Official Title: A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Adult Subjects With Borderline Personality Disorder

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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Adult Subjects With Borderline Personality Disorder

Open-label Trial of Brexpiprazole in the Treatment of Borderline Personality Disorder

Protocol No. 331-201-00195
IND No. 141091
EudraCT No. 2019-002897-30

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	2/3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety CCI [redacted]
Amendment 1 Approval:	01 Jul 2020
Original Approval:	21 Aug 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 relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

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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.: 331-201-00195

IND No.: 141091

EudraCT No.: 2019-002897-30

Protocol Title: A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Adult Subjects With Borderline Personality Disorder

Protocol Lay Person Short Title: Open-label Trial of Brexpiprazole in the Treatment of Borderline Personality Disorder

Clinical Phase/Trial Type: Phase 2/3 / Therapeutic use

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

Objectives and Endpoints:

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

Objectives	Endpoints
[redacted]	[redacted]

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; [redacted]; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptom; ET = early termination; [redacted]; SAS = Simpson Angus Scale; [redacted] Schedule; [redacted]

Note: The assessments from the last scheduled treatment visit of the previous double-blind trial will serve as the baseline measures for Trial 331-201-00195.

Trial Design:

This will be a 12-week, multicenter, open-label trial designed to evaluate the safety and tolerability of brexpiprazole treatment in adult subjects diagnosed with BPD. Subjects will receive 2 to 3 mg/day brexpiprazole.

Enrollment into the trial will be drawn from eligible subjects who completed the last visit of the previous double-blind, brexpiprazole BPD trials (and took the investigational medicinal product [IMP] through the last scheduled treatment visit) and, in the investigator's judgment, could potentially benefit from treatment with brexpiprazole for BPD.

Subjects will be screened for eligibility at the last scheduled treatment visit of the previous double-blind trial. Subjects will sign a separate informed consent form (ICF) at the last scheduled treatment visit of the previous double-blind trial for participation in Trial 331-201-00195 before any procedures specific to the open-label trial are performed. The assessments from the last scheduled treatment visit of the previous double-blind trial will serve as the baseline measures for Trial 331-201-00195 for any assessment that is not new (unique) to the open-label trial. Medical history will be updated, if necessary. Informed consent cannot be obtained after the last scheduled treatment visit of the previous double-blind trial without all screening/baseline assessments being repeated. If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor (Note: assessments from the last scheduled treatment visit in the previous double-blind trial that are going to be used as the baseline measures for Trial 331-201-00195 will not need to be repeated if the subject enters Trial 331-201-00195 within 3 days).

Eligible subjects will receive up to 12 weeks of daily treatment with open-label brexpiprazole. A safety follow-up telephone contact or clinic visit will occur 21 (± 3) days after the last dose of brexpiprazole.

Trial Population:

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

- Subjects who participated in a double-blind brexpiprazole BPD trial will be eligible for Trial 331-201-00195 if they have completed the last scheduled treatment visit of the previous double-blind trial and did not terminate early.
- Subjects must qualify for Trial 331-201-00195 at the last scheduled treatment visit of the previous double-blind trial and must be able to continue treatment without interruption between the double-blind and open-label trials (if a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor).

Key Inclusion/Exclusion Criteria:

Male or female outpatients, ages 18 to 65 years (at the time of informed consent of the previous double-blind trial), with a BPD diagnosis who completed the last treatment visit of the previous double-blind brexpiprazole BPD trial and who, in the opinion of the investigator, could potentially benefit from administration of brexpiprazole for the treatment of BPD. Eligible subjects must not have a major protocol deviation during the course of their participation in the previous double-blind brexpiprazole BPD trial (if the major protocol deviation is due to the coronavirus disease of 2019 [COVID-19], eligibility for the subject to continue can be discussed with medical monitor).

Trial Site(s):

This trial will be conducted at multiple sites globally.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

All subjects will receive a starting dose of 1 mg/day at the screening/baseline visit, followed by an increase to 2 mg/day at the end of Week 1. Subjects may increase their dose to 3 mg/day at the investigator's discretion on or after the Week 2 visit, depending on treatment response and tolerability. Subjects taking 3 mg/day may down-titrate to 2 mg/day based on tolerability at any time during the course of the trial. Subjects unable to tolerate 2 mg/day will be discontinued from the trial. Dose adjustments to brexpiprazole must be made in increments of 1 mg/day. Dose decreases for brexpiprazole can occur at unscheduled visits and dose increases for brexpiprazole can only occur at scheduled visits.

As applicable, dose changes of background antidepressant therapy (ADT) can be modified to achieve optimum efficacy and tolerability. Dose adjustments of ADT should not occur at the same visit as a dose adjustment of brexpiprazole and a recommended minimum of 5 days should occur between any dose adjustments of brexpiprazole or ADT at any point during the trial.

Dosing Schedule			
IMP	**Screening/Baseline - Week 1**	**Week 1 - Week 2**	**Week 2 - Week 12[a]**
Brexpiprazole	1 mg/day	2 mg/day	2 or 3 mg/day[b]

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

[b]Option to titrate to 2 or 3 mg/day (ie, 2 mg, or 3 mg) based on clinical response and tolerability; changes must occur in 1 mg/day increments.

