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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

Brexpiprazole (OPC-34712)

A 12-week, Multicenter, Active-treatment Extension Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-201-00182
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Statistical Analysis Plan

Version: Final
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CONFIDENTIAL – PROPRIETARY INFORMATION

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAD	Agitation in Alzheimer's dementia
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-S	Clinical Global Impression - Severity
CRF	Case Report Form
CMAI	Cohen-Mansfield Agitation Inventory
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ET	Early termination
FDA	(United States) Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
IAF	Informed assent form
ICF	Informed consent form
ID	Identification
IMP	Investigational medicinal product
IRE	Immediately reportable event
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
PE	Physical examination
QD	Once Daily
QTc	Corrected QT interval
QTcF	QT interval as corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAS	Simpson Angus Scale
SAS®	Statistical Analysis System®
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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1 Introduction

This statistical analysis plan (SAP) expands the statistical section of the protocol 331-201-00182 and documents in detail the statistical methodologies and data analysis algorithms and conventions to be applied to the analysis and reporting of the safety and tolerability data collected in the study. All amendments to the protocol have been taken into consideration in developing this SAP.

2 Study Objectives

Primary: To assess the long-term safety and tolerability of oral brexpiprazole as treatment in adult subjects with AAD.

3 Trial Details

3.1 Study Design

This is a multicenter, active-treatment extension trial designed to assess the long-term safety and tolerability of oral brexpiprazole (2 and 3 mg/day) as treatment in adults with AAD. Enrollment into the trial will consist of eligible subjects who completed the 12-week treatment in the double-blind, phase 3 efficacy Trial 331-14-213.

The trial will be organized as follows:

Screening/baseline: Subjects who completed Week 12 of the double-blind trial and had no substantial protocol deviations will be screened for eligibility at the last visit of the double-blind trial (ie, Week 12 or ET, if the trial is terminated, visit of Trial 331-14-213). Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-201-00182 before any procedures specific to the extension trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-201-00182 for any assessment that is not unique to the extension trial. Medical history will be updated, if necessary.

Active Extension Treatment: Eligible subjects from Trial 331-14-213 will receive 12 weeks of daily treatment with brexpiprazole (target doses of 2 or 3 mg/day) in Trial 331-201-00182. Visits will occur at the end of Weeks 1, 2, 6, and 12.

Follow-up: All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP

during a clinic visit at either the investigator's site or residential facility, as applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver. For all subjects who terminate early from the trial, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 (relative to baseline visit).

