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Otsuka Pharmaceutical
Development & Commercialization, Inc

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

Protocol 331-10-238
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A Long-term, Phase 3, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Oral OPC-34712 as Adjunctive Therapy in Adults with Major Depressive Disorder, the Orion Trial

Statistical Analysis Plan

Version 1.0
(Final)

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADT	Antidepressant Therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case report form
ECG	Electrocardiogram
ET	Early termination
ICF	Informed consent form
IMP	Investigational medicinal product
LOCF	Last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed case
SAP	Statistical analysis plan
SAS	Simpson Angus Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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 safety and tolerability data of Study 331-10-238. All amendments to the protocol are taken into consideration in developing this SAP.

2 Trial Objectives

Primary: To assess the long-term safety and tolerability of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD.

Secondary: To assess the long-term efficacy of oral brexpiprazole as adjunctive therapy in the treatment of adult patients with MDD.

3 Trial Design

3.1 Type/Design of Study

3.1.1 Trial Design Before Protocol Amendment 3

This is a multicenter, **52-week**, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed one of the double-blind, phase 3 brexpiprazole MDD trial and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD. A schematic of the study design is presented in Figure 3.1-1.

The trial will be organized as follows:

Screening/Baseline: Subjects will be screened for eligibility at the last scheduled visit of the prior double-blind phase 3 trial. Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-10-238 before any procedures specific to the open-label trial are performed. The assessments from the last scheduled visit of the prior double-blind phase 3 trial will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

Treatment Phase: Eligible subjects will receive daily treatment with open-label brexpiprazole and ADT as described in the Investigational Medicinal Product (IMP), Dose, Formulation, Mode of Administration section. Visits will occur at the end of

Weeks 1, 2, 4, 8, 14, 20, 26 32, 28, 44, and 52. All subjects will receive up to 52 weeks of open-label treatment in Trial 331-10-238.

Follow-up: Subjects will be followed up for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.

