Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-34712

# REVISED CLINICAL PROTOCOL

A Multicenter, Randomized, Flexible-dose, Double-blind Trial of Brexpiprazole Versus Placebo for the Treatment of Adults With Borderline Personality Disorder

A Trial of Brexpiprazole in the Treatment of Borderline Personality Disorder

Protocol No. 331-201-00242
IND No. 141091
EudraCT No. 2019-002813-20

CONFIDENTIAL — PROPRIETARY INFORMATION

| | |
|---|---|
| Clinical Development Phase: | 2 |
| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>2440 Research Boulevard<br>Rockville, Maryland 20850, United States |
| Immediately Reportable Event | Syneos Health Pharmacovigilance & Drug Safety<br>Fax: +1 877.464.7787<br>Email: safetyreporting@syneoshealth.com |
| Amendment 1 Approval:<br>Original Approval: | 07 Jul 2020<br>09 Jul 2019 |

## Trial Conduct for COVID-19

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

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# 1 Protocol Summary

## 1.1 Synopsis

**Name of Sponsor:** Otsuka Pharmaceutical Development & Commercialization, Inc.

**Name of Investigational Medicinal Product:** Brexpiprazole (OPC-34712)

**Protocol No.:** 331-201-00242

**IND No.:** 141091

**Protocol Title**: A Multicenter, Randomized, Flexible-dose, Double-blind Trial of Brexpiprazole Versus Placebo for the Treatment of Adults With Borderline Personality Disorder

**Protocol Lay Person Short Title**:

A Trial of Brexpiprazole in the Treatment of Borderline Personality Disorder

**Clinical Phase/Trial Type:** Phase 2 / Therapeutic confirmatory

**Treatment/Indication:** For the treatment of borderline personality disorder (BPD)

**Objectives and Endpoints:**

| **Trial Objectives and Endpoints** | |
|---|---|
| **Objectives** | **Endpoints** |
| Primary: To compare the efficacy of brexpiprazole versus placebo for the treatment of subjects with a diagnosis of BPD | Primary efficacy: Change from baseline in the ZAN-BPD total score |
| | Key secondary efficacy: Change from baseline in the CGI-S score |
| | Secondary efficacy:<br>• Change from baseline in the PGI-S for each trial visit during the double-blind treatment period<br>• PGI-C score<br>• CGI-I score |

| | |
|---|---|
| | Exploratory efficacy:<br>• Change from baseline in the ZAN-BPD total score for each trial visit during the double-blind treatment period<br>• Change from baseline in the CGI-S score for each trial visit during the double-blind treatment period<br>• Change from baseline in the WHODAS 2.0 score<br>• Change from baseline in the HADS-A and HADS-D scores<br>• Change from baseline in the ZAN-BPD sector scores<br>• Change from baseline in the CGI-SS-extended scale |
| Secondary: To evaluate the safety and tolerability of brexpiprazole for the treatment of subjects with a diagnosis of BPD | • Frequency and severity of AEs<br>• Changes in ECGs, vital signs, clinical laboratory tests including blinded prolactin, body weight, and physical examinations<br>• Extrapyramidal symptoms: SAS, the AIMS, and the BARS<br>• Suicidal ideation and behavior will be assessed using the C-SSRS |

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = CGI-I = Clinical Global Impression-Improvement of Illness; CGI-S = Clinical Global Impression-Severity of Illness; CGI-SS = Clinical Global Impression- Severity of Suicidality; C-SSRS = Columbia-Suicide Severity Rating Scale; Barnes Akathisia Rating Scale; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression Scale; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; SAS = Simpson Angus Scale; WHODAS = World Health Organization Disability Assessment Schedule; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

**Trial Design:**

This will be a 12-week, multicenter, randomized, double-blind, placebo-controlled, 2-arm trial evaluating the efficacy and safety of brexpiprazole treatment in adult subjects with BPD. Subjects will be randomized (1:1) to 2-3 mg/day brexpiprazole (n = 120) or placebo (n = 120).

The trial will consist of a screening period (up to 21 days), a 12-week, double-blind treatment period, and safety follow-up (21 [±2] days after the last dose of investigational medicinal product [IMP]).

**Trial Population:**

Approximately 350 subjects will be screened to have 240 subjects randomized into the trial.

**Key Inclusion Criteria:**

The trial population will consist of male and female outpatients, aged 18 to 65 years, inclusive. Subjects will have a BPD diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) and confirmed by a valid diagnostic instrument (Structured Clinical Interview for DSM-5 Personality Disorders [SCID-5-PD]) and a total score of ≥ 12 on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) at the screening visit and at Day 0. In addition, a score of ≥ 2 in at least 2 of the following 4 ZAN-BPD subscale items will be required at screening and Day 0: 1) "inappropriate, intense anger or difficulty controlling anger" (hereafter referred to as inappropriate anger), 2) "transient stress-related paranoid ideation or severe dissociative symptoms" (paranoid ideation), 3) "affective instability due to a marked reactivity of mood" (affective instability), and 4) "impulsivity in at least other two areas that are potentially self-damaging" (impulsivity).

**Trial Sites:**

This trial will be conducted in the United States (US) and Europe.

**Investigational Medicinal Product, Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:**

During the double-blind treatment period, subjects will receive IMP, consisting of up to 3 mg/day brexpiprazole or placebo, depending on the subject's treatment assignment.

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

**Trial Assessments:**

Assessments for Efficacy: ZAN-BPD, Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Patient's Global Impression of Change (PGI-C), Patient's Global Impression of Severity (PGI-S), Clinical Global Impression -

Severity of Suicidality (CGI-SS)-extended, Hospital Anxiety and Depression Scale (HADS), World Health Organization Disability Assessment Schedule (WHODAS) 2.0.

Assessments for Pharmacokinetics: blood sampling for IMP plasma concentrations.

Assessments for Pharmacogenomics: blood sampling for cytochrome P450 2D6 metabolism assessment.

Assessments for future biospecimen research (FBR): blood sampling for deoxyribonucleic acid, ribonucleic acid, and genomic analysis, proteomics, metabolomics, and/or measurement of other analytes.

Assessments for Safety: AE, clinical laboratory tests (hematology, serum chemistry [including glycosylated hemoglobin (HbA1c), thyroid-stimulating hormone (TSH), and blinded prolactin], and urinalysis), electrocardiogram (ECG), vital signs, physical examination findings, Columbia-Suicide Severity Rating Scale (C-SSRS), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).

Screening/Other: SCID-5-PD, Mini International Neuropsychiatric Interview (MINI) for Psychotic Disorders, medical history, psychiatric history (including BPD history and BPD therapy), urine drug screen/blood alcohol test, and urine pregnancy test.

**Data Monitoring Committee:** None

**Statistical Methods:**

In general, descriptive statistics will be provided for all efficacy and safety endpoints. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. The change from baseline in the ZAN-BPD total score will be analyzed using a mixed-effect model repeated measures (MMRM) methodology with the unstructured variance covariance matrix. The model will include fixed class-effect terms for treatment, trial center, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of ZAN-BPD total score by visit week as a covariate. Other continuous efficacy endpoints will also be analyzed using MMRM methodology**.**

Completed details of the planned statistical analysis will be presented in the blinded addendum to this protocol and in the statistical analysis plan.

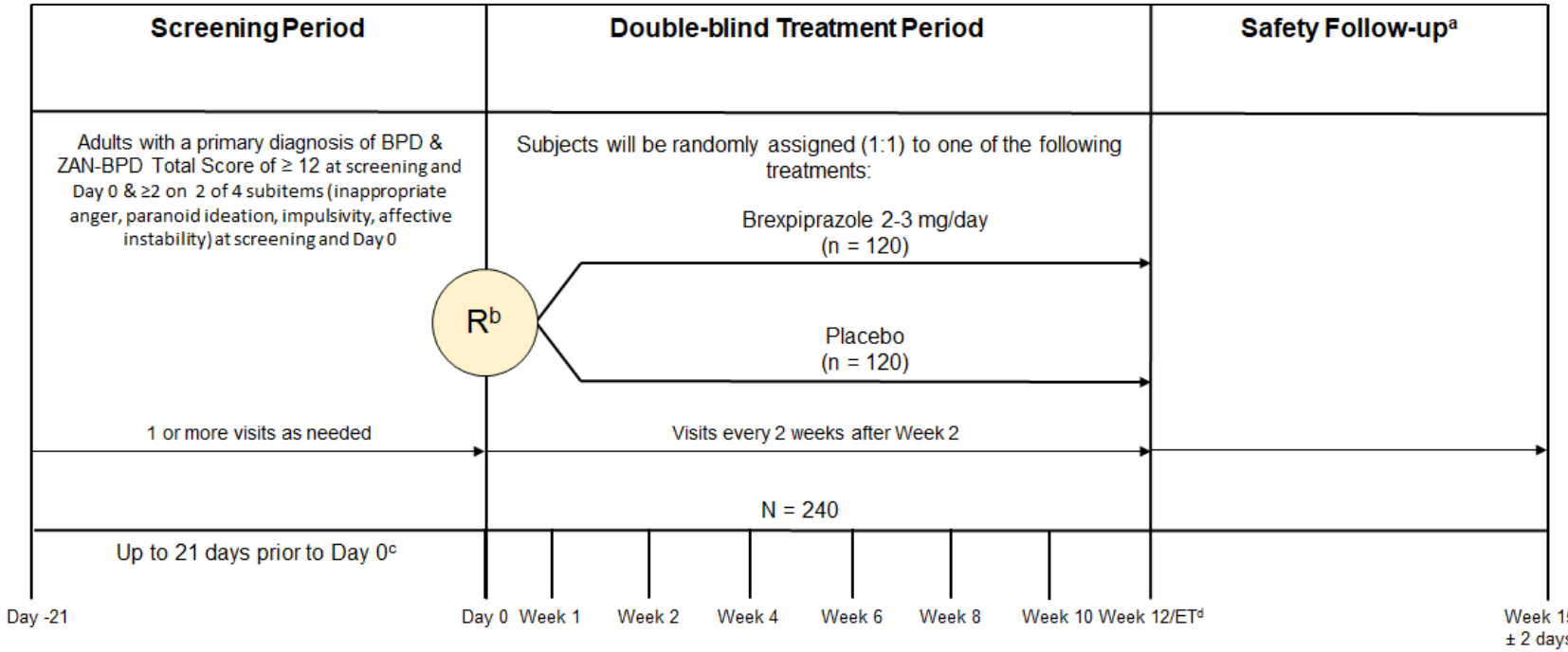
**Trial Duration:**

Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed):

- Eligibility screening period (up to 21 days)
- Double-blind randomized treatment period (12 weeks)
- Post-treatment safety follow-up period (21 days; for subjects who do not enroll in the open-label extension trial)

Overall, the trial duration from first informed consent form signed to the final subject assessment is expected to be approximately 15.5 months.

