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- **Document title: A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder**
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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 Subjects with Bipolar I Disorder

Protocol No. 331-201-00083
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Statistical Analysis Plan

Version: Final

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CONFIDENTIAL – PROPRIETARY INFORMATION

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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 331-201-00083. All amendments to the protocol are taken into consideration in developing this SAP.

2 Study Objectives

The purpose of this trial is to assess the safety and tolerability of brexpiprazole (OPC-34712) in the treatment of subjects with bipolar I disorder.

3 Trial Details

3.1 Study Design

This is a multicenter, open-label trial designed to assess the safety and tolerability of oral brexpiprazole (OPC-34712) (2-4 mg/day) as treatment in adults with bipolar I disorder. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who will include subjects who completed the 3-week treatment in the double-blind, phase 3 efficacy trials (ie, Trials 331-201-00080 or 331-201-00081) and, in the investigator's judgment, could potentially benefit from treatment with oral brexpiprazole (OPC-34712) for bipolar I disorder. In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at select sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

The trial will be organized as follows:

Rollover Subjects:

Screening/Baseline: Subjects who completed Day 21 of the double-blind trial and had no major protocol deviation will be screened for eligibility at the last visit of the double-blind trial (i.e., Week 3 [Day 21] visit of Trials 331-201-00080 or 331-201-00081). Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-201-00083 before any procedures specific to the open-label trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-201-00083 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

Open-label Treatment Phase: Eligible subjects from Trials 331-201-00080 or 331-201-00081 will receive 26 weeks of daily treatment with open-label brexpiprazole (OPC-34712) (2-4 mg/day) in open-label treatment phase of Trial 331-201-00083, as described in Section 3.2. Visits will occur at the end of Weeks 1, 2, 4, 8, 12, 18, and 26.

Follow-up: Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of open-label investigational medicinal product (IMP).

De Novo Subjects

There are no de novo subjects enrolled in the study.

See Figure 3.1-1 for schematics of the trial design for rollover subjects.

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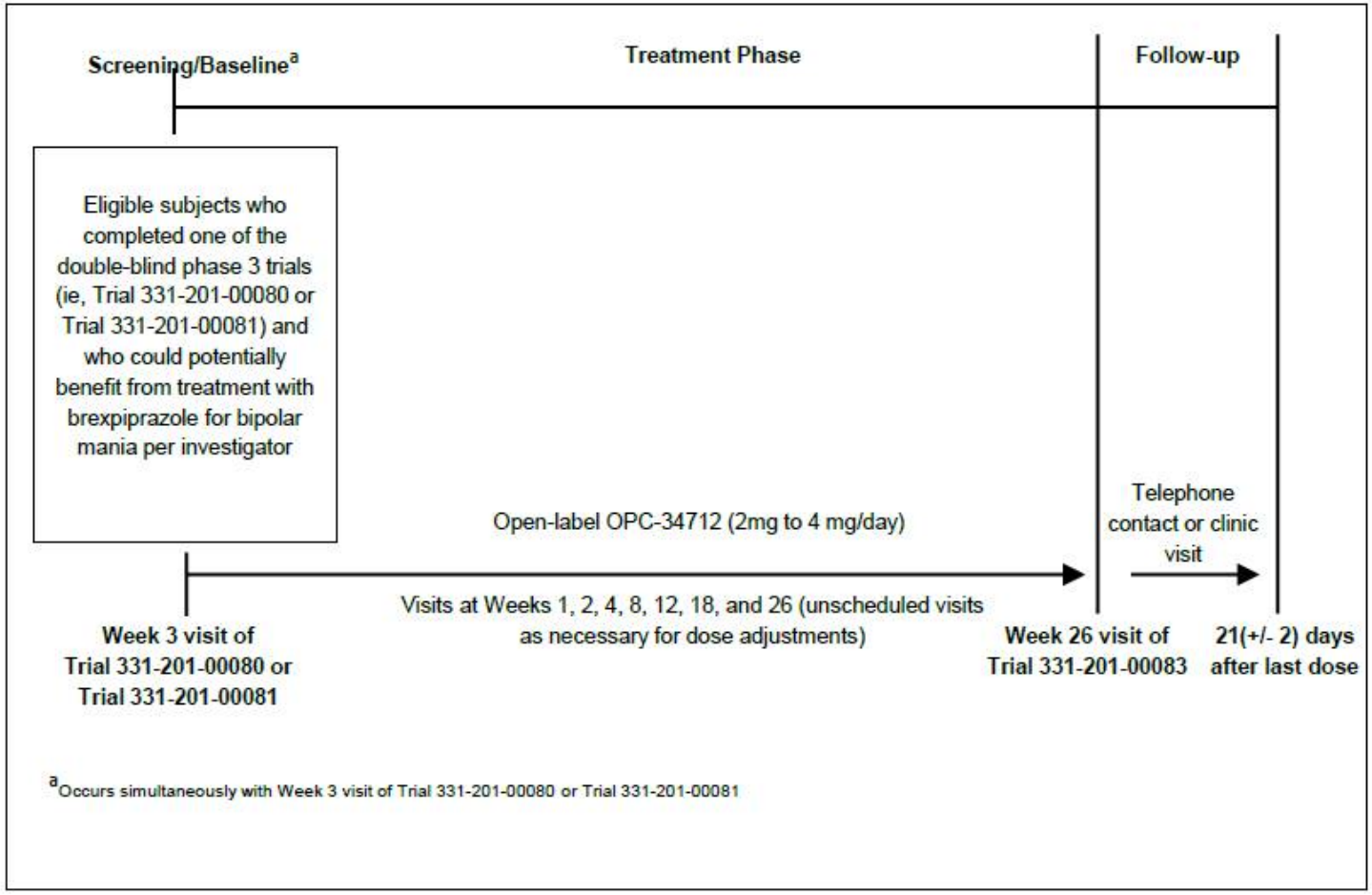