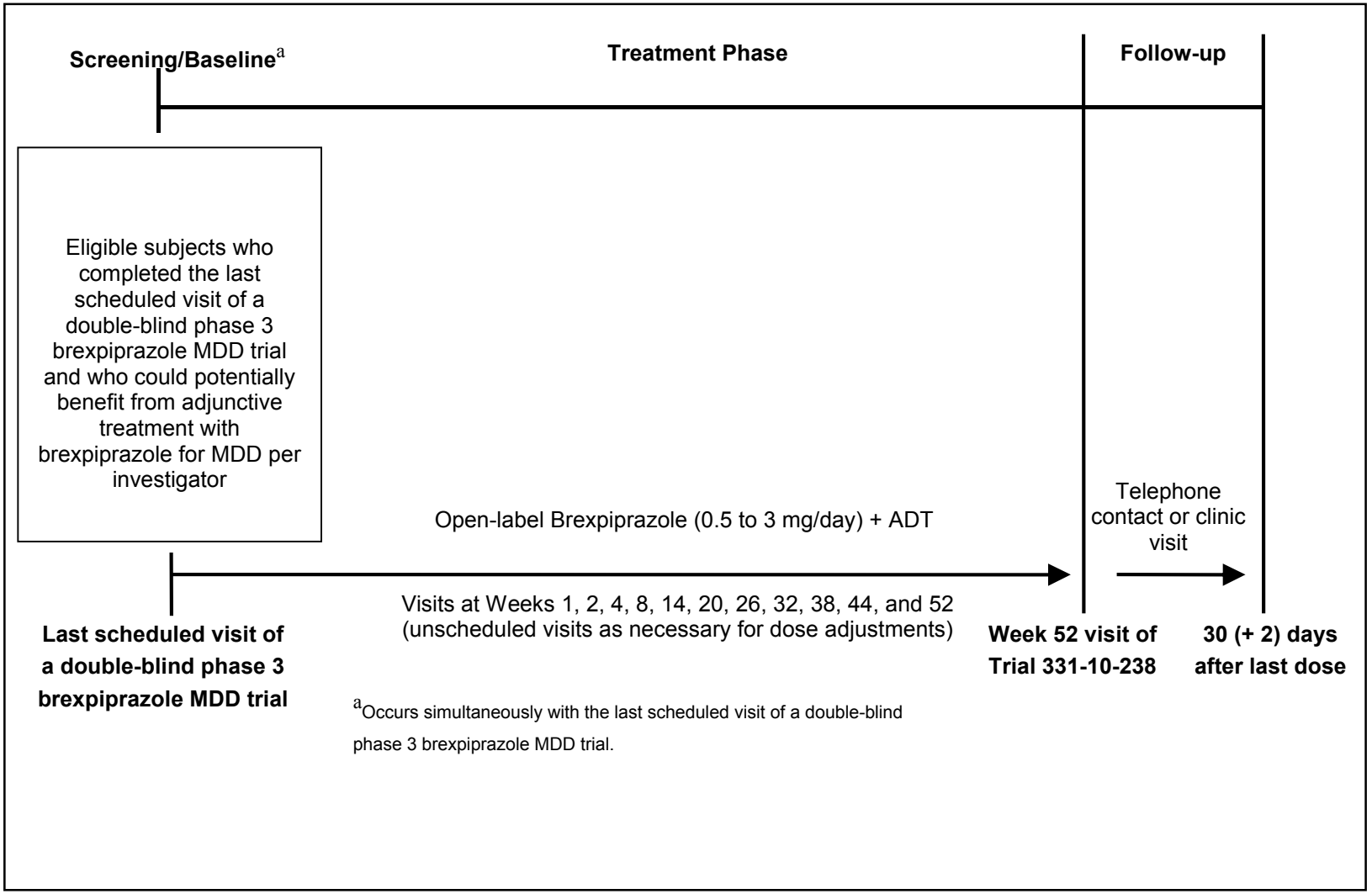

Figure 3.1-1 Trial Design Schematic

3.1.2 Trial Design After Protocol Amendment 3

This is a multicenter, **26-week**, open-label trial designed to assess the long-term safety, tolerability, and efficacy of adjunctive brexpiprazole in depressed adults on concurrent antidepressant therapy (ADT). The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible subjects who have completed one of the double-blind, phase 3 brexpiprazole MDD trial and who, in the investigator's judgment, could potentially benefit from adjunctive treatment with oral brexpiprazole for MDD. A schematic of the study design is presented in Figure 3.1-2.

The trial will be organized as follows:

Screening/Baseline: Subjects will be screened for eligibility at the last scheduled visit of the prior double-blind phase 3 trial. Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-10-238 before any procedures specific to the open-label trial are performed. The assessments from the last scheduled visit of the prior double-blind phase 3 trial will serve as the baseline measures for Trial 331-10-238 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

Treatment Phase: Eligible subjects will receive daily treatment with open-label brexpiprazole and ADT as described in the Investigational Medicinal Product (IMP), Dose, Formulation, Mode of Administration section. Visits will occur at the end of Weeks 1, 2, 4, 8, 14, 20, and 26. All subjects will receive up to 26 weeks of open-label treatment in Trial 331-10-238.

Follow-up: Subjects will be followed up for safety via telephone contact or clinic visit 30 (+ 2) days after the last dose of open-label medication.

