- **Protocol number: 331-201-00083**
- **Document title: A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder**
- **Version number: 2.0**
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

# CLINICAL PROTOCOL

A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder

Protocol No. 331-201-00083
IND No. 134115
EudraCT No. 2017-002225-38

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase: 3

| | |
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| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>2440 Research Boulevard<br>Rockville, Maryland 20850, United States |
| Immediately Reportable Event | INC Research Pharmacovigilance & Drug Safety<br>Fax: PPD<br>E-mail: PPD |
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| Version No.: | 2.0 |

Protocol 331-201-00083

# Protocol Synopsis

| | |
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| Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712) | Protocol No.:<br>331-201-00083<br>IND No.: 134115<br>EudraCT No.:<br>2017-002225-38 |
| Protocol Title: | A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder |
| Clinical Phase/Trial Type: | Phase 3/Therapeutic use |
| Treatment Indication: | Bipolar I disorder |
| Objective(s): | Primary: To assess the safety and tolerability of brexpiprazole (OPC-34712) in the treatment of subjects with bipolar I disorder. |
| Trial Design: | Multicenter, open-label |
| Subject Population: | Men and women 18 to 65 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of bipolar I disorder will be enrolled in the trial and will include eligible rollover subjects who completed one of the double-blind, phase 3 efficacy trials (ie, Trials 331-201-00080 or 331-201-00081) and could, in the opinion of the investigator, potentially benefit from treatment with brexpiprazole (OPC-34712). In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at select sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor. Approximately 60% of subjects will be enrolled from North America and 40% of subjects will be enrolled from the rest of the world (ROW). |
| Inclusion/Exclusion Criteria: | Diagnosis of bipolar I disorder, as confirmed by the Mini International Neuropsychiatric Interview (MINI), and a history of at least 1 previous manic episode, with or without mixed features, and 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 not currently have |

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| | severity of bipolar symptoms that, in the opinion of the investigator, would require hospitalization. |
| Trial Site(s): | It is estimated that approximately 384 rollover subjects may be enrolled in the trial to achieve a target completion of approximately 175 subjects at 6 months at approximately 90 trial sites in North America and the ROW. |
| Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration: | All subjects will receive a starting dose of 2 mg/day of brexpiprazole from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole, 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.<br><br>Subjects experiencing tolerability issues in-between visits may have their doses adjusted at any time during an unscheduled in-clinic visit. |
| Trial Assessments: | CCI [redacted]<br><br>Pharmacokinetic: None.<br><br>Safety: Adverse event (AE) reporting, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, waist circumference, physical examination, CCI [redacted]<br><br>Screening/Other: Medical, psychiatric, and medication history, urine drug and alcohol screening, serum pregnancy test, and MINI. |
| Criteria for Evaluation: | **Primary Endpoint:** The primary endpoint is the safety and tolerability of brexpiprazole (OPC-34712), as assessed by the frequency and severity of AEs.<br>CCI [redacted] |

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| | • CCI [redacted]<br><br>**Additional Safety Endpoints:**<br><br>Standard safety variables will include clinically significant changes in: ECGs, vital signs, clinical laboratory tests, use of concomitant medications, changes in body weight, and physical examinations.<br><br>CCI [redacted] |
| Statistical Methods: | The sample size is not based on statistical power considerations but on International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) requirements. The trial population will be derived from eligible subjects from the double-blind, phase 3 trials (ie, Trial 331-201-00080 and Trial 331-201-00081) to achieve a target completion of approximately 175 subjects at 6 months.<br><br>The primary safety analysis is the frequency and severity of AEs in the open-label treatment phase (Phase B). All AEs will |

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| | be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of treatment-emergent adverse events (TEAEs) will include the following summaries:<br>• TEAEs by severity<br>• Potentially drug-related TEAEs<br>• TEAEs with an outcome of death<br>• Serious TEAEs<br>• Discontinuations due to TEAEs<br><br>A TEAE is defined as an AE that starts after the first dose of investigational medicinal product (IMP) or an AE that is reported at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption, or reduction of IMP.<br><br>Descriptive statistics will be provided for each endpoint, and will be summarized at each trial visit using the observed cases (OC) dataset and at the last visit using the last observation carried forward (LOCF) dataset. Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment phase. |
| Trial Duration: | The duration of this trial for an individual subject who completes the trial without ET early withdrawal is approximately 29 to 35 weeks. This is inclusive of a maximum 14-day screening period, a 4 week conversion phase (if applicable), a 26-week open-label treatment period, and a safety follow-up period via telephone contact or clinic visit 21 (± 2) days after the last dose of IMP. |

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# List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| 5-HT | Serotonin |
| ADHD | Attention-deficit hyperactivity disorder |
| AE | Adverse event |
| CCI | [redacted] |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| CCI | [redacted] |
| BMI | Body mass index |
| CCI | [redacted] |
| CNS | Central nervous system |
| CPK | Creatine phosphokinase |
| CCI | [redacted] |
| CYP | Cytochrome P450 |
| DBP | Diastolic blood pressure |
| D/C | Discontinue |
| 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 |
| FDA | Food and Drug Administration |
| CCI | [redacted] |
| GCP | Good Clinical Practice |
| HbA1c | Glycosylated hemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| 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 |
| IDDM | Insulin-dependent diabetes mellitus |
| IEC | Independent ethics committee |
| IMP | Investigational medicinal product |
| IND | Investigative new drug |
| INR | International normalized ratio |
| IRB | Institutional review board |
| IRE | Immediately reportable event |
| IR IM | Immediate-release intramuscular |
| IWRS | Interactive web response system |
| LOCF | Last observation carried forward |

| | |
|---|---|
| CCI | [redacted] |
| MAOI | Monoamine oxidase inhibitor |
| MDD | Major depressive disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINI | Mini International Neuropsychiatric Interview |
| OC | Observed cases |
| OTC | Over-the-counter |
| PK | Pharmacokinetics |
| PQC | Product quality complaint |
| PT | Prothrombin time |
| 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 |
| ROW | Rest of world |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| CCI | [redacted] |
| SBP | Systolic blood pressure |
| SSRI | Selective serotonin reuptake inhibitors |
| TEAE | Treatment-emergent adverse event |
| TSH | Thyroid-stimulating hormone |
| $T_4$ | Free thyroxine |
| US | United States |
| ULN | Upper limit of normal |
| WBC | White blood cell |
| WOCBP | Women of childbearing potential |
| CCI | [redacted] |

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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 (OPC-34712) 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 (OPC-34712) in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole (OPC-34712) 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 (OPC-34712) 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 (OPC-34712) 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 bipolar I disorder.

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## 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]

## 1.2 Clinical Data

Currently, brexpiprazole (OPC-34712) 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. In addition to the proposed trial in the treatment of bipolar I disorder, the current brexpiprazole clinical development program includes ongoing investigations in the following indications: adjunctive treatment of adult attention-deficit hyperactivity disorder (ADHD) coadministered with marketed stimulant therapy; treatment of agitation associated with dementia of the Alzheimer's type; and adjunctive treatment of adult post-traumatic stress disorder (PTSD) coadministered with selective serotonin reuptake inhibitors (SSRIs).[7]

As of 17 Apr 2016, the brexpiprazole (OPC-34712) clinical development program consisted of a total of 65 clinical trials conducted in North America, Latin America, Europe, and Asia (53 completed and 12 ongoing). This includes 59 trials conducted under US Investigational New Drug Applications (INDs) (47 completed and 12 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of ADHD, agitation associated with dementia of the Alzheimer's type, or PTSD; and 6 non-US IND trials, completed in either South Korea or Japan, conducted in healthy subjects and subjects with schizophrenia.[7]

Please refer to the IB for more detailed information.[7]

## 1.3 Known and Potential Risks and Benefits

Phase 1 data indicated that brexpiprazole (OPC-34712) 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 (OPC-34712) 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; as adjunctive therapy in elderly subjects (70-85 years of age) with MDD up to 3 mg/day; 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 (OPC-34712) is a novel atypical 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] Like other atypical antipsychotics that have demonstrated efficacy across the indications of schizophrenia, MDD, and bipolar I disorder, brexpiprazole's (OPC-34712) specific receptor activity profile likely correlates with its established efficacy in schizophrenia and MDD, and may also prove to be an effective target for the treatment of the acute mania of bipolar I disorder. This 26-week, multicenter, open-label trial will be conducted to evaluate the long-term safety and tolerability of brexpiprazole (OPC-34712) for the treatment of subjects with bipolar I disorder.

## 2.2 Dosing Rationale

The dosing paradigm of brexpiprazole (OPC-34712) to be used in Trial 331-201-00083 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.[7]

The dosing 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

The purpose of this trial is to assess the safety and tolerability of brexpiprazole (OPC-34712) in the treatment of subjects with bipolar I disorder.

## 3 Trial Design

### 3.1 Type/Design of Trial

This is a multicenter, open-label trial designed to assess the safety and tolerability of oral brexpiprazole (OPC-34712) (2-4 mg/day) as treatment in adults with bipolar I disorder. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who will include subjects who completed the 3-week treatment in the double-blind, phase 3 efficacy trials (ie, Trials 331-201-00080 or 331-201-00081) and, in the investigator's judgment, could potentially benefit from treatment with oral brexpiprazole (OPC-34712) for bipolar I disorder. In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at select sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

The trial will be organized as follows:

Rollover Subjects:

*Screening/Baseline:* Subjects who completed Day 21 of the double-blind trial and had no major protocol deviation will be screened for eligibility at the last visit of the double-blind trial (ie, Week 3 [Day 21] visit of Trials 331-201-00080 or 331-201-00081). Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-201-00083 before any procedures specific to the open-label trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-201-00083 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

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*Open-label Treatment Phase (Phase B):* Eligible subjects from Trials 331-201-00080 or 331-201-00081 will receive 26 weeks of daily treatment with open-label brexpiprazole (OPC-34712) (2-4 mg/day) in Phase B of Trial 331-201-00083, as described in Section 3.2. Visits will occur at the end of Weeks 1, 2, 4, 8, 12, 18, and 26.

*Follow-up:* Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of open-label investigational medicinal product (IMP).

De Novo Subjects (The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor):

*Screening:* Subjects will enter a pretreatment screening phase that will range from a minimum of 1 day to a maximum of 14 days to assess eligibility criteria and to washout from prohibited concomitant medications, if applicable. A screening number will be assigned for each subject with a signed ICF. Subjects with a lapse in antipsychotic treatment ("lapse" defined as > 7 consecutive days without oral antipsychotic medication) will proceed directly to the baseline of the open-label treatment phase (Phase B) after completing screening assessments, provided that all eligibility criteria are met, including washout of all prohibited medications. All other subjects will undergo conversion to oral brexpiprazole in the conversion phase (Phase A).

*Conversion Phase (Phase A):* Any subject receiving antipsychotic treatment(s) at the initial screening visit will undergo cross-titration to oral brexpiprazole (OPC-34712) for 4 weeks in Phase A, as described in Section 3.2. Those subjects on mood stabilizers and antipsychotics will need to be on monotherapy brexpiprazole (OPC-34712) by end of the conversion phase. Visits will occur at the end of Conversion Weeks 1, 2, 3, and 4 during Phase A. The goal in Phase A is for the de novo subjects to achieve a brexpiprazole (OPC-34712) target dose of 2 mg daily by the Conversion Week 4 visit, which will also be the baseline visit of Phase B. Therefore, the assessments from the Conversion Week 4 visit of Phase A will serve as the baseline measures for Phase B.

*Baseline and Open-label Treatment Phase (Phase B):* After completing baseline assessments (Phase B baseline visit for subjects entering Phase B directly from screening or Conversion Week 4 visit of Phase A for subjects who participated in Phase A), eligible subjects will receive daily treatment with open-label brexpiprazole (OPC-34712) in Phase B, as described in Section 3.2. Subjects will receive 26 weeks of open-label brexpiprazole (OPC-34712) (2-4 mg/day) in Phase B. Visits will occur at the end of Weeks 1, 2, 4, 8, 12, 18, and 26.

*Follow-up:* Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of open-label medication.

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See Figure 3.1-1 and Figure 3.1-2 for schematics of the trial design for rollover and de novo subjects, respectively.

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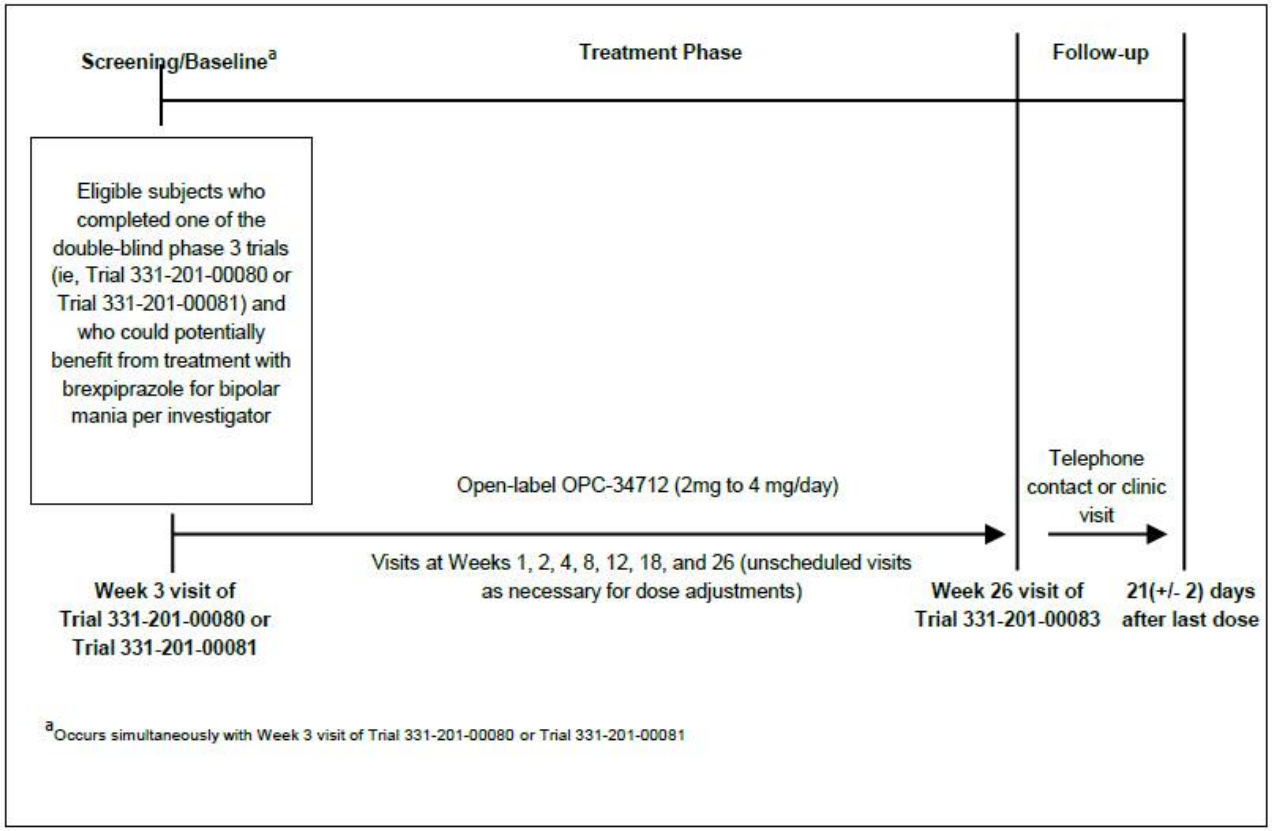


