 331-10-238 study if they have completed the last scheduled visit of the prior double-blind phase 3 trial.***
- Subjects must qualify for Trial 331-10-238 at the last ***scheduled*** visit of the ***prior*** double-blind ***phase 3*** trial and must be able to continue therapy without interruption between the double-blind and open label trials. Based on the projected enrollment estimates for the ***prior*** double-blind phase 3 ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 and Trial 331-10-228)**~~, ***up to approximately*** ~~**up to 1280**~~***3,000*** subjects may enroll into Trial 331-10-238.

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, *Brexpiprazole*, bulleted list, Paragraph 1, Sentences 1 and 2:

- The first dose of open-label brexpiprazole will be taken one day after the last dose is taken for the ***prior*** double-blind, phase 3 ***brexpiprazole MDD*** ~~efficacy~~ trial so that adjunctive treatment will continue without interruption. It is anticipated that

the last dose of the double-blind, phase 3 ***brexpiprazole MDD***~~efficacy~~ trial will be taken the day of the ***last scheduled visit*****~~Week 14 visit of Trial 331-10-227 or Trial 331-10-228~~**, **~~(~~**ie, the day of the Screening/Baseline visit for the open-label trial**~~)~~**.

SYNOPSIS, Investigational Medicinal Product, Dose, Formulation, Mode of Administration, *ADT*, Paragraph 1, Sentences 1 and 2:

ADT: During the Treatment Phase of Trial 331-10-238, subjects will remain on the same assigned open-label ADT from the ***prior*** double-blind, phase 3 ***brexpiprazole MDD***~~efficacy~~ trial **~~(ie, Trial 331-10-227 or Trial 331-10-228)~~**. The initial dose of ADT will be the same as the ADT dose taken on the last ***scheduled*** visit of ***the prior double-blind phase 3 trial*****~~Trial 331-10-227 or Trial 331-10-228~~**.

SYNOPSIS, Trial Duration, Sentence 1:

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately **~~30~~*63*** months, of which approximately **~~17~~*51*** months are allotted for rollover of subjects from the ***prior*** double-blind phase 3 ***brexpiprazole MDD*** trials **~~(ie, Trial 331-10-227 or Trial 331-10-228)~~**.

List of Abbreviations and Definitions of Terms:

~~Incomplete response~~	**~~A term employed to assess prospective response to ADT during Phase A of the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228) as part of eligibility criteria for entrance into Phase B. Incomplete response is defined as < 50% reduction in depressive symptom severity between baseline and the Week 8 visit as measured by the 17-item Hamilton Depression Rating Scale (HAM-D17) Total Score; AND a HAM-D17 Total Score ≥ 14 at the Week 8 visit; AND a Clinical Global Impression – Improvement scale (CGI-I) score ≥ 3 at the Week 8 visit. Note: The visit of interest for this definition is the Week 8 visit of the double-blind phase 3 trial (ie, Trial 331-10-227 and Trial 331-10-228).~~**

~~**Response**~~	~~**A term employed to assess prospective response to ADT during Phase A of the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228) and representing the logical complement of "incomplete response." Response is defined as ≥ 50% reduction in depressive symptom severity between baseline and the Week 8 visit as measured by the HAM-D17 Total Score; OR a HAM-D17 Total Score of < 14 at the Week 8 visit; OR a CGI-I score of < 3 at the Week 8 visit. Note: The visit of interest for this definition is the Week 8 visit of the double-blind phase 3 trial (ie, Trial 331-10-227 and Trial 331-10-228).**~~

Section 2.1, Trial Rationale, Paragraph 2, Sentence 4:

The current trial (Trial 331-10-238) provides an open-label rollover option for ~~**the**~~ double-blind phase 3 ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 andTrial 331-10-228)**~~ and will expand on the knowledge gained in these trials by assessing the long-term safety, tolerability, and efficacy of brexpiprazole when administered concomitantly with antidepressant medications.

Section 3.1, Type/Design of Trial, Paragraph 1, Sentence 3:

This is a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent ADT. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed ~~**one**~~***the last scheduled visit*** of the double-blind, phase 3 ~~**efficacy**~~ ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~ and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD.

Section 3.1, Type/Design of Trial, Paragraph 3, *Screening/Baseline*, Sentences 1 and 3:

Subjects will be screened for eligibility at the last ***scheduled*** visit ***of the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228 (ie, Week 14)**~~. Subjects will sign a separate informed consent form for participation in Trial 331-10-238 before any procedures specific to the open-label trial are performed. The assessments from the ***last scheduled visit of the prior double-blind phase 3 trial*** ~~**(Week 14 visit of Trial 331-10-227 or Trial 331-10-228)**~~ will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial.

Section 3.1, Type/Design of Trial, Paragraph 3, *Follow-up*:

Subjects will be followed ~~**up**~~ for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.

Figure 3.1-1, Population and screening/baseline visit descriptions:

[a]Occurs simultaneously with **the** last scheduled visit of **a** double-blind phase 3 brexpiprazole MDD ~~T~~trial ~~331-10-227 or Trial 331-10-228~~.

Section 3.2.1.1, Brexpiprazole, Paragraph 1, Sentence 2:

The first dose of open-label brexpiprazole will be taken one day after the last dose is taken for the ***prior*** double-blind, phase 3 efficacy trial so that adjunctive treatment will continue without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the ***last scheduled visit*** ~~**Week 14 visit of Trial 331-10-227 or Trial 331-10-228, (**~~ie, the day of the Screening/Baseline visit for the open-label trial~~)~~.

Table 3.2.1.1-1, Footnote d:

[d]Throughout Trial 331-10-238, the subject must remain on the same ADT that was assigned in the ***prior*** double-blind phase 3 trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~.

Section 3.2.1.2, ADT, Sentences 1 and 3:

During the Treatment Phase of Trial 331-10-238, subjects will remain on the same assigned open-label ADT from the ***prior*** double-blind, phase 3 efficacy trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~. Numbered ADT bottles to be dispensed to the subject will be assigned by the IVRS or IWRS. The initial dose of ADT for the open-label trial will be the same as the ADT dose taken on the last ***scheduled*** visit of the prior double-blind ***phase 3*** trial.

Section 3.2.2.1, Brexpiprazole, Paragraph 2:

Subjects who are unable to tolerate the 0.5 -mg/day dose of brexpiprazole must be withdrawn from the trial. However, subjects whose brexpiprazole dose is decreased to 0.5 mg/day and who demonstrate adequate tolerability at this dose should be rechallenged with a 1 -mg/day dose within approximately 6 to 8 weeks after the dose is decreased to 0.5 mg/day. If tolerability issues arise following the rechallenge, the dose may be decreased again to 0.5 mg/day. Further rechallenge at 1 mg/day may be performed at the investigator's discretion. The dose of brexpiprazole can be ***increased***~~**re-escalated**~~ as necessary following a dose decrease at any other dose if, in the investigator's judgment, rechallenge with a higher dose is warranted in order to identify an optimum dose for the subject. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

Section 3.2.2.2, ADT, Paragraph 2:

The Sponsor reserves the right to use a generic equivalent should any marketed antidepressant become unavailable during the course of the trial.

Section 3.3, Trial Population, Paragraphs 1, 2, 4, 5, 6, and 7:

The ~~subject~~ trial population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD ***according to the following criteria***~~**and who meet one of the following conditions**~~:

- ***Subjects who participated in Trial 331-10-227 or Trial 331-10-228 will be eligible for the 331-10-238 study if they meet one of the following conditions:***
  - Subjects who completed participation in the ~~**D**~~***d***ouble-blind ~~**R**~~***r***andomization ~~**P**~~***p***hase (ie, Week 14 visit of Phase B) in Trial 331-10-227 or Trial 331-10-228 or
  - Subjects who ~~**met criteria for a response**~~ ***continued into Phase A+ (were not randomized into Phase B)*** at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227 or Trial 331-10-228, **BUT DID NOT** meet criteria for remission (defined as a ***Montgomery Asberg Depression Rating Scale*** ~~MADRS~~ Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227 or Trial 331-10-228.

- ***Subjects who participated in another double-blind phase 3 brexpiprazole MDD trial will be eligible for the 331-10-238 study if they have completed the last scheduled visit of the prior double-blind phase 3 trial.***
- Subjects must qualify for Trial 331-10-238 at the last ***scheduled*** visit of the ***prior*** double-blind ***phase 3*** trial and must be able to continue therapy without interruption between the double-blind and open label trials. Based on the projected enrollment estimates for the ***prior*** double-blind phase 3 ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 and Trial 331-10-228)**~~, ***up to approximately*** ~~**up to 1280**~~***3,000*** subjects may enroll into Trial 331-10-238.

Section 3.4.1, Informed Consent, Paragraph 2, Sentence 3:

The ICF for the open-label trial may be provided to potential candidates for review and discussion toward completion of the ***prior*** double-blind ***phase 3*** trial, but the form must not be signed until the day of the Screening/Baseline visit for Trial 331-10-238 (ie, the ***the last scheduled visit of the prior double-blind phase 3 trial*** ~~**Week 14 visit of Trial 331-10-227 or Trial 331-10-228**~~).

