Official Title:	A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Adult Subjects With Borderline Personality Disorder
NCT Number:	NCT04186403
Document Date:	Statistical Analysis Plan Final Version: 20 September 2021

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

Brexpiprazole (OPC-34712)

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

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

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

Statistical Analysis Plan

Version: Final

Date: September 20, 2021

CONFIDENTIAL – PROPRIETARY INFORMATION

Table of Contents

List of In-text Tables

List of In-text Figures

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of study 331-201-00195. All amendments and addendums to the protocol are taken into consideration in developing this SAP. In addition, if the analyses described in the protocols differ from those in this SAP, the methods of the SAP prevail.

2 Study Objectives

Primary Safety: To evaluate the safety and tolerability of brexpiprazole for the treatment of subjects with a diagnosis of BPD.

3 Trial Details

3.1 Study Design

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

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

The trial will be organized as follows:

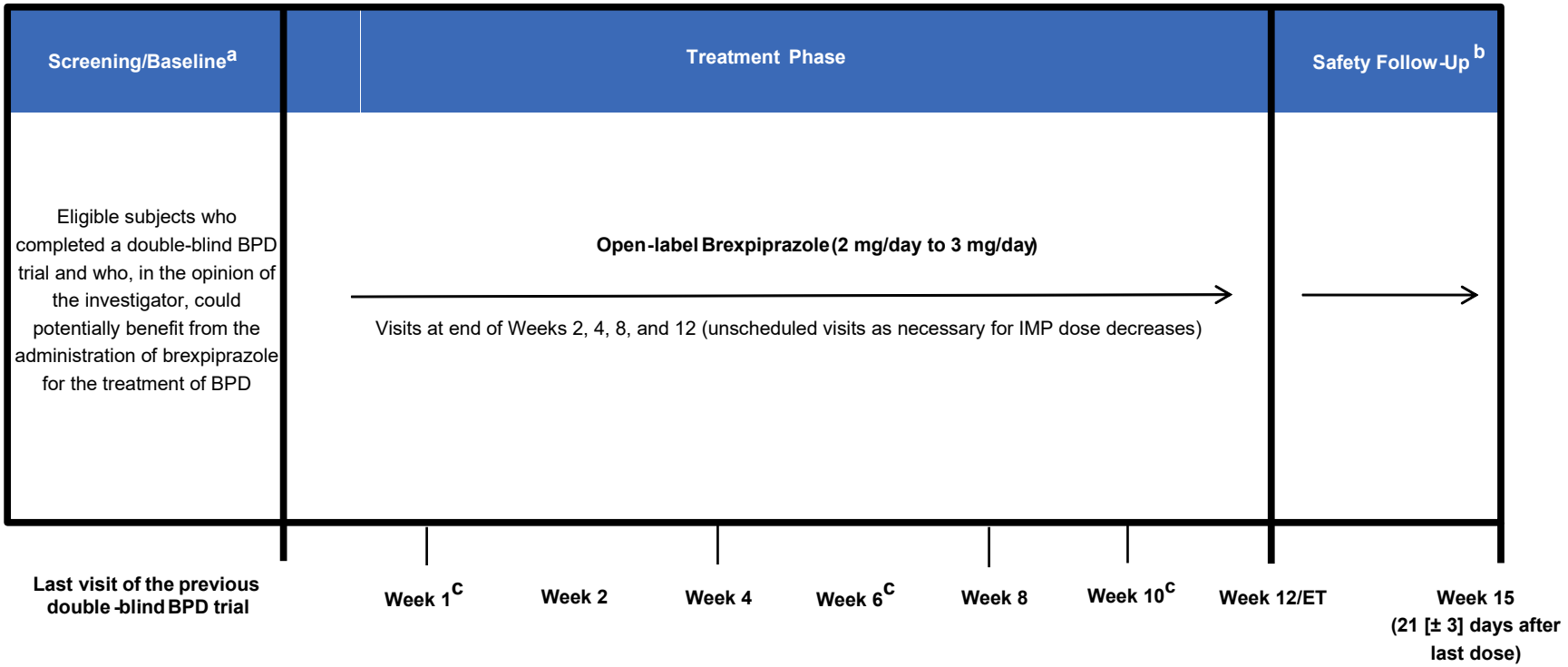
Screening/Baseline: Subjects will be screened for eligibility at the last scheduled treatment visit of the previous double-blind trial. Subjects will sign a separate informed consent form (ICF) at the last scheduled treatment visit of the previous double-blind trial for participation in this trial before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