**Figure 3.1-1 Trial Design Schematic - Rollover Subjects**

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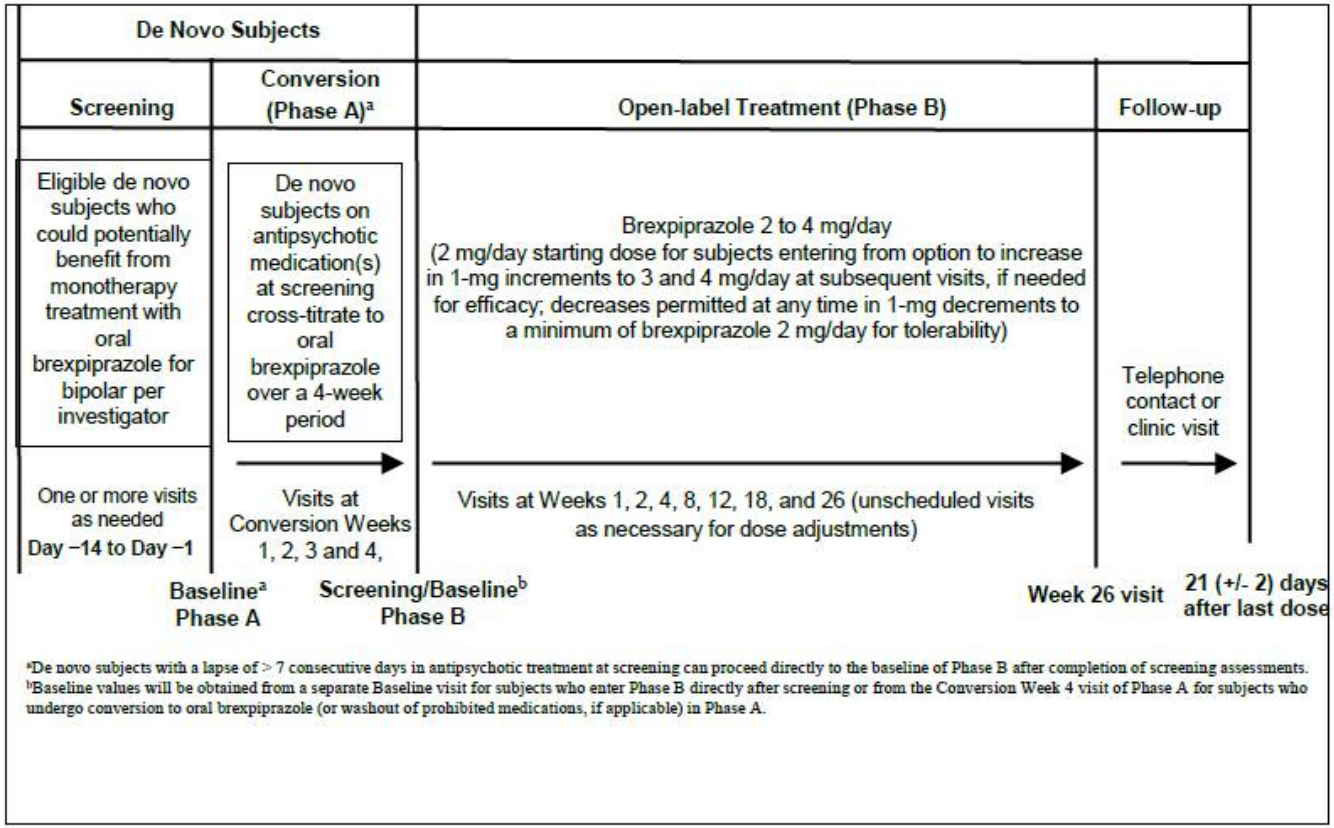


**Figure 3.1-2 Trial Design Schematic - De Novo Subjects**

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## 3.2 Trial Treatments

### 3.2.1 De Novo Subjects

**The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.**

#### 3.2.1.1 Conversion Phase (Phase A)

For de novo subjects, Conversion (Phase A) applies only to subjects who are receiving antipsychotic medication(s) when being considered for entry into Trial 331-201-00083. All other de novo subjects will enter the trial at Phase B (see Section 3.2.2.1) after completing screening assessments. The purpose of Phase A is to cross-titrate de novo subjects from current antipsychotic treatment(s) to monotherapy with brexpiprazole (OPC-34712) 2 mg/day over a 4-week period to minimize the possibility of rebound (eg, cholinergic or histaminergic) from abrupt changes in antipsychotic medication. The procedure as it pertains to this protocol is summarized in Table 3.2.1.1-1.

**Table 3.2.1.1-1 Recommendation for Switching from Other Antipsychotics to Oral Brexpiprazole Monotherapy**

| Trial Visit | Phase A Baseline[a] | Conversion Week 1[b] | Conversion Week 2 | Conversion Week 3 | Conversion Week 4/ Baseline of Phase B[c] |
|---|---|---|---|---|---|
| Dose of brexpiprazole (OPC-34712) | 1 mg/day | 1 mg/day | 1 or 2 mg/day | 2 mg/day | 2 mg/day |
| Dose of other antipsychotic(s) | No change | No change | Decrease | Decrease | D/C |

D/C = discontinue.

[a]Add short-term concomitant medications as needed to control symptoms (eg, agitation and insomnia).

[b]Gradually withdraw concomitant medications.

[c]Monotherapy with brexpiprazole 2 mg/day will begin at the Conversion Week 4 visit/baseline of Phase B which will occur the day after discontinuation of all other antipsychotic treatment(s).

The scheme in Table 3.2.1.1-1 represents the optimal approach for conversion of subjects from other antipsychotic(s) to brexpiprazole and is highly recommended for use in this trial; however, the investigator may adjust the dose(s) of other antipsychotic(s) during the 4-week cross-titration as deemed appropriate for individual subjects. The dose of brexpiprazole (OPC-34712) can increase during cross-titration, but cannot decrease. Subjects must achieve a monotherapy dose of brexpiprazole (OPC-34712) 2 mg/day at the Conversion Week 4 visit/baseline of Phase B in order to progress to Phase B. Although de novo subjects must be outpatient at screening, the investigator has the option

to hospitalize subjects during the conversion phase (Phase A), if deemed medically necessary. The need for hospitalization should be discussed with the medical monitor in advance. However, de novo subjects must be outpatient at baseline of Phase B.

### 3.2.2 Rollover and De Novo Subjects

#### 3.2.2.1 Open-label Treatment Phase (Phase B)

The only antipsychotic treatment permitted during Phase B will be open-label brexpiprazole (OPC-34712). Any subject who requires additional antipsychotic treatment must be withdrawn from the trial. Timing of the first dose of brexpiprazole (OPC-34712) in Phase B will be as follows:

**De Novo Subjects (The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.)**

- For de novo subjects who undergo conversion in Phase A, open-label dosing of brexpiprazole (OPC-34712) in Phase B will begin the day after discontinuation of all other antipsychotic treatment(s), which is the Conversion Week 4 visit/baseline of Phase B.
- De novo subjects with a lapse in oral antipsychotic treatment of > 7 consecutive days at screening will receive the first dose of open-label brexpiprazole (OPC-34712) in Phase B as soon as all screening and baseline evaluations are completed, including washout of all other prohibited medications.

**Rollover Subjects**

- The first dose of open-label brexpiprazole (OPC-34712) will be taken one day after the last dose of double-blind IMP is taken in Trials 331-201-00080 or 331-201-00081 so that treatment continues without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Day 21 (Week 3) visit of Trial 331-201-00080 or 331-201-00081 (ie, the day of the screening/baseline visit for the open-label trial).
- All subjects will start on 2 mg/day of brexpiprazole (OPC- 34712) regardless of treatment assignment in the double-blind trial.

All subjects will receive a starting dose of 2 mg/day of brexpiprazole from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole, 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.

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Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial.

The dosing strategy is summarized in Table 3.2.2.1-1. Subjects must return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response. All doses of brexpiprazole should be taken orally once daily and can be administered without regard to meals. Subjects are to take IMP at approximately the same time each day.

**Table 3.2.2.1-1 Dosing Schedule - Open-label Treatment Phase**

| IMP | Trial Visit | | |
|---|---|---|---|
| | Days 1-3 | Day 4[a] | Day 7-Week 26 |
| Brexpiprazole (OPC-34712) | 2 mg/day | 3 mg/day | 2-4 mg/day[b] |

[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 to 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.

## 3.3 Trial Population

### 3.3.1 Number of Subjects and Description of Population

It is estimated that approximately 384 rollover subjects may be enrolled into Trial 331-201-00083 to achieve a target completion of approximately 175 subjects at 6 months at approximately 90 trial sites in North America and the rest of world (ROW). Men and women 18 to 65 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of bipolar I disorder will be enrolled in the trial and will include rollover subjects from the double-blind, phase 3 efficacy trials (ie, Trials 331-201-00080 or 331-201-00081). In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at select sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

Diagnosis will be confirmed by the Mini International Neuropsychiatric Interview (MINI)[8,9] and a history of at least 1 previous manic episode with or without mixed features and 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 not currently have severity of bipolar symptoms that, in the opinion of the investigator, would require hospitalization. Approximately 60% of subjects will be enrolled from North America and 40% of subjects will be enrolled from the rest of world (ROW).

### 3.3.2 Subject Selection and Numbering

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

## 3.4 Eligibility Criteria

### 3.4.1 Informed Consent

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

Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[10] and local regulatory requirements. The investigator will ensure that the sponsor 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.

### 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**

| | **De Novo Subjects[a]** |
|---|---|
| 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 and/or consent obtained from a legally acceptable representative (as required by IRB/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; 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 who do not have severity of bipolar symptoms that, in the opinion of the investigator, would require 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. | Subjects who, in the investigator's judgment, require treatment with an antipsychotic medication for their bipolar I disorder. |
| 6. | Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period. |
| 7. | Outpatient status. Subjects hospitalized at the investigator's discretion during conversion to oral brexpiprazole (OPC-34712) in Phase A and hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) will be considered outpatient status for the purpose of enrollment in Trial 331-201-00083. Subjects hospitalized during the conversion phase (Phase A) must be outpatient at the baseline of Phase B. |
| **Rollover Subjects from Trial 331-201-00080 or 331-201-00081** | |
| 8. | Subjects remaining in hospital at the Day 21 (Week 3) visit of Trial 331-201-00080 or Trial 331-201-00081 (for other than psychosocial reasons) will be permitted to enroll in Trial 331-201-00083 at the Week 3 visit of the double-blind trial if they are planned to be discharged from the hospital before the Week 1 visit of Trial 331-201-00083. Subjects not discharged by the Week 1 visit of Trial 331-201-00083 must be withdrawn. |
| 9. | Subjects who, in the opinion of the investigator, could potentially benefit from administration of oral brexpiprazole for the treatment of bipolar I disorder and who completed 3 weeks of post-randomization treatment in Trial 331-201-00080 or Trial 331-201-00081. |

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IEC = independent ethics committee; IRB = institutional review board.

[a]The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

### 3.4.3 Exclusion Criteria

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

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| **Table 3.4.3-1 Exclusion Criteria** | |
|---|---|
| **De Novo Subjects**[a] | |
| | **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 in Trial 331-201-00083. |
| | **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 with manic symptoms that are better accounted for by another general medical condition or direct physiological effects of a substance (eg, medications). |
| 5. | Subjects considered unresponsive to clozapine or who are only responsive to clozapine. |
| 6. | Subjects with bipolar I disorder who are considered resistant or refractory to treatment for manic symptoms by history. |
| 7. | Electroconvulsive treatment within the past 2 months of the screening/baseline visit for Trial 331-201-00083. |
| 8. | Use of psychotropic medications (other than benzodiazepines) within 7 days of the baseline YMRS. |
| 9. | Rapid cyclers with more than 6 episodes in the previous year. |
| 10. | Subjects whose current manic episode has lasted for more than 4 weeks overall, or who require hospitalization for the current acute episode at the time of the screening visit, excluding hospitalization for psychosocial reasons. |
| | **Medical History and Concurrent Diseases** |
| 11. | 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. |
| 12. | Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months, **OR**<br>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**<br>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**<br>Subjects who, in the opinion of the investigator, present a serious risk of suicide or homicide. |
| 13. | 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. |

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| **Table 3.4.3-1 Exclusion Criteria** | |
|---|---|
| 14. | Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as the following:<br>• any history of myocardial infarction or congestive heart failure (whether controlled or uncontrolled),<br>• HIV seropositive status or acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN).<br><br>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. |
| 15. | Subjects with IDDM (ie, any subjects using insulin) are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:<br>• HbA1c < 7.0%, AND<br>• 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 retested value must be ≤ 125 mg/dL, AND<br>• 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<br>• Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND<br>• Subject's diabetes is not newly diagnosed during screening for the trial. |
| 16. | 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.<br><br>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. |
| 17. | Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile, post traumatic, or alcohol withdrawal seizure. |

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**Table 3.4.3-1 Exclusion Criteria**

| | |
|---|---|
| | **Physical and Laboratory Results** |
| 18. | 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:<br>• Platelets ≤ 75000/$mm^3$<br>• Hemoglobin ≤ 9 g/dL<br>• Neutrophils, absolute ≤ 1000/$mm^3$<br>• AST > 2 × ULN<br>• ALT > 2 × ULN<br>• CPK > 3 × ULN, unless discussed with and approved by the medical monitor<br>• Creatinine ≥ 2 mg/dL<br>• QTcF ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing.<br><br>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. |
| 19. | Subjects with a positive drug screen for cocaine or other drugs of abuse (excluding stimulants and other prescribed medications and marijuana) are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or OTC medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor. |
| 20. | 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. |
| | **Disallowed and Concomitant Medication** |
| 21. | 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. |
| 22. | Subjects who would be likely to require prohibited concomitant therapy during the trial. |
| 23. | Subjects who received brexpiprazole (OPC-34712) in any prior clinical trial or currently taking commercially available brexpiprazole (Rexulti®). |
| | **Allergies and Adverse Drug Reactions** |
| 24. | Subjects with a history of neuroleptic malignant syndrome, serotonin syndrome, or clinically significant tardive dyskinesia. |
| 25. | Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications. |
| 26. | Subjects who are known to be allergic or hypersensitive to brexpiprazole (OPC-34712) or other quinolinones. |
| | **Other** |
| 27. | 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. |
| 28. | Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial. |
| 29. | 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. |

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| **Table 3.4.3-1 Exclusion Criteria** | |
|---|---|
| **Rollover Subjects from Trial 331-201-00080 or 331-201-00081** | |
| 30. | Subjects with a major protocol violation during the course of their participation in the double-blind phase 3 trial (ie, Trial 331-201-00080 or 331-201-00081). Minor violations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-201-00083; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the prior double-blind trial would be considered a major violation that would result in exclusion from Trial 331-201-00083. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility. |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CPK = creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; ECG = electrocardiogram; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; IDDM = insulin dependent diabetes mellitus; OTC = over-the-counter; QTcF = QT interval as corrected by Fridericia's formula; SBP = systolic blood pressure; $T_4$ = free thyroxine; ULN = upper limit of normal; WOCBP = women of childbearing potential.

[a]The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

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.