Table 3.4.2-1, Inclusion Criteria 3, 4, 5, and 6:

	All Subjects
3. ~~**4**~~.	Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent for Trial 331-10-238.
4. ~~**5**~~.	Subjects willing to discontinue all prohibited psychotropic medications starting from the time of signing the ICF and during the trial period (refer to Section 4).
	331-10-227 and 331-10-228 Subjects Only
5. ~~3~~.	Subjects who, in the opinion of the investigator, could potentially benefit from administration of brexpiprazole as adjunctive therapy to their antidepressant therapy and who meet one of the following criteria: a) Subjects who completed participation in the d~~D~~ouble-blind r~~R~~andomization p~~P~~hase (ie, Week 14 visit of Phase B) in Trial 331-10-227 or Trial 331-10-228 or b) Subjects who ~~**met criteria for a response**~~ ***continued into Phase A+ (were not randomized into Phase B)*** at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227 or Trial 331-10-228, **BUT DID NOT** meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331-10-227 or Trial 331-10-228.
	Eligible Subjects From Other Double-Blind Phase 3 Brexipiprazole MDD Trials
6. ~~**4.**~~	***Subjects who completed*** ~~***participation***~~***the last scheduled visit of the prior double-blind phase 3 trial and who in the opinion of the investigator, could potentially benefit from administration of brexpiprazole as adjunctive therapy to their antidepressant therapy.***

Section 3.4.3, Exclusion Criteria, Paragraph 1:

Subjects entering the open-label trial at the last ***scheduled*** visit ***of the prior double-blind phase 3 trial*** ~~**of Trial 331-10-227 or Trial 331-10-228 (ie, Week 14)**~~ will be excluded from Trial 331-10-238 if they meet any of the following exclusion criteria.

Table 3.4.3-1, Exclusion Criteria 1, 3, 6, 10, 11, 15, and 20:

Sex and Reproductive Status	
1.	Sexually active females of childbearing potential (see Section 5.5) and male subjects who are not practicing two different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who will not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use two of the following precautions: vasectomy, tubal ligation ***(subject or partner)***, vaginal diaphragm, IUD, birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide.
Administrative	
3.	Subjects with a major protocol violation during the course of their participation in the ***prior*** double-blind phase 3 trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~. Minor violations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-10-238; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the prior double-blind ***phase 3*** trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~ would be considered a major violation that would result in exclusion from Trial 331-10-238. **The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.**
Target Disease	
6.	Subjects with a current need for involuntary commitment or who have been hospitalized during ***the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228**~~ for the current major depressive episode.
10.	Subjects receiving new onset psychotherapy (individual, group, marriage, or family therapy) during ***the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228**~~.
Medical History and Concurrent Diseases	
11.	Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) at entry, **OR** Subjects with a response of "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) at entry, **OR** Subjects with a response of "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) at entry, **OR** Subjects who, in the opinion of the investigator (including consideration of responses on the C-SSRS throughout ***the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228**~~), present a serious risk of suicide. Note: "Entry" is defined as ***the last scheduled visit of the prior double-blind phase 3 trial*** ~~**Week 14 of Trial 331-10-227 or Trial 331-10-228**~~.
15.	Subjects with IDDM (ie, any subjects using insulin) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying **ALL** of the following criteria: • Screening/baseline HbA1c < 7.0%, **AND** • Screening/baseline fasting glucose must be ≤ 125 mg/dL, **AND** • Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) or diabetes has been well-controlled by diet during ***the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228**~~, **AND** • Subject has not had any hospitalizations ~~**during Trial 331-10-227 or Trial 331-10-228**~~ due to diabetes or complications related to diabetes ***during the prior double-blind phase 3 trial*** ~~**Trial 331-10-227, or Trial 331-10-228**~~, **AND** • Subject's diabetes is not newly diagnosed during screening/baseline for Trial 331-10-238.
Physical and Laboratory Results	
20.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75,000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) AST > 2 × ULN

	5) ALT > 2 × ULN 6) CPK > 3 × ULN, unless discussed with and approved by the medical monitor 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) QTcF ≥ 450 msec 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 are medically significant and that would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in Appendix 3, Appendix 4, and Appendix 5 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Eligibility should be based on the last available measurement during ***the prior double-blind phase 3 trial*** ~~**Trial 331-10-227 or Trial 331-10-228**~~. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
22.	Subjects with a history of neuroleptic malignant syndrome ~~(NMS)~~ or serotonin syndrome.

Section 3.4.3, Exclusion Criteria, Paragraph 2, Sentence 2:

Subjects who do not qualify for the open-label trial at the Screening/Baseline visit may not be rescreened at a later date. If results of clinical laboratory tests from the last ***scheduled*** visit of the prior double-blind ***phase 3*** trial ~~**(ie, Week 14 of Trial 331-10-227 or Trial 331-10-228)**~~ are not available to assess eligibility, the assessment for the affected criteria should be based on the last available measurement during the respective double-blind trial.

Section 3.6, Trial Procedures, Sentence 1:

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately ***63*** ~~**30**~~ months, of which approximately ***51*** ~~**17**~~ months are allotted for rollover of subjects from the ***prior*** double-blind phase 3 ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~.

Table 3.6-1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)											Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26	32	38	44	52/ET[b]	
ENTRANCE CRITERIA													
Informed consent[d]	X												
Inclusion/exclusion criteria	X												
Medical history	X[e]												
EFFICACY													
CGI-S	X[f]	X	X	X	X	X	X	X	X	X	X	X	
CGI-I[gf]		X	X	X	X	X	X	X	X	X	X	X	
SDS	X[f]				X			X				X	
IDS-SR	X[fq]				X	X	X	X		X		X	
SAFETY													
Physical examination	X[f]				X			X				X	
Waist circumference	X[f]				X	X	X	X	X	X	X	X	
Vital signs[hg]	X[f]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[ih]	X[f]	X		X	X	X		X		X		X	
Clinical laboratory tests[ji]	X[f,kj]	X[lk]		X[lk]	X[lk]	X[lk]		X[lk]		X[lk]		X[lk]	
ACTH, cortisol, and HbA1c	X[m]	X[lk]		X[lk]	X[lk]	X[lk]		X[lk]		X[lk]		X[lk]	
Drug screen/blood alcohol[nl]	X[f]	X		X	X	X		X		X		X	
Urine pregnancy test (WOCBP only)[om]	X[f]	X	X	X	X	X	X	X	X	X	X	X	
SAS	X[f]	X	X	X	X	X	X	X	X	X	X	X	
AIMS	X[f]	X	X	X	X	X	X	X	X	X	X	X	
BARS	X[f]	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[pn]	X[f]	X	X	X	X	X	X	X	X	X	X	X	
MSFQ	X[f]	X	X		X			X				X	

Table 3.6-1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)											Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26	32	38	44	52/ET[b]	
Adverse events	X~~[q]~~*[o]*	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications~~[r]~~*[p]*	X	X	X	X	X	X	X	X	X	X	X	X	X
OTHER													
Dose adjustments*[q]*		X	X	X	X	X	X	X	X	X	X		
RUF~~[t]~~*[r]*	X				X			X				X	
Register visit in IVRS/IWRS~~[u]~~*[s]*	X	X	X	X	X	X	X	X	X	X	X	X	
IMP dispensing	X	X	X	X	X	X	X	X	X	X	X		
IMP accountability		X	X	X	X	X	X	X	X	X	X	X	

IVRS = interactive voice response system; IWRS = interactive web response system; WOCBP = women of childbearing potential.

[a] Screening for Trial 331-10-238 occurs simultaneously with Baseline at the ***last scheduled visit of the prior double-blind trial*** ~~**Week 14 visit of Trial 331-10-227 or Trial 331-10-228**~~. ***All assessments listed under screening need to be performed at Screening/Baseline of Trial 331-10-238; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.***

[b] If a subject discontinues prematurely before Week 52, procedures noted for Week 52 must be completed at the early termination (ET) visit.

[c] Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety and applies to all subjects (completers and early withdrawals).

[d] Informed consent for Trial 331-10-238 will occur at Screening/Baseline and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e] Update, if necessary.

~~[f] **Screening/Baseline value will be obtained from the Week 14 visit of Trial 331-10-227 or Trial 331-10-228.**~~

~~[g]~~*[f]* Improvement should be based on the subject's status at the last ***scheduled*** visit of the ***prior*** double-blind phase 3 trial ~~**(ie, the Week 14 visit of Trial 331-10-227 or Trial 331-10-228)**~~.

~~[h]~~*[g]* Vital signs include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (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.

~~[i]~~*[h]* Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Subjects will be enrolled in Trial 331-10-238 based on the screening/baseline ECG results from the trial site. If the

screening/baseline ECG results from the central reader (ie, ~~**Week 14 visit of Trial 331-10-227 or Trial 331-10-228**~~***the last scheduled visit of the prior double-blind phase 3 trial***), when available, indicate a QTcF ≥ 450 msec at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

~~**j**~~***i*** Includes hematology (including PT, aPTT, and INR), serum chemistry (including prolactin and TSH, with reflex to free thyroxine [T_4] if the result for TSH is abnormal), and urinalysis.

k~~**k**~~***j*** Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline laboratory assessments (ie, ~~**Week 14 *visit* of Trial 331-10-227 and Trial 331-10-228**~~***the last scheduled visit of the prior double-blind phase 3 trial***).

~~**l**~~***k*** Clinical laboratory tests should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 52/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

~~**m**~~ ~~**A fasting blood sample for analysis of ACTH, cortisol, and HbA1c must be drawn at Screening/Baseline from subjects entering Trial 331-10-238 after completing Phase A+ of Trial 331-10-227 or Trial 331-10-228. This is not required for subjects entering Trial 331-10-238 from Phase B of Trial 331-10-227 or Trial 331-10-228 because the screening/baseline values will be obtained from the last visit of the double-blind protocols.**~~

~~**n**~~***l*** 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.