Trial Assessments:

CCI [redacted]

Assessments for Pharmacokinetics/Pharmacodynamics: None.

Assessments for Safety: Adverse event (AE) reporting, clinical laboratory tests (including prolactin and glycosylated hemoglobin [HbA1c]), electrocardiogram (ECG), vital signs, physical examination, Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Columbia-Suicide Severity Rating Scale (C-SSRS).

Screening/Other: Medical, psychiatric, and medication history; urine drug and blood alcohol screening; and urine pregnancy test.

Data Monitoring Committee: None.

Statistical Methods:

The sample size is not based on statistical power considerations but on the number of subjects rolling over from the lead-in trials. The trial population will be derived from eligible subjects who completed the previous double-blind brexpiprazole BPD trials. The number of eligible subjects will be limited by the number of subjects enrolled into the double-blind trials.

The primary safety analysis is the frequency and severity of AEs in the open-label treatment phase. All AEs will be coded by system organ class and the Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by the prior treatment group:

1) Treatment-emergent adverse events (TEAEs)
2) TEAEs by severity,
3) TEAEs potentially causally related to the IMP,
4) TEAEs with an outcome of death,
5) Serious TEAEs,
6) TEAEs leading to discontinuation of the IMP,
7) Adverse events of special interest (AESI).

A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or IMP-related or results in death, discontinuation, interruption or reduction of IMP. Information about new onset or exacerbation of "Pathological Gambling and Other Compulsive Behaviors" will be collected and analyzed as an AE of special interest.

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

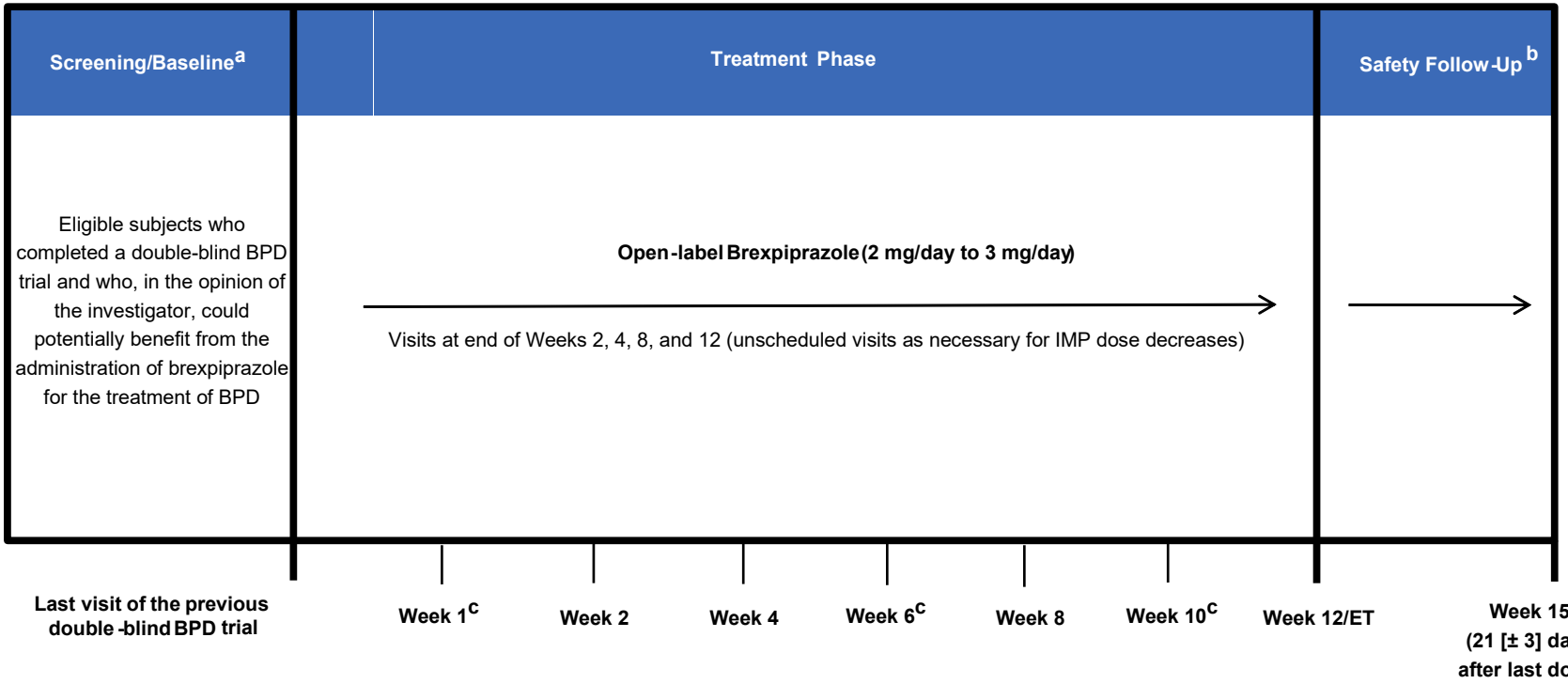
Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed), for approximately 15 weeks:

- Eligibility screening period (1 day) (If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor.)
- Treatment period (12 weeks)
- Post-treatment follow-up period (21 ± 3 days)

Eligible subjects from the previous double-blind trials will be eligible to roll over into this open-label extension trial. Overall, the trial duration from first ICF signed to the final subject assessment is expected to be several years.