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 over-the-counter (OTC) medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results or the subject does not meet DSM-5 criteria for substance abuse or dependence, may continue evaluation for the trial following consultation and approval by the medical monitor.

Screen failures 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 the safety and tolerability of brexpiprazole (OPC-34712), as assessed by the frequency and severity of adverse events (AEs).

### 3.5.2 Secondary Endpoints

None.

### 3.5.3 CCI

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### 3.5.4 Additional Safety Endpoints

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

CCI

[redacted]

## 3.6 Measures to Minimize/Avoid Bias

This trial is open-label.

## 3.7 Trial Procedures

This is a multicenter, open-label trial designed to assess the safety and tolerability of oral brexpiprazole (OPC-34712) (2-4 mg/day) as treatment in adults with bipolar I disorder. The trial will be conducted on an outpatient basis. The trial comprises a 26-week open-label treatment period with a 21 (± 2) day follow-up.

Trial assessment time points are summarized in Table 3.7-1 (open-label treatment phase [Phase B]) and Table 3.7-2 (conversion phase [Phase A]).

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**Table 3.7-1 Schedule of Assessments - Open-label Treatment (Phase B)**

| Assessment | Screening / Baseline[a] (Rollover) | Phase B Baseline[a] (De Novo) | Open-Label Treatment Phase Trial Week Visit (± 2 days) | | | | | | | Follow-up 21 (± 2) days[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 4 | 8 | 12 | 18 | 26/ ET[b] | |
| **ENTRANCE CRITERIA** | | | | | | | | | | |
| Informed consent | X[d] | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Medical history | X[e] | | | | | | | | | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **SAFETY** | | | | | | | | | | |
| Physical examination | X[f] | X[g] | | | | | | | X | |
| Waist circumference | X[f] | X[g] | | | | | | | X | |
| Vital signs[i] | X[f] | X[g] | X | X | X | X | X | X | X | |
| 12-lead ECG[j] | X[f] | X[g] | | | | | X | | X | |
| Clinical laboratory tests[k] | X[f,l] | X[g,l] | | | | | X[m] | | X[m] | |
| HbA1c | X[f,l] | X[g,l] | | | | | X[m] | | X[m] | |
| Drug screen/blood alcohol[n] | X[f] | X[g] | | | X | | X | | X | |
| Urine pregnancy test (WOCBP only)[o] | X[f] | X[g] | X | X | X | X | X | X | X | |
| CCI | | | | | | | | | | |

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**Table 3.7-1 Schedule of Assessments - Open-label Treatment (Phase B)**

| Assessment | Screening / Baseline[a] (Rollover) | Phase B Baseline[a] (De Novo) | Open-Label Treatment Phase Trial Week Visit (± 2 days) | | | | | | | Follow-up 21 (± 2) days[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 4 | 8 | 12 | 18 | 26/ ET[b] | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| Adverse events[q] | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| **OTHER** | | | | | | | | | | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| Dose adjustment[r] | | | X | X | X | X | X | X | X | |
| Register visit in IWRS | X | X | X | X | X | X | X | X | X | |
| IMP dispensing | X | X | X | X | X | X | X | X | | |
| IMP accountability | | | X | X | X | X | X | X | X | |

CCI IWRS = interactive web response system.

[a]For rollover subjects, screening for Trial 331-201-00083 occurs simultaneously with baseline which will be at the same day as the Day 21 (Week 3) visit of Trial 331-201-00080 or Trial 331-201-00081. Separate screening and baseline visits are required for de novo subjects to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

[b]If a subject discontinues early before Week 26, procedures noted for Week 26 must be completed at the ET visit. Attempts should be made to complete ALL evaluations, particularly efficacy assessments, for the Week 26/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes.

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

[d]Informed consent for Trial 331-201-00083 will occur at screening/baseline for rollover subjects and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e]Update, if necessary, for rollover subjects.

[f]Screening/baseline value will be obtained from the Day 21 (Week 3) visit of Trial 331-201-00080 or Trial 331-201-00081.

[g]Baseline assessment will be performed at baseline of Phase B for de novo subjects who enter Phase B directly after screening, but will be obtained from the Conversion Week 4 visit of Phase A for subjects who participate in Phase A.

CCI [redacted]

[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. However, ECG results will also be evaluated at the investigational site to monitor safety during the trial. Rollover subjects will be enrolled in Trial 331-201-00083 based on the screening/baseline ECG results from the trial site. If the screening/baseline ECG results from the central reader, when available, indicate a QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing.at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. For de novo subjects, ECG results from the central reader must be reviewed for exclusion criteria prior to the first dose of open-label brexpiprazole in Phase B. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[k]Includes hematology (including prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]), 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 urinalysis.

[l]Rollover subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline 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. A fasting blood sample is required at baseline prior to dosing. De novo subjects must fast for a minimum of 8 hours prior to blood draws for baseline laboratory assessments.

[m]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at Week 26/ET and should be drawn after a minimum 8-hour fast at all other visits, if possible. Vital sign and ECG assessments should be completed before any blood samples are collected.

[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. If results of either or both are positive, the investigator must contact the medical monitor to discuss the subject's eligibility for continued participation in the trial.

[o] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at screening, baseline, or screening/baseline must not be enrolled in Trial 331-201-00083. 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.

CCI [redacted]

[q] AE recording will begin with the signing of the ICF for Trial 331-201-00083.

[r] Adjustments to the dose of brexpiprazole can be made at scheduled and unscheduled visits during the 26-week open-label treatment phase (ie, Phase B) to optimize efficacy and tolerability as described in the protocol. Subjects must return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits.

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**Table 3.7-2 Schedule of Assessments - Screening and Conversion (Phase A): De Novo Subjects**

The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

| Assessment | Screening (Days -14 to -1)[a] | Phase A Baseline | Conversion Week 1 (± 2 days) | Conversion Week 2 (± 2 days) | Conversion Week 3 (± 2 days) | Conversion Week 4/ Phase B Baseline[b] (± 2 days) |
|---|---|---|---|---|---|---|
| **ENTRANCE CRITERIA** | | | | | | |
| Informed consent[c] | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | X |
| Medical history | X | | | | | |
| Demography | X | | | | | |
| Psychiatric history | X | | | | | |
| MINI | X | | | | | |
| Prior medication washout[d] | X | | | | | |
| HIV, HBsAg, and anti-HCV | X | | | | | |
| CCI [redacted] | | | | | | |
| **SAFETY** | | | | | | |
| Physical examination[e] | X | | | | | X |
| Waist circumference | | X | | | | X |
| Vital signs[f] | X | X | X | X | X | X |
| 12-lead ECG[g] | X | | | | | X |
| Clinical laboratory tests (hematology, serum chemistry [including prolactin], and urinalysis)[h] | X[i] | | | | | X |
| TSH with reflex to free $T_4$ if abnormal[h] | X[i] | | | | | X |

**Table 3.7-2 Schedule of Assessments - Screening and Conversion (Phase A): De Novo Subjects**

The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

| Assessment | Screening (Days -14 to -1)[a] | Phase A Baseline | Conversion Week 1 (± 2 days) | Conversion Week 2 (± 2 days) | Conversion Week 3 (± 2 days) | Conversion Week 4/ Phase B Baseline[b] (± 2 days) |
|---|---|---|---|---|---|---|
| HbA1c[h] | X[i] | X | | | | X |
| PT, aPTT, and INR[h] | X | X | | | | X |
| Drug screen/blood alcohol[j] | X | | | | | X |
| Urine pregnancy test (WOCBP only)[k] | X | | | | | X |
| CCI | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| Adverse events | X[m] | X | X | X | X | X |
| Concomitant medications[n] | X | X | X | X | X | X |
| **OTHER** | | | | | | |
| CCI | | | | | | |
| | | | | | | |
| | | | | | | |
| Register visit in IWRS | X | X | X | X | X | X |
| Cross-titration[o] | | X | X | X | X | X |
| IMP dispensing | | X | X | X | X | X |
| IMP accountability | | | X | X | X | X |

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

[a]All de novo subjects (ie, subjects who did not participate in one of the double-blind phase 3 trials) will enter a screening period to determine eligibility for the open-label trial. 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 prior to baseline. Review of inclusion/exclusion criteria at baseline will be based on some assessments performed during screening.

[b]If a subject discontinues early before Week 4, procedures noted for Week 26/ ET must be completed at the ET visit. Attempts should be made to complete **ALL** evaluations, particularly efficacy assessments for the Week 26/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes.

[c]Informed consent must be obtained before any trial-related procedures are performed.

[d]Washout of prohibited medications begins after signing the ICF. Details of medications requiring washout are provided in Section 4.1. Prohibited and restricted medications are also provided in Section 4.1. In addition, all antipsychotic medications used within 30 days of the first dose of IMP will be recorded.

[e]To include measurement of height at screening only.

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

[g]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. However, ECGs will also 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. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[h]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at screening and Conversion Week 4, 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. Vital sign and ECG assessments should be completed before any blood samples are collected.

[i]See Section 3.4.3 for exclusions based on screening laboratory results.

[j]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator. If results of either or both are positive, the investigator must contact the medical monitor to discuss the subject's eligibility for continued participation in the trial.

[k]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.

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[m]AE recording will begin with the signing of the ICF.

[n]All prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in Section 4.1.

[o]Cross-titration will occur over a 4-week period in order to bring about a stable transition from previous antipsychotic treatment(s) to oral brexpiprazole.

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### 3.7.1 Schedule of Assessments

#### 3.7.1.1 Screening and Baseline

##### 3.7.1.1.1 Rollover Subjects

Subjects who completed Day 21 of the double-blind trial and had no major protocol deviation will be screened for eligibility at the last visit of the double-blind trial (ie, Week 3 [Day 21] visit of Trials 331-201-00080 or Trial 331-201-00081). Subjects will sign a separate ICF for participation in Trial 331-201-00083 before any procedures specific to the open-label trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-201-00083 for the following assessments: CCI physical examination, waist circumference, vital signs, ECG, clinical laboratory tests, urine drug screen, blood alcohol, and urine pregnancy test.

Additional procedures to be performed for rollover subjects at screening/baseline of the open-label trial are as follows:

- Inclusion/exclusion criteria for Trial 331-201-00083 will be reviewed to ensure the subject's eligibility.
- Trial personnel will register the visit in the interactive web response system (IWRS).
- Medical history will be updated, if necessary.
- Concomitant medications will be reviewed to assure that the subject is not receiving any prohibited medications.
- CCI
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Recording of AEs will begin with the signing of the ICF for Trial 331-201-00083.

##### 3.7.1.1.2 De Novo Subjects

**The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.**

###### 3.7.1.1.2.1 Screening

Screening procedures for de novo subjects are shown in Table 3.7-2 and begin after written informed consent has been obtained. These procedures can be performed at any time from Day −14 to Day −1. Although the screening period continues up to administration of the first dose of IMP, 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 enrollment/baseline. 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. After a subject has signed the ICF, sites will access the IWRS and enter a screening number. Completion of screening activities may require more than 1 visit; however, only the initial visit will be registered in the IWRS. Screening evaluations for de novo subjects will include the following:

- 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 the first dose of IMP) 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]
- A complete physical examination (including height) 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 Section 3.4.3 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) 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.
- Blood samples will be drawn for human immunodeficiency virus (HIV) serology and the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV). Subjects with a positive result for any of these tests will be excluded from the trial. Vital sign and ECG assessments should be completed before any blood samples are collected.

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- Samples will be obtained for blood alcohol testing. See Section 3.4.3 for details regarding subjects with a positive blood alcohol test.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Section 3.4.3 for exclusions based on outcome of screening urinalysis and urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all women of childbearing potential (WOCBP). All positive results must be confirmed by a serum pregnancy test. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- Adverse events will be recorded beginning with the completion of the consent process.
- Trial personnel will access the IWRS or equivalent to register the visit.

Subjects with a lapse in antipsychotic treatment ("lapse" defined as > 7 consecutive days without oral antipsychotic medication) will proceed directly to the baseline of the open-label treatment phase (Phase B) after completing screening assessments, provided that all eligibility criteria are met, including washout of all prohibited medications (Section 3.7.1.1.2.2). All other subjects will undergo conversion to oral brexpiprazole in the conversion phase (Phase A) (Section 3.7.1.1.2.3).

#### 3.7.1.1.2.2 Baseline (Phase B)

If the subject continues to be eligible for the trial after the screening period, and does not require titration to oral brexpiprazole (OPC-34712), 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.
- CCI [redacted]
- A complete physical examination (including waist circumference) will be performed.
- 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.

- Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and TSH with reflex to $T_4$ if the result for TSH is abnormal) should be drawn after a minimum 8-hour fast.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected from all potential 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. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- Adverse events and concomitant medications will be recorded.
- Site staff will distribute the wearable device and provide instructions on its use.
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Trial personnel will access the IWRS or equivalent to register the visit.
- CCI [redacted]

#### 3.7.1.1.2.3 Baseline (Phase A)

If the subject continues to be eligible for the trial after the screening period, and requires titration to oral brexpiprazole, the following procedures will be performed:

- 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.
- Waist circumference will be measured.
- Blood samples for clinical laboratory tests (coagulation parameters and HbA1c) must be collected after a minimum 8-hour fast.
- Adverse events and concomitant medications will be recorded.
- CCI [redacted]
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Trial personnel will access the IWRS or equivalent to register the visit.
- CCI [redacted]

- Cross-titration will occur over a 4-week period in order to bring about a stable transition from previous antipsychotic treatment(s) to oral brexpiprazole (OPC-34712).

#### 3.7.1.1.2.4 Conversion to Oral Brexpiprazole (Conversion Weeks 1, 2, 3, and 4 of Phase A)

Cross-titration will occur over a 4-week period in order to bring about a stable transition from previous antipsychotic treatment(s) to oral brexpiprazole (OPC-34712). De novo subjects will receive oral brexpiprazole (OPC-34712) in Phase A and will attend weekly visits (± 2 days) during which the following assessments and procedures will be performed as specified (see Table 3.7-2):

Conversion Weeks 1, 2, and 3:

- 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.
- AEs and concomitant medications will be recorded.
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Drug accountability will be performed.
- CCI [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

Conversion Week 4/Baseline of Phase B:

- An assessment of all inclusion and exclusion criteria will be made to confirm the subject's eligibility for the trial.
- CCI [redacted]
- A complete physical examination (including waist circumference) will be performed.
- 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 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 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 all potential 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. Subjects with a positive serum pregnancy test result will be excluded from the trial.
- Adverse events and concomitant medications will be recorded.
- A confirmation of data download from the wearable device will be performed.
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Drug accountability will be performed.
- Trial personnel will access the IWRS or equivalent to register the visit.

### 3.7.1.2 Open-Label Treatment (Phase B - All Subjects)

#### 3.7.1.2.1 Week 1

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

- 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.
- A confirmation of data download from the wearable device will be performed.
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.
- Drug accountability will be performed.
- Electronic sleep diary accountability will be performed.

- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.2 Week 2

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

- 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.
- CCI [redacted]
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.
- Drug accountability will be performed.
- CCI [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.3 Week 4

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

- 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.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected from all subjects for 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. Subjects with a positive serum pregnancy test result will be withdrawn from the trial.

