Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product
REXULTI® (brexpiprazole, OPC-34712, OPC-331, Lu AF41156)

REVISED CLINICAL PROTOCOL

A Phase 4, Multicenter, Open-label, Interventional Trial to Assess the Effects on Engagement of Flexible-dose Brexpiprazole (OPC-34712) as Adjunctive Therapy for the Treatment of Adults With Major Depressive Disorder

A Phase 4, Canadian Interventional Trial to Assess Brexpiprazole (OPC-34712) as Adjunctive Therapy in Adults With Major Depressive Disorder

Protocol No. 331-201-00289

CONFIDENTIAL — PROPRIETARY INFORMATION

Drug Development Phase:	4
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
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List of Abbreviations

Abbreviation	Definition
AAD	Agitation associated with dementia
ADHD	Attention deficit hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
BMI	Body mass index
bpm	Beats per minute
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBC	Complete blood count
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CIOMS	Council for International Organizations of Medical Science
C_{max}	Maximum (peak) plasma concentration
CRF	Case report form
CYP	Cytochrome P450
D	dopamine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ET	Early termination
FOCBP	Females of childbearing potential
GAD-7	Generalized Anxiety Disorder 7-item
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDS-SR	Inventory of Depressive Symptomatology Self-Report
IEC	Independent ethics committee
IND	Investigational New Drug
IRB	Institutional review board
IRE	Immediately reportable event
K_i	Inhibition constant
LAI	Long-acting injectable
LOCF	Last observation carried forward
MAR	Missing at random
MDD	Major Depressive Disorder
MDE	Major depressive episode
mmHg	Millimeter of mercury
MMRM	Mixed model repeated measure
MNAR	Missing not at random
N	Number of patients
OC	Observed cases

Abbreviation	Definition
OCD	Obsessive-compulsive disorder
PD	Pharmacodynamic
PGI-I	Patient Global Impression – Improvement
PGI-S	Patient Global Impression – Severity
PHQ-9	Patient Health Questionnaire 9-item scale
PK	Pharmacokinetic
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Sheehan Disability Scale
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
UFIE	Unusual failure in efficacy
US or USA	United States or United States of America
WHODAS	World Health Organization Disability Assessment Schedule
5-HT	5-hydroxytryptamine

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1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product:

REXULTI® (brexpiprazole, OPC-34712, OPC-331, Lu AF41156)

Protocol No.:

331-201-00289

Protocol Title:

A Phase 4, Multicenter, Open-label, Interventional Trial to Assess the Effects on Engagement of Flexible-dose Brexpiprazole (OPC-34712) as Adjunctive Therapy for the Treatment of Adults With Major Depressive Disorder

Protocol Lay Person Short Title:

A Phase 4, Canadian Interventional Trial to Assess Brexpiprazole (OPC-34712) as Adjunctive Therapy in Adults With Major Depressive Disorder

Clinical Phase:

4

Treatment/Indication:

Major Depressive Disorder (MDD)

Objectives:

The primary objective of the trial is:

- To prospectively characterize the effect of brexpiprazole on the concept of engagement, by evaluating Inventory of Depressive Symptomatology Self-Report (IDS-SR)-10-engagement, and the IDS-SR Total score, in patients with MDD with a current depressive episode.

The secondary objectives of the trial are:

- To evaluate patients' impression of improvement of their depression symptoms over time.
- To explore the relationship between engagement and other clinical effects of brexpiprazole, such as improvement in depressive symptoms and functioning.

- To evaluate the safety and tolerability of brexpiprazole (flexible dose; 0.5 to 2 mg once daily [QD]) as adjunctive therapy to antidepressant therapy (ADT) in the proposed patient population with MDD.

Trial Design:

This is a phase 4, multicenter, open-label, flexible dose trial designed to assess the effects of brexpiprazole (flexible dose; 0.5 to 2 mg QD) as adjunctive therapy to ADT in patients with MDD. This trial is being conducted in line with the Canadian Product Monograph.

The trial will be organized as follows:

Screening Phase: The screening period of up to 14 days (Days -14 to -1) will begin when the informed consent form (ICF) is signed. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant pharmacotherapy, if applicable.

Open-Label Treatment Phase: Patients meeting all of the inclusion and none of the exclusion criteria will be enrolled at the baseline visit into an 8-week open-label treatment phase. The screening and baseline visits can occur on the same day if the patient meets all required enrollment criteria. During the open-label treatment phase, all patients will receive brexpiprazole (that is, adjunctive brexpiprazole as a flexible dose; 0.5 to 2 mg/day) and will continue on the stable dose of ADT that they were taking at screening. Patients will attend visits at Weeks 2, 4, and 8 during the open-label treatment phase. If any patient discontinues the trial early, every effort should be made to complete the Week 8/early termination (ET) evaluations.

Following the completion of all scheduled visits, patients will be asked if they are interested in taking part in an exit interview, which will be separate from trial assessments and should occur within 30 days of the Week 8/ET visit. This also applies to patients withdrawn prematurely from the trial.

Trial Population:

The trial population will include male and female outpatients between the regional age of majority (18 or 19 years of age) and 65 years of age, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of a single or recurrent, non-psychotic episode of MDD with or without symptoms of anxiety. Additionally, patients must have a treatment history for the current major depressive episode (MDE) of an inadequate response (assessment of inadequate response is per investigator judgment) to at least 1 and no more than 2 adequate antidepressant treatments (including the antidepressant that the patient is taking at screening).

Patients with a historical diagnosis of any concurrent condition that is exclusionary may be permitted if the investigator determines and documents this prior diagnosis was not appropriate based on current and historical presentation.

Patients with attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), panic disorders, or generalized anxiety disorder can be included under the following conditions:

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

It is anticipated that approximately 210 patients will be screened and approximately 134 enrolled into the open-label treatment phase from approximately 15 sites (to complete 100 patients).

Inclusion/Exclusion Criteria:

Patients are required to meet the following inclusion criteria:

1) Patients who are able to provide informed consent, understand the nature of the trial, follow protocol requirements, and read and understand English or French.
2) Male and female patients (outpatients) between the regional age of majority (18 or 19 years of age) to 65 years of age, inclusive, at the time of informed consent.
3) Primary diagnosis of MDD and in a current non-psychotic MDE as defined by DSM-5 criteria, who have been outpatients for at least 4 weeks, and have an inadequate response, per investigator judgment, to 1 or 2 adequate treatments of ADTs in their current MDE, including current ADT.
4) Patients with a Patient Health Questionnaire 9-item scale (PHQ-9) $\geq$ 15 at the screening and baseline visits, if separate.

Patients will be excluded if they meet any of the following exclusion criteria:

1) Females who are breast-feeding and/or who are pregnant at the time of trial enrollment, or who plan to become pregnant during the trial.
2) Patients currently or previously treated with brexpiprazole including patients who received brexpiprazole in any prior clinical trial.
3) Patients with a concurrent DSM-5 diagnosis of the following will be excluded:
   a) Schizophrenia or schizoaffective disorder
   b) Bipolar I or bipolar II disorder
   c) Post-traumatic stress disorder

   d) Dementia
   e) Eating disorder
   f) Borderline personality disorder
   g) Antisocial personality disorder
4) Patients with a suicidality score of 3 based on IDS-SR suicidality item 18 or patients who, in the opinion of the investigator, presents a serious risk of suicide.
5) Psychotherapy administered at baseline that is not expected to remain stable throughout the trial.
6) Patients who have received neurostimulation when used for treatment resistant depression.
7) Current, prior (lifetime treatment history), or planned use (during trial participation) of ketamine and/or esketamine for treatment of depression.
8) Current use of oral, immediate release intramuscular, or long-acting injectable (LAI) antipsychotics at Baseline and within 7 days prior to trial participation (one treatment cycle for LAIs).
9) Subjects who are currently participating in another clinical trial.
10) Any patient who does not have baseline blood glucose and complete blood count (CBC) including white blood cell counts as required prior to initiating treatment with brexpiprazole as per the Canadian Product Monograph. Has a medical condition (eg, moderate or severe substance use disorder) that would expose them to undue risk or interfere with the trial endpoints, or any other reason that, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial. Please review the contraindications and warnings and precautions of the Canadian Product Monograph..

Trial Site(s):

Approximately 15 trial sites in Canada.

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

During the open-label treatment phase, all patients will receive brexpiprazole (that is, adjunctive brexpiprazole as a flexible dose; 0.5 to 2 mg/day) and will continue on the stable dose of ADT that they were taking at screening. Brexpiprazole should be taken at approximately the same time each day and can be taken at the same time as the ADT. Antidepressant therapy is not considered trial drug in this trial.

Patients will take the first dose of brexpiprazole with or without food on the day after they are enrolled in the trial (Day 1). In accordance with the Canadian Product Monograph, the starting dose will be 0.5 mg or 1 mg QD. Up-titration will occur at weekly intervals to reach a dose of at least 1 mg QD by the Week 2 visit. After the

Week 2 visit, the dose may be decreased to a minimum of 0.5 mg QD or increased to a maximum of 2 mg QD based on the investigator's clinical judgment. Dose increases may occur at weekly intervals based on the patient's clinical response and tolerability. Dose decreases can occur at unscheduled trial visits. This dosing regimen is consistent with the Canadian Product Monograph and with clinical practice in Canada.

Allowable brexpiprazole doses that may be given starting the day after the Week 2 visit will be [redacted]. The dose of 2 mg QD is the recommended target dose and is also the maximum recommended dose.

The trial drug will not be provided by the sponsor to the investigators. Instead, the trial drug will be supplied directly to enrolled patients by their retail pharmacists through a trial cards system.

Trial Assessments:

Assessments for Efficacy: IDS-SR, Patient Health Questionnaire 9-item (PHQ-9), Generalized Anxiety Disorder 7-item scale (GAD-7), World Health Organization Disability Assessment Schedule (WHODAS) 2.0 short, Sheehan Disability Scale (SDS), Clinical Global Impression - Severity (CGI-S), Clinical Global Impression - Improvement (CGI-I), Patient Global Impression – Severity (PGI-S), and Patient Global Impression – Improvement (PGI-I) scales.