## 1.2 Schema




ADT = antidepressant therapy; BPD = borderline personality disorder; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

[a]For subjects who do not enroll in the open-label extension trial.

[b]Randomization will be stratified by site and the status of background ADT therapy (with or without background ADT).

[c]Extension of screening may be requested and discussed with the medical monitor prior to the expiration of the screening period.

[d]Subjects who complete all trial visits through Week 12 with no major protocol deviations may be offered entry into an open-label extension trial.

**Figure 1.2-1 Trial Design Schematic**

## 1.3 Schedule of Assessments

**Table 1.3-1 Schedule of Assessments**

| | Visit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Double-Blind Treatment Period | | | | | | | | |
| | | 12 weeks | | | | | | | | |
| Assessment | Screening[a] (Day -21 to Day -1) | Day 0 | Week 1[b] | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | End of treatment (Week 12) or ET[c] | Post-treatment Follow-up (21 ± 2 days)[d] |
| | | | ± 2 days | | | | | | | |
| **ENTRANCE and HISTORY** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | |
| Confirmation of eligibility | X[e] | | | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Psychiatric history, including BPD history | X | | | | | | | | | |
| Confirm use/no use of ADTs | X | | | | | | | | | |
| SCID-5-PD[f] | X | | | | | | | | | |
| Diagnostic for concurrent excluded diseases (MINI for Psychotic Disorders) | X | | | | | | | | | |
| Prior medication washout[g] | X | | | | | | | | | |
| HIV, HBsAg, and anti-HCV | X | | | | | | | | | |
| **EFFICACY** | | | | | | | | | | |
| ZAN-BPD | X | X | X | X | X | X | X | X | X | |
| CGI-S | | X | X | X | X | X | X | X | X | |
| CGI-I | | | X | X | X | X | X | X | X | |
| PGI-S | | X | X | X | X | X | X | X | X | |
| PGI-C | | | X | X | X | X | X | X | X | |
| CGI-SS-extended | | X | X | X | X | X | X | X | X | |

**Table 1.3-1 Schedule of Assessments**

| Assessment | Visit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Double-Blind Treatment Period | | | | | | | | Post-treatment Follow-up (21 ± 2 days)[d] |
| | | 12 weeks | | | | | | | | |
| | Screening[a] (Day -21 to Day -1) | Day 0 | Week 1[b] | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | End of treatment (Week 12) or ET[c] | |
| | | ± 2 days | | | | | | | | |
| WHODAS 2.0 | | X | | | | | | | X | |
| HADS | | X | X | | X | X | | X | X | |
| **SAFETY** | | | | | | | | | | |
| Physical examination[h] | X | | | | | | | | X | |
| Vital signs[i] | X | X | X | X | X | X | X | X | X | |
| Clinical laboratory tests (hematology, serum chemistry, and urinalysis) | X[j] | | | | | X | | | X | |
| Prolactin (blinded) | X | | | | | | | | X | |
| TSH with reflex to free $T_4$ if abnormal | X | | | | | | | | | |
| HbA1c | X | | | | | | | | X | |
| ECG[k] | X | | | | | | | | X | |
| Urine pregnancy test (FOCBP only)[l] | X | X | | | X | | X | | X | |
| Urine drug screen and blood alcohol test[m] | X | | | | | X | | | X | |
| C-SSRS[n] | X | X | X | X | X | X | X | X | X | |
| Extrapyramidal symptoms scales (SAS, AIMS, and BARS) | | X | | | | X | | | X | |
| Adverse events[o] | X | X | X | X | X | X | X | X | X | X |
| Concomitant therapy[p] | X | X | X | X | X | X | X | X | X | X |

**Table 1.3-1 Schedule of Assessments**

| Assessment | Visit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Double-Blind Treatment Period | | | | | | | | |
| | | 12 weeks | | | | | | | | |
| | Screening[a] (Day -21 to Day -1) | Day 0 | Week 1[b] | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | End of treatment (Week 12) or ET[c] | Post-treatment Follow-up (21 ± 2 days)[d] |
| | | | ± 2 days | | | | | | | |
| **PHARMACOKINETIC AND PHARMACOGENOMIC SAMPLING** | | | | | | | | | | |
| Pharmacokinetic sampling[q] | | | | | | X | | | X | |
| PGx sampling[r] | | X | | | | | | | | |
| Optional FBR sampling[r] | | X | | | | | | | | |
| **OTHER PROCEDURES** | | | | | | | | | | |
| IMP dispensing[s] | | X[t] | X | X | X | X | X | X | | |
| IMP accountability | | | X | X | X | X | X | X | X | |
| Schedule optional phone contact/other communication | | | | X[u] | X[u] | X[u] | X[u] | X[u] | | |

anti-HCV = antibodies to hepatitis C virus; CST = Clinical Surveillance Team; ET = Early Termination; FBR = future biospecimen research; FOCBP = females of childbearing potential; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IRE = immediately reported events; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; PGx = Pharmacogenomic; PK = pharmacokinetic; $T_4$ = thyroxine.

[a]Extension of screening may be requested and discussed with the medical monitor prior to the expiration of the screening period. Screening visit may be split over two days.

[b]Week designations correspond to the end of the week (eg, Week 4 visit occurs at the end of week 4 of the trial).

[c]If a subject discontinues early, every effort should be made to complete the "Week 12/End of treatment/ET" evaluations as soon as possible and, whenever possible, prior to starting any new medication or treatment.

[d]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety (AEs) for all subjects who do not enroll in the open-label extension trial.

[e]An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial by the CST. Subjects cannot be enrolled until site personnel have received the final CST notification from the Medical Monitor or Clinical Scientist.

[f]The BPD and antisocial personality disorder modules must be conducted as part of screening in order to meet inclusion/exclusion criteria; however, per investigator discretion other PD modules may be administered at baseline in order to decrease the length of the screening visit. The investigator is responsible for determining that BPD is the primary personality disorder diagnosis at screening.

[g]Washout of prohibited medications begins after completion of the consent process and must comply with the required washout periods (see Section 6.5).

[h]To include measurement of height (at screening only) and waist circumference.

[i]Vital sign measurements include body weight, body temperature, systolic and diastolic blood pressure, 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]Blood samples for clinical laboratory tests should be drawn after a minimum 8-hour fast at screening, if possible. If the Screening Visit laboratory samples were not obtained under fasting conditions, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], HbA1c, TSH with reflex to free $T_4$ if the result for TSH is abnormal, and urinalysis) need to be obtained under fasting conditions at the Day 0 Visit. Vital sign and ECG assessments should be completed before any blood samples are collected.

[k]Standard ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to ensure reproducibility of the abnormality before excluding a subject. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the subject must be excluded.

[l]All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

[m]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. See the exclusion criteria for exclusions based on urine drug screen and blood alcohol tests at screening.

[n]The “Baseline/Screening” C-SSRS form will be completed for all subjects at screening to determine eligibility and the “Since Last Visit” C-SSRS form will be completed at the Day 0 Visit to ensure that the subject continues to qualify for the trial. The “Since Last Visit” C-SSRS form will also be completed at all visits after the Day 0 Visit.

[o]Adverse events will be recorded starting after the subject completes the consent process and through the last scheduled trial visit (IREs will be collected through the last trial contact).

[p]All prescription and non-prescription therapy (pharmacological or other therapy) taken during the trial will be recorded. Details of prohibited therapies are provided in Section 6.5.1.

[q]A PK sample will be collected at the same time of collection of clinical laboratory assessments, where applicable. Time of last 3 doses will be recorded at the time of PK sampling.

[r]FBR (optional) and PGx sample will be collected from consenting subjects (separate consent needed for optional FBR samples only). Samples can be collected at any visit during the trial after Day 0.

[s]Decreases in the dose of brexpiprazole (from 3 mg/day to 2 mg/day) can be made at scheduled and unscheduled visits after week 3. Increases in the dose of brexpiprazole (from 2 mg/day to 3 mg/day) can be made at scheduled visits only after week 3 and are not allowed after the Week 8 visit. Subjects must return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits.

[t]The subject will be instructed to take their first dose of IMP during the Day 0 Visit.

[u]Schedule an optional phone call or other form of communication with subject for approximately 1 week (± 2 days) after clinic visit (ie, at Weeks 3, 5, 7, 9, and 11) to check on status.

# 2 Introduction

Borderline personality disorder (BPD) is a mental disorder consisting of a pervasive pattern of instability in regulation of emotions, impulse control, interpersonal relationships, and self image.[1,2] Patients with BPD are prone to self-harm (including suicidal behavior/ideation), other dangerous behaviors, substance abuse, depression and eating disorders.[3] The prevalence of BPD has been reported to be as high as 5.9% in the general population[4] but represents 15% to 29% of patients in psychiatric clinics and hospitals.[5,6] Because the personality of children and adolescents is developing, the features of BPD do not become recognizable until late adolescence or early adulthood.[7,8] There is a high comorbidity of BPD with other psychiatric disorders (approximately 85%), including anxiety disorders, mood disorders, impulse-control disorders, and substance-use disorders.[9]

Brexpiprazole (REXULTI®) is an atypical antipsychotic that is a serotonin-dopamine activity modulator and is indicated in the United States (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 major depressive disorder (MDD) (2 - 3 mg/day).[10]

While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high-binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-$HT_{1A}$ and at dopaminergic $D_2$ receptors with antagonist activity at serotonergic 5-$HT_{2A}$ receptors, with similar high affinities at all of these receptors (inhibition constant [$K_i$]: 0.1 - 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ receptors with affinity in the same sub-nanomolar $K_i$ range ($K_i$: 0.2 - 0.6 nM). The 5-$HT_{1A}$/$D_2$ receptor partial agonist activity in combination with 5-$HT_{2A}$ and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy, reduced impulsive behavior, and cognitive improvement.[10]

Please refer to the Brexpiprazole Investigator's Brochure for more detailed information.