- Adverse events and concomitant medications will be recorded.
- A confirmation of data download from the wearable device will be performed.
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.
- Drug accountability will be performed.
- CCI [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.4 Week 8

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

- 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.
- CCI [redacted]
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.
- Drug accountability will be performed.
- CCI [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.5 Week 12

All subjects will attend a visit at Week 12 (± 2 days) for the following evaluations:

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 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 TSH with reflex to $T_4$ if the result for TSH is abnormal) should be drawn after a minimum 8-hour fast.
- Samples will be obtained for blood alcohol testing.
- Urine will be collected from all 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. Subjects with a positive serum pregnancy test result will be withdrawn from the trial.
- Adverse events and concomitant medications will be recorded.
- CCI [redacted]
- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.
- Drug accountability will be performed.
- CCI [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.6 Week 18

All subjects will attend a visit at Week 18 (± 2 days) for the following evaluations:

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.

CCI [redacted]

- Open-label brexpiprazole (OPC-34712) will be dispensed to the subject.
- Adjustment of brexpiprazole (OPC-34712) dose, if needed.

- Drug accountability will be performed.
- [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

#### 3.7.1.2.7 End of Treatment - Week 26/Early Termination

The following procedures will be performed at the Week 26, or ET, visit:

- [redacted]
- A complete physical examination (including waist circumference) will be performed.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine 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 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.
- Adverse events and concomitant medications will be recorded.
- Drug accountability will be performed.
- [redacted]
- Trial personnel will access the IWRS or equivalent to register the visit.

### 3.7.1.3 Post-treatment Follow-up Period

Subjects will be contacted to monitor for safety events via telephone contact or clinic visit (investigator's discretion) for 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. [redacted] 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 Otsuka Pharmaceutical Development & Commercialization, Inc. or a designee.

[redacted]

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CCI [redacted]

### 3.7.2.4 Other Assessments

The MINI[8,9,14] will be conducted at the screening visit (where applicable) 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 4.

CCI [redacted]

### 3.7.3 Safety Assessments

Refer to Section 5, Reporting of Adverse Events.

#### 3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

#### 3.7.3.2 Clinical Laboratory Assessments

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

reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically.

**Table 3.7.3.2-1 Clinical Laboratory Assessments**

| | |
|---|---|
| Hematology:<br>White Blood Cell (WBC) count with differential<br>Red Blood Cell (RBC) count<br>Hematocrit<br>Hemoglobin<br>Platelet count<br><br>Urinalysis:<br>pH<br>Specific Gravity<br>Protein<br>Ketones<br>Glucose<br>Blood<br>Microscopic analysis (performed only if any part of the urinalysis is not negative)<br><br>Urine Drug Screen:<br>Amphetamines<br>Barbiturates<br>Benzodiazepines<br>Cannabinoids<br>Cocaine<br>Marijuana<br>Methadone<br>Opiates<br>Phencyclidine<br>Propoxyphene<br><br>Other:<br>Blood Alcohol | Serum Chemistry:<br>Alkaline Phosphatase (ALP)<br>Alanine Aminotransferase (ALT)<br>Albumin<br>Aspartate Aminotransferase (AST)<br>Bicarbonate<br>Bilirubin, total<br>Blood Urea Nitrogen (BUN)<br>Creatine phosphokinase (CPK)<br>Calcium<br>Chloride<br>Cholesterol (total, low density lipoprotein, and high density lipoprotein)<br>Creatinine<br>Gamma Glutamyl Transferase (GGT)<br>Glucose<br>HbA1c<br>Inorganic phosphorus<br>Insulin<br>Lactic Dehydrogenase (LDH)<br>Magnesium<br>Potassium<br>Prolactin<br>Protein, total<br>Sodium<br>Thyroid Stimulating Hormone (TSH)<br>Thyroxine, Free ($T_4$) (if needed)<br>Uric acid<br>Triglycerides<br><br>Additional Tests:<br>Urine or serum pregnancy for WOCBP<br>Prothrombin time (PT)<br>Activated partial thromboplastin time (aPTT)<br>International normalized ratio (INR)<br>HbA1c<br>Additional Tests (screening only):<br>HIV<br>HbsAg<br>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 5 for criteria for identifying values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets $\leq 75000/mm^3$
- Hemoglobin $\leq 9$ g/dL
- Neutrophils, absolute $\leq 1000/mm^3$
- 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 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).

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- 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.[16]

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 6 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 7 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical significance. Exclusion criteria for screening do not apply as mandatory discontinuation

criteria for subjects who are already enrolled in the trial. Please consult the medical monitor in case of questions.

### 3.7.3.5 Other Safety Assessments

It is required that a trained and experienced clinician administer the safety assessments, CCI [redacted] 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.

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[redacted]

CCI

[redacted]

CCI [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 the first dose of IMP 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) on the case report form.

### 3.7.5 Pharmacokinetic Assessments

None.

### 3.7.6 End of Trial

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

### 3.7.7 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, 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. The treatment interruption will be recorded in the ePlatform and also recorded as a protocol deviation (Section 3.13).

#### 3.8.3.2 Treatment Discontinuation

After starting open-label IMP, 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 Interruption/Discontinuation

A subject may temporarily interrupt or 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)
    - Serious adverse event (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 (complete written withdrawal of consent form)
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

If the subject temporarily interrupts or 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 3.8.3.1 and 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 interrupt or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1 and 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 started on treatment, whether through randomization or open assignment.

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 the Week 26 visit will be defined as trial completers.

### 3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the Week 26 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 (ie, brexpiprazole). Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also noncompliant and should be considered for discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

### 3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

## 4 Restrictions

### 4.1 Prohibited Medications

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP. 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 enrollment. 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<br>Oral (or IR IM) aripiprazole<br>Other oral (or IR IM) antipsychotics<br>Depot or long-acting injectable antipsychotics | <br>14 days<br>7 days<br>One full cycle plus 1/2 cycle[a]<br>(length of 1 cycle based on the prescribing label) |
| Antidepressants<br>Fluoxetine or Symbyax<br>MAOIs<br>Citalopram and escitalopram<br>Venlafaxine and desvenlafaxine<br>All other antidepressants | <br>28 days[a]<br>14 days<br>8 days<br>3 days<br>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[b] | 14 days |

CYP = cytochrome P450; 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.

[b]Concomitant use of CYP3A4 inducers or CYP2D6/CYP3A4 inhibitors may be allowed with prior approval from the medical monitor, including a discussion with the medical monitor for potential dose adjustments of the IMP prior to initiation of therapy.

**Table 4.1-2 List of Medications Prohibited During the Trial**

| | |
|---|---|
| 1. | All psychotropic agents including, but not limited to, the following:<br>a) Antipsychotics, including depot or long-acting injectable formulations<br>b) Anticonvulsants |

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| Table 4.1-2 List of Medications Prohibited During the Trial | |
|---|---|
| | c) Antidepressants (including MAOIs)<br>d) Mood stabilizers (ie, lithium and/or anticonvulsants)<br>e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy[a]<br>f) Prescription stimulants (including appetite suppressants and treatments for ADHD or narcolepsy)<br>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).<br>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.) |

ADHD = attention-deficit hyperactivity disorder; CNS = central nervous system; CYP = cytochrome p450; MAOIs = monoamine oxidase inhibitors.

[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 intramuscular benzodiazepines and continual use of oral benzodiazepines is prohibited during this trial. However, limited use of oral lorazepam (up to 4 mg/day) as a

rescue medication for the short-term management of treatment-emergent AEs (TEAEs) of anxiety, agitation, and insomnia will be allowed during the trial. 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. 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 and 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.

## 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.[20]
- 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 in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.

  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (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 on the eSource platform provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF.

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

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 the upper limit of normal (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 ePlatform.

## 5.5 Pregnancy

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

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

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

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

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

A urine and/or serum pregnancy test for human chorionic gonadotropin 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

Not applicable. This is an open-label trial.

## 5.7 Follow-up of Adverse Events

For this trial, information on AEs will be followed for up to 21 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 noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until resolution of the AE is confirmed or the condition is considered clinically stable. 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 21days 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.

### 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 Pharmacokinetic Analysis

No PK analysis is planned.

# 7 Statistical Analysis

## 7.1 Sample Size

The sample size is not based on statistical power considerations but on ICH/GCP requirements. The trial population will be derived from eligible subjects from the double-blind, phase 3 trials (ie, Trials 331-201-00080 and 331-201-00081). In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at select sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

## 7.2 Datasets for Analysis

The following datasets are defined for this trial:

- Enrolled Sample, which comprises all subjects who sign an ICF for the trial.
- Safety Sample, which comprises all subjects that will receive at least 1 dose of IMP.
- CCI [redacted]

CCI [redacted]

[redacted]

## 7.4 Primary and Secondary Endpoint Analyses

### 7.4.1 Primary Endpoint Analysis

The primary safety endpoint analysis is the frequency and severity of AEs in the open-label treatment phase (Phase B). All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of TEAEs will include the following summaries:

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

A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption, or reduction of IMP.

### 7.4.2 Secondary Endpoint Analysis

Not applicable.

### 7.4.3 CCI

[redacted]

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- CCI [redacted]

[redacted]

### 7.4.4 Interim Analysis

No interim analysis is planned for this trial.

## 7.5 Analysis of Demographic and Baseline Characteristics

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

## 7.6 Additional Safety Analysis

Standard safety variables to be analyzed include clinical laboratory tests, vital signs, ECGs, and physical examinations. 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 waist circumference. Details of safety analyses will be provided in the statistical analysis plan (SAP).

### 7.6.1 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements 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.

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### 7.6.2 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.

### 7.6.3 Electrocardiogram Data

Mean change from baseline will be summarized by visit.

The incidence of clinically relevant changes will be calculated for ECG parameters and summarized 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's 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.

### 7.6.4 CCI

[redacted]

## 8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the brexpiprazole (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 as 1-mg, 2-mg, 3-mg, and 4-mg tablets. 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 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 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 identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

### 8.5.3 Return Process

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

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

### 8.5.4 Assessment/Evaluation

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

# 9 Records Management

## 9.1 Source Documents

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

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

## 9.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;

- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

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

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

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

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

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

At the end of the trial, the investigator must certify that the data entered 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, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science 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 eSource, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

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

## 12 Confidentiality

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

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

## 13 Amendment Policy

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

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the

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

# 14 Publication Authorship Requirements

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

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

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

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

# 15 References

1 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC, American Psychiatric Association, 2013.

2 Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 3: The clinical guidelines. Int J Neuropsychopharmacol. 2017;20(2):180-95.

3 Ostacher MJ, Tandon R, Suppes T. Florida Best Practice Psychotherapeutic Medication Guidelines for Adults With Bipolar Disorder: A Novel, Practical, Patient-Centered Guide for Clinicians. J Clin Psyciatry. 2016;77(7):920-6.

4 The Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington, DC: Department of Veterans Affairs and Department of Defense; 2010.

5 Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1-44.

6 Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. Bipolar Disord. 2009:11(Suppl 2):S45-54.

7 Brexpiprazole (OPC-34712) Investigator's Brochure, Otsuka Pharmaceutical Development & Commercialization, Inc. Version No. 9, 09 Sep 2013.

8 Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, et al. Reliability and validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. Eur Psychiatry. 1997;12:232-41.

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

10 US Food and Drug Administration [homepage on the Internet]. Rockville, MD: Guideline for industry: Structure and content of clinical study reports. ICH E3 [Jul 1996; cited 20 Aug 2013]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073113.pdf

C
Cl
[redacted]

14 Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, et al. The Mini International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview. J Clin Psychiatry. 1998;59(Suppl 20):22-33.

15 Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.

16 The Practical Guide: Identification, evaluation, and treatment of overweight and obesity in adults. Developed by National Institutes of Health National Heart, Lung and Blood Institute. North American Association for the Study of Obesity. NIH Publication Number 00-4084, October 2000.

17 Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publication No. ADM 76-338). Rockville, MD, US Department of Health, Education, and Welfare, 1976:534-7.

[redacted]

20 Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2008;27:31-40.

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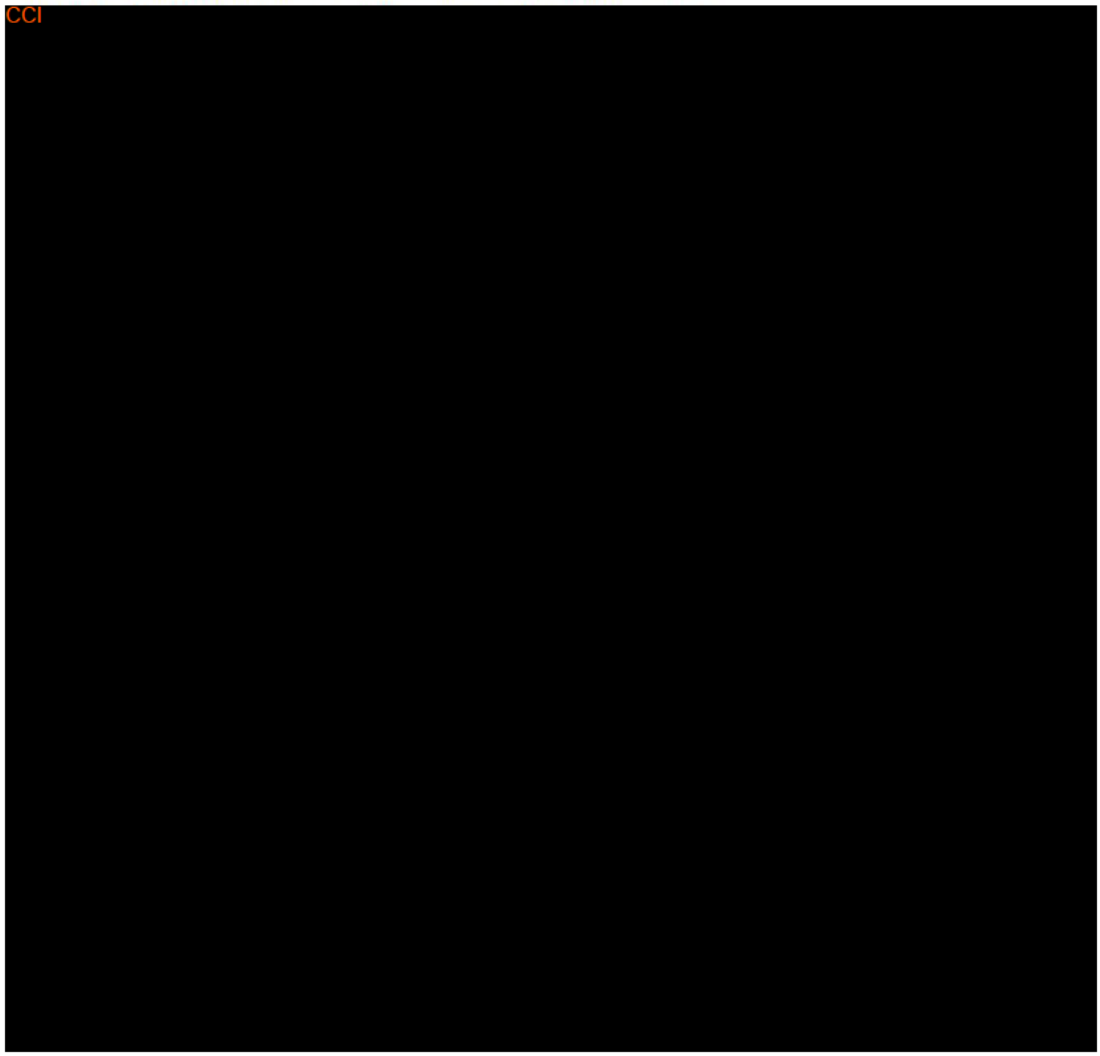

