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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Phase 3, Multicenter, Randomized, Double-blind Trial of Brexpiprazole as Combination Therapy with Sertraline in the Treatment of Adults with Post-traumatic Stress Disorder

A Trial of Brexpiprazole with Sertraline in the Treatment of Post-traumatic Stress Disorder

Protocol No. 331-201-00071
IND No. 117,549

CONFIDENTIAL — PROPRIETARY INFORMATION

Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Safety and Pharmacovigilance Fax: 877-464-7787 Email: safetyreporting@syneoshealth.com
Amendment 4 Approval:	04 Jan 2023

CCI [redacted]

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 coronavirus disease 2019 (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.: 331-201-00071

IND No.: 117,549

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind Trial of Brexpiprazole as Combination Therapy with Sertraline in the Treatment of Adults with Post-traumatic Stress Disorder

Protocol Lay Person Short Title: A Trial of Brexpiprazole with Sertraline in the Treatment of Post-traumatic Stress Disorder

Clinical Phase/Trial Type: 3

Treatment/Indication: Post-traumatic stress disorder (PTSD)

Objectives and Endpoints:

Trial Objectives and Endpoints	
Objectives	**Endpoints**
Primary: To evaluate the efficacy of brexpiprazole + sertraline in adult subjects with PTSD.	Primary Efficacy: Change from baseline to the end of the efficacy period in the CAPS-5 total score Key Secondary Efficacy: • Change from baseline to the end of the efficacy period in the CGI-S score • Change from baseline to the end of the efficacy period in B-IPF score Other Efficacy: • Change from baseline to the end of the efficacy period in the PCL-5 score • Change from baseline to the end of the efficacy period in the HADS-A and HADS-D score • Response defined by decrease ≥ 30% from baseline to the end of the efficacy period in the CAPS-5 total score • Change from baseline to the end of the efficacy period in the CAPS-5 subscales/domain scores

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Trial Objectives and Endpoints	
Objectives	**Endpoints**
Primary: To evaluate the efficacy of brexpiprazole + sertraline in adult subjects with PTSD.	CCI [redacted]
Secondary: To evaluate the safety and tolerability of brexpiprazole + sertraline in adult subjects with PTSD	Safety: Standard safety variables will include AEs, clinical laboratory tests (hematology, serum chemistry [including HbA1c and blinded prolactin], and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured. Extrapyramidal symptoms will be evaluated by calculating the mean change from baseline in the SAS total score, AIMS movement rating score, and BARS global score. The C-SSRS will be used to assess and classify reported suicidal behavior.

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; ECG = electrocardiogram; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale - Depression subscale; HbA1c = glycosylated hemoglobin; MCS = mental component summary; PCL-5 = PTSD Checklist for DSM-5; PCS = physical component summary; SAS = Simpson-Angus Scale; CCI [redacted]

Trial Design:

This will be a 12-week, multicenter, randomized, double-blind trial evaluating the efficacy, safety, and tolerability of brexpiprazole + sertraline combination treatment in adult subjects with PTSD.

The trial will consist of a screening period (up to 14 days), a 12-week, double-blind treatment period, and follow-up (21 [+2] days after the last dose of investigational medicinal product [IMP]).

Trial Population:

Approximately 448 male and female outpatients, aged 18 to 65 years, inclusive, will be enrolled.

Key Inclusion/Exclusion Criteria:

The trial population will consist of subjects with a PTSD diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) and

confirmed by the Mini International Neuropsychiatric Interview (MINI) at the screening visit. Subjects are required to have been symptomatic for at least 6 months prior to screening and to have a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score ≥ 33 at screening and baseline (Day 0) visits in order to be considered for enrollment.

Trial Sites:

This trial will be conducted in the United States.

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

During the double-blind treatment period, subjects will receive IMP, consisting of brexpiprazole + sertraline, or sertraline, or placebo, depending on the subject's treatment assignment. IMP assignments can change during the double-blind treatment period.

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

Trial Assessments:

Assessments for Efficacy: CAPS-5, Clinical Global Impression - Severity (CGI-S), PTSD Checklist for DSM-5 (PCL-5), Hospital Anxiety and Depression Scale (HADS), CCI and Brief Inventory of Psychosocial Function (B-IPF).

Assessments for Safety: Adverse event (AE), clinical laboratory tests (hematology, serum chemistry [including glycosylated hemoglobin (HbA1c) and blinded prolactin], and urinalysis), thyroid-stimulating hormone (TSH), 12-lead electrocardiogram (ECG), vital signs, physical examination findings, Columbia Suicide Severity Rating Scale (C-SSRS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).

Assessments for Pharmacokinetics: Blood sampling for IMP plasma concentrations.

Screening/Other: Life Events Checklist for DSM-5 (LEC-5), MINI, and Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID), medical history, psychiatric history (including PTSD history), and PTSD treatments (pharmacological, nonpharmacological, and Emory Treatment Resistance Interview for PTSD [E-TRIP]), urine drug screen/blood alcohol test, and urine pregnancy test.

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Data Monitoring Committee: No

Statistical Methods:

It is anticipated that approximately 448 subjects will be enrolled into the trial.

The change from baseline to the end of the efficacy period in the CAPS-5 total score will be analyzed using a mixed-effect model repeated measures (MMRM) analysis with an unstructured variance covariance structure. The model will include fixed class-effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week, and will include the interaction term of baseline values of the CAPS-5 total score by visit week as a covariate. All scheduled visits after baseline during the double-blind treatment period will be included in the model.

Trial Duration:

The anticipated duration for participants to complete the trial is approximately 17 weeks. This is inclusive of a screening period (up to 14 days), a 12-week double-blind treatment period, and a safety follow-up period (21 [+2] days after the last dose of IMP).

Overall, the trial duration from first informed consent form signed to the final subject assessment is expected to be approximately 46 months.