## 2.1 Trial Rationale

There are currently no pharmacological treatments approved for BPD. The first-line of treatment is psychotherapy, including dialectic behavior therapy to manage emotions,

help with tolerating distress, and managing relationships.[7] Pharmacotherapy is used to treat targeted symptoms that fall within the following categories: 1) affective dysregulation, mood lability, and anger, 2) impulsive and self-harming behavior, and 3) cognitive perceptual symptoms. Based on off-label prescribing practices and on clinical trial data, there is evidence that atypical antipsychotics may be efficacious at treating patients with BPD, especially symptoms of mood, self-harm, impulsivity, and aggression. Reductions in overall BPD symptomatology have been demonstrated in clinical trials of quetiapine[11] olanzapine[12,13,14] clozapine[15,16] and aripiprazole.[17,18]

This receptor activity profile may allow for effective pharmacotherapy for the treatment of BPD. More specifically, the serotonergic and dopaminergic stabilization and modulation provided by brexpiprazole may directly address the pathways implicated in the BPD features of impulse aggression (serotonergic) and emotional dysregulation and impulsivity (dopaminergic).

The proposed 12-week, double-blind, placebo-controlled trial will be conducted to evaluate the efficacy and safety of brexpiprazole for the treatment of subjects diagnosed with BPD.

## 2.2 Background

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 IB.[10]

Currently, brexpiprazole is approved in multiple countries for use in adult patients for the treatment of schizophrenia, and for the use as an adjunctive therapy to antidepressants for the treatment of MDD. Additionally, the current clinical development program is designed to show safety and efficacy of brexpiprazole for the treatment of the following indications: treatment of adult post-traumatic stress disorder (PTSD), bipolar mania, adolescent schizophrenia, and the treatment of agitation in Alzheimer's disease (AAD).[10]

As of 17 Apr 2018, the brexpiprazole clinical development program consisted of a total of 74 clinical trials conducted in North America, Latin America, Europe, and Asia (66 completed and 8 ongoing). This includes 67 trials conducted under US Investigational New Drug (IND) Applications (59 completed and 8 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of attention-deficit/hyperactivity disorder (ADHD), AAD, PTSD, or bipolar; and 7 non-US IND trials (7 completed and 0 ongoing) in either South Korea or Japan conducted in healthy subjects and subjects with schizophrenia.[10]

Please refer to the IB for a detailed summary of available clinical data.[10]

## 2.3 Known and Potential Risks and Benefits

As of 17 Apr 2018, a total of 9153 unique subjects were exposed to single or multiple doses of brexpiprazole (either alone or with another marketed drug) in US IND trials. This total includes 877 subjects in the collective phase 1 clinical pharmacology trials (593 healthy subjects or subjects in special populations and 284 subjects diagnosed with either schizophrenia or schizoaffective disorder [N = 236], MDD [N = 36], or ADHD [N = 12]) and 8276 subjects diagnosed with either schizophrenia or schizoaffective disorder (N = 2404), MDD (N = 5265), AAD (N = 429), ADHD (N = 155), or PTSD (N = 23) in the collective phase 2 and phase 3/3b trials.

Overall, the total number of subject years of exposure (SYE) in the completed phase 1 clinical pharmacology trials (N = 877) and all phase 2 and phase 3/3b trials combined (N = 8276) was 28.5 and 3590.3 SYEs, respectively. Exposure to brexpiprazole in the completed phase 2 and phase 3/3b US IND trials is summarized by duration of exposure and indication in the current IB.[10] The majority of subjects within each of the 5 indications have received at least 6 weeks of brexpiprazole, including 3139 subjects with at least 26 weeks of exposure and 1612 subjects with at least 52 weeks of exposure.

Completed phase 2 and phase 3 clinical trials have evaluated multiple oral doses up to 6 mg/day in subjects with schizophrenia, up to 3 mg/day when coadministered with marketed antidepressant therapy in subjects with MDD, up to 3 mg/day in subjects with PTSD, up to 2 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD, and up to 2 mg/day in subjects with AAD. Dose selection for the ongoing multiple-dose trials was derived from the collective safety, efficacy, and receptor occupancy data from completed phase 1, phase 1b, phase 2, and phase 3 trials of brexpiprazole.

Overall, 9062 subjects received brexpiprazole either alone or coadministered with another marketed medication from the 59 completed brexpiprazole trials conducted under US INDs. Overall, 6403/9062 subjects (70.7%) reported at least 1 treatment-emergent adverse event (TEAE) compared with 1498/2781 subjects (53.9%) who received placebo either alone or coadministered with another marketed medication. The most frequently reported TEAEs (incidence ≥ 5% of the total brexpiprazole group and more than total placebo) in all subjects who received brexpiprazole were increased weight (12.1%), headache (9.1%), insomnia (7.8%), akathisia (7.2%), somnolence (6.2%), and dizziness (5.3%). In the total placebo group, headache (8.2%) was the most frequently reported TEAE (incidence ≥ 5% of subjects).

Please refer to the IB for a summary of available nonclinical and clinical safety data.[10]

Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

# 3 Objectives and Endpoints

**Table 3-1 Trial Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| Primary: To compare the efficacy of brexpiprazole versus placebo for the treatment of subjects with a diagnosis of BPD | Primary efficacy: Change from baseline in the clinician-administered ZAN-BPD total score |
| | Key secondary efficacy: Change from baseline in the CGI-S score |
| | Secondary efficacy:<br>• Change from baseline in the PGI-S for each trial visit during the double-blind treatment period<br>• PGI-C score<br>• CGI-I score |
| | Exploratory efficacy:<br>• Change from baseline in the ZAN-BPD total score for each trial visit during the double-blind treatment period<br>• Change from baseline in the CGI-S score for each trial visit during the double-blind treatment period<br>• Change from baseline in the WHODAS 2.0 score<br>• Change from baseline in the HADS-A and HADS-D scores<br>• Change from baseline in the ZAN-BPD sector scores<br>• Change from baseline in the CGI-SS-extended scale |

| | |
|---|---|
| Secondary: To evaluate the safety and tolerability of brexpiprazole for the treatment of subjects with a diagnosis of BPD | • Frequency and severity of AEs<br>• Changes in ECGs, vital signs, clinical laboratory tests including blinded prolactin, changes in body weight, and physical examinations<br>• EPS: SAS, the AIMS, and the BARS<br>• Suicidal ideation and behavior will be assessed using the C-SSRS |

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = CGI-I = Clinical Global Impression-Improvement of Illness; CGI-S = Clinical Global Impression-Severity of Illness; CGI-SS = Clinical Global Impression- Severity of Suicidality; C-SSRS = Columbia-Suicide Severity Rating Scale; Barnes Akathisia Rating Scale; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression Scale; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; SAS = Simpson Angus Scale; WHODAS = World Health Organization Disability Assessment Schedule; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Section 9.4 describes the statistical analysis of the endpoints.

# 4 Trial Design

## 4.1 Type/Design of Trial

This will be a 12-week, multicenter, randomized, double-blind, placebo-controlled trial of brexpiprazole in subjects diagnosed with BPD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and confirmed by a valid diagnostic instrument (Structured Clinical Interview for DSM-5 Personality Disorders [SCID-5-PD]).

The trial will be organized as follows:

*Screening Period:* The screening period will begin after written informed consent has been obtained and will take place between Day −21 and Day −1 prior to enrollment. Eligible subjects are required to meet all inclusion criteria at both screening and Day 0, including a total score of ≥ 12 on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). In addition, a score of ≥ 2 in at least 2 of the following 4 ZAN-BPD subscale items will be required at screening and Day 0: 1) "inappropriate, intense anger or difficulty controlling anger" (hereafter referred to as inappropriate anger), 2) "transient stress-related paranoid ideation or severe dissociative symptoms" (paranoid ideation), 3) "affective instability due to a marked reactivity of mood" (affective instability), and 4) "impulsivity in at least other two areas that are potentially self-damaging" (impulsivity). Following screening, eligible subjects will enter the trial

and be randomly assigned to brexpiprazole 2 to 3 mg/day or placebo in a 1:1 fashion. Randomization will be stratified by site and the status of background antidepressant therapy (ADT) use (with background ADT or without background ADT).

*Treatment Period*: Subjects will receive their assigned treatment during a 12-week, double-blind treatment period. The primary endpoint and the key secondary endpoint will be the change from baseline in the ZAN-BPD total score and Clinical Global Impression Scale - Severity of Illness (CGI-S) score, respectively. Visits will occur at Day 0 and at the end of Weeks 1, 2, 4, 6, 8, 10, and 12, with phone contact to check on subject status on the weeks the subject does not visit the clinic.

*Safety Follow-up*: Subjects who do not continue treatment in the open-label extension trial will be followed up for safety reasons via telephone contact or in clinic visit 21 (± 2) days after the last dose of investigational medicinal product (IMP). This contact also applies to subjects who are withdrawn prematurely from the trial.

See Figure 1.2-1 for a schematic of the trial.

## 4.2 Scientific Rationale for Trial Design

Given its clinical efficacy in treating both schizophrenia and MDD as well as its multimodal mechanism of action, brexpiprazole may offer added benefit to patients suffering from BPD. Like other psychological disorders, BPD has been linked to aberrations in monoaminergic neurotransmission. While dysfunctions related to dopamine and serotonin have been historically cited, recent evidence has also implicated noradrenergic dysfunction in BPD as well.[19,20,21,22] Since brexpiprazole possesses a multi-modal mechanism of drug action, pharmacologically, it may improve defects in monoamine circuitry that have gone awry in this psychiatric disorder. Notably, brexpiprazole is a partial agonist at dopamine $D_2/D_3$ and serotonin 5-$HT_{1A}$ receptors. It is also an antagonist at serotonin 5-$HT_{2A}$ and adrenergic $\alpha_{1B}$ and $\alpha_{2C}$ receptors. Its pharmacological effects at each receptor subtype may be beneficial in treating the diverse symptomology present in patients diagnosed with BPD. For example, as a partial dopamine $D_2/D_3$ receptor agonist, brexpiprazole may quell the hyperresponsiveness in the dopaminergic circuitry purported to exist in patients with BPD.[23] By dampening dopaminergic tone in overactivated circuits, brexpiprazole may improve impulsivity and cognitive and emotional processing. Conversely, brexpiprazole may also improve dopaminergic tone in those circuits that are understimulated to improve mood. Likewise, brexpiprazole may normalize aberrations that are believed to exist in a heightened adrenergic system.[23] Since the noradrenergic system is one of the effectors of the stress

response and likely activated with childhood trauma, it is postulated that noradrenergic genetic variants may confer BPD risk.[22] Furthermore, 5-$HT_{2A}$ receptors are expressed on locus coeruleus noradrenergic neurons.[24] In this regard, brexpiprazole may improve BPD symptomology like affective dysregulation, anxiety and impulsive-aggression by modulating noradrenergic drive.[25] Impulsive-aggressive behavior is a core feature of BPD that may also result from hyperactivation of the amygdala. The amygdala is part of the limbic system that controls negative emotions. In BPD, loss of inhibitory regulation of the amygdala may occur from alterations in the 5-$HT_{1A}$ receptor gene, HTR1A, in some individuals.[21] In these individuals, serotonergic function is reduced. Low levels of serotonin may lead to anger, suicidality, impulsivity, and aggressive behavior. Given its agonistic effects on both pre- and post-synaptic 5-$HT_{1A}$ receptors, brexpiprazole may help negatively modulate these behaviors, respectively, by normalizing serotonin neurotransmission.