Assessments for Safety: adverse events (AEs), vital signs, and physical examination findings.

Screening/Other: Demographic information, medical and psychiatric history, medication history, and urine pregnancy test.

Patient diary: Word of the day. Patients will be provided a list of words and will select one each day as their "word of the day". The meaningful word list was generated based on interviews with MDD patients.

Criteria for Evaluation:

The co-primary efficacy endpoints are as follows:

1) Change from baseline to Week 8 in IDS-SR-10-engagement.
2) Change from baseline to Week 8 in IDS-SR Total score.

The other efficacy endpoints are as follows:

1) Change from baseline to Weeks 2 and 4 in IDS-SR-10-engagement.
2) Change from baseline to Weeks 2 and 4 in IDS-SR Total score.

3) Change from baseline to Weeks 2, 4, and 8 in IDS-SR patient-selected engagement items.
4) Change from baseline to Weeks 2, 4, and 8 in IDS-SR engagement items selected by both clinicians and patients.
5) Change from baseline to Weeks 2, 4, and 8 in CGI-S score.
6) CGI-I score at Weeks 2, 4, and 8.
7) Change from baseline to Weeks 4 and 8 in SDS Mean score and SDS individual item scores.
8) Change from baseline to Weeks 4 and 8 in WHODAS 2.0 short form score.
9) Change from baseline to Weeks 2, 4, and 8 in PHQ-9 score.
10) Change from baseline to Weeks 2, 4, and 8 in GAD-7 score.
11) Change from baseline to each timepoint (ie, being measured weekly at home) in depression as measured by PGI-I score.
12) PGI-I response rate at each timepoint (ie, being measured weekly at home), where response is defined as a PGI-I score of 1 or 2 (very much improved or much improved).
13) Time to first PGI-S response, where response is defined as a reduction of 2 points in PGI-S score from baseline.

[redacted]

Safety endpoints to be examined in this trial will include AEs, vital signs, change from baseline in body weight and body mass index (BMI), and potentially clinically significant changes in body weight.

Data Monitoring Committee: No

Statistical Methods:

Sample Size: This is a single-arm trial to assess the effect of brexpiprazole on patient engagement in MDD patients through the following co-primary endpoints: 1) change from baseline to Week 8 in IDS-SR-10-engagement 2) change from baseline to Week 8 in IDS-SR Total score. A sample size of 100 completers (ie, patients who have an evaluation on IDS-SR Total score and IDS-SR-10-engagement at Week 8) will yield 95% power to show a difference from baseline in IDS-SR Total score and at least 95% power to show a difference from baseline in IDS-SR-10-engagement at a two-sided significance level of 0.05, respectively. It will ensure the overall power is at least 90%. After considering an ET rate of 25%, a total of 134 patients need to be enrolled in this trial.

Efficacy: The primary efficacy analysis is to evaluate if changes from baseline to Week 8 in both co-primary endpoints will differ from 0, separately. Each of the endpoints will be tested by fitting a mixed model repeated measure (MMRM) analysis with an unstructured variance covariance structure at a two-sided significance level of 0.05 on observed cases (OC) dataset on Efficacy Sample. The model will include fixed effect terms for visit, baseline value, an interaction term of baseline value by visit, and trial center. The trial will be claimed positive if both p-values are less than 0.05. Therefore, the overall type I error is controlled at 0.05 level.

Safety: Adverse events and vital signs will be summarized by descriptive statistics. Descriptive statistics will be also used to summarize body weight and BMI at screening, baseline, and Weeks 2, 4, and 8/ET. The incidence of potentially clinically significant changes in body weight will be tabulated in incidence tables.

Trial Duration:

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

- Screening period (14 days [Day -14 to Day -1])
- Outpatient treatment period (8 weeks; including assessments at baseline and Weeks 2, 4, and 8)
- End of Trial (Week 8 visit/ET)

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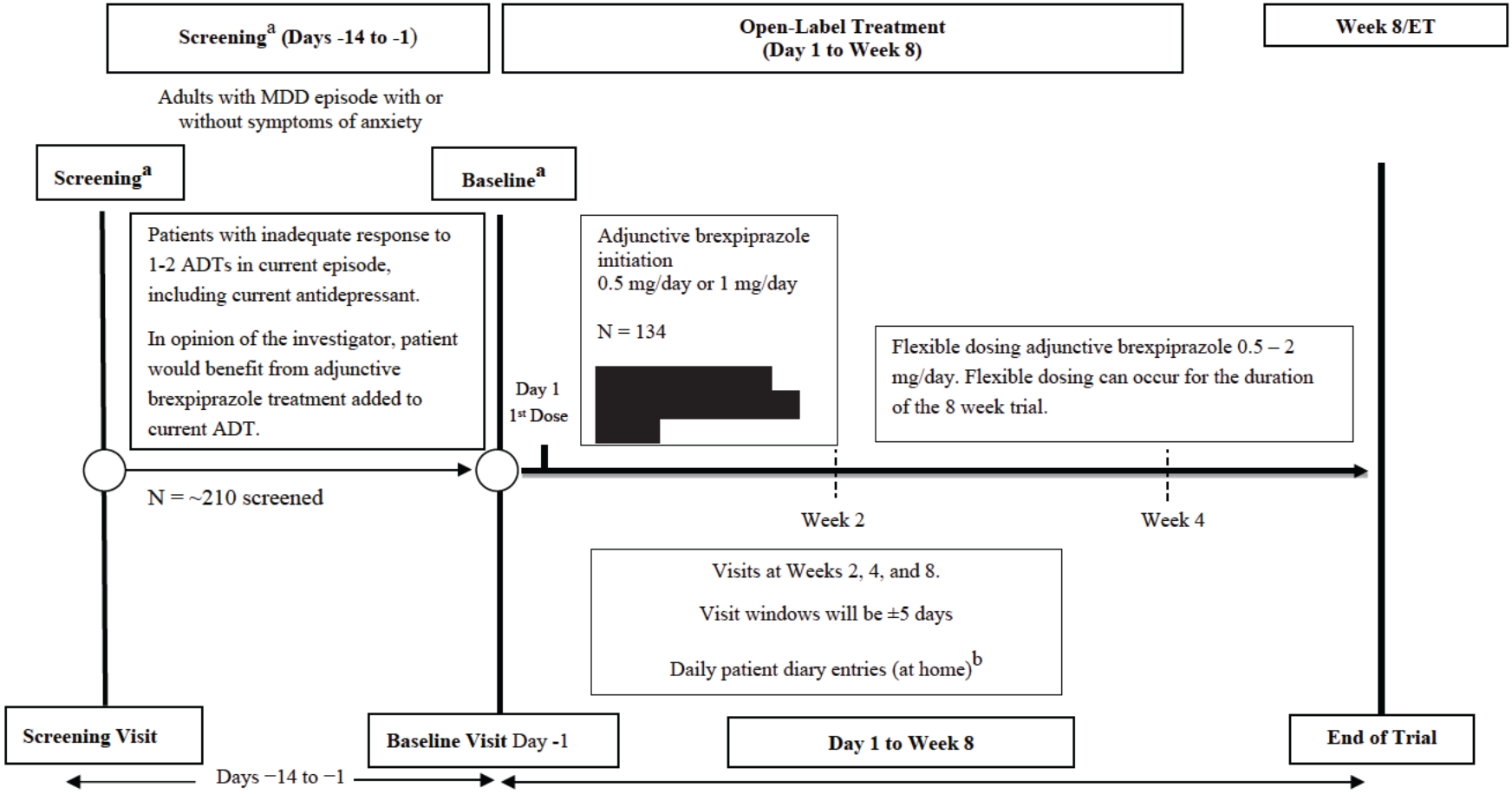
1.2 Trial Schematic



N = number of patients.

[a]The screening visit can comprise 1 or more visits as needed. The screening and baseline visits can occur the same day if the patient meets all required enrollment criteria.

[b]Patient diary entries will be reduced in frequency from daily to twice weekly from the day after the Week 4 visit to Week 8 (word of the day and PGI-S).

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Assessment	Visit				
	Screening[a] (Days -14 to -2)	Baseline[a] (Day -1)	Week 2	Week 4	Week 8 /ET[b]
		± 5 days			
ENTRANCE/HISTORY					
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demography	X				
Medical history	X				
Psychiatric history	X				
Prohibited medication washout[c]	X				
Urine pregnancy test	X	X			
EFFICACY[d]					
IDS-SR (patient reported)		X	X	X	X
PHQ-9 (patient reported)[e]	X	X	X	X	X
GAD-7 (patient reported)		X	X	X	X
WHODAS 2.0 short (patient reported)		X		X	X
SDS (patient reported)		X		X	X
CGI-S		X	X	X	X
CGI-I			X	X	X
SAFETY					
Brief physical examination[f]	X				X
Height and body weight[g]	X	X	X	X	X
Vital signs[h]	X	X		X	X
Adverse events	X	X	X	X	X
Concomitant medications[i]	X	X	X	X	X

Table 1.3-1 Schedule of Assessments

Assessment	Visit				
	Screening[a] (Days -14 to -2)	Baseline[a] (Day -1)	Week 2	Week 4	Week 8 /ET[b]
		± 5 days			
Clinical evaluation for suicidality[e]	X	X	X	X	X
OTHER					
Trial drug prescribed[j]		X	X	X	
Trial drug accountability (patient reported)			X	X	X
Review of Patient Diary (word of the day, PGI-S, and PGI-I)[k]		X	X	X	X

ADT = antidepressant therapy; CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; ET = early termination; GAD-7 = Generalized Anxiety Disorder 7-item scale; ICF = informed consent form; IDS-SR = Inventory of Depressive Symptomatology Self-Report; PGI-I = Patient Global Impression – Improvement; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire 9-item scale; SDS = Sheehan Disability Scale; WHODAS = World Health Organization Disability Assessment Schedule.