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

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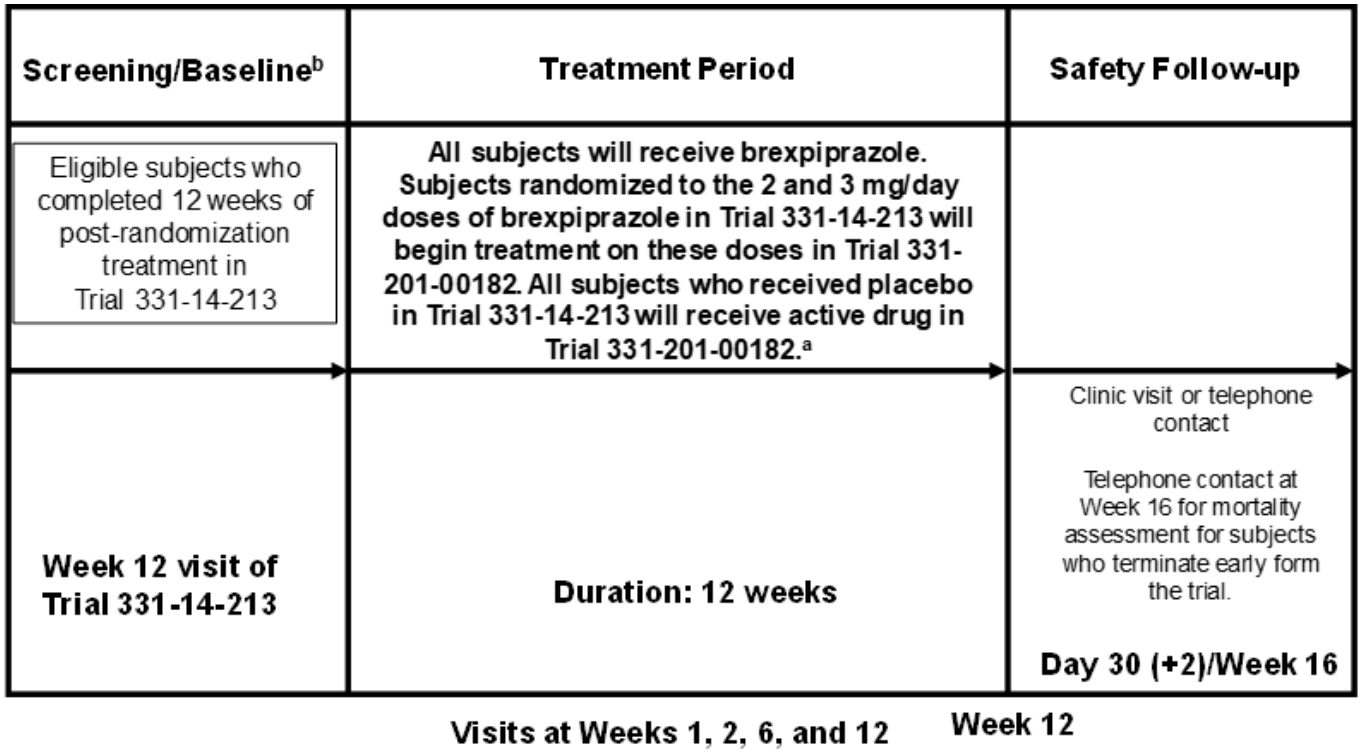

[a]Starting at week 4, 1 dose decrease can occur at any time (scheduled or unscheduled visits) until the end of the trial. In addition, one dose increase can occur but only at the Week 6 scheduled visit. Subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. Subjects randomized to brexpiprazole and who completed the titration schedule in Trial 331-14-213 (ie, completed Week 4 visit in 331-14-213) will begin treatment on the same dose in this trial. Subjects randomized to brexpiprazole and who have not completed the titration schedule will restart drug in Trial 331-201-00182 dependent on the point in the titration scheme for Trial 331-14-213 that early termination occurred.

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[b]For subjects who may be offered entry into this trial as a result of early termination of Trial 331-14-213 due to overwhelming efficacy from the interim analysis, the Screening/Baseline will occur at the last visit of the double-blind trial (ie, ET visit of Trial 331-14-213).

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

All subjects will receive target doses of 2 or 3 mg/day brexpiprazole in Trial 331-201-00182; these doses were those studied in Trial 331-14-213.

To preserve the blind in Trial 331-14-213, all doses in Trial 331-201-00182 will remain blinded. The first dose taken in Trial 331-201-00182 should be taken one day after the Week 12.

Subjects randomized to the 2 mg/day and 3 mg/day doses of brexpiprazole in Trial 331-14-213 will begin treatment on these same doses in the active-treatment extension Trial 331-201-00182. All subjects who received placebo in Trial 331-14-213 will receive active drug (ie, brexpiprazole) in Trial 331-201-00182.

All subjects will receive target doses of 2 or 3 mg/day brexpiprazole during the trial. Dose adjustments are allowed during the trial. Starting at week 4, one dose decrease can occur at any time (scheduled or unscheduled visits) until the end of the trial. In addition, one dose increase is permitted but only at the Week 6 scheduled visit. Subjects who require an additional dose increase or decrease will be discontinued from the trial. Timing of dose adjustments as outlined above is summarized in the table below.

Dosing Adjustments		
Visit	**Decrease**[a]	**Increase**
Week 6	Permitted	Permitted
Unscheduled (week 4 or anytime thereafter)	Permitted	Not Permitted

[a]Starting at week 4, 1 dose decrease can occur at any time (scheduled or unscheduled visits) until the end of the trial.

