- **Protocol number: 331-201-00080**
- **Document title: A Multicenter, Randomized, Double-blind Trial of Brexpiprazole Versus Placebo for the Acute Treatment of Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder**
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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

CLINICAL PROTOCOL

A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment of Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder

Protocol No. 331-201-00080
IND No. 134115
EudraCT No. 2017-002222-20

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	INC Research Pharmacovigilance & Drug Safety Fax: PPD E-mail: PPD
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-201-00080 IND No.: 134115 EudraCT No.: 2017-002222-20
Protocol Title:	A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment of Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder
Clinical Phase/Trial Type:	Phase 3/Therapeutic use
Treatment Indication:	Bipolar I disorder
Objective(s):	Primary: To demonstrate the efficacy of brexpiprazole for the acute treatment of manic episodes, with or without mixed features, in subjects with a diagnosis of bipolar I disorder. Secondary: To demonstrate the safety and tolerability of brexpiprazole in this same population.
Trial Design:	Multicenter, randomized, double-blind, placebo-controlled
Subject Population:	Men and women 18 to 65 years of age with a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnosis of bipolar I disorder displaying an acute manic episode with or without mixed features requiring hospitalization will be enrolled in the trial. Approximately 60% of subjects will be randomized in North America and 40% in Europe.
Inclusion/Exclusion Criteria:	Subjects with bipolar I disorder, diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI) and a history of at least 1 previous manic episode with or without mixed features with manic symptoms of sufficient severity to require one of the following interventions: hospitalization or treatment with a mood stabilizer, or treatment with an antipsychotic agent. Eligible subjects must have a Young-Mania Rating Scale (YMRS) score $\geq$ 24 at screening and baseline.

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Trial Site(s):	It is planned that approximately 320 subjects will be randomized into the trial at approximately 45 trial sites in North America and Europe.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	During the double-blind period, subjects will receive a starting dose of 2 mg/day of brexpiprazole (or corresponding placebo) from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole (or placebo) on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole (or placebo), up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Subjects who are unable to tolerate their current dose can be titrated down at any time to a minimum of 2 mg/day. Dose adjustments must be made in increments of 1 mg/day. Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial.
Trial Assessments:	Efficacy: YMRS, Clinical Global Impression-Bipolar (CGI-BP), CCI [redacted] CCI [redacted] and CCI [redacted] Safety: Adverse event (AE) reporting, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, body weight, physical examination (PE), CCI [redacted] and CCI [redacted] Screening/Other: Medical, psychiatric, and medication history, urine drug and alcohol screening, serum pregnancy test, MINI, lithium, valproate, and carbamazepine levels.
Criteria for Evaluation:	**Primary Endpoint:** Change from Baseline to Day 21 of the double-blind treatment phase in the YMRS Total Score **Key Secondary Endpoint:** Change from Baseline to Day 21 in the double-blind treatment period in CGI-BP severity score in mania CCI [redacted]

	CCI [redacted] **Safety Endpoints:** Standard safety variables will include AEs, clinically significant changes in: ECGs, vital signs, clinical laboratory tests, use of concomitant medications, changes in body weight, and PE. CCI [redacted] Suicidality will be assessed using the C-SSRS.
Statistical Methods:	For analysis of the double-blind treatment phase data, baseline is defined as the last available measurement prior to the first dose of double-blind IMP. The primary analysis will be performed on the Efficacy Sample which includes all randomized subjects who took at least 1 dose of IMP in the double-blind treatment phase and who have both a baseline

value and at least 1 post-randomization YMRS Total Score during the double blind treatment phase. CCI [redacted]

The primary efficacy endpoint is the change from baseline to Day 21 in the double-blind treatment phase in the YMRS Total Score. The trial will compare the placebo arm to the brexpiprazole arm, randomized at a ratio of 1:1, with an overall significance level of 0.05 for the primary endpoint.

[redacted] CCI The planned sample size of 304 evaluable subjects (152 in each treatment arm) will yield at least 90% power to detect the treatment effects at a 2-tailed significance level of 0.05.

A sufficient number of subjects will be enrolled and randomized to achieve approximately 304 evaluable subjects in the double-blind treatment phase CCI [redacted] the total number of subjects to be randomized is 320 (160 in each treatment arm).

In order to ensure 304 evaluable subjects, CCI [redacted]

	CCI [redacted]
Trial Duration:	The duration of this trial for an individual subject who completes the trial without early withdrawal is approximately 8 weeks. This is inclusive of a maximum 14-day screening period, a 3-week double-blind treatment period, and a safety follow-up via telephone contact or clinic visit 21 (± 2) days after the last dose of IMP. Subjects who complete all trial visits through the Day 21 visit may be offered entry into an optional open-label rollover trial.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
CCI	[redacted]
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CCI	[redacted]
BMI	Body mass index
CGI-BP	Clinical Global Impression- Bipolar
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CCI	[redacted]
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ET	Early termination
EudraCT	European Clinical Trial Data Base
CCI	[redacted]
FDA	Food and Drug Administration
CCI	[redacted]
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigative new drug
INR	International normalized ratio
IRB	Institutional review board
IRE	Immediately reportable event
IWRS	Interactive web response system
LOCF	Last observation carried forward
LOE	Lack of efficacy

CCI	[redacted]
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MI	Multiple imputation
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-effect model repeated measure
MNAR	Missing not at random
OC	Observed cases
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PE	Physical examination
PK	Pharmacokinetics
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcN	QT interval corrected for heart rate by the FDA Neuropharm Division formula
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
CCI	[redacted]
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
T_4	Free thyroxine
US or USA	United States or United States of America
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
YMRS	Young-Mania Rating Scale

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1 Introduction

Bipolar I disorder is a lifelong episodic illness characterized by manic and depressive episodes. Psychotic symptoms (ie, delusions, hallucinations, thought disorders) often accompany the manic phase of bipolar I disorder. The lifetime prevalence of bipolar I disorder is estimated to be 0.4% to 1.6% with a mean age of onset for first manic episode in the early 20s.[1]

Atypical antipsychotics are currently recommended as first-line treatment for acute mania across multiple United States (US) and international treatment guidelines based on established evidence.[2,3,4,5] Although the availability of newer atypical antipsychotics has increased the therapeutic options in the treatment of manic and depressive episodes of bipolar I disorder, there still remains a need for safer and more effective therapies to expand the current options.[6]

Brexpiprazole (also referred to as OPC-34712 and Lu AF41156) is a novel atypical antipsychotic synthesized by Otsuka that is being codeveloped by Otsuka and Lundbeck. Brexpiprazole is currently approved in Canada and the US as monotherapy for the treatment of schizophrenia and the US for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD). While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin (5-HT) and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (K_i: 0.1 - 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ with affinity in the same subnanomolar K_i range (K_i: 0.2 - 0.6 nM). The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy, reduced impulsive behavior, and cognitive improvement.[7] This receptor activity profile may also prove an effective target for the treatment of acute mania of bipolar I disorder.

1.1 Nonclinical Data

A complete description of the available efficacy and safety pharmacology data from nonclinical studies, including pharmacokinetic (PK) and toxicology studies in different animal species can be found in the current Investigator's Brochure (IB).[7]

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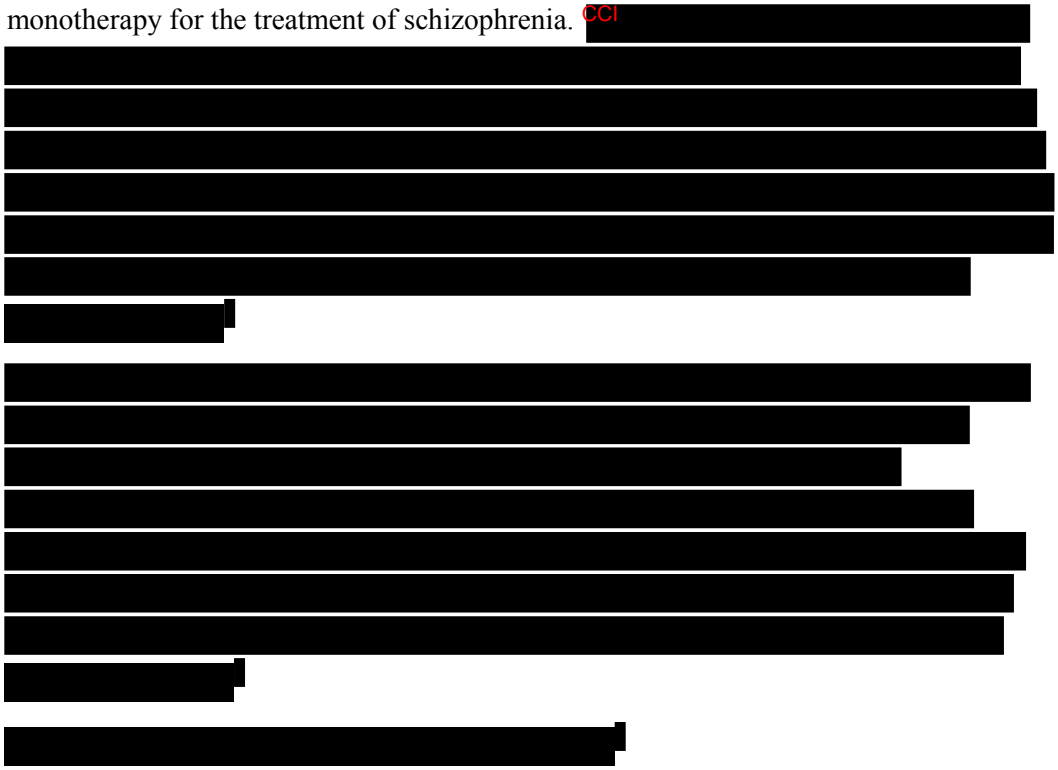
1.2 Clinical Data

Currently, brexpiprazole is approved in the US for use in adult patients as an adjunctive therapy to antidepressants for the treatment of MDD and in Canada and the US as monotherapy for the treatment of schizophrenia. CCI



1.3 Known and Potential Risks and Benefits

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

Please refer to the current IB for a summary of available nonclinical and clinical safety data.[7]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Current guidelines for the treatment of acute mania in bipolar I disorder advocate first-line use of atypical antipsychotics, such as aripiprazole, as monotherapy or in combination with lithium or divalproex[2,3,4,5]

Brexpiprazole is a novel antipsychotic that is a serotonin-dopamine activity modulator and is indicated in the US as monotherapy for the treatment of schizophrenia in adult patients (2-4 mg/day) and as an adjunctive therapy to antidepressants for the treatment of MDD (2-3 mg/day).[7] Brexpiprazole, like other atypical antipsychotics, targets the specific receptor profile of agents that have proven efficacy in the treatment of bipolar I disorder. This multicenter, randomized, double-blind, placebo-controlled trial will be conducted to evaluate the safety and efficacy of brexpiprazole monotherapy (2-4 mg/day, with a starting dose of 2 mg/day) for the acute treatment of manic episodes, with or without mixed features, in subjects with bipolar I disorder.

2.2 Dosing Rationale

The dosing paradigm of brexpiprazole to be used in Trial 331-201-00080 has been determined based on the current approved dosing ranges and phase 3 trial results across related psychiatric indications (MDD and schizophrenia) and on dosing paradigms used in the development of other atypical antipsychotics used for bipolar I disorder. In general, for most atypical antipsychotics, the recommended dosing range and maximal doses tend to be comparable for subjects with either schizophrenia or bipolar I acute mania.

During the double-blind period, subjects will receive a starting dose of 2 mg/day of brexpiprazole (or corresponding placebo) from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole (or placebo) on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole (or placebo), up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Subjects who are unable to tolerate their current dose can be titrated down at any time to a minimum of 2 mg/day. Dose adjustments must be made in increments of 1 mg/day. Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial. This paradigm is within the currently approved recommended dose range for schizophrenia, ie, 2 to 4 mg/day, but with a more rapid titration schedule. A higher starting dose and faster titration for acute mania is proposed to reach the target dose quickly, without resulting in undesirable side effects. This decision is consistent with

clinical trial programs and labeling for other atypical antipsychotics, where similar differences are seen between schizophrenia and acute mania dosing paradigms with respect to the starting doses and recommended dose ranges. In addition, this is consistent with previously tested dosing paradigms for brexpiprazole in schizophrenia that resulted in similar safety and tolerability profiles as seen with the labeled dosing paradigm. This includes trials with higher starting doses without titration (up to 12 mg/day), and with more rapid titration schedules (Trials 331-07-203, 331-08-205, and 14644A).

2.3 Trial Objectives

Primary: To demonstrate the efficacy of brexpiprazole for the acute treatment of manic episodes, with or without mixed features, in subjects with a diagnosis of bipolar I disorder.

Secondary: To confirm the safety and tolerability of brexpiprazole in this same population.

3 Trial Design

3.1 Type/Design of Trial

This will be a 3-week, multicenter, randomized, double-blind, placebo-controlled trial of brexpiprazole in subjects diagnosed with bipolar I disorder (current manic episode with or without mixed features) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; updated terminology replaces "mixed episodes" with the descriptor of "mixed features"). The total duration of the trial is up to 8 weeks, including screening, double-blind treatment, and follow-up. See Figure 3.1-1 for a schematic of the trial design.

The trial will be organized as follows:

Screening Phase: The screening period will begin after written informed consent has been obtained and will take place between Day −14 and Day −1 prior to randomization. Hospitalization will begin with the signing of the informed consent form (ICF) for subjects who are not already hospitalized at the time of the initial screening visit. The purpose of the screening period is to assess eligibility criteria and to washout prohibited concomitant medication. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening, will have a diagnosis of bipolar I disorder, and will be experiencing a manic episode with or without mixed features as defined by the DSM-5 criteria. An interactive web response system (IWRS) or equivalent will be used to obtain an

identification (ID) number for each subject with documented consent. Although the screening period will continue up to administration of the first dose of investigational medicinal product (IMP), screening procedures should be initiated with a sufficient amount of time allotted in order to obtain laboratory results and electrocardiogram (ECG) results from the central reader prior to randomization. The sponsor reserves the right to utilize external quality oversight methods to ensure the validity of diagnosis, severity of illness, and other factors determining appropriateness of subject selection.

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods.

Treatment Phase: Following the screening period, subjects who meet all inclusion criteria, including a score of ≥ 24 on the Young-Mania Rating Scale (YMRS)[8] at screening and baseline, and meet none of the exclusion criteria, will be randomized in a 1:1 ratio to receive either placebo or brexpiprazole for 3 weeks. Subjects will receive a starting dose of 2 mg/day of brexpiprazole (or corresponding placebo) from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole (or placebo) on Day 4. Further dose increases up to 4 mg/day may occur no earlier than Day 7 at the investigator's discretion based on treatment response. Subjects who are unable to tolerate their current dose can be titrated down at any time to a minimum of 2 mg/day. Subjects may be re-titrated back to higher dose levels based on investigator discretion. Dose adjustments must be made in increments of 1 mg/day. Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial. All subjects will remain hospitalized for a minimum of the first 2 weeks of the 3-week treatment phase. However, subjects who, in the opinion of the investigator, have clinically improved from their baseline assessments with mild to no manic symptoms, and are stable enough to be treated on an outpatient basis, including no risk of suicide as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS), may be discharged and will continue as outpatients for the last week of double-blind treatment. Subjects who do not meet these criteria will remain hospitalized for the duration of the 3 week treatment phase.