Due to COVID-19, delayed entry subjects are permitted to be screened for Trial 331-201-00195 up to 90 days after completing the last scheduled treatment visit of the previous double-blind BPD trial (discussion with the medical monitor is required if > 90 days have passed). These subjects will be screened for eligibility at a separate screening visit for Trial 331-201-00195, where they will undergo full assessments to determine eligibility. The screening period will be up to 21 days and may be extended upon discussion with the medical monitor. The delayed entry subjects will also undergo a separate baseline visit, and the assessments from that visit will serve as the baseline measures for Trial 331-201-00195. Delayed entry subjects will receive the first dose of IMP at the baseline visit.

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

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

See Figure 3.1-1for a schematic of the trial design.



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

[b]Telephone contact or clinic visit.

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

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

The first dose of open-label brexpiprazole will be taken one day after the last dose of double-blind IMP is taken for the previous double-blind, brexpiprazole BPD trial so that treatment continues without interruption. It is anticipated that the last dose of IMP of the double-blind trial will be taken the day of the treatment last visit of the previous double-blind brexpiprazole BPD trial (i.e., the day of the screening/baseline visit for the open-label trial). If a subject is unable to rollover immediately, up to 3 days may be permitted between the end of the double-blind trial and the start of IMP in the open-label extension trial; however, this must be discussed with the medical monitor. Delayed entry subjects will receive the first dose of IMP at the baseline visit.All subjects will receive a starting dose of 1 mg/day at the screening/baseline visit, followed by an increase to 2 mg/day at the end of Week 1 (Table 3.2-1). Subjects may increase their dose to 3 mg/day at the investigator's discretion on or after the Week 2 visit, depending on treatment response and tolerability. Subjects taking 3 mg/day may down-titrate to 2 mg/day based on tolerability at any time during the course of the trial. Subjects unable to tolerate 2 mg/day will be discontinued from the trial. Dose adjustments to brexpiprazole must be made in increments of 1 mg/day. Dose decreases for brexpiprazole can occur at unscheduled visits and dose increases for brexpiprazole can only occur at scheduled visits.

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

Table 3.2-1 Dosing Schedule

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

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

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

4 Sample Size and Power Justification

The sample size is not based on statistical power considerations but on the number of subjects rolling over from the lead-in trials. The trial population will be derived from eligible subjects

who completed the previous double-blind brexpiprazole BPD trials. The number of eligible subjects will be limited by the number of subjects enrolled into the double-blind trials.

5 Data Sets for Analysis and Missing Data

5.1 Data Sets for Analysis

The following datasets are defined for this trial:

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

5.2 Handling of Missing Data

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

6 Study Conduct

6.1 Subject Disposition, Completion Rate and Reasons for Discontinuation

Subject disposition will be summarized for the Enrolled Sample by parent study treatment group and overall.

Subject completion rate and reasons for discontinuation will be summarized for the Enrolled Sample by parent study treatment group and overall.

6.2 Treatment Compliance

Based on the Investigational medicinal product (IMP) panel of the CRF, compliance in taking IMP is calculated by dividing the number of tablets/capsules taken by the total number of

tablets/capsules the patients were scheduled to take during the study period. For lost-to-follow up patients, last IMP end date record will be used as the treatment end date.