[a]Brexpiprazole dosing will take place on Day 1 of Week 1. The screening visit can comprise 1 or more visits as needed. Screening and baseline visits can occur the same day if the patient meets all required enrollment criteria. Where screening and baseline visits occur on the same day, assessments will not be duplicated.

[b]If a patient discontinues prematurely before Week 8, every effort should be made to complete the "Week 8/ET" evaluations.

[c]Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods.

[d]Where possible, sites should follow the order of efficacy assessments and patient reported outcomes as listed.

[e]If the PHQ-9 indicates suicidal ideation (eg, a patient has suicidality on item 9 of the PHQ-9 scale [≥ 1] and/or IDS item 18 ≥ 3), then clinical evaluation of suicidality is essential on that particular visit and the investigator will conduct a more in-depth clinical assessment of the patient per the site's standard protocol.

[f]The extent of the physical examination will be at the discretion of the investigator.

[g]Height and body weight at screening and body weight at baseline and at Weeks 2, 4, and 8/ET. When screening and baseline visits occur on the same day, assessments will not be duplicated.

[h]Vital signs include systolic and diastolic blood pressure and heart rate.

[i]All medications taken within 30 days prior to informed consent will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. All ADTs taken within 12 months prior to informed consent will be recorded.

[j]Trial drug will not be prescribed at the Week 8 visit. The ADT regimen will be left to the discretion of the investigator.

[k]Patient diary entries will be reduced in frequency from daily to twice weekly from Week 5 to Week 8 (word of the day and PGI-S). The PGI-I will be administered weekly throughout the trial.

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2 Introduction

Major depressive disorder (MDD) is a serious medical illness associated with significant suicide risk and marked disability. Symptoms are heterogenous, spanning emotional, physical and cognitive domains, and lead to impairments in personal and social functioning, as well as diminished quality of life. Importantly, patients want a treatment that will help them to regain optimism and self-confidence, feel like their usual selves, and regain their pre-morbid level of functioning[1] and feelings of well-being. The return to premorbid levels of functioning are often rated by patients as more important than symptom relief.[2] Given that full symptomatic and functional recovery is the goal of MDD treatment, early identification of treatments that can address a broad range of symptoms of the illness are needed in order to effectively treat the consequences on overall functioning and well-being, and help the patient return to their premorbid state.

Canadian clinical practice guidelines emphasize the importance of adequate treatment for MDD, including a timely change in treatment (ie, medication switch or addition of adjunct therapy) if improvement is not observed within 2-4 weeks of dose-optimized therapy.[3] Second-generation antipsychotics such as aripiprazole, brexpiprazole, olanzapine, quetiapine, and risperidone are recommended by the Canadian Network for Mood and Anxiety Treatments (CANMAT) as adjunct treatments with Level 1 evidence for patients who have not experienced an adequate response to prior antidepressant medications; however not all of these treatments are approved by Health Canada as adjunctive MDD treatments, and patients respond differently in terms of efficacy and tolerability to different medications. Consequently, there is an ongoing medical need to identify adjunctive strategies that offer a broad efficacy to enable patients to regain their premorbid functioning and personal well-being, and ultimately to return to their premorbid state.

Brexpiprazole (OPC-34712 and Lu AF41156) is an atypical antipsychotic synthesized by Otsuka that is being codeveloped by Otsuka and Lundbeck. Brexpiprazole is currently approved in Canada, the United States (US), Mexico, United Arab Emirates, and other countries as monotherapy for the treatment of schizophrenia and in the US and Canada for use as an adjunctive therapy to antidepressants for the treatment of MDD. Brexpiprazole is a serotonin (5-hydroxytryptamine [5-HT]) –dopamine (D) activity modulator which is a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors, and an antagonist at serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all with subnanomolar affinities.

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2.1 Nonclinical Data

Efficacy and safety pharmacology of brexpiprazole are summarized in Section 2.1.1 and Section 2.1.2. A complete description of the available data from nonclinical studies, including pharmacokinetic and toxicology studies in different animal species can be found in the Investigator's Brochure (IB).[4]

2.1.1 Efficacy Pharmacology

While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (inhibition constant [K_i]: 0.1 - 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ 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. These mechanisms of actions have previously shown activity in preclinical models for MDD.

Please refer to the IB[4] for more detailed information.

2.1.2 Safety Pharmacology

Please refer to the IB[4] for information.

2.2 Clinical Data

As of 17 Apr 2020, the brexpiprazole clinical development program consisted of a total of 96 clinical trials conducted in North America, Latin America, Europe, and Asia (74 completed and 22 ongoing). This total includes 77 trials conducted under US Investigational New Drug (IND) Applications (65 completed and 12 ongoing) for healthy subjects, schizophrenia, adjunctive treatment of MDD, adjunctive treatment of attention deficit hyperactivity disorder (ADHD), agitation associated with dementia (AAD) of the Alzheimer's type, post-traumatic stress disorder (PTSD), bipolar disorder, or autism spectrum disorder; and 19 non-US IND trials (9 completed and 10 ongoing in China, South Korea, and Japan) conducted in healthy subjects, subjects with schizophrenia, subjects with MDD, and subjects with AAD.

Please refer to the IB[4] for more detailed information.

2.2.1 Pharmacokinetics/Pharmacodynamics

The pharmacokinetics (PK) of single and multiple doses of brexpiprazole was studied in healthy subjects and in subjects with MDD, ADHD, and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, brexpiprazole and 1 metabolite, DM-3411, were identified as the major analytes that are present in human plasma. In vitro, the activity of DM-3411 is 17 times lower than that of brexpiprazole and thus is considered a minimally active metabolite. Both brexpiprazole and DM-3411 pharmacokinetics were linear in healthy subjects following single oral doses of brexpiprazole 0.2 to 6.0 mg. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Steady state PK was linear following multiple daily doses of brexpiprazole in the range of 0.5 to 2.0 mg to healthy subjects. The accumulation factor based on maximum (peak) plasma concentration (C_{max}) and area under the concentration-time curve calculated to the last observable concentration at time t (AUC_t) was approximately 4 times. After multiple dose administration of brexpiprazole (1.0 to 12.0 mg/day) to subjects with schizophrenia or schizoaffective disorder, brexpiprazole and DM-3411 mean terminal elimination half-life at steady state was 95.4 and 89.3 hours, respectively; median time to maximum (peak) plasma concentration was 3.0 and 8.0 hours, respectively.

In drug interaction trials in healthy subjects, brexpiprazole was shown to be metabolized by cytochrome P450 (CYP) 3A4 and CYP2D6 isozymes and was not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein. Coadministration of potent CYP3A4 or CYP2D6 inhibitors with brexpiprazole resulted in about a 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half-life of brexpiprazole. Of note, administration of brexpiprazole with fluoxetine, paroxetine, and duloxetine (medications for treatment of MDD coadministered in this trial) may potentially increase brexpiprazole plasma concentrations by up to 2-fold.

In a single-dose trial in healthy subjects, approximately 46.0% and 24.6% of administered radioactivity following an oral dose of ^{14}C-brexpiprazole was excreted in feces and urine, respectively. In this same trial, brexpiprazole did not preferentially bind to red blood cells. Brexpiprazole showed high protein binding in human serum (≥ 99.8%) in vitro.

The binding of brexpiprazole to dopamine receptors was assessed using positron emission tomography. The mean D_2/D_3 receptor occupancies at 4 and 24 hours postdose

after 0.25, 0.5, 1.0, 2.0, 4.0, 5.0, and 6.0 mg single-dose administration of brexpiprazole to healthy subjects were 11.4% to 17.4%, 36.5% to 46.3%, 45.6% to 60.2%, 52.7% to 68.6%, 67.9% to 79.5%, 71.9% to 88.2%, and 69.5% to 92.6%, respectively (Trial 331-07-202). Based on the single-dose D_2/D_3 receptor occupancy data and steady state PK/pharmacodynamic (PD) modeling, it was predicted that the D_2/D_3 receptor occupancy after multiple daily dose administration of 1.0 to 2.0 mg and higher doses of brexpiprazole will result in at least 80% to 90% D_2/D_3 receptor occupancy.

Population PK analysis of phase 1 through phase 3 trials demonstrated no differences in the PK of brexpiprazole between healthy subjects, subjects with MDD, and subjects with either schizophrenia or schizoaffective disorder (in phase 1 trials).

Please refer to the IB[4] for more detailed information.

2.2.2 Major Depressive Disorder

The data derived from 6 adequate and well-controlled short-term trials provides evidence that brexpiprazole 2 mg/day and 3 mg/day is efficacious as adjunctive treatment in adults with MDD who had a persistent inadequate response to antidepressant therapy (ADT). The maximum dose approved in Canada is 2 mg/day.

Please refer to the IB[4] for more detailed information.

2.3 Known and Potential Risks and Benefits

Phase 1 data indicated that brexpiprazole demonstrated good safety and tolerability when administered to healthy volunteers at single doses of 0.2 to 6 mg and at a repeated dose of 2 mg/day. Data from completed repeated dosing trials indicate that brexpiprazole demonstrated good tolerability when administered to subjects with schizophrenia or schizoaffective disorder at doses of up to 12 mg/day; when administered to subjects with MDD at doses of up to 4 mg/day in combination with a marketed antidepressant (brexpiprazole in MDD is approved only to 2 mg/day); up to 3 mg/day as adjunctive therapy in elderly subjects (70 - 85 years of age) with MDD; and when administered to subjects with ADHD at doses of up to 4 mg/day in combination with a marketed stimulant (brexpiprazole is approved for doses of up to 2 mg for the adjunct treatment of MDD in Canada). Please refer to the Canadian Product Monograph[5] for details of known and potential risks and benefits of brexpiprazole.