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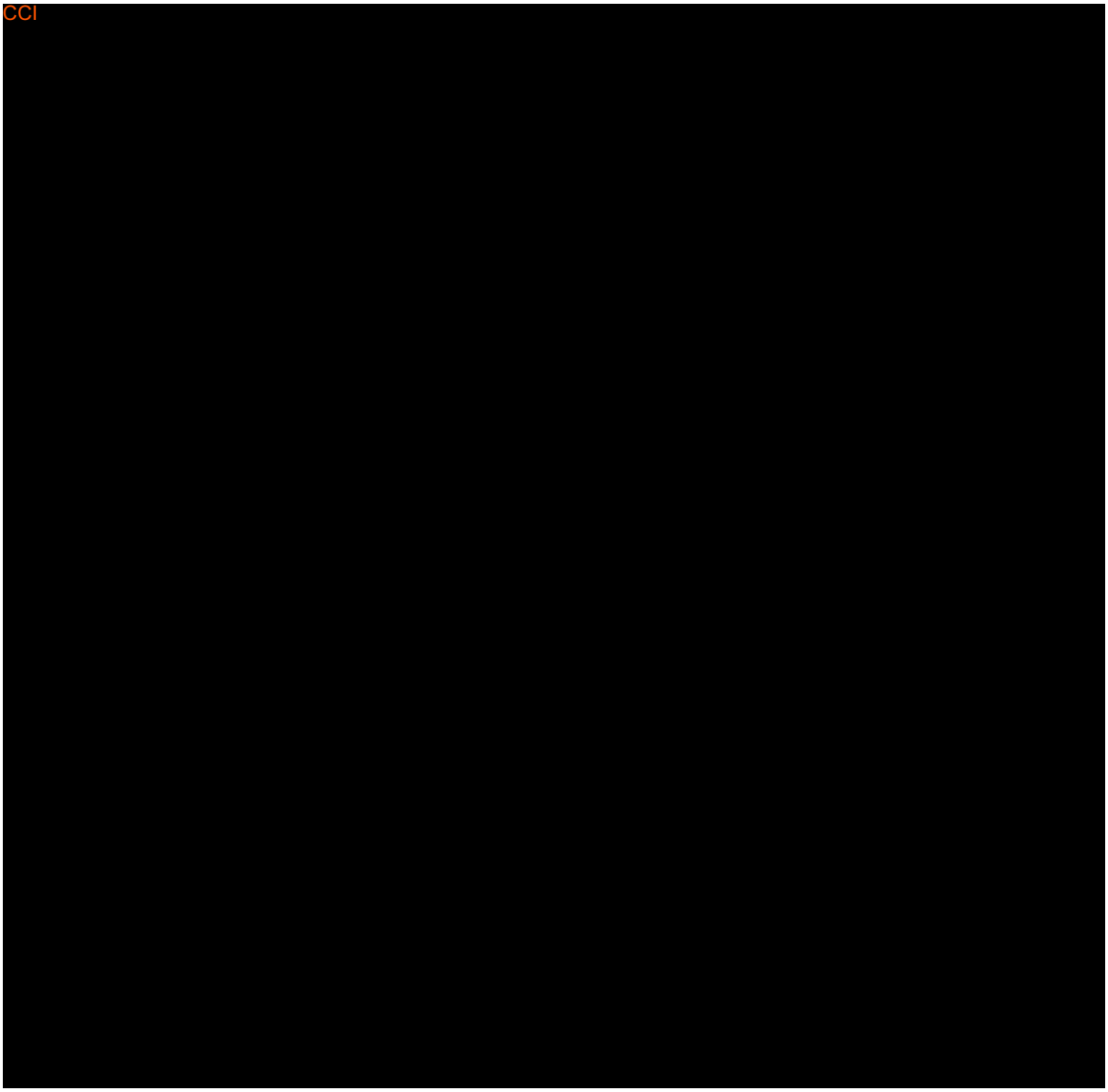

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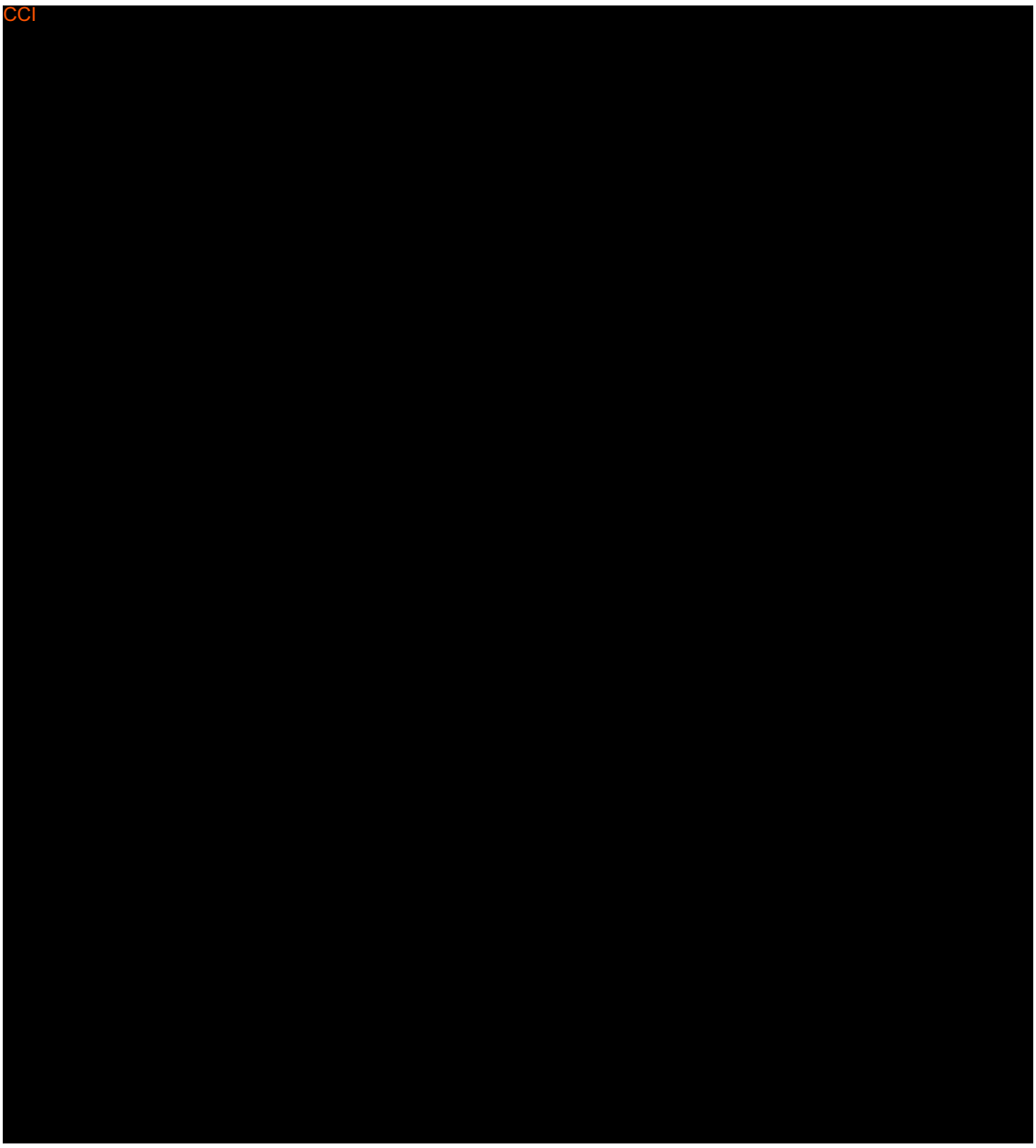

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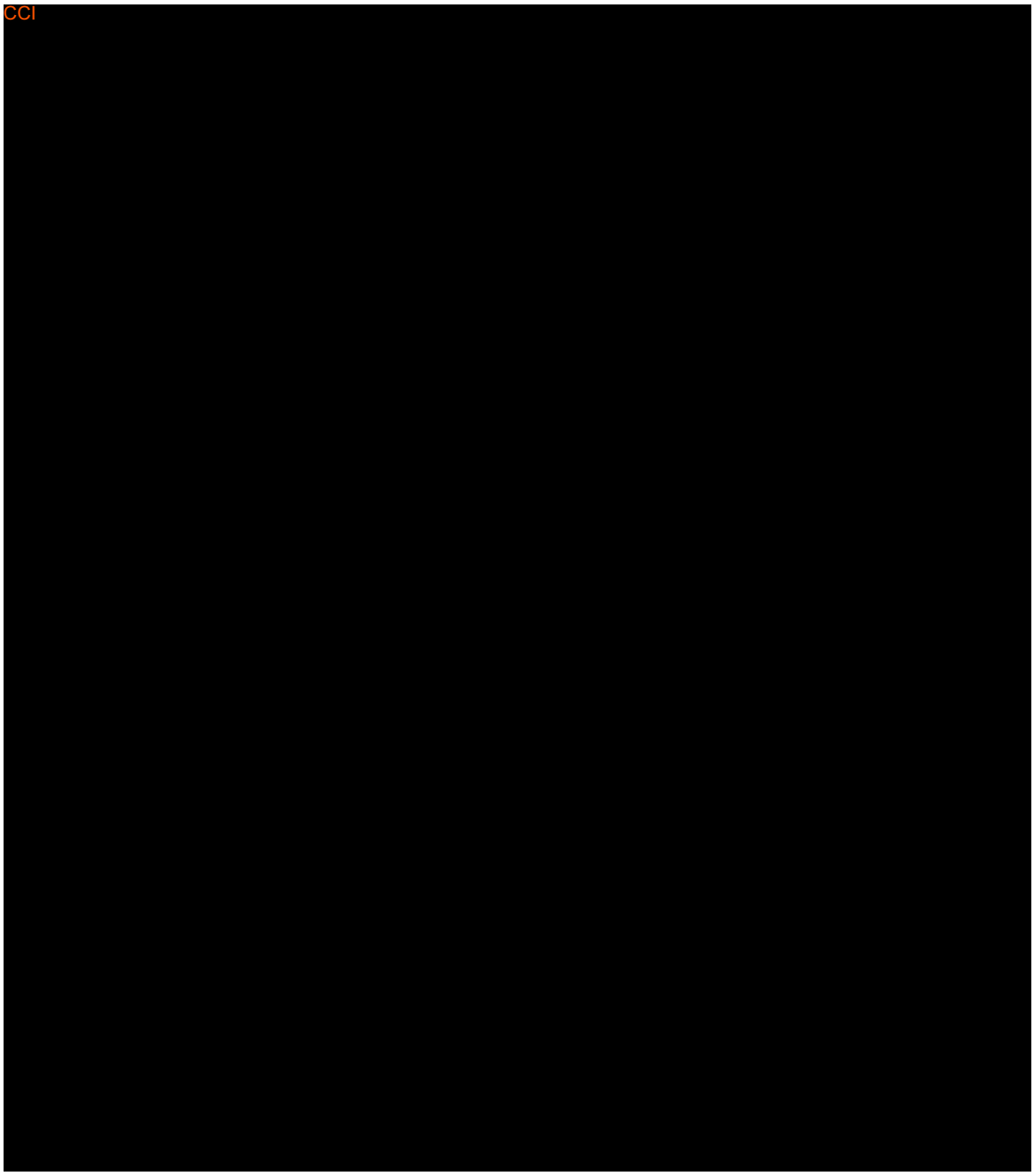