All doses of brexpiprazole will be taken orally once daily, preferably in the morning, and will be administered without regard to meals, and should be taken at approximately the same time each day.

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 who rollover from the double-blind phase 3 Trial 331-14-213.

5 Data Sets for Analysis and Missing Data

5.1 Data Sets for Analysis

To adequately describe the statistical analyses and reporting, three analysis populations are defined as follows.

- Enrolled Sample: comprises all subjects who sign an ICF for the trial and are enrolled into the trial.
- Safety Sample: comprised of those subjects who sign an ICF for the trial and receive at least one dose of brexpiprazole in Trial 331-201-00182.
- Efficacy Sample: comprises all subjects in the Safety Sample who have a baseline assessment and at least one post-baseline assessment for CMAI (Cohen-Mansfield Agitation Inventory) total score.

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, ie, 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.

The above summaries will be repeated in subject subgroups as defined by gender (Female and Male), age group (< 65; ≥ 65 and < 75; or ≥ 75), race (white or other), geographical region (North America or other), and dementia severity (severe, moderate, and mild), where dementia severity will be defined based on Mini Mental State Examination (MMSE) score at baseline as follows:

- Severe: MMSE score ≤ 12
- Moderate: MMSE score > 12 and ≤ 18
- Mild: MMSE score > 18

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6.2 Treatment Compliance

Compliance in taking investigational medicinal product is calculated by dividing the number of tablets taken by the total number of tablets the subjects were scheduled to take during the trial period. For lost-to-follow-up subjects, last IMP end date record will be used as the treatment end date.

Number (%) of subjects meeting compliance cut-offs ($< 70\%$, $\geq 70\%$ and $< 80\%$, $\geq 80\%$ and $< 90\%$, $\geq 90\%$) will be summarized by treatment group.

6.3 Protocol Deviation

Protocol deviations including the types of deviations (eg, deviations in entry criteria, dosing, concomitant medications, procedurals, etc.) will be summarized on the Enrolled Sample by trial center, and prior treatment group. A listing of protocol deviations will be provided.

7 Baseline Characteristics

7.1 Baseline Definition

Individual subject's baseline value is defined as the observation or assessment taken on the subject at the last scheduled visit (i.e., the Week 12 visit) in the double-blind treatment period of the parent trial (Trial 331-14-213). There will be no imputation for baseline values if missing or unknown.

7.2 Demographic Characteristics

Demographic and baseline characteristics including age, race, ethnicity, gender, weight, height, waist circumference, 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 Baseline Psychiatric Evaluations

Baseline psychiatric evaluations for the open-label extension trial are the ones taken at the last assessment visit of the parent trial. The baseline values in the following parameters will be summarized on the OC data on the Enrolled Sample using descriptive statistics: CMAI total score; CMAI derived agitation factors of aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior; Clinical Global Impression-Severity of Illness Scale (CGI-S) score, MMSE score, Sheehan Suicidality Tracking Scale (Sheehan-STS) score. Refer to Section 10 for of all the scales and the scoring via the aggregation of component items of the scales.

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8.1 COVID-19 Related Supplementary Analyses

Summary statistics for mean and mean change from baseline in CMAI total score, 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: MMSE score, assessments of suicidality (eg, Sheehan-STS), and extrapyramidal symptoms (EPS; eg, the Simpson-Angus Scale, abnormal involuntary movement scale [AIMS], and Barnes Akathisia Rating Scale [BARS]).

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 specified.

The long-term 24 weeks (6 months) safety analysis for subjects who received brexpiprazole in the parent trial 331-14-213 will be described in the SAP for the Summary of Clinical Safety (SCS) for Agitation in Alzheimer's dementia (AAD) and the results will be presented in the SCS.

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

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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, eg, 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) Treatment-emergent AEs (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 discontinuation 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.