6.3 Protocol Deviation

Protocol deviations will be summarized by center and type of deviation for enrolled subjects by parent study treatment group. A listing of protocol deviations will be provided. In addition, protocol deviations affected by the COVID-19 will be summarized. Listing of subjects with protocol deviations affected by the COVID-19 will also be provided.

7 Baseline Characteristics

7.1 Baseline Definition

Baseline is defined as the last available measurement prior to the first dose of open-label IMP in the open-label treatment phase.

7.2 Demographic Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and body mass index (BMI) will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable) for the Enrolled Sample by parent study treatment group and overall.

7.3 Medical and Psychiatric History

A summary of medical, psychiatric, and borderline personality disorder history will be presented for the Enrolled Sample (by parent study treatment group and overall).

7.4 Baseline Psychiatric Evaluation

For the Enrolled Sample, baseline psychiatric scale evaluation will be summarized by parent study treatment group and overall. The mean, median, range and standard deviation will be used to summarize the assessments of: CCI [redacted].

8 Efficacy Analysis

CCI [redacted]

CCI

8.1 COVID-19 Related Supplementary Analyses

Summary statistics for mean and mean change from baseline in CCI , by trial visit and at the last visit (i.e., Week 12/ET) and by visit type (face-to-face vs. remote) based on the Efficacy Sample will be provided by parent study treatment group for rollover subjects and overall.

9 Safety Analysis

The primary safety endpoint analysis is the frequency and severity of AEs in the open-label treatment phase (see Section 9.1). Other standard safety variables to be analyzed include clinical laboratory tests, vital signs, body weight, waist circumference, BMI, 12-lead electrocardiograms (ECGs), and physical examinations. In addition, data from the following safety scales will be evaluated: Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Columbia-Suicide Severity Rating Scale (C-SSRS).

Safety analyses will be conducted based on the Safety Sample, and summary statistics will be provided by parent study treatment group and overall, unless otherwise indicated.

Unless otherwise specified, in general, analysis of safety data will be performed on observed case and for last visit.

9.1 Adverse Events

All adverse events will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs that are sex-specific, e.g., ovarian cancer, will have their incidence rates evaluated for the specific sex.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the first dose of IMP. In more detail, TEAEs are all adverse events which started after start of IMP; or if the event was continuous from baseline and was worsening, serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy. Adverse events occurring up to 30 days after the last day of IMP will be included in the summary tables.

The incidence of the following events in the open-label treatment phase will be tabulated by treatment group and overall using the Safety Sample:

a) TEAEs

b) TEAEs by severity

c) TEAEs potentially causally related to the IMP

d) TEAEs with an outcome of death

e) Serious TEAEs

f) TEAEs leading to discontinuations of the IMP

g) AESI

The above summaries (b), (e) and (f) will also be prepared for TEAEs potentially causally related to the IMP.

In addition, incidence of TEAE during the open-label treatment phase of at least 5% by SOC and PT will be provided.

Incidence of TEAEs by SOC and PT will be summarized for sex, race, age and region subgroups.

Extrapyramidal symptoms (EPS)-related AEs will be grouped into five categories.

1) Dystonic Events, which include cervical spasm, dystonia, emprosthotonos, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle spasticity, myotonia, nuchal rigidity, oculogyration, opisthotonos, pleurothotonus, risus sardonicus, torticollis, and trismus;

2) Parkinsonian Events, which include akinesia, asterixis, athetosis, bradykinesia, cogwheel rigidity, essential tremor, extrapyramidal disorder, freezing phenomenon, gait festinating, hypertonia, hypokinesia, hypokinesia neonatal, intention tremor, masked facies, parkinson's disease, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, tremor, and tremor neonatal;

3) Akathisia Events, which include akathisia, hyperkinesia, and psychomotor hyperactivity;

4) Dyskinetic Events, which include ballismus, buccoglossal syndrome, choreoathetosis, clumsiness, dyskinesia, dyskinesia neonatal, dyskinesia oesophageal, fumbling, nodding of head, on and off phenomenon, and tardive dyskinesia;

5) Residual Events, which include chorea, Huntington's chorea, muscle twitching, and myoclonus.