Please refer to the current brexpiprazole IB[4] for a summary of available nonclinical and clinical safety data.

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2.4 Trial Rationale

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

Post-marketing reports from various sources have revealed a clinical observation of brexpiprazole-treated patients, initially described as an increase or improvement in "engagement," "positivity," or "brightening." This unique effect was reported by physicians from multiple countries, and was also observed in reports received by the company call centers. Based on this spontaneous feedback, a post-hoc analysis of specific "engagement items" of the Inventory of Depressive Symptomatology Self-Report (IDS-SR) from the brexpiprazole pivotal trial data was conducted to explore patient ratings of this so-called "engagement effect," and patient interviews from previous MDD exploratory studies were analyzed for spontaneous use of "engagement" lexicon. Briefly, results indicated that MDD patients treated with adjunctive brexpiprazole demonstrated improvements vs adjunctive placebo on items that represented patient well-being and engagement.[6] Furthermore, a majority of patients (~89%) that consented to participate in exit interviews after exploratory studies used language reflecting an improvement in at least one of four engagement domains (social, emotional, physical or cognitive).[7] Canadian healthcare providers confirmed that improvement in engagement has been observed in Canadian MDD patients, with reports of patients experiencing "increased motivation," "improved anhedonia," "clarity of mind," and being "more engaged" indicating that further prospective investigation of this effect is warranted. Furthermore, interviews recently conducted with MDD patients support the relevance of the previously-identified IDS-SR items in the measurement of patient engagement.

3 Objectives

The primary objective of this trial is:

- To prospectively characterize the effect of brexpiprazole on the concept of engagement, by evaluating IDS-SR-10-engagement, and the IDS-SR Total score, in patients with MDD with a current depressive episode.

The secondary objectives of this trial are:

- To evaluate patients' impression of improvement of their depression symptoms over time.
- To explore the relationship between engagement and other clinical effects of brexpiprazole, such as improvement in depressive symptoms and functioning.

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- To evaluate the safety and tolerability of brexpiprazole (flexible dose; 0.5 to 2 mg once daily [QD]) as adjunctive therapy to ADT in the proposed patient population with MDD.

4 Trial Design

4.1 Type/Design of Trial

This is a phase 4, multicenter, open-label, flexible dose trial designed to assess the effects of brexpiprazole (flexible dose; 0.5 to 2 mg QD) as adjunctive therapy to ADT in patients with MDD. This trial is being conducted in line with the Canadian Product Monograph.[5]

The trial will be organized as follows:

Screening Phase: The screening period of up to 14 days (Days -14 to -1) will begin when the informed consent form (ICF) is signed. The purpose of the screening period is to assess eligibility criteria at 1 or more visits (as necessary to complete screening assessments) and to washout prohibited concomitant pharmacotherapy, if applicable.

Open-Label Treatment Phase: Patients meeting all of the inclusion and none of the exclusion criteria will be enrolled at the baseline visit into an 8-week open-label treatment phase. The screening and baseline visits can occur on the same day if the patient meets all required enrollment criteria. During the open-label treatment phase, all patients will receive brexpiprazole (that is, adjunctive brexpiprazole as a flexible dose; 0.5 to 2 mg/day) and will continue on the stable dose of ADT that they were taking at screening. Patients will attend visits at Weeks 2, 4, and 8 during the open-label treatment phase. If any patient discontinues the trial early, every effort should be made to complete the Week 8/early termination (ET) evaluations.

Following the completion of all scheduled visits, patients will be asked if they are interested in taking part in an exit interview, which will be separate from trial assessments and should occur within 30 days of the Week 8/ET visit. This also applies to patients withdrawn prematurely from the trial.

A schematic of the trial design is presented in Figure 1.2-1.

4.2 Scientific Rationale for Trial Design

The current clinical trial will be the first prospective investigation to further characterize the effect of brexpiprazole on patient engagement.

The engagement items of the IDS-SR (which were previously identified by clinicians and subsequently confirmed by MDD patients) will serve as one of the co-primary outcome

measures. The relationship between engagement and other outcomes of interest (such as functioning, and depressive symptoms) will be explored in order to further characterize this engagement effect. The majority of the clinical assessments to be used in this trial are patient-reported, which is aligned with current views that patient-reported outcomes are imperative to demonstrating the clinical effectiveness of MDD treatments.[8]

While the current trial is interventional, the trial design is intended to assess the effect of adjunctive brexpiprazole on MDD patients when administered in a real-world setting. The open-label nature of the trial, as well as the patient population, the timing of the visits, the clinical assessments used, and the dosing parameters are intended to mimic Canadian clinical practice as closely as possible. Patient diaries will assess the patient's clinical experience in a manner that is as non-invasive as possible.

4.3 Dosing Rationale

Dosing is in line with the instructions for use in the Canadian Product Monograph[5] while providing flexibility to adjust based on tolerability and treatment response.

The dosing regimen for brexpiprazole in this trial is presented in Section 6.1.

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 case report form (CRF) page for the last patient completing or withdrawing from the trial.

4.5 Definition of Completed Patients

The treatment period is defined as the time period during which patients are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the patient actually consumes all doses of the trial drug. Patients who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, patients who complete the Week 8 visit will be defined as trial completers.

5 Trial Population

The trial population will include male and female outpatients between the regional age of majority (18 or 19 years of age) and 65 years of age, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis of a single or recurrent, non-psychotic episode of MDD with or without symptoms of anxiety. Additionally, patients must have a treatment history for the current major depressive episode (MDE) of an inadequate response (assessment of inadequate response is per

investigator judgment) to at least 1 and no more than 2 adequate antidepressant treatments (including the antidepressant that the patient is taking at screening).

Patients with a historical diagnosis of any concurrent condition that is exclusionary may be permitted if the investigator determines and documents this prior diagnosis was not appropriate based on current and historical presentation.

Patients with ADHD, obsessive compulsive disorder (OCD), panic disorders, or generalized anxiety disorder can be included under the following conditions:

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

It is anticipated that approximately 210 patients will be screened and approximately 134 enrolled into the open-label treatment phase from approximately 15 sites (to complete 100 patients).

5.1 Patient Selection and Numbering

All patients will be given a unique identification (ID; site number [3 digits] + patient number ['S' + 5 digits] upon providing consent [or assent if applicable]). The site number will be designated by the sponsor. For each site, the patient number will be given sequentially from S00001.

Demographic information (collection date, date of birth, sex, gender identity, childbearing potential, race, ethnicity, native language, years of education) and medical history will be recorded in the CRF at the screening visit.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, either by the investigator or by the medical monitor.

5.2.1 Inclusion Criteria

Patients are required to meet the following inclusion criteria:

1) Patients who are able to provide informed consent, understand the nature of the trial, follow protocol requirements, and read and understand English or French.
2) Male and female patients (outpatients) between the regional age of majority (18 or 19 years of age) to 65 years of age, inclusive, at the time of informed consent.

3) Primary diagnosis of MDD and in a current non-psychotic MDE as defined by DSM-5 criteria, who have been outpatients for at least 4 weeks, and have an inadequate response, per investigator judgment, to 1 or 2 adequate treatments of ADTs in their current MDE, including current ADT.
4) Patients with a Patient Health Questionnaire 9-item scale (PHQ-9) ≥ 15 at the screening and baseline visits, if separate.

5.2.2 Exclusion Criteria

Patients will be excluded if they meet any of the following exclusion criteria:

1) Females who are breast-feeding and/or who are pregnant at the time of trial enrollment, or who plan to become pregnant during the trial (see Section 10.2).
2) Patients currently or previously treated with brexpiprazole including patients who received brexpiprazole in any prior clinical trial.
3) Patients with a concurrent DSM-5 diagnosis of the following will be excluded:
   a) Schizophrenia or schizoaffective disorder
   b) Bipolar I or bipolar II disorder
   c) PTSD
   d) Dementia
   e) Eating disorder
   f) Borderline personality disorder
   g) Antisocial personality disorder
4) Patients with a suicidality score of 3 based on IDS-SR suicidality item 18 or patients who, in the opinion of the investigator, presents a serious risk of suicide.
5) Psychotherapy administered at baseline that is not expected to remain stable throughout the trial.
6) Patients who have received neurostimulation when used for treatment resistant depression.
7) Current, prior (lifetime treatment history), or planned use (during trial participation) of ketamine and/or esketamine for treatment of depression.
8) Current use of oral, immediate release intramuscular, or long-acting injectable (LAI) antipsychotics at Baseline and within 7 days prior to trial participation (one treatment cycle for LAIs).
9) Subjects who are currently participating in another clinical trial.
10) Any patient who does not have baseline blood glucose and CBC including white blood cell counts as required prior to initiating treatment with brexpiprazole as per the Canadian Product Monograph. Has a medical condition (eg, moderate or severe substance use disorder) that would expose them to undue risk or interfere with the trial endpoints, or any other reason that, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial. Please review

the contraindications and warnings and precautions of the Canadian Product Monograph.

Full requirements for contraception along with a definition of females of childbearing potential (FOCBP) are described in Section 10.2.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Brexpiprazole dosing is in line with the instructions for use and restrictions indicated in the Canadian Product Monograph.[5] There are no other restrictions on food or water intake prior to or after administration of brexpiprazole.

5.3.2 Caffeine and Alcohol

Alcohol may interact with brexpiprazole. Patients will be informed of the risks of interaction between alcohol and brexpiprazole.

5.4 Screen Failures

Patients who sign an ICF but who are not started on treatment will be considered screen failures and are permitted to be re-screened with consent of the medical monitor. In the event that the patient is re-screened for trial participation, and the re-screening was not completed within the original screening window, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

A screen failure is a patient from whom informed consent is obtained and is documented in writing (ie, patient signs an ICF), but who is not assigned trial treatment. All adverse events (AEs) must be reported after patient informed consent has been obtained, including screening failures due to AEs, irrespectively of trial drug administration.