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

1) Dystonic Events, which include blepharospasm, cervical spasm, clumsiness, dystonia, dystonic tremor, emprosthotonus, essential tremor, facial spasm, fumbling, gait inability, head titubation, intention tremor, Meige's syndrome, muscle contractions involuntary, muscle spasms, muscle spasticity, muscle tightness, muscle tone disorder, musculoskeletal stiffness, myotonia, nuchal rigidity, oculogyration, oesophageal spasm, opisthotonos, opisthotonus, oromandibular dystonia, oropharyngeal spasm, pharyngeal dystonia, pleurothotonus, risus

sardonicus, spasmodic dysphonia, tongue spasm, torticollis, torticollis psychogenic, trismus, uvular spasm;

2) Parkinsonian Events, which include action tremor, akinesia, asterixis, bradykinesia, bradyphrenia, cogwheel rigidity, dysphonia, fine motor skill dysfunction, freezing phenomenon, gait disturbance, gait festinating, hypertonia, hypokinetic dysarthria, laryngeal tremor, masked facies, micrographia, mobility decreased, muscle rigidity, on and off phenomenon, parkinsonian crisis, parkinsonian gait, parkinsonian rest tremor, parkinsonism, parkinsonism hyperpyrexia syndrome, parkinsons disease, parkinson's disease, parkinson's disease psychosis, postural reflex impairment, postural tremor, propulsive gait, reduced facial expression, resting tremor, tremor, walking disability;

3) Akathisia Events, which include akathisia, extrapyramidal disorder, hyperkinesia, movement disorder, psychomotor hyperactivity, and restlessness;

4) Dyskinetic Events, which include abnormal involuntary movement scale, athetosis, ballismus, buccoglossal syndrome, chorea, choreoathetosis, chronic tic disorder, complex tic, dopamine dysregulation syndrome, drooling, dyskinesia, dyskinesia oesophageal, grimacing, motor dysfunction, muscle twitching, nodding of head, oculogyric crisis, pharyngeal dyskinesia, protrusion tongue, provisional tic disorder, rabbit syndrome, respiratory dyskinesia, secondary tic, tardive dyskinesia, tic;

5) Residual Events, which include huntingtons disease and myoclonus.

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

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

9.2 Clinical Laboratory Tests

9.2.1 Change from Baseline in Lab Tests

Summary statistics for mean and mean change from baseline in the routine clinical laboratory measurements, prolactin concentrations, coagulation parameters (prothrombin time, activated partial thromboplastin time, and international normalized ratio), HbA1c, and thyroid-stimulating hormone will be provided by parent study treatment and by visit.

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9.2.2 Potentially Clinically Relevant Values

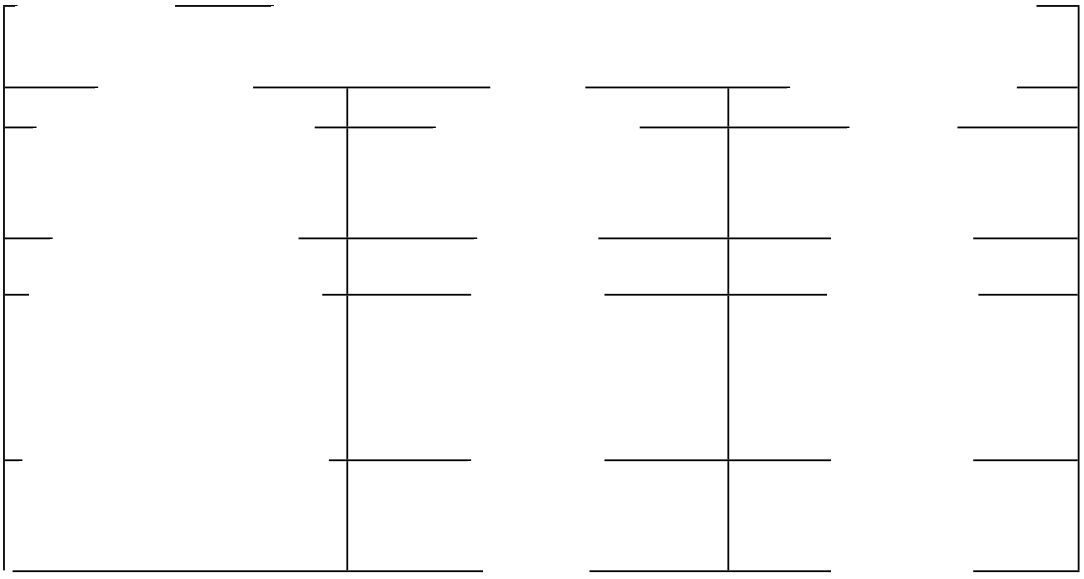
In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria for laboratory tests will be summarized by parent study treatment group. A listing of PCRs by subject and by test will be provided.