~~**o**~~***m*** All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at Screening/Baseline must not be enrolled in Trial 331-10-238 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.

~~**p**~~***n*** "Since Last Visit" C-SSRS form.

~~**q**~~~~**r**~~***o*** AE recording will begin with the signing of the ICF for Trial 331-10-238.

~~**r**~~***p*** 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.

q*~~**s**~~ Adjustments to the dose of brexpiprazole or ADT are permitted to optimize efficacy and tolerability as described in Section 3.2. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). At least 5 days must elapse between dose increases for brexpiprazole and ADT. An interval of at least 5 days between dose adjustments is also recommended for dose decreases; however, the investigator may decrease the dose of brexpiprazole or ADT as needed for tolerability according to the rules described in Section 3.2.2. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole or ADT (increases or decreases) are required between scheduled visits. ***All eligible subjects entering from prior double-blind phase 3 brexpiprazole MDD trials must be able to continue therapy without interruption between the double-blind and open label trials.

***r*~~**t**~~ Baseline RUF is completed at Screening/Baseline for all subjects. The Follow-up RUF is completed at all other visits.

***s*~~**u**~~ The IVRS/IWRS will be accessed at unscheduled visits if new blister cards are dispensed for dose adjustment of brexpiprazole.

Section 3.6.1.1, Screening/Baseline, Paragraph 1 and bulleted list:

Subjects entering Trial 331-10-238 must sign the ICF for the open-label trial before any procedures specific to Trial 331-10-238 can be performed. Subjects will retain the same subject identification (Subject ID) number assigned in the ***prior*** double-blind phase 3 trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228). Screening/baseline values will be derived from the last visit of the double-blind phase 3 trial (ie, Week 14 *visit* of Trial 331-10-227 or Trial 331-10-228) for the following assessments: CGI-S, SDS, IDS-SR, MSFQ, SAS, AIMS, BARS, C-SSRS, physical examination, waist circumference, vital signs, ECG, clinical laboratory tests (except for ACTH, cortisol, and HbA1c for some subjects), urine drug screen, blood alcohol, and urine pregnancy test**~~. The ~~**only additional***following*~~** procedures ***need*** to be performed at Screening/Baseline of ***Trial 331-10-238*~~**the open-label trial are as follows:**~~***; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.***

- Inclusion/exclusion criteria for Trial 331-10-238 will be reviewed to assure the subject's eligibility.
- Medical history will be updated, if necessary***, using information from the prior double-blind phase 3 trial.***
- ***Subjects will submit to a physical examination and assessments of waist circumference, vital signs, and ECG.***
- ***The investigator (or qualified designee) will administer any scale (ie, CGI-I and CGI-S).***
- ***Subjects will complete any Baseline instrument (ie, SDS, IDS-SR, and MSFQ).***
- ***An adequately trained and experienced clinician will administer any EPS scale (ie, SAS, AIMS, and BARS).***
- ***The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.***
- Concomitant medications will be reviewed to assure that the subject is not receiving any prohibited medications.
- Subjects will complete the Baseline RUF.
- For subjects entering Trial 331-10-238 after completing ***the last scheduled visit of the prior double-blind phase 3 trial***~~**Phase A+ of Trial 331-10-227 or Trial 331-10-228**~~, a fasting blood sample will be drawn for analysis of ***any clinical laboratory parameter (ie, the clinical laboratory parameters specified in Table 3.6.2.1-1) that was not analyzed at the last scheduled visit of the prior double-blind phase 3 trial***~~ACTH, cortisol, and HbA1c to obtain screening/baseline values for these parameters.~~ ~~**For all other, the screening/baseline values for these parameters will be obtained from the last visit of the double-blind trial.**~~

- AE recording will begin with the signing of the ICF for Trial 331-10-238.
- Trial personnel will call the interactive voice response system (IVRS) or access the interactive web response system (IWRS) to register the visit and to obtain blister card and ADT bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed. Treatment will begin with brexpiprazole 0.5 mg/day for 1 week. The ADT will be the same as the one taken during the ***prior*** double-blind phase 3 trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~. The dose of ADT should not be changed at this time.

Section 3.6.2.1, Clinical Laboratory Tests, Paragraph 1, Sentences 1 and 3:

As it is unlikely that the final laboratory test results from ***the last scheduled visit of the prior*** double-blind phase 3 trial ~~**(ie, Week 14 of Trial 331-10-227 and Trial 331-10-228)**~~ will be available at the time of enrollment in Trial 331-10-238, the investigator is to review the subject's most recent laboratory test results from the ***prior*** double-blind ***phase 3*** trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~ for compliance with the exclusion criteria and the presence of abnormal laboratory test results that, in the investigator's judgment, are medically significant and would impact the safety of the subject or the interpretation of the trial results. Subjects meeting any of these criteria will be excluded from Trial 331-10-238. Appendix 4 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. If one or more results from the screening/baseline sample are clinically significant and/or exclusionary when the results from the last ***scheduled*** visit of the ***prior*** double-blind ***phase 3*** trial become available, the test(s) should be repeated.

Section 3.6.2.2.1, Physical Examination, Paragraph 1, Sentences 1 and 3:

The complete physical examination at the last ***scheduled*** visit of the ***prior*** double-blind phase 3 trial ~~**(ie, Week 14 visit of Trial 331-10-227 or Trial 331-10-228)**~~ will serve as the screening/baseline physical examination for the current protocol. A complete physical examination will consist of a review of the following body systems: HEENT, thorax, abdomen, urogenital, extremities, neurological, and skin and mucosae. Repeat measurement of height is not required during Trial 331-10-238 if a ***S~~s~~***creening/***B~~b~~***aseline value is available from the last ***scheduled*** visit of the ***prior*** double-blind phase 3 trial.

Section 3.6.2.2.1, Physical Examination, Paragraph 5, Sentences 1, 3, and 4:

The principal investigator or his/her appointed designee is primarily responsible to perform the physical exam***ination***. If the appointed designee is to perform the physical exam***ination***, 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 exam***inations***. Any condition present at the post-treatment physical exam***ination*** that was not present at the screening/baseline exam***ination*** should be documented as an AE and followed to a satisfactory conclusion.

Section 3.6.2.4.4

Suicidality will be monitored during the trial using the C-SSRS. Subjects completed the "Baseline/Screening" C-SSRS form at the beginning of the ***prior*** double-blind phase 3 trial ~~**(ie, Trial 331-10-227 or Trial 331-10-228)**~~; therefore, only the "Since Last Visit" C-SSRS form will be used in Trial 331-10-238. A copy of the "Since Last Visit" C-SSRS form is provided in Appendix 13.

Section 3.6.3.2, Clinical Global Impression - Improvement Scale (CGI-I), Sentence 2

The efficacy of trial treatment will be rated for each subject using the CGI-I.26 The rater or investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared to the subject's condition at Screening/Baseline (ie, ~~**Week 14**~~ ***last scheduled*** visit of ***the prior double-blind phase 3 trial***~~**Trial 331-10-227 or Trial 331-10-228**~~). Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. A sample of the CGI-I is provided in Appendix 7.

Section 3.6.3.3.3, Resource Utilization Form (RUF), Sentences 2 and 3:

The RUF is a self-report tool designed to collect information regarding the extent of medical care sought by subjects while participating in the trial (Appendix 15). The number of hospitalizations and days of hospitalization within the past 12 months will be collected on the Baseline Form at Screening/Baseline, including any hospitalizations that may have occurred during the subject's participation in ***the prior double-blind phase 3 trial***~~**Trial 331-10-227 or Trial 331-10-228**~~. The number of visits to various practitioners for mental health and other reasons within the 3 months prior to Screening/Baseline (excluding any visits from ***the prior***

***double-blind phase 3 trial*~~Trial 331-10-227 or Trial 331-10-228~~) will be collected on the Baseline Form and the number of such visits occurring during the trial (excluding visits related to the trial) will be collected on the Follow-up Form at Weeks 8, 26, and 52/ET.

Section 3.8, Screen Failures, Sentence 3:

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment, whether through randomization or open assignment. For the purposes of Trial 331-10-238, treatment begins with the first dose of open-label brexpiprazole in the Treatment Phase. Subjects who do not qualify for Trial 331-10-238 at the last ***scheduled*** visit of the ***prior*** double-blind phase 3 trial ~~(ie, Week 14 of Trial 331-10-227 or Trial 331-10-228)~~ may not be rescreened.

Section 4.1, Prohibited Medications, Sentence 1:

Concomitant medications taken by subjects who are rolling over into Trial 331-10-238 from ~~one of the~~***a prior*** double-blind phase 3 trial~~s (ie, Trial 331-10-227 or Trial 331-10-228)~~ should be reviewed for the prohibited medications listed in Table 4.1-1.

Section 4.2.1, Restricted Therapies and Precautions, Paragraph 4, Sentence 1:

ECT was prohibited during the ***prior*** double-blind phase 3 trials ~~(ie, Trial 331-10-227 and Trial 331-10-228)~~ and is also prohibited for the duration of Trial 331-10-238.

Section 4.2.2.2, Restrictions, Paragraph 1:

Subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they initiated the therapy at least 42 days before enrollment in ~~one of~~ the ***prior*** double-blind phase 3 trials ~~(ie, Trial 331-10-227 or Trial 331-10-228)~~, participated in the therapy regularly during the ***prior*** double-blind phase 3 trial, and commit to maintain their participation during the course of Trial 331-10-238, or unless permission is obtained from the medical monitor.