This phase 2, 2-arm trial is intended to provide preliminary evidence that treatment of subjects with BPD with brexpiprazole is superior to placebo.

## 4.3 Dosing Rationale

The dosing paradigm of brexpiprazole to be used in Trial 331-201-00242 has been determined based on the dosing ranges investigated in other related psychiatric indications (bipolar I disorder, MDD, PTSD, and schizophrenia).[10]

In other psychiatric indications, brexpiprazole has been shown to be safe and well tolerated within the proposed dose range to be investigated in this trial (ie, 2 to 3 mg/day). In addition, the effective dose range for approved indications (MDD and schizophrenia) is 2 to 4 mg/day; the 1 mg/day dose has not been shown to be effective.

## 4.4 End of Trial Definition

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

## 4.5 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 Week 12 will be defined as trial completers.

# 5 Trial Population

It is planned that approximately 240 subjects will be enrolled at approximately 65 trial sites in the US and Europe. An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial. Subjects should not be enrolled until the Clinical Surveillance Team (CST) review and feedback has been completed and the site has received final notification from the Medical Monitor or Clinical Scientist.

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.

Decisions regarding inclusion of subjects at time of enrollment and assessment of subject safety throughout the trial primarily remain at the discretion of the investigator; however, the medical monitor may recommend exclusion or discontinuation of a subject based on individual subject data.

## 5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number [‘S’ + 5 digits] upon providing consent [or assent if applicable]). Site number will be designated by the sponsor. The subject number will be given sequentially from S00001 as the serial numbers in the trial sites.

Demographic information (collection date, date of birth, sex, childbearing potential, race, ethnicity) and medical history will be recorded in eSource at screening visit.

Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for treatment sequence assignment. Results of the eligibility assessment, date of randomization (or date of treatment assignment) and subject ID (or treatment group) will be recorded in eSource.

## 5.2 Eligibility Criteria

### 5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

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 Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) prior to the initiation of any protocol-required procedures.

3) Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited medication, and to read and understand the written word in order to be reliably rated on assessment scales.
4) Subjects with a primary DSM-5 diagnosis of BPD confirmed by the SCID-5-PD at screening.
5) At screening and Day 0, subjects must have a total score of ≥ 12 on the ZAN-BPD scale. In addition, a score of ≥ 2 in at least 2 of the following 4 ZAN-BPD subscale items will be required at screening and Day 0: 1) inappropriate anger, 2) paranoid ideation, 3) affective instability, and 4) impulsivity.
6) Subjects who, in the investigator's judgment, require treatment with a medication for BPD.
7) Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

### 5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

*Sex and Reproductive Status*

1) Sexually active males or females of childbearing potential (FOCBP) 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.

   Consensual sexual activity that cannot biologically result in pregnancy may not be subject to required birth control methods, following discussion with the medical monitor.

   Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.
2) Women who are breastfeeding and/or who have a positive pregnancy test result prior to receiving IMP.

*Target Disease*

3) Subjects with a concurrent DSM-5 diagnosis of schizophrenia or schizoaffective disorder are excluded. Subjects with a historical diagnosis of schizophrenia or schizoaffective disorder may be permitted if the investigator determines and documents that this prior diagnosis was not appropriate based on current and historical presentation. Also, subjects with a concurrent diagnosis of bipolar I disorder, bipolar II disorder, delirium, dementia, amnesia, eating disorder, antisocial personality disorder, or other cognitive disorders are excluded. Subjects with MDD, PTSD, ADHD, panic disorder, or generalized anxiety disorder can be included under the following conditions: symptoms have been stable for at least 60 days prior

to screening, these disorders are not the primary focus of treatment, and changes in any treatment for these disorders (permitted medication and/or psychotherapy) would not likely be required for the duration of the trial. All other concurrent psychiatric or neurological diagnoses must be discussed with the medical monitor.

4) Subjects who are currently in psychotherapy specifically used to target BPD symptoms at the time of screening (eg, dialectical behavior therapy, mentalization-based therapy) or who have participated in BPD-targeted psychotherapy within 60 days of screening are excluded. Individual or group supportive talk therapy, or other non-pharmacological interventions, may be permitted provided the treatment has not been initiated or a changed within 60 days prior to the screening visit, and if is not anticipated that that the subject will require changes in this treatment during the trial.
5) Subjects who have had electroconvulsive treatment or transcranial magnetic stimulation within 90 days prior to the screening visit.

*Medical History and Concurrent Diseases*

6) Subjects who have a current diagnosis of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) within 90 days prior to the screening visit.
7) Subjects who fulfill the following criteria related to suicide and/or suicidal ideation are excluded:
   - Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide based on history or routine psychiatric status examination, or those who are homicidal or considered to be a high risk to others, or subjects with a response of "yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) within the 90 days prior to screening or at Day 0, **OR**
   - Subjects with a response of "yes" on the C-SSRS Suicidal Behavior Items Actual Attempt, Interrupted Attempt, or Aborted Attempt within the 90 days prior to screening or at Day 0, **OR**
   - Subjects who have had 3 suicide attempts within 2 years prior to screening, **OR**
   - Subjects who have had 3 or more hospitalizations due to suicidal behavior within 12 months prior to screening.

   Note that subjects who have engaged in non-suicidal self-injurious behavior within the 90 days prior to screening or at Day 0 are eligible, unless the behavior is better described as an actual attempt, interrupted attempt, or aborted attempt according to C-SSRS definition and/or investigator judgment and therefore exclusionary.

   Subjects with a response of "yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan and Intent) within the 90 days prior to screening or at Day 0 may be included following discussion with the medical monitor.
8) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least 90 days prior to screening) or an abnormal result for free $T_4$ at screening.

9) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as the following:
   - Any history of myocardial infarction or congestive heart failure (whether controlled or uncontrolled)
   - Human immunodeficiency virus (HIV) seropositive status or acquired immunodeficiency syndrome
   - Chronic hepatitis B or C (defined as positive serology and aspartate aminotransferase [AST] or alanine aminotransferase [ALT] elevated to > 2 × upper limit of normal [ULN])

   Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a correspondingly high body mass index (BMI), need to be reviewed and discussed with the medical monitor.
10) Subjects with diabetes mellitus (both insulin-dependent and non-insulin-dependent) may be eligible for the trial if their condition is stable and well-controlled as determined by satisfying ALL of the following criteria:
    a) Glycosylated hemoglobin (HbA1c) < 8.0%, **AND**
    b) Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non-fasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, **AND**
    c) Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes.

    Subjects with non-insulin-dependent diabetes mellitus (ie, any subjects not using insulin) must also satisfy the below criterion:
    a) Subject has been maintained on a stable regimen of antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening.

    Subjects with newly diagnosed diabetes during screening are excluded.
11) Subjects with uncontrolled hypertension, symptomatic hypotension, or orthostatic hypotension (see Section 8.7.3).

    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.
12) Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile, post traumatic, or alcohol withdrawal seizure.

*Physical and Laboratory Results*

13) 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.

    In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial:

    - Platelets $\leq 75000/mm^3$
    - Hemoglobin $\leq 9$ g/dL
    - Neutrophils, absolute $\leq 1000/mm^3$
    - AST $> 2 \times$ ULN
    - ALT $> 2 \times$ ULN
    - Creatine phosphokinase (CPK) $> 3 \times$ ULN, unless discussed with and approved by the medical monitor
    - Creatinine $\geq 2$ mg/dL
    - QTcF $\geq 450$ msec in men and $\geq 470$ msec in women, unless due to ventricular pacing.

    Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the subject must be excluded.

14) 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 cannabis, or prescription or over-the counter 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. Subjects with positive results for alcohol use will require consultation and approval by the medical monitor in order to verify use does not indicate a substance-use disorder.

*Disallowed and Concomitant Medication*

15) Recent treatment with a prohibited therapy (a table of prohibited therapies along with required wash-out periods is provided in Section 6.5.1)
16) Subjects who would be likely to require prohibited concomitant therapy during the trial (see Section 6.5).
17) Subjects who received brexpiprazole in any prior clinical trial or subjects who have taken or are currently taking commercially available brexpiprazole (Rexulti®).

*Allergies and Adverse Drug Reactions*

18) Subjects with a history of neuroleptic malignant syndrome, serotonin syndrome, or clinically significant tardive dyskinesia.

19) Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
20) Subjects who are known to be allergic or hypersensitive to brexpiprazole or other quinolinones.

*Other*

21) 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.
22) Subjects who are currently either inpatient or partially hospitalized should not participate in the trial.
23) Subjects who participated in a clinical trial within 90 days prior to screening or who participated in more than 2 clinical trials within a year prior to screening.
24) Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications described in Section 6.5. No restrictions to activity, food, caffeine, alcohol or tobacco or any other lifestyle considerations are needed during this trial.

## 5.3 Lifestyle Considerations

Not applicable.

### 5.3.1 Meals and Dietary Restrictions

Not applicable.

### 5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

### 5.3.3 Activity

Not applicable.

## 5.4 Screen Failures

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

Subjects who sign an ICF but who are not started on treatment are permitted to be re-screened. In the event that the subject is re-screened for trial participation, and the

re-screening is not completed within the original screening window, a new ICF must be signed.