9.2.3 Potentially Liver Injury Related Laboratory Test

Total bilirubin level will be checked for any subjects with increased alanine transaminase (ALT) or aspartate transaminase (AST) levels greater or equal to three times the upper normal limits (or baseline).

Liver injury related laboratory test results will be summarized for subjects who met following criteria for Safety Sample during the open-label treatment period. The corresponding listing will be provided as well.

- AST or ALT ≥ 3 × upper limit of normal (ULN) and
- T_Bili ≥ 2 × ULN



9.3 Physical and Neurological Examination and Vital Signs

Physical and neurological examination findings will be listed by subject.

Summary statistics for change from baseline in vital signs, body weight, BMI, and waist circumference will be provided by parent study treatment group.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria for vital signs and body weight will be summarized by parent study treatment group. Listing of PCRs by subject and by test will be provided.

9.4 12-Lead ECG

Summary statistics for change from baseline in ECG parameters will be provided by parent study treatment group and by visit.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria for ECG will be summarized by parent study treatment group. Listing of PCRs by subject and by test will be provided.

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:

- QTcB is the length of the QT interval corrected for heart rate by the Bazett formula: QTcB=QT/(RR)0.5
- QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: QTcF=QT/(RR)0.33
- 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 during the open-label treatment period will be summarized based on the criteria in Table 9.4-1.

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Table 9.4-1 Categorical Change Criteria in QT/QTc Parameters		
Classification	**Category**	**Criteria**
QT	New onset (≥ 450 msec for men or ≥ 470 msec for women)	New onset in QT means a subject who attains a cut off value during treatment period but not at baseline.
QTc[a]	New onset (≥ 450 msec for men or ≥ 470 msec for women)	New onset in QTc means a subject who attains a cut-off value during treatment period but not at baseline.
	New onset (≥ 450 msec for men or ≥ 470 msec for women) and > 10% increase	New onset and > 10% increase in QTc means a subject who attains a cut off value 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

[a] QTc categorical change criteria apply to QTcB, QTcF and QTcN.

9.5 Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale

The mean 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 Mini-Mental State Examination

The mean changes from baseline in MMSE for trial visits during the open-label treatment phase will be summarized by descriptive statistics. 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.

9.7 Suicidality Data

The mean changes from baseline in Sheehan-STS individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score for trial visits during the open-label treatment phase using the Safety Sample will be summarized by descriptive statistics. 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.Incidence of treatment emergent suicidal ideation, suicidal behavior will be summarized by treatment, and overall.

9.8 Concomitant Medications

Number and proportion of subjects taking concomitant medications prior to IMP, during the open-label treatment period, and after IMP are tabulated by drug classification using the World Health Organization drug dictionary.

9.9 Extent of Exposure

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

The number and percentage of completers will be presented by week and by parent study treatment group.

The mean daily dosage will be summarized by week and parent study treatment group using descriptive statistics. The mean daily dosage per subject per week will be determined for each week of the trial. 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 for each parent study treatment group the number of subjects receiving open-label IMP, and the mean and range of the mean daily dose for each week.

10 Conventions

10.1 Study Visit Windows

Trial visit windows will be used to map visits using trial day intervals. This visit window convention applies to tables and listings for all efficacy and safety scales (CMAI, CGI-S, SAS, AIMS, BARS, MMSE and Sheehan-STS). This derived trial window variable will be named as WEEK and will be footnoted. In listings it will be listed along with the case report form (CRF) trial visit.