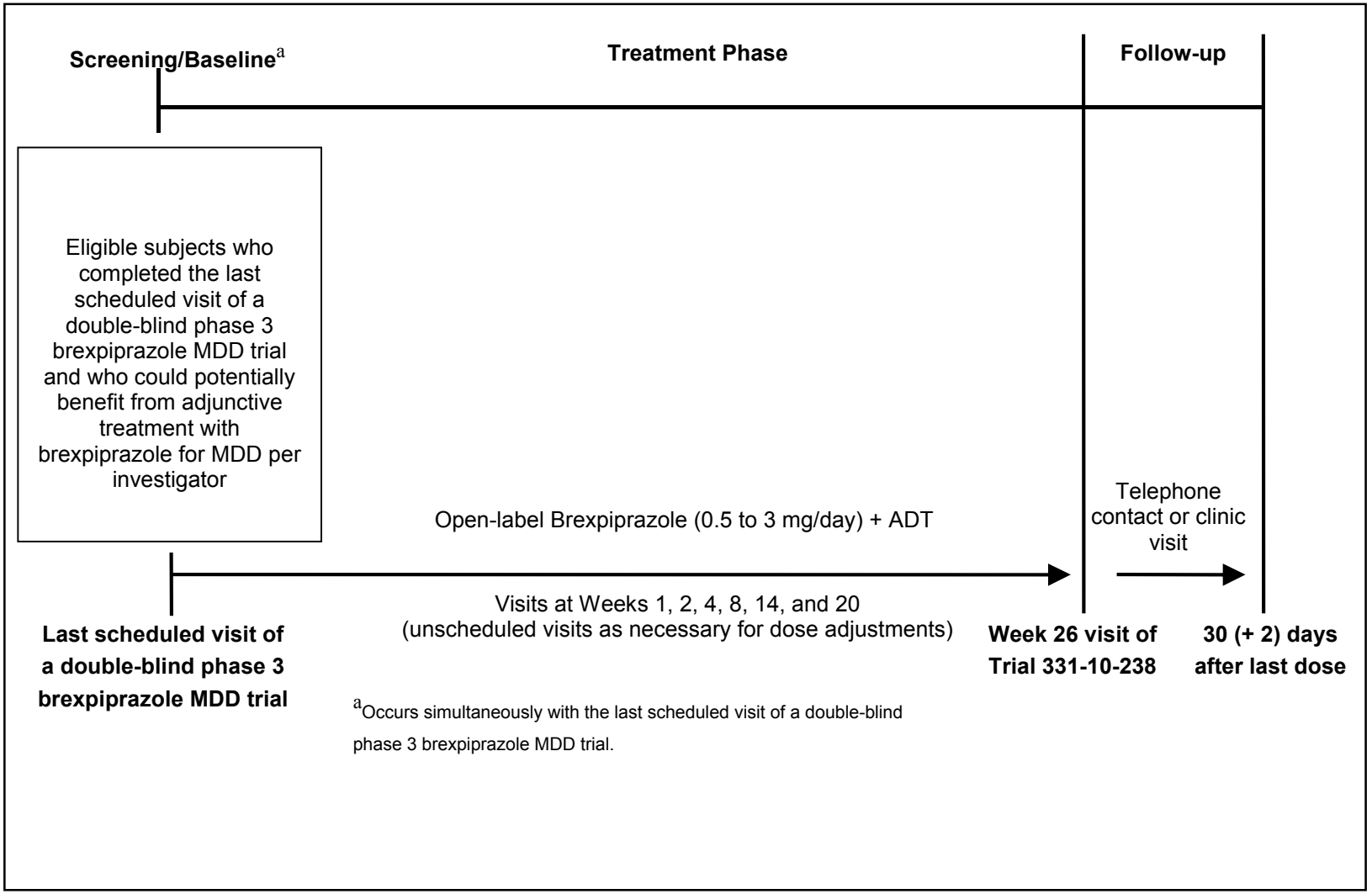

Figure 3.1-2 Trial Design Schematic

3.2 Study Population

The subject population will consist of eligible subjects who, in the investigator's judgment, could potentially benefit from adjunctive treatment with brexpiprazole for MDD and who meet one of the following conditions:

- Subjects who completed participation in the Double-blind Randomization Phase (ie, Week 14 visit of Phase B) in Trial 331-10-227 or Trial 331-10-228 or
- Subjects who met criteria for a response at the end of prospective treatment (ie, Week 8 visit of Phase A) in Trial 331-10-227 or Trial 331-10-228, **BUT DID NOT** meet criteria for remission (defined as a MADRS Total Score of $\leq$10) at the Week 14 visit of Phase A+ in Trial 331-10-227 or Trial 331-10-228.

Subjects must qualify for Trial 331-10-238 at the last visit of the double-blind trial and must be able to continue therapy without interruption between the double-blind and open label trials. Based on the projected enrollment estimates for the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228), up to 1280 subjects may enroll into Trial 331-10-238.

4 Sample Size and Power Justification

The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects from the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228). Therefore, the number of eligible subjects will be limited by the number of subjects enrolled into these protocols. Based on the projected enrollment estimates for the double-blind phase 3 trials (ie, Trial 331-10-227 and Trial 331-10-228), up to 1280 subjects may enroll into Trial 331-10-238.

5 Statistical Methods

5.1 Data Sets Analyzed

The following datasets are defined for this study:

- Enrolled Sample: comprises all subjects who sign an ICF for the trial.
- Safety Sample: comprises those subjects who receive at least one dose of open-label brexpiprazole as adjunctive therapy to one of the allowed ADTs.
- Efficacy Sample: comprises those subjects in the Safety Sample who have at least one post-baseline efficacy evaluation of CGI-S.