Adverse Events of Special Interest

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

Unless otherwise specified, in general, analysis of safety data will be performed on observed case and for last visit.

9.2 Clinical Laboratory Tests

Summary statistics for mean and mean change from baseline in the routine clinical laboratory measurements, prolactin concentrations, coagulation parameters (PT, aPTT, and INR), HbA1c, and TSH will be provided by parent study treatment group and by visit.

Potentially clinically relevant laboratory measurement test results in the open-label treatment period will be identified for the Safety Sample and will be summarized by parent study treatment group and listed. Criteria for identifying laboratory values of potential clinical relevance are provided in Appendix 2.

9.2.1 Drug Induced Liver Injury (DILI)

Total bilirubin level should be checked for any subject with increased ALT or AST levels ≥ three times the upper normal limits (ULN) or baseline.

- Reporting all DILI as SAE to the FDA based on Hy's Law:
  - AST or ALT $\geq$ 3 x ULN or baseline and
  - T_Bili $\geq$ 2 x ULN or baseline

A separate incidence table will be provided for DILI cases, and the corresponding listing will be provided for Safety Sample during the open-label treatment period.

9.2.2 Metabolic Change

In addition to mean change from baseline, incidence of treatment emergent significant changes in fasting lipids, fasting glucose, and metabolic syndrome will be summarized by parent study treatment group using the following criteria.

Criteria for Treatment-Emergent Significant Change in Lipids and Glucose

LAB PARAMETER	BASELINE[1]	ANYTIME POST BASELINE
LDL Direct, Fasting (MG/DL)	Borderline 100-<160	High >=160
	Normal/Borderline <160	High >=160
	Normal <100	Borderline/High >=100
	Any Value	Increased >=30
HDL Cholesterol, Fasting (MG/DL)	Normal >=40	Low <40
	Any Value	Decreased >=20
Triglycerides, Fasting (MG/DL)	Normal <150	High 200-<500
	Borderline 150-<200	High 200-<500
	Normal/Borderline <200	High 200-<500
	Normal <150	Borderline/High/Very High >=150
	Any Value	Increased >=50
Glucose Fasting, Serum (MG/DL)	Normal <100	High >=126
	Impaired 100-<126	High >=126
	Normal/Impaired <126	High >=126
	Any Value	Increased >=10

[1] BASELINE IS DEFINED AS THE LAST AVAILABLE MEASUREMENT PRIOR TO THE FIRST DOSE OF OPEN-LABEL IMP IN THE OPEN-LABEL TREATMENT PHASE.

Criteria for Treatment-Emergent Metabolic Syndrome

DESCRIPTION	ANYTIME POST BASELINE[1]
Central Obesity	Waist Circumference >=102cm(MALE), >=88cm (FEMALE)
Dyslipidemia	Triglycerides >= 150mg/dl
Dyslipidemia	HDL < 40mg/dl (MALE), <50mg/dl (FEMALE)
Supine Blood Pressure	Systolic>=130mmHg and Diastolic>=85mmHg

Criteria for Treatment-Emergent Metabolic Syndrome	
DESCRIPTION	**ANYTIME POST BASELINE[1]**
Glucose Fasting, Serum	>=100mg/dl
Metabolic Syndrome	Met 3 Or More of the Above Criteria at a Visit

[1] BASELINE IS DEFINED AS THE LAST AVAILABLE MEASUREMENT PRIOR TO THE FIRST DOSE OF OPEN-LABEL IMP IN THE OPEN-LABEL TREATMENT PHASE.

9.3 Physical Examination and Vital Signs

Summary statistics for changes from baseline in vital signs will be provided for the Safety Sample. By-patient listings will be provided for physical examination.

Potentially clinically relevant vital signs measurements identified in the open-label treatment phase for the Safety Sample will be listed and summarized. Criteria for identifying vital signs of potential clinical relevance are provided in Appendix 1.