A drug screen and alcohol test are required at the Day 21/Early Termination (ET) visit for subjects who are discharged from the hospital at the end of Week 2 (Day 14) to verify continued compliance with the protocol.

Follow-up Phase: If any subject discontinues the trial early, every effort should be made to complete the Day 21/ET assessments as soon as possible and prior to starting any new medication or treatment. Subjects who complete all trial visits through the Day 21 visit and had no major protocol violations may be offered entry into an optional open-label

rollover trial. Subjects who do not enter the open-label trial will be followed up for safety reasons via telephone contact or in clinic visit 21 (± 2) days after the last dose of IMP. This contact also applies to subjects who are withdrawn prematurely from the trial.

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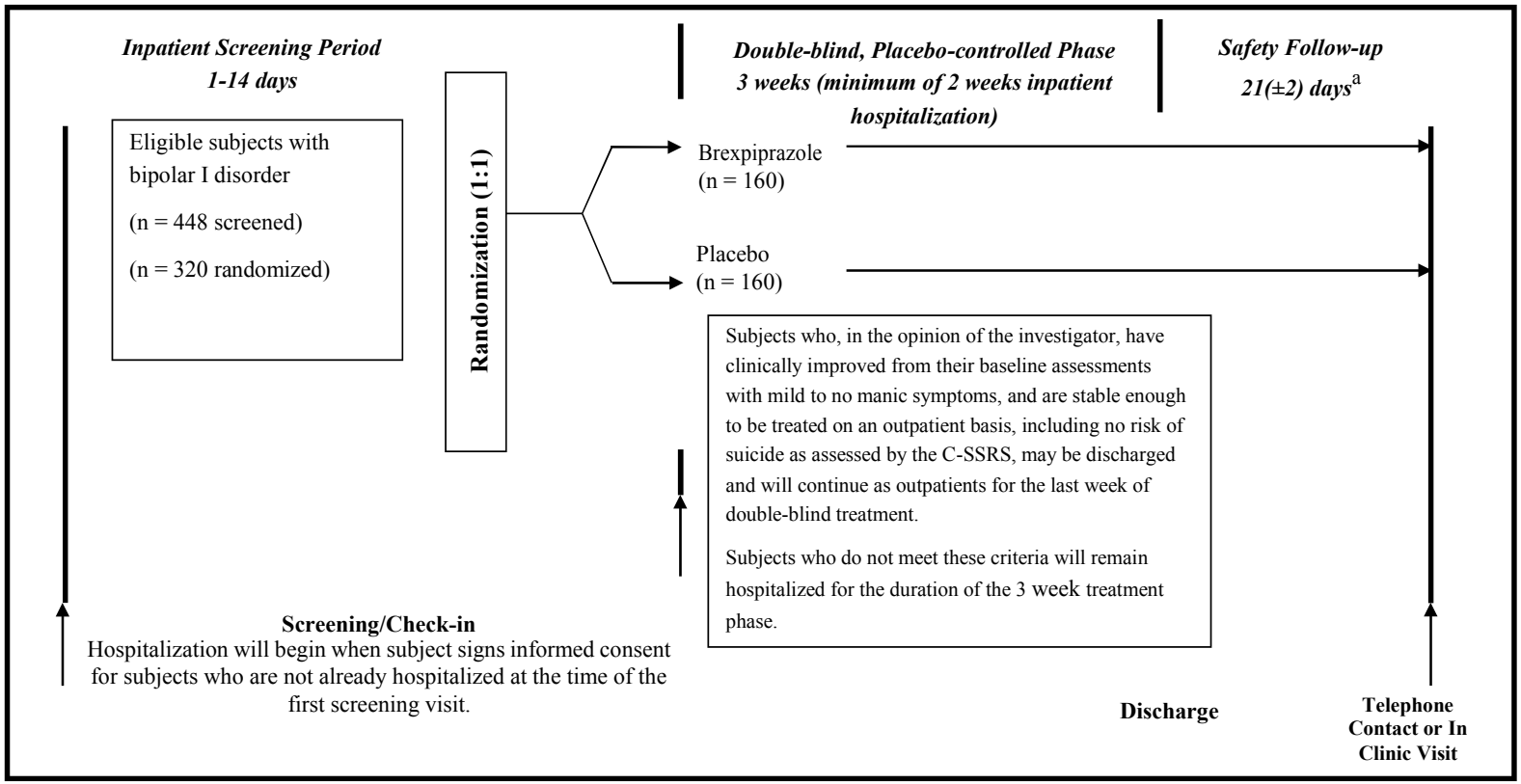

C-SSRS = Columbia-Suicide Severity Rating Scale.

[a]Subjects who complete all trial visits through the Day 21 visit may be offered entry into an optional open-label rollover trial.

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

During the double-blind treatment phase, subjects will receive IMP consisting of brexpiprazole monotherapy or placebo, depending on the subject's treatment assignment.

As shown in Table 3.2-1, subjects will receive a starting dose of 2 mg/day of brexpiprazole (or corresponding placebo) from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole (or placebo) on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole (or placebo), up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Subjects who are unable to tolerate their current dose can be titrated down at any time to a minimum of 2 mg/day. Dose adjustments must be made in increments of 1 mg/day. Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial.

Table 3.2-1 Dosing Schedule

Dose	Days 1-3	Days 4[a]	Days 7-21[b]
Brexpiprazole	2 mg	3 mg	2-4 mg
Placebo	Placebo	Placebo	Placebo

[a]Down titration can occur at any time due to tolerability after Day 4. The minimum dose allowed is 2 mg/day.

[b]Option to titrate 2 to 4 mg (ie, 2 mg, 3 mg, or 4 mg) based on clinical response and tolerability; changes must occur in 1 mg/day increments. Increases up to 4 mg/day may occur no earlier than Day 7.

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

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

It is planned that approximately 320 subjects will be randomized into the trial at approximately 45 trial sites in the North America and Europe. Approximately 60% of subjects will be randomized in North America and 40% in Europe.

The trial population will include men and women 18 to 65 years of age, inclusive, with a DSM-5 diagnosis of bipolar I disorder displaying an acute manic episode with or without mixed features requiring hospitalization. Diagnosis will be confirmed by the Mini

International Neuropsychiatric Interview (MINI)[9,10] and a history of at least 1 previous manic episode with or without mixed features with manic symptoms of sufficient severity to require one of the following interventions: hospitalization or treatment with a mood stabilizer, or treatment with an antipsychotic agent. Eligible subjects must also have an YMRS score ≥ 24 at screening and baseline.

3.3.2 Subject Selection and Numbering

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

3.4 Eligibility Criteria

3.4.1 Informed Consent

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

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

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

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

Prospective trial participants will be provided with controlled access to the electronic informed consent application by site staff. When the site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign the electronic ICF application and an electronic date and time stamp will be applied to the signature. The participant will be given a printed, signed copy of the consent form. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These

signatures cannot be altered, removed, or copied. In the event electronic ICFs are not allowed per local or country regulations, a paper consent will be utilized.

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

CCI

[redacted]

3.4.2 Inclusion Criteria

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

Table 3.4.2-1 Inclusion Criteria

1.	Male or female subjects, ages 18 to 65 years, inclusive, at the time of informed consent.
2.	Subjects who are able to complete the consent process as required by IRB or IEC prior to the initiation of any protocol-required procedures.
3.	Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited medication; and to read and understand written word in order to be reliably rated on assessment scales.
4.	Subjects with a DSM-5 diagnosis of bipolar I disorder displaying an acute manic episode with or without mixed features requiring hospitalization. Diagnosis confirmed by the MINI and a history of at least one previous manic episode with or without mixed features with manic symptoms of sufficient severity to require one of the following interventions: hospitalization or treatment with a mood stabilizer, or treatment with an antipsychotic agent. "Require" is defined as an intervention that occurred rather than one that was recommended.
5.	YMRS score of ≥ 24 at screening and baseline.
6.	Subjects who, in the investigator's judgment, require treatment with an atypical antipsychotic medication for their bipolar I disorder.
7.	Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria

	Sex and Reproductive Status
1.	Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.
2.	Females who are breastfeeding and/or who have a positive pregnancy test result prior to receiving IMP.
	Target Disease
3.	Subjects with a history of DSM-5 diagnosis other than bipolar I disorder, including schizophrenia, schizoaffective disorder, major depressive disorder, attention-deficit/hyperactivity disorder, delirium, dementia, amnestic, or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder. All other current diagnoses must be discussed with the medical monitor.
4.	Subjects whose current manic episode has lasted for more than 4 weeks overall, or who have required hospitalization > 21 days for the current acute episode at the time of the screening visit, excluding hospitalization for psychosocial reasons.
5.	Subjects who have had initiation of, or a change in, psychotherapy for the treatment of bipolar disorder symptoms within 28 days prior to the screening visit or if it is anticipated that the subject will have a change in psychotherapy during the trial.
6.	Subjects with manic symptoms that are better accounted for by another general medical condition or direct physiological effects of a substance (eg, medications).
7.	Subjects considered unresponsive to clozapine or who are only responsive to clozapine.
8.	Subjects with bipolar I disorder who are considered resistant or refractory to treatment for manic symptoms by history.
9.	Subjects who have had electroconvulsive treatment within the past 2 months.
10.	Use of psychotropic medications (other than benzodiazepines) within 7 days of the baseline YMRS.
11.	Rapid cyclers with more than 6 episodes in the previous year.
12.	Subjects with serum concentrations of lithium ≥ 0.6 mmol/L, serum concentrations of valproate ≥ 50 µg/mL, or serum concentrations of carbamazepine ≥ 4 µg/mL (if any of these parameters are outside of the listed exclusionary range, they may be reassessed prior to randomization, if necessary).
	Medical History and Concurrent Diseases
13.	Subjects who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the screening visit.
14.	Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months, **OR** Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months **OR** Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide or homicide.

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Table 3.4.3-1 Exclusion Criteria	
15.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) or an abnormal result for free T_4 at screening.
16.	Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as the following: • any history of myocardial infarction or congestive heart failure (whether controlled or uncontrolled), • HIV seropositive status or acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN). Medical conditions that are minor or well−controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a correspondingly high BMI, need to be reviewed and discussed with the medical monitor.
17.	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: • HbA1c < 7.0%, AND • Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND • Subject has been maintained on a stable regimen of oral anti-diabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, AND • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND • Subject's diabetes is not newly diagnosed during screening for the trial.
18.	Subjects with uncontrolled hypertension (DBP > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms. NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above.
19.	Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile, post traumatic, or alcohol withdrawal seizure.
20.	Subjects with a history of a gastric bypass surgery that creates a malabsorptive state, including Roux-en-Y gastric bypass and biliopancreatic bypass with duodenal switch. This does not include gastric banding, gastric stapling, and sleeve gastrectomy procedures.

Table 3.4.3-1 Exclusion Criteria

	Physical and Laboratory Results
21.	Subjects with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subject or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Criteria are provided in Section 3.7.3.2. In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: • Platelets ≤ 75000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 • AST > 2 × ULN • ALT > 2 × ULN • CPK > 3 × ULN, unless discussed with and approved by the medical monitor • Creatinine ≥ 2 mg/dL • QTcF ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing. Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the subject must be excluded.
22.	Subjects with a positive drug screen for cocaine, or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of marijuana, 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.
	Disallowed and Concomitant Medication
23.	Recent treatment with a long acting or depot antipsychotic in which the last dose was less than one full cycle plus 1/2 cycle from baseline visit (Section 4.1).
24.	Subjects who would be likely to require prohibited concomitant therapy during the trial (Section 4.1).
25.	Subjects who received brexpiprazole in any prior clinical trial or currently taking commercially available brexpiprazole (Rexulti®).
26.	Subjects who may require CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers during this trial.
	Allergies and Adverse Drug Reactions
27.	Subjects with a history of neuroleptic malignant syndrome, serotonin syndrome, or clinically significant tardive dyskinesia.
28.	Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
29.	Subjects who are known to be allergic or hypersensitive to brexpiprazole or other quinolinones.
	Other
30.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
31.	Subjects who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
32.	Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CPK = creatine phosphokinase; CYP = cytochrome P450; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; OTC = over-the-counter; QTcF = QT interval corrceted

for heart rate by Fridericia's formula; SBP = systolic blood pressure; ULN = upper limit of normal; WOCBP = women of childbearing potential.

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

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

During screening, subjects with a positive blood alcohol screen should be reassessed for alcohol abuse and dependence before consultation with medical monitor about approval for inclusion. Subjects with a positive drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results should be excluded from the trial. Subjects with a positive drug screen for cocaine or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of marijuana, 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 or the subject does not meet DSM-5 criteria for substance abuse or dependence, may continue evaluation for the trial following consultation and approval by the medical monitor.

Screen failures may be rescreened at any time if the exclusion characteristic has changed. Subjects who sign an ICF but who are not started on treatment are permitted to be rescreened. If a subject is rescreened for trial participation, and the rescreening is not completed within the original screening window, a new ICF must be signed.

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is change from baseline to Day 21 of the double-blind treatment phase in YMRS Total Score.

3.5.2 Secondary Endpoints

The key secondary endpoint is the change from baseline to Day 21 in the double-blind treatment period in Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness score in mania.

CCI

[redacted]

3.5.3 CCI

[redacted]

3.5.4 CCI

[redacted]

3.5.5 Safety Endpoints

Standard safety variables will include adverse events (AEs), clinical laboratory tests (hematology, serum chemistry [including prolactin and glycosylated hemoglobin (HbA1c)], coagulation parameters, and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured.

CCI

[redacted] The C-SSRS will be used to assess and classify reported suicidal behavior.

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CCI [redacted]

3.5.6 CCI [redacted]

[redacted]

3.6 Measures to Minimize/Avoid Bias

During the entire trial, treatment will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment at any given visit.

Treatment assignments will be based on a fixed-block computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department. The randomization will be stratified by trial site and designed to allocate subjects to a treatment regimen in a 1:1 ratio. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the IWRS, and reporting serious adverse events (SAEs) to regulatory agencies.

3.7 Trial Procedures

This trial is a phase 3, double-blind, placebo-controlled trial to investigate the efficacy, safety, and tolerability of brexpiprazole (2-4 mg/day) for the treatment of subjects with bipolar I disorder experiencing a manic episode with or without mixed features. The trial comprises a 3-week, double-blind treatment period with a 21 (± 2) day follow-up.

Trial assessment time points are summarized in Table 3.7-1.