All the summaries will be done for all subjects, 52-week enrollers (before Protocol Amendment 3), and 26-week enrollers (after Protocol Amendment 3), and will be done by parent study treatment group. Selected summaries will also be done by ADT. Details of those summaries will be specified in the following sections.

The Safety Sample will be used for all baseline and safety summaries. The Efficacy Sample will be used for the efficacy summaries.

The observed case (OC) dataset will consist of the actual observations recorded at each visit and will be used to present summaries per trial week.

The last-observation-carried-forward (LOCF) data set will include data recorded at a given visit in the Treatment Phase or, if no observation is recorded at that visit, data carried forward from the previous visit in the Treatment Phase. Data collected prior to or on the first day of Treatment Phase dosing will not be carried forward or averaged with Treatment Phase data to impute missing values for the LOCF data set.

5.2 Handling of Missing Data

In order to assess sensitivity of results due to missing data, 2 types of analyses will be performed: LOCF and 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 carried forward from the previously scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF dataset. The OC data set will be used for analyses at each study visit and the LOCF data set 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.

Subject completion rate by week, and reasons for discontinuation will be summarized for the Enrolled Sample. In addition, these summaries will also be done by ADT

6.2 Treatment Compliance

Treatment compliance will be reported, by percentage of patients taking investigational medicinal product based on investigational medicinal product (IMP) panel of the case report form (CRF).

6.3 Protocol Deviations

Protocol deviations data will be summarized by type of deviations (eg, deviations in entry criteria, dosing, concomitant medication, procedural, etc.). In addition, a patient listing will be provided describing the deviations for each subject.

7 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable)

8 Efficacy Analysis

Efficacy is secondary objective for the study. Efficacy endpoints are as follows:

1) Change from baseline in CGI-S score, by trial week and at the last visit (ie, Week 26/ET or Week 52/ET);
2) Mean CGI-I score, by trial week and at the last visit (ie, Week 26/ET or Week 52/ET);
3) Change from baseline in SDS score, by trial week and at the last visit (ie, Week 26/ET or Week 52/ET);
4) Change from baseline in IDS-SR Total Score, by trial week and at the last visit (ie, Week 26/ET or Week 52/ET).

Descriptive statistics will be provided for each endpoint. The analysis will be carried out on the Efficacy Sample. Descriptive statistics will be summarized at each trial visit using the OC data set and at the last visit using the LOCF data set.

9 Safety Analyses

The primary safety analysis is the frequency and severity of AEs (see Section 9.1). Other standard safety variables to be analyzed include clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and BMI. In addition, data from the following safety scales will be evaluated: SAS, AIMS, BARS, C-SSRS, and MSFQ. Analyses regarding safety and tolerability will be conducted based on the Safety Sample, which is defined in Section 5.1. In general, baseline measurements of safety variables are defined as their last measurements prior to the first dose of open-label brexpiprazole.

9.1 Adverse Events

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

- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

A TEAE is defined as an AE that starts after the first dose of IMP or an AE that is reported at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption or reduction of IMP.

In addition, incidence of TEAE during 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 and age 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.

Incidence of EPS-related TEAEs will be summarized by EPS category. This summary will also be provided by ADT.

9.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, prolactin concentrations, coagulation parameters (PT, aPTT, and INR), HbA1c, cortisol, ACTH, and TSH will be provided. In addition, potentially clinically significant results in laboratory tests identified using prospectively defined criteria will be summarized.

9.2.1 Potential Hy's Law Cases

Total bilirubin level should be checked for any subject with increased ALT or AST levels greater or equal to three times the upper limit of normal (or baseline). If total bilirubin level is greater or equal to twice upper limit of normal (or baseline), IRE form with the lab values will be sent to INC Research within 24 hours. The corresponding pages of the eCRF should be filled.

Reporting all potential cases as SAE to the FDA based on Hy's Law:

- AST or ALT ≥ 3 x ULN and
- Total Bilirubin ≥ 2 x ULN

A separate incidence table will be provided for Hy's Law cases, and the corresponding listing will be provided.

9.3 Physical Examination and Vital Signs Data

By-patient listings will be provided for physical examination. Summary statistics for changes from baseline in vital signs will be provided. Potentially clinically significant results in vital signs will also be summarized. In addition, the change from baseline in weight, BMI, and waist circumference, and potentially clinically relevant abnormalities in weight, will also be summarized by ADT and by Gender, separately.