Section 5.4, Potential Hy's Law Cases:

For a subject that experiences an elevation in AST or ALT that is ≥ 3 times the upper normal limit ~~**or whose levels increase ≥ 3 times their initial screening value**~~, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the upper normal limit ~~**or ≥ 2 times their screening value**~~, ***confirmatory repeat laboratory samples should be drawn within 48 to 72 hours of the initial draw. If these values are confirmed, trial personnel will*** complete an IRE form with all values listed and also report as an AE on the eCRFs. ***Please note: If the subject was enrolled into the trial with non-exclusionary elevated transaminase levels at baseline, please discuss any potential drug-induced liver injury events with the Medical Monitor.***

Section 5.5, Pregnancy:

WOCBP and men who are sexually active must use an effective method of birth control during the course of the trial and for at least 30 days after the last dose in a manner such that risk of failure is minimized. Unless the subject is sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remains abstinent, two of the following precautions must be used: vasectomy ***or*** ~~**,**~~ tubal ligation ***(subject and partner)***, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Section 7.2, Sample Size:

The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects from the ***prior*** double-blind phase 3 ***brexpiprazole MDD*** trials ~~**(ie, Trial 331-10-227 and Trial 331-10-228)**~~. Therefore, the number of eligible subjects will be limited by the number of subjects enrolled into these protocols. Based on the projected enrollment estimates for the ***prior*** double-blind phase 3 trials ~~**(ie, Trial 331-10-227 and Trial 331-10-228)**~~, ***up to approximately*** ~~**up to**~~ ***3,000*** **1280** subjects may enroll into Trial 331-10-238.

Section 8.1, Packaging and Labeling, Paragraph 3, Sentence 2:

ADTs 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.***

Appendix 1, Names of Sponsor Personnel:

Primary Medical Contact:

[redacted]

Phone [redacted]
Fax [redacted]

Backup Medical Contact:

[redacted]

Phone [redacted]
Fax [redacted]

~~**Backup Medical Contact:**~~

[redacted]

~~**Phone**~~ [redacted]

~~**Fax** [redacted]~~

Appendix 2, Institutions Concerned with the Trial, Safety Reporting:

Country	**Safety Fax Line**
United States	[redacted]
Canada	[redacted]
~~**Czech Republic**~~	[redacted]
France	[redacted]
Germany	[redacted]
Hungary	[redacted]
Poland	[redacted]
Romania	[redacted]
Russia	[redacted]
Slovakia	[redacted]
Ukraine	[redacted]
All other countries	[redacted]

Appendix 7, Clinical Global Impression - Improvement Scale (CGI-I), Sentence 2:

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at the last ***scheduled*** visit of ***the prior double-blind phase 3 trial***~~**Trial 331-10-227 or Trial 331-10-228**~~ (ie, prior to enrollment into Trial 331-10-238), how much has patient changed?

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects as a result of this protocol amendment.

Amendment Number: 3

Issue Date: 11 Apr 2014

PURPOSE:

The sponsor has determined the need for a third formal amendment to the original protocol. Due to a well-established safety profile in the completed double-blind and long-term Phase 2 and Phase 3 trials the study duration has been reduced from 52 weeks to 26 weeks and the number of assessments has been decreased. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency and correct typographical errors. The purpose of amending Protocol 331-10-238, issued on 16 Nov 2012 (amendment 2), was to:

- reduce the trial duration from 52 weeks to 26 weeks.
- reduce the number of visits to match the reduction in trial duration.
- minimize safety assessments performed at each visit.
- reduce the safety scale administration performed at each visit.
- reduce the efficacy scale administration performed at each visit.
- make administrative changes.

BACKGROUND:

Due to a well-established safety profile in the completed double-blind and long-term Phase 2 and Phase 3 trials the study duration has been reduced from 52 weeks to 26 weeks and the number of assessments has been decreased. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency and correct typographical errors.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Changes made to Protocol 331-10-238 in this third amendment are as outlined above.
- All the references to Week 52 were changed to Week 26. The word “study” was replaced by “trial” throughout the document.
- All visits and assessments from Week 26 to Week 52 were removed.
- Reference to Trial 331-13-214 was added wherever Trial 331-10-227 and Trial 331-10-228 were referred. .
- Sections 8.5 to 8.5.4 (Reporting of Product Quality Complaints) were added.

General Revisions:

Changes made to Protocol 331-10-238 in this third amendment are as outlined above. Changes by section are provided below.

Revisions by Protocol Section:

Location	Current Text	Revised Text
Title Page	[redacted] [redacted] Phone Fax E-mail [redacted] [redacted] [redacted]	[redacted] [redacted] Phone Fax E-mail: [redacted] [redacted]
Synopsis: Trial Design	This is a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). Visits will occur at the end of	This is a multicenter, 26-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be

	Weeks 1, 2, 4, 8, 14, 20, 26, 32, 38, 44, and 52. All subjects will receive up to 52 weeks of open-label treatment in Trial 331-10-238.	drawn from eligible subjects who have completed the last scheduled visit of a double-blind, phase 3 brexpiprazole MDD trial and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD. The original 52 week open-label trial design has been modified in this Amendment 3 to shorten the duration of the trial to 26 weeks; ongoing subjects who have not reached their Week 26 visit will be re-consented and will follow Amendment 3 schedule of assessments. Ongoing subjects who have already completed their Week 26 visit at the time of Amendment 3 will follow Amendment 3 week 26/ET schedule of assessments at their next scheduled visit Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20 and 26. All subjects will receive up to 26 weeks of open-label treatment in Trial 331-10-238.

Synopsis: Trial Duration	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 63 months, of which approximately 51 months are allotted for rollover of subjects from the prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 56 weeks (52 weeks of treatment and 30-day follow-up).	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 57 months, of which approximately 51 months are allotted for rollover of subjects from the prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 30 weeks (26 weeks of treatment and 30-day follow-up).
Section 3.1: Type/Design of Trial	Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20, 26, 32, 38, 44, and 52. All subjects will receive up to 52 weeks of open-label treatment in Trial 331-10-238 and follow the schedule of assessments described in Table 3.6-1. See Current Figure at the end of the table. Figure 3.1-1 Trial Design	Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20, and 26. All subjects will receive up to 26 weeks of open-label treatment in Trial 331-10-238 and follow the schedule of assessments described in Table 3.6-1. See Revised Figure at the end of the table. Figure 3.1-1 Trial Design Schematic

	Schematic	
	See current Table 3.2.1.1-1 Dosing Schedule for Brexpiprazole at the end of this table.	See revised Table 3.2.1.1-1 Dosing Schedule for Brexpiprazole at the end of this table.
	See curent Table 10.2-1 Schedule of Assessments at the end of this table	See revised Table 10.2-1 Schedule of Assessments at the end of this table.
Section 3.3: Trial Population	The trial population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD according to the following criteria: • Subjects who participated in Trial 331-10-227, Trial 331-10-228 or Trial 331 13 214 will be eligible for Trial 331-10-238 if they meet one of the following conditions: Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of phase B) in Trial 331-10-227, Trial 331-10-228 or	The trial population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD according to the following criteria: • Subjects who participated in Trial 331-10-227, Trial 331-10-228 or Trial 331 13 214 will be eligible for Trial 331-10-238 if they meet one of the following conditions: Subjects who completed participation in the double-blind randomization phase (ie, Week 14 visit of phase B) in Trial 331-10-227, Trial 331-10-228 or

	Trial 331 13 214 or Subjects who continued into Phase A+ (were not randomized into Phase B) at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214, BUT DID NOT meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331 10 227, Trial 331-10-228 or Trial 331-13-214. • Subjects who participated in a double-blind phase 3 brexpiprazole MDD trial will be eligible for the 331-10-238 trial if they have completed the last scheduled visit of the double-blind phase 3 trial. • Subjects must qualify for Trial 331-10-238 at the last scheduled visit of the prior double-blind phase 3 trial and must be able to continue therapy without interruption between the double-blind and open label	Trial 331 13 214 or Subjects who continued into Phase A+ (were not randomized into Phase B) at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227, Trial 331-10-228 or Trial 331-13-214, BUT DID NOT meet criteria for remission (defined as a MADRS Total Score of ≤ 10) at the Week 14 visit of Phase A+ in Trial 331 10 227, Trial 331-10-228 or Trial 331-13-214. • Subjects who participated in a double-blind phase 3 brexpiprazole MDD trial will be eligible for the 331-10-238 trial if they have completed the last scheduled visit of the double-blind phase 3 trial. • Subjects must qualify for Trial 331-10-238 at the last scheduled visit of the prior double-blind phase 3 trial and must be able to continue therapy without interruption between the double-blind and open label

	trials. Based on the projected enrollment estimates for the prior double-blind phase 3 brexpiprazole MDD trials, up to approximately 3,000 subjects may enroll into Trial 331-10-238.	trials. Based on the projected enrollment estimates for the prior double-blind phase 3 brexpiprazole MDD trials, up to approximately 3,000 subjects may enroll into Trial 331-10-238.
Section 3.4.2: Inclusion Criteria	Subjects willing to discontinue all prohibited psychotropic medications starting from the time of signing the ICF and during the trial period (refer to Section 4). 331-10-227 331-10-228 Subjects Only.	Subjects willing to discontinue all prohibited psychotropic medications starting from the time of signing the ICF and during the trial period (refer to Section 4). 331-10-227 331-10-228 and 331-13-214 Subjects Only.
Section 3.4.3: Exclusion Criteria.	5. 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 for management of treatment-resistant depression.	5. 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 management of treatment-resistant depression. Subjects who have had Transcranial Magnetic Stimulation during the current major depressive episode. 15. Continuation of subjects excluded based on abnormal test results from the

		screening/baseline visit should be discussed with the medical monitor, if in the investigator's judgement, the subject is a suitable candidate for the trial.
	20. Eligibility should be based on the last available measurement during the prior double-blind phase 3 trial. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.	20. Eligibility should be based on the Screening/baseline laboratory test and ECG results. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility. Continuation of subjects excluded based on abnormal test and ECG results should be discussed with the medical monitor, if in the investigator's judgement, the subject is a suitable candidate for the trial.
Section 3.5.2.2: Safety Variables	Mean change from baseline will be calculated for coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], and International Normalized Ratio [INR]), glycosylated hemoglobin	Mean change from baseline will be calculated for coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], and International Normalized Ratio [INR]), glycosylated hemoglobin