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

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

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6 Trial Treatments

6.1 Trial Treatments Administered

Treatment will consist of open-label brexpiprazole plus an ADT. The investigator must be able and willing to prescribe brexpiprazole to the patient per the approved Canadian Product Monograph.[5] Brexpiprazole should be taken at approximately the same time each day and can be taken at the same time as the ADT. Antidepressant therapy is not considered trial drug in this trial. The dosing schedule for brexpiprazole is presented in Table 6.1-1.

Table 6.1-1 Brexpiprazole Dosing Schedule

Trial Days	Week	Brexpiprazole Adjunctive Therapy[a]
1-7	1	Starting dose: Single oral 0.5 or 1 mg tablet QD. Up-titration at weekly intervals [redacted]
8-14	2	
15-21	3	Single oral 0.5, 1, 1.5, or 2 mg tablet(s) QD. (Dose increases must occur at weekly intervals. The maximum recommended target dose is 2 mg QD).
22-28	4	
29-35	5	
36-42	6	
43-49	7	
50-56	8	

[a]Brexpiprazole tablet strengths are 0.25, 0.5, 1, and 2 mg per the Canadian Product Monograph.[5]

Patients will take the first dose of brexpiprazole with or without food on the day after they are enrolled in the trial (Day 1). In accordance with the Canadian Product Monograph, the starting dose will be 0.5 mg or 1 mg QD. Up-titration will occur at weekly intervals to reach a dose of at least 1 mg QD by the Week 2 visit. After the Week 2 visit, the dose may be decreased to a minimum of 0.5 mg QD or increased to a maximum of 2 mg QD based on the investigator's clinical judgment. Dose increases may occur at weekly intervals based on the patient's clinical response and tolerability. Dose decreases can occur at unscheduled trial visits. This dosing regimen is consistent with the Canadian Product Monograph[5] and with clinical practice in Canada.

Allowable brexpiprazole doses that may be given starting the day after the Week 2 visit will be [redacted]. The dose of 2 mg QD is the recommended target dose and is also the maximum recommended dose.

For information regarding the dose regimen see Section 4.1.

6.2 Management of Investigational Medicinal Product

For full details on trial drug management, please refer to the brexpiprazole IB.[4]

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6.2.1 Packaging and Labeling

The trial drug will not be provided by the sponsor to the investigators. Instead, the trial drug will be supplied directly to enrolled patients by their retail pharmacists through a trial cards system.

6.2.2 Storage

The trial drug will be labeled at the patient's retail pharmacy and storage instructions should be provided to the patient by their retail pharmacist at the time that the patient fills the prescription. The trial drug will also be labeled with appropriate storage conditions. Patients will be instructed by their retail pharmacist to adhere to trial drug storage requirements for the duration of the trial.

6.2.3 Accountability

For the entire duration of trial participation, the trial drug will be dispensed to patients by retail pharmacists through a trial cards system (Section 6.2.1).

6.2.4 Returns and Destruction

Patients will be instructed that upon completion or termination of the trial, all unused trial drug and partially used trial drug must be returned to the patient's retail pharmacy for proper disposal.

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, patient, medical representative, regulatory agency, Partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a Medical Device or Medicinal Product after it is released for distribution to a clinical trial.

Examples include, but are not limited to, communications involving:

- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Bottle defects (eg, under-fill, over-fill, no safety seal)
- 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 notify the sponsor (or sponsor's designee) by telephone or email within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Report all PQCs by calling 1-877-341-9245 or by sending PQC reporting information to the OPCI Medical Information mailbox email: OCPI-MedInfo@otsuka-ca.com.
- Also indicate whether or not the complaint sample is available for return.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, patient, 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
- Was any patient at risk due to the identified issue?

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 sponsor will provide return instructions, when applicable.

6.2.5.4 Assessment/Evaluation

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

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

6.4 Patient Compliance

There will be a question in the patient's daily diary asking the patient if they have taken their daily medication. Sites and investigators will assess compliance with patients at the scheduled visits. The actual start and finish dates for each dose strength of trial drug administered will be recorded on the CRF. Information regarding any inappropriately administered dose will also be documented on the CRF.

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Patients will be required to comply with medication restrictions outlined in Section 6.5.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (including prescription medications, over-the-counter medications, herbal remedies, etc.) and therapies taken by the patient from the time of signing the ICF through the end of the evaluation period (defined as the time period during which patients are evaluated for primary and/or secondary objectives) in the CRF. The investigator will also record all medications and therapies taken by the patient for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the CRF.

The clinical site will record all concomitant medications taken 30 days prior to baseline in the CRF, including the ADT for the patient's current MDE.

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

6.5.1 Prohibited Medications or Therapies

Concomitant medications that are contraindicated in the Canadian Product Monograph[5] are prohibited in this trial. In addition, benzodiazepines and/or hypnotics (including non-benzodiazepine sleep aids) should not be ingested within 8 hours prior to a scheduled visit due to the possibility of impacting efficacy assessments.

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, Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

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

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7.3 Individual Patient Discontinuation

7.3.1 Treatment Discontinuation

After the baseline visit, a patient may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a patient for any reason or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. If a patient discontinues treatment, their participation in the trial will be discontinued. Discontinued patients should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the patient is withdrawn.

7.3.2 Documenting Reasons for Treatment Interruption or Discontinuation

Brief treatment interruptions/periods of non-adherence will be allowed and managed according to the clinical judgment of the investigators.

A patient may discontinue trial drug for the reasons listed below:

- Adverse event
  - Patient decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing trial drug places the patient at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to trial drug)
    - Serious adverse event (SAE)
    - Other potentially trial drug-related safety concerns or AEs
- Death
- Failure to meet continuation criteria
- Lack of efficacy
- Lost to follow-up
- Noncompliance with trial drug
- Physician decision
- Pregnancy (see Section 10.2)
- Protocol deviation
- Protocol-specific withdrawal criterion met
- Site terminated by sponsor
- Trial terminated by sponsor
- Technical problems
- Withdrawal by patient

- Other

If the patient discontinues trial drug 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 must be followed.

7.3.3 Withdrawal of Consent

Each patient has the right to withdraw their consent from further participation in the trial at any time without prejudice. Patients can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator can also discontinue a patient's participation in the trial at any time if medically necessary. Unless the patient provides their written withdrawal of consent or there is other written documentation by the investigator confirming the patient's verbal intent to completely withdraw from the trial, patients should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a patient'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 a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by patient and trial site staff).
- Contact of the patient by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical 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 patient'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 patient's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the patient and the integrity of the trial. A patient may initially express their desire to discontinue trial drug administration, which

is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.1). A patient 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 7.3.2 to determine if the patient can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated (Section 6.1). Only patients who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4 Definition of Patients Lost to Follow-up

Patients who cannot be contacted on or before the Week 8 visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the patient, medical records, successful telephone contact with the patient, statement by a family member or primary care physician, or public records).

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

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

8 Trial Procedures

Individual participation for patients who complete the trial without early withdrawal will consist of a 14-day screening period and an 8-week outpatient treatment period.

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

8.1 Efficacy Assessments

Where possible, sites should follow the order of efficacy assessments and patient reported outcomes as listed below and in Table 1.3-1.

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8.1.1 Inventory of Depressive Symptomatology Self-Report (IDS-SR)

The IDS-SR[9] is a 30-item self-report measure used to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of MDD (see Section 9.3 for more details). Symptom severity is rated using the following scale: 0-13: None, 14-25: Mild, 26-38: Moderate, 39-48: Severe, and 49-84: Very severe. The investigator or designated trial personnel should encourage patients to complete this instrument completely and legibly.

8.1.1.1 IDS-SR-10-Engagement

The IDS-SR-10-engagement consists of selected 10 item scores, including the following 10 items for the co-primary endpoint (clinician-selected): item 8 - Response of your mood to good or desired events, item 15 - Concentration/decision making, item 16 - View of myself, item 17 - View of my future, item 19 - General interest, item 20 - Energy level, item 21 - Capacity for pleasure or enjoyment (excluding sex), item 22 - Interest in sex (please rate interest, not activity), item 23 - Feeling slowed down, and item 29 - Interpersonal sensitivity. The IDS-SR-10-engagement will be determined based on these 10 items as described in Section 9.3.

IDS-SR patient-selected engagement items will be included in the other efficacy endpoint analysis and the exploratory endpoint analysis. Details will be provided in the statistical analysis plan (SAP).

8.1.2 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a standardized, self-administered rating scale that assesses the severity of depressive symptoms. The scale consists of 9 items, representing the 9 criteria upon which the diagnosis of DSM-5 depressive disorders is based. A higher score on the PHQ-9 represents a higher severity of depressive symptoms.

8.1.3 Generalized Anxiety Disorder-7 (GAD-7)

The Generalized Anxiety Disorder 7-item (GAD-7) scale is designed to assess anxiety in patients. The scale contains 7 items and each item is rated from 0 (not at all) to 3 (nearly every day). The score ranges from 0 to 21. A higher score on the GAD-7 represents greater anxiety symptomatology.

8.1.4 World Health Organization Disability Assessment Schedule 2.0 (WHODAS) Short Form Questionnaire

The World Health Organization Disability Assessment Schedule (WHODAS) 2.0 short form[10] is a 12-item self-assessment questionnaire to assess a patient's activity limitations

and participation restrictions (ie, disability) across 6 domains of life: cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating, staying alone), getting along (interacting with others), life activities (domestic responsibilities, leisure, work and school), and participation (community and society).

8.1.5 Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS)[11,12] is a self-rated instrument used to measure the effect of the patient's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0 = not at all, to 10 = extremely. For the work/school item, no response was to be entered if the patient did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS Score will be calculated over the three item scores. All three item scores need to be available with the exception of the work/school item score when this item is not applicable.

8.1.6 Clinical Global Impression - Severity of Illness (CGI-S)

The severity of illness for each patient will be rated using the Clinical Global Impression - Severity (CGI-S) scale.[13] 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 patient 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 patients.