9.4 ECG Data

Mean change from baseline and incidence of clinically significant changes will be calculated 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: $QTcB=QT/(RR)^{0.5}$
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: $QTcN=QT/(RR)^{0.37}$

Categorical changes in ECG parameters will be summarized based on the following criteria:

Table 9.4-1 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)	New onset (> 450 msec) in QTc means a subject who attains a value > 450 msec during treatment period but not at baseline.
	New Onset (> 450 Msec) And > 10% Increase	New onset (> 450 msec) and > 10% increase in QTc means a subject who attains a value > 450 msec 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 Suicidality Data

Suicidality will be monitored during the study using the C-SSRS 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.

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.

9.6 Concomitant Medications

Number and proportion of patients taking concomitant medications prior to Treatment Phase, during Treatment Phase, and after study therapy are tabulated by drug classification and medication preferred name using the WHO drug dictionary.

9.7 Extent of Exposure

The start date of double-blind IMP will be the first day of double-blind dosing. The number and percentage of patients who receive brexpiprazole will be presented by 4-week interval. This summary will be performed on the Safety Sample, and will also be done by ADT.

The number and percentage of patients who receive each dose of brexpiparzole (0.5mg/day, 1mg/day, 2mg/day and 3mg/day) will be summarized by 4-week interval. This summary will also be done by ADT.

The number and percentage of patients who receive ADT medications will also be summarized by ADT.

9.8 Other Safety Data

Descriptive statistics will be provided for the SAS, AIMS, BARS, and MSFQ scales. Change from baseline in body weight will be summarized by descriptive statistics, as well as incidence of clinically significant changes in body weight. Descriptive statistics will also be provided for change from baseline in waist circumference and BMI. Descriptive statistics will be summarized at each visit using the OC data set and at the last visit (Week 52/ET) using the LOCF data set.

9.8.1.1.1 Post-baseline concomitant Medications

Concomitant medications used post-baseline will be summarized in 2 categories of time interval - during IMP treatment period and after IMP treatment period. In each case, use of concomitant medication will be summarized by number and percentage of users.

10 Other Outcomes

The percentage of subjects hospitalized for exacerbation of symptoms (including emergency department visits) will be tabulated as a measure of healthcare resource utilization. The frequency of outpatient visits to various healthcare providers (eg, primary care physician, psychiatrists, other mental health practitioners, etc.) not required per the protocol will also be examined.

11 Conventions

11.1 Study Visit Windows

Study visit windows will be used to map visits using study day intervals. This visit window convention applies to tables and listings for all efficacy and safety scales (CGI-S, CGI-I, SDS, IDS-SR, SAS, AIMS, BARS and MSFQ). This derived study window variable will be named as WEEK and will be footnoted. In listings it will be listed along with the CRF study visit.

Table 11.1-1 shows classifications for study day intervals. The variable "target day" is defined using the number of days since the start of open-label OPC dosing in the study. The first day of open-label OPC 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 seven days after the last dosing date will be excluded from the analysis.

Table 11.1-1 Study Day and Visit Windows

Week	Target Day [a]	Study Day Interval [a]
1	7	2-10
2	14	11-21
4	28	22-35
6	42	36-49
8	56	50-77
14	98	78-119
20	140	120-161
26	182	162-203
32 [c]	224	204-245
38 [c]	266	246-287
44 [c]	308	288-336
52 [c]	364	337-385 [b]

[a] Relative to the first day of open-label OPC dosing.

[b] Evaluations occurring more than seven days after the last OPC dosing will be excluded from summaries of change from baseline analyses.

[c] Evaluations The duration of the length of the treatment phase was reduced to 26 weeks in Protocol Amendment 3. Therefore, the 26-week enrollers didn't have these visits.

11.2 Scales: Rules for Scoring and Handling of Missing Data

11.2.1 Clinical Global Impression (CGI)

CGI consists of two scales: CGI Severity (CGI-S), and CGI Improvement (CGI-I). CGI-S items are: 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, 7 = among the most extremely ill patients. The score 0 (= not assessed) will be set to missing. The CGI-S is therefore a 7-point scale from 1 through 7.

CGI-I items are: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. The score of 0 (= not assessed) will be set to missing. The CGI-I is therefore a 7-point scale from 1 through 7. CGI improvement is judged with respect to the patient's condition at baseline.

11.2.2 Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS) 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 except for the work/school item score when this item is not applicable.