1.2 Schema

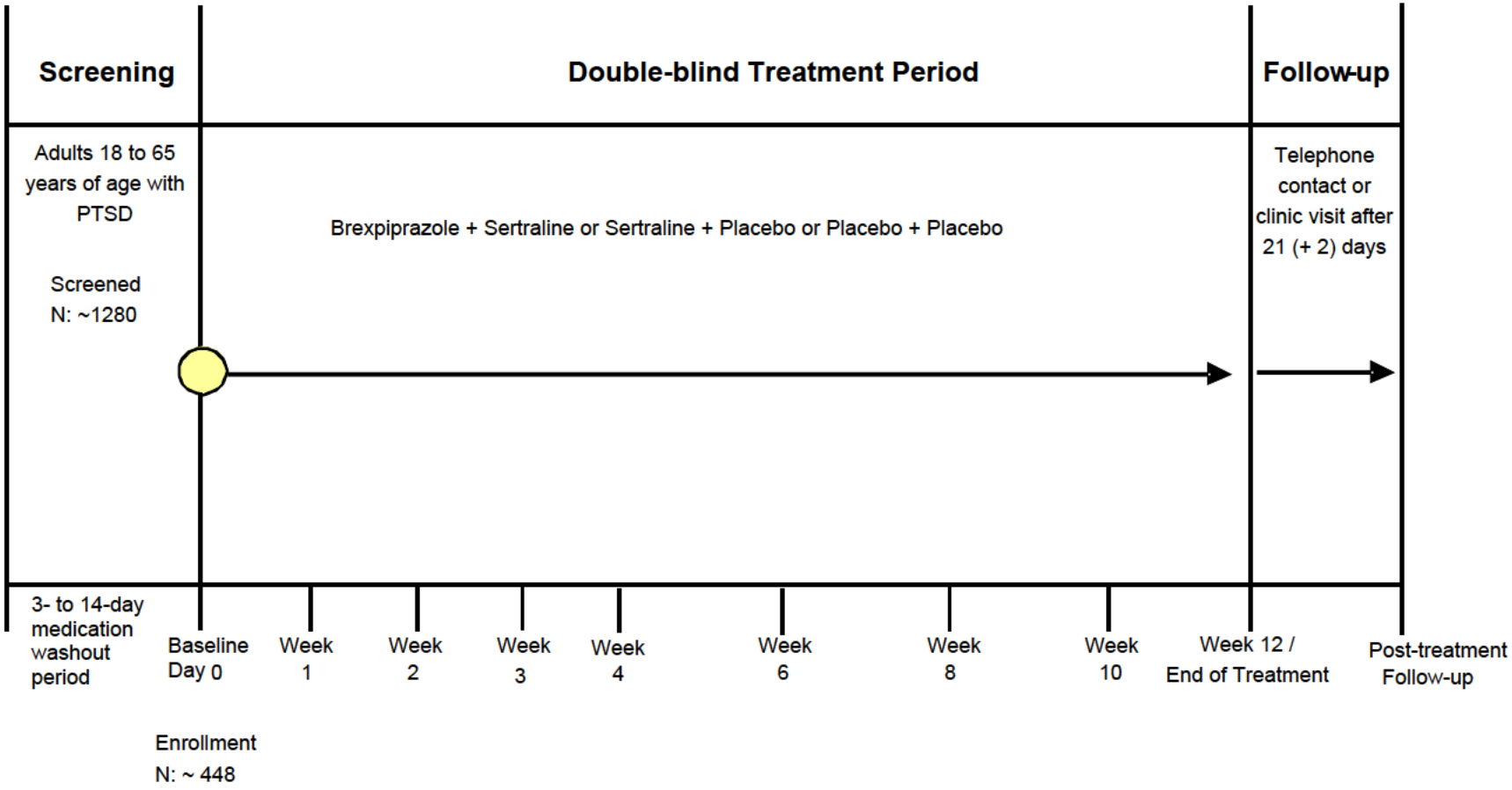

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Assessment	Screening (Day −14 to Day −1)[a]	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 3 days)	Week 8 Visit (± 3 days)	Week 10 Visit (± 3 days)	Week 12/ ET Visit (± 3 days)	Post-treatment Follow-up (21 [+ 2] days)	Notes:
ENTRANCE CRITERIA												
Informed Consent	X											Section 10.1.2 (Appendix 1)
Inclusion/exclusion criteria	X	X										Section 5.2
Demography	X											Section 5.1
Medical history	X											Section 5.1
Psychiatric history (including PTSD history)	X											Section 5.1
PTSD treatments (pharmacological, non-pharmacological, and E-TRIP)	X											Section 6.5
Prior medication washout	X											Section 6.5.1
LEC-5[b]	X											Section 8.1.7.2
MINI	X											Section 8.1.7.3
OSU TBI-ID	X											Section 8.1.7.4
HIV, HBsAg, and anti-HCV	X											Section 10.2 (Appendix 2)
Review of birth control methods	X	X	X	X	X	X	X	X	X	X	X	Section 10.3 (Appendix 3)
EFFICACY												
CAPS-5	X	X	X		X	X	X		X	X		Section 8.1.1
CGI-S		X	X	X	X	X	X	X	X	X		Section 8.1.2
PCL-5[c]		X	X		X		X		X	X		Section 8.1.3
HADS[c]		X	X		X		X		X	X		Section 8.1.4

Table 1.3-1 Schedule of Assessments

Assessment	Screening (Day −14 to Day −1)[a]	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 3 days)	Week 8 Visit (± 3 days)	Week 10 Visit (± 3 days)	Week 12/ ET Visit (± 3 days)	Post-treatment Follow-up (21 [+ 2] days)	Notes:
CCI												
B-IPF[c]		X						X		X		Section 8.1.6
SAFETY												
Assessment of need for dose modification						X	X					Section 6.1
Clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], urinalysis), TSH	X	X					X			X		Section 8.7.1
HbA1c	X									X		Section 8.7.1
Physical examination	X									X		Section 8.7.2
Vital signs	X	X	X	X	X	X	X	X	X	X		Section 8.7.3
12-lead ECG	X	X								X		Section 8.7.4
Urine drug screen/blood alcohol	X						X			X		Section 10.2 (Appendix 2)
Urine pregnancy test	X	X					X			X		Section 10.2 (Appendix 2)
C-SSRS	X	X	X	X	X	X	X	X	X	X		Section 8.7.5
AIMS		X		X			X			X		Section 8.7.6.1
BARS		X		X			X			X		Section 8.7.6.2
SAS		X		X			X			X		Section 8.7.6.3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	Section 8.8
Concomitant medications		X	X	X	X	X	X	X	X	X	X	Section 6.5
OTHER												
Drug dispensing		X	X	X	X	X	X	X	X			Section 6.2.3
Drug accountability			X	X	X	X	X	X	X	X		Section 6.2.3

Table 1.3-1 Schedule of Assessments

Assessment	Screening (Day −14 to Day −1)[a]	Baseline (Day 0)	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 3 days)	Week 8 Visit (± 3 days)	Week 10 Visit (± 3 days)	Week 12/ ET Visit (± 3 days)	Post-treatment Follow-up (21 [+ 2] days)	Notes:
Pharmacokinetic and Pharmacogenomic Sampling												
PK sample							X			X		Section 8.2
Pharmacogenomic sample							X					Section 8.4
FBR sample (optional)[d]		X										Section 8.6

anti-HCV = antibodies to hepatitis C virus; E-TRIP = Emory Treatment Resistance Interview for PTSD; FBR = future biospecimen research; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; LEC-5 = Life Events Checklist for DSM-5; PK = pharmacokinetic TSH = thyroid-stimulating hormone.

[a]Screening assessments may be completed over more than 1 day. In the event that a subject cannot be enrolled prior to expiration of the 14-day screening period, an additional 14-day extension of screening may be requested from the medical monitor.

[b]LEC-5 is a self-reported assessment to be completed on the clinical ink tablet (this assessment is not available on a direct electronic application, ie, the 'subject-facing Engage app').

[c]Assessment to be completed directly by the subject using the 'subject-facing Engage app'.

[d]The FBR sample can be taken at baseline or at any other scheduled visit where lab samples are taken if subjects choose to consent to collection after the baseline visit. Only one FBR sample should be collected.

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2 Introduction

Post-traumatic stress disorder (PTSD) is a prevalent, debilitating, and often chronic neuropsychiatric illness that may develop in a person who has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others. The person's response involves intense fear, helplessness, or horror. According to *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5), the diagnostic criteria for PTSD include a history of exposure to a traumatic event that meets specific stipulations and symptoms from each of 4 symptom clusters: intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity. The sixth criterion concerns duration of symptoms, the seventh assesses functioning, and the eighth criterion clarifies symptoms as not attributable to a substance or co-occurring medical condition. The United States (US) National Comorbidity Survey Replication found a PTSD lifetime prevalence of 6.8%, and a 12-month prevalence of 3.6%, with rates of 5.2% for women and 1.8% for men.[1,2]

The risk of developing PTSD depends on the type of trauma, with interpersonal violence carrying the highest risk.[3,4] In the World Health Organization World Mental Health Surveys, the most common traumas at the respondent level were as follows: traumas of loved ones or were witnessed (35.7%), accidents (34.3%), and unexpected death of a loved one (31.4%). These were followed by physical violence (22.9%), intimate partner or sexual violence (14.0%), war-related trauma (13.1%), and 'other' traumas (8.4%). The trauma type associated with the highest PTSD risk is intimate partner or sexual violence (11.4%). The risk of developing PTSD based on the other types of trauma is as follows: 'other' traumas (9.2%), unexpected death of loved one (5.4%), war-related trauma (3.5%), physical violence (2.8%), traumas of loved ones or were witnessed (2.4%), and accidents (2.0%).[4]

Like many other psychiatric disorders, PTSD has been purported to result from a dysregulation in monoaminergic neurotransmission. While dysfunction of the dopaminergic system has emerged as one of the most important hypotheses, recent reports have found higher levels of norepinephrine and epinephrine in PTSD patients as well.[3,4]

Brexpiprazole (REXULTI®, OPC-34712, OPC-331, and Lu AF41156) is a new chemical entity discovered by Otsuka Pharmaceutical Development and Commercialization (OPDC) that is being co-developed by OPDC and Lundbeck Inc. Brexpiprazole is a novel atypical antipsychotic that is a serotonin-dopamine activity modulator and is

indicated in the US as monotherapy for the treatment of schizophrenia in adult patients (2 - 4 mg/day) and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) (2 - 3 mg/day) in adult patients.