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Table 3.7-1 Schedule of Assessments

	Screening[a]	Double-blind Treatment Phase					Follow-up[c]
	Day -14 to -1	Baseline (Day 1)	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21/ET[b] (± 2 days)	21 (± 2) days after last dose
Screening Assessments and Randomization							
Informed Consent[d]	X						
Demographics	X						
Medical History	X						
Psychiatric History	X						
MINI	X						
Concomitant Medications[e]	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Efficacy Assessments							
YMRS[f]	X	X	X	X	X	X	
CGI-BP[g]		X	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]		[redacted]				[redacted]	
Safety Assessments							
Physical Examination[h]	X					X	
Vital Signs[i]	X	X	X	X	X	X	
Body Weight	X					X	
12-lead ECG[j]	X	X				X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis), including prolactin[k]	X					X	
HbA1c[j]	X					X	

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Table 3.7-1 Schedule of Assessments							
	Screening[a]	**Double-blind Treatment Phase**					**Follow-up[c]**
	Day -14 to -1	**Baseline (Day 1)**	**Day 4 (± 1 day)**	**Day 7 (± 1 day)**	**Day 14 (± 1 day)**	**Day 21/ET[b] (± 2 days)**	**21 (± 2) days after last dose**
TSH, with reflex to T4 if TSH is abnormal	X					X	
Coagulation parameters (PT, aPTT, INR)[k]	X					X	
Lithium, Valproate, Carbamazepine Levels[l]	X						
HIV, HBsAg, and anti-HCV	X						
Pregnancy Test[m]	X		X			X	
Drug Screen[n]	X					X	
Blood Alcohol Test[n]	X					X	
C-SSRS[o]	X	X	X	X	X	X	
CCI							
AEs[p]	X	X	X	X	X	X	X
CCI							
Other							
IMP dispensing[r]		X	X	X	X		
IMP accountability			X	X	X	X	

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aPTT = activated partial thromboplastin time; HBsAg = Hepatitis B surface antigen; Anti-HCV = Antibodies to hepatitis C virus; INR = International Normalized Ratio; T_4 = free thyroxine; TSH = thyroid-stimulating hormone.

[a]Screening begins when the ICF is signed and will take place between Day −14 and Day −1; however, screening procedures should be initiated with a sufficient amount of time allotted in order to obtain laboratory results and ECG results from the central reader prior to randomization. Review of inclusion/exclusion criteria at baseline will be based on assessments performed during screening. Hospitalization will begin with the signing of the ICF for subjects who are not already hospitalized at the initial screening visit. Note: In the rare circumstance when a subject must leave the inpatient facility temporarily (eg, family emergency or doctor visit), a temporary day pass may be granted. For such a request, sites must first contact the medical monitor for explicit authorization and guidance on procedures. A medical monitor approved day pass is good for the day requested only, and subjects must return to the site the same day (eg, in the evening).

[b]If a subject discontinues prematurely before Day 21, procedures noted for Day 21 must be completed at the ET visit.

[c]Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety 21 days after the last dose of IMP and applies only to subjects who do not enter the optional open-label rollover trial.

[d]Informed consent must be obtained prior to any trial-related procedures. CCI [redacted]

[e]All medications taken within 30 days of screening will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications.

[f]To be eligible for the trial, subjects must have a YMRS score ≥ 24 at screening and baseline.

CCI [redacted]

[h]To include measurement of height at screening only and waist circumference at screening and Day 21.

[i]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 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.

[j]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. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Subjects will be randomized based on screening ECG results from the central reader and baseline ECG results from the trial site. If the baseline ECG results from the central reader, when available, indicate a QT interval corrected for heart rate by Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing, at 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.

[k]Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. Clinical laboratory tests must be drawn after a minimum 8-hour fast at Day 21/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

[l]If lithium, valproate, or carbamazepine levels are outside of the listed exclusionary range, they may be reassessed prior to randomization.

[m]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at screening must not be enrolled. Subjects with positive urine and serum pregnancy test results 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]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]The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine elgibility and the "Since Last Visit" C-SSRS form will be completed at the baseline visit to assure that the subject continued to qualify for the trial. Any subject with suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Table 3.4.3-1). The "Since Last Visit" C-SSRS form will be completed at all visits after the baseline visit.

[p]Adverse events will be recorded starting after the subject signs the ICF.

[q]CCI [redacted]

[r]Site staff will provide IMP to hospitalized subjects daily from assigned blister cards. If a subject is discharged at Day 14, the site should counsel the subject on the importance of taking IMP as directed.

3.7.1 Schedule of Assessments

3.7.1.1 Screening (Day -14 to -1)

The screening period begins after consent has been obtained. Consent should also be obtained for optional FBR for those subjects that want to participate. Although the screening period takes place between Day −14 and Day −1, subjects will participate in screening activities for a minimum of 1 day. After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing the IWRS or equivalent. Screening evaluations will include the following:

- Hospitalization will begin once the subject signs the ICF for subjects who are not already hospitalized at the time of the screening visit.
- A qualified and certified rater will administer the YMRS CCI [redacted]
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years which is considered to be clinically relevant per the investigator's judgment.
- Psychiatric history will be recorded, including the DSM-5 diagnosis of bipolar I disorder that will be made by an adequately trained and experienced clinician and will be confirmed by the administration of the MINI.
- Medications (including those that were taken within 30 days of screening) will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited/restricted medications are provided in Table 4.1-1 and Table 4.1-2.
- Washout from prohibited concomitant medications, if applicable (Table 4.1-1).
- CCI [redacted]
- The investigator (or qualified designee) who is adequately trained will complete the "Baseline/Screening" C-SSRS form to exclude subjects with a significant risk of suicidal behavior (see Table 3.4.3-1).
- A complete physical examination (including height and waist circumference) will be performed.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3-1 for exclusions based on outcome of screening vital sign measurements.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. See Table 3.4.3-1 for exclusions based on ECG results.

- Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T_4] if the result for TSH is abnormal, and lithium, valproate, and carbamazepine levels) should be drawn after a minimum 8-hour fast at screening. See Table 3.4.3-1 for exclusions based on outcome of screening clinical laboratory tests. Note: if lithium, valproate, or carbamazepine levels are outside of the listed exclusionary range, they may be reassessed prior to randomization.
- Samples will be obtained for blood alcohol testing. See Section 3.4.3 for details regarding subjects with a positive blood alcohol test.
- CCI [redacted]
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Section 3.4.3 for exclusions based on outcome of screening urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all women of childbearing potential (WOCBP). All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- Adverse events will be recorded beginning with the completion of the consent process.
- Trial personnel will access the IWRS or equivalent to register the visit (initial visit only).

3.7.1.2 Baseline (Day 1)

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

- An assessment of all inclusion and exclusion criteria will be made to confirm the subject's eligibility for the trial.
- A qualified and certified rater will administer the YMRS, CGI-BP, CCI [redacted]
- The investigator (or qualified designee) who is adequately trained will complete the "Baseline/Screening" C-SSRS form.
- Vital sign measurements (body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3-1 for exclusions based on outcome of screening vital sign measurements.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. See Table 3.4.3-1 for exclusions based on ECG results.
- Adverse events and concomitant medications will be recorded.

3.7.1.3 Randomization

Once subject eligibility has been confirmed at baseline, the following will be performed on Day 1:

- Trial personnel will access the IWRS or equivalent to register the visit and to obtain blister card assignment(s) for double-blind IMP. The assigned IMP will be dispensed to the subject.

3.7.1.4 Treatment Phase - Day 4

The following procedures will be performed on Day 4 (± 1 day):

- A qualified and certified rater will administer the YMRS and CGI-BP.
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
- CCI [redacted]
- Vital sign measurements (body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- A urine pregnancy test will be performed for all WOCBP. All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be withdrawn from the trial.
- Adverse events and concomitant medications will be recorded.
- IMP will be dispensed to the subject (Days 4, 5, and 6).
- Drug accountability will be performed.

3.7.1.5 Treatment Phase - Day 7

The following procedures will be performed on Day 7 (± 1 day):

- A qualified and certified rater will administer the YMRS and CGI-BP.
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
- CCI [redacted]
- Vital sign measurements (body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- Adverse events and concomitant medications will be recorded.

- IMP will be dispensed to the subject (Days 7 through 13).
- Drug accountability will be performed.

3.7.1.6 Treatment Phase - Day 14

The following procedures will be performed on Day 14 (± 1 day):

- A qualified and certified rater will administer the YMRS, CGI-BP, CCI
- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
- CCI
- Vital sign measurements (body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine and standing after the subject has been in each position at least 3 minutes.
- Adverse events and concomitant medications will be recorded.
- IMP will be dispensed to the subject (Days 14 through 21).
- Drug accountability will be performed.
- Subjects who, in the opinion of the investigator, have clinically improved from their baseline assessments with mild to no manic symptoms, and are stable enough to be treated on an outpatient basis, including no risk of suicide assessed by the C-SSRS, may be discharged and will continue as outpatients for the last week of double-blind treatment.
- Those subjects who are discharged early will be administered IMP for the last week of treatment that is clearly labeled with the trial number, subject ID, and subject initials. Subjects will be counseled on the importance of taking the IMP.

3.7.1.7 End of Treatment Phase - Day 21/Early Termination Visit

All subjects will undergo a complete evaluation at Day 21 (± 2 days). In addition, Day 21 evaluations are to be completed for any subject withdrawn at any time after randomization into the trial. Attempts should be made to complete all evaluations, particularly efficacy assessments, for the Day 21/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new rescue medication for worsening manic symptoms prior to ET procedures prior to the Day 21/ET procedures, no efficacy assessments should be performed.

The following procedures will be performed on Day 21(± 2 day) or the ET visit:

- A qualified and certified rater will administer the YMRS, CGI-BP, CCI

- The investigator (or qualified designee) who is adequately trained will complete the "Since Last Visit" C-SSRS form.
- CCI [redacted]
- A complete physical examination 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 and standing after the subject has been in each position at least 3 minutes.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes.
- Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and thyroid-stimulating hormone [TSH] with reflex to T_4 if the result for TSH is abnormal) must be drawn after a minimum 8-hour fast.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected from subjects for urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all WOCBP. All positive results must be confirmed by a serum pregnancy test.
- CCI [redacted]
- CCI [redacted]
- Adverse events and concomitant medications will be recorded.
- Trial personnel will access the IWRS or equivalent to register the visit.
- Drug accountability will be performed.

3.7.1.8 Post-treatment Follow-up Period

Subjects will be contacted for a safety follow-up either via telephone or in-clinic visit (at the investigator's discretion) scheduled 21 (± 2) days after the last dose of IMP. Adverse events and concomitant medications will be recorded. This contact also applies to subjects withdrawn prematurely from the trial.

3.7.2 Efficacy Assessments

It is required that trained and experienced clinicians administer all rating scales. In addition, the raters must be certified for this trial to administer the YMRS CCI [redacted] scales. 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, certification, and materials for rating will be provided by OPDC or designee.

3.7.2.1 Young-Mania Rating Scale

The YMRS consists of 11 items assessing the core symptoms of mania[8] and is based on questions asked of the subject regarding his or her clinical condition. Additional information is based upon clinical observations made during the course of the clinical interview. Each item has 5 defined categories of severity with 4 items graded on a 0 to 8 scale (irritability, speech, content, and disruptive-aggressive behavior) and 7 items graded on a 0 to 4 scale. A copy of the YMRS is provided in Appendix 7.

3.7.2.2 Clinical Global Impression - Bipolar Version

The CGI-BP scale refers to the global impression of the subject with respect to bipolar disorder.[12] The scale rates the subject's Severity of Illness (CGI-BP Severity of Illness: mania, depression, and overall bipolar illness) based on a 7-point scale and rates the subject's Change from Baseline (CGI-BP change from baseline: mania, depression, and overall bipolar illness) based on a 7-point scale. Severity of Illness (CGI-BP Severity of Illness) should be rated at visits indicated in Table 3.7-1. The CGI-BP Change from Baseline is not assessed at the baseline visit. At each visit other than baseline, the Change from Baseline will be judged with respect to subject's condition at baseline. It is important that the point of reference for assessing improvement or worsening on the CGI-BP Change from Baseline be the condition of the subject at the baseline visit and not the condition of the subject at any post-baseline visit preceding the current visit. A copy of the CGI-BP is provided in Appendix 9.

3.7.2.3 CCI

[redacted]

3.7.2.4 Other Assessments

3.7.2.4.1 Mini International Neuropsychiatric Interview

The MINI[9,10,14] will be conducted at the screening visit to confirm the subject's diagnosis of bipolar I disorder and to rule out exclusionary comorbid psychiatric diagnoses.

Detailed instructions for administration of this structured interview will be provided. A copy of the score sheet is provided in Appendix 5.

3.7.2.4.2 CCI

[redacted]

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. The central laboratory will provide laboratory results electronically. A list of clinical laboratory assessments is provided in Table 3.7.3.2-1.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
White Blood Cell (WBC) count with differential	Alkaline Phosphatase (ALP)
Red Blood Cell (RBC) count	Alanine Aminotransferase (ALT)
Hematocrit	Albumin
Hemoglobin	Aspartate Aminotransferase (AST)
Platelet count	Bicarbonate
	Bilirubin, total
	Blood Urea Nitrogen (BUN)
Urinalysis:	Creatine phosphokinase (CPK)
pH	Calcium
Specific Gravity	Chloride
Protein	Cholesterol (total, low density lipoprotein, and high

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Table 3.7.3.2-1 Clinical Laboratory Assessments

Ketones Glucose Blood Microscopic analysis (performed only if any part of the urinalysis is not negative) Urine Drug Screens: Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Opiates Phencyclidine Propoxyphene <u>Other:</u> Blood Alcohol	density lipoprotein) Creatinine Gamma Glutamyl Transferase (GGT) Glucose HbA1c Inorganic phosphorus Insulin Lactic Dehydrogenase (LDH) Magnesium Potassium Prolactin Protein, total Sodium Thyroid Stimulating Hormone (TSH) Thyroxine, Free (T_4) (if needed) Uric acid Triglycerides <u>Additional Tests:</u> Urine or serum pregnancy for WOCBP Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ration (INR) HbA1c <u>Additional Tests (screening only):</u> HIV HbsAg anti-HCV

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; LDH = lactic dehydrogenase; MCHC = mean corpuscular hemoglobin concentration; RBC = red blood cell; WBC = white blood cell.

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 3 for criteria for identifying values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets $\leq 75000/mm^3$

- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/mm^3
- Aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2 × ULN
- Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
- Creatinine ≥ 2 mg/dL

The total volume of blood to be collected during the trial per subject is expected to be approximately 50 mL.

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

3.7.3.3 Physical Examination and Vital Signs

3.7.3.3.1 Physical Examination

A complete physical examination will consist of measurement of height and waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. Height will be measured with a stadiometer, measuring stick, or tape. Waist circumference will be measured with each physical examination. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- The waist circumference measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[15]

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 Food and Drug Administration (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 baseline examination should be documented as an AE and followed to a satisfactory conclusion.

3.7.3.3.2 Measurement of Vital Signs

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

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

Blood pressure and heart rate measurements will be made in the supine 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 standing.