	(HbA1c), cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), waist circumference, and body mass index (BMI; derived programmatically from body weight and height measurements).	(HbA1c), thyroid-stimulating hormone (TSH), waist circumference, and body mass index (BMI; derived programmatically from body weight and height measurements).
Section 3.6: Trial Procedures	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 63 months, of which approximately 51 months are allotted for rollover of subjects from prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 56 weeks (52 weeks of treatment and 30-day follow-up).	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 57 months, of which approximately 51 months are allotted for rollover of subjects from prior double-blind phase 3 brexpiprazole MDD trials. Individual participation for subjects who complete the trial without early withdrawal will be approximately 30 weeks (26 weeks of treatment and 30-day follow-up).
Section 3.6.1: Screening/Baseline	• The investigator (or qualified designee) will administer any scale (ie,the CGI-I and CGI S).	• The investigator (or qualified designee) will administer the CGI-S and CGI .
Section 3.6.1.2: Week 1	• The investigator (or qualified designee) will administer the	• The investigator (or qualified designee) will administer the

	CGI-S and CGI-I. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • The subject will complete the MSFQ. • 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 is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry,	CGI-S. • An adequately trained and experienced clinician will administer the SAS AIMS,and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • 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. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. • Women of childbearing potential (WOCBP) will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test. WOCBP with a positive serum

	including prolactin, HbA1c, ACTH, cortisol, and TSH, with reflex to free thyroxine [T_4] if the result for TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. • Women of childbearing potential (WOCBP) will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The dose of brexpiprazole will be increased to 1 mg/day. Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit. It is recommended that the dose of ADT not be changed	pregnancy test result must discontinue the IMP and be withdrawn from the trial. • Drug accountability will be performed for brexpiprazole and ADT. • The dose of brexpiprazole will be increased to 1 mg/day. Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.

	while the dose of brexpiprazole is being optimized. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.	
Section 3.6.1.3: Week 2	• The investigator (or qualified designee) will administer the CGI-S and CGI-I. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • The subject will complete the MSFQ. • 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	• The investigator (or qualified designee) will administer the CGI-S. • An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • 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

	standing after the subject has been in each position at least 3 minutes. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized. Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain	minutes. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized. Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-labelbrexpiprazole and

	blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.	ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.
Section 3.6.1.4: Week 4	• The investigator (or qualified designee) will administer the CGI-S and CGI-I. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • 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 investigator (or qualified designee) will administer the CGI-S. • An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • 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. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urine screen(s) for drugs of

	The ECG is to be completed before any blood is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, ACTH, cortisol, and TSH, with reflex to free T4 if the result for TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary as described in	abuse. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary as described in Section 3.2 to achieve optimal efficacy and tolerability. If necessary, the dose of ADT can be changed after the Week 4 visit, but not at the same visit as a change to the dose of brexpiprazole (see Section 3.2.2.2). Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned

	Section 3.2 to achieve optimal efficacy and tolerability. If necessary, the dose of ADT can be changed after the Week 4 visit, but not at the same visit as a change to the dose of brexpiprazole (see Section 3.2.2.2). Any subject unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial. Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.	open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.
Section 3.6.1.5: Week 8	• The investigator (or qualified designee) will administer the CGI-S and CGI-I. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS	• The investigator (or qualified designee) will administer the CGI-S. • An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS. • Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be

	form. • The subject will complete the MSFQ, SDS, IDS-SR, and the Follow-up RUF. • 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 is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, ACTH, cortisol, and TSH, with reflex to free T4 if TSH	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. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urine screen(s) for drugs of abuse. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the

	is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle	IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.

	number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.	
Section 3.6.1.6:	**Section 3.6.1.6: Long-term Treatment Visits (Weeks 14, 20, 26, 32, 38, and 44)** All subjects will attend visits at Weeks 14, 20, 26, 32, 38, and 44 (± 2 days). The following evaluations will be performed at each visit, unless otherwise specified: • The investigator (or qualified designee) will administer the CGI-S and CGI-I. • Waist circumference will be measured. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The subject will complete the IDS-SR (except for Weeks 32 and 44). • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.	**Section 3.6.1.6 Week 14** All subjects will attend a visit at Week 14 (± 2 days) where the following evaluations will be performed: • The investigator (or qualified designee) will administer the CGI-S and CGI-I. • Waist circumference will be measured. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The subject will complete the IDS-SR and SDS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured

	• 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. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter	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 is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, and TSH, with reflex to free T4 if the result for TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. Additional blood alcohol testing may be performed at any other time at the discretion of the investigator. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. Additional urine drug screens may be performed at any

	dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded. • The following additional evaluations will be performed at Weeks 14, 26, and 38 only: • 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 is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, ACTH, cortisol, and TSH, with reflex to free T4 if the result for TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. Additional blood alcohol	other time at the discretion of the investigator. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded.

	testing may be performed at any other time at the discretion of the investigator. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. Additional urine drug screens may be performed at any other time at the discretion of the investigator. The following additional evaluations will be performed at Week 26 only: • A complete physical examination will be performed. • The subject will complete the MSFQ, SDS, and the Follow-up RUF.	
Section 3.6.1.7: Week 20	**Section 3.6.1.7: End of Treatment (Week 52/ET)**	**Section 3.6.1.7:** All subjects will attend a visit at Week 20 (± 2 days) where the following evaluations will be performed: • The investigator (or qualified designee) will administer the CGI-S.

		• An adequately trained and experienced clinician will administer the SAS and BARS to assess EPS. • 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. • WOCBP will be given a urine pregnancy test. 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. • Drug accountability will be performed for brexpiprazole and ADT. • The investigator will adjust the dose of brexpiprazole as necessary within the range of 0.5 to 3 mg daily as described in Section 3.2. If necessary, the dose of ADT can also be adjusted (see

		Section 3.2.2.2). Trial personnel will call the IVRS or access the IWRS to register the visit, to enter dose details for brexpiprazole and ADT, and to obtain blister card and bottle number assignments. The assigned open-label brexpiprazole and ADT will be dispensed to the subject. • AEs and concomitant medications will be recorded
Section 3.6.1.8: End of Treatment (Week 26/ET)	**NA**	• The Week 26 visit signifies the end of treatment. Therefore, all subjects will undergo a complete evaluation at Week 26 (±2 days). In addition, Week 26 evaluations are to be completed, if possible, for any subject withdrawn from the trial prematurely. Since the original 52 week open-label trial design has been modified as a part of Amendment 3 to shorten the duration of the trial to 26 weeks; ongoing subjects who have not reached their Week 26 visit will be re-consented and will follow Amendment 3 schedule of assessments. Ongoing subjects who have

		already completed their Week 26 visit at the time Amendment 3 is approved will follow Amendment 3 week 26/ET schedule of assessments at their next scheduled visit. The following activities and assessments will occur at Week 26 (or at the ET visit, if applicable):The investigator (or qualified designee) will administer the CGI-S and CGI-I. • An adequately trained and experienced clinician will administer the SAS, AIMS, and BARS to assess EPS. • The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form. • The subject will complete the MSFQ, SDS, IDS-SR, and the Follow-up RUF. • 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 is drawn. • A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin, HbA1c, ACTH,cortisol and TSH, with reflex to free T_4 if TSH is abnormal). Vital sign and ECG assessments should be completed before any blood samples are collected. • Samples will be obtained for blood alcohol testing. • Urine will be collected for urinalysis and urine screen(s) for drugs of abuse. • WOCBP will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test.