Screen failures due to exclusionary criteria may be rescreened at any time if the exclusion characteristic has changed. In the event that a subject cannot be randomized prior to expiration of the 21-day screening period, additional extension of screening may be requested and discussed with the medical monitor. Any extension should be requested prior to the expiration of the previous extension or screening period, as applicable. If no extension is granted, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Subjects may be rescreened twice for this trial.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in eSource:

- Date of informed consent
- Visit date (screening visit and Day 0)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

# 6 Trial Treatments

## 6.1 Trial Treatments Administered

During the first 3 weeks of the trial, subjects will have their dose titrated according to the blinded titration schedule, based on the treatment group to which they are randomized. Per this schedule, at the start of week 3, subjects will receive one of the following:

- Brexpiprazole 3 mg/day
- Placebo

The dose of IMP can be adjusted to optimize efficacy and safety/tolerability according to the following rules:

- Subjects who had their dose increased to 3 mg/day can have this reduced back to 2 mg/day due to tolerability issues at any time during the trial after week 3. If a subject requires a dose reduction for tolerability issues outside of a regularly scheduled visit, they need to complete an unscheduled clinic visit.
- Subjects unable to tolerate 2 mg/day will be discontinued from the trial.
- Dose increases can be made up until Week 8. No dose increases may occur following the Week 8 visit.

- Subjects who had their dose decreased to 2 mg/day can have this increased back to 3 mg/day until Week 8. Dose increases are only permitted at scheduled visits. Only 1 dose increase is permitted for subjects who had their dose decreased to 2 mg/day.

For information regarding the dose regimen and treatment periods, including any follow-up period, for each treatment group/arm of the trial, see Section 4.1.

### 6.1.1 Medical Devices

Not applicable.

## 6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the Brexpiprazole IB.[10]

### 6.2.1 Packaging and Labeling

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

### 6.2.2 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 conditions indicated on the IMP label. The clinical site staff will maintain a temperature log in the IMP storage area to record the temperature and report any excursions.

### 6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational or placebo) received, dispensed, administered, and returned. Neither the investigator nor any designees may provide IMP to any subject not participating in this protocol.

### 6.2.4 Returns and Destruction

The IMP will be destroyed by the clinical trial site. 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. Accountability of the IMP must be completed and verified by the assigned trial monitor prior to destruction. The trial site(s) may utilize qualified third-party vendors for IMP destruction.

### 6.2.5 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 the following:

- 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

#### 6.2.5.1 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 within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Send information required for reporting purposes (listed below) to IMP-PQC@otsuka-us.com.

  It should also be indicated if the complaint sample is available or not available for return.

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

#### 6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- 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

#### 6.2.5.3 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.

#### 6.2.5.4 Assessment/Evaluation

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

### 6.3 Measures to Minimize/Avoid Bias

Procedures for breaking the blind can be found in Section 8.8.7.

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

Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department. The randomization will be stratified by site and the status of background ADT use (with background ADT or without background ADT). Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization

files, packaging IMP, operating the Interactive Response Technology, and reporting serious adverse events (SAEs) to regulatory agencies.

## 6.4 Subject Compliance

Responsible trial personnel will dispense the IMP (ie, brexpiprazole or placebo). 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 compliance issues merits discontinuation from the trial.

## 6.5 Concomitant Medications or Therapies

The investigator will record all available information for medications and therapies used for treatment of symptoms of BPD and other psychiatric conditions prior to the trial and 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 eSource. Therapies used for the treatment of other conditions will be recorded from 30 days prior to signing the ICF through the end of the evaluation period on eSource. The investigator will also 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 eSource.

For concomitant medications, the following will be recorded in eSource: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in eSource: therapy, indication, start date and end date, and frequency.

### 6.5.1 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 6.5-1 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.

Extensions to the screening period in order to achieve the appropriate wash-out periods may be permitted following discussion with the medical monitor.

| Table 6.5-1 List of Medications Prohibited Before the Trial | | |
|---|---|---|
| 1. | Neuroleptic agents (depot or long-acting injectable) | One full cycle plus 1/2 cycle |
| 2. | Monoamine oxidase inhibitor | 14 days |
| 3. | Antipsychotic agents (oral)[a]<br>• Oral aripiprazole<br>• Oral cariprazine<br>• Other oral antipsychotic agents (except for quetiapine when used for insomnia)[b] | <br>14 days<br>28 days<br>7 days |
| 4. | Benzodiazepines (stable doses of short-acting [eg, lorazepam up to 2 mg/day or equivalent] and long-acting, [eg, clonazepam up to 1 mg/day] may be allowed)[c] | 7 days |
| 5. | Hypnotics, including ramelteon[d] | 7 days |
| 6. | Mood stabilizers (ie, lithium) | 7 days |
| 7. | Anticonvulsants (except for gabapentin when used to treat anxiety or pain, after discussion with the medical monitor). | 7 days |
| 8. | Antidepressant therapy<br>•<br>• Multiple concurrent ADTs at a therapeutic dose range (for depressive symptoms) are not permitted[e]<br>• Tricyclic antidepressants and trazodone are excluded unless they are being used for sleep management (further discussion with the medical monitor is required before allowing these medications) | 14 days |
| 9. | Ketamine, esketamine, arketamine within 90 days prior to screening | 90 days |
| 10. | Investigational agents within 90 days prior to screening | 90 days |

[a]If a subject was exposed to 2 or more atypical antipsychotic agents in the 12 months prior to screening or if the subject did not show improvement on their previous atypical antipsychotic therapy, additional discussion with the medical monitor is required.

[b]Quetiapine, if being used for treatment of insomnia at low doses (eg, 25 to 50 mg), may be washed out 24 hours prior to enrollment.

[c]Chronic, stable (ie, regularly scheduled maintenance dose that has not changed within 60 days of screening) use of specific oral benzodiazepines is permitted for the treatment of anxiety up to a maximum of 2 mg/day lorazepam (or equivalent) or 1 mg/day clonazepam.

[d]Chronic, stable (ie, regularly scheduled maintenance dose that has not changed within 60 days of screening) use of non-benzodiazepine sleep aids is permitted for the management of sleep.

[e]Chronic, stable (ie, regularly scheduled maintenance dose that has not changed within 60 days of screening) treatment with 1 ADT is permitted; however, doses may not exceed > 60 mg/day for fluoxetine and > 50 mg/day for paroxetine.

Table 6.5-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

| Table 6.5-2 | List of Medications Prohibited During the Trial |
|---|---|
| 1. | Psychotropic agents including, but not limited to, the following:<br>a) Antipsychotics, including depot or long-acting injectable formulations<br>b) Anticonvulsants (except gabapentin when used to treat anxiety or pain after further discussion with the medical monitor)<br>c) Monoamine oxidase inhibitors, tricyclic antidepressants,[a] trazodone,[a] nefazodone, fluoxetine (> 60 mg/day) and paroxetine (> 50 mg/day)<br>d) Mood stabilizers (ie, lithium)<br>e) Benzodiazepine use is restricted to chronic, stable treatment or when used to manage treatment-emergent AEs such as agitation and anxiety[b]<br>f) Hypnotics, including ramelteon[c]<br>g) Stimulants and atomoxetine<br>h) Opioid analgesics, unless approval is obtained from the medical monitor. Approval 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. Buprenorphine is also excluded.<br>i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric acid supplements, etc)<br>j) Disulfiram<br>k) Prazosin - allowed if currently being taken for an appropriate indication at a stable dose for at least 60 days prior to screening. Should be continued throughout trial participation |
| 2. | Investigational agents |
| 3. | Cytochrome P450 (CYP) 2D6 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, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone. The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial. |
| 4. | Barbiturates |
| 5. | Beta receptor antagonists[d] |
| 6. | Anticholinergic agents are prohibited within 8 hours of schedule EPS scale assessments. |

[a]Unless they are being used for sleep management (further discussion with the medical monitor is required before allowing these medications)

[b]See Section 6.5.2.

[c]Chronic, stable (ie, regularly scheduled maintenance dose that has not changed within 60 days of screening) use of non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, and eszopiclone only) is permitted for the management of sleep but not on the same day as administration of a benzodiazepine, regardless of indication. Intermittent use of specific non-benzodiazepine sleep aids is permitted for the short term management of treatment-emergent AEs related to sleep problems. For the non-benzodiazepine sleep aids, only 1 of the listed medications that are approved for this indication in the respective countries should be used 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.

[d]Propranolol is permitted for akathisia or tremor up to a maximum of 20 mg 3 times daily (total of 60 mg/day). Propranolol must not be administered within 8 hours prior to scheduled efficacy and safety assessments, including EPS scales.

### 6.5.2 Benzodiazepine Use During the Trial

Chronic, stable (ie, regularly scheduled maintenance dose that has not changed within 60 days of screening) use of specific oral benzodiazepines is permitted for the treatment of anxiety up to a maximum of 2 mg/day lorazepam (or equivalent) or 1 mg/day clonazepam in divided doses. Intermittent use of specific oral benzodiazepines is permitted for the short term management of treatment-emergent AEs up to a maximum of 2 mg/day lorazepam (or equivalent) or 1 mg/day clonazepam in divided doses. Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. If required for intermittent treatment of agitation, 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 should not be administered within 8 hours prior to scheduled efficacy and safety assessments, including extrapyramidal symptom 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 benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eSource. For subjects entering the trial on regularly scheduled maintenance doses of benzodiazepines, routine doses may be taken at scheduled times per investigator instructions as long as drug name, dose, date, and time taken are clearly documented in eSource.

### 6.5.3 Permitted Medications

All medications that are not specifically prohibited (see Section 6.5.1) are permitted but need to be recorded on eSource as described in Section 6.5.

### 6.5.4 Rescue Medications

Not applicable.

### 6.6 Intervention after the End of the Trial

Subjects who complete all trial visits through the Week 12 visit and meet the inclusion and exclusion criteria of the open-label extension trial may be offered entry into the optional open-label extension trial.

# 7 Stopping Rules, Withdrawal Criteria, and Procedures

## 7.1 Entire Trial or Treatment

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.