Subjects with uncontrolled hypertension (screening DBP > 95 mmHg in any position) or symptomatic hypotension are excluded from the trial as are subjects with orthostatic hypotension defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure OR development of symptoms (see Table 3.4.3-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Appendix 2 is included to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.7.3.4 Electrocardiogram Assessments

All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee

will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

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

Refer to Appendix 4 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical significance postrandomization. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. Please consult the medical monitor in case of questions.

3.7.3.5 CCI [redacted]

[redacted] 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.

3.7.3.5.1 CCI [redacted]

[redacted]

Protocol 331-201-00080

CCI [redacted]

3.7.3.5.2 CCI [redacted]

[redacted]

3.7.3.5.3 CCI [redacted]

[redacted]

Protocol 331-201-00080

CCI [redacted]

3.7.3.5.4 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject with active suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Table 3.4.3-1). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening. Copies of the C-SSRS forms are provided in Appendix 13and Appendix 14.

3.7.3.5.5 CCI [redacted]

[redacted]

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the case report form. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an

AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the ePlatform.

3.7.5 CCI [redacted]

[redacted]

3.7.5.1 CCI [redacted]

[redacted]

3.7.6 CCI [redacted]

[redacted]

3.7.7 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 ePlatform page for the last subject completing or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

Not applicable.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

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

3.8.2 Individual Site

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

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

All attempts should be made to avoid treatment interruption during the trial. For subjects who have an interruption of treatment, the investigator or designee will contact the medical monitor as soon as possible. The investigator and medical monitor 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 medical monitor. The treatment interruption will be recorded via eSource and also recorded as a protocol deviation (Section 3.13).

3.8.3.2 Treatment Discontinuation

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

3.8.3.3 Documenting Reasons for Treatment Discontinuation

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

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death

- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

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

3.8.3.4 Withdrawal of Consent

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

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

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

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

3.8.3.5 Procedures to Encourage Continued Trial Participation

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

3.9 Screen Failures

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

Screen failures may be rescreened at any time if the exclusion characteristic has changed. Subjects who sign an ICF but who are not started on treatment are permitted to be rescreened. In the event that the subject is rescreened for trial participation, and the rescreening is not completed within the original screening window, a new ICF must be signed.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete Day 21 visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 21 visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the medical monitor at the earliest possible time by telephone. The investigator and medical monitor 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 medical monitor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP. Subjects who are receiving prohibited medications that would require a washout of more than 14 days (eg, current use of depot or long-acting injectable antipsychotics) are excluded from the trial. However, subjects whose last injection of antipsychotic occurred at least one full cycle (based on the prescribing label) before the initial screening visit are eligible to enter the 14-day screening period if at least one full cycle plus 1/2 cycle (length of 1 cycle based on the prescribing label) will have elapsed before randomization. Subjects with serum concentrations of lithium ≥ 0.6 mmol/L, valproate ≥ 50 µg/mL, or carbamazepine ≥ 4 µg/mL at screening may repeat a clinical laboratory test for these parameters prior to randomization. The results of the additional test will be reviewed and confirmed before the subject can be randomized into the trial. Other therapies restricted or prohibited prior to enrollment and during the trial are presented in Section 4.2.

Table 4.1-1 List of Medications Prohibited Before the Trial

Medication	Required Washout Prior to Dosing
Antipsychotics Oral (or IR IM) aripiprazole Other oral (or IR IM) antipsychotics Depot or long-acting injectable antipsychotics	 14 days 7 days One full cycle plus 1/2 cycle[a] (length of 1 cycle based on the prescribing label)
Antidepressants Fluoxetine or Symbyax MAOIs Citalopram and escitalopram Venlafaxine and desvenlafaxine All other antidepressants	 28 days[a] 14 days 8 days 3 days 14 days
Mood stabilizers (ie, lithium and/or anticonvulsants)	7 days
Varenicline	5 days
Benzodiazepines	Refer to Section 4.1.1 for details on benzodiazepine use during the trial
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers	14 days

IR IM = immediate-release intramuscular; MAOIs = monoamine oxidase inhibitors.

[a]Subjects must satisfy the washout restriction within the 14-day screening period. Therefore, subjects currently receiving depot or long-acting injectable antipsychotics, fluoxetine, or Symbyax at screening are excluded from the trial. However, if these medications were recently discontinued prior to the initial screening visit for reasons unrelated to this trial and the required washout will be met within 14 days of the initial screening visit, the subject may be screened for the trial.

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

Table 4.1-2 List of Medications Prohibited During the Trial

1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants c) Antidepressants (including MAOIs) d) Mood stabilizers (ie, lithium and/or anticonvulsants) e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy[a] f) Prescription stimulants (including appetite suppressants and treatments for ADHD or narcolepsy) g) 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). h) Nutritional supplements and non-prescription herbal preparations with CNS effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc)
2.	Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage treatment-emergent AEs related to insomnia[b]
3.	Antihistamines (except for loratadine and cetirizine)
4.	Varenicline
5.	Vitamins, other nutritional supplements, and non-prescription herbal preparations, unless approved in advance by the medical monitor
6.	Investigational agents.
7.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. Selected CYP2D6 inhibitors 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.)

[a]Refer to Section 4.1.1 for details on benzodiazepine use during the trial.

[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 8 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to

delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eSource.

4.1.1 Use of Benzodiazepines During the Trial

The use of IM benzodiazepines and continual use of oral benzodiazepines is prohibited during this trial. However, limited use of oral lorazepam as a rescue medication for the short-term management of treatment-emergent AEs (TEAEs) of anxiety, agitation, and insomnia will be allowed both during the washout period between the screening and baseline assessments, and during the treatment phase. Lorazepam equivalents are prohibited unless explicitly authorized by the medical monitor. During the washout period, the prior use of other benzodiazepines must be discontinued in favor of oral lorazepam. During the treatment phase, use of oral lorazepam must follow the daily dose schedule listed in Table 4.1.1-1 for Days 1 through 14. All benzodiazepine use, including lorazepam, is prohibited after Day 14.

In countries where lorazepam is not commercially available, the use of oral oxazepam, alprazolam, diazepam, or clonazepam is only acceptable with prior authorization 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 8 hours prior to any scheduled efficacy or safety scale assessments. Investigators are encouraged to delay scale administration until a full 8 hours have elapsed since the last benzodiazepine dose, if at all possible, including at screening and baseline assessments. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eSource.

Table 4.1.1-1 Oral Benzodiazepine Rescue Therapy During the Trial

Oral Benzodiazepine	Maximum Allowable Dose (mg/day)			
	Days 1-4	Days 5-7	Days 8-10	Days 11-14
Lorazepam[a]	6	4	2	1

[a] In countries or institutions where lorazepam is not commercially available, use of oral lorazepam equivalents, as described in Section 4.1.1and dosed based on the schedule in Table 4.1.1-1 is

acceptable only with prior authorization from the medical monitor. All benzodiazepine use, including lorazepam, is prohibited after Day 14.

4.2 Other Restrictions

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

- Non-steroidal anti-inflammatory drugs, aspirin, or other drugs that interfere with coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of upper gastrointestinal bleeding.[19]
- 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 serotonin-norepinephrine reuptake inhibitors and these drugs.

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 3 times daily (total of 60 mg/day). Sites should only utilize medications that are approved for these indications in their respective countries.

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

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical

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

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

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

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

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

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on the clinical trial pregnancy and breastfeeding form, or other designated form, to the sponsor.

Pregnancy will only be documented on the AE ePlatform if there is an abnormality or complication.

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

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

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

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

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

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded within the eSource platform provided by the sponsor. All AE collection is to begin after a subject has signed the ICF.

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

A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the ePlatform.

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

5.3 Immediately Reportable Events

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

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

5.4 Potential Serious Hepatotoxicity

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

5.5 Pregnancy

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

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had

a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

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

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

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

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

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

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

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

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

5.7 Follow-up of Adverse Events

For this trial, information on AEs will be followed for up to 21 (+2) days after the last dose of IMP has been administered.

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE ePlatform with the current status (ongoing or resolved/recovered) noted. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the ePlatform. For any AE having been identified throughout the trial, during

analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to 21 (+2) days after the last dose of IMP is administered.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE ePlatform and reported to the sponsor 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, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved, stabilized, or the subject is lost to follow-up.

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

6 CCI [redacted]

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CCI [redacted]

7 Statistical Analysis

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

7.1 Sample Size

It is anticipated that approximately 320 subjects will be randomized from an estimated 45 sites in the US and Europe. The primary efficacy endpoint is the change from baseline to Day 21 in the double-blind treatment phase in the YMRS Total Score. The trial will compare the placebo arm to the brexpiprazole arm, randomized at a ratio of 1:1, with an overall significance level of 0.05 (2-sided) for the primary endpoint.

[redacted]

CCI [redacted] The planned sample size of 304 evaluable subjects (152 in each treatment arm) will yield at least 90% power to detect the treatment effects at a 2-tailed significance level of 0.05.

A sufficient number of subjects will be enrolled and randomized to achieve approximately 304 evaluable subjects in the double-blind treatment phase CCI [redacted] the total number of subjects to be randomized is 320 (160 in each treatment arm).

In order to ensure 304 evaluable subjects, CCI [redacted]

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: comprises all subjects who signed an ICF for the trial and enrolled into the trial.

Randomized Sample: comprises all subjects who were randomized in the double-blind treatment phase. Subjects are considered randomized when they are assigned a treatment number by IWRS at the end of screening. A subject receiving IMP outside of the IWRS will not be considered randomized, but safety will be reported.

Safety Sample: comprises those randomized subjects in the double-blind treatment phase who received at least 1 dose of double-blind IMP as indicated on the dosing record. Subjects will be excluded from this population only if there is documented evidence (ie, drug dispensed = drug returned or no IMP dispensed) that the subject did not take IMP. If a subject is dispensed IMP and is lost to follow up, he/she will be considered exposed.

Efficacy Sample: the Full Analysis Set comprises all subjects in the Safety Sample who have a baseline value and at least 1 valid post-randomization efficacy evaluation for YMRS Total Score in the double-blind treatment phase.

7.3 Handling of Missing Data

The YMRS is utilized as the primary efficacy assessment of a subject's level of manic symptoms. The YMRS consists of 11 items: 1) elevated mood, 2) increased motor activity-energy, 3) sexual interest, 4) sleep, 5) irritability, 6) speech (rate and amount), 7) language-thought disorder, 8) content, 9) disruptive-aggressive behavior, 10) appearance, and 11) insight. Seven items are rated on a 0- to 4-scale, while four items (Items 5, 6, 8, and 9) are rated on a 0- to 8-scale with 0, 2, 4, 6, and 8 being the possible scores (twice the weight of the other items). For all items, 0 is the "best" rating and the highest score (4 or 8) is the 'worst' rating. The YMRS Total Score is the sum of ratings for all 11 items; therefore, possible total scores range from 0 to 60. The YMRS Total Score is set to be missing if less than 9 of the 11 items are recorded. If 10 of the 11 items are available and the item missing is from items 5, 6, 8 or 9, then the YMRS Total Score is the sum of scores for items 1 to 4, 7, 10 to 11 plus the mean of the recorded items from 5, 6, 8 and 9 times four. If 10 of the 11 items are available and the item missing is from items 1 to 4, 7, 10 to 11, then the YMRS Total Score is the sum of scores for items 5, 6, 8 and 9 plus the mean of the recorded items from 1 to 4, 7, 10 to 11 times seven. If 9 of the 11 items are available and both missing items are from items 5, 6, 8 and 9, then the YMRS Total Score is set to be missing. If 9 of the 11 items are available and both missing items are from items 1 to 4, 7, 10 to 11, then the Total Score was the sum of scores for items 5, 6, 8 and 9 plus the mean of the recorded items from 1 to 4, 7, 10 to 11 times seven. If 9 of the 11 items are available and one of the missing items is from items 1 to 4, 7, 10 to 11, and one of the missing items is from items 5, 6, 8 and 9, then the YMRS Total Score is the mean of the recorded items from 5, 6, 8 and 9 times

four, plus the mean of the recorded items from 1 to 4, 7, 10 to 11 times seven. All imputed scores are rounded to the first decimal place.

CCI

[redacted]

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary efficacy endpoint is the change from baseline to Day 21 of the double-blind treatment phase in YMRS Total Score. For analysis of the double-blind treatment phase data, baseline is defined as the last available measurement prior to the first dose of double-blind IMP.

The primary analysis will be performed on the Efficacy Sample which includes all randomized subjects who took at least 1 dose of IMP in the double-blind treatment phase and who have both a baseline value and at least 1 post-randomization YMRS Total Score during the double-blind treatment phase. The primary efficacy analysis will be performed by fitting a mixed-effect model repeated measure (MMRM) analysis with an unstructured variance covariance structure in which the change from the baseline in YMRS Total Score during the double-blind treatment phase will be the dependent variable based on the observed cases (OC) data set. CCI

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[redacted]

CCI

[redacted].

7.4.2 Secondary Endpoint Analysis

The key secondary efficacy endpoint is the change from baseline to Day 21 in the double-blind treatment phase in CGI-BP Severity of Illness score in mania. This endpoint will be analyzed by fitting the same MMRM model described in the primary analysis.

CCI

[redacted]

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CCI [redacted]

7.4.3 CCI [redacted]

[redacted]

7.4.4 CCI [redacted]

[redacted]

7.4.5 Interim Analysis

Not applicable.

7.5 Analysis of Demographic and Baseline Characteristics

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

Baseline disease severity and psychiatric history will also be summarized by descriptive statistics for the Safety Sample to identify any potential lack of balance between the treatment groups.

7.6 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (C-SSRS) and CCI [redacted] Safety analysis will be conducted based on the Safety Sample defined in Section 7.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for

clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

7.6.1 Adverse Events

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

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

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

7.6.2 Clinical Laboratory Data

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

7.6.3 Physical Examination and Vital Signs Data

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

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

7.6.4 Electrocardiogram Data

Mean change from baseline will be summarized by treatment group and by visit.

The incidence of clinically relevant changes will be calculated for ECG parameters and summarized by treatment group and by visit.

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

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB=QT/(RR)^{0.5}$, and

2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$

3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Results will be summarized by visit.

7.6.5 CCI [redacted]

[redacted]

Suicidality (eg, C-SSRS) will be summarized by treatment group based on the OC dataset of the Safety Sample. Details will be described in SAP.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC-34712 IB.[7]

8.1 Packaging and Labeling

The IMP will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as blister cards. Each blister card used in the dosing period will be labeled to include a section for the sites to indicate the subject initials and ID, as well as compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

8.2 Storage

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

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

8.3 Accountability

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

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial site(s) (if applicable). The IMP may only be destroyed by the trial site(s), if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be clearly identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction (if applicable) of used IMP containers, unused IMP, and 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 the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to PPD
- Phone - Rocky Mountain Call Center at PPD

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

8.5.3 Return Process

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

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

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

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

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of 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.