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

The IDS-SR is a 30-item self-report measure used to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of major depressive disorders. 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 "worst" 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. The IDS-SR Total Score will be un-evaluable if less

than 23 of the 28 items are recorded. If the number of items recorded is at least 23 and at most 27, the IDS-SR Total Score will be the mean of the recorded items multiplied by 28 and then rounded to the first decimal place.

11.2.4 Simpson-Angus Scale (SAS)

The SAS is a rating scale used to measure EPS. The SAS is a 10-item scale, with each item rated from 0 to 4, with 0 being normal and 4 being the worst. 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 unevaluable 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.

11.2.5 Abnormal Involuntary Movement Scale (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 unevaluable 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.

11.2.6 Barnes Akathisia Rating Scale (Barnes)

The Barnes Akathisia Rating Scale will be used to assess the presence and severity of akathisia. This scale consists of 4 items. Only the 4th item, the Global Clinical Assessment of Akathisia, will be evaluated in this study. This item is rated on a 6-point scale, with 0 being best (absent) and 5 being worst (severe akathisia).

11.2.7 Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ)

The MSFQ is a measure of a patient's self-reported sexual functioning. The MSFQ includes 5 items, each addressing experiences over the last month: a) interest in sex, b) ability to get sexually aroused, c) ability to achieve orgasm, d) ability to get and maintain an erection, and e) overall sexual satisfaction. For items a) through e), a score of 1 indicates 'greater than normal', and 6 indicates 'totally absent'.

All item scores are analyzed separately. No total or mean score is derived.

11.2.8 Resource Utilization Scale

The Resource Utilization Form is a self-report tool designed to collect information regarding the extent of medical care sought by patients while participating in the study. Incidence rates (related to number of visits to a health care provider, number of times hospitalized, or number of days hospitalized) will be expressed through the average use per person-year. For each group, the number of events across all patients in that group will be divided by the total person year (study duration in days / 365.25) during the open-label study across all patients.

12 Appendices

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
LDH	≥ 3 x ULN
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
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 ≥ 0.20 second	increase of ≥ 0.05 second
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 ≥ 0.12 second	increase of ≥ 0.02 second
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	QTc > 450 msec (men or 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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CT-10.5.1.1.3 Incidence of Treatment-Emergent Significant Change in Lipids – 26-Week Enrollers

CT-10.5.1.2.2 Listing of Treatment-Emergent Significant Change in Lipids

CT-10.5.2.1.1 Incidence of Treatment-Emergent Significant Change in Glucose – All Subjects

CT-10.5.2.1.2 Incidence of Treatment-Emergent Significant Change in Glucose – 52-Week Enrollers

CT-10.5.2.1.3 Incidence of Treatment-Emergent Significant Change in Glucose – 26-Week Enrollers

CT-10.5.2.2.1 Listing of Treatment-Emergent Significant Change in Glucose – All Subjects

CT-10.5.2.2.2 Listing of Treatment-Emergent Significant Change in Glucose – 52-Week Enrollers

CT-10.5.2.2.3 Listing of Treatment-Emergent Significant Change in Glucose – 26-Week Enrollers

CT-10.5.3.1.1 Incidence of Treatment-Emergent Metabolic Syndrome – All Subjects

CT-10.5.3.1.2 Incidence of Treatment-Emergent Metabolic Syndrome – 52-Week Enrollers

CT-10.5.3.1.3 Incidence of Treatment-Emergent Metabolic Syndrome – 26-Week Enrollers

CT-10.5.3.2.1 Listing of Treatment-Emergent Metabolic Syndrome – All Subjects

CT-10.5.3.2.2 Listing of Treatment-Emergent Metabolic Syndrome – 52-Week Enrollers

CT-10.5.3.2.3 Listing of Treatment-Emergent Metabolic Syndrome – 26-Week Enrollers

CT-10.6 Criteria for Potential Clinical Relevant Laboratory Test Abnormalities

CT-11.1.1.1 Mean Change from Baseline in Vital Signs – All Subjects

CT-11.1.1.2 Mean Change from Baseline in Vital Signs – 52-Week Enrollers

CT-11.1.1.3 Mean Change from Baseline in Vital Signs – 26-Week Enrollers

CT-11.1.2.1 Mean Change from Baseline in Weight, BMI and Waist Circumference – All Subjects

CT-11.1.2.2 Mean Change from Baseline in Weight, BMI and Waist Circumference – 52-Week Enrollers