1.2 Schema



[a]The last visit of the previous double-blind BPD trial will serve as the baseline measures for Trial 331-201-00195. If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor.

[b]Telephone contact or clinic visit.

[c]Telephone contact will be made at Weeks 1, 6, and 10 to assess AEs and concomitant therapy.

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Assessment	Visit: Screening/ Baseline[a,b]	Treatment Period: Week 1[c,d]	Week 2[c]	Week 4[c]	Week 6[c,d]	Week 8[c]	Week 10[c,d]	Week 12 or ET[c,e]	Post-treatment Follow-up[f]
		± 3 days							21 ± 3 days
ENTRANCE CRITERIA									
Informed consent[g]	X								
Inclusion and exclusion criteria[g]	X								
Confirmation of eligibility[g]	X								
Medical history[g]	X								
Psychiatric history, including BPD history[g]	X								
CCI									
SAFETY									
Physical examination[i]	X							X	
Vital signs[j]	X		X	X		X		X	

Table 1.3-1 Schedule of Assessments

Assessment	Visit: Screening/ Baseline[a,b]	Treatment Period: Week 1[c,d]	Week 2[c]	Week 4[c]	Week 6[c,d]	Week 8[c]	Week 10[c,d]	Week 12 or ET[c,e]	Post-treatment Follow-up[f]
		± 3 days							21 ± 3 days
Clinical laboratory tests (hematology [including HbA1c], serum chemistry [including prolactin], urinalysis)	X[k]							X[l]	
ECG[m]	X							X	
Urine pregnancy test (FOCBP only)[n]	X			X		X		X	
Urine drug screen and blood alcohol test[o]	X							X	
C-SSRS[p]	X		X	X		X		X	
EPS scales (SAS, AIMS, BARS)	X			X		X		X	
Adverse events[q]	X	X	X	X	X	X	X	X	X
Concomitant therapy[r]	X	X	X	X	X	X	X	X	X
OTHER PROCEDURES									
IMP dispensing[g]	X		X	X		X			
IMP accountability			X	X		X		X	
Dose adjustment[s]			X	X		X		X	
Schedule optional telephone contact/other communication[t]			X	X	X	X	X		

FOCBP = female of childbearing potential.

[a]Screening for Trial 331-201-00195 occurs on the same day as baseline but prior to any procedures specific to the open-label trial. Informed consent for Trial 331-201-00195 should be signed at the start of the last double-blind treatment visit. The screening/baseline for Trial 331-201-00195 will be the same day as the last visit of the previous double-blind trial.

[b]The assessments from the last scheduled treatment visit of the previous double-blind trial will serve as the baseline measures for Trial 331-201-00195 for any assessment that is not new (unique) to the open-label trial. If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor (Note: assessments from the last scheduled treatment visit in the previous double-blind trial that are going to be used as the baseline measures for Trial 331-201-00195 will not need to be repeated if the subject enters Trial 331-201-00195 within 3 days).

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

[d]Telephone contact will be made at Weeks 1, 6, and 10 to assess AEs and concomitant therapy.

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

[f]Telephone contact or clinic visit (investigator's discretion) for evaluation of safety, 21 days after the last dose.

[g]New (unique) assessments for Trial 331-201-00195 include informed consent, inclusion/exclusion criteria, confirmation of eligibility, changes in medical and psychiatric history, and dispensing of IMP.

[h]Any post-screening/baseline visit should refer to screening/baseline when assessing change.

[i]To include measurement of waist circumference.

[j]Vital sign measurements include body weight, body temperature, systolic blood pressure, 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.

[k]Subjects should be fasting for a minimum of 8 hours prior to blood draws for screening/baseline laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening/baseline, nonfasting blood samples may be obtained initially for determining eligibility for the trial and need to be repeated at the next visit at the discretion of the investigator.

[l]Blood samples for clinical laboratory tests should be drawn after a minimum 8-hour fast at Week 12/ET, if possible. Vital sign and ECG assessments should be completed before any blood samples are collected.

[m]Standard ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. Subjects will be enrolled in Trial 331-201-00195 based on the screening/baseline ECG results from the trial site. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

[n]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.

[o]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/baseline.

[p]The "Since Last Visit" C-SSRS form will be completed at all visits for all subjects.

[q]Adverse events recording will begin with the signing of the ICF for Trial 331-201-00195 and through the last scheduled trial visit (immediately reportable events will be collected through the last trial contact).

[r]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.

[s]See Section 6.1 for dose adjustment details.

[t]Schedule an optional telephone call or other form of communication with the subject approximately 1 week (± 2 days) after the visit (eg, 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 suicide), 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 (84.5%), including anxiety, mood, impulse control, and substance disorders.[9]

Brexpiprazole (REXULTI®) is a novel 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 Investigator's Brochure (IB) 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 dialectical 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 of brexpiprazole may allow for effective pharmacotherapy for the treatment of BPD. More specifically, the serotonergic and dopaminergic stabilization and normalization 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, open-label trial (Trial 331-201-00195) will be conducted to evaluate the safety and tolerability 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 dementia (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 or subjects with schizophrenia.[10]

Please refer to the current 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 current 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 Safety: To evaluate the safety and tolerability of brexpiprazole for the treatment of subjects with a diagnosis of BPD.	Primary Safety: Frequency and severity of AEs. Secondary Safety: • Changes in: ECGs, vital signs, clinical laboratory tests including prolactin, changes in body weight, and physical examinations; • EPS: SAS, AIMS, and BARS; • Suicidal ideation and behavior will be assessed using the C-SSRS.

Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
CCI [redacted]	

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CCI [redacted]; CCI [redacted]; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptom; ET = early termination; CCI [redacted]; CCI [redacted]; CCI [redacted]; SAS = Simpson Angus Scale; CCI [redacted] Schedule; CCI [redacted].

Note: The assessments from the last scheduled treatment visit of the previous double-blind trial will serve as the baseline measures for Trial 331-201-00195.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a 12-week, multicenter, open-label trial designed to evaluate the safety and tolerability of brexpiprazole treatment in adult subjects diagnosed with BPD. Subjects will receive 2 to 3 mg/day brexpiprazole.

Enrollment into the trial will be drawn from eligible subjects who completed the last treatment visit of the previous double-blind brexpiprazole BPD trials (and took the investigational medicinal product [IMP] through the last scheduled treatment visit) and, in the investigator's judgment, could potentially benefit from treatment with brexpiprazole for BPD.

The trial will be organized as follows:

Screening/Baseline: Subjects will be screened for eligibility at the last scheduled treatment visit of the previous double-blind trial. Subjects will sign a separate informed consent form (ICF) at the last scheduled treatment visit of the previous double-blind trial for participation in this trial before any procedures specific to the open-label trial are performed. The assessments from the last scheduled treatment visit of the previous double-blind trial will serve as the baseline measures for this trial for any assessment that is not new (unique) to the open-label trial. Medical history will be updated, if necessary. Informed consent cannot be obtained after the last scheduled treatment visit of the previous double-blind trial without all screening/baseline assessments being repeated. If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor (Note: assessments from the last scheduled treatment visit in the previous double-blind trial that are going to be used as the baseline measures for Trial 331-201-00195 will not need to be repeated if the subject enters Trial 331-201-00195 within 3 days).

Treatment Phase: Eligible subjects will receive daily treatment with open-label brexpiprazole beginning at the screening/baseline visit, as described in Section 6.1. Visits will occur at the end of Weeks 2, 4, 8, and 12. Telephone contact will be made at Weeks 1, 6, and 10 to assess adverse events (AEs) and concomitant therapy. In addition, an optional telephone call or other form of communication will be made with the subject approximately 1 week (± 2 days) after the visit (eg, at Weeks 3, 5, 7, 9, and 11) to check on status. All subjects will receive up to 12 weeks of open-label treatment in this trial.

Follow-up: Subjects will be followed for safety via telephone contact or clinic visit 21 (± 3) days after the last dose of open-label brexpiprazole.

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

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]

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, as noted in Section 2. Together, the broad pharmacological profile of brexpiprazole may provide for a unique treatment strategy for BPD. More specifically, the serotonergic and dopaminergic stabilization and modulation provided by brexpiprazole may directly address some of the key features and symptoms noted in the disease including impulsivity, aggression, affective instability, and suicidality. It is anticipated that the brexpiprazole safety profile for BPD will be comparable to the safety profiles of the currently approved indications.

Trial 331-201-00195 is being conducted to evaluate the safety and tolerability of brexpiprazole in subjects diagnosed with BPD who have completed a double-blind BPD trial.

4.3 Dosing Rationale

The dosing paradigm of brexpiprazole to be used in Trial 331-201-00195 has been determined based on the dosing ranges investigated in other related psychiatric indications (bipolar I disorder, MDD, PTSD, and schizophrenia) and the dosing ranges used in the previous double-blind trials for the open-label extension.[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 follow-up page in eSource 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 visit will be defined as trial completers.

5 Trial Population

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

- Subjects who participated in a double-blind brexpiprazole BPD trial will be eligible for Trial 331-201-00195 if they have completed the last scheduled treatment visit of the previous double-blind trial and did not terminate early.
- Subjects must qualify for Trial 331-201-00195 at the last scheduled treatment visit of the previous double-blind trial and must be able to continue treatment without interruption between the double-blind and open-label trials (if a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor).

Decisions regarding inclusion of subjects at the 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 retain a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] that was given upon providing consent [or assent if applicable]) for the previous double-blind trial.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

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) Subjects, who completed the last treatment visit of the previous double-blind brexpiprazole BPD trial and who, in the opinion of the investigator, could potentially benefit from administration of brexpiprazole for the treatment of BPD.
2) Male or female outpatients, ages 18 to 65 years, inclusive, at the time of informed consent of the previous double-blind brexpiprazole BPD trial.
3) Subjects who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by the institutional review board [IRB]/independent ethics committee [IEC]) prior to the initiation of any protocol-required procedures.
4) 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.

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, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) 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/baseline 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.

Medical History and Concurrent Disease

3) Subjects who fulfill the following criteria related to suicide and/or suicidal ideation at entry are excluded:
   - Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide, or those who are homicidal or considered to be a high risk to others, or subjects with a response of "yes" on the Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent), OR
   - Subjects with a response of "yes" on the C-SSRS Suicidal Behavior Items Actual Attempt, Interrupted Attempt, or Aborted Attempt
   - Subjects who endorse engaging in preparatory acts and/or non-suicidal self-injury may be included according to investigator judgment, provided the behavior has not increased significantly in frequency or severity during the preceding double-blind trial period, and after discussion and approval by the medical monitor.