## 7.2 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 Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

## 7.3 Individual Subject Discontinuation

### 7.3.1 Treatment Interruption

All attempts should be made to avoid treatment interruptions during the trial. If a subject's IMP treatment must be interrupted for medical or surgical reasons; liver test abnormalities; use of a prohibited concomitant medication; or other reasons (eg, hospital admission for an invasive procedure, a major medical condition, surgery; dental work, or a temporary situation that prevents subject compliance with the IMP dosing schedule), the subject's IMP should be resumed as early as the situation allows (see Section 7.3.4). If > 4 consecutive doses of IMP are missed, a discussion should occur with the medical monitor to determine if the subject should be discontinued from the trial as a result of the treatment interruption.

### 7.3.2 Treatment Discontinuation

After treatment assignment, 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 7.3.5.

### 7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may temporarily interrupt or discontinue IMP for a number of reasons, including those listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with IMP
- Physician decision
- Pregnancy (see Section 10.3)
- Protocol deviation
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal by subject

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 7.3.1 and Section 7.3.2 must be followed.

### 7.3.4 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:

- 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 modify or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.1 and Section 7.3.2, respectively). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3 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 methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

### 7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) 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.

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

Subjects who cannot be contacted on or before Week 12 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". 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 or other contact methods 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.

If the subject was classified as "lost to follow-up", "Were you able to contact the subject?", "Date of contact/Date of final contact attempt" and "Contact method" will be recorded in the source documents.

## 8 Trial Procedures

The assessments to be conducted during the trial and timing of assessments are summarized in Section 1.3.

### 8.1 Efficacy Assessments

It is required that trained and experienced clinicians administer all rating scales. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by OPDC or designee. Quality reviews of audio recording may be performed for some assessments, including eligibility review, in order to verify the quality of the assessment/interview and accuracy of scoring.

#### 8.1.1 Clinician Administered

##### 8.1.1.1 Zanarini Rating Scale for Borderline Personality Disorder

The ZAN-BPD is a clinician-administered scale for the assessment of change in Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) borderline psychopathology.[26] Although the DSM-IV was updated to DSM-5, the diagnostic criteria

for BPD remain unchanged. The ZAN-BPD is designed to assess severity of disease symptoms in patients with BPD based on clinician rating.

The questions for the ZAN-BPD reflect a 1-week time frame. Each of the 9 criteria for BPD is rated on a 5-point anchored rating scale of 0 to 4. These scores are clustered into 4 sector scores (akin to domains) and a total score. The 3 affective symptoms have a sector score range from 0 to 12. The 2 cognitive symptoms have a sector score range from 0 to 8. The 2 impulsive symptoms have a sector range from 0 to 8. The 2 interpersonal symptoms have a sector score range of 0 to 8. These 4 sector scores add up to provide the overall total score for the ZAN-BPD, which ranges from 0 to 36.

#### 8.1.1.2 Clinical Global Impression-Severity of Illness Scale

The severity of illness for each subject will be rated using the CGI-S.[27] To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with borderline personality disorder, how ill is the subject at this time?" Response choices are 0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects.

#### 8.1.1.3 Clinical Global Impression-Improvement Scale

Change from baseline in the subject's condition will be assessed using the CGI-I scale.[27] The investigator (or designee) will answer the following question: "Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at Day 0, how much has the patient changed?". All responses will be compared with the subject's condition at baseline (Day 0). Response choices are 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

#### 8.1.1.4 Clinical Global Impression-Severity of Suicidality - Extended

The severity of suicidality for each subject will be rated using an extended version of the CGI-SS. To perform this assessment, the investigator (or designee) will rate the severity of the subject's suicidal ideation, behavior, overall suicidality, and non-suicidal self-injurious behavior over the past 7 days. Ratings are based on a 7-point scale from lowest to highest level of severity. The CGI-SS-extended used for this trial includes components from the CGI-SS[28] and the CGI-SS-Revised[29] with additional questions of interest for BPD.

### 8.1.2 Patient Completed

#### 8.1.2.1 Patient's Global Impression - Severity

The PGI-S is a 7-point single-item self-report scale for the patient to rate the severity of symptoms of BPD. Subjects answer the following question: "Taking into account all of your symptoms, how severe is your Borderline Personality Disorder at this time?" Scores range from 1 "no symptoms" to 7 "very severe".

#### 8.1.2.2 Patient's Global Impression - Change

The Patient's Global Impression of Change (PGI-C) is a 7-point single-item self-report scale depicting a patient's rating of overall change in their condition since starting trial medication. Subjects answer the following question: "Since starting study medication, how much have your symptoms of Borderline Personality Disorder changed?" Scores range from 1 "very much improved" to 7 "very much worse".

#### 8.1.2.3 World Health Organization Disability Assessment Schedule 2.0

The WHODAS 2.0[30,31] is a 36-item self-assessment scale to measure a subject's function and disability across 6 domains of life: cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating, staying alone), getting along (interacting with others), life activities (domestic responsibilities, leisure, work and school), and participation (community and society).

#### 8.1.2.4 Hospital Anxiety and Depression Scale

The HADS[32] is a subject-rated scale designed to screen for anxiety and depressive states in medical subjects. The HADS consists of 2 subscales: The D-scale measures depression and the A-scale measures anxiety. Each subscale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each subscale ranges from 0 to 21, and the subscales are analyzed separately.

### 8.1.3 Screening Assessments

#### 8.1.3.1 Structured Clinical Interview for DSM-5 Personality Disorders

The SCID-5-PD[33] is a validated diagnostic instrument and will be conducted at screening to confirm the subject's diagnosis of BPD. Detailed instructions for administration of this diagnostic interview will be provided.

#### 8.1.3.2 Mini International Neuropsychiatric Interview for Psychotic Disorders

The Mini International Neuropsychiatric Interview (MINI) version 7.0.2 for Psychotic Disorders[34,35,36,37] will be conducted at screening to rule out exclusionary comorbid psychiatric diagnoses. This version of the MINI is suitable for settings where specific psychotic disorders are a focus of interest (ie, for exclusionary purposes). Detailed instructions for administration of this structured interview will be provided.

## 8.2 Pharmacokinetic Assessments

The PK samples will be collected as described in the schedule of assessments (Table 1.3-1). The time of last 3 doses of IMP will be recorded at the time of PK sampling.

### 8.2.1 Pharmacokinetic Blood Samples

Blood samples will be collected in vacutainers containing sodium heparin and processed into plasma to determine the concentrations of brexpiprazole. Metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed. The total volume of blood to be collected during the trial will be documented in the ICF.

Blood samples for PK analysis will be collected at the time points as shown in Table 1.3-1 (schedule of assessments). The actual date and time of the PK sample collection will be recorded in eSource.

When vital signs or ECGs are scheduled at the same nominal time as PK sample collections, vital signs should be measured and ECGs should be performed before PK samples are collected.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70° C or −20°C, unless otherwise instructed in the Operations/Laboratory Manual.

All plasma samples will be shipped to the bioanalytical laboratory for analysis. Additional information will be provided in the Operations Manual.

## 8.3 Pharmacodynamic Assessments

Not applicable.

## 8.4 Pharmacogenomic Assessments

A pharmacogenomics (PGx) sample to assess the CYP2D6 metabolism status will be collected from consenting subjects only. Whole blood samples will be collected in 4-mL potassium ethylenediaminetetraacetic acid vacutainer tubes for pharmacogenomic testing. The total volume of blood to be collected during the trial will be documented in the ICF. Genomic deoxyribonucleic acid (DNA) will be extracted from a whole blood sample and used to determine genotypes and related phenotypes for CYP2D6. The method used to determine these genotypes may also generate genotype data for additional genes related to absorption, distribution, metabolism, and excretion. Phenotyping of these additional genes is not currently planned but may be considered in the future. If so, the genotyping data may be included as part of covariate analysis in a population PK analysis to be reported separately.

The date and time of sample collected for PGx analysis will be recorded in eSource.

All PGx samples will be shipped to the PGx laboratory. Additional information will be provided in the Operations/Laboratory Manual.

## 8.5 Biomarker Assessments

Not applicable.

## 8.6 Future Biospecimen Research Samples

### 8.6.1 Scope of Future Biospecimen Research

Future Biospecimen Research (FBR) samples will be collected from subjects who consent to this sample collection. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics, and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for future biospecimen research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

### 8.6.2 Summary of Procedures for Future Biospecimen Research Samples

All subjects enrolled in the clinical trial will be considered for enrollment in the optional FBR substudy.

After obtaining informed consent, a whole blood sample for FBR will be collected from consenting subjects only. The total volume of blood to be collected during the trial will be documented in the ICF. The blood sample will be used for:

- DNA analysis
- RNA analysis
- genomic analysis (includes both DNA and RNA)
- measurement of proteins, sugars, and other molecules

If a subject provides consent to FBR collection, back-up PK samples may be used for FBR. The date and time of the sample collection will be recorded in eSource. Additional information will be provided in the Operations Manual. If a FBR substudy is planned, a separate document describing the analysis may be prepared and the results may be reported separately from the clinical study report.

### 8.6.3 Retention of Future Biospecimen Research Specimens

The FBR specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Samples may be stored for longer if a regulatory or governmental agency has active questions that are being answered. In this special circumstance, samples will be stored until these questions have been adequately addressed.

## 8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

### 8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2. Vital sign and ECG assessments should be completed before any blood samples are collected. Refer to Section 10.5 for criteria for identifying laboratory values of potential clinical relevance.

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. A fasting blood sample is required at Day 0 prior to dosing. If a fasting blood sample was not obtained at the Screening Visit, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], $HbA_{1c}$, TSH with reflex to $T_4$ if the result for TSH is abnormal, and urinalysis) need to be repeated at the Day 0 Visit. 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.

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, 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 (Section 10.5) for criteria for identifying values of potential clinical relevance. Refer to Section 5.2.2 for laboratory test results that are exclusionary at screening.

The total volume of blood to be collected during the trial is documented in the ICF.

A pregnancy test will be conducted in FOCBP (refer to Section 10.3 for definition) 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.

### 8.7.2 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1).

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 mucosa. At screening, height will be measured with a stadiometer, measuring stick or tape. Repeat measurement of height is not required at the physical examinations scheduled for the

Week 12 or ET visit. Waist circumference will be measured at each physical examination (screening and Week 12 or ET), using the provided measuring tape. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- Measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[38]

The investigator (or designee) is responsible for performing the physical examination. If the appointed designee is to perform the physical examination, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. 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.

### 8.7.3 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1). Vital sign measurements scheduled for the same visit as blood samples are to be completed before blood is drawn. Subjects should be monitored for potentially clinically significant vital signs values (Section 10.6).