CT-11.1.2.3 Mean Change from Baseline in Weight, BMI and Waist Circumference – 26-Week Enrollers

CT-11.1.3.1 Mean Change from Baseline in Weight, BMI and Waist Circumference by ADT – All Subjects

CT-11.1.3.2 Mean Change from Baseline in Weight, BMI and Waist Circumference by ADT – 52-Week Enrollers

CT-11.1.3.3 Mean Change from Baseline in Weight, BMI and Waist Circumference by ADT – 26-Week Enrollers

CT-11.1.4.1 Mean Change from Baseline in Weight, BMI and Waist Circumference by Gender – All Subjects
CT-11.1.4.2 Mean Change from Baseline in Weight, BMI and Waist Circumference by Gender – 52-Week Enrollers
CT-11.1.4.3 Mean Change from Baseline in Weight, BMI and Waist Circumference by Gender – 26-Week Enrollers
CT-11.2.1.1 Incidence of Potentially Clinically Relevant Abnormalities in Vital Signs – All Subjects
CT-11.2.1.2 Incidence of Potentially Clinically Relevant Abnormalities in Vital Signs – 52-Week Enrollers
CT-11.2.1.3 Incidence of Potentially Clinically Relevant Abnormalities in Vital Signs – 26-Week Enrollers
CT-11.2.2.1 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Visit – All Subjects
CT-11.2.2.2 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Visit – 52-Week Enrollers
CT-11.2.2.3 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Visit – 26-Week Enrollers
CT-11.2.3.1 Incidence of Potentially Clinically Relevant Abnormalities in Weight by ADT – All Subjects
CT-11.2.3.2 Incidence of Potentially Clinically Relevant Abnormalities in Weight by ADT – 52-Week Enrollers
CT-11.2.3.3 Incidence of Potentially Clinically Relevant Abnormalities in Weight by ADT – 26-Week Enrollers
CT-11.2.4.1 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Gender – All Subjects
CT-11.2.4.2 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Gender – 52-Week Enrollers
CT-11.2.4.3 Incidence of Potentially Clinically Relevant Abnormalities in Weight by Gender – 26-Week Enrollers
CT-11.3.1 Listing of Potentially Clinically Relevant Abnormalities in Vital Signs – All Subjects
CT-11.3.2 Listing of Potentially Clinically Relevant Abnormalities in Vital Signs – 52-Week Enrollers
CT-11.3.3 Listing of Potentially Clinically Relevant Abnormalities in Vital Signs – 26-Week Enrollers
CT-11.4 Criteria for Potentially Clinically Relevant Abnormalities in Vital Signs

CT-12.1.1 Mean Change from Baseline in Electrocardiogram Results – All Subjects
CT-12.1.2 Mean Change from Baseline in Electrocardiogram Results – 52-Week Enrollers
CT-12.1.3 Mean Change from Baseline in Electrocardiogram Results – 26-Week Enrollers
CT-12.2.1 Incidence of Potentially Clinically Relevant Changes in ECG Evaluations – All Subjects
CT-12.2.2 Incidence of Potentially Clinically Relevant Changes in ECG Evaluations – 52-Week Enrollers
CT-12.2.3 Incidence of Potentially Clinically Relevant Changes in ECG Evaluations – 26-Week Enrollers
CT-12.3.1.1 Listing of Potentially Clinically Relevant Abnormalities in ECG Evaluations – All Subjects
CT-12.3.1.2 Listing of Potentially Clinically Relevant Abnormalities in ECG Evaluations – 52-Week Enrollers
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CT-12.3.2.1 Criteria for Potentially Clinically Relevant Abnormalities in ECG Evaluations
CT-12.3.3.1 ECG Diagnosis Mapping for Potentially Clinically Relevant Electrocardiogram Abnormalities
CT-12.4.1.1 Incidence of Categorical Changes in QT Evaluations – All Subjects
CT-12.4.1.2 Incidence of Categorical Changes in QT Evaluations – 52-Week Enrollers

CT-12.4.1.3 Incidence of Categorical Changes in QT Evaluations – 26-Week Enrollers
CT-12.4.2.1 Listing of Categorical Changes in QT Evaluations – All Subjects
CT-12.4.2.2 Listing of Categorical Changes in QT Evaluations – 52-Week Enrollers
CT-12.4.2.3 Listing of Categorical Changes in QT Evaluations – 26-Week Enrollers

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