		• Final drug accountability will be performed. • Trial personnel will call the IVRS or access the IWRS to register completion or discontinuation from the trial. • AEs and concomitant medications will be recorded.
Section 3.6.2.1: Clinical Laboratory Tests	See the current table at the end of this table	See the revised table at the end of this table
Section 3.6.2.2.1: Physical Examination	Repeat measurement of height is not required during Trial 331-10-238 if a Screening/Baseline value is available from the last scheduled visit of the prior double blind phase 3 trial. Waist circumference will be measured at each physical examination (ie, Weeks 8, 26, and 52), and in addition, at Weeks 14, 20, 32, 38, and 44.	Repeat measurement of height is not required during Trial 331-10-238 if a Screening/Baseline value is available from the prior double blind phase 3 trial. Waist circumference will be measured at Screening/Baseline Week 14 and Week 26/ET.
Section 3.10: Definition of Lost to Follow-up	Subjects who cannot be contacted on or before the Week 52 visit during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as “lost to follow-up” as the	Subjects who cannot be contacted on or before the Week 26 visit during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as “lost to follow-up” as the

	reason for discontinuation.	reason for discontinuation. The site will make three 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.
Section 5.1: Definitions	Examples of AEs that are considered extrapyramidal symptoms include, but are not limited to: generalized rigidity, hyperkinesia, bradykinesia, akinesia, dystonia, hypertonia, akathisia, tremor, flexed posture, involuntary muscle contractions, athetosis, and chorea. • Potential Hy's Law cases (Any increase of AST or ALT ≥ 3 times the upper normal limit or screening value with an increase in total bilirubin ≥ 2 times the upper normal limit or screening value.)	Examples of AEs that are considered extrapyramidal symptoms include, but are not limited to: generalized rigidity, hyperkinesia, dyskinesia, bradykinesia, akinesia, dystonia, hypertonia, akathisia, tremor, flexed posture, involuntary muscle contractions, athetosis, and chorea. • Potential Hy's Law cases (Any increase of AST or ALT ≥ 3 times the upper normal limit with an increase in total bilirubin ≥ 2 times the upper normal limit.
Section 7.1.2:	In order to assess sensitivity of results due to missing data, two types of analyses will be performed for analyses by visit:	In order to assess sensitivity of results due to missing data, two types of analyses will be performed for analyses by visit:

	LOCF and OC. The LOCF and OC data sets are defined in Section 7.1.1. The OC data set will be used for analyses at each visit and the LOCF data set will be used for the last visit analyses (ie, Week 26, LOCF).	LOCF and OC. The LOCF and OC data sets are defined in Section 7.1.1. The OC data set will be used for analyses at each visit and the LOCF data set will be used for the last visit analyses
Section 7.1.4: Secondary outcome analysis	Secondary efficacy endpoints are as follows: 1) Change from baseline in CGI-S score, by trial week and at the last visit (ie, Week 26/ ET); 2) Mean CGI-I score, by trial week and at the last visit (ie, Week 26/ET); 3) Change from baseline in SDS score, by trial week and at the last visit (ie, Week 26/ET); 4) Change from baseline in IDS-SR Total Score, by trial week and at the last visit (ie, Week 26/ET). Descriptive statistics will be provided for each endpoint. The analysis will be carried out on the Efficacy Sample. Descriptive statistics will be summarized at	Secondary efficacy endpoints are as follows: 1) Change from baseline in CGI-S score, by trial week and at the last visit. 2) Mean CGI-I score, by trial week and at the last visit. 3) Change from baseline in SDS score, by trial week and at the last visit. 4) Change from baseline in IDS-SR Total Score, by trial week and at the last visit Descriptive statistics will be provided for each endpoint. The analysis will be carried out on the Efficacy Sample. Descriptive statistics will be summarized at each trial visit using the OC data set and at the last visit.

	each trial visit using the OC data set and at the last visit using the LOCF data set.	
Section 7..4.5: Other Safety Data	Descriptive statistics will be summarized at each visit using the OC data set and at the last visit (Week 26/ET) using the LOCF data set. Suicidality monitored during the trial using the C-SSRS	Descriptive statistics will be summarized at each visit using the OC data set and at the last visit using the LOCF data set. Suicidality monitored during the trial using the C-SSRS
Section 8.1: Packaging and Labeling	Each blister card used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, Subject ID (to be filled in by the site staff/investigator), subject's initials, name of the investigator (to be filled in by the site staff/investigator), site number (to be filled in by the site staff/investigator), subject's initials (to be filled in by the site staff/investigator), date dispensed (to be filled in by the site staff/investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary	Each blister card used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, Subject ID (to be filled in by the site staff/investigator), subject's initials or other unique identifier, name of the investigator (to be filled in by the site staff/investigator), site number (to be filled in by the site staff/investigator), subject's initials (to be filled in by the site staff/investigator), date dispensed (to be filled in by the site staff/investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and

	statements. Subjects must remain on the same ADT for the duration of the trial (ie, Screening/Baseline through Week 52/ET).	appropriate precautionary statements. Subjects must remain on the same ADT for the duration of the trial (ie, Screening/Baseline through Week 26/ET).
Section 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
Section 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 sponsor through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) must be notified within 24 hours of becoming aware of the PQC by e-mail or telephone and 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.
Section 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
Section 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 OAPI-EQC. It should be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to OAPI-EQC for complaint investigation.
Section 8.5.4: Assessment/Evaluation		Assessment and evaluation of Product Quality complaints will be handled by OAPI EQC QM group.
Section 9.4: Records Retention at the Trial Site	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 3 years following the date on which a New Drug Application is approved by the FDA. • A period of 3 years after the sponsor notifies the investigator that no further application is to be filed with the FDA.	Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following three periods • A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR • A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with

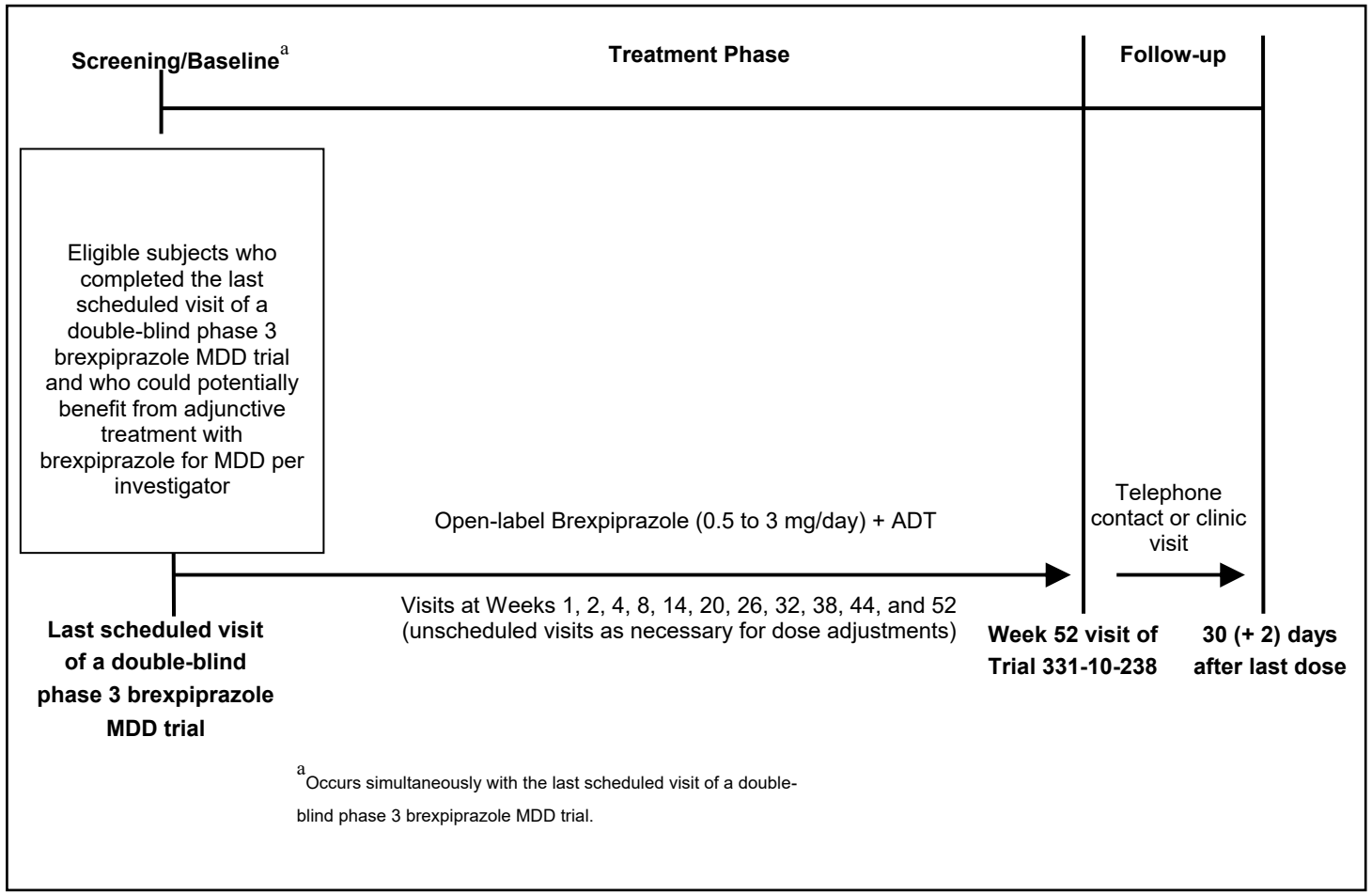
	The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor or designated agent to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial, including the eCRF data on the CD-ROM and any data clarification forms received from the sponsor (or sponsor's designee). Such documentation is subject to inspection by the sponsor, sponsor's designee, and relevant regulatory agencies. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial related records should be transferred to a	regulatory authorities. • Longer, region-specific storage requirements, if applicable. 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 the sponsor or designated agent 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 the eCRF data on the CD ROM and any data clarification forms received from the sponsor (or sponsor's designee). Such documentation is subject to inspection by the sponsor, sponsor's designee, and relevant regulatory agencies. 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

	mutually agreed upon designee. Notice of such transfer will be given to the sponsor (or designee) in writing.	within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor (or designee) in writing.
Section 12: Confidentiality	Subjects will be identified only by initials and unique subject numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.	Subjects will be identified only by initials and unique subject numbers in eCRFs. Per country regulations, if subject initials cannot be collected, another unique identifier will be used. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.
Appendix 1	**Current Contacts** ~~**Primary Medical Contact:**~~ [redacted] ~~**Phone**~~ ~~**Fax**~~ [redacted] ***Primary Medical Contact:*** [redacted]	**Revised Contacts** [redacted] Phone [redacted] Mobile [redacted] Backup Medical Contact: [redacted]