In addition, the change from baseline in weight, BMI, and waist circumference, and potentially clinically relevant abnormalities in weight, will also be summarized.

9.4 12-Lead ECG

Summary statistics and incidence of potentially clinically relevant changes will be provided for ECG parameters.

For the analysis of QT and QTc, data from three consecutive complexes (representing three consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: $QTcB=QT/(RR)^{0.5}$ and
2) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Potentially clinically relevant changes in the 12-lead ECG identified in the open-label treatment phase for the Safety Sample will be listed and summarized by treatment group. Criteria for identifying ECG measurements of potential clinical relevance are provided in Appendix 3.

Categorical changes in ECG parameters during the open-label treatment phase will be summarized based on the following criteria:

Categorical Change Criteria in QT/QTc Parameters		
Classification	**Category**	**Criteria**
QT	New Onset (> 450 Msec)	New onset (>450 msec) in QT means a subject who attains a value > 450 msec during treatment period but not at baseline.
QTc *	New Onset (≥ 450 Msec for men and ≥ 470 Msec for women)	New onset (≥ 450 Msec for men and (≥ 470 Msec for women) in QTc means a subject who attains a value ≥ 450 Msec for men or ≥ 470 Msec for women during treatment period but not at baseline.
	New Onset (≥ 450 Msec for men and ≥ 470 Msec for women) And > 10% Increase	New onset (≥ 450 Msec for men and ≥ 470 Msec for women) and > 10% increase in QTc means a subject who attains a value ≥ 450 Msec for men or ≥ 470 Msec for women, and > 10% increase during treatment period but not at baseline
	New Onset (> 500 Msec)	New onset (> 500 msec) in QTc means a subject who attains a value > 500 msec during treatment period but not at baseline.
	Increase 30 - 60 Msec	Increase from baseline value > 30 and ≤ 60 msec in QTc
	Increase > 60 Msec	Increase from baseline value > 60 msec in QTc

* QTc categorical change criteria apply to QTcB, QTcF and QTcN.

9.5 SAS, AIMS, and BARS

Change from baseline in SAS, AIMS, and BARS scales for trial visits during the open-label treatment phase using the Safety Sample will be summarized by descriptive statistics. In addition, incidence of BARS Global Clinical Assessment of Akathisia during the open-label treatment phase by severity category will be provided. Descriptive statistics will be summarized at each visit using the OC data set and at the last visit (Week 12/ET) using the LOCF data set.

9.6 Suicidality Data

Suicidality will also be monitored during the study using the C-SSRS CCI [redacted] and will be summarized as number and percentage of subjects reporting any suicidal behavior, ideation, behavior by type (4 types), ideation by type (5 types) and treatment emergent suicidal behavior and ideation. Summary will be provided for the open-label treatment phase.

Suicidality is defined as report of at least one occurrence of any type of suicidal ideation or at least one occurrence of any type of suicidal behavior during assessment period (count each person only once).

Treatment emergent suicidal behavior and ideation is summarized by four types: Emergence of suicidal ideation, Emergence of serious suicidal ideation, Worsening of suicidal ideation, Emergence of suicidal behavior.

Emergence of suicidal behavior/ideation is defined as report of any type of suicidal behavior/ideation during treatment when there was no baseline suicidal behavior/ideation.

Emergence of serious suicidal ideation is defined as observation of suicidal ideation severity rating of 4 or 5 during treatment when there was no baseline suicidal ideation.

Worsening of suicidal ideation is defined as a suicidal ideation severity rating that is more severe than it was at baseline.

9.7 Concomitant Medications

Number and proportion of patients taking concomitant medications prior to the open-label treatment phase, during the open-label treatment phase, and after study therapy are tabulated by drug classification using the WHO drug dictionary

9.8 Extent of Exposure

The start date of the open-label study therapy - brexpiprazole - will be the first day of dosing during the open-label treatment phase. The number and percentage of patients who receive study medication during the open-label treatment phase, will be presented by week. Each dosing week will be based on the actual week; i.e., Day 1-7 in Week 1, Day 8-14 in Week 2, etc. This summary will be performed on the Safety Sample.