   Note that 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) may be included following discussion with the medical monitor.

Physical and Laboratory Results

4) Subjects with abnormal laboratory tests results, vital signs results, or electrocardiogram (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 ≤ 9 g/dL
   - Neutrophils, absolute $\leq 1000/mm^3$
   - Aspartate aminotransferase (AST) $> 2 \times$ the upper limit of normal (ULN)
   - Alanine aminotransferase (ALT) $> 2 \times$ ULN
   - Creatine phosphokinase (CPK) $> 3 \times$ ULN, unless discussed with and approved by the medical monitor
   - Creatinine ≥ 2 mg/dL
   - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing.

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

5) 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.

Other

6) Subjects with a major protocol deviation during the course of their participation in the previous double-blind brexpiprazole BPD trial. Minor deviations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-201-00195; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the previous double-blind trial would be considered a major deviation that would result in exclusion from Trial 331-201-00195. If the major protocol deviation is due to the coronavirus disease of 2019 (COVID-19), eligibility for the subject to continue can be discussed with medical monitor. The medical monitor should be contacted if the investigator is unsure of any subject's eligibility.
7) Subjects who participated in a clinical trial within 90 days prior to screening/baseline (with the exception of a previous brexpiprazole double-blind BPD trial) or who participated in more than 2 clinical trials within a year prior to screening/baseline.
8) 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 ICF), but who is not assigned trial treatment.

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/baseline visit)
- Demographics (collection date, birth date, sex)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

Rescreening of subjects is not permitted.

6 Trial Treatments

6.1 Trial Treatments Administered

The first dose of open-label brexpiprazole will be taken one day after the last dose of double-blind IMP is taken for the previous double-blind, brexpiprazole BPD trial so that treatment continues without interruption. It is anticipated that the last dose of IMP of the double-blind trial will be taken the day of the treatment last visit of the previous double-blind brexpiprazole BPD trial (ie, the day of the screening/baseline visit for the open-label trial). If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor.

All subjects will receive a starting dose of 1 mg/day at the screening/baseline visit, followed by an increase to 2 mg/day at the end of Week 1 (Table 6.1-1). Subjects may increase their dose to 3 mg/day at the investigator's discretion on or after the Week 2 visit, depending on treatment response and tolerability. Subjects taking 3 mg/day may down-titrate to 2 mg/day based on tolerability at any time during the course of the trial. Subjects unable to tolerate 2 mg/day will be discontinued from the trial. Dose adjustments to brexpiprazole must be made in increments of 1 mg/day. Dose decreases

for brexpiprazole can occur at unscheduled visits and dose increases for brexpiprazole can only occur at scheduled visits.

As applicable, dose changes of background antidepressant therapy (ADT) can be modified to achieve optimum efficacy and tolerability. Dose adjustments of ADT should not occur at the same visit as a dose adjustment of brexpiprazole and a recommended minimum of 5 days should occur between any dose adjustments of brexpiprazole or ADT at any point during the trial.

Table 6.1-1 Dosing Schedule

IMP	Screening/Baseline - Week 1	Week 1 - Week 2	Week 2 - Week 12[a]
Brexpiprazole	1 mg/day	2 mg/day	2 or 3 mg/day[b]

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

[b]Option to titrate to 2 or 3 mg/day (ie, 2 mg, or 3 mg) based on clinical response and tolerability; changes must occur in 1 mg/day increments.

For information regarding the dose regimen and treatment period(s), including any follow-up period(s), 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 cards 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.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, 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 oral communication by a healthcare professional, consumer, subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or medicinal product or a falsified, tampered, or diverted product after it is released for distribution to a clinical trial. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

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 PQC reporting information to the OPDC IMP complaints mailbox email: CCI
  Also indicate whether or not the complaint sample is available for return.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow the reporting mechanism 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 of complaint sample (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the return instructions 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

This trial is open-label.

6.4 Subject Compliance

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

6.5 Concomitant Medications or Therapies

The investigator will record all medications and therapies taken by the subject from the screening/baseline visit through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in 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) in 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, end date, and frequency.

6.5.1 Prohibited Medications

Table 6.5.1-1 lists all medications prohibited during the trial, including exceptions, where appropriate. This table is consistent with the prohibited medications across the double-blinded trials. However, in this open-label extension, exceptions to prohibited medications or dose adjustments to allowed medications (ie, benzodiazepines) may be considered on a case-by-case basis following discussion with the medical monitor. This will provide greater flexibility in treatment as subject needs arise.