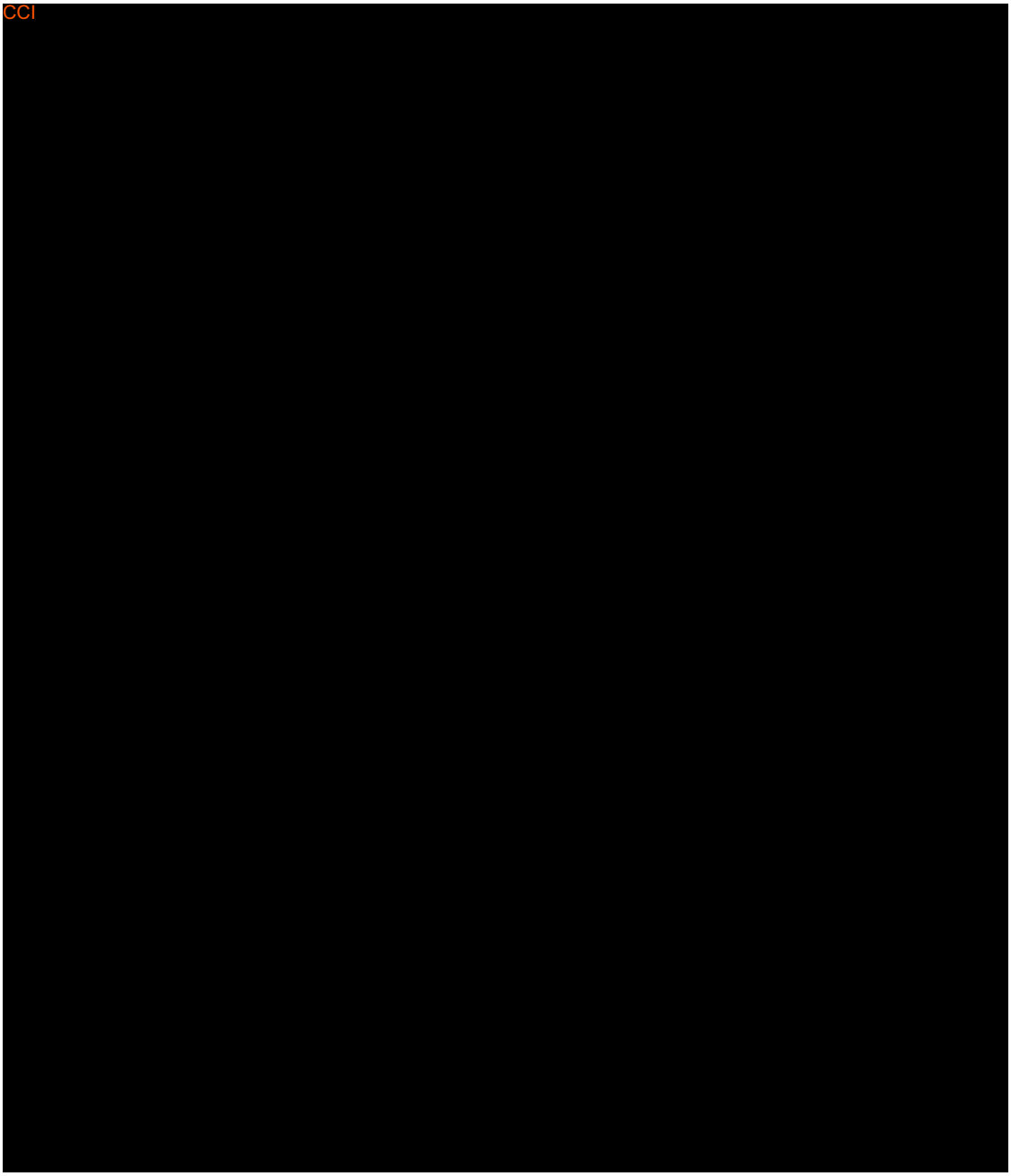

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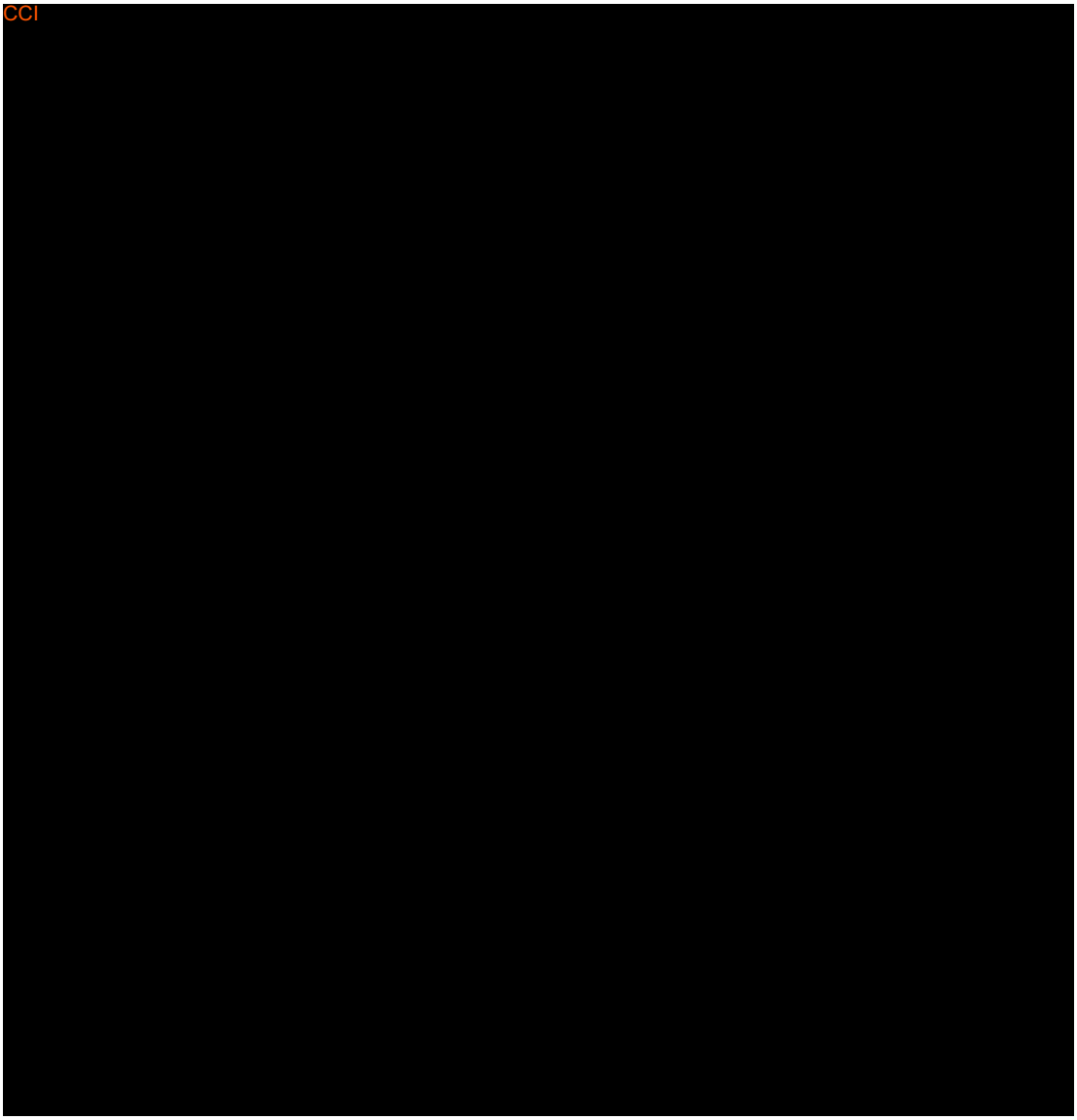

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## Appendix 4 Mini International Neuropsychiatric Interview

# 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) | ☐ | F32.x | ☐ |
| | | Past | ☐ | F32.x | ☐ |
| | | Recurrent | ☐ | F33.x | ☐ |
| B | SUICIDALITY | Current (Past Month) | ☐ | | ☐ |
| | | Lifetime attempt | ☐ | ☐ Low ☐ Moderate ☐ High | ☐ |
| | SUICIDE BEHAVIOR DISORDER | Current | ☐ | (In Past Year) | ☐ |
| | | In early remission | ☐ | (1 - 2 Years Ago) | ☐ |
| C | MANIC EPISODE | Current | ☐ | | |
| | | Past | ☐ | | |
| | HYPOMANIC EPISODE | Current | ☐ | | |
| | | Past | ☐ | ☐ Not Explored | |
| | BIPOLAR I DISORDER | Current | ☐ | F31.0 - F31.76 | ☐ |
| | | Past | ☐ | F31.0 - F31.76 | ☐ |
| | BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES | Current | ☐ | F31.2/31.5/F31.64 | ☐ |
| | | Past | ☐ | F31.2/31.5/F31.64 | ☐ |
| | BIPOLAR II DISORDER | Current | ☐ | F31.81 | ☐ |
| | | Past | ☐ | F31.81 | ☐ |
| | OTHER SPECIFIED BIPOLAR AND RELATED DISORDER | Current | ☐ | F31.89 | ☐ |
| | | Past | ☐ | F31.89 | ☐ |
| D | PANIC DISORDER | Current (Past Month) | ☐ | F41.0 | ☐ |
| | | Lifetime | ☐ | 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<br>Lifetime | ☐<br>☐ | F20.81-F29<br>F20.81-F29 | ☐<br>☐ |
| | MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES | Current<br>Past | ☐<br>☐ | F32.3/F33.3<br>F32.3/F33.3 | ☐<br>☐ |
| | BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES | Current<br>Past | ☐<br>☐ | F31.2/F31.5/F31.64<br>F31.2/F31.5/F31.64 | ☐<br>☐ |
| 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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## Appendix 5 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 6 Criteria for Identifying Vital Signs of Potential Clinical Relevance

| Variable | Criterion Value[a] | Change Relative to Baseline[a] |
|---|---|---|
| Heart rate[b] | > 120 bpm<br>< 50 bpm | ≥ 15 bpm increase<br>≥ 15 bpm decrease |
| Systolic blood pressure[b] | > 180 mmHg<br>< 90 mmHg | ≥ 20 mmHg increase<br>≥ 20 mmHg decrease |
| Diastolic blood pressure[b] | > 105 mmHg<br>< 50 mmHg | ≥ 15 mmHg increase<br>≥ 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<br>≥ 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 New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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## Appendix 7 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<br>≥ 12 weeks post trial entry |
| **ST/T Morphological** | | |
| Myocardial ischemia | all | not present → present |
| Symmetrical T-wave inversion | all | not present → present |
| Increase in QTc | QTcF ≥ 450 msec (men)<br>QTcF ≥ 470 msec (women) | |

[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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CCI [redacted]

CCI [redacted]

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Protocol 331-201-00083

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Protocol 331-201-00083

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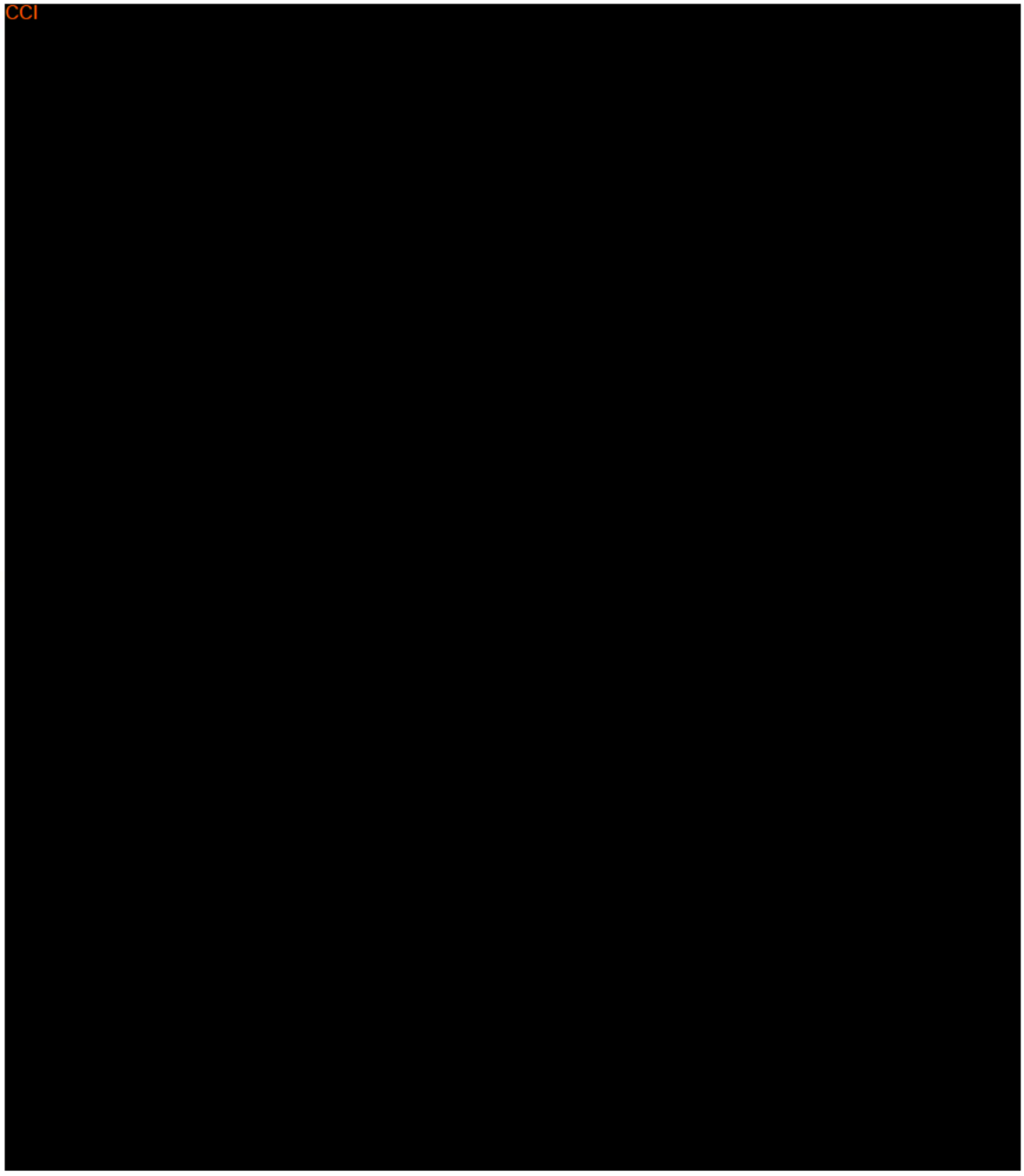
Protocol 331-201-00083



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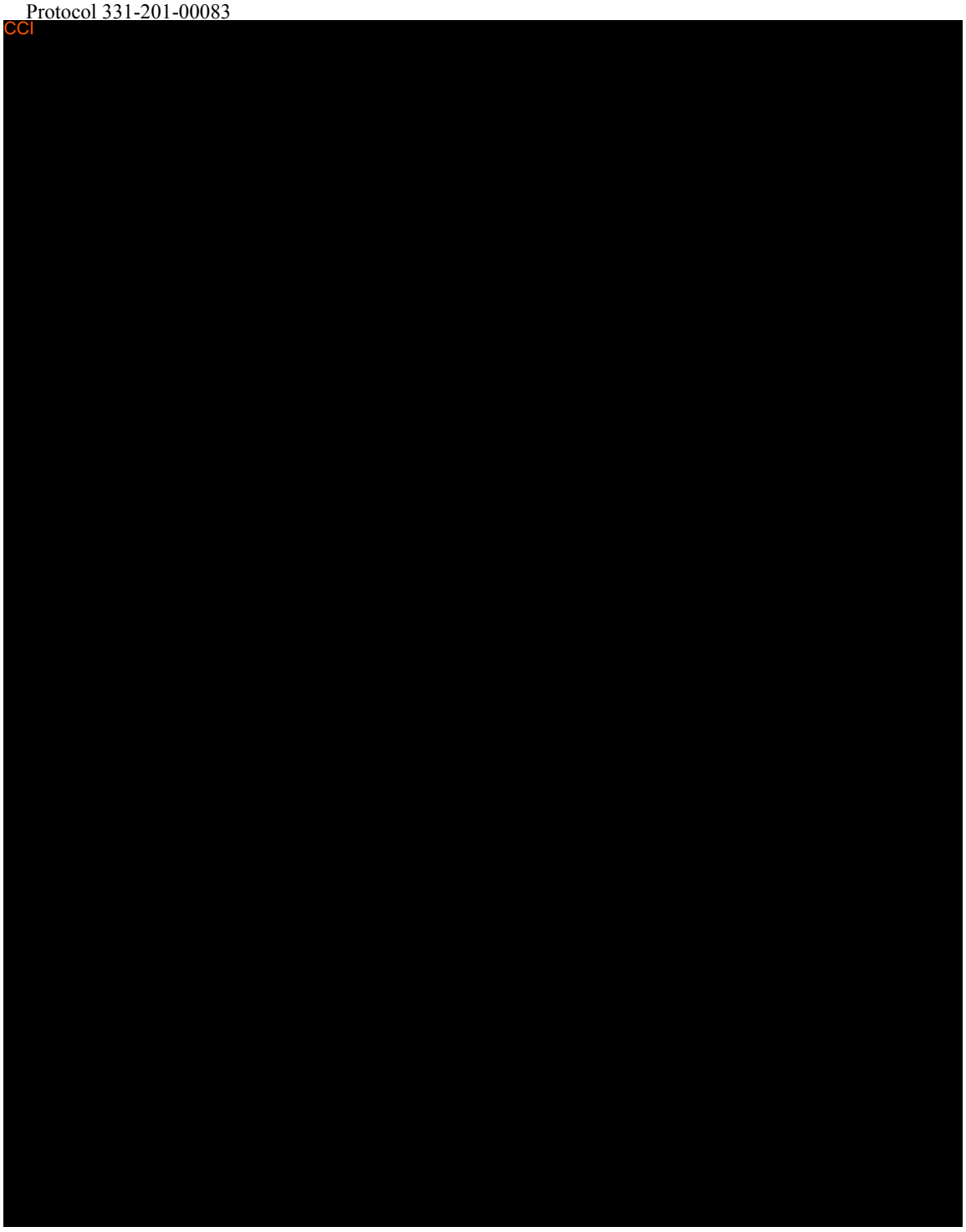