8.1.7 Clinical Global Impression - Improvement (CGI-I)

The efficacy of trial treatment will be rated for each patient using the Clinical Global Impression - Improvement (CGI-I) scale.[14] The rater or investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

8.1.8 Word of the Day

The "Word of the Day" is a word contained in a previously-generated list of meaningful words that has been developed through patient interviews. Words in this list have been

assigned a valence (ie, positive, negative, or neutral) and will be selected by patients to best describe how the patient has felt that day.

8.1.9 Patient Global Impression - Severity (PGI-S)

The Patient Global Impression – Severity (PGI-S) scale is a 7-point single-item self-report scale for the patient to rate the severity of symptoms of MDD. Patients answer the following question: "Taking into account all of your symptoms, how severe is your Major Depressive Disorder at this time?" Scores range from 1 "no symptoms" to 7 "very severe."

8.1.10 Patient Global Impression - Improvement (PGI-I)

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

8.2 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.3.

8.2.1 Physical Examination

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

The investigator or designee is primarily responsible for performing the physical examination and the extent of the physical examination will be at the discretion of the investigator. Whenever possible, the same individual should perform all physical examinations for any individual patient. Any clinically significant condition present at a post treatment physical examination that was not present at the baseline physical examination should be documented as an AE and followed to a satisfactory conclusion.

Body height and weight will also be measured during screening for calculation of body mass index (BMI) and weight will be measured at baseline and at Weeks 2, 4, and 8/ET. Where screening and baseline visits occur on the same day, assessments will not be duplicated.

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8.2.2 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1). Patients should be monitored for potentially clinically significant vital signs values (Section 10.3).

Vital signs will include systolic and diastolic blood pressure and heart rate. At each time point for vital signs, blood pressure (systolic and diastolic) and heart rate will be taken after patients have been in the seated position for at least 5 minutes. If the patient has any symptoms suggestive of orthostatic hypotension, the sitting and standing vital signs can be performed at the investigator's discretion.

8.2.3 Suicidality Monitoring

A suicidality assessment will be conducted using the PHQ-9 suicidality item and/or as per the trial site's standard operating procedures (SOPs). If the PHQ-9 indicates suicidal ideation (eg, a patient has suicidality on item 9 of the PHQ-9 scale [≥ 1] and/or IDS item 18 ≥ 3), then clinical evaluation of suicidality is essential on that particular visit and the investigator will conduct a more in-depth clinical assessment of the patient per the site's SOPs.

8.3 Adverse Events

8.3.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial patient administered a trial drug 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 a trial drug related to any dose administered.

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

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

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A serious AE (SAE) includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the patient 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 patient 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 (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Lack of efficacy cases should be evaluated for unusual failure in efficacy (UFIE) and must be reported in an expedited fashion.
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate trial drug discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the patient or the partner of the patient. Pregnancy will only be documented on the AE CRF if the pregnancy occurs in a female patient and there is an abnormality or complication. Please refer to Section 10.2 for contraceptive guidance and collection of pregnancy information.

Clinical Laboratory Test Value Changes: Clinical laboratory assessments will be conducted at the investigator's discretion to ensure safety of the patient. However, aside

from the urine pregnancy test at screening, ongoing clinical laboratory assessments are not required for this trial. In the event that the investigator orders a laboratory test in the interest of patient safety, it is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is abnormal (eg, clinically significant) for that individual patient. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the CRF. The severity of an AE 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.

Trial Drug Causality: Assessment of causal relationship of an AE to the use of the trial drug is defined as follows:

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

8.3.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess patients for the occurrence of AEs. To avoid bias in eliciting AEs, patients should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the patient must be recorded on the source documents and CRF provided by the sponsor. Adverse event collection will begin after a patient signs the ICF, and will continue until the Week 8/ET visit. All AEs must be reported after patient informed consent has been obtained, including screening failures due to AEs, irrespective of trial drug administration.

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.

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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 8.3.3. Special attention should be paid to recording hospitalization and concomitant medications.

The adverse event, start date and time, end date and time, seriousness, severity, relationship to trial treatment (trial drug causality), action taken with trial treatment, and outcome will be recorded on the source documents and in the CRF.

8.3.3 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, UFIE, 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 CRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.3.5.2.

8.3.4 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.3.5 Follow-up of Adverse Events

8.3.5.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE CRF 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 the CRF. 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).

8.3.5.2 Follow-up of Immediately Reportable Events

This trial requires that patients be actively monitored for IREs up to the Week 8/ET visit.

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Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE CRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a patient'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 CRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.3.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the patient and will provide prompt updates on the patient's status to the sponsor. The investigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- The patient is lost to follow-up, or
- Has died.

Resolution means that the patient has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the patient'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 patient is lost to follow-up, or has died.

Refer to Section 10.2 for additional information regarding the follow-up period for patients that become pregnant or for pregnant partners of male patients.

8.3.5.3 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 trial drug, should be reported to the sponsor according to the procedures outlined in Section 8.3.3. 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 patient is lost to follow-up or has died.

9 Statistical Considerations

9.1 Sample Size

This is a single-arm trial to assess the effect of brexpiprazole on patient engagement in MDD patients through the following co-primary endpoints: 1) change from baseline to

Week 8 in IDS-SR-10-engagement; 2) change from baseline to Week 8 in IDS-SR Total score.

Based on the results of the appropriate brexpiprazole-plus-ADT arms from four previous Phase 2/3 brexpiprazole MDD trials, it is reasonable to expect a mean change of -2.5 (standard deviation = 6.5) in IDS-SR-10-engagement and a mean change of -5 (standard deviation = 13.5) in IDS-SR Total score from baseline to Week 8. A sample size of 100 completers (ie, patients who have an evaluation on IDS-SR Total score and IDS-SR-10-engagement at Week 8) will yield 95% power to show a difference from baseline in IDS-SR Total score and at least 95% power to show a difference from baseline in IDS-SR-10-engagement at a two-sided significance level of 0.05, respectively. It will ensure the overall power is at least 90%. After considering an ET rate of 25%, a total of 134 patients need to be enrolled in this trial.

9.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: comprises all patients who signed an ICF for the trial and enrolled into the open-label treatment phase.

Safety Sample: comprises all enrolled patients who received at least one dose of open-label brexpiprazole.

Efficacy Sample: the Full Analysis Set comprises all patients in the Safety Sample who have a baseline value and at least one post-baseline efficacy evaluation for IDS-SR Total score and IDS-SR-10-engagement during the open-label treatment phase.

9.3 Handling of Missing Data

IDS-SR is utilized as the primary efficacy measurement to assess core diagnostic depressive symptoms as well as the atypical and melancholic symptom features of MDD. The IDS-SR consists of 30 items, all rated on a 0 to 3 scale with 0 being the “best” rating and 3 being the “worse” rating. Besides item 9, two sub-items 9A and 9B exist, with possible scores of 1, 2 or 3 for item 9A, and 0 or 1 for item 9B. The scores for these two sub-items are not included in the calculation of the total score. Item 11 or item 12 should be completed but not both, and similarly, item 13 or item 14 should be completed but not both. Should items 11 and 12 be rated both, then the maximum of the two scores will be used. The same approach will be used for handling items 13 and 14.

The IDS-SR Total Score is the sum of ratings of 28 item scores. The possible IDS-SR Total Score ranges from 0 to 84.

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The IDS-SR-10-engagement is the sum of ratings of the selected 10 item scores, including item 8 - Response of your mood to good or desired events, item 15 - Concentration/decision making, item 16 - View of myself, item 17 - View of my future, item 19 - General interest, item 20 - Energy level, item 21 - Capacity for pleasure or enjoyment (excluding sex), item 22 - Interest in sex (please rate interest, not activity), item 23 - Feeling slowed down, and item 29 - Interpersonal sensitivity. The possible IDS-SR-10-engagement ranges from 0 to 30.

The mixed model repeated measure (MMRM) method assumes data are missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials in MDD.[15] However, the possibility of "missing not at random" (MNAR) data can never be ruled out. Sensitivity analyses based on MNAR will be performed and details will be provided in the SAP.

The observed cases (OC) data set will consist of actual observations recorded at each scheduled visit during the open-label treatment phase, and no missing data will be imputed. MMRM and sensitivity analyses based on MNAR will be performed on the OC dataset. The last observation carried forward (LOCF) approach will also be used to impute missing data for continuous and categorical efficacy endpoints. The LOCF data set will include data recorded at a scheduled visit during the open-label treatment phase or, if no observation is recorded at that visit, data carried forward from the previous scheduled visit at the open-label treatment phase. Baseline data will not be carried forward to impute missing values for the LOCF data set.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The co-primary efficacy endpoints are as follows:

1) Change from baseline to Week 8 in IDS-SR-10-engagement.
2) Change from baseline to Week 8 in IDS-SR Total score.

The primary hypothesis is that the mean changes from baseline to Week 8 in both co-primary endpoints will differ from 0, separately. Each of the endpoints will be tested by fitting a MMRM analysis with an unstructured variance covariance structure at a two-sided significance level of 0.05 on OC dataset on Efficacy Sample. The model will include fixed effect terms for visit, baseline value, an interaction term of baseline value

by visit, and trial center. The trial will be claimed positive if both p-values are less than 0.05. Therefore, the overall type I error is controlled at 0.05 level.

In case there is a convergence problem with MMRM model with the unstructured variance covariance matrix, the following structures other than unstructured will be used in order of 1) heterogeneous Toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. Details will be provided in SAP.

One-sample Wilcoxon signed rank test will also be performed for each endpoint in case that the normality assumptions are violated.

9.4.1.2 Control of Experiment-wise Type I Error

Each of the co-primary endpoints will be tested by fitting a MMRM analysis at a two-sided significance level of 0.05 on OC dataset on Efficacy Sample, and the trial will be claimed positive if both p-values are less than 0.05. Therefore, the overall type I error is controlled at 0.05 level.