Source documents and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected

into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

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

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

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

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

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

9.3 File Management at the Trial Site

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

The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after 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 sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

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

10.2 Auditing

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

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

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling ePlatform, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID code will be used to identify each subject.

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

12 Confidentiality

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

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

13 Amendment Policy

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

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

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

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

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

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

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

No publication will be made without Otsuka authorization.

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Appendix 1

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Appendix 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

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

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

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

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Appendix 3 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

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Appendix 4 Criteria for Identifying Electrocardiogram Measurements of Potential Clinical Relevance

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

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

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

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

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

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Appendix 5 Mini International Neuropsychiatric Interview

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

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Patient Number:	
Time Interview Began:	
Time Interview Ended:	
Total Time:	

	MODULES	TIME FRAME	MEETS CRITERIA	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Past Recurrent	☐ ☐ ☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks) Past Recurrent	☐ ☐ ☐	F32.x F32.x F33.x	☐ ☐ ☐
B	SUICIDALITY	Current (Past Month) Lifetime attempt	☐ ☐	 ☐ Low ☐ Moderate ☐ High	☐ ☐
	SUICIDE BEHAVIOR DISORDER	Current In early remission	☐ ☐	(In Past Year) (1 - 2 Years Ago)	☐ ☐
C	MANIC EPISODE	Current Past	☐ ☐		
	HYPOMANIC EPISODE	Current Past	☐ ☐	 ☐ Not Explored	
	BIPOLAR I DISORDER	Current Past	☐ ☐	F31.0 - F31.76 F31.0 - F31.76	☐ ☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past	☐ ☐	F31.2/31.5/F31.64 F31.2/31.5/F31.64	☐ ☐
	BIPOLAR II DISORDER	Current Past	☐ ☐	F31.81 F31.81	☐ ☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current Past	☐ ☐	F31.89 F31.89	☐ ☐
D	PANIC DISORDER	Current (Past Month) Lifetime	☐ ☐	F41.0 F40.0	☐ ☐
E	AGORAPHOBIA	Current	☐	F40.00	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10/F10.20	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10/F11.20 - F19.20	☐

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K	ANY PSYCHOTIC DISORDER	Current Lifetime	☐ ☐	F20.81-F29 F20.81-F29	☐ ☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current Past	☐ ☐	F32.3/F33.3 F32.3/F33.3	☐ ☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current Past	☐ ☐	F31.2/F31.5/F31.64 F31.2/F31.5/F31.64	☐ ☐
L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?) -

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CCI [redacted]

CCI [redacted]

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Appendix 7 Young-Mania Rating Scale

What is the YMRS?

The YMRS is an 11-item scale which aims to provide a continuous measure rating the intensity of symptoms associated with mania. The YMRS was developed as an instrument to be used by clinicians. Young et al. suggested the ratings should be based on a 15-30 minute clinical interview which takes into consideration the patients' subjective report as well as the raters' observation. Young and his collaborators intended to improve upon previous scales by providing a larger number of items for increased sensitivity and better rater reliability through the use of defined anchor points.

Optimizing the YMRS for Research

To reduce sources of error associated with the YMRS, we would like you to use the attached scripted interview when administering the YMRS.

Conventions for the YMRS

- Use the extremes of the rating scale when the anchor points accurately describe the patient's condition. Zero really means the symptom is absent. The YMRS extremes are not meant to be held in reserve for the worst imaginable case. Rather, they include common manifestations of severe manic states.
- Always score in whole numbers, but note items 5, 6, 8, and 9 not only allow but also encourage scores between the defined anchor points.
- When in doubt between two ratings, assign the higher rating, or, on 0 – 8 scaled items, the middle rating.
- Be sure that you have enough time to conduct the interview properly – you may be able to complete the YMRS in 15 minutes, but interviews with symptomatic patients often require 30-45 minutes.
- Clarify the patient's understanding and usage of terms like "paranoid", "irritable", "hyper", and "sexual interest".

YMRS

DIRECTIONS

For each item below begin inquiry using the script. Ask additional questions if necessary to assign ratings. Rate each item using your judgement in addition to the patient's self report. Also, include any information obtained outside the interview (e.g., reports by family members, etc.).

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (always in whole points) is possible and encouraged after experience with the scale is acquired.

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I will now be asking you questions to rate symptoms you may have had during the past week.

Information given in italics is intended to guide the interviewer in clarifying severity levels for each rating.

1. Elevated Mood

The first item probes for the presence of elevated mood. Using the questions below you will inquire about "high" or elevated mood, euphoria, self-confidence, optimism, and inappropriate humor.

This past (week or seven days) how has your mood been?

Did you feel optimistic about the future? (Was there reason to feel that way?)

Distinguish here between healthy optimism, e.g., a sense that things might be improving, from an overly optimistic viewpoint. For example, a patient who is recovering from a depressive episode and is feeling simply less discouraged, would not be rated as "overly optimistic." Take into account if there is reason for the patient to feel more optimistic.

Did you feel especially self confident (especially good about yourself)?

Rate here a sense of feeling particularly good or self-confident about one's abilities.

Were there any times you felt too good or even a little high? [If yes] Were the good days really too good, or just better than the bad days?

It is helpful here to inquire if others noticed that they were in more than just a good mood. If necessary, clarify the use of the term feeling "high," e.g., feeling on top of the world, feeling so good it is like being on a drug, etc. Remember, you are rating abnormal mood elevation, not simply an improvement from depressed mood.

Were there times when you laughed about things you ordinarily wouldn't find funny? Or did you laugh or joke about things that other people don't find funny (or thought in poor taste)?

You are probing here for an increased or inappropriate sense of humor. You may clarify this item by asking if, in retrospect, they viewed their behavior as inappropriate or if others seemed offended by their humor. Also, use your clinical judgement in rating whether the use of humor was inappropriate (e.g., making sexual jokes or innuendos at work).

0 Absent

A rating of 0 indicates that there has been no observed or reported mood elevation in the past week. The symptom is completely absent.

1 Mildly or possibly increased on questioning

A rating of 1 is typically given if there has been mild or possible mood elevation, e.g., a patient reports feeling slightly more optimistic at one time during the past week.

2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content

A rating of 2 is given if the patient reports feeling clearly more cheerful, self-confident, or optimistic. This should be rated even if there is an appropriate stimulus for feeling this way, e.g., a patient receives positive feedback from his boss and feels higher or more self-confident in response to that feedback.

3 Elevated, inappropriate to content; humorous

A rating of 3 is given if the patient's mood is elevated or high, and is clearly out of proportion with the circumstances. Take into account both the severity and duration of the elevated mood, e.g., in order to rate a 3, patient's mood should be clearly elevated for more days than not.

4 Euphoric; inappropriate laughter; singing

A rating of 4 is given if the patient's mood is euphoric or high nearly every day in the past week. A rating of 4 is given if the patient is so high that he or she is exhibiting laughter or singing during the interview or at inappropriate times during the past week.

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2. Increased Motor Activity/Energy

This item probes for motor excitement, excessive energy, restlessness, and hyperactivity.

What's your energy been like?

Were there times you felt particularly full of energy?

[If yes] Was it hard to calm down?

Take into account both the patient's report and your observation of their restlessness or hyperactivity in the interview. Take into account whether the patient was able to function during the past week (e.g., sitting still when required at work, etc.)

Be sure to distinguish whether or not the patient was able to calm down.

Did you feel physically restless? (have trouble sitting still?) Have you been more active than usually? Did you get a lot more done than usual?

Notes: _____

0 Absent

A rating of 0 indicates that the patient exhibited no motor excitement, excessive energy, restlessness, and hyperactivity during the interview or in the past week.

1 Subjectively increased

A rating of 1 indicates that the patient felt possibly more energetic than usual, with no excessive hyperactivity or physical restlessness.

2 Animated; gestures increased

A rating of 2 is given if the patient appears animated, with increased gestures. Patient may report having felt increased energy on several occasions during the past week.

3 Excessive energy; hyperactive at times; restless (can be calmed)

A rating of 3 is given if the patient has been clearly restless or hyperactive more days than not. A rating of 3 indicates that the patient is able to calm himself down when necessary.

4 Motor excitement; continuous hyperactivity (cannot be calmed)

A rating of 4 is given if the patient has demonstrated hyperactivity, restlessness, or motor activity nearly constantly in the past week. In order to rate a 4 on this item, the patient should appear restless during the interview itself and have difficulty sitting still.

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3. Sexual Interest

Was sex more interesting to you than usual?

Here, you want to probe for increased sexual interest whether or not the patient has access to a sexual partner. For example, if the patient responds to this question by stating that they are not currently involved in a sexual relationship, re-phrase this question as "If you had had the opportunity to be more sexual this past week, do you think that you would have been?" or "Did you find yourself thinking about wanting to be sexual more often this past week?"

Did you do anything sexual that is unusual for you?

Get a sense of any behaviors that were out of character for the patient (e.g., going home with someone they just met; engaging in any out of the ordinary sexual practices).

Were you talking or joking about sex more than you normally do?

Probe here for the use of sexual humor or the discussion of sexual matters during the past week.

Notes: _____

0 Normal, not increased

A rating of 0 is given if the patient denies any increased interest in sex.

1 Mildly or possibly increased

A rating of 1 is given if the patient felt slightly more interested in sex during the past week, with no major change in behavior or practices.

2 Definite subjective increase on questioning

A rating of 2 is given if the patient feels clearly more interested in sex than usual, e.g., engaged in sexual activity with regular partner twice as frequently as usual or clearly thought about sex much more often than usual.

3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report

A rating of 3 is indicated if the patient reports heightened sexual interest, with some change in behavior that is out of the ordinary (e.g., talking, joking about sex in inappropriate situations; engaging in uncharacteristic sexual practices; actively seeking out sexual partners; spontaneously mentioning sexual behavior during the interview).

4 Overt sexual acts (toward patients, staff, or interviewer)

A rating of 4 is indicated if the patient makes sexual gestures toward the interviewer or staff. A rating of 4 is also indicated if the patient's behavior outside of the interview appears clearly out of control (risky sexual indiscretions; overt sexual advances toward strangers; other extremely inappropriate behaviors, etc.).

4. Sleep

How many hours of sleep are you getting?

Obtain an estimate of the number of hours of sleep obtained per night during the past week. Also, inquire about the amount of sleep that is typical for the patient. This can be tricky, particularly if the patient spends little time euthymic and often fluctuates between episodes of depression and increased sleep and (hypo)mania and decreased sleep. Do your best to obtain the amount that is most typical, and compare the current sleeping patterns to that amount..

Did you need less sleep than usual (and still feel rested)?

The key here is to probe for a decreased need for sleep, with a sense of still feeling rested.

Notes:_____

0 Reports no decrease in sleep

Self- explanatory. A rating of 0 is assigned if patient's sleep is normal or increased.

1 Sleeping less than normal amount by up to one hour

A rating of 1 is assigned if sleep is decreased by one hour or less. If your rating is between a 1 or a 2, round up to a 2.

2 Sleeping less than normal by more than one hour

A rating of 2 is assigned if sleep is decreased by greater than one hour.

3 Reports decreased need for sleep

Assign a 3 if patient reports sleeping less by more than one hour without feeling tired.

4 Denies need for sleep

A rating of 4 is warranted if the patient reports no need for sleep.

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5. Irritability

This item probes for increased irritability, anger, and annoyance. Take into consideration both the degree and persistence of reported irritability in the past week, as well as the patient's behavior in the interview.

Were you annoyed about things that happened or how people treated you?

Did you notice these things bothered you more than they usually do?

Rate degree of annoyance even in response to justifiable stressor (e.g., being caught in a traffic jam, being made to wait in line).

Were you often irritable?

Get a sense of the frequency of irritable or angry behavior.

How did you show your anger?

Inquire about the patient's response to situations in which they felt irritated, e.g., shouting, arguments, etc.

Notes: _____

0 Absent

Assign a rating of 0 if the patient denies any increased irritability in the past week and if there is no evidence of irritability in the interview.

1

2 Subjectively increased

A rating of 2 is warranted if the patient reports increased irritability during the past week, with no serious displays of anger by the patient (e.g., patient reports feeling more irritated or frustrated by traffic jams than usual, patient feels more snappy or less polite, with no overt anger expressed to others).

3

4 Irritable at times during interview; recent episodes of anger or annoyance on ward

A rating of 4 is given if the patient either exhibits irritability during the interview or if the patient (or others) report that the patient has expressed anger towards others due to irritability (e.g., shouting at others in traffic; yelling at store clerk).

5

6 Frequently irritable during interview; short, curt throughout

A rating of 6 is given if the patient is clearly irritable during most of the interview; a rating of 6 would also be given if the patient has been irritable nearly every day in the past week and has exhibited frequent displays of anger towards others.

7

8 Hostile, uncooperative; interview impossible

A rating of 8 is assigned if the patient is extremely irritable or hostile during the interview, making completion of the interview impossible; patient is incapable of interactions with others.

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6. Speech (Rate and Amount)

Have you been more talkative than usual?

Get a sense here if the patient feels more likely to speak with others, e.g., have they been more likely to strike up conversations or to make phone calls.

Did anyone complain that they couldn't get a word in?

Probe to see if others commented on patient's increased talking, e.g., others had difficulty contributing to the conversation.

Did you find it hard to stop talking once you got started?

Did the patient have a sense of difficulty controlling the rate or amount of speech?

Were there times you spoke so fast people had trouble understanding you?

Did others comment that the patient's speech was jumbled or difficult to follow?

Notes: _____

0 No increase

A rating of 0 is given if no increased speech is reported or observed in the interview.

1

2 Feels talkative

A rating of 2 is assigned if patient feels more likely to speak with others, e.g., starts conversations with others; makes more phone calls than usual. However, a rating of 2 indicates that there are no aberrant processes in speech patterns, e.g. patient is clearly understood; others are able to contribute to the conversation.

3

4 Increased rate or amount at times, verbose at times

A rating of 4 indicates that the patient is clearly speaking at an increased rate and amount. Take your observation into account, as well as the patient's self-report.

5

6 Push; consistently increased rate and amount; difficult to interrupt

A rating of 6 is warranted if the patient feels a pressure to keep talking, e.g. others have difficulty getting a word in edgewise. Patient must make an effort to stop self from talking.

7

8 Pressured; uninterruptible continuous speech

A rating of 8 is indicated if patient's speech is pressured and impossible to interrupt. Patient is not able to control or slow down speech.

7. Language – Thought Disorder

This item probes for a range of difficulties with language and thought processes, ranging from mild distractibility to racing thoughts, flight of ideas, and incoherent communication.

Have you had more ideas than usual or any particularly good ideas?

Get a sense here if patient has been thinking more about special ideas or has had an increased number of ideas.

Was your thinking especially keen or clear over the past week?

Did you often get distracted?

Get a sense of the intensity and frequency of distraction, e.g., was the patient able to focus and concentrate on reading or work activities; was the patient able to stay on track in conversations?

Has your mind seemed to be going very fast?