	[redacted] ***Phone*** [redacted] ***Mobile*** [redacted] ***Fax*** [redacted] [redacted]: [redacted] Phone [redacted]94 Fax [redacted] Primary Clinical Contact: [redacted] Phone [redacted] Fax [redacted]	[redacted] Phone [redacted] Fax [redacted] E-mail [redacted] [redacted] Phone [redacted] Fax [redacted] Primary Clinical Contact: [redacted] Phone: [redacted] Fax: [redacted] Mobile: [redacted] email: [redacted] Backup Clinical Contact: [redacted]

		[redacted] Phone Fax [redacted] Phone Fax

Current Figure 3.1-1



Revised Figure 3.1-1

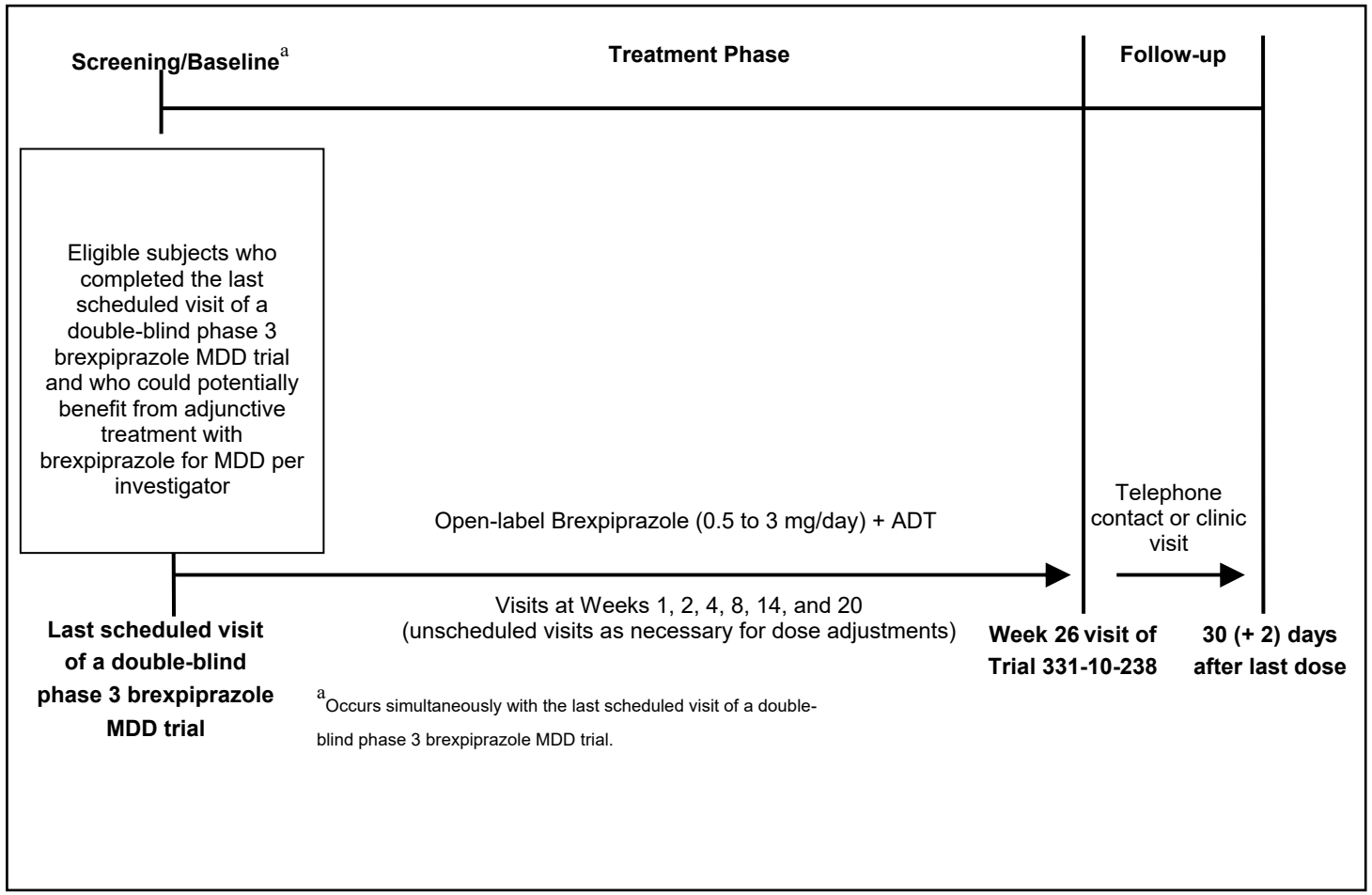


Table 4.2.2.2-2 Dosing Schedule for Brexpiprazole

IMP	Trial Visit				
	Screening/ Baseline	**Week 1**[a]	**Week 2**[b]	**Week 4**[b]	**Visits at Weeks 8, 14, 20, 26, 32, 38, and 44**[b]
Brexpiprazole (mg/day)[c]	0.5	1	0.5, 1 or 2	0.5, 1, 2 or 3	0.5, 1, 2, or 3
ADT[d]	Final dose from double-blind trial	No change[e]	No change[e]	No change[e]	Change to ADT dose is permitted as described in Section 3.2.2.2.

[a]Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit.

[b]Step-wise increases in the dose of brexpiprazole must be separated by at least 5 days. Although step-wise decreases in the brexpiprazole dose are permitted at any time after the Week 1 visit to a minimum of 0.5 mg/day, an interval of at least 5 days between dose adjustments is recommended. See Section 3.2.2.1 for additional information on dose adjustments. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

[c]Subjects unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial.

[d]Throughout Trial 331-10-238, the subject must remain on the same ADT that was assigned in the prior double-blind phase 3 trial.

[e]It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized.

Revised Table 4.2.2.2-3 Dosing Schedule for Brexpiprazole

IMP	Trial Visit				
	Screening/ Baseline	**Week 1**[a]	**Week 2**[b]	**Week 4**[b]	**Visits at Weeks 8, 14, and 20**[b]
Brexpiprazole (mg/day)[c]	0.5	1	0.5, 1 or 2	0.5, 1, 2 or 3	0.5, 1, 2, or 3
ADT[d]	Final dose from double-blind trial	No change[e]	No change[e]	No change[e]	Change to ADT dose is permitted as described in Section 3.2.2.2.

[a]Subjects unable to tolerate brexpiprazole 1 mg/day may decrease to 0.5 mg/day at any time after the Week 1 visit.

[b]Step-wise increases in the dose of brexpiprazole must be separated by at least 5 days. Although step-wise decreases in the brexpiprazole dose are permitted at any time after the Week 1 visit to a minimum of 0.5 mg/day, an interval of at least 5 days between dose adjustments is recommended. See Section 3.2.2.1 for additional information on dose adjustments. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole (increases or decreases) are required between scheduled visits.

[c]Subjects unable to tolerate the minimum dose of brexpiprazole (ie, 0.5 mg/day) must be withdrawn from the trial.

[d]Throughout Trial 331-10-238, the subject must remain on the same ADT that was assigned in the prior double-blind phase 3 trial.

[e]It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized.

Current Table 3.6.1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)											Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26	32	38	44	52/ET[b]	
ENTRANCE CRITERIA													
Informed consent[d]	X												
Inclusion/exclusion criteria	X												
Medical history	X[e]												
EFFICACY													
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-I[f]		X	X	X	X	X	X	X	X	X	X	X	
SDS	X				X			X				X	
IDS-SR	X				X	X	X	X		X		X	
SAFETY													
Physical examination	X				X			X				X	
Waist circumference	X				X	X	X	X	X	X	X	X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X	X		X	X	X		X		X		X	
Clinical laboratory tests[i]	X[j]	X[k]		X[k]	X[k]	X[k]		X[k]		X[k]		X[k]	
ACTH, cortisol, and HbA1c	X	X[k]		X[k]	X[k]	X[k]		X[k]		X[k]		X[k]	
Drug screen/blood alcohol[l]	X	X		X	X	X		X		X		X	
Urine pregnancy test (WOCBP only)[m]	X	X	X	X	X	X	X	X	X	X	X	X	
SAS	X	X	X	X	X	X	X	X	X	X	X	X	
AIMS	X	X	X	X	X	X	X	X	X	X	X	X	
BARS	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	X	X	
MSFQ	X	X	X		X			X				X	

Current Table 3.6.1 Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)											Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26	32	38	44	52/ET[b]	
Adverse events	X[o]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[p]	X	X	X	X	X	X	X	X	X	X	X	X	X
OTHER													
Dose adjustments[q]		X	X	X	X	X	X	X	X	X	X		
RUF[r]	X				X			X				X	
Register visit in IVRS/IWRS[s]	X	X	X	X	X	X	X	X	X	X	X	X	
IMP dispensing	X	X	X	X	X	X	X	X	X	X	X		
IMP accountability		X	X	X	X	X	X	X	X	X	X	X	

IVRS = interactive voice response system; IWRS = interactive web response system; WOCBP = women of childbearing potential.

[a] Screening for Trial 331-10-238 occurs simultaneously with Baseline at the last scheduled visit of the prior double-blind phase 3 trial. All assessments listed under screening need to be performed at Screening/Baseline of Trial 331-10-238; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.