Table 6.5.1-1 List of Medications Prohibited During the Trial	
1.	Psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Anticonvulsants (except for gabapentin when used to treat anxiety or pain, after discussion with the medical monitor) c) Monoamine oxidase inhibitors, tricyclic antidepressants,[a] trazodone,[a] nefazodone, fluoxetine (> 60 mg/day), and paroxetine (> 50 mg/day) d) Mood stabilizers (ie, lithium) e) Benzodiazepine use is restricted to chronic, stable treatment or when used to manage TEAEs such as agitation and anxiety[b] f) Hypnotics, including ramelteon[c] g) Stimulants and atomoxetine 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. 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) j) Disulfiram k) Prazosin - allowed if currently being taken for an appropriate indication at a stable dose. Should be continued throughout trial participation.
2.	Investigational agents
3.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, clomipramine, pyrilamine, diphenhydramine, quinidine, terbinafine, halofantrine, and 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, and verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, and troglitazone. The medical monitor should be consulted for any questions regarding the potential for PK 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 scheduled EPS scale assessments.

CYP = cytochrome P450.

[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 during the previous double-blind trial) 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 TEAEs 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. Other changes to hypnotic medications must be discussed with the medical monitor.

[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. Other changes to beta receptor antagonists must be discussed with the medical monitor.

6.5.2 Benzodiazepine Use During the Trial

Chronic, stable (ie, regularly scheduled maintenance dose that has not changed during the previous double-blind trial) 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 TEAEs 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 (EPS) scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration in 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 the drug name, dose, date, and time taken are clearly documented in eSource.

6.5.3 Permitted Medications or Therapies

Initiation of treatment with new medications or initiation of dose changes in current medications should not occur without discussion with the medical monitor. For subjects who are on ADT treatment at trial entry, dose changes of brexpiprazole and dose changes of ADT, if applicable, should not occur at the same visit and should have a minimum of 5 days occurring between a dose change. Doses of paroxetine cannot exceed 50 mg/day and doses of fluoxetine cannot exceed 60 mg/day.

Initiation of psychotherapy or change in current psychotherapy treatment during the trial may be considered after consultation with the medical monitor.

6.5.4 Rescue Medications

Not applicable.

6.6 Intervention after the End of the Trial

Not applicable.

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 starting open-label IMP, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 7.3.5.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

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

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

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

Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed), for approximately 15 weeks:

- Eligibility screening period (1 day) (If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor.)
- Treatment period (12 weeks)
- Post-treatment follow-up period (21 ± 3 days)

Eligible subjects from the previous double-blind trials will be able to roll over into this open-label extension trial. Overall, the trial duration from first ICF signed to the final subject assessment is expected to be several years.

The assessments to be conducted during the trial are summarized in Table 1.3-1.

8.1 Efficacy Assessments

It is required that trained and experienced clinicians administer all rating scales. The number of raters within each trial site 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.

Subject assessment recordings are summarized in Section 8.10.

CCI

CCI

[redacted]

8.2 Pharmacokinetic Assessments

Not applicable.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

Not applicable.

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. 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 (hematology [including HbA1c], serum chemistry [including prolactin], and urinalysis) 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/baseline, nonfasting blood samples may be obtained initially for determining eligibility for the trial and need to be repeated at the next visit at the discretion of the investigator. 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 at screening/baseline, 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.

The total volume of blood to be collected during the trial will be 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/baseline, 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/early termination (ET) visit. Waist circumference will be measured at each physical examination (screening/baseline and Week 12/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.[24]

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). Subjects should be monitored for potentially clinically significant vital signs values (Section 10.9).

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 lying for at least 3 minutes. The supine measurements will be performed first, followed by standing.

Subjects with uncontrolled hypertension (screening/baseline DBP > 95 mmHg in any position) or symptomatic hypotension at screening/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 to 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/baseline that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening/baseline vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial.

8.7.4 Electrocardiogram

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

Rollover subjects will be enrolled in trial based on the screening/baseline ECG results from the trial site. If at screening/baseline, 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), the subject should be excluded from the trial. Abnormal results for ECGs should be repeated once at screening/baseline 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. If the screening/baseline ECG results from the central reader, when available, indicate a QTcF $\geq$ 450 msec in men and $\geq$ 470 msec in women (unless due to ventricular pacing at screening/baseline), the investigator must contact the medical monitor to discuss the subject's continued participation in the trial.

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. The “Since Last Visit” version of the scale will be completed at all visits for all subjects. Any subject with active suicidal ideation and intent at entry or who has engaged in prohibited suicidal behaviors, or who, in the clinical judgment of the investigator, presents a serious risk of suicide should be excluded from the trial (see Section 5.2.2).

8.7.6 Other Safety Variables

It is required that an adequately trained and experienced clinician administer the safety assessments, including the EPS scales (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]). The number of raters within each trial site 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[25] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until the required time frame has 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 in eSource.

8.7.6.2 Abnormal Involuntary Movement Scale

The AIMS[23] 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, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until the required time frame has 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 in 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[26] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 6.5.1). Investigators are encouraged to delay scale administration until the required time frame has 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 in 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/baseline 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 open-label treatment. In more detail, TEAEs are all AEs which started after start of open-label 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 page in 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 in 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 provided by the sponsor and in eSource. 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 medications.

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 page in 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 in eSource.

8.8.7 Procedure for Breaking the Blind

This trial will not use blinding procedures.

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 page in 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 in 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 (± 3) 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 page in eSource 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 page in eSource 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 the current IB section for overdose.[10]

8.10 Subject Assessment Recording

CCI

[redacted]

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

The sample size is not based on statistical power considerations but on the number of subjects rolling over from the lead-in trials. The trial population will be derived from eligible subjects who completed the previous double-blind brexpiprazole BPD trials. The number of eligible subjects will be limited by the number of subjects enrolled into the double-blind trials.