The mean daily dosage will be summarized by week using descriptive statistics. The mean daily dosage per patient per week will be determined for each week of the study. This will be calculated by dividing the sum of individual total doses by the number of days in the week interval. The summary will contain the number of patients receiving study medication during the open-label treatment phase, and the mean and range of the mean daily dose for each week.

10 Conventions

10.1 Study Visit Windows

Study visit windows will be used to map visits using study day intervals. Observations at each scheduled visit and Early Termination will be assigned to Week 2, Week 4, Week 8 and Week 12 visits based on their visit windows as shown in Table 10.1A. This visit window convention applies to tables and listings for all efficacy and safety scales (CCI

CCI SAS, AIMS and BARS). This derived study window variable will be named as DAY and will be footnoted. In listings, it will be listed along with the CRF study visit.

Table 10.1A shows classifications for study day intervals in the open-label treatment phase. The variable "target day" is defined using the number of days since the start of open-label brexpiprazole dosing. The first day of open-label brexpiprazole dosing is defined as "Day 1".

If more than one observation falls within a particular study day interval, then the last observation within that interval is used. Evaluations occurring more than 7 days after the last open-label brexpiprazole dosing date will not be mapped into study visit windows, and will be excluded from the analysis.

Table 10.1A: Study Day and Visit Windows in the Open-label Treatment Phase

Week	Target Day [a]	Study Day Interval [a]
2	14	2-21
4	28	22-42
8	56	43-70
12	84	71-91 [b]

[a] Relative to the first day of open-label brexpiprazole in the open-label treatment phase.

[b] Evaluations occurring more than seven days after the last dosing date of open-label brexpiprazole in the open-label treatment phase will be excluded from the efficacy analyses.

10.2 Scales: Rules for Scoring and Handling of Missing Data

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

10.2.9 SAS

The SAS will be used to evaluate extrapyramidal symptoms (EPS). It consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4

representing a severe condition. The SAS Total score is the sum of ratings for all 10 items, with possible Total scores from 0 to 40. The SAS Total score will be un-evaluable if less than 8 of the 10 items are recorded. If 8 or 9 of the 10 items are recorded, the Total score will be the mean of the recorded items multiplied by 10 and then rounded to the first decimal place.

10.2.10 AIMS

The AIMS is a 12-item scale. The first 10 items are rated from 0 to 4 (0=best, 4=worst). An item score of 0, depending on the item, either means: no abnormal involuntary movement (AIM), or no incapacitation due to AIM, or no awareness of AIM. An item score of 4 either means: severe AIM, or severe incapacitation due to AIM, or being aware of, and severe distress caused by AIM. Items 11 and 12, related to dental status, have dichotomous responses, 0=no and 1=yes. The AIMS Total Score is the sum of the ratings for the first seven items. The possible total scores are from 0 to 28. The AIMS Total Score will be un-evaluable if less than 6 of the first 7 items are recorded. If 6 of the items are recorded, then the total score will be the mean of the recorded items multiplied by 7 and then rounded to the first decimal place.

10.2.11 BARS

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

10.2.12 C-SSRS

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

11 Potential Clinical Relevance Criteria from Protocol

Appendix 1 Criteria for Identifying Vital Signs of Potential Clinical Relevance

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

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

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
Lactate dehydrogenase (LDH)	≥ 3 x ULN
Blood urea nitrogen (BUN)	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
Creatine phosphokinase (CPK)	≥ 3 x ULN
Prolactin	> ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTcF ≥ 450 msec (men) QTcF ≥ 470 msec (women)	