2.1 Trial Rationale

The selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline are currently approved for the treatment of PTSD by the Food and Drug Administration (FDA) in the US. Response rates with SSRIs in PTSD are modest and vary from a low of 24.3% to a high of 60%.[5] There is relatively low satisfaction with paroxetine and sertraline, as evidenced by the low use of these products (2.1% and 19.1%, respectively) as first-line therapy for PTSD treatment.[6] In addition, sertraline's efficacy for the treatment of PTSD has been inconsistent with in the short-term randomized, controlled trials: 2 of the 4 US registrational trials were negative on the primary efficacy endpoint. Physicians are seeking alternative options and there are several products that are registered for other indications that are used off-label for symptom relief in patients with PTSD. There is an important unmet medical need for new efficacious and safe treatments for individuals suffering from PTSD.

A more detailed scientific rationale for the trial is provided in Section 4.2.

2.2 Background

2.2.1 Nonclinical Pharmacology

The pharmacology of brexpiprazole has been extensively investigated both in vitro and in vivo. 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 serotoninergic (5-HT) and dopaminergic (DA) systems that combines partial agonist activity at 5-HT_{1A} and at D_2 receptors with antagonist activity at 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 $\alpha_{1B/2C}$ with affinity in the same subnanomolar K_i range (K_i: 0.2 - 0.6 nM). The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy, reduced impulsive behavior, and cognitive improvement.[7]

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Adjunctive treatment with brexpiprazole and escitalopram reduced behavioral stress responses and increased hypothalamic neuropeptide Y (NPY) immunoreactivity in a rat model of PTSD-like symptoms.[8]

2.2.2 Nonclinical Pharmacokinetics

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

2.2.3 Clinical

Currently, brexpiprazole is approved in the US for use in adult patients as an adjunctive therapy to antidepressants for the treatment of MDD and monotherapy treatment of schizophrenia. Additionally, the current clinical development program is designed to show safety and efficacy of brexpiprazole for the treatment of the following indications: treatment of agitation associated with dementia of the Alzheimer's type (AAD), and treatment of adult PTSD.[7]

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 Applications (INDs) (59 completed and 8 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of attention-deficit hyperactivity disorder (ADHD), AAD, PTSD, or bipolar disorder; and 7 non-US IND trials completed in either Korea or Japan conducted in healthy subjects and subjects with schizophrenia.[7]

2.3 Known and Potential Risks and Benefits

Phase 1 data indicated that brexpiprazole had good safety and tolerability when administered to healthy volunteers at single doses of 0.2 to 6 mg and at a repeated dose of 2 mg/day. Data from completed repeated dosing trials in the US indicate that brexpiprazole had good tolerability when administered to patients with schizophrenia or schizoaffective disorder at doses of up to 12 mg/day; when administered to patients with MDD at doses of up to 4 mg/day in combination with a marketed antidepressant; and when administered to patients with ADHD at doses of up to 4 mg/day in combination with a marketed stimulant.[7]

In subjects who participated in the 59 completed brexpiprazole trials conducted under US INDs, the most frequently reported treatment-emergent adverse events (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%). Please refer to the brexpiprazole IB for a summary of available nonclinical and clinical safety data.[7]

In Trial 331-201-00061, brexpiprazole + sertraline combination therapy was shown to be efficacious in the improvement of PTSD-related symptoms as demonstrated by superiority versus placebo as well as superiority over sertraline monotherapy and brexpiprazole monotherapy on the primary efficacy endpoint, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score. Concordant support for the efficacy of brexpiprazole + sertraline therapy was also seen in multiple other clinician- and subject-assessed secondary endpoints including the Clinical Global Impression - Severity (CGI-S), PTSD Checklist for DSM-5 (PCL-5), Hospital Anxiety and Depression Scale - Depression subscale (HADS-D), CAPS-5 response rate, and CAPS-5 subscale domains. Brexpiprazole + sertraline combination therapy was safe and well tolerated when administered for up to 12 weeks in adults with PTSD; no new safety signals were observed in this population. The TEAEs that occurred at an incidence of > 5% and twice more than placebo in the active treatment groups were as follows: brexpiprazole + sertraline: decreased appetite (7.5%) and akathisia (6.3%); brexpiprazole monotherapy: fatigue (8.0%), decreased appetite (6.7%), akathisia (13.3%), and sedation (6.7%); and sertraline monotherapy: nausea (20.3%).[9]

Zoloft (sertraline) is indicated for the treatment of PTSD at dose of 50-200 mg/day. Per the US package insert, the most common TEAEs (≥ 5% for Zoloft and twice placebo) in pooled placebo-controlled MDD, obsessive-compulsive disorder, panic disorder, PTSD, social anxiety disorder, and premenstrual dysphoric disorder clinical trials were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido.[10]

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

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3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To evaluate the efficacy of brexpiprazole + sertraline in adult subjects with PTSD.	Primary Efficacy: Change from baseline to the end of the efficacy period in the CAPS-5 total score Key Secondary Efficacy: • Change from baseline to the end of the efficacy period in the CGI-S score • Change from baseline to the end of the efficacy period in B-IPF score Other Efficacy: • Change from baseline to the end of the efficacy period in the PCL-5 score • Change from baseline to the end of the efficacy period in the HADS-A and HADS-D score • Response defined by decrease ≥ 30% from baseline to the end of the efficacy period in the CAPS-5 total score • Change from baseline to the end of the efficacy period in the CAPS-5 subscales/domain scores
	CCI [redacted]

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Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
Secondary: To evaluate the safety and tolerability of brexpiprazole + sertraline in adult subjects with PTSD	Safety: Standard safety variables will include AEs, clinical laboratory tests (hematology, serum chemistry [including HbA1c and blinded prolactin], and urinalysis), physical examinations, vital sign measurements, and ECGs. Body weight, height, and waist circumference will also be measured. Extrapyramidal symptoms will be evaluated by calculating the mean change from baseline in the SAS total score, AIMS movement rating score, and BARS global score. The C-SSRS will be used to assess and classify reported suicidal behavior.

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale; HbA1c = glycosylated hemoglobin; MCS = mental component summary; PCS = physical component summary; SAS = Simpson-Angus Scale; CCI [redacted]

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This will be a 12-week, multicenter, randomized, double-blind trial of brexpiprazole + sertraline combination treatment in adult subjects with PTSD.

The trial will consist of a screening period (up to 14 days), a 12-week, double-blind treatment period, and follow-up (21 [+2] days after the last dose of investigation medicinal product [IMP]).

Screening Period:

Screening will begin when consent has been obtained. The screening visit will take place between Day −14 and Day −1 prior to enrollment and subjects will participate in screening activities for a minimum of 3 days. In the event that a subject cannot be enrolled prior to expiration of the 14-day screening period, an additional 14-day extension of screening may be requested from the medical monitor.

The purpose of the screening period is to assess eligibility criteria at 1 or more visits and to washout prohibited concomitant pharmacotherapy, if applicable. An eSource method will be used to obtain an identification (ID) number for each subject with documented consent.

Subjects will be between 18 and 65 years of age, inclusive, at the time of screening and will have a diagnosis of PTSD as defined by DSM-5 criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI). All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods.

Double-blind Treatment Period:

During the double-blind treatment period, subjects will receive IMP, consisting of brexpiprazole + sertraline, or sertraline, or placebo, depending on the subject's treatment assignment. IMP assignments can change during the double-blind treatment period.

Subjects will attend visits at Weeks 1, 2, 3, 4, 6, 8, 10, and 12/early termination (ET) during the treatment period.

Follow-up:

For any subject who discontinues the trial early, the site should make every effort to complete the ET evaluations as soon as possible and prior to the subject starting any new medication or treatment. All subjects (completers and early withdrawals) will be monitored for safety events via telephone or clinic visit (at the investigator's discretion) 21 (+ 2) days after the last dose of IMP. For any subject who withdraws due to a serious adverse event (SAE), every effort should be made to ensure that the safety follow-up is performed face-to-face. Given that this may not be feasible in all circumstances, safety follow-up via phone is permitted in cases where face-to-face follow up cannot be performed.

Upon completion of the 12-week trial period, participants may be eligible to receive up to a six months' supply of sertraline or paroxetine through TrialCard®. Participants in this program will have prescribed medication shipped directly to their home by a designated retail mail-in pharmacy free of charge.