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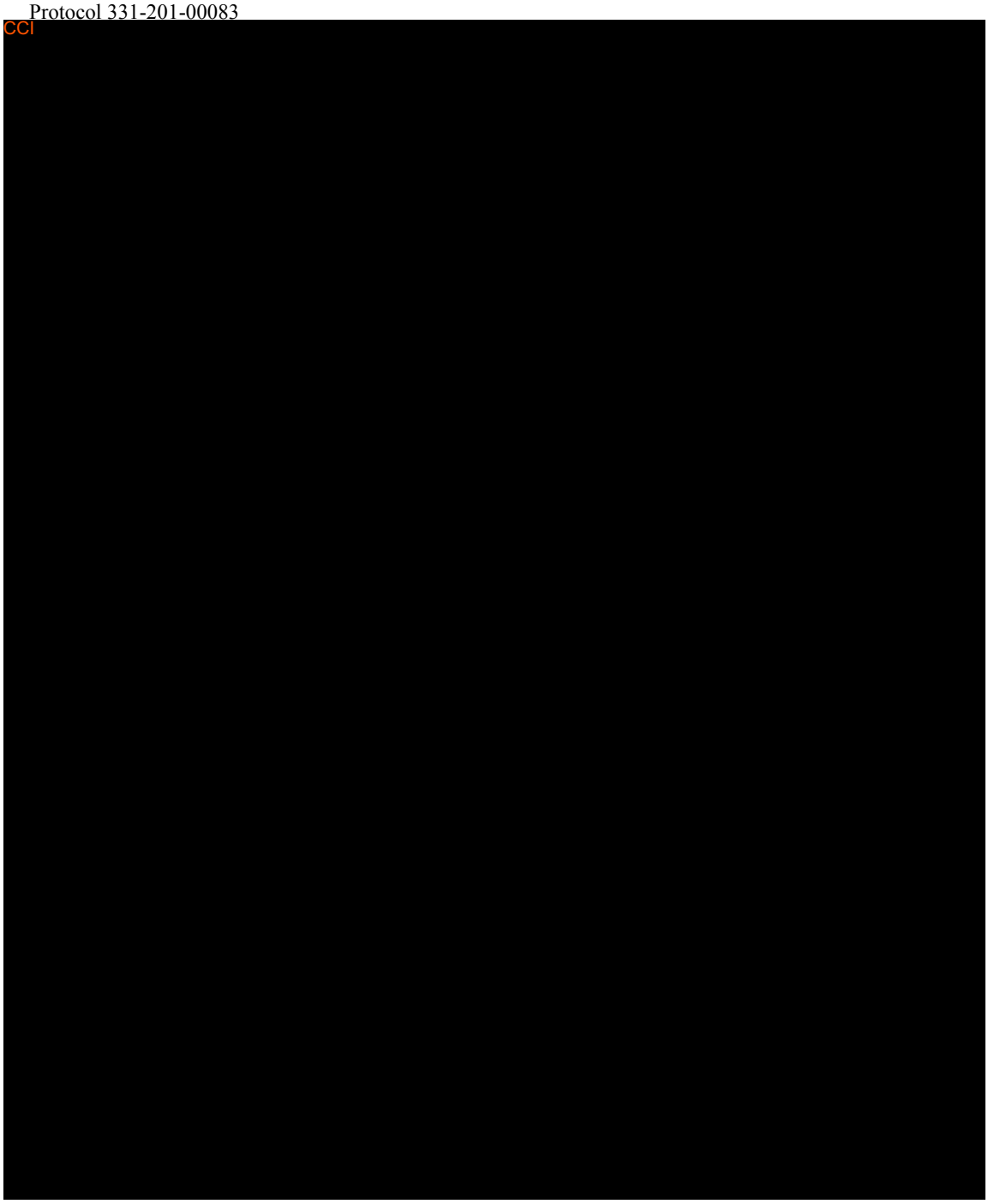

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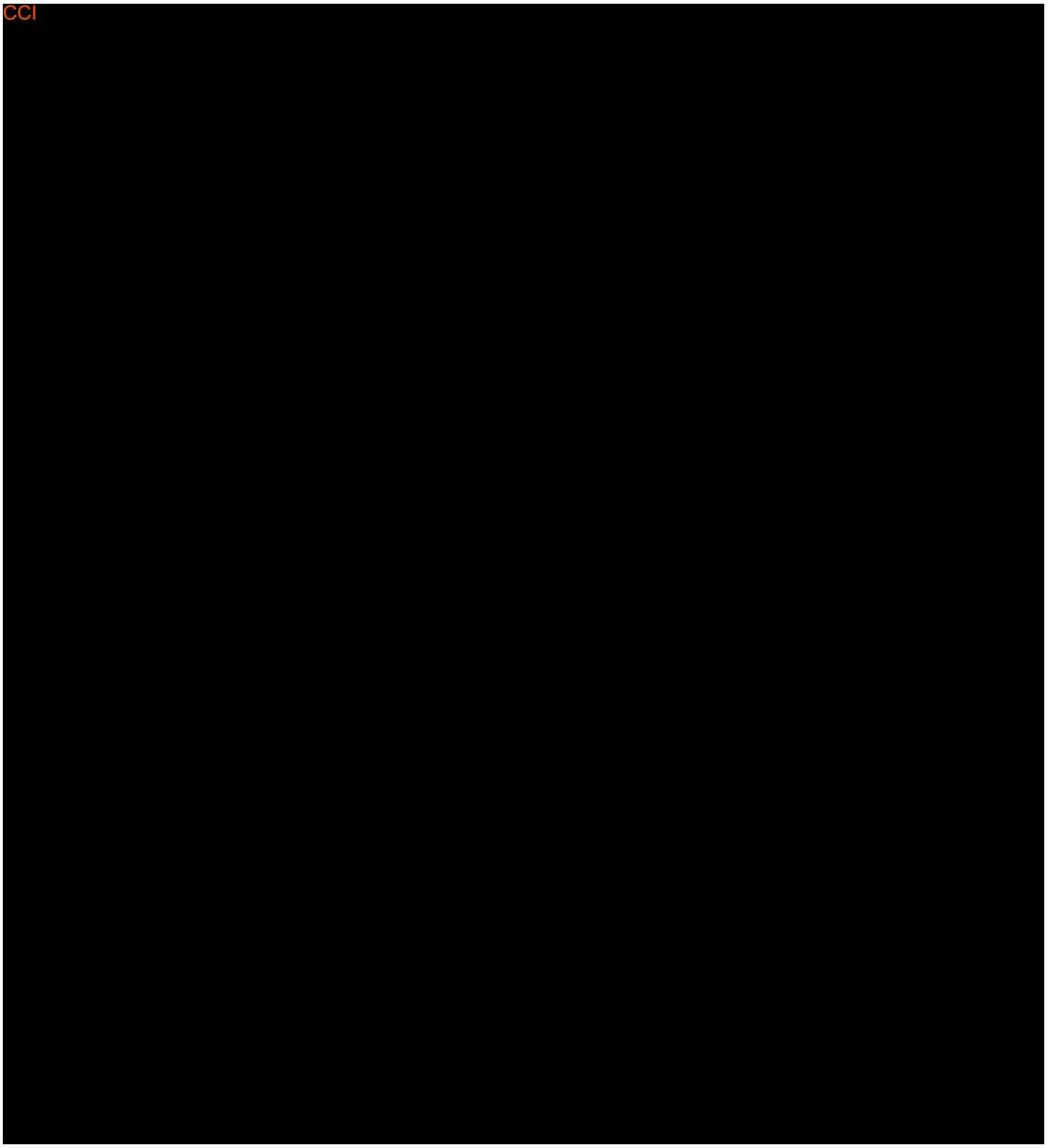

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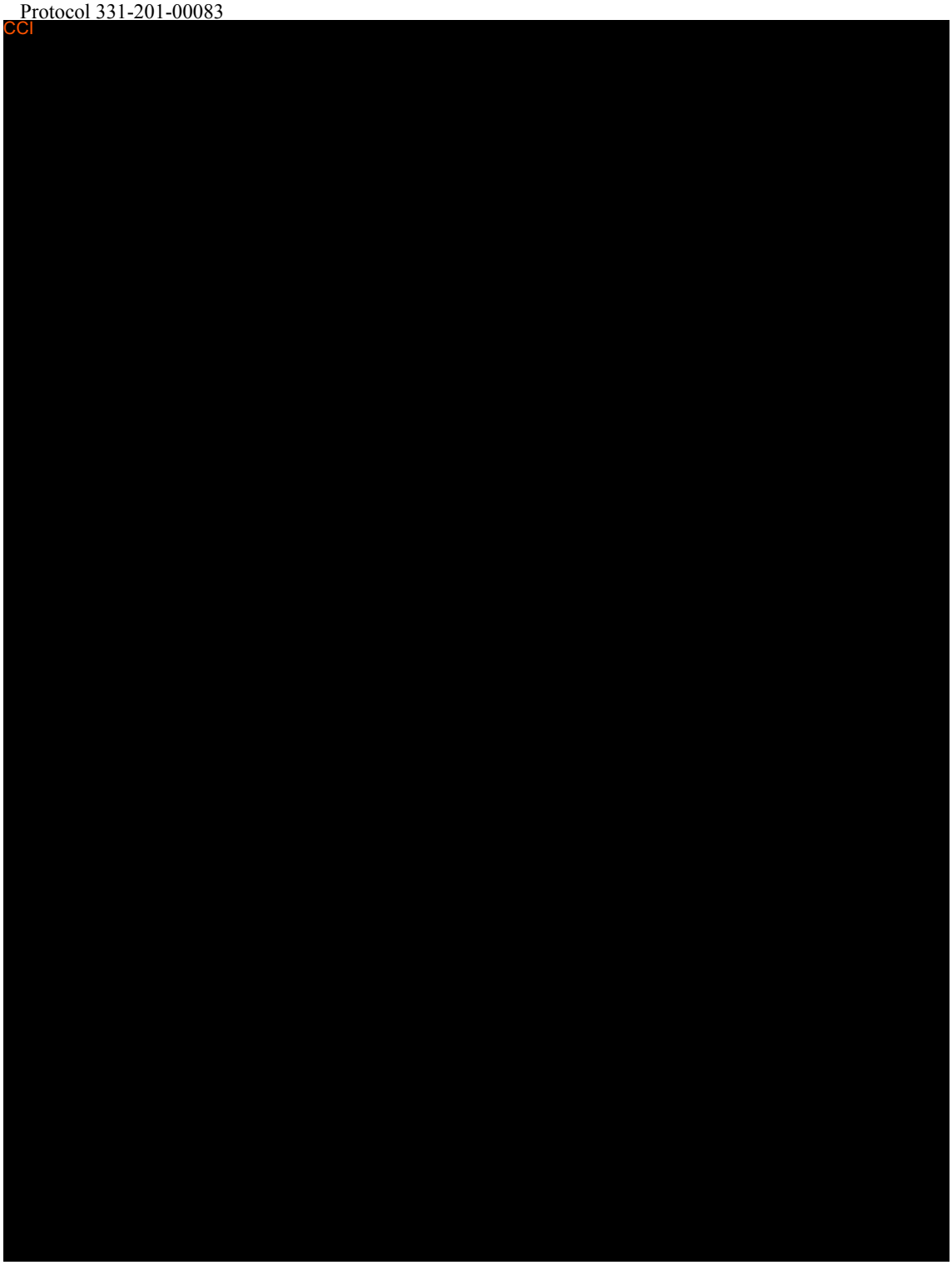

Protocol 331-201-00083

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Protocol 331-201-00083

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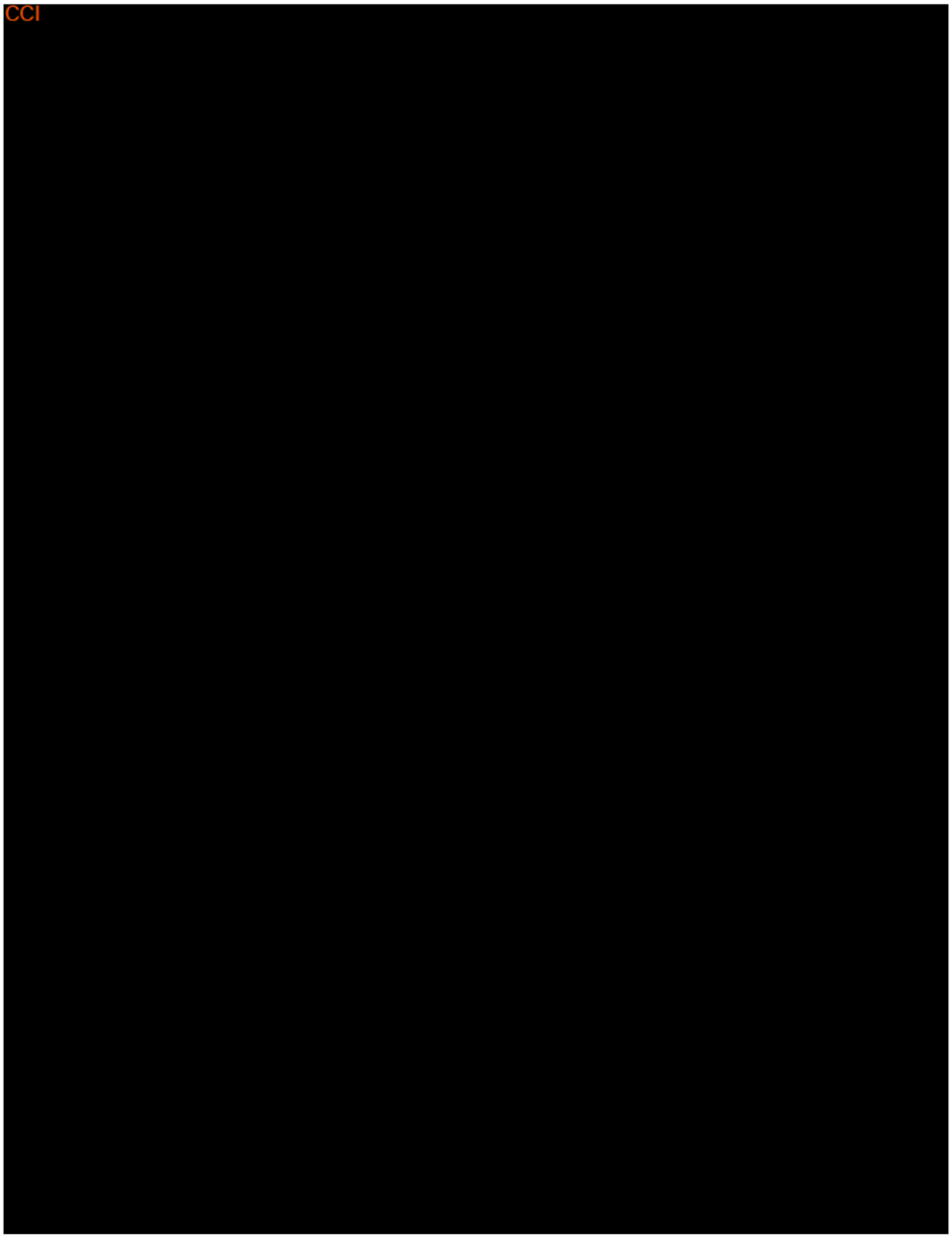

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**Appendix 14 Protocol Amendment(s)/Administrative Change(s)**

**Amendment Number:** 1

**Issue Date:** 20 Oct 2017

**PURPOSE:**

The purpose of amending the Protocol 331-201-00083, issued 07 Jun 2017, was to:

- Update the document with minor wording revisions for grammatical and administrative clarification
- Clarify when evaluations were conducted during the trial in the Schedule of Assessments
- CCI [redacted]
- Remove language indicating a confirmation of data download from the wearable device will be performed
- Remove laboratory tests for adrenocorticotropic hormone and cortisol
- Allow anticholinergics and propranolol with daily limits
- Update the way pregnancy is reported in Section 5 "Reporting of Adverse Events"

CCI [redacted]

**BACKGROUND:**

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

- After consultation with experts in the field of sleep medicine, it was determined that a daily sleep diary filled out by subjects would add accuracy to the actigraphic data being collected by the wearable device. Trial personnel will instruct subjects on how to complete the daily electronic sleep diary and electronic sleep diary accountability will be performed
- Language in Section 3.7.1.3 was removed indicating that a confirmation of data download from the wearable device will be performed in the post-treatment follow-up period. The wearable device will be turned in at the End of Treatment - Week 26/Early Termination Visit and there will be no data collected or downloaded during the Post-treatment follow up period

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- Laboratory tests for ACTH and cortisol are not included in the 331-201-00080 or 331-201-00081 protocols and were inadvertently included in the 331-201-00083 protocol

CCI [redacted]

- The Sponsor has changed the way pregnancies are to be reported. Language was added to Section 5 of the protocol to clarify how pregnancies should be reported

CCI [redacted]

**MODIFICATIONS TO PROTOCOL:**

**General Revisions:**

All changes by section are provided below.