Figure 3.1-1 Trial Design Schematic - Rollover Subjects

3.2 Trial Treatments

Rollover Subjects

- The first dose of open-label brexpiprazole (OPC-34712) will be taken one day after the last dose of double-blind IMP is taken in Trials 331-201-00080 or 331-201-00081 so that treatment continues without interruption. It is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Day 21 (Week 3) visit of Trial 331-201-00080 or 331-201-00081 (ie, the day of the screening/baseline visit for the open-label trial).
- All subjects will start on 2 mg/day of brexpiprazole (OPC- 34712) regardless of treatment assignment in the double-blind trial.

All subjects will receive a starting dose of 2 mg/day of brexpiprazole from Days 1 to 3, followed by titration to 3 mg/day brexpiprazole on Day 4. Subjects may be titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Subjects who are unable to tolerate their current dose can be titrated down at any time to a minimum of 2 mg/day. Dose adjustments must be made in increments of 1 mg/day. Subjects who are unable to tolerate 2 mg/day brexpiprazole will be discontinued from the trial.

The dosing strategy is summarized in Table 3.2.2.1-1. Subjects must return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response. All doses of brexpiprazole should be taken orally once daily and can be administered without regard to meals. Subjects are to take IMP at approximately the same time each day.

Table 3.2.2.1-1 Dosing Schedule - Open-label Treatment Phase

IMP	Trial Visit		
	Days 1-3	Day 4[a]	Day 7-Week 26
Brexpiprazole (OPC-34712)	2 mg/day	3 mg/day	2-4 mg/day[b]

[a]Down titration can occur at any time due to tolerability after Day 4. The minimum dose allowed is 2 mg/day.

[b]Option to titrate to 2 to 4 mg (ie, 2 mg, 3 mg, or 4 mg) based on clinical response and tolerability; changes must occur in 1 mg/day increments. Increases up to 4 mg/day may occur no earlier than Day 7.

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4 Sample Size and Power Justification

The sample size is not based on statistical power considerations but on ICH/GCP requirements. The trial population will be derived from eligible subjects from the double-blind, phase 3 trials (ie, Trials 331-201-00080 and 331-201-00081). In the event the sponsor determines that the enrollment rate of rollover subjects will not be sufficient to meet the target completion of approximately 175 subjects at 6 months, de novo subjects may be enrolled at selected sites. The enrollment of de novo subjects at any site will not be permitted until initiation and notification by the sponsor.

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.
- Safety Sample, which comprises all subjects who will receive at least 1 dose of IMP.

[redacted]

6 Study Conduct

There are no de novo subjects enrolled in the study.

6.1 Subject Disposition, Completion Rate and Reasons for Discontinuation

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

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

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 for rollover subjects and overall.