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 PTSD. More specifically, as a partial dopamine D_2/D_3 receptor agonist, brexpiprazole may quell the hyper-responsiveness in the dopaminergic circuitry purported to exist in PTSD patients.[11,12] By dampening dopaminergic tone, brexpiprazole may improve upon symptoms such as memory/cognitive dysfunction, mood, and impulsivity. Similarly, brexpiprazole may help normalize aberrations that are believed to exist in a heightened adrenergic system as well. It is postulated that

noradrenaline release is accentuated in PTSD, which is linked with the establishment of long-term aversive memories that induce strong emotions and arousal such as fear, hyper-responsiveness, and anxiety. The effect of brexpiprazole as an α_{1B} and α_{2C} receptor antagonist may be advantageous in this regard. Furthermore, 5-HT_{2A} and α_1 receptors are co-localized in GABAergic interneurons in the prefrontal cortex, which is involved in behavioral control and cognitive processing.[13] Brexpiprazole may exert an added beneficial effect on cortical functioning, impulsivity, and contextual fear by simultaneous blocking α_1 and 5-HT_{2A} receptors. Data also suggest that 5-HT_{2A} plays a significant role in learning and may contribute to the autonomic dysregulation and maladaptive re-experiencing of traumatic memories in PTSD.[14] Attenuation of contextual fear appears to involve 5-HT_{1A} in the extended amygdala. SSRIs administered concomitantly with extinction training in mice facilitate a rapid and enduring loss of conditioned fear memory. A similar process appears to occur in humans with PTSD who ingest SSRIs while engaged in trauma-focused psychotherapy.[14,15] Taken together and given its effects as a 5-HT_{1A} partial receptor agonist, brexpiprazole may lessen the anxiety noted in these patients as well.

Two clinical trials have been conducted with brexpiprazole in subjects with PTSD. Trial 14865A was a phase 3 trial for adjunctive treatment with brexpiprazole in subjects with PTSD who had an inadequate response to treatment with paroxetine or sertraline. Trial 14865A was terminated prematurely when the Sponsor realized that it would likely be unable to enroll enough participants to fully power the trial. No safety concerns factored into the decision to terminate the trial and the recruited population at the time of termination was too small to analyze from an efficacy perspective. Trial 331-201-00061 was a phase 2 trial of brexpiprazole as monotherapy or combination therapy with sertraline in the treatment of adults with PTSD. Results demonstrated that brexpiprazole + sertraline was more effective in relieving PTSD symptoms (as determined by improvements in the Clinician-Administered PTSD Scale for DSM-5 [CAPS-5] total score) than sertraline alone, brexpiprazole alone, or placebo. Brexpiprazole + sertraline combination therapy resulted in significant improvement on both clinician- and subject-assessed endpoints and was safe and well tolerated when administered for up to 12 weeks in adults with PTSD.[9]

This phase 3 trial is intended to provide persuasive evidence that treatment of PTSD with combination treatment with brexpiprazole + sertraline is efficacious, safe, and well-tolerated.

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4.3 Dosing Rationale

The dosing paradigm to be used in this trial has been determined based on completed phase 1 clinical pharmacology trials as well as phase 2/3 trials in PTSD.

The maximum tolerated dose (MTD) for healthy subjects has been determined to be 6 mg for single-dose administration and 2 mg for once-daily (QD), multiple-dose administration. The MTD of brexpiprazole administered as monotherapy in subjects with schizophrenia or schizoaffective disorder or coadministration with marketed antidepressant in subjects with MDD has not been established. The following doses of brexpiprazole have been tolerated in completed QD, multiple-dose, phase 1 clinical pharmacology trials: up to 12 mg/day in adult subjects with schizophrenia or schizoaffective disorder, and up to 4 mg/day in adult subjects with MDD when coadministered with a marketed antidepressant.[7]

The efficacy, safety, and tolerability of brexpiprazole coadministered with sertraline has been investigated in 2 completed phase 2/3 trials. Trial 14865A was a phase 3 trial for adjunctive treatment with brexpiprazole in subjects with PTSD who had an inadequate response to treatment with paroxetine or sertraline. Trial 14865A was terminated early due to challenges with patient eligibility. There were not enough subjects randomized for any efficacy analyses; the decision to terminate was not based on any safety concerns.[16] A second trial, 331-201-00061, a phase 2 trial which evaluated brexpiprazole as combination treatment with sertraline in adult subjects with PTSD, was then conducted. In that trial, brexpiprazole + sertraline combination therapy was shown to be efficacious in the improvement of PTSD-related outcomes. At the trial endpoint, combination treatment with brexpiprazole + sertraline demonstrated statistically significant results over placebo as well as superiority over sertraline monotherapy and brexpiprazole monotherapy. The incidence of TEAEs were similar across treatment groups. No new safety signals were observed in the PTSD population.[9]

Based on the collective safety, tolerability, and efficacy data, doses of up to a maximum of 3 mg/day brexpiprazole and 150 mg/day sertraline will be evaluated in this phase 3 trial. The doses given in the phase 2 PTSD trial (331-201-00061) were within this range and were well tolerated. In addition, Zoloft (sertraline) is indicated for the treatment of PTSD at doses of 50-200 mg/day.[10]

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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 eSource page for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period (Week 12) will be defined as trial completers.

5 Trial Population

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (site number [3 digits] + subject number ['S' + 5 digits] upon providing consent). Site number will be designated by the sponsor. The subject number will be given sequentially from S00001.

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

Eligible subjects will be randomized.

5.2 Eligibility Criteria

Up to 20% of subjects with an index trauma related to combat can be enrolled.

Exceptions for eligibility criteria will not be permitted during the trial.

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 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.
2) Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete

subject-reported outcomes measures; and to be reliably rated on assessment scales.

3) Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent.
4) Subjects who have PTSD, diagnosed according to DSM-5, and confirmed by the MINI.
5) Subjects have a CAPS-5 total score ≥ 33 at screening and baseline (Day 0) Visits.
6) Onset of symptoms meeting the DSM-5 criteria for PTSD symptoms for a minimum of 6 months prior to screening.
7) Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

   NOTE: Prohibited medications and therapies are discussed in Section 6.5.1. Permitted medications and rescue medications are discussed in Section 6.5.2 and Section 6.5.3.

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).

1) Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of IMP.
2) Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3) Subjects who are receiving disability payments because of PTSD or any other psychiatric disorder; unless the disability payments will not be impacted by potential improvements demonstrated in the trial, OR the subject is engaged in compensation litigation or other processes whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.
4) The index traumatic event that led to development of PTSD took place > 9 years before screening.
5) The index traumatic event occurred before age 16.
6) Subjects who are currently experiencing trauma, have ongoing contact with their assailant/abuser, or have ongoing legal matters related to their assault/abuse.
7) Subjects with PTSD who, in the investigator's opinion, are considered resistant/refractory to psychotropic treatment by history.
8) Subjects who are currently receiving sertraline with adequate dose and duration (> 50 mg/day for a minimum of 8 weeks).

9) Subjects who have had initiation of, or a change in, psychotherapy or any other intervention for the treatment of PTSD within 28 days prior to the screening visit or it is anticipated that the subject will have a change in psychotherapy or in any other intervention for PTSD (eg, equine therapy, yoga, mindfulness, etc) during the trial.
10) Subjects who meet the DSM-5 criteria for a current major depressive episode (ie, currently symptomatic).
11) Subjects who have current or recent history (within 6 months prior to the screening visit) of an anxiety disorder that has been the primary focus of psychiatric treatment including generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive, and other related disorders.
12) Subjects who have a DSM-5 diagnosis of delirium, major neurocognitive, or other cognitive disorder; schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or II disorder, or bipolar disorder not otherwise specified; eating disorder (including anorexia nervosa or bulimia); or borderline or antisocial personality disorders, or intellectual disability.
13) Subjects who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the screening visit.
14) Subjects who have a positive urine drug screen that, in the judgment of the investigator with concurrence of the medical monitor, indicates substance abuse that could compromise the subject's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results.
15) Subjects who have a history of moderate or severe head trauma as assessed by the OSU TBI-ID or other neurological disorders or systemic medical diseases where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact subject safety, in the investigator's opinion.
16) Subjects who have experienced a traumatic event within 3 months of screening.
17) Subjects with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or C-SSRS answer of "yes" to question 4 or 5 (current or within the last 90 days) or subjects with any suicidal behavior during the last year prior to the screening visit.
18) Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days prior to the baseline [Day 0] Visit).
19) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, gastrointestinal, pulmonary, or cardiovascular disorders such as ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevated to > 2 × upper limit of normal [ULN]),

or bariatric surgeries that may cause malabsorption. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation. Subjects who are severely obese, as confirmed by a corresponding high body mass index (BMI; ≥ 40 kg/m^2), need to be reviewed and discussed with the medical monitor.