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

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

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

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

12 Proposed List of Summary Tables

CT-1.1 Subject Disposition (Enrolled Sample)
CT-1.2 Subject Disposition by Center (Enrolled Sample)
CT-1.3 Subject Completion Rates by Week (Enrolled Sample)
CT-1.4 Enrollment by Country (Enrolled Sample)
CT-1.5 Enrollment by Country by Age Group (Enrolled Sample)
CT-1.6 Summary of Proportion of the Face-to-Face and Virtual Visits by Study Week (Enrolled Sample)
CT-2 Reasons for Discontinuation (Enrolled Sample)
CT-3.1 Demographic Characteristics (Enrolled Sample)
CT-3.2.1 Medical History (Enrolled Sample)
CT-3.2.2 Psychiatric History (Enrolled Sample)
CT-3.2.3 Borderline Personality Disorder Disease History (Enrolled Sample)
CT-3.3 Baseline Psychiatric Scale Evaluation (Enrolled Sample)
CT-4.1.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy (Safety Sample)
CT-4.1.2 Concomitant Medications: Medications Taken During Study Therapy Period (Safety Sample)
CT-4.1.3 Concomitant Medications: Medications Taken Post Study Therapy Period (Safety Sample)
CT-4.2.1 Psychiatric Concomitant Medications: Medications Taken Prior to Start of Study Therapy (Safety Sample)
CT-4.2.2 Psychiatric Concomitant Medications: Medications Taken During Study Therapy Period (Safety Sample)
CT-4.2.3 Psychiatric Concomitant Medications: Medications Taken Post Study Therapy (Safety Sample)

CCI

CCI

[redacted]

CT-6.1 Summary of Mean Change from Baseline in Simpson-Angus Scale (SAS) Total Score (Safety Sample)

CT-6.2 Summary of Mean Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score and Item Scores 8, 9 and 10 (Safety Sample)

CT-6.3.1 Summary of Mean Change from Baseline in Barnes Akathisia Rating Scale (BARS) Global Clinical Assessment of Akathisia (Safety Sample)

CT-6.3.2 Incidence of Barnes Akathisia Rating Scale (BARS) Global Clinical Assessment of Akathisia (Safety Sample)

CT-6.4.1 Columbia-Suicide Severity Rating Scale(C-SSRS), Suicidality (Safety Sample)

CT-6.4.2 Columbia-Suicide Severity Rating Scale(C-SSRS), Suicidal Behavior by Type (Safety Sample)

CT-6.4.3 Columbia-Suicide Severity Rating Scale(C-SSRS), Suicidal Ideation by Type (Safety Sample)

CT-6.4.4 Columbia-Suicide Severity Rating Scale(C-SSRS), Treatment Emergent Suicidal Behavior and Ideation (Safety Sample)

CT-6.4.5 Columbia-Suicide Severity Rating Scale (C-SSRS) – Listing of Treatment Emergent Suicidal Ideation (Safety Sample)

CT-6.4.6 Columbia-Suicide Severity Rating Scale (C-SSRS) – Listing of Treatment Emergent Suicidal Behavior (Safety Sample)

CT-6.4.7 Columbia-Suicide Severity Rating Scale (C-SSRS) – Listing of Treatment Emergent Serious Suicidal Ideation (Safety Sample)

CT-6.4.8 Columbia-Suicide Severity Rating Scale (C-SSRS) – Listing of Worsening Suicidal Ideation (Safety Sample)

CT-7.1 Extent of Exposure to Study Medication (Safety Sample)

CT-7.2 Number and Percentage of Subjects Receiving Study Medication and Mean and Range of Average Daily Dose (Safety Sample)

CT-8.1 Adverse Events (All Causalities) (Safety Sample)

CT-8.2.1 Incidence of TEAEs by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.2.2 Incidence of TEAEs by System Organ Class, MedDRA Preferred Term and Severity (Safety Sample)

CT-8.2.3 Incidence of TEAE of at Least 5% by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.2.4 Incidence of TEAEs by System Organ Class and MedDRA Preferred Term, by Sex (Safety Sample)