Probe here for the presence of racing thoughts, e.g., a sense that one's thoughts are going so quickly that they are too difficult to hold onto.

Did you sometimes have so many ideas that you lost track of what you were saying?

Be sure to use your observation and clinical judgement here, e.g., is the patient able to stay on track to express a coherent message? Also note any abnormal speech processes, such as rhyming or repeating nonsensical phrases.

Were you getting lost in details?

Notes: _____

0 Absent

A rating of 0 is assigned if neither observation nor self-report indicates any difficulty with language or thought processes.

1 Circumstantial; mild distractibility; quick thoughts

A rating of 1 is assigned if patient reports slight distractibility or mild increase in flow of thoughts. A rating of 1 should also be assigned if patient exhibits circumstantiality in the interview.

2 Distractible; loses goal of thought; changes topics frequently; racing thoughts

A rating of 2 is assigned if patient endorses a sense that thoughts are racing. Patient is clearly distracted and expresses some difficulty in maintaining focus or concentration.

3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia

A rating of 3 should be assigned if patient exhibits any of the following: a sense that ideas are jumping from one topic to another, making conversation difficult to follow; an observation of aberrant speech processes such as nonsensical rhyming or repeating words.

4 Incoherent; communication impossible

A rating of 4 is reserved for patients whose racing thoughts, distractibility, or flight of ideas is so severe that communication is impossible.

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8. Content

This item probes for a wide range of symptoms related to mania: starting "special" plans or projects, seeing special meanings or understanding things more deeply; more involvement in religion or religious insights; a sense of grandiosity or the capacity for special powers or abilities; a sense of paranoia, and the presence of hallucinations or delusions.

Did you make any new plans or get new projects started?

Evaluate the nature of the patient's new plans or projects, e.g., is this something the patient has been planning for a long time (returning to school) or is it something more spontaneous or potentially risky?

Did you accomplish anything special? Were you more capable than usual?

Probe here for a sense of grandiosity.

Did you find you could understand things more deeply than usual?

Probe here for a sense of seeing special significance or deeper meaning than usual.

Did you have any religious insight?

In addition to religious insights, probe for increased religious participation.

Did you find you were more aware of coincidences?

Did you find special significance in things that happened or the way things were arranged around you?

Did you notice things that other people missed, or have the sense that people were talking about you, or even trying to hurt you?

Probe here for paranoia.

Did you have any thoughts that didn't make sense to other people?

Did you have any hallucinations?

It is important to clarify use of the term hallucinations, e.g. did you see things that others couldn't see or did you hear things that others couldn't hear?

0 Normal

A rating of 0 indicates that the patient has exhibited none of the symptoms counting towards this item.

1

2 Questionable plans, new interests

A rating of 2 indicates that the patient has engaged in some new plans or interests of a possibly questionable nature, e.g., planned a spontaneous vacation (within budget), scheduled more social plans than usual; shopped more than usual without spending extravagantly. You must take into account the patient's typical budget and financial situation when judging monetary decisions. Impulsive purchases clearly out of line with patient's budget should be rated a 3 or higher depending on level of excessiveness.

3

4 Special project(s); hyperreligious

A rating of 4 indicates that the patient has taken on new projects or plans of a clearly questionable nature, e.g., spending impulsively and out of budget, impulsively building an addition to one's home without prior planning, etc. A rating of 4 would also be warranted for a sudden increase in religious participation, e.g., an individual who usually attends church on a weekly basis has attended every day in the past week and not due to some external stressor or crisis, i.e., a mother who attends church on a daily basis to pray for her child who has recently been hospitalized would not qualify as "hyper-religious".

5

6 Grandiose or paranoid ideas; ideas of reference

A rating of 6 is warranted if the patient describes having special powers or abilities, e.g., being able to predict the future or being the "best in the world" at a particular talent or ability. An example might be the student who believes that the insights in his term paper will radically alter his professor's life. A rating of 6 might also be given if a patient reports finding special meaning or significance in everyday situations (e.g., seeing a particular sign on the street and "knowing" that it is pointing him towards a new career. If the patient exhibits clearly paranoid thinking, a rating of 6 is also justified. Be sure to clarify the patient's use of the term paranoid, e.g., use your judgment to ascertain evidence of true vs. imagined negative intentions of others.

7

8 Delusions; hallucinations

A rating of 8 is warranted for clearly psychotic sx, e.g., hallucinations or delusions.

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9. Disruptive – Aggressive Behavior

In this item, you will probe for information related to the patient's ability to get along with others, e.g., argument; demanding or destructive behaviors.

How have you gotten along with other people? (Have you been cooperative?)

Were there times when you were loud, demanding, or sarcastic?

Have you had any confrontations with people? (What happened?)

Did you find yourself shouting, throwing things, or doing anything destructive?

Notes: _____

0 Absent, cooperative
A rating of 0 indicates that the patient was fully cooperative in the interview and reported no incidents of disruptive or aggressive behavior in the past week.

1

2 Sarcastic; loud at times, guarded
A rating of 2 indicates that the patient is either guarded or somewhat uncooperative during the interview; or the patient reports one or two incidents of sarcastic, loud, or uncooperative behavior during the past week. A rating higher than 2 would be given if patient exhibited this behavior frequently during the past week or if the incidents resulted in shouting or destructive behavior.

3

4 Demanding, threats on ward
A rating of 4 is given if patient has been demanding or threatening several times in the past week, e.g., patient reports several incidents during the past week in which he lost his temper and shouted at store clerks, family members, etc.

5

6 Threatens interviewer; shouting; interview difficult
A rating of 6 is given if the interview is difficult to complete due to the patient's threats or confrontational behavior.

7

8 Assaultive; destructive; interview impossible
A rating of 8 is given if the patient's behavior has been assaultive in the past week. A rating of 8 would also be given if the interview cannot be completed due to the patient's aggressive behavior.

Protocol 331-201-00080

10. Appearance

This item probes for abnormal appearance and grooming. Patients who are manic may neglect their grooming, or alternatively may dress in a flashy, overly fancy, immodest, or bizarre fashion.

How well did you keep up your appearance and grooming?

Was it hard to do?

Were there occasions when people thought you were over-dressed or under-dressed?

Did you choose to wear different colors than usual this past week?

What about wearing more jewelry or make-up than usual?

Were there times you neglected your grooming?

Notes: _____

0 Appropriate dress and grooming

A rating of 0 is given if the patient is groomed and dressed appropriately.

1 Minimally unkempt

A rating of 1 is given if the patient is slightly unkempt (e.g., messy hair, unshaven, clothing slightly wrinkled, etc.).

2 Poorly groomed; moderately disheveled; overdressed

A rating of 2 is given if the patient is poorly groomed by most people's standards (e.g., unwashed hair) or is overdressed for the situation (e.g., wearing a fancy dress or excessive jewelry for a casual work setting).

3 Disheveled; partly clothed; garish make-up

A rating of 3 is given if the patient is clearly disheveled (clothing is dirty; smells of body odor) or if patient is dressed in an extremely skimpy or inappropriate way (e.g., wearing a revealing cocktail dress to an afternoon appointment). A rating of 3 is also assigned if the patient is wearing makeup that most people would consider garish or overdone.

4 Completely unkempt; decorated; bizarre garb.

A rating of 4 is given if the patient is completely unkempt (clothing is torn, patient has not bathed in a week, etc.) or the patient is adorned in extremely unusual attire or costume.

Protocol 331-201-00080

11. Insight

This item inquires about the patient's explanation for their behavior and insight.

As you look back on the past week, were there things you did that stand out as unusual behavior for you? [If yes] Was that because your mood was high?

How do you understand: _____?

(example patient's possible behavioral symptoms)

Notes: _____

0 Present; admits illness; agrees with need for treatment

A rating of 0 is assigned (no matter how severely manic the patient) if he/she attributes the symptoms to bipolar disorder or manic-depression and agrees with the need for treatment.

1 Possibly ill

A rating of 1 is assigned if the patient is possibly attributing the symptoms to bipolar disorder, but is not entirely convinced of the diagnosis.

2 Admits behavior change, but denies illness

A rating of 2 is assigned if the patient acknowledges symptoms or changes in behavior (e.g., risky behaviors, sleep changes, etc.) but refuses to attribute the symptoms to a diagnosis of bipolar disorder.

3 Admits possible change in behavior, but denies illness

A rating of 3 is given if the patient acknowledges possible symptoms, but is somewhat ambivalent in admitting such changes in behavior, and clearly denies having a mood disorder.

4 Denies any behavior change

Self-explanatory. Patient denies symptoms and behavior changes.

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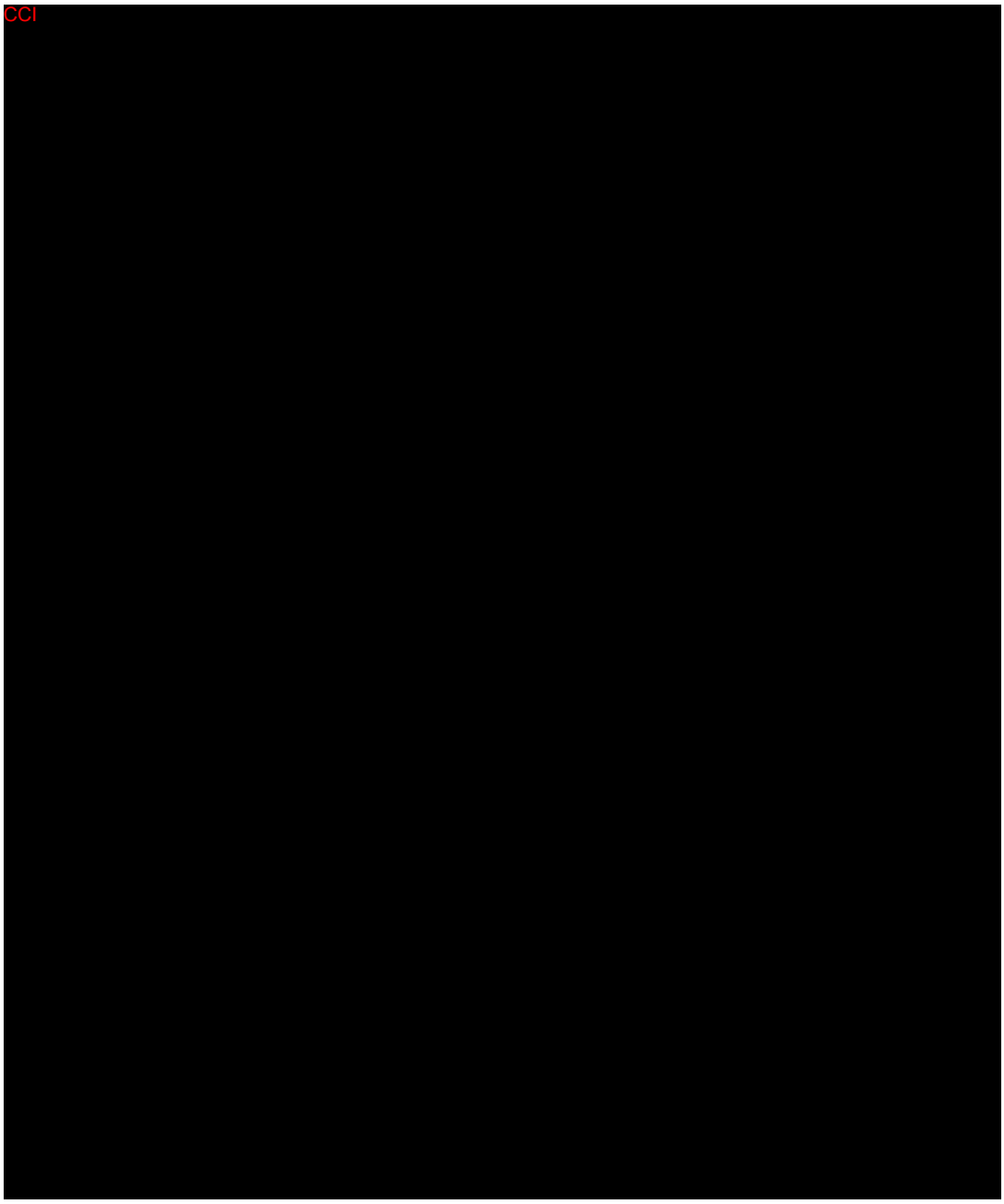

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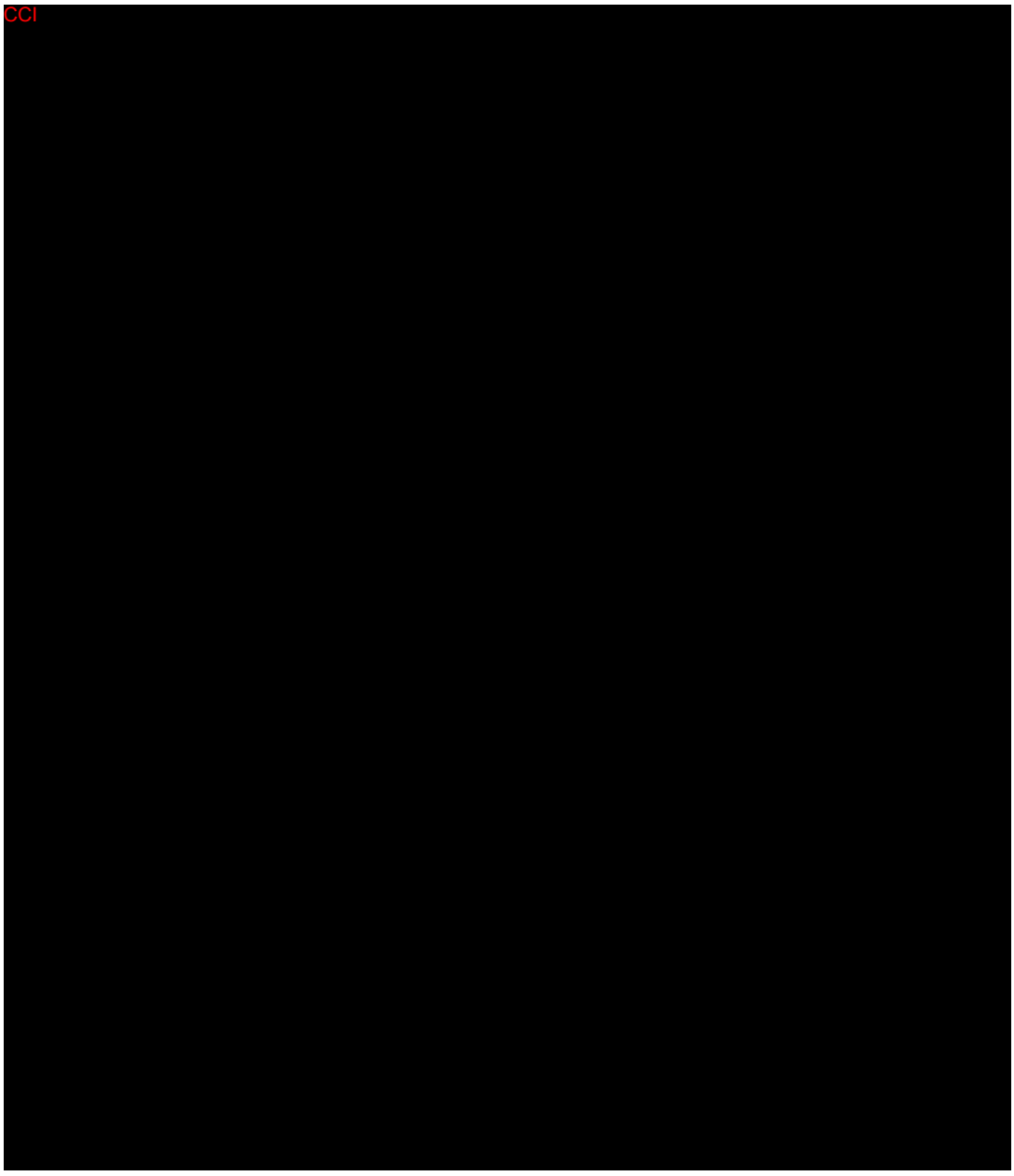