20) Subjects with diabetes mellitus (both insulin-dependent and non-insulin-dependent) may be eligible for the trial if their condition is stable and well-controlled as determined by satisfying **ALL** of the following criteria:
    a) Glycosylated hemoglobin (HbA1c) < 8.0%, **AND**
    b) Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non-fasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, **AND**
    c) Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes.

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

    Subjects with newly diagnosed diabetes during screening are excluded.
21) Subjects with uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure (SBP) and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms.

    NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a subject based on the criteria noted above.
22) Subjects with epilepsy or a history of seizures, except for a single seizure episode; for instance, childhood febrile seizure, a post traumatic seizure episode, or an alcohol withdrawal seizure.
23) 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 any of the following laboratory test and ECG results at screening must be excluded from the trial:

a) Platelets ≤ 75000/mm^3
b) Hemoglobin ≤ 9 g/dL
c) Neutrophils, absolute ≤ 1000/mm^3
d) AST > 2 × ULN
e) ALT > 2 × ULN
f) Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
g) Creatinine ≥ 2 mg/dL
h) 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 once to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the subject must be excluded

24) Subjects who would be likely to require prohibited concomitant therapy during the trial.
25) Subjects who received brexpiprazole in any prior clinical trial or subjects who have taken or are currently taking commercially available brexpiprazole (Rexulti®).
26) Subjects with a history of neuroleptic malignant syndrome or serotonin syndrome.
27) Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
28) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
29) Subjects who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
30) 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 (Appendix 3).

Subjects must agree to restrictions to medications and lifestyle described in Section 6.5.1 and Section 5.3, respectively.

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5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to dosing and during the trial is prohibited.

For subjects with NIDDM, their diabetes must be well-controlled by diet for at least 28 days prior to screening if they have not been maintained on a stable regimen of oral antidiabetic medication(s) during that time.

5.3.2 Caffeine, Alcohol, and Tobacco

Excessive alcohol consumption will be prohibited.

Subjects with a prescription for medical marijuana may continue at their prescribed dose (see Section 6.5.2). Recreational marijuana use is not exclusionary if, in the investigator's documented opinion, the subject does not meet DSM-5 criteria for substance abuse or dependence, and its use would remain stable during the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.

Consumption of caffeine and use of tobacco products are permitted.

5.3.3 Activity

Subjects may only receive psychotherapy (including, but not limited to, individual, group, marriage, family, pet therapy, etc.) or other intervention if they have been participating in the therapy regularly for at least 28 days prior to screening and commit to maintain their participation during the course of the trial at the current frequency or unless permission is obtained from the medical monitor.

Current participation in substance abuse treatment will require consultation with the medical monitor prior to potential enrollment.

5.4 Screen Failures

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

Subjects who sign an ICF but who are not started on treatment are permitted to be re-screened one time. Screen failures due to exclusionary criteria may be re-screened one time if the exclusion characteristic has changed. In the event that a subject cannot be enrolled prior to expiration of the 14-day screening period, an additional 14-day

extension of screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension screening period. In the event that the subject is re-screened for trial participation, and the re-screening is not completed within the original screening window, a new ICF must be signed.

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

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

6 Trial Treatments

6.1 Trial Treatments Administered

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

Should a subject forget to ingest a dose of IMP, he/she can take the scheduled dose later that same day. However, if a subject forgets to ingest a dose on the scheduled day, he/she should be encouraged to leave the missed dose in the blister card and return all unused IMP to the site.

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

- Dose increases can occur only at the Week 4 visit
- Dose decreases can occur at scheduled or unscheduled visits starting after the first dose following Week 4 and are not allowed after the Week 6 visit.
- Dose must be maintained for the remainder of the treatment period after the Week 6. If subjects are unable to maintain the Week 6 dose due to tolerability issues, the subject must be withdrawn from the trial.

6.1.1 Medical Devices

Not applicable.

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6.2 Management of Investigational Medicinal Product

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

6.2.1 Packaging and Labeling

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

The clinical site staff will maintain a temperature log in the IMP storage area to record the temperature. The monitor will inspect the storage area and verify the temperature logs to ensure that the site is maintaining the security of all IMP.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, 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 in accordance with local regulations after obtaining Sponsor approval. In cases where local regulations do not allow the clinical trial site to destroy IMP, sites will contact the Sponsor to work out a plan to destroy the IMP which complies with 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 provided 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: IMP-PQC@otsuka-us.com. 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

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

Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department. Randomization will be stratified. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the IRT, and reporting SAEs to regulatory agencies.

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

6.4 Subject Compliance

Responsible trial personnel will dispense the IMP. Accountability and compliance verification should be documented in the subject's trial records. Subjects must be counseled on the importance of taking the IMP as directed at all trial visits. Dosing compliance will be assessed by a pill count of doses remaining in the returned blister cards. Subjects will also record daily doses in a subject diary, which will be reviewed by site staff. If poor compliance with dosing is observed and 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 will be permitted to complete site visits within ± 2 days of the scheduled visit day during Weeks 1 to 4 and within ± 3 days of the scheduled visit day during Weeks 6

to 12 in order to allow flexibility with the goal of decreasing the number of missed visits. However, 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 beginning when they sign the informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on 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.

6.5.1 Prohibited Medications and Therapies

All subjects must agree to discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods, as shown in Table 6.5.1-1. Washout of prohibited medications begins after completion of the consent process.

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Table 6.5.1-1 List of Medications Prohibited Prior to the Trial and Required Washout Period	
Prohibited Medication	**Required Washout Period**
Psychotropic agents: antipsychotic agents (oral), anticonvulsants, antidepressants, mood stabilizers, benzodiazepines (except as permitted in Section 6.5.2), hypnotics, opioid analgesics, and disulfiram	at least 7 days
Varenicline	at least 5 days
Controlled stimulants (eg, amphetamine and dextroamphetamine)	at least 7 days
Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, kava extracts, gamma-aminobutyric acid supplements, etc)	at least 7 days
CYP2D6 inhibitors: celecoxib, hydroxyzine, chloroquine, chlorpheniramine, moclobemide, clemastine, pyrilamine, diphenhydramine, quinidine, terbinafine, halofantrine, and tripelennamine	at least 7 days
CYP3A4 inhibitors: amiodarone, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, and verapamil	at least 7 days
CYP3A4 inducers: dexamethasone, primidone, efavirenz, rifampin, nevirapine, and troglitazone	at least 7 days
Barbiturates	at least 7 days
Diazepam and MAOIs	at least 14 days
Cariprazine, fluoxetine, and aripiprazole	at least 28 days
Neuroleptic agents (depot or long acting injectable)	1 full cycle plus half cycle

CYP = cytochrome P450; MAOI = monoamine oxidase inhibitors.

A complete list of medications prohibited during the trial is provided in Table 6.5.1-2.

Table 6.5.1-2 List of Medications Prohibited/Restricted During the Trial

All psychotropic agents including, but not limited to, the following:

- Antipsychotics, including depot or long-acting injectable formulations
- Anticonvulsants used for the purposes of mood stabilization or the treatment of seizures are prohibited. Low dose anticonvulsants, such as gabapentin, used for the purposes of promoting sleep, treating neuropathic pain, treating headaches/migraines, or relieving acute anxiety, are permitted with medical monitor approval.
- Antidepressants
- MAOIs, anti-platelet drugs, and any drugs mentioned in the sertraline label as having clinically significant drug interactions with sertraline
- Mood stabilizers (ie, lithium)
- Benzodiazepines, except when used to manage TEAEs such as agitation and anxiety
- Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage TEAEs related to insomnia
- Non-controlled stimulants and atomoxetine are allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to Baseline (Day 0) Visit and should be continued throughout trial participation.
- 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.
- Nutritional supplements and non-prescription herbal preparations with central nervous system effects (eg, St. John's Wort, kava extracts, gamma-aminobutyric acid supplements, etc)
- Disulfiram
- Prazosin is allowed if currently being taken for an appropriate indication at a stable dose for at least 14 days prior to Baseline (Day 0) Visit and should be continued throughout trial participation.