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

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

Blood pressure and heart rate measurements will be made in the supine and standing positions after the subject has been in 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 at screening or baseline are excluded from the trial as are subjects with orthostatic hypotension, which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared with the previous supine blood pressure or development of symptoms. In addition, subjects should be excluded if they have any other vital sign measurement at screening or baseline that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening or baseline vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial.

### 8.7.4 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1). Vital sign and ECG assessments should be completed before any blood samples are collected. Subjects should be monitored for potentially clinically significant ECG results (Section 10.7).

Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. The ECG 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 used for reading all ECGs in order to standardize interpretations for the safety analysis.

If during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2.2), 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 as 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.

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

### 8.7.5 Suicidality Monitoring - Columbia-Suicide Severity Rating Scale

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1).

Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening and Day 0 to determine eligibility. Any subject who presents a serious risk of suicide should be excluded from the trial (see Section 5.2.2). The "Since Last Visit" C-SSRS form will also be completed at all visits after screening.

Discussion with the medical monitor during regarding any concerns or guidance regarding the C-SSRS during the trial is recommended.

### 8.7.6 Other Safety Variables

It is required that an adequately trained and experienced clinician administer the safety assessments, including the EPS scales (SAS, AIMS, and BARS). 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 a rater training group.

#### 8.7.6.1 Simpson Angus Scale

The SAS[39] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero

representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

Anticholinergics, benzodiazepines, non-benzodiazepine sleep aids, and propranolol are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

#### 8.7.6.2 Abnormal Involuntary Movement Scale

The AIMS[27] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4, indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes or no questions that address the subject's dental status.

Anticholinergics, benzodiazepines, non-benzodiazepine sleep aids, and propranolol are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

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

#### 8.7.6.3 Barnes Akathisia Rating Scale

The BARS[40] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated

and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning.

Anticholinergics, benzodiazepines, non-benzodiazepine sleep aids, and propranolol are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

## 8.8 Adverse Events

### 8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned 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.

Treatment-emergent AEs are defined as AEs with an onset date on or after the start of double-blind treatment. In more detail, TEAEs are all adverse events which started after start of double-blind IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.

  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable events (IREs).

Immediately Reportable Event:

- Any SAE.
- Any AE related to occupational exposure.
- Any AESIs (pathological gambling and other compulsive behaviors)
- Potential serious hepatotoxicity (see Section 8.8.6).
- 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 and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication. This includes pregnancy of the subject or the partner of the subject.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. 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 (ie, clinically significant) 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 eSource. The severity 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. |

### 8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eSource provided by the sponsor. Adverse event collection will begin after a subject signs the ICF.

Medical terminology should be used for 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 8.8.3. Special attention should be paid to recording hospitalization and concomitant therapy.

Adverse event, start date, end date, seriousness, severity, relationship to trial treatment (IMP Causality), action taken with trial treatment and outcome will be recorded on the source documents and in eSource.

### 8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational

exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (Please note that the IRE form is NOT the AE eSource.).

### 8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

### 8.8.5 Adverse Events of Special Interest

The new onset or exacerbation of "Pathological Gambling and Other Compulsive Behaviors" will be analyzed as an AESI.

### 8.8.6 Potential Serious Hepatotoxicity

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

### 8.8.7 Procedure for Breaking the Blind

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

### 8.8.8 Follow-up of Adverse Events

#### 8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on eSource. For any AE having been identified throughout the trial, during

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

#### 8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 21 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

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. The investigator will follow IREs until the events are:

- resolved,
- stabilized,
- the subject is lost to follow-up, or
- has died.

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 resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

#### 8.8.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant

follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

### 8.9 Treatment of Overdose

For treatment of overdose, please refer to IB Section 6.3, Overdosage.

### 8.10 Subject Assessment Recording

Subject assessment recordings are included under efficacy assessments in Section 8.1.

### 8.11 Other Assessments

Not applicable.

## 9 Statistical Considerations

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

### 9.1 Sample Size

Approximately 240 subjects will be enrolled in the trial. Details will be presented in the blinded addendum to this protocol.

### 9.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: comprises all subjects who signed an ICF for the trial and enrolled into the trial on Day 0.

Safety Sample: comprises those randomized subjects in the double-blind treatment period who received at least 1 dose of double-blind IMP as indicated on the dosing record.

Intent-to-treat: Sample: comprises all subjects in the Safety Sample who have measurements of ZAN-BPD total score before randomization and at least 1 post-randomization time point.

### 9.3 Handling of Missing Data for Primary and Key Secondary Endpoint Analysis

Details will be presented in the blinded addendum to this protocol.

## 9.4 Statistical Analyses

### 9.4.1 Efficacy Analyses

#### 9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy analysis will be performed by fitting a mixed-effect model repeated measure (MMRM) analysis with an unstructured variance covariance structure in which the change from the baseline in ZAN-BPD total score during the double-blind treatment period will be the dependent variable based on the observed cases data set. The model will include fixed class effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week. The model will also include the interaction term of baseline values of ZAN-BPD total score by visit week as covariates. All scheduled visits after baseline during the double-blind treatment period will be included in the model.

Complete details of the planned statistical analysis will be presented in the blinded protocol addendum and in the SAP.

#### 9.4.1.2 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoint will be analyzed by fitting the same MMRM model described in the primary analysis.

#### 9.4.1.3 Secondary Efficacy Endpoint Analysis

Details will be presented in the blinded addendum to this protocol.

#### 9.4.1.4 Control of Experiment-wise Type 1 Error

Details will be presented in the blinded addendum to this protocol.

#### 9.4.1.5 Exploratory Efficacy Endpoint Analysis

Details will be presented in the blinded addendum to this protocol.

### 9.4.2 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. In addition, data from the following safety scales will be evaluated: assessments of suicidality (C-SSRS) and EPS (eg, the SAS, AIMS, and BARS). Safety analysis will be conducted based on the Safety Sample defined in Section 9.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analyses will be provided in the SAP.

#### 9.4.2.1 Adverse Events

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

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

#### 9.4.2.2 Clinical Laboratory Data

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

#### 9.4.2.3 Physical Examination and Vital Signs Data

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

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

#### 9.4.2.4 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 corrected QT interval (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:

$$QTcB=QT/(RR)^{0.5}, \text{ and}$$

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 Food and Drug Administration (FDA) Neuropharm Division formula:

$$QTcN=QT/(RR)^{0.37}$$

Results will be summarized by visit.

#### 9.4.2.5 Other Safety Data

Change from baseline in scores for EPS (eg, SAS, AIMS, and BARS) will be evaluated using descriptive statistics. The analyses will be based on the observed case (OC) and last observation carried forward datasets of the Safety Sample.

Suicidality (eg, C-SSRS) will be summarized by treatment group by descriptive statistics. Details will be described in SAP.

### 9.4.3 Other Analyses

#### 9.4.3.1 Analysis of Demographic and Baseline Characteristics

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

#### 9.4.3.2 Pharmacokinetic Analysis

Pharmacokinetic samples will be analyzed for brexpiprazole (OPC-34712) and its metabolite(s) and descriptive statistics will be calculated. No formal statistical comparisons are planned.

#### 9.4.3.3 Pharmacodynamic Analysis

Not applicable.

#### 9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

A separate population or pharmacokinetic/pharmacodynamic modeling may be performed using the data from this trial and other trials.

#### 9.4.3.5 Pharmacogenomic Analysis

CYP2D6 genotype and predicted phenotype will be listed for brexpiprazole-treated subjects..

#### 9.4.3.6 Other Endpoint Analysis

Analysis of other efficacy endpoints will be described in the SAP.

## 9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design are planned.

### 9.5.1 Data Monitoring Committee

Not applicable.

# 10 Supporting Documentation and Operational Considerations

## 10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

### 10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, Food and Drug Administration (FDA) regulations, International Conference for Harmonisation (ICH) GCP: Consolidated Guideline (E6[R2]), 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, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

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

### 10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The electronic ICF will be approved by the same IRB/IEC that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6(R2)[41] 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 subjects will be provided with controlled access to the electronic ICF application by trial site staff. When the trial site staff and the subject agree that the

subject has enough information to make an informed decision to participate, the subject will electronically sign in the electronic ICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. 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.

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

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 continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

A separate and similar consent process will be followed for the optional blood samples for future biospecimen research. Consent must be obtained before the blood sample is collected.

### 10.1.3 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 ID in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

### 10.1.4 Quality Control and Quality Assurance

#### 10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6[R2]), 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 trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

#### 10.1.4.2 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 a review of eSource with source documents, as applicable. 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.

### 10.1.5 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 or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in eSource along with the start date and details of the deviation.

### 10.1.6 Records Management

#### 10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the 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.

#### 10.1.6.2 Data Collection

During each subject's visit to the site or remote visit, an investigator or their designee participating in the trial will record information 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 the investigator (or designee) who made an entry in the medical record.

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 (where permitted by local regulation) 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 according to 21 CFR Part 11. Changes to the data will be captured by an automatic audit trail.

Designated trial site staff will not be given access to the electronic source 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 per the monitoring plan 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 investigator or their designee.

Another exception will be safety laboratory (or central ECG data), where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records 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.

#### 10.1.6.3 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: Consolidated Guideline (E6[R2]) and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

#### 10.1.6.4 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.

#### 10.1.6.5 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 subjects 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 subjects consent to such acknowledgement in any publications resulting from its conduct.