9.4.1.3 Other Efficacy Endpoint Analysis

The other efficacy endpoints are as follows. All of them will be evaluated at a nominal 0.05 level (2-sided) without adjusting for multiplicity on Efficacy Sample:

1) Change from baseline to Weeks 2 and 4 in IDS-SR-10-engagement.
2) Change from baseline to Weeks 2 and 4 in IDS-SR Total score.
3) Change from baseline to Weeks 2, 4, and 8 in IDS-SR patient-selected engagement items.
4) Change from baseline to Weeks 2, 4, and 8 in IDS-SR engagement items selected by both clinicians and patients.
5) Change from baseline to Weeks 2, 4, and 8 in CGI-S score.
6) CGI-I score at Weeks 2, 4, and 8.
7) Change from baseline to Weeks 4 and 8 in SDS Mean score and SDS individual item scores.
8) Change from baseline to Weeks 4 and 8 in WHODAS 2.0 short form score.
9) Change from baseline to Weeks 2, 4, and 8 in PHQ-9 score.
10) Change from baseline to Weeks 2, 4, and 8 in GAD-7 score.
11) Change from baseline to each timepoint (ie, being measured weekly at home) in depression as measured by PGI-I score.

12) PGI-I response rate at each timepoint (ie, being measured weekly at home), where response is defined as a PGI-I score of 1 or 2 (very much improved or much improved).
13) Time to first PGI-S response, where response is defined as a reduction of 2 points in PGI-S score from baseline.

Endpoint (1) - (5), (7) - (11) will be analyzed by fitting the same MMRM model described in the primary analysis on OC dataset. Endpoint (6) will be analyzed using one-sample t-test on LOCF dataset. Endpoint (12) will be evaluated using descriptive statistics on LOCF dataset. Endpoint (13) will be evaluated by time-to-event analysis with Kaplan-Meier curve on OC dataset.

[redacted]

9.4.2 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics (including age, weight, BMI, sex, race, and ethnicity) for Enrolled Sample will be summarized using descriptive statistics (frequency,

mean, median, standard deviation (SD), maximum, minimum, and percentage when applicable).

9.4.3 Safety Analysis

Safety analysis will be performed on the Safety Sample. Safety variables of interest mainly include AEs, body weight, BMI, and vital signs.

9.4.3.1 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 descriptive statistics:

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

Adverse event data will also be presented in listings.

9.4.3.2 Physical Examination and Vital Signs Data

Physical examination data will be presented in a listing.

Descriptive statistics will be used to summarize body weight and BMI at screening, baseline, and Weeks 2, 4, and 8/ET. The incidence of potentially clinically significant changes in body weight will be tabulated in incidence tables.

Descriptive statistics for changes from baseline in vital signs will also be provided. Potentially clinically significant results in vital signs will be summarized.

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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, applicable ICH GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the CRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting patient privacy. To this end, a patient ID will be used to identify each patient.

Financial aspects, patient 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 patients (or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB/IEC that approves this protocol.

Each ICF will comply with the International Council for Harmonisation (ICH) GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial before submission to the IRB/IEC. Trial sites will have patients review and sign the ICF prior to starting any trial procedures.

Investigators may discuss trial availability and the possibility for entry with a potential patient 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 patients 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 patients will be provided with study protocol information by the trial site staff. When the trial site staff and the patient agree that the patient has enough

information to make an informed decision to participate, the patient will sign the ICF. The patient will be given a printed, signed copy of the ICF. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign the 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 patient by the investigator (or a qualified designee), and it has been documented that the patient has had the opportunity to ask questions, the IRB/IEC-approved ICF will be signed and dated by both the patient and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The patient will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

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

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Patient confidentiality requirements of Canada 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 and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Patients will be identified only by unique patient ID in the CRF. If further patient identification is required, patients' full names may be made known to a regulatory agency or other authorized officials if necessary, patient 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 applicable ICH GCP guidance, and applicable

regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and 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, trial drug supply, presence of required documents, the informed consent process, site operations, delegation of authority and training, and a review of the CRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, patient dosing error, patient 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 patient'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 the CRF 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, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

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

10.1.6.2 Data Collection

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

Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the patient visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications.

Source data will be source data verified by the trial clinical research associate, and the location of the source data (ie, 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, right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Remote monitoring and on-site monitoring will take place in order to review data entry source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess 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 source system are complete and accurate. After database lock, the investigator will receive an electronic copy of the patient data. Additional details for data collection will be provided in the Operations Manual.

10.1.6.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

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

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if trial drug development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the 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 patient to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.6.5 Publication Authorship Requirements

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

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

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

Investigators or other trial patients 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 patients consent to such acknowledgement in any publications resulting from its conduct.

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10.2 Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of nonchildbearing potential do not meet definition of FOCBP.

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the patient 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 trial drug. Unless the patient is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) or remains abstinent during the trial and for 30 days after the last dose of trial drug, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, 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 the CRF or source document. Male patients must also agree not to donate sperm from trial screening through 30 days after the last dose of trial drug.

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
- ICF
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

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

A urine pregnancy test for human chorionic gonadotropin will be performed at screening and baseline on all FOCBP.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male patients 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 patient is suspected to be pregnant before she receives trial drug, the trial drug administration must be withheld. If the pregnancy is confirmed, the patient must not receive the trial drug and must not be enrolled in the trial. If pregnancy is suspected while the patient is taking trial drug, the trial drug 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 trial drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for patient safety) and the patient 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 trial drug exposure during the trial and for at least 30 days after the last dose of trial drug, 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 patient unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.3 Appendix 3: Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 100 bpm < 50 bpm	≥ 10 bpm increase ≥ 10 bpm decrease
Systolic blood pressure[b]	≥ 140 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure[b]	≥ 90 mmHg < 60 mmHg	≥ 10 mmHg increase ≥ 10 mmHg decrease
Weight	–	≥ 7% increase ≥ 7% decrease

bpm = beats per minute; mmHg = millimeter of mercury.

[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 patient'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," Food and Drug Administration Division of Neuropharmacological Drug Products draft (2/27/87).

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10.4 Appendix 4: Protocol Amendments

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

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

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[redacted]

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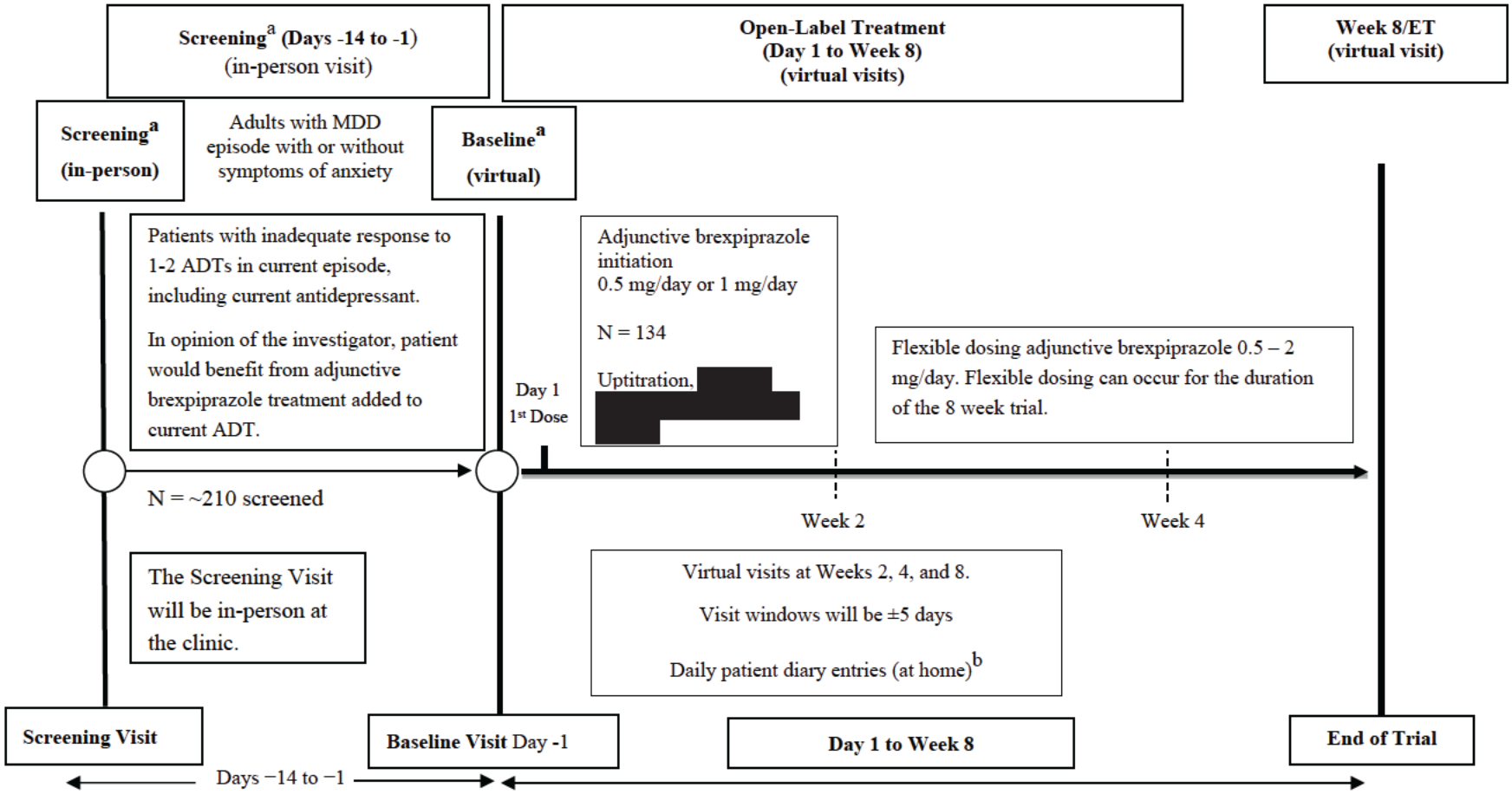
10.5 Appendix 5: Trial Continuity Plan

10.5.1 Trial Continuity Plan Appendix

All procedures and assessments in the main body of the protocol are to be followed to the fullest extent possible. In the event that the ability to conduct the trial (ie, perform specified procedures and assessments) is impacted by extenuating circumstances (eg, pandemic, natural disaster, national or international conflict), the sponsor, in coordination with the site, investigator(s), and medical monitor, may implement the trial continuity measures provided in this appendix.