Varenicline.

Investigational agents within 60 days prior to Baseline (Day 0) Visit.

CYP2D6 inhibitors or CYP3A4 inhibitors and inducers.

- Selected CYP2D6 inhibitors: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, clomipramine, pyrilamine, diphenhydramine, quinidine, terbinafine, halofantrine, tripelennamine
- Selected CYP3A4 inhibitors: amiodarone, fluvoxamine, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil

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Table 6.5.1-2 List of Medications Prohibited/Restricted During the Trial
• Selected CYP3A4 inducers: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone The medical monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial.
Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate

In particular, the investigator should caution the subject about concomitant use of the following during the trial:

- Non-steroidal anti-inflammatory drugs, aspirin, or other drugs that interfere with coagulation, since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of upper gastrointestinal bleeding.[17]
- Triptans (eg, sumatriptan, naratriptan, almotriptan, frovatriptan, rizatriptan, eletriptan, and zolmitriptan), linezolid, and methylene blue, since there have been rare post-marketing reports of serotonin syndrome or serotonin syndrome-like reactions (eg, mental status changes, hyperreflexia, autonomic effects, lack of coordination, and diarrhea) following the concomitant use of SSRIs or serotonin-norepinephrine reuptake inhibitors and these drugs.[18,19,20]

Use of intramuscular benzodiazepines is prohibited throughout the trial.

Use of controlled stimulants (e.g. methylphenidate, amphetamine, methamphetamine, dextroamphetamine, lisdextroamphetamine) is prohibited throughout the trial.

Electroconvulsive therapy and transcranial magnetic stimulation are prohibited within 60 days of screening. In addition, subjects may not undergo implantation of a device for vagus nerve stimulation or deep brain stimulation during the trial.

For subjects who discontinue early, attempts should be made to complete ALL evaluations for the Week 12/ET visit prior to the administration of any new medications for the treatment of PTSD.

6.5.2 Permitted Medications

The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator.

Administration of specific oral benzodiazepines is permitted for the short-term management of TEAEs such as anxiety and agitation up to a maximum of 6 mg/day lorazepam (or equivalent) in divided doses. The dose of 6 mg/day may be taken for up to 2 days.

Short-acting benzodiazepines are to be used whenever possible. In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam or clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 15 mg oxazepam = 0.5 mg alprazolam = 5 mg diazepam = 0.5 mg clonazepam. The prescribed benzodiazepine should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects. Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including extrapyramidal symptoms (EPS) scales. Investigators should delay scale administration until 12 hours have elapsed.

Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, suvorexant, and eszopiclone only) are permitted for the treatment of TEAEs related to insomnia for up to 4 days per week, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize 1 of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators should delay scale administration until 12 hours have elapsed.

Anticholinergics are permitted for the treatment of EPS up to a maximum of 4 mg/day benztropine or its equivalent and propranolol is permitted for akathisia or tremor up to a maximum of 20 mg 3 times daily (total of 60 mg/day). Sites should only utilize medications that are approved for these indications. Daily administration of propranolol for the treatment of chronic hypertension or chronic anxiety is not permitted.

If a benzodiazepine, non-benzodiazepine sleep aid, anticholinergic, or propranolol is given within 12 hours of scale administration the drug name, dose, and time of administration should be documented in eSource. The use of the benzodiazepine, non-benzodiazepine sleep aid, anticholinergic, or propranolol, including a notation of the drug name, dose, and time of administration, should be documented in eSource.

Subjects who are prescribed atomoxetine and other non-controlled stimulants can continue those medications if they are being taken for an appropriate indication at a stable

dose for at least 14 days prior to the baseline (Day 0) visit and will be continued throughout trial participation.

When given for an appropriate indication, marijuana as a medical treatment and prazosin may be continued during the trial if maintained at a stable dose for at least 14 days prior to the baseline visit and should be continued throughout trial participation.

6.5.3 Rescue Medications

Short-term use of benzodiazepines and non-benzodiazepine sleep aids are permitted as specified in Section 6.5.2.

Use of antidepressants, barbiturates, and antipsychotics for rescue purposes are not permitted.

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 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 by the IRB 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 at the site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

In this approximately 3-month trial, it is expected that subjects may have one or more treatment interruptions during the treatment phase. 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. 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 (see Section 7.3.4).

7.3.2 Treatment Discontinuation

After enrollment, 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 permanently discontinue IMP for a number of reasons, including those listed below:

- Reasons related to adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Withdrawal of informed consent
- Lost to follow-up
- Pregnancy (see Section 10.3 [Appendix 3])
- Failure to meet enrollment criteria
- Physician decision
- Noncompliance with IMP
- Termination of all or part of the trial by the sponsor

If the subject temporarily interrupts or permanently 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.

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7.3.4 Withdrawal of Consent or Assent

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 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.

Details on the withdrawal of consent from the optional Future Biospecimen Research (FBR) substudy are provided in the ICF.

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 Visit 12 during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

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

8 Trial Procedures

The duration of this trial for an individual subject who completes the trial without ET is approximately 17 weeks. This is inclusive of a screening period (up to 14 days), a 12-week double-blind treatment period, and a safety follow-up period (21 [+2] days after the last dose of IMP).

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

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8.1 Efficacy Assessments

It is required that trained and experienced clinicians administer all clinician-rated psychometric scales. In addition, the raters must be certified for this trial to administer the CAPS-5. The number of raters within each trial center should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by OPDC or designee.

8.1.1 Clinician-Administered PTSD Scale for DSM-5

The CAPS-5[21,22] is a clinician-rated, structured interview designed to assess PTSD diagnostic status and symptoms severity as defined by the DSM-5. This trial will use the CAPS-5 Past Month version (at screening only) and CAPS-5 Past Week version (at all other assessment timepoints) of the scale. The CAPS-5 Past Month version will be completed for all subjects at screening to determine eligibility. The CAPS-5 Past Week version will be completed at the Baseline (Day 0) Visit to assure that the subject continues to qualify for the trial and at all visits after the Baseline (Day 0) Visit when the assessment is scheduled for collection.

The CAPS-5 comprises questions that target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS-5 administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization).

The CAPS-5 is scored by summing severity scores for the 20 DSM-5 PTSD symptoms. Similarly, CAPS-5 symptom cluster severity scores are calculated by summing the individual item severity scores for symptoms corresponding to a given DSM-5 cluster: Criterion B (items 1-5); Criterion C (items 6-7); Criterion D (items 8-14); and, Criterion E (items 15-20). A symptom cluster score may also be calculated for dissociation by summing items 29 and 30.

The CAPS-5 will be administered by a qualified and certified rater on the visits as specified in Section 1.3. It takes on average between 45 and 60 minutes to administer the CAPS-5.

The CAPS-5 interviews may be audio recorded and randomly selected interviews subjected to quality reviews to verify accuracy of CAPS-5 scoring and reduce potential therapeutic benefit to participants derived from overly long and detailed CAPS-5 interviews by investigators.

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8.1.2 Clinical Global Impression - Severity

The severity of illness for each subject will be rated using the CGI-S.[23] To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects. The CGI-S will be administered on the visits as specified in Section 1.3.

8.1.3 PTSD Checklist for DSM-5

The PCL-5[24] is a subject-rated instrument intended to assess the degree to which individual DSM-5 PTSD symptoms have impaired a patient's functioning. Subjects need to indicate a number to the right of each problem to indicate how much they have been bothered by that problem in the past week. The scale rates items from 0 (not at all), 1 (a little bit), 2 (moderately), 3 (quite a bit), and 4 (extremely). The PCL-5 will be administered on the visits as specified in Section 1.3.

8.1.4 Hospital Anxiety and Depression Scale

The HADS[25] is a subject-rated scale designed to screen for anxiety and depressive states in medical subjects. The HADS consists of 2 subscales: The D-scale measures depression and the A-scale measures anxiety. Each subscale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each subscale ranges from 0 to 21, and the subscales are analyzed separately. It takes approximately 5 to 10 minutes to complete the HADS. The HADS will be administered on the visits as specified in Section 1.3.