**Sectional Revisions:**

| Location | Old Text | Updated Text |
|---|---|---|
| Title Page | Issue Date: 30 May 2017<br><br>Version No.: 1.0 | Issue Dates:<br>Original Protocol: 30 May 2017<br>Date of Amendment 1: **19 Oct 2017**<br><br>Version No.: **2.0** |
| Synopsis, Criteria for Evaluation | CCI [redacted] | [redacted] |

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| Location | Old Text | Updated Text |
|---|---|---|
| Synopsis, Criteria for Evaluation | [redacted] | [redacted] |
| List of Abbreviations | ACTH Adrenocorticotropic hormone | Abbreviation removed. |
| List of Abbreviations | [redacted] | Abbreviation removed. |
| 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.** |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| | Changes to Table 3.7-1 and Table 3.7-2 are summarized on the next page and are indicated by **bold, underlined text**. | |

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**Table 3.7-1 Schedule of Assessments - Open-label Treatment (Phase B)**

| Assessment | Screening / Baseline[a] (Rollover) | Phase B Baseline[a] (De Novo) | Open-Label Treatment Phase Trial Week Visit (± 2 days) | | | | | | | Follow-up 21 (± 2) days[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 4 | 8 | 12 | 18 | 26/ ET[b] | |
| **ENTRANCE CRITERIA** | | | | | | | | | | |
| Informed consent | X[d] | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Medical history | X[e] | | | | | | | | | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| **SAFETY** | | | | | | | | | | |
| Physical examination | X[f] | X[g] | | | | | | | X | |
| Waist circumference | X[f] | X[g] | | | | | | | X | |
| Vital signs[i] | X[f] | X[g] | X | X | X | X | X | X | X | |
| 12-lead ECG[j] | X[f] | X[g] | | | | | X | | X | |
| Clinical laboratory tests[k] | X[f,l] | X[g,l] | | | | | X[m] | | X[m] | |
| HbA1c | X[f,l] | X[g,l] | | | | | X[m] | | X[m] | |
| Drug screen/blood alcohol[n] | X[f] | X[g] | | | X | | X | | X | |
| Urine pregnancy test (WOCBP only)[o] | X[f] | X[g] | X | X | X | X | X | X | X | |
| SAS | X[f] | X[g] | X | X | X | X | X | X | X | |

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**Table 3.7-1 Schedule of Assessments - Open-label Treatment (Phase B)**

| Assessment | Screening / Baseline[a] (Rollover) | Phase B Baseline[a] (De Novo) | Open-Label Treatment Phase Trial Week Visit (± 2 days) | | | | | | | Follow-up 21 (± 2) days[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 4 | 8 | 12 | 18 | 26/ ET[b] | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| Adverse events[q] | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| **OTHER** | | | | | | | | | | |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| Dose adjustment[r] | | | X | X | X | X | X | X | X | |
| Register visit in IWRS | X | X | X | X | X | X | X | X | X | |
| IMP dispensing | X | X | X | X | X | X | X | X | | |
| IMP accountability | | | X | X | X | X | X | X | X | |

CCI IWRS = interactive web response system.

[a]For rollover subjects, screening for Trial 331-201-00083 occurs simultaneously with baseline which will be at the same day as the Day 21 (Week 3) visit of Trial 331-201-00080 or Trial 331-201-00081. Separate screening and baseline visits are required for de novo subjects to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

[b]If a subject discontinues early before Week 26, procedures noted for Week 26 must be completed at the ET visit. Attempts should be made to complete ALL evaluations, particularly efficacy assessments, for the Week 26/ET visit prior to the administration of any new psychotropic medications. However, if the subject

receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes.

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

[d]Informed consent for Trial 331-201-00083 will occur at screening/baseline for rollover subjects and must be obtained before any trial-related procedures specific to the open-label trial are performed.

[e]Update, if necessary, for rollover subjects.

[f]Screening/baseline value will be obtained from the Day 21 (Week 3) visit of Trial 331-201-00080 or Trial 331-201-00081.

[g]Baseline assessment will be performed at baseline of Phase B for de novo subjects who enter Phase B directly after screening, but will be obtained from the Conversion Week 4 visit of Phase A for subjects who participate in Phase A.

CCI [redacted]

[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. However, ECG results will also be evaluated at the investigational site to monitor safety during the trial. Rollover subjects will be enrolled in Trial 331-201-00083 based on the screening/baseline ECG results from the trial site. If the screening/baseline ECG results from the central reader, when available, indicate a QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing.at screening/baseline, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial. For de novo subjects, ECG results from the central reader must be reviewed for exclusion criteria prior to the first dose of open-label brexpiprazole in Phase B. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[k]Includes hematology (including prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]), 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 urinalysis.

[l]Rollover subjects must be fasting for a minimum of 8 hours prior to blood draws for screening/baseline 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. A fasting blood sample is required at baseline prior to dosing. De novo subjects must fast for a minimum of 8 hours prior to blood draws for baseline laboratory assessments.

[m]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at Week 26/ET and should be drawn after a minimum 8-hour fast at all other visits, if possible. Vital sign and ECG assessments should be completed before any blood samples are collected.

[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. If results of either or both are positive, the investigator must contact the medical monitor to discuss the subject's eligibility for continued participation in the trial.

[o]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with positive urine and serum pregnancy test results at screening, baseline, or screening/baseline must not be enrolled in Trial 331-201-00083. 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.

CCI [redacted]

[q]AE recording will begin with the signing of the ICF for Trial 331-201-00083.

[r]Adjustments to the dose of brexpiprazole can be made at scheduled and unscheduled visits during the 26-week open-label treatment phase (ie, Phase B) to optimize efficacy and tolerability as described in the protocol. Subjects must return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits.

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**Table 3.7-2 Schedule of Assessments - Screening and Conversion (Phase A): De Novo Subjects**

The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

| Assessment | Screening (Days -14 to -1)[a] | Phase A Baseline | Conversion Week 1 (± 2 days) | Conversion Week 2 (± 2 days) | Conversion Week 3 (± 2 days) | Conversion Week 4/ Phase B Baseline[b] (± 2 days) |
|---|---|---|---|---|---|---|
| **ENTRANCE CRITERIA** | | | | | | |
| Informed consent[c] | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | X |
| Medical history | X | | | | | |
| Demography | X | | | | | |
| Psychiatric history | X | | | | | |
| MINI | X | | | | | |
| Prior medication washout[d] | X | | | | | |
| HIV, HBsAg, and anti-HCV | X | | | | | |
| CCI [redacted] | | | | | | |
| **SAFETY** | | | | | | |
| Physical examination[e] | X | | | | | X |
| Waist circumference | | X | | | | X |
| Vital signs[f] | X | X | X | X | X | X |
| 12-lead ECG[g] | X | | | | | X |
| Clinical laboratory tests (hematology, serum chemistry [including prolactin], and urinalysis)[h] | X[i] | | | | | X |
| TSH with reflex to free $T_4$ if abnormal[h] | X[i] | | | | | X |
| HbA1c[h] | X[i] | X | | | | X |

**Table 3.7-2 Schedule of Assessments - Screening and Conversion (Phase A): De Novo Subjects**

The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

| Assessment | Screening (Days -14 to -1)[a] | Phase A Baseline | Conversion Week 1 (± 2 days) | Conversion Week 2 (± 2 days) | Conversion Week 3 (± 2 days) | Conversion Week 4/ Phase B Baseline[b] (± 2 days) |
|---|---|---|---|---|---|---|
| PT, aPTT, and INR[h] | X | X | | | | X |
| Drug screen/blood alcohol[j] | X | | | | | X |
| Urine pregnancy test (WOCBP only)[k] | X | | | | | X |
| CCI | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| Adverse events | X[m] | X | X | X | X | X |
| Concomitant medications[n] | X | X | X | X | X | X |
| **OTHER** | | | | | | |
| CCI | | | | | | |
| | | | | | | |
| | | | | | | |
| Register visit in IWRS | X | X | X | X | X | X |
| Cross-titration[o] | | X | X | X | X | X |
| IMP dispensing | | X | X | X | X | X |
| IMP accountability | | | X | X | X | X |

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

[a]All de novo subjects (ie, subjects who did not participate in one of the double-blind phase 3 trials) will enter a screening period to determine eligibility for the open-label trial. 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 prior to baseline. Review of inclusion/exclusion criteria at baseline will be based on some assessments performed during screening.

[b]If a subject discontinues early before Week 4, procedures noted for Week 26/ ET must be completed at the ET visit. Attempts should be made to complete **ALL** evaluations, particularly efficacy assessments for the Week 26/ET visit prior to the administration of any new psychotropic medications. However, if the subject receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation in the source notes.

[c]Informed consent must be obtained before any trial-related procedures are performed.

[d]Washout of prohibited medications begins after signing the ICF. Details of medications requiring washout are provided in Section 4.1. Prohibited and restricted medications are also provided in Section 4.1. In addition, all antipsychotic medications used within 30 days of the first dose of IMP will be recorded.

[e]To include measurement of height at screening only.

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

[g]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. However, ECGs will also 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. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[h]Blood samples for clinical laboratory tests must be drawn after a minimum 8-hour fast at screening and Conversion Week 4, 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. Vital sign and ECG assessments should be completed before any blood samples are collected.

[i]See Section 3.4.3 for exclusions based on screening laboratory results.

[j]A urine drug screen and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator. If results of either or both are positive, the investigator must contact the medical monitor to discuss the subject's eligibility for continued participation in the trial.

[k]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.

CCI [redacted]

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[m]AE recording will begin with the signing of the ICF.

[n]All prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in Section 4.1.

[o]Cross-titration will occur over a 4-week period in order to bring about a stable transition from previous antipsychotic treatment(s) to oral brexpiprazole.

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| | | |
|---|---|---|
| Section 3.7.1.1.2.1, Screening | • CCI [redacted] | [redacted] |
| Section 3.7.1.1.2.2, Baseline (Phase B) | Not applicable (newly added text) | CCI [redacted] |
| Section 3.7.1.1.2.2, Baseline (Phase B) | CCI [redacted] | [redacted] |
| Section 3.7.1.1.2.3, Baseline (Phase A) | • Blood samples for clinical laboratory tests (coagulation parameters, adrenocorticotropic hormone (ACTH), cortisol, and HbA1c) must be collected after a minimum 8-hour fast. | • Blood samples for clinical laboratory tests (coagulation parameters and HbA1c) must be collected after a minimum 8-hour fast. |
| Section 3.7.1.1.2.3, Baseline (Phase A) | Not applicable (newly added text) | CCI [redacted] |
| Section 3.7.1.1.2.3, Baseline (Phase A) | CCI [redacted] | Evaluation deleted by Amendment 1. |
| Section 3.7.1.1.2.3, Baseline (Phase A) | Not applicable (newly added text) | • **Trial personnel will instruct subjects on how to complete a daily electronic sleep diary during the course of the trial.** |
| Section 3.7.1.1.2.4, Conversion to Oral Brexpiprazole (Conversion Weeks 1, 2, 3, and 4 of Phase A) | Not applicable (newly added text) | <u>Conversion Weeks 1, 2, and 3:</u><br>CCI [redacted] |
| Section 3.7.1.1.2.4, Conversion to Oral Brexpiprazole (Conversion Weeks 1, 2, 3, and 4 of Phase A) | <u>Conversion Week 4/Baseline of Phase B:</u><br>• Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, ACTH, cortisol, and TSH with reflex to $T_4$ if the result for TSH is abnormal) must be collected after a minimum 8-hour fast. | <u>Conversion Week 4/Baseline of Phase B:</u><br>• Blood samples for clinical laboratory tests (hematology, coagulation parameters, and serum chemistry, including prolactin, HbA1c, and TSH with reflex to $T_4$ if the result for TSH is abnormal) must be collected after a minimum 8-hour fast. |
| Section 3.7.1.2.1, Week 1 | Not applicable (newly added text) | CCI [redacted] |
| Section 3.7.1.2.2, Week 2 | Not applicable (newly added text) | CCI [redacted] |

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| | | |
|---|---|---|
| Section 3.7.1.2.3, Week 4 | • Urine will be collected from all subjects for urinalysis and urine screen(s) for drugs of abuse. | • Urine will be collected from all subjects for urine screen(s) for drugs of abuse. |
| Section 3.7.1.2.3, Week 4 | Not applicable (newly added text) | • CCI |
| Section 3.7.1.2.4, Week 8 | Not applicable (newly added text) | • CCI |
| Section 3.7.1.2.5, Week 12 | Not applicable (newly added text) | • CCI |
| Section 3.7.1.2.6, Week 18 | Not applicable (newly added text) | • CCI |
| Section 3.7.1.2.7, End of Treatment - Week 26/Early Termination | Not applicable (newly added text) | • CCI |
| Section 3.7.1.3 | Adverse events and concomitant medications will be recorded and a confirmation of data download from the wearable device will be performed. | Adverse events and concomitant medications will be recorded. |
| CCI | | |
| CCI | | |

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| | | |
|---|---|---|
| Section 3.7.2.4, Other Assessments | Not applicable (newly added text) | CCI [redacted] |
| Table 3.7.3.2-1, Clinical Laboratory Assessments | Adrenocorticotropic hormone (ACTH)<br>Cortisol | Assessments removed. |
| 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.** |
| 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. |
| Sction 5.2, Eliciting and Reporting Adverse Events | To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" <u>All</u> AEs (serious and nonserious) reported by the subject must be recorded on the eSource and ePlatform provided by the sponsor. | To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" <u>All</u> AEs (serious and nonserious) reported by the subject must be recorded on the eSource platform provided by the sponsor. |
| CCI [redacted] | [redacted] | [redacted] |

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| Section 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).<br><br>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. | Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and body mass index (BMI) will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable). |
| Section 7.6.3, Electrocardiogram Data | Mean change from baseline will be summarized by treatment group and by visit.<br><br>The incidence of clinically relevant changes will be calculated for ECG parameters and summarized by treatment group and by visit. | Mean change from baseline will be summarized by visit.<br><br>The incidence of clinically relevant changes will be calculated for ECG parameters and summarized by visit. |
| CCI [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| Appendix 5, Criteria for Identifying Laboratory Values of Potential Clinical Relevance | Laboratory test criteria updated to match text of the protocol. | |
| CCI [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

Agreement

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

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, 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 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.

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|---|---|---|
| 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

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