10.5.1.1 Trial Design Schematic - Trial Continuity



[a]The screening visit can comprise 1 or more visits as needed. The screening and baseline visits can occur the same day if the patient meets all required enrollment criteria.

[b]Patient diary entries will be reduced in frequency from daily to twice weekly from the day after the Week 4 visit to Week 8 (word of the day and PGI-S).

Figure 10.5.1.1-1 Trial Design Schematic - Trial Continuity

10.5.1.2 Schedule of Assessments - Trial Continuity

Table 10.5.1.2-1 Schedule of Assessments - Trial Continuity

Assessment	Visit				
	Screening[a] (Days -14 to -2) (in-person visit)	Baseline[a] (Day -1)	Week 2	Week 4	Week 8 /ET[b]
		virtual visits (± 5 days)			
ENTRANCE/HISTORY					
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demography	X				
Medical history	X				
Psychiatric history	X				
Prohibited medication washout[c]	X				
Urine pregnancy test	X	X			
EFFICACY[d]					
IDS-SR (patient reported)		X	X	X	X
PHQ-9 (patient reported)[e]	X	X	X	X	X
GAD-7 (patient reported)		X	X	X	X
WHODAS 2.0 short (patient reported)		X		X	X
SDS (patient reported)		X		X	X
CGI-S		X	X	X	X
CGI-I			X	X	X
SAFETY					
Brief physical examination[f]	X				X
Height and body weight[g]	X	X	X	X	X
Vital signs[h]	X	X		X	X
Adverse events	X	X	X	X	X
Concomitant medications[i]	X	X	X	X	X
Clinical evaluation for suicidality[e]	X	X	X	X	X

Table 10.5.1.2-1 Schedule of Assessments - Trial Continuity

Assessment	Visit				
	Screening[a] (Days -14 to -2) (in-person visit)	Baseline[a] (Day -1)	Week 2	Week 4	Week 8 /ET[b]
		virtual visits (± 5 days)			
OTHER					
Trial drug prescribed[j]		X	X	X	
Trial drug accountability (patient reported)			X	X	X
Review of Patient Diary (word of the day, PGI-S, and PGI-I)[k]		X	X	X	X

ADT = antidepressant therapy; CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression - Severity; ET = early termination; GAD-7 = Generalized Anxiety Disorder 7-item scale; ICF = informed consent form; IDS-SR = Inventory of Depressive Symptomatology Self-Report; PGI-I = Patient Global Impression – Improvement; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire 9-item scale; SDS = Sheehan Disability Scale; WHODAS = World Health Organization Disability Assessment Schedule.

[a]Brexpiprazole dosing will take place on Day 1 of Week 1. The screening visit can comprise 1 or more visits as needed. Screening and baseline visits can occur the same day if the patient meets all required enrollment criteria. Where screening and baseline visits occur on the same day, assessments will not be duplicated. The Screening Visit will be an in-person visit at the clinic. All other visits will be virtual.

[b]If a patient discontinues prematurely before Week 8, every effort should be made to complete the "Week 8/ET" evaluations.

[c]Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods.

[d]Where possible, sites should follow the order of efficacy assessments and patient reported outcomes as listed.

[e]If the PHQ-9 indicates suicidal ideation (eg, a patient has suicidality on item 9 of the PHQ-9 scale [≥ 1]), then clinical evaluation of suicidality is essential on that particular visit and the investigator will conduct a more in-depth clinical assessment of the patient per the site's standard protocol.

[f]The extent of the physical examination will be at the discretion of the investigator.

[g]Height and body weight at screening and body weight at baseline and at Weeks 2, 4, and 8/ET. When screening and baseline visits occur on the same day, assessments will not be duplicated.

[h]Vital signs include systolic and diastolic blood pressure and heart rate.

[i]All medications taken within 30 days of informed consent will be recorded. In addition, all prescription and non-prescription medications taken during the trial will be recorded as concomitant medications. All ADTs taken within 12 months of informed consent will be recorded.

[j]Trial drug will not be prescribed at the Week 8 visit. The ADT regimen will be left to the discretion of the investigator.

[k]Patient diary entries will be reduced in frequency from daily to twice weekly from Week 5 to Week 8 (word of the day and PGI-S). The PGI-I will be administered weekly throughout the trial.

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10.5.2 General Considerations

10.5.2.1 Telemedicine

Sites should collect information from subjects via phone or video in a standardized approach to minimize confusion and risk of errors that could occur from utilizing varying collection strategies. All applicable guidances and local regulations will be followed when implementing telemedicine options.

10.5.2.2 Reconsent

If there is an immediate need to reconsent subjects to maintain trial continuity, a paper reconsent process may be followed and sites are encouraged to contact the CRO and sponsor with questions. In regions where remote capacity exists to collect remote consent, information will be provided by the CRO and sponsor.

10.5.2.3 Protocol Deviations

Deviations from this Trial Continuity Plan, once implemented, must be recorded by the site in the source system separately from other protocol deviations as soon as they are identified and will be recorded as “Other” in the source system for data capture purposes. Sites will be instructed to indicate “Trial Continuity:” at the start of the description field for the “Other” protocol deviation. Examples of the types of trial continuity-related deviations to be reported include: missed visits, missed assessments, assessments performed remotely (completed outside of protocol procedure), missed IMP dose, IMP dispensed/returned via courier, IMP not returned to site/site unable to verify medication compliance, out of window visits, changes in rater, and prohibited concomitant medication. All other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

10.5.2.4 Guidance to Record Adverse Events and Discontinuations Due to Extenuating Circumstances

If a subject experiences an AE as a direct result of the extenuating circumstances, the reason will be recorded in the source system. Subjects who experience an AE as a direct result of the extenuating circumstances must be reviewed with the medical monitor and approval must be received for the subject to continue in the trial with remote visits. Experiencing such an AE is not automatically an SAE, unless an SAE criterion is met (eg, hospitalization). If the event meets the criterion for an SAE, then the subject will be discontinued from the trial.

Upon implementation of this appendix, the criteria that require consideration for the appropriateness of subject continuation in the trial will be determined by the sponsor in

coordination with the sites, investigator(s), and medical monitor. The medical monitor will be consulted for consideration of individual subjects that meet those criteria.

10.5.2.4.1 Novel Coronavirus 19 (COVID-19)

An AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result" must be recorded on the AE page in the source system if a subject tests positive OR is presumed positive with COVID-19. The subject may continue in the trial with remote visits only as long as they remain asymptomatic for COVID-19. Subjects who are symptomatic for COVID-19 must be reviewed with the medical monitor and approval must be received for the subject to continue in the trial with remote visits. A positive test result or a presumed positive subject is not automatically an SAE, unless an SAE criterion is met (eg, hospitalization). If the event meets the criterion for an SAE, then the subject will be discontinued from the trial.

10.5.2.5 Statistical Analyses

Any impact of changes made to maintain trial continuity on the planned statistical analyses for the trial will be described in the final SAP.

10.5.2.6 Clinical Outcomes

To decrease variability, sites should attempt to standardize the method of administering a scale to an individual subject and across all subjects in the trial. Assessments should be administered by the same qualified/trained rater who previously rated the subject; if this is not possible due to staff availability and/or technological limitations, discuss relevant information with previous raters to obtain clinical context (note that per protocol raters must be trained/qualified to conduct assessments in all cases). Raters should conduct all assessments for that visit during the same remote session, where possible.

Please refer to guidance provided to clinical sites regarding the administration methods for remote visits.

10.5.3 Trial Procedures

10.5.3.1 Safety Assessments

10.5.3.1.1 Vital Signs

Blood pressure, heart rate, and weight will all be measured as described in the protocol at the time points defined in this Schedule of Assessments - Trial Continuity (Table 10.5.1.2-1) with the following changes, if remote visits are necessary:

- Subjects will be asked to use their own collection device, if available, until devices can be provided to subjects;

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  - Site staff will remotely supervise the collection of measurements via video or guide by telephone, if video is not possible.
  - All remote measurements should be performed at a consistent time of day.
  - Site staff will be instructed to record the measurement in the source system, and if there are believed to be any errors, inconsistencies, or safety concerns with the home measurement, the medical monitor should be notified.
- Site staff will instruct the subjects to follow the procedures in the protocol for blood pressure and heart rate collection.

10.5.3.1.2 Pregnancy

Pregnancy tests will be performed as described in the protocol at the time points defined in this Schedule of Assessments - Trial Continuity (Table 10.5.1.2-1) with the following changes:

- For the baseline visit that requires a pregnancy test for FOCBP, the site will provide the necessary tests and instructions so the test may be performed at home;
- Applicable subjects will perform a pregnancy test prior to dosing with IMP, ensuring a date and time-stamped picture or video of the result is taken, followed by notification to the site staff of the results via telephone, or other means, on the appropriate visits. Subjects will also provide the site staff with the date- and time stamped picture/video.
  - If negative, site to inform subject to proceed with dosing.
  - If positive, the site must instruct the subject to immediately stop taking IMP, and the site will refer to the Pregnancy section of the protocol for appropriate IRE reporting.
    - Further instruction must be agreed upon in consultation with the sponsor.

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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, 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 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB/IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on CRF 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 patients screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to patients, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all patients 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

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SIGNATURE PAGE

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Document Number: [redacted]

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