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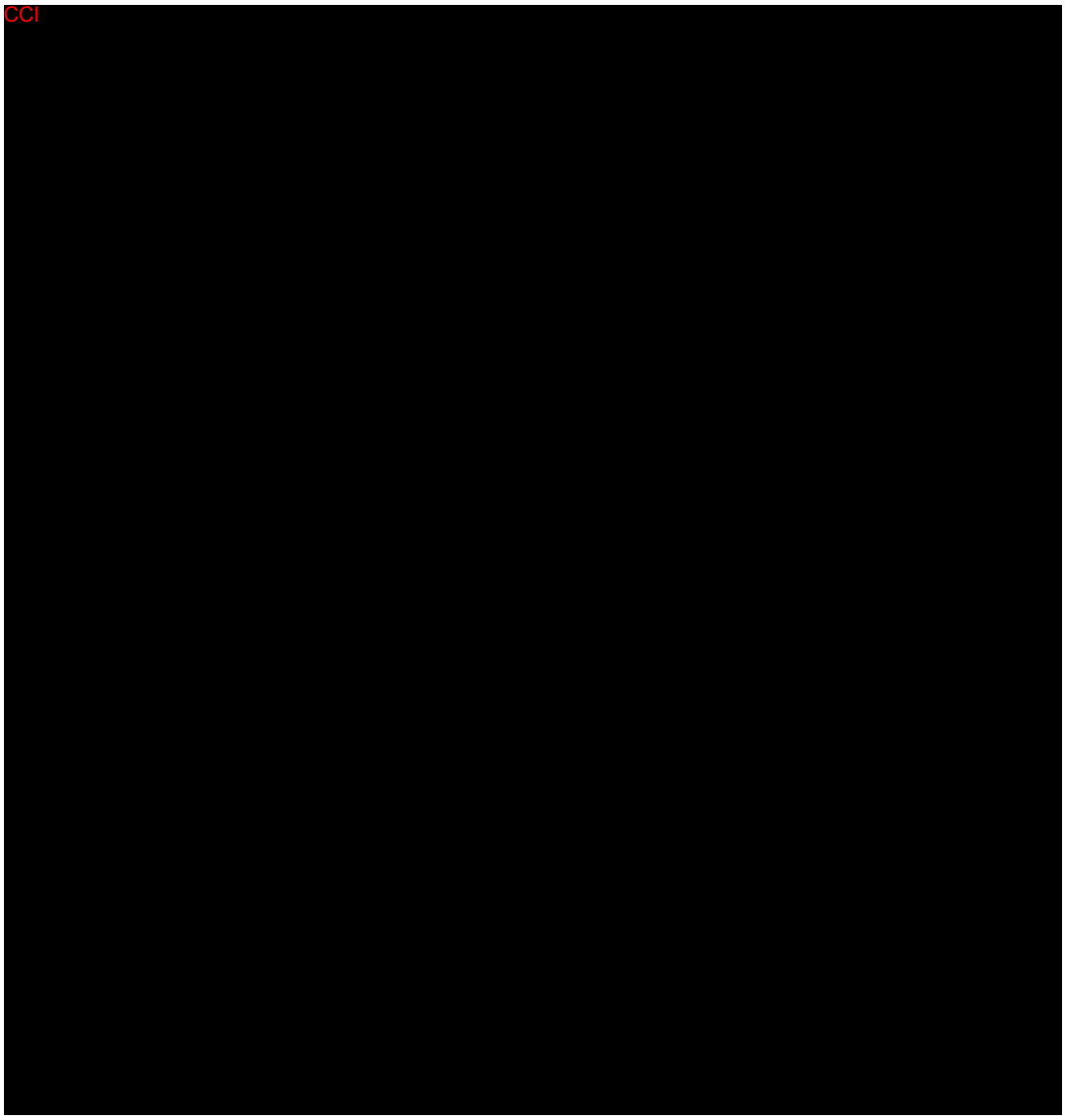

Appendix 9 Clinical Global Impression - Bipolar Version

SEVERITY of Illness

Considering your total clinical experience with bipolar patients, how severely ill has the patient been during the assessment period (the past seven days)?

a. Mania:

- ☐ 1 = Normal, not ill (no symptoms, not at all ill)
- ☐ 2 = Minimally ill (minimal symptoms, continued effective functioning)
- ☐ 3 = Mildly ill (low level symptoms, subjective distress, little to no functional impairment)
- ☐ 4 = Moderately ill (some prominent symptoms, moderate functional impairment)
- ☐ 5 = Markedly ill (significant symptoms, very substantial functional impairment)
- ☐ 6 = Severely ill (very notable symptoms, unable to function in most areas)
- ☐ 7 = Very severely ill (extreme symptoms, completely incapacitated, requiring extra care)

b. Depression:

- ☐ 1 = Normal, not ill (no symptoms, not at all ill)
- ☐ 2 = Minimally ill (minimal symptoms, continued effective functioning)
- ☐ 3 = Mildly ill (low level symptoms, subjective distress, little to no functional impairment)
- ☐ 4 = Moderately ill (some prominent symptoms, moderate functional impairment)
- ☐ 5 = Markedly ill (significant symptoms, very substantial functional impairment)
- ☐ 6 = Severely ill (very notable symptoms, unable to function in most areas)
- ☐ 7 = Very severely ill (extreme symptoms, completely incapacitated, requiring extra care)

c. Overall Bipolar Illness:

- ☐ 1 = Normal, not ill (no symptoms, not at all ill)
- ☐ 2 = Minimally ill (minimal symptoms, continued effective functioning)
- ☐ 3 = Mildly ill (low level symptoms, subjective distress, little to no functional impairment)
- ☐ 4 = Moderately ill (some prominent symptoms, moderate functional impairment)
- ☐ 5 = Markedly ill (significant symptoms, very substantial functional impairment)
- ☐ 6 = Severely ill (very notable symptoms, unable to function in most areas)
- ☐ 7 = Very severely ill (extreme symptoms, completely incapacitated, requiring extra care)

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Change from BASELINE Visit

Compared to the Baseline Visit, how much has the patient changed?

a. Mania:

- ☐ 1 = Very much improved (all better or nearly all better; very good level of functioning; minimal residual symptoms; represents a very substantial change)
- ☐ 2 = Much improved (notably better with significant reduction of symptoms; increase in the level of functioning, but some symptoms remain)
- ☐ 3 = Minimally improved (slightly better with little or no clinically meaningful reduction of symptoms; represents very little change in basic clinical status, level of care, or functional capacity)
- ☐ 4 = No change (symptoms remain essentially unchanged)
- ☐ 5 = Minimally worse (slightly worse but not clinically meaningful and represents very little change in basic clinical status or functional capacity)
- ☐ 6 = Much worse (notably worse with significant increase in symptoms and loss of functioning in several areas of usual social or occupational roles)
- ☐ 7 = Very much worse (distinctly worse with severe exacerbation of symptoms and loss of functioning)
- ☐ 8 = Not applicable (a particular mood state, i.e. mania or depression, cannot be rated at this time because it has not occurred during this rating period)

b. Depression:

- ☐ 1 = Very much improved (all better or nearly all better; very good level of functioning; minimal residual symptoms; represents a very substantial change)
- ☐ 2 = Much improved (notably better with significant reduction of symptoms; increase in the level of functioning, but some symptoms remain)
- ☐ 3 = Minimally improved (slightly better with little or no clinically meaningful reduction of symptoms; represents very little change in basic clinical status, level of care, or functional capacity)
- ☐ 4 = No change (symptoms remain essentially unchanged)
- ☐ 5 = Minimally worse (slightly worse but not clinically meaningful and represents very little change in basic clinical status or functional capacity)
- ☐ 6 = Much worse (notably worse with significant increase in symptoms and loss of functioning in several areas of usual social or occupational roles)
- ☐ 7 = Very much worse (distinctly worse with severe exacerbation of symptoms and loss of functioning)
- ☐ 8 = Not applicable (a particular mood state, i.e. mania or depression, cannot be rated at this time because it has not occurred during this rating period)

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c. Overall Bipolar Illness:

- ☐ 1 = Very much improved (all better or nearly all better; very good level of functioning; minimal residual symptoms; represents a very substantial change)
- ☐ 2 = Much improved (notably better with significant reduction of symptoms; increase in the level of functioning, but some symptoms remain)
- ☐ 3 = Minimally improved (slightly better with little or no clinically meaningful reduction of symptoms; represents very little change in basic clinical status, level of care, or functional capacity)
- ☐ 4 = No change (symptoms remain essentially unchanged)
- ☐ 5 = Minimally worse (slightly worse but not clinically meaningful and represents very little change in basic clinical status or functional capacity)
- ☐ 6 = Much worse (notably worse with significant increase in symptoms and loss of functioning in several areas of usual social or occupational roles)
- ☐ 7 = Very much worse (distinctly worse with severe exacerbation of symptoms and loss of functioning)
- ☐ 8 = Not applicable (a particular mood state, i.e. mania or depression, cannot be rated at this time because it has not occurred during this rating period)

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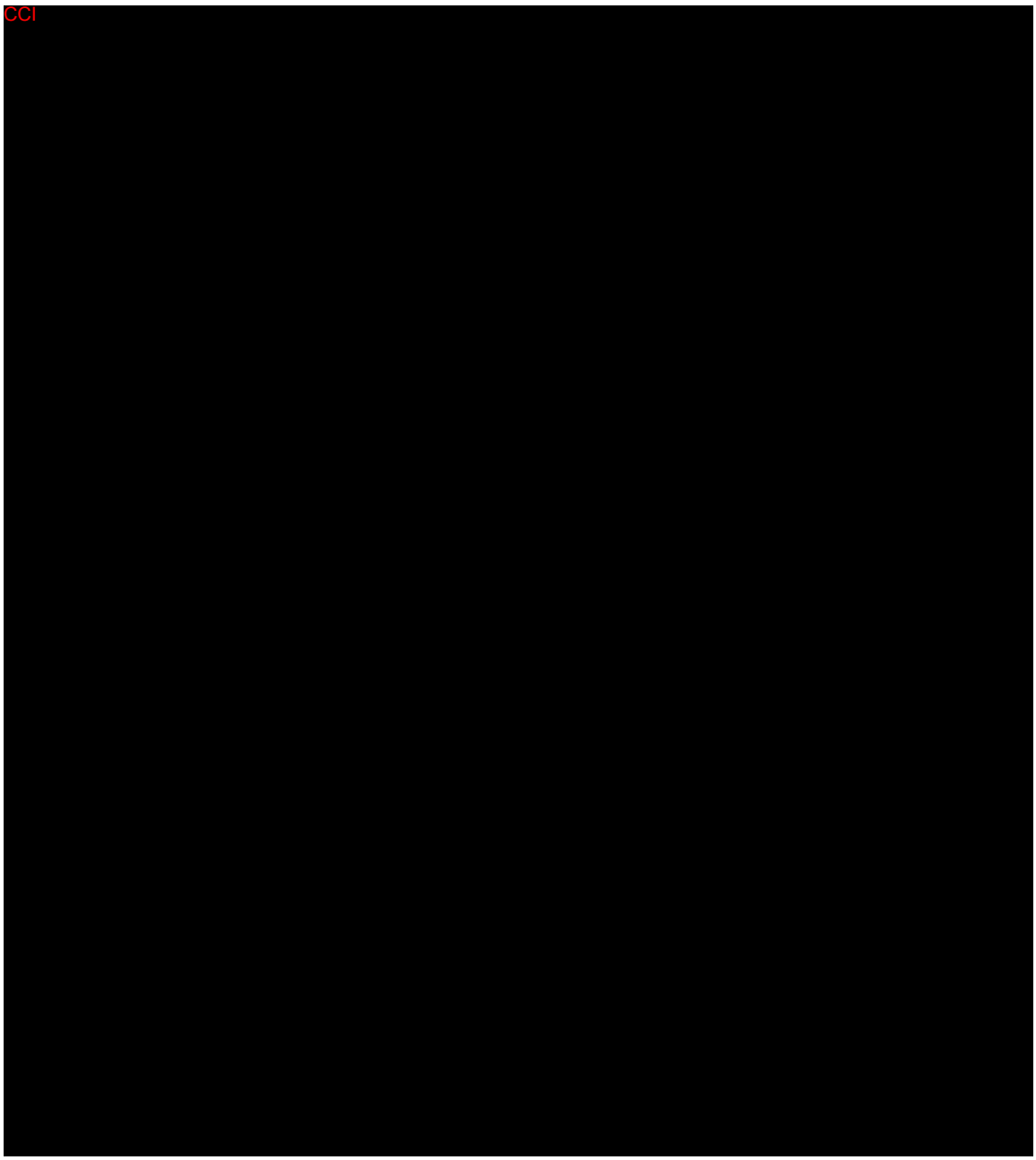

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Appendix 13 Baseline Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

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 PPD *New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

Protocol 331-201-00080

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.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Month(s)**
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 ☐	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 ☐	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 ☐	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 ☐	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 ☐	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). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation* Past 6 Month - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation*	Most Severe	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	___	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 24 Month(s)
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 ☐	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 _____	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 _____	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 ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First 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* _____	*Enter Code* _____	*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* _____	*Enter Code* _____	*Enter Code* _____

Protocol 331-201-00080

Appendix 14 Since Last Visit Columbia Suicide-Severity Rating Scale

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.