9.2 Datasets for Analysis

The following datasets are defined for this trial:

- Enrolled Sample, which comprises all subjects who sign an ICF for the trial and are enrolled into the trial.
- Safety Sample, which comprises all subjects who will receive at least 1 dose of IMP.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

In order to assess the sensitivity of results due to missing data, 2 types of analyses will be performed: last observation carried forward (LOCF) and observed cases (OC). The OC dataset will consist of the actual observations recorded at each visit. The LOCF dataset will include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data will be carried forward from the previously scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF dataset. The OC dataset will be used for analyses at each trial visit and the LOCF dataset will be used for analyses at the last visit.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

CCI [redacted].

9.4.2 Safety Analysis

The primary safety endpoint analysis is the frequency and severity of AEs in the open-label treatment phase. 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.

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 the prior treatment group:

- Treatment-emergent AEs (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

A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or IMP-related or results in death, discontinuation, interruption or reduction of IMP. Information about new onset or exacerbation of "Pathological Gambling and Other Compulsive Behaviors" will be collected and analyzed as an AE of special interest.

9.4.2.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined in the statistical analysis plan (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 using Bazett's formula:

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

2) QTcF is the length of the QT interval corrected for heart rate using Fridericia's formula:

$$QTcF=QT/(RR)^{0.33}$$

3) QTcN is the length of the QT interval corrected for heart rate using 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 OC and LOCF datasets of the Safety Sample.

Suicidality (eg, C-SSRS) will be summarized by the prior 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, sex, weight, height, and body mass index will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

9.4.3.2 Pharmacokinetic Analysis

No PK analysis is planned.

9.4.3.3 Pharmacodynamic Analysis

No pharmacodynamic (PD) analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No pharmacogenomic analysis is planned.

CCI

[redacted]

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, FDA regulations, International Council 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 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)[27] 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. In support of the site's standard process for administering informed consent, this trial will also allow for electronic informed consent (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB/IEC-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however if local regulations does not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

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 eICF 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 eICF 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 eICF 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.

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, 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/baseline 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 Code of

Federal Regulations 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: HbA1c Hemoglobin Hematocrit MCH MCHC MCV Platelet count RBC count RBC morphology RDW WBC count with differential Urinalysis: Specimen Appearance Color Occult Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific Gravity Ketones Urine Drug Screens: Amphetamines/MDMA Barbiturates Benzodiazepines Cannabinoids Cocaine Methadone Opiates Phencyclidine Propoxyphene Drug and Alcohol Screening: Blood alcohol	Serum Chemistry: ALP ALT AST Bilirubin, total BUN Calcium Cholesterol (total, LDL, and HDL) CPK Creatinine GGT Glucose LDH Magnesium Potassium Prolactin Protein, total Sodium Triglycerides Uric acid Additional Tests: Urine and serum pregnancy for FOCBP[a]

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; 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]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening/baseline must not be enrolled and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing 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 orchiectomy) 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. Male subjects must also agree not to donate sperm from trial screening/baseline 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/baseline and at each check-in to the inpatient facility 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 dementia
ADHD	Attention-deficit/hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BARS	Barnes Akathisia Rating Scale
BPD	Borderline personality disorder
bpm	Beats per minute
BUN	Blood urea nitrogen
CCI	[redacted]
CCI	[redacted]
COVID-19	Coronavirus disease of 2019
CPK	Creatine phosphatase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D	Dopamine
DBP	Diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	Electrocardiogram
eICF	Electronic informed consent
EPS	Extrapyramidal symptoms
ET	Early termination
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
CCI	[redacted]
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational New Drug

Abbreviation	Definition
IRB	Institutional review board
IRE	Immediately reportable event
K_i	Inhibition constant
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine
OC	Observed cases
PD	Pharmacodynamic
CCI [redacted]	[redacted]
PK	Pharmacokinetic
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcN	QT interval corrected for heart rate using the Food and Drug Administration Neuropharm Division formula
RBC	Red blood cell
RDW	Red cell distribution width
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SYE	Subject years of exposure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]

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]	> 100 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
Systolic blood pressure[b]	≥ 140 mmHg Supine < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure[b]	≥ 90 mmHg Supine < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Orthostatic hypotension	≥ 30 mmHg decrease in systolic blood pressure and/or a decrease of ≥ 20 mmHg in diastolic blood pressure after at least 3 minutes of standing compared to the previous supine blood pressure.	Not applicable (baseline status not considered)
Orthostatic tachycardia	≥ 25 bpm increase in heart rate from supine to standing	Not applicable (baseline status not considered)
Weight	–	≥ 7% increase ≥ 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 ≥ 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) QTcF > 470 msec (females)	

QTc = corrected QT interval; QTcF = QT interval corrected for heart rate using Fridericia's formula.

[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: 01 Jul 2020

PURPOSE:

The purpose of this protocol amendment is to introduce an addendum for COVID-19 for any protocol-specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. Refer to the COVID-19 Addendum (dated 01 Jul 2020) for the appropriate measures to be followed. Additional administrative changes were made to the protocol and are documented below. Finally, minor editorial revisions were made for consistency with Otsuka style and for internal consistency.