## 10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

**Table 10.2-1 Clinical Laboratory Assessments**

| | |
|---|---|
| Hematology:<br>Hemoglobin<br>Hematocrit<br>MCH<br>MCHC<br>MCV<br>Platelet count<br>RBC count<br>RBC morphology<br>RDW<br>WBC count with differential<br><br>Urinalysis:<br>Specimen Appearance<br>Color<br>Occult Blood<br>Glucose<br>Microscopic analysis, WBC/RBC counts per high powered field<br>pH<br>Protein<br>Specific Gravity<br>Ketones<br><br>Urine Drug Screens:<br>Amphetamines/MDMA<br>Barbiturates<br>Benzodiazepines<br>Cannabinoids<br>Cocaine<br>Methadone<br>Opiates<br>Phencyclidine<br>Propoxyphene<br><br>Drug and Alcohol Screening<br>Blood alcohol | Serum Chemistry:<br>ALP<br>ALT<br>AST<br>Bilirubin, total<br>BUN<br>Calcium<br>Cholesterol (total, LDL, and HDL)<br>CPK<br>Creatinine<br>GGT<br>Glucose<br>Lactic Dehydrogenase<br>Magnesium<br>Potassium<br>Prolactin[a]<br>Protein, total<br>Sodium<br>Triglycerides<br>Uric acid<br><br>Additional Tests:<br>Urine and serum pregnancy for FOCBP[b]<br>TSH, with reflex to free $T_4$ if TSH is abnormal<br>Prothrombin time, Activated partial thromboplastin time, and International normalized ratio (screening only)<br>$HbA_{1c}$<br><br>Additional Tests (screening only):<br>HIV<br>HBsAg<br>Anti-HCV |

ALP = alkaline phosphatase; anti-HCV = hepatitis C antibodies; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HBsAg = hepatitis B surface antigen; HDL = high density lipoprotein; LDH = lactic dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDMA = methylenedioxymethamphetamine; RBC = red blood cell; RDW = red cell distribution width; WBC = white blood cell.

[a] Prolactin results will be blinded to the investigators and trial staff.

[b] All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

## 10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of child-bearing potential are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For males and FOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) 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, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchidectomy) or remains abstinent during the trial and for 30 days after the last dose of IMP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control implant, birth control depot injection, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide.

Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in eSource. Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Consensual sexual activity that cannot biologically result in pregnancy may not be subject to required birth control methods, following discussion with the medical monitor. The contraceptive method will be documented in eSource. Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

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

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

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

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 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 the Pregnancy Surveillance Form(s) to the investigator 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 the 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.

## 10.4 Appendix 4: Abbreviations

| Abbreviation | Definition |
|---|---|
| 5-HT | Serotonin |
| AAD | Agitation in Alzheimer's disease |
| ADHD | Attention-deficit/hyperactivity disorder |
| ADT | Antidepressant therapy |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AIMS | Abnormal Involuntary Movement Scale |
| ALT | Alanine aminotransferase |
| ALP | Alkaline phosphatase |
| anti-HCV | Hepatitis C antibodies |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| BARS | Barnes Akathisia Rating Scale |
| BMI | Body mass index |
| BPD | Borderline personality disorder |
| BPM | Beats per minute |
| BUN | Blood urea nitrogen |
| CGI-I | Clinical Global Impression-Improvement of Illness |
| CGI-S | Clinical Global Impression-Severity of Illness |
| CGI-SS | Clinical Global Impression- Severity of Suicidality |
| CPK | Creatine phosphokinase |
| CRO | Contract research organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CST | Clinical Surveillance Team |
| CYP | Cytochrome P450 |
| D | Dopamine |
| DBP | Diastolic blood pressure |
| DNA | Deoxyribonucleic acid |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4th edition |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, 5th edition |
| ECG | Electrocardiogram |
| EPS | Extrapyramidal symptoms |
| ET | Early termination |
| FBR | Future Biospecimen Research |
| FDA | Food and Drug Administration |
| FOCBP | Females of childbearing potential |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| HADS | Hospital Anxiety and Depression Scale |
| $HbA_{1c}$ | Glycosylated hemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HDL | High-density lipoprotein |
| HIV | Human immunodeficiency virus |

| Abbreviation | Definition |
|---|---|
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product(s) |
| IND | Investigational New Drug |
| INR | International normalized time |
| IRB | Institutional Review Board |
| IRE | Immediately reportable event |
| $K_i$ | Inhibitory constant |
| LDH | Lactate dehydrogenase |
| LDL | Low-density lipoprotein |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MDD | Major depressive disorder |
| MDMA | Methylenedioxymethamphetamine |
| MINI | Mini International Neuropsychiatric Interview |
| MMRM | Mixed-effect model repeated measure |
| OC | Observed case |
| OPDC | Otsuka Pharmaceutical Development & Commercialization, Inc |
| PGI-C | Patient's Global Impression of Change |
| PGI-S | Patient's Global Impression of Severity |
| PGx | Pharmacogenomic(s) |
| PK | Pharmacokinetic(s) |
| PQC | Product Quality Complaint |
| PT | Prothrombin time |
| PTSD | Post-traumatic stress disorder |
| QTcB | QT interval as corrected by Bazett's formula |
| QTcF | QT interval as corrected by Fridericia's formula |
| QTcN | QT interval as corrected by the FDA Neuropharm Division formula |
| RBC | Red blood cell |
| RNA | Ribonucleic acid |
| RR | Response rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Simpson Angus Scale |
| SBP | Systolic blood pressure |
| SCID-5-PD | Structured Clinical Interview for DSM-5 Personality Disorders |
| SYE | Subject years of exposure |
| $T_4$ | Thyroxine |
| TEAE | Treatment-emergent adverse event |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| US | United States |
| WBC | White blood cell |

| Abbreviation | Definition |
|---|---|
| WHODAS | World Health Organization Disability Assessment Schedule |
| ZAN-BPD | Zanarini Rating Scale for Borderline Personality Disorder |

## 10.5 Appendix 5: Criteria for Identifying Laboratory Values of Potential Clinical Relevance

| Laboratory Tests | Criteria |
|---|---|
| **Chemistry** | |
| AST (SGOT) | ≥ 3 x ULN |
| ALT (SGPT) | ≥ 3 x ULN |
| Alkaline phosphatase | ≥ 3 x ULN |
| Lactate dehydrogenase | ≥ 3 x ULN |
| Blood urea nitrogen | ≥ 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 |
| Creatine phosphokinase | > 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 |
| WBC count | ≤ 2,800 mm3 or ≥ 16,000 mm3 |
| Eosinophils | ≥ 10% |
| Neutrophils | ≤ 15% |
| Absolute neutrophil count | ≤ 1,500/$mm^3$ |
| 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 |
| Nonfasting | ≥ 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 |

## 10.6 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 standing | Not applicable (baseline status not considered) |
| Weight | – | ≥ 7% increase<br>≥ 7% decrease |

bpm = beats per minute.

[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).

## 10.7 Appendix 7: Criteria for Identifying ECG Measurements of Potential Clinical Relevance

| Variable | Criterion Value[a] | Change Relative to Baseline[a] |
|---|---|---|
| **Rate** | | |
| Tachycardia | ≥ 120 bpm | increase of ≥ 15 bpm |
| Bradycardia | ≤ 50 bpm | decrease of ≥ 15 bpm |
| **Rhythm** | | |
| Sinus tachycardia[b] | ≥ 120 bpm | increase of ≥ 15 bpm |
| Sinus bradycardia[c] | ≤ 50 bpm | decrease of ≥ 15 bpm |
| Supraventricular premature beat | all | not present → present |
| Ventricular premature beat | all | not present → present |
| Supraventricular tachycardia | all | not present → present |
| Ventricular tachycardia | all | not present → present |
| Atrial fibrillation | all | not present → present |
| Atrial flutter | all | not present → present |
| **Conduction** | | |
| 1 atrioventricular block | PR ≥ 200 msec | increase of ≥ 50 msec |
| 2 atrioventricular block | all | not present → present |
| 3 atrioventricular block | all | not present → present |
| Left bundle-branch block | all | not present → present |
| Right bundle-branch block | all | not present → present |
| Pre-excitation syndrome | all | not present → present |
| Other intraventricular conduction block[d] | QRS ≥ 120 msec | increase of ≥ 20 msec |
| **Infarction** | | |
| Acute or subacute | all | not present → present |
| Old | all | not present → present<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 (males)<br>QTcF > 470 msec (females) | |

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

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

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

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

## 10.8 Appendix 8: Protocol Amendments

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 "nonsubstantial" 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.

### 10.8.1 Protocol Amendment(s)/Administrative Change(s)

#### 10.8.1.1 Protocol Amendment 1

**Amendment 1 Approval Date:** 07 Jul 2020

**PURPOSE:**

The purpose of this protocol amendment is to introduce a COVID-19 Addendum for any protocol-specified activities that are not able to be performed per protocol or cannot be performed due to COVID-19 considerations. Refer to the COVID-19 Addendum (dated 02 Jul 2020) for the appropriate measures to be followed. Additional changes were made to the protocol and are documented below in this change memo. Minor editorial revisions were also made, for consistency with Otsuka style and for internal consistency.

**BACKGROUND:**

These changes to clinical trial protocol 331-201-00242, originally issued on 09 Jul 2019, were made to introduce a COVID-19 addendum including a revised schedule of assessments able to be conducted remotely, as well as to incorporate items from the protocol clarification memo (dated 05 Mar 2020).

**MODIFICATIONS TO PROTOCOL:**

**General Revisions:**

- Added footnotes for SCID-5-PD and Screening (column heading) under Table 1.3-1 “Schedule of Assessments”.
- Revised exclusion criterion #1 and deleted the word “oral” in exclusion criterion #10 in Section 5.2.2 “Exclusion Criteria”.
- Updated email address and changed text in Section 6.2.5.1 “Eliciting and Reporting Product Quality Complaints”.
- Added text “including ramelteon” in Table 6.5-1 “List of Medications Prohibited Before the Trial”.
- Revised Section 9.4.3.5 “Pharmacogenomic Analysis”.
- Deleted text “pharmacogenomic testing and” in Section 10.1.2 “Informed Consent”.
- Added text “or remote visit” in Section 10.1.6.2 “Data Collection”.

- Incorporated the following items from the protocol clarification memos:
  - Revised the following text: Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Male or female subjects identifying as homosexual with exclusively same-sex partners may not be required to practice birth control methods following discussion with the investigator and medical monitor.
  - Revised the following text: Multiple concurrent ADTs at a therapeutic dose range (for depressive symptoms) are not permitted. Tricyclic antidepressants and trazodone are excluded unless they are being used for sleep management (further discussion with the medical monitor is required before allowing these medications).
  - Revised the following text: Monoamine oxidase inhibitors, tricyclic antidepressants,[a] trazodone,[a] nefazodone, fluoxetine (> 60 mg/day) and paroxetine (> 50 mg/day).

**ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

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Agreement

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

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, 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/IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eSource 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 subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

| _____ | _____ | _____ |
|---|---|---|
| Principal Investigator Print Name | Signature | Date |

**This page is a manifestation of an electronically captured signature**

# SIGNATURE PAGE

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| Raoufinia_Arash | Approved for Clinical Pharmacology and Nonclinical | 07-Jul-2020 16:31:47 |
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