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For reprints of the C-SSRS contact PPD *, New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact* PPD

Protocol 331-201-00080

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	____

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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:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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 ☐
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* _____

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Appendix 15 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 21 Dec 2017

PURPOSE:

The purpose of amending the Protocol 331-201-00080, issued 24 May 2017, was to:

- Update the document with minor wording revisions for grammatical and administrative clarification
- Remove an incorrect exclusion criteria in Section 3.1
- Add clarifying details on administration of the Clinical Global Impressions – Bipolar Scale assessment
- Add information on retesting subjects with elevated lithium, valproate, or carbamazepine at screening
- Add information on use of anticholinergics
- Update the efficacy scales in the appendices to match the licensed versions currently available

BACKGROUND:

The rationale for the changes in this protocol amendment is as follows:

- The exclusion criteria of ≥ 30% decrease in YMRS between screening and baseline was removed from Section 3.1 because the criteria was inadvertently left in the document from earlier drafts of the protocol. This criteria was removed in all other sections of the protocol and this removal is an administrative change only.
- Instructions were added to clarify how the 2 different parts of the alternate version of the CGI-BP should be administered. Specifically, there is no change to the way the Severity of Illness portion of the CGI-BP is administered. The CGI-BP Change from Baseline portion of the scale uses the baseline visit as the frame of reference. At each visit subsequent to baseline visit, the subject is scored based on change from the baseline visit. In the previous version of the scale, the reference point was "preceding phase" and this caused some confusion among raters. As a result, the version of the CGI-BP that uses “change from baseline” was used to avoid any confusion about the point of reference will be used
- The use of anticholinergics was intended from the beginning of study, as this is consistent with current clinical practice, but was omitted by accident in original version of the protocol. This change is not based on any new findings from the ongoing studies.

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- The efficacy scales in the appendices were updated to match the licensed versions currently available. No changes to the scale grading system or scoring were made, and the correct versions of the scales have been used since the initiation of the trial

MODIFICATIONS TO PROTOCOL:

General Revisions:

All changes by section are provided below.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder	A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment **of** Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder
Title Page	Issue Date: 24 May 2017 Version No.: 1.0	Issue Date**s**: **Original Protocol:** 24 May 2017 **Date of Amendment 1: 21 Dec 2017** Version No.: **2.0**
CCI [redacted]	[redacted]	[redacted]
Section 3.1, Type/Design of Trial	*Screening Phase*: An interactive web response system (IWRS) will be used to obtain an identification (ID) number for each subject with documented consent.	*Screening Phase*: An interactive web response system (IWRS) **or equivalent** will be used to obtain an identification (ID) number for each subject with documented consent.

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Location	Old Text	Updated Text
Section 3.1, Type/Design of Trial	*Treatment Phase:* Following the screening period, subjects who meet all inclusion criteria, including a score of ≥ 24 on the Young-Mania Rating Scale (YMRS)[8] at screening and baseline, and meet none of the exclusion criteria, including ≥ 30% decrease in YMRS between screening and baseline, will be randomized in a 1:1 ratio to receive either placebo or brexpiprazole for 3 weeks.	*Treatment Phase:* Following the screening period, subjects who meet all inclusion criteria, including a score of ≥ 24 on the Young-Mania Rating Scale (YMRS)[8] at screening and baseline, and meet none of the exclusion criteria, will be randomized in a 1:1 ratio to receive either placebo or brexpiprazole for 3 weeks.
Section 3.1, Type/Design of Trial	*Follow-up Phase:* If any subject discontinues the trial early, every effort should be made to complete the Day 21/ET assessments as soon as possible and prior to starting any new medication or treatment. Subjects who complete all trial visits through the Day 21 visit may be offered entry into an optional open-label rollover trial. Subjects who do not enter the open-label trial will be followed up for safety reasons via telephone contact or in clinic visit 21 (± 2) days after the last dose of IMP. This contact also applies to subjects who are withdrawn prematurely from the trial.	*Follow-up Phase:* If any subject discontinues the trial early, every effort should be made to complete the Day 21/ET assessments as soon as possible and prior to starting any new medication or treatment. Subjects who complete all trial visits through the Day 21 visit **and had no major protocol violations** may be offered entry into an optional open-label rollover trial. Subjects who do not enter the open-label trial will be followed up for safety reasons via telephone contact or in clinic visit 21 (± 2) days after the last dose of IMP. This contact also applies to subjects who are withdrawn prematurely from the trial.
Section 3.4.1, Informed Consent	Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.	Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied. **In the event electronic ICFs are not allowed per local or country regulations, a paper consent will be utilized.**
Table 3.4.3-1, Exclusion Criteria 12	Subjects with serum concentrations of lithium ≥ 0.6 mmol/L, serum concentrations of valproate ≥ 50 µg/mL, or serum concentrations of carbamazepine ≥ 4 µg/mL (may be reassessed at randomization, if necessary).	Subjects with serum concentrations of lithium ≥ 0.6 mmol/L, serum concentrations of valproate ≥ 50 µg/mL, or serum concentrations of carbamazepine ≥ 4 µg/mL (**if any of these parameters are outside of the listed exclusionary range, they** may be reassessed **prior to** randomization, if necessary).

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Location	Old Text	Updated Text
CCI [redacted]	[redacted]	[redacted]
Table 3.7-1	Changes to Table 3.7-1 are summarized on the next page and are indicated by **bold, underlined text**.	

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Table 10.2-1 Schedule of Assessments

	Screening[a]	Double-blind Treatment Phase					Follow-up[c]
	Day -14 to -1	Baseline (Day 1)	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21/ET[b] (± 2 days)	21 (± 2) days after last dose
Screening Assessments and Randomization							
Informed Consent[d]	X						
Demographics	X						
Medical History	X						
Psychiatric History	X						
MINI	X						
Concomitant Medications[e]	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Efficacy Assessments							
YMRS[f]	X	X	X	X	X	X	
CGI-BP[g]		X	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]			[redacted]	[redacted]	
[redacted]		[redacted]				[redacted]	
Safety Assessments							
Physical Examination[h]	X					X	
Vital Signs[i]	X	X	X	X	X	X	
Body Weight	X					X	
12-lead ECG[j]	X	X				X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis), including prolactin[k]	X					X	
HbA1c[i]	X					X	

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Table 10.2-1 Schedule of Assessments							
	Screening[a]	Double-blind Treatment Phase					Follow-up[c]
	Day -14 to -1	Baseline (Day 1)	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 21/ET[b] (± 2 days)	21 (± 2) days after last dose
TSH, with reflex to T4 if TSH is abnormal	X					X	
Coagulation parameters (PT, aPTT, INR)[k]	X					X	
Lithium, Valproate, Carbamazepine Levels[l]	X						
HIV, HBsAg, and anti-HCV	X						
Pregnancy Test[m]	X		X			X	
Drug Screen[n]	X					X	
Blood Alcohol Test[n]	X					X	
C-SSRS[o]	X	X	X	X	X	X	
CCI							
AEs[p]	X	X	X	X	X	X	X
CCI							
Other							
IMP dispensing[r]		X	X	X	X		
IMP accountability			X	X	X	X	

aPTT = activated partial thromboplastin time; HBsAg = Hepatitis B surface antigen; Anti-HCV = Antibodies to hepatitis C virus; INR = International Normalized Ratio; T_4 = free thyroxine; TSH = thyroid-stimulating hormone.

[a]Screening begins when the ICF is signed and will take place between Day −14 and Day −1; however, screening procedures should be initiated with a sufficient amount of time allotted in order to obtain laboratory results and ECG results from the central reader prior to randomization. Review of inclusion/exclusion criteria at baseline will be based on assessments performed during screening. Hospitalization will begin with the signing of the ICF for subjects who are not already hospitalized at the initial screening visit. **Note: In the rare circumstance when a subject must leave the inpatient facility temporarily (eg, family emergency or doctor visit), a temporary day pass may be granted. For such a request, sites must first contact the medical monitor for explicit authorization and guidance on procedures. A medical monitor approved day pass is good for the day requested only, and subjects must return to the site the same day (eg, in the evening).**

[b]If a subject discontinues prematurely before Day 21, procedures noted for Day 21 must be completed at the ET visit.

[c]Consists of telephone contact or clinic visit (investigator's discretion) for evaluation of safety 21 days after the last dose of IMP and applies only to subjects who do not enter the optional open-label rollover trial.

CCI [redacted]

[e]All medications taken within 30 days of screening will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications.

[f]To be eligible for the trial, subjects must have a YMRS score ≥ 24 at screening and baseline.

CCI [redacted]

[h]To include measurement of height at screening only and waist circumference at screening and Day 21.

[i]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 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.

[j]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. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Subjects will be randomized based on screening ECG results from the central reader and baseline ECG results from the trial site. If the baseline ECG results from the central reader, when available, indicate a QT interval corrected for heart rate by Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing, at 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.

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[k] Subjects must be fasting for a minimum of 8 hours prior to blood draws for screening laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. Clinical laboratory tests must be drawn after a minimum 8-hour fast at Day 21/ET. Vital sign and ECG assessments should be completed before any blood samples are collected.

[l] **If lithium, valproate, or carbamazepine levels are outside of the listed exclusionary range, they may be reassessed prior to randomization.**

[m] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at screening must not be enrolled. Subjects with positive urine and serum pregnancy test results 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] 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] The "Baseline/Screening" C-SSRS form will be completed for all subjects at screening to determine elgibility and the "Since Last Visit" C-SSRS form will be completed at the baseline visit to assure that the subject continued to qualify for the trial. Any subject with suicidal ideation within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Table 3.4.3-1). The "Since Last Visit" C-SSRS form will be completed at all visits after the baseline visit.

[p] Adverse events will be recorded starting after the subject signs the ICF.

CCI [redacted]

[r] Site staff will provide IMP to hospitalized subjects daily from assigned blister cards. If a subject is discharged at Day 14, the site should counsel the subject on the importance of taking IMP as directed.

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Section 3.7.1.1, Screening (Day -14 to -1)	After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing the IWRS.	After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing the IWRS **or equivalent**.
Section 3.7.1.1, Screening (Day -14 to -1)	• Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T4] if the result for TSH is abnormal, and lithium valproate and carbamazepine levels) should be drawn after a minimum 8-hour fast at screening. See Table 3.4.4-1 for exclusions based on outcome of screening clinical laboratory tests. Note: if lithium, valproate, or carbamazepine levels are outside of the listed exclusionary range, they may be reassessed prior to randomization.	• Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and thyroid-stimulating hormone [TSH] with reflex to free thyroxine [T4] if the result for TSH is abnormal, and lithium**,** valproate**,** and carbamazepine levels) should be drawn after a minimum 8-hour fast at screening. See Table 3.4.4-1 for exclusions based on outcome of screening clinical laboratory tests. **Note: if lithium, valproate, or carbamazepine levels are outside of the listed exclusionary range, they may be reassessed prior to randomization.**
Section 3.7.1.4, Treatment Phase - Day 4	The following procedures will be performed on Day 4:	The following procedures will be performed on Day 4 **(± 1 day)**:
Section 3.7.1.5, Treatment Phase - Day 7	The following procedures will be performed on Day 7:	The following procedures will be performed on Day 7 **(± 1 day)**:
Section 3.7.1.6, Treatment Phase - Day 14	The following procedures will be performed on Day 14:	The following procedures will be performed on Day 14 **(± 1 day)**:
Section 3.7.1.7, End of Treatment Phase - Day 21/Early Termination Visit	Not applicable (newly added text)	**All subjects will undergo a complete evaluation at Day 21 (± 2 day). In addition, Day 21 evaluations are to be completed for any subject withdrawn at any time after randomization into the trial. Attempts should be made to complete all evaluations, particularly efficacy assessments, for the Day 21/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new rescue medication for worsening manic symptoms prior to ET procedures prior to the Day 21/ET procedures, no efficacy assessments should be performed.** The following procedures will be performed on Day 21**(± 2 day)** or the ET visit:

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Section 3.7.2.2, Clinical Global Impression - Bipolar Version	The scale rates the subject's severity of illness (CGI-BP severity of illness: mania, depression, and overall bipolar illness) and Change from Preceding Phase (CGI-BP change from preceding phase: mania, depression, and overall bipolar illness) based on a 7-point scale. CCI [redacted]	The scale rates the subject's Severity of Illness (CGI-BP **S**everity of **I**llness: mania, depression, and overall bipolar illness) **based on a 7-point scale and rates the subject's** Change from **Baseline** (CGI-BP change from **Baseline**: mania, depression, and overall bipolar illness) based on a 7-point scale. CCI [redacted]
Section 3.7.3.2, Clinical Laboratory Assessments	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.	The central laboratory will provide laboratory results electronically.
Section 3.8.3.1, Treatment Interruption	No treatment interruptions are permitted in this trial.	**All attempts should be made to avoid treatment interruption during the trial. For subjects who have an interruption of treatment, the investigator or designee will contact the medical monitor as soon as possible. The investigator and medical monitor 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 medical monitor. The treatment interruption will be recorded via eSource and also recorded as a protocol deviation (Section 3.13).**

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Section 3.13, Protocol Deviations	In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.	In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the **medical monitor** at the earliest possible time by telephone. The investigator and **medical monitor** 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 **medical monitor**, and reviewed by the site monitor.
Section 4.1, Prohibited Medications	However, subjects whose last injection of antipsychotic occurred at least one full cycle (based on the prescribing label) before the initial screening visit are eligible to enter the 14-day screening period if at least one full cycle plus 1/2 cycle (length of 1 cycle based on the prescribing label) will have elapsed before randomization. Other therapies restricted or prohibited prior to enrollment and during the trial are presented in Section 4.2.	However, subjects whose last injection of antipsychotic occurred at least one full cycle (based on the prescribing label) before the initial screening visit are eligible to enter the 14-day screening period if at least one full cycle plus 1/2 cycle (length of 1 cycle based on the prescribing label) will have elapsed before randomization. **Subjects with serum concentrations of lithium ≥ 0.6 mmol/, valproate ≥ 50 µg/mL, or carbamazepine ≥ 4 µg/mL at screening may repeat a clinical laboratory test for these parameters prior to randomization. The results of the additional test will be reviewed and confirmed before the subject can be randomized into the trial.** Other therapies restricted or prohibited prior to enrollment and during the trial are presented in Section 4.2.
Section 4.2, Other Restrictions	Not applicable (newly added text)	**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 3 times daily (total of 60 mg/day). Sites should only utilize medications that are approved for these indications in their respective countries.**

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Section 5.1, Definitions	Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE ePlatform if there is an abnormality or complication.	Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on **the clinical trial pregnancy and breastfeeding** form**, or other designated form,** to the sponsor. Pregnancy will only be documented on the AE ePlatform if there is an abnormality or complication.
Section 5.2, Eliciting and Reporting Adverse Events	All AEs (serious and nonserious) reported by the subject must be recorded within the esource provided by the sponsor.	All AEs (serious and nonserious) reported by the subject must be recorded within the e**S**ource **platform** provided by the sponsor.
Section 7.4.2, Secondary Endpoint Analysis	CCI [redacted]	[redacted]
Appendix 7, Young-Mania Rating Scale	Assessment updated to the latest version.	
CCI [redacted]	[redacted]	
	[redacted]	
	[redacted]	

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Agreement

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

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, brexpiprazole (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 receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where brexpiprazole (OPC-34712) will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- 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 and designee 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 substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and 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 before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

Principal Investigator Print Name	Signature	Date

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

OPC-34712

SIGNATURE PAGE

Document Name: Protocol 331-201-00080 Amendment 1

Document Number: 0001260106

Document Version: 4.0

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