CCI

CCI [redacted]

8.1.6 Brief Inventory of Psychosocial Function

The Brief Inventory of Psychosocial Function (B-IPF)[27] is a short patient-reported questionnaire consisting of 7 questions which measure PTSD-specific psychosocial function on a 7 point Likert scale (0 = not at all to 6 = very much, and a not applicable option) with a recall period of 30 days. The B-IPF measures the concepts of romantic relationships, parenting, family, friendships and socializing, work, education, and self-care. The B-IPF will be administered on the visits as specified in Section 1.3.

8.1.7 Screening Assessments

8.1.7.1 Emory Treatment Resistance Interview for PTSD

The E-TRIP[28] consists of clinician-administered questions to assess the adequacy and benefit derived from past treatment trials. For each adequately delivered treatment to which the subject failed to respond, a score is assigned depending on the strength of evidence supporting the treatment's efficacy.

8.1.7.2 Life Events Checklist for DSM-5

The LEC-5[29] is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. The LEC-5 will be administered as specified in Section 1.3.

8.1.7.3 Mini International Neuropsychiatric Interview

The MINI[30,31,32,33] will be conducted as specified in Section 1.3 to confirm the subject's diagnosis of PTSD and to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided.

8.1.7.4 Ohio State University Traumatic Brain Injury Identification Method

The OSU TBI-ID[34] is a standardized procedure for eliciting a person's lifetime history of TBI via a 3 to 5-minute structured interview. The OSU EBI-ID will be conducted as specified in Section 1.3.

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8.2 Pharmacokinetic Assessments

A PK sample will be collected at the same time of collection of clinical laboratory samples as specified in Section 1.3. Time and date of the last 3 doses of brexpiprazole and sertraline will be recorded at the time of PK sampling.

8.2.1 Pharmacokinetic Blood Samples

Blood samples (4 mL) will be collected in vacutainers containing sodium heparin and processed into plasma to determine the concentrations of brexpiprazole and sertraline. Metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

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

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

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

All plasma samples will be shipped to the central laboratory, who will then subsequently ship the samples to the bioanalytical laboratory for analysis. Additional information will be provided in the Operations/Laboratory Manual.

8.3 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

A pharmacogenomics sample to assess the CYP2D6 metabolism status will also be collected at the same time of collection of clinical laboratory samples as specified in Section 1.3

8.4.1 Pharmacogenomic Samples

Whole blood samples (4 mL) will be collected in 4-mL potassium ethylenediaminetetraacetic acid vacutainer tubes for pharmacogenomic testing. Genomic deoxyribonucleic acid (DNA) will be extracted from a whole blood sample and used to

determine genotypes and related phenotypes for CYP2D6. The method used to determine these genotypes may also generate genotype data for additional genes related to absorption, distribution, metabolism, and excretion. Phenotyping of these additional genes is not currently planned but may be considered in the future. If so, the genotyping data may be included as part of covariate analysis in a population PK analysis to be reported separately.

The date and time of the sample collection for pharmacogenomics (PGx) analysis will be recorded in eSource.

All PGx samples will be shipped to the central laboratory, who will then subsequently ship the PGx samples to the PGx laboratory for analysis. Additional information will be provided in the Operations/Laboratory Manual.

8.5 Biomarker Assessments

Not applicable.

8.6 Future Biospecimen Research Samples

8.6.1 Scope of Future Biospecimen Research

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

8.6.2 Summary of Procedures for Future Biospecimen Research Samples

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

After obtaining informed consent for FBR, a whole blood sample (up to 10 mL) for FBR will be collected prior to dosing. Samples can be taken at baseline or at any other scheduled visit where lab samples are taken if subjects consent after the baseline visit.

The blood sample may be used for:

- DNA analysis

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

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

8.6.3 Retention of Future Biospecimen Research Specimens

The FBR specimens will be stored in the biorepository for potential analysis.

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 (Appendix 2). Refer to Section 10.5 (Appendix 5) for criteria for identifying laboratory values of potential clinical relevance.

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. If a fasting blood sample was not obtained at the screening visit and if more than 10 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], HbA1c, TSH with reflex to T_4 if the result for TSH is abnormal, and urinalysis) need to be repeated at the baseline (Day 0) visit. The results of these tests at screening must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory will be retained electronically within the

lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eSource.

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

The following laboratory test results at screening are exclusionary:

- Platelets ≤ 75000/mm^3
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/mm^3
- AST > 2 × ULN
- ALT > 2 × ULN
- CPK > 3 × ULN, unless discussed with and approved by the medical monitor
- Creatinine ≥ 2 mg/dL
- HbA1c ≥ 8%
- Blood glucose > 125 mg/dL (fasting)

Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.

The total volume of blood to be collected during the trial is expected to be approximately 100 to 115 mL.

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

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; extremities; neurological; and skin and mucosae. Height will be measured at screening only with a stadiometer, measuring stick, or tape. Waist circumference will be measured at each physical examination. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- The waist circumference measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[35]

The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the 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 10.6 [Appendix 6]).

Measurement of vital signs will include body weight, body temperature, SBP, DBP, and heart rate. The following guidelines will aid in the standardization of body weight measurements:

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

Blood pressure and heart rate measurements will be made in the supine and standing positions after the subject has been in each position for at least 3 minutes. The supine measurements will be performed first followed by standing.

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

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 [Appendix 7]).

All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review the ECG tracing and cardiology report within the central ECG vendor's online portal, assess the findings, noting whether or not any abnormal results are clinically significant within eSource.

The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis.

If, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject and/or the interpretation of the trial results) or meets an exclusion criterion, the subject should be excluded from the trial. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already enrolled. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG

recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each time point). The central ECG service will provide the corrections for the 3 ECGs performed. Based on QTcF reported by the central service, a subject will be excluded if the corrections are ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of ≥ 450 msec in men and ≥ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.

8.7.5 Suicidality Monitoring

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

Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "baseline/screening" and "since last visit" versions of the scale. The "baseline/screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility. Any subject who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial. The "since last visit" C-SSRS form will also be completed at all visits after screening.

8.7.6 Other Safety Variables

8.7.6.1 Abnormal Involuntary Movement Scale

The AIMS assessment will be conducted at the time points described in the schedule of assessments (Table 1.3-1).

The AIMS[36] 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/no questions that address the subject's dental status. Investigators should delay scale administration until 12 hours have elapsed after a benzodiazepene, non-benzodiazepene sleep aid, anticholinergic, or propranolol is given.

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).

8.7.6.2 Barnes Akathisia Rating Scale

The BARS assessment will be conducted at the time points described in the schedule of assessments (Table 1.3-1).

The BARS[37] 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. Investigators should delay scale administration until 12 hours have elapsed after a benzodiazepene, non-benzodiazepene sleep aid, anticholinergic, or propranolol is given.

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

8.7.6.3 Simpson-Angus Scale

The SAS assessment will be conducted at the time points described in the schedule of assessments (Table 1.3-1).

The SAS[38] evaluates 10 symptoms associated with antipsychotic-induced Parkinsonism, including gait changes, 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. Investigators should delay scale administration until 12 hours have elapsed after a benzodiazepene, non-benzodiazepene sleep aid, anticholinergic, or propranolol is given.

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8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

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

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

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

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

blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

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

Immediately Reportable Event:

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancies are also defined as immediately reportable events (IREs). Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication. This includes pregnancy of the subject or the partner of the subject.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated 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.

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8.8.2 Eliciting and Reporting Adverse Events

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

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

Adverse event, start date (and time, if possible), end date (and time, if possible), 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, 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.) Details regarding the follow-up of IREs is included in Section 8.8.8.2.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

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.

If the total bilirubin is < 2 times the ULN, weekly AST or ALT should be obtained until the value has either normalized or the value has decreased on two consecutive laboratory draws, whichever occurs first. If AST, ALT, or total bilirubin increase on 2 consecutive laboratory draws or increase to > 5 ULN, stop all IMP immediately, report the event as an SAE in eSource, and provide whatever supportive medical care is needed to stabilize the participant. After stabilization, the subject should be discontinued from the trial.

8.8.7 Procedure for Breaking the Blind

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

8.8.8 Follow-up of Adverse Events

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE 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 for 21 days after the last dose of IMP is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE 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 (Appendix 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.