CT-8.2.5 Incidence of TEAEs by System Organ Class and MedDRA Preferred Term, by Race (Safety Sample)

CT-8.2.6 Incidence of TEAEs by System Organ Class and MedDRA Preferred Term, by Age (Safety Sample)

CT-8.2.7 Incidence of TEAEs by System Organ Class and MedDRA Preferred Term, by Region (Safety Sample)

CT-8.2.8 Incidence of Non-Serious TEAE of at Least 5% by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.2.9 Occurrence (Number of Events) of Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.2.10 Occurrence (Number of Events) of Potentially Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.2.11 Occurrence (Number of Events) of Non-Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.3.1 Incidence of Potentially Drug-Related TEAEs by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.3.2 Incidence of Potentially Drug-Related TEAEs by System Organ Class, MedDRA Preferred Term and Severity (Safety Sample)

CT-8.4 Incidence of Deaths Due to TEAEs by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.5.1 Incidence of Serious TEAEs by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.5.2 Incidence of Serious TEAEs by System Organ Class, MedDRA Preferred Term and Severity (Safety Sample)

CT-8.6.1 Incidence of TEAEs Resulting in Discontinuation from Study by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-8.6.2 Incidence of TEAEs Resulting in Discontinuation from Study by System Organ Class, MedDRA Preferred Term and Severity (Safety Sample)

CT-8.7.1 Incidence of TE EPS-related AEs by EPS Category and MedDRA Preferred Term (Safety Sample)

CT-8.7.2 Incidence of Onset of Akathisia Adverse Event by Week (Safety Sample)

CT-8.8.1 Listing of TEAEs that Are Related or Probably Related to COVID-19 (Safety Sample)

CT-8.8.2 Listing of Serious TEAEs or Deaths that Are Related or Probably Related to COVID-19 (Safety Sample)

CT-8.9 Incidence of Treatment-Emergent Adverse Events of Special Interests (AESIs) by System Organ Class and MedDRA Preferred Term (Safety Sample)

CT-9.1 Listing of Deaths

CT-9.2 Listing of Serious Adverse Events

CT-9.3 Listing of Discontinuations Due to Adverse Events

CT-10.1 Criteria for Laboratory Test Values with Potential Clinical Relevance

CT-10.2.1 Listing of Laboratory Test Values with Potential Clinical Relevance by Subject (Safety Sample)

CT-10.2.2 Listing of Laboratory Test Values with Potential Clinical Relevance by Test (Safety Sample)

CT-10.2.3 Incidence of Laboratory Test Values with Potential Clinical Relevance (Safety Sample)

CT-10.3.1 Mean Change from Baseline in Clinical Laboratory Test Results - Serum Chemistry (Safety Sample)

CT-10.3.2 Mean Change from Baseline in Clinical Laboratory Test Results - Hematology (Safety Sample)

CT-10.3.3 Mean Change from Baseline in Clinical Laboratory Test Results - Urinalysis (Safety Sample)

CT-10.3.4 Mean Change from Baseline in Clinical Laboratory Test Results - Prolactin, by Sex (Safety Sample)

CT-10.3.5 Mean Change from Baseline in Clinical Laboratory Test Results - Other Tests (Safety Sample)

CT-10.4.1 Incidence of Laboratory Test Values with Potential Clinical Relevance - Prolactin (Safety Sample)

CT-10.4.2 Listing of Laboratory Test Values with Potential Clinical Relevance - Prolactin (Safety Sample)

CT-10.5.1.1 Incidence of Treatment-Emergent Significant Change in Lipids (Safety Sample)

CT-10.5.1.2 Listing of Treatment-Emergent Significant Change in Lipids (Safety Sample)

CT-10.5.2.1 Incidence of Treatment-Emergent Significant Change in Glucose (Safety Sample)

CT-10.5.2.2 Listing of Treatment-Emergent Significant Change in Glucose (Safety Sample)

CT-10.5.3.1 Incidence of Treatment-Emergent Metabolic Syndrome (Safety Sample)