BACKGROUND:

These changes to clinical trial protocol 331-201-00195, originally issued on 21 Aug 2019, were made to introduce a COVID-19 addendum. In addition, administrative changes were incorporated as described in the protocol clarification memos (dated 20 Nov 2019 and 12 Feb 2020).

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Clarified in the trial design sections, for consistency with the schedule of assessments, that an optional telephone call or other form of communication will be made with the subject approximately 1 week (± 2 days) after the visit (eg, at Weeks 3, 5, 7, 9, and 11) to check on status.
- Modified exclusion criterion #1 to indicate that consensual sexual activity that cannot biologically result in pregnancy may not be subject to required birth control methods (following discussion with the medical monitor).
- Added to exclusion criterion #6 that if the major protocol deviation is due to COVID-19, eligibility for the subject to continue can be discussed with medical monitor.
- Added that rescreening of subjects is not permitted.
- For medications prohibited during the trial, added an exception for gabapentin when used to treat anxiety or pain (after discussion with the medical monitor).
- Added trazodone to the list of medications prohibited during the trial (unless it is being used for sleep management, in which case further discussion with the medical monitor is required).

- CCI [redacted]
- Added that the investigator (or their designee participating in the trial) will record information to document all significant observations at remote visits (in addition to site visits).
- Incorporated the following items from the protocol clarification memos:
  - Revised the following text: "Note: assessments from the last scheduled treatment visit in the previous double-blind trial that are going to be used as the baseline measures for Trial 331-201-00195 will not need to be repeated if the subject enters Trial 331-201-00195 within 3 days CCI [redacted]
  - Revised the following text: "Weight should be recorded before a subject's meal and at approximately the same time at each visit CCI [redacted]
  - Added a definition of abstinence: "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."
  - Removed insulin and added HbA1c to the list of laboratory tests.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

11 References

1 Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet. 2004;364(9432):453-461.

2 Gask L, Evans M, Kessler D. Clinical review: personality disorder. BMJ. 2013;347(10):f5276.

3 National Institute of Mental Health [homepage on the Internet]. Bethesda: Borderline Personality Disorder. Available from: http://www.nimh.nih.gov/health/topics/borderline-personality-disorder/index.shtml. [Updated December 2017, Accessed 28 Aug 2018]

4 Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008;69(4):533-545.

5 Truven Marketscan Treatment Pathways; January 2016-December 2017, Otsuka Data on File.

6 National Comorbidity Survey Replication. Biol Psychiatry. 2007.

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

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

9 Lenzenweger MF, Lane MC, Loranger AW, Kessler RC. DSM-IV personality disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;62(6):553-564.

10 Otsuka Pharmaceutical Co, Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., H. Lundbeck A/S. REXULTI® (brexpiprazole) Investigator's Brochure, Edition 14. Otsuka Report, issued 01 Aug 2018.

11 Black DW, Zanarini MC, Romine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2014;171(11):1174-1182.

12 Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Lin D, et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2011;72(10):1353-1362.

13 Schulz SC, Camlin KL, Berry SA, Jesberger JA. Olanzapine safety and efficacy in patients with borderline personality disorder and comorbid dysthymia. Biol Psychiatry. 1999;46(10):1429-1435.

14 Schulz SC, Zanarini MC, Bateman A, Bohus M, Detke HC, Trzaskoma Q, et al. Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. Br J Psychiatry. 2008;193(6):485-492.

15 Chengappa KN, Ebeling T, Kang JS, Levine J, Parepally H. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. J Clin Psychiatry. 1999;60(7):477-484.

16 Belli H, Ural C, Akbudak M. Borderline personality disorder: bipolarity, mood stabilizers and atypical antipsychotics in treatment. J Clin Med Res. 2012;4(5):301-308.

17 Nickel MK, Muehlbacher M, Nickel C, Kettler C, Pedrosa Gil F, Bachler E, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2006;163(5):833-838.

18 Nickel MK, Loew TH, and Pedrosa Gil, F. Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. Psychopharmacology. 2007;191:1023-1026.

19 DeBellis MD, Lefter L, Trickett PK, Putnam FW. Urinary catecholamine excretion in sexually abused girls. J Am Acad Child Adol Pschiatry. 1997;33(3):320-327.

20 Friedel RO. Dopamine dysfunction in borderline personality disorder: a hypothesis. Neuropsychopharmacol. 2004;29:1029-1039.

21 Joyce PR, Stephenson J, Kennedy M, Mulder RT, McHugh PC. The presence of both serotonin 1A receptor (HTR1A) and dopamine transporter (DAT1) gene variants increase the risk of borderline personality disorder. Frontiers in Genetics. 2014;4(313):1-7.

22 Martin-Blanco A, Ferrer M, Soler J, Arranz MJ, Vega D, Bauza J, et al. An exploratory association study of the influence of noradrenergic genes and childhood trauma in borderline personality disorder. Psychiatry Research. 2015;229:589-592.

CCI [redacted]

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

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

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

27 International Council for Harmonisation (ICH) [homepage on the Internet]. E6(R2): Good Clinical Practice: Integrated Addendum to ICH E6(R1) [finalized 2016 November; cited 2019 Jul 8]. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf.

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 in 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