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8.9 Treatment of Overdose

For treatment of overdoses, please refer to IB Section 6.3.[7]

8.10 Subject Assessment Recording

8.10.1 Subject Diary

Each subject will complete a subject diary in order to record daily IMP administration.

8.10.2 Quality of Life

Quality of life assessments are detailed in Section 8.1.5 and Section 8.1.6.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

Complete details of the planned statistical analysis will be presented in the unblinded addendum to this protocol and in the statistical analysis plan (SAP).

9.1 Sample Size

It is anticipated that approximately 448 subjects will be enrolled in this trial.

9.2 Datasets for Analysis

The following samples are defined for this trial:

- Enrolled sample: all subjects who are enrolled at baseline
- Intent-to-treat sample: all randomized subjects administered at least one dose of double-blind IMP, who have measurements on the CAPS-5 total score at or prior to randomization and at least one post-randomization time point
- Safety sample: all randomized subjects administered at least one dose of double-blind IMP

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

The handling of missing data for primary and key secondary endpoint analysis is described in the unblinded addendum and in the SAP.

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9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline to the end of the efficacy period in the CAPS-5 total score. The change from baseline to the end of the efficacy period in the CAPS-5 total score will be analyzed using a mixed-effect model repeated measures (MMRM) analysis with an unstructured variance covariance structure. The model will include fixed class-effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week, and will include the interaction term of baseline values of the CAPS-5 total score by visit week as a covariate. All scheduled visits after baseline during the double-blind treatment period will be included in the model.

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

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy endpoints are the change from baseline to the end of the efficacy period in the CGI-S score and the change from baseline to the end of the efficacy period in B-IPF score. Both endpoints will be analyzed using an MMRM model similar to that prespecified for the primary efficacy endpoint, correcting for the relevant values at randomization.

9.4.1.3 Secondary Efficacy Endpoint Analysis

Not applicable.

9.4.1.4 Control of Experiment-wise Type 1 Error

Control of experiment-wise Type 1 error is described in the unblinded addendum and in the SAP.

9.4.1.5 Other Efficacy Endpoint Analysis

Analysis of the other efficacy endpoint analysis is described in the unblinded addendum and in the SAP.

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9.4.2 Safety Analysis

9.4.2.1 Adverse Events

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

- 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

9.4.2.2 Clinical Laboratory Data

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

9.4.2.3 Physical Examination and Vital Signs Data

Physical examination findings will be listed by subject.

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

Potentially clinically relevant results in vital signs and body weight will also be summarized.

9.4.2.4 Electrocardiogram Data

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

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

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

1) QT interval corrected for heart rate using Bazett's formula (QTcB) is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB=QT/(RR)^{0.5}$, and
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the Food and Drug Administration 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 the EPS (eg, the SAS, the AIMS, and the BARS) and suicidality (eg, C-SSRS) will be summarized by treatment group based on the OC dataset of the safety sample. Details will be described in SAP.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Demographic characteristics and disease severity at baseline will be summarized by descriptive statistics, eg, proportion, mean, median, SD, and minimum and maximum values.

9.4.3.2 Pharmacokinetic Analysis

No pharmacokinetic analysis is planned as only sparse samples will be obtained. Plasma concentrations of brexpiprazole and sertraline will be summarized using descriptive statistics by dose and timepoint.

9.4.3.3 Pharmacodynamic Analysis

No PD analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

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

9.4.3.5 Pharmacogenomic Analysis

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

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9.5 Interim Analysis and Adaptive Design

No interim analysis is planned for this study.

9.5.1 Data Monitoring Committee

Not applicable.

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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 Conference on Harmonisation (ICH) GCP: Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB 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 that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6[39] 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. 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-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. Irrespective of the format used, subjects must sign informed consent prior to any trial procedures being conducted.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and

documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

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

Prospective trial subjects will be provided with controlled access to the electronic ICF application by trial site staff. When the trial site staff and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the electronic ICF application, and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB-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. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

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

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel

(or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

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

10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), 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/major deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be

documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

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

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, progress notes, paper-based assessments and scales, 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 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, 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, accurate, and complete) 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.

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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) 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

Food and Drug Administration regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

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
8) Drafting the work or revising it critically for important intellectual content; AND
9) Final approval of the version to be published; AND
10) 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.

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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: Hemoglobin Hematocrit MCHC MCV RBC count WBC count with differential Platelet count Urinalysis: Appearance Color 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 Potassium Prolactin[a] Protein, total Sodium Triglycerides Chloride Magnesium Bicarbonate Inorganic phosphorus Uric acid Albumin Additional Tests: Urine pregnancy for WOCBP TSH HbA1c Additional Tests (screening only): HIV HBsAg Anti-HCV

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; MDMA = methylenedioxymethamphetamine; WBC = white blood cell.

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

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

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

For males and WOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchidectomy) or remains abstinent during the trial and for 30 days after the last dose of IMP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control implant, birth control depot injection, condom with spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in eSource. Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.

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

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

Before trial enrollment, males and WOCBP 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, Week 6, and Week 12/ET on all WOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

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

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10.4 Appendix 4: Abbreviations

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
B-IPF	Brief Inventory of Psychosocial Function
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CGI-S	Clinical Global Impression - Severity
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
ECG	Electrocardiogram
eICF	Electronic informed consent
ET	Early termination
E-TRIP	Emory Treatment Resistance Interview for PTSD
FBR	Future Biospecimen Research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HADS-A	Hospital Anxiety and Depression Scale - Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale - Depression subscale
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
IRE	Immediately reportable event
K_i	Inhibition constant
LDH	Lactate dehydrogenase

Abbreviation	Definition
LDL	Low-density lipoprotein
MCHC	Mean corpuscular hemoglobin concentration
MCS	Mental component summary
MCV	Mean corpuscular volume
MDD	Major depressive disorder
NIDDM	Non-insulin-dependent diabetes mellitus
NPY	Neuropeptide Y
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
PCL-5	PTSD Checklist for DSM-5
PCS	Physical component summary
PGx	Pharmacogenomic(s)
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 by the Food and Drug Administration Neuropharm Division formula
RBC	Red blood cell count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
CCI	[redacted]
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US or USA	United States or United States of America
WBC	White blood cell count
WOCBP	Women of childbearing potential

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

Laboratory Tests	Criteria
Chemistry	
Aspartate aminotransferase	≥ 3 × ULN
Alanine aminotransferase	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
Lactate dehydrogenase	≥ 3 x ULN
Urea nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Urate	
Males	≥ 10.5 mg/dL
Females	≥ 8.5 mg/dL
Bilirubin	≥ 2.0 mg/dL
Creatine kinase	> 3 × ULN
Prolactin[a]	> ULN
Hematology	
Hematocrit	
Males	≤ 37% and decrease of ≥ 3 percentage points from baseline
Females	≤ 32% and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Males	≤ 11.5 g/dL
Females	≤ 9.5 g/dL
Leukocyte count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Eosinophils/Leukocyte	≥ 10%
Neutrophils/Leukocyte	≤ 15%
Neutrophil	≤ 1,500/mm^3
Platelet	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	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
Cholesterol, fasting	≥ 240 mg/dL
LDL cholesterol, fasting	≥ 160 mg/dL
HDL cholesterol, fasting	
Males	< 40 mg/dL
Females	< 50 mg/dL
Triglycerides, fasting	≥150 mg/dL

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

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10.6 Appendix 6: Criteria for Identifying Vital Signs of Potential Clinical Relevance

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

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).

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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)	

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

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

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

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

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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. 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, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB 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 notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, 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, 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.

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Agreement

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

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

I understand that this IRB-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 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 within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB 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
_____	_____	_____
Sponsor Representative Print Name	Signature	Date

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PPD	Clinical Approval	04-Jan-2023 17:20:27
	Approved for Clinical Pharmacology and Nonclinical	09-Jan-2023 14:48:28
	Biostatistics Approval	04-Jan-2023 22:35:35

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Document Number: CCI [redacted]

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Biostatistics Approval	07-Jul-2020 21:15:45
	Approved for Clinical Pharmacology and Nonclinical	07-Jul-2020 16:31:09
	Clinical Approval	09-Jul-2020 19:38:23