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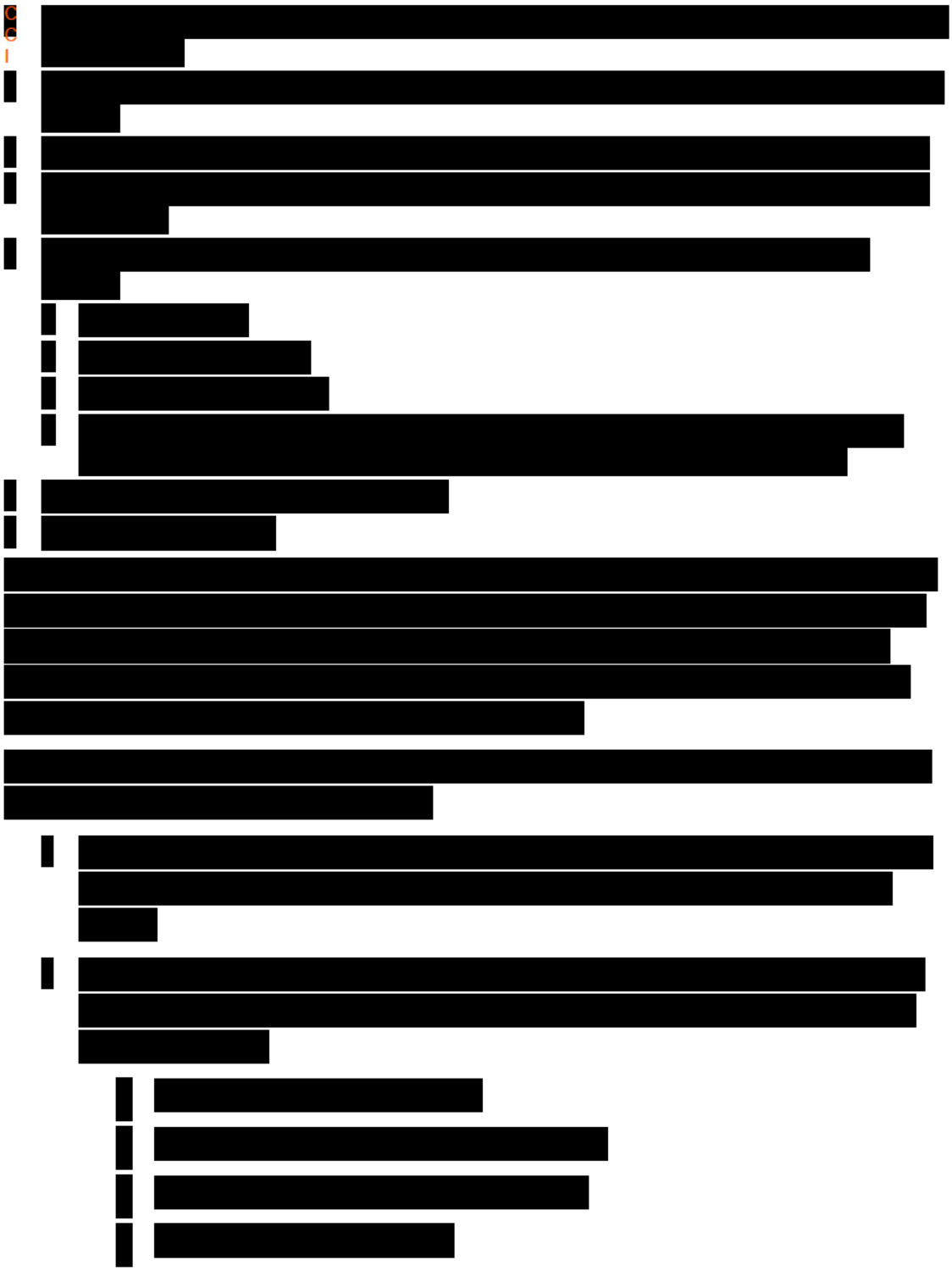

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9 Safety Analysis

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. CCI [redacted]

Safety analyses will be conducted based on the Safety Sample, and summary statistics will be provided by parent study treatment group for rollover subjects 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 21 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 summarized 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

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.

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.

9.2 Clinical Laboratory Tests

Summary statistics for mean and mean change from baseline in the routine clinical laboratory measurements, prolactin concentrations, and HbA1c will be provided. Potentially clinically relevant results in laboratory tests will also be summarized.

Potentially clinically relevant laboratory measurement test results in the open-label treatment phase will be identified, summarized, 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 ≥ 3 x ULN or baseline and
  - T_Bili ≥ 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 phase.

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 for rollover subjects and overall 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
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 Data

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. 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

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Categorical Change Criteria in QT/QTc Parameters		
Classification	**Category**	**Criteria**
		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.

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9.6 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.

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9.7 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.

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10 Conventions

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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	≤ 1,000/ 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.

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