[b] If a subject discontinues prematurely before Week 52, procedures noted for Week 52 must be completed at the early termination (ET) visit.

[c] Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety and applies to all subjects (completers and early withdrawals).

[d] Informed consent for Trial 331-10-238 will occur at Screening/Baseline and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e] Update, if necessary.

[f] Improvement should be based on the subject's status at the last scheduled visit of the prior double-blind phase 3 trial.

[g] Vital signs include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (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.

[h] Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Subjects will be enrolled in Trial 331-10-238 based on the screening/baseline ECG results from the trial site. If the screening/baseline ECG results from the central reader (ie, the last scheduled visit of the prior double-blind phase 3 trial), when available, indicate a QTcF

≥ 450 msec at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[i] Includes hematology (including PT, aPTT, and INR), serum chemistry (including prolactin and TSH, with reflex to free thyroxine [T_4] if the result for TSH is abnormal), and urinalysis.

[j] Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline laboratory assessments (ie, the last scheduled visit of the prior double-blind phase 3 trial).

[k] Clinical laboratory tests should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 52/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

[l] 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.

[m] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at Screening/Baseline must not be enrolled in Trial 331-10-238 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.

[n] "Since Last Visit" C-SSRS form.

[o] AE recording will begin with the signing of the ICF for Trial 331-10-238.

[p] 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.

[q] Adjustments to the dose of brexpiprazole or ADT are permitted to optimize efficacy and tolerability as described in Section 3.2. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). At least 5 days must elapse between dose increases for brexpiprazole and ADT. An interval of at least 5 days between dose adjustments is also recommended for dose decreases; however, the investigator may decrease the dose of brexpiprazole or ADT as needed for tolerability according to the rules described in Section 3.2.2. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole or ADT (increases or decreases) are required between scheduled visits. All eligible subjects entering from prior double-blind phase 3 brexpiprazole MDD trials must be able to continue therapy without interruption between the double-blind and open label trials.

[r] Baseline RUF is completed at Screening/Baseline for all subjects. The Follow-up RUF is completed at all other visits.

[s] The IVRS/IWRS will be accessed at unscheduled visits if new blister cards are dispensed for dose adjustment of brexpiprazole.

Revised Table 3.6-1Schedule of Assessments

Assessment	Screening/ Baseline[a]	Open-Label Treatment Phase Visit Week (± 2 days)							Follow-up[c] 30 (+2) days
		1	2	4	8	14	20	26/ET[b]	
ENTRANCE CRITERIA									
Informed consent[d]	X								
Inclusion/exclusion criteria	X								
Medical history	X[e]								
EFFICACY									
CGI-S	X	X	X	X	X	X	X	X	
CGI-I[f]	X					X		X	
SDS	X					X		X	
IDS-SR	X					X		X	
SAFETY									
Physical examination	X							X	
Waist circumference	X					X		X	
Vital signs[g]	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X					X		X	
Clinical laboratory tests[i]	X[j]					X[k]		X[k]	
HbA1c	X[j]					X[k]		X[k]	
Drug screen/blood alcohol[l]	X	X		X	X	X		X	
Urine pregnancy test (WOCBP only)[m]	X	X	X	X	X	X	X	X	
SAS	X	X	X	X	X	X	X	X	
AIMS	X					X		X	
BARS	X	X	X	X	X	X	X	X	
C-SSRS[n]	X	X	X	X		X		X	
MSFQ	X							X	
Adverse events	X[o]	X	X	X	X	X	X	X	X

Concomitant medications[p]	X	X	X	X	X	X	X	X	X
OTHER									
Dose adjustments[q]		X	X	X	X	X	X		
RUF[r]	X							X	
Register visit in IVRS/IWRS[s]	X	X	X	X	X	X	X	X	
IMP dispensing	X	X	X	X	X	X	X		
IMP accountability		X	X	X	X	X	X	X	

IVRS = interactive voice response system; IWRS = interactive web response system; WOCBP = women of childbearing potential.

[a]Screening for Trial 331-10-238 occurs simultaneously with Baseline at the last scheduled visit of the prior double-blind phase 3 trial. All assessments listed under screening need to be performed at Screening/Baseline of Trial 331-10-238; if any of these assessments were conducted at the last scheduled visit of the prior double-blind phase 3 trial, then Screening/Baseline values for those assessments will be derived from that visit and those assessments will not need to be repeated at Screening/Baseline of Trial 331-10-238.

[b]If a subject discontinues prematurely before Week 26, procedures noted for Week 26 must be completed at the early termination (ET) visit. Subjects who have completed 26 weeks or more, will have the Week 26/ET procedures at their next scheduled visit.

[c]Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety and applies to all subjects (completers and early withdrawals).

[d]Informed consent for Trial 331-10-238 will occur at Screening/Baseline and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e]Update, if necessary.

[f]Improvement should be based on the subject's status at the last scheduled visit of the prior double-blind phase 3 trial.

[g]Vital signs include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (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.

[h]Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Subjects will be enrolled in Trial 331-10-238 based on the screening/baseline ECG results from the trial site. If the screening/baseline ECG results from the central reader (ie, the last scheduled visit of the prior double-blind phase 3 trial), when available, indicate a QTcF ≥ 450 msec at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[i]Includes hematology (including PT, aPTT, and INR), serum chemistry (including prolactin and TSH, with reflex to free thyroxine [T_4] if the result for TSH is abnormal), and urinalysis.

[j] Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline laboratory assessments (ie, the last scheduled visit of the prior double-blind phase 3 trial).

[k] Clinical laboratory tests should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 26/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

[l] 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.

[m] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at Screening/Baseline must not be enrolled in Trial 331-10-238 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.

[n] "Since Last Visit" C-SSRS form.

[o] AE recording will begin with the signing of the ICF for Trial 331-10-238.

[p] 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.

[q] Adjustments to the dose of brexpiprazole or ADT are permitted to optimize efficacy and tolerability as described in Section 3.2. It is recommended that the dose of ADT not be changed while the dose of brexpiprazole is being optimized (ie, no change to ADT up to and including the Week 4 visit). At least 5 days must elapse between dose increases for brexpiprazole and ADT. An interval of at least 5 days between dose adjustments is also recommended for dose decreases; however, the investigator may decrease the dose of brexpiprazole or ADT as needed for tolerability according to the rules described in Section 3.2.2. Subjects must return to the clinic for unscheduled visits if changes to the dose of brexpiprazole or ADT (increases or decreases) are required between scheduled visits. All eligible subjects entering from prior double-blind phase 3 brexpiprazole MDD trials must be able to continue therapy without interruption between the double-blind and open label trials.

[r] Baseline RUF is completed at Screening/Baseline for all subjects. The Follow-up RUF (as well as hospitalization questions) is completed at ET visit.

[s] The IVRS/IWRS will be accessed at unscheduled visits if new blister cards are dispensed for dose adjustment of brexpiprazole.

Section 3.6.2.1: Clinical Laboratory Tests		

Current Table

Table 3.6.2.1-1 Safety Clinical Laboratory Tests

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis: pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (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 or SGPT AST or SGOT BUN CPK Creatinine LDH Total bilirubin Triglycerides Cholesterol (total, LDL, and HDL) Calcium Chloride Glucose Insulin Magnesium Bicarbonate Inorganic phosphorous Sodium Potassium Total protein Uric acid GGT Prolactin Albumin Additional Tests: Urine pregnancy (WOCBP)[a] TSH, with reflex to free T_4 if TSH is abnormal PT, aPTT, and INR ACTH Cortisol HbA1c

Revised Table

Table 3.6.2.1-1 Safety Clinical Laboratory Tests

Hematology: WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis: pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (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 or SGPT AST or SGOT BUN CPK Creatinine LDH Total bilirubin Triglycerides Cholesterol (total, LDL, and HDL) Calcium Chloride Glucose Insulin Magnesium Bicarbonate Inorganic phosphorous Sodium Potassium Total protein Uric acid GGT Prolactin Albumin Additional Tests: Urine pregnancy (WOCBP)[a] TSH, with reflex to free T_4 if TSH is abnormal PT, aPTT, and INR HbA1c

Amendment Number: 4

Issue Date: 13 Jun 2014

PURPOSE:

The sponsor has determined the need for a fourth Amendment to make the following administrative changes:

- include C-SSRS assessment at week 8 and week 20 (removed in error from amendment 3 issued on 11 Apr 2014)
- update sponsor contact details

General Revisions:

- Changes made to Protocol 331-10-238 in this fourth amendment are as outlined above. Changes by section are provided below.

Location	Current Text	Revised Text
Title Page	[redacted] [redacted] Phone Fax [redacted] E-mail: [redacted] [redacted]	[redacted] [redacted] Phone Fax [redacted] E-mail: [redacted] [redacted]
Table 3.6-1 Schedule of Assessments		C-SSRS added X at week 8 and 20
3.6.1.5 **Week 8**		The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
3.6.1.7 **Week 20**		The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.

Agreement

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

I will provide copies of the protocol to all physicians, nurses and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-34712, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where 331-10-238 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in Paragraph I of the sponsor's Clinical Research Agreement, at which time I agree to adhere strictly to the protocol as amended).

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

I agree to await IRB/IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.

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

_____

Principal or Coordinating Investigator Signature and Date

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically captured signature

OPC-34712

SIGNATURE PAGE

Document Name: 331-10-238 Amendment 04

Document Number: 0001108835

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
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