Table 10.1-1 below shows classifications for trial day intervals in the open-label treatment period. 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 trial 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 10.1-1 Mapping of the Analysis Visit for the Open-label Treatment Period

Analysis Visit	Target Study Day [a] per Protocol	Study Day Interval[a] (endpoint inclusive)
Day 1	1	1
Week 1	7	2 to 10
Week 2	14	11 to 28
Week 6	42	29 to 63
Week 12	84	64 to 91

[a] Relative to the first day of IMP in the open-label treatment period.

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

The preceding algorithm ensures that all observations collected at an ET visit or any other unscheduled visit will be mapped to an analysis visit. In instances where multiple observations (of same parameter on the same subject) fall into one study day interval, all values of the multiple observations in the study interval will be included for listings, but only the last observation will be used for the by-visit analysis or summary.

10.2 Scales: Rules for Scoring and Handling of Missing Data

10.2.1 Cohen-Mansfield Agitation Inventory

The CMAI consists of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. The CMAI total score is the sum of ratings for all 29 items. The possible total scores are from 29 to 203. The CMAI total score will be unevaluable if less than 24 of the 29 items are recorded. If 24 to 28 of the 29 items are recorded, the total score will be the mean of the recorded items multiplied by 29 and then rounded to the first decimal place.

Factor 1: Aggressive behavior: Hitting (including self), kicking, scratching, grabbing onto people, pushing, hurt self or other (cigarette, hot water, etc.), throwing things, cursing or verbal aggression, spitting (include at meals), tearing things or destroying property, screaming, biting.

Criteria for agitated status based on Factor 1:

- at least one aggressive behavior occurring at a frequency of at least 4; or
- at least two aggressive behaviors occurring at a frequency of at least 3; or
- at least three aggressive behaviors occurring at a frequency of at least 2;

Factor 2: Physically nonaggressive behavior: Pace, aimless wandering, trying to get to a different place, general restlessness, inappropriate dress or disrobing, handling things inappropriately, performing repetitious mannerisms.

Criteria for agitated status based on Factor 2:

- at least one physically nonaggressive behavior occurring at a frequency of at least 5; or
- at least two physically nonaggressive behavior occurring at a frequency of at least 4; or
- at least three physically nonaggressive behavior occurring at a frequency of at least 3; or
- at least four physically nonaggressive behavior occurring at a frequency of at least 2;

Factor 3: Verbally agitated behavior: Complaining, constant unwarranted request for attention or help, repetitious sentences or questions, negativism.

Criteria for agitated status based on Factor 3:

- at least one verbally agitated behavior occurring at a frequency of at least 5; or
- at least two verbally agitated behavior occurring at a frequency of at least 4; or
- at least three verbally agitated behavior occurring at a frequency of at least 3; or
- at least four verbally agitated behavior occurring at a frequency of at least 2;

Factor 4: Hiding things, hoarding things.

The following items are not included in factors derivation[1]: Intentional Falling; Making Verbal Sexual Advances; Making Physical Sexual Advances; Strange Noises (weird laughter or crying); Eating or Drinking Inappropriate Substances.

10.2.2 Clinical Global Impression-Severity of Illness Scale

The severity of agitation for each subject will be rated using the Clinical Global Impression-Severity of Illness Scale (CGI-S). To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the subject at this time?" Response choices 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; and 7 = among the most extremely ill subjects. The score 0 (not assessed) will be set to missing. The CGI-S is therefore a 7-point scale from 1 through 7.

10.2.3 Simpson-Angus Scale

The Simpson-Angus Scale is a rating scale used to measure EPS. The Simpson-Angus Scale is a 10-item scale, with each item rated from 0 to 4, with 0 being normal and 4 being the worst. The Simpson-Angus Scale total score is the sum of ratings for all 10 items, with possible total scores from 0 to 40. The Simpson-Angus Scale 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.

10.2.4 Abnormal Involuntary Movement Scale

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.

10.2.5 Barnes Akathisia Rating Scale

Barnes Akathisia Rating Scale (BARS) 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 trial. This item is rated on a 6-point scale, with 0 being best (absent) and 5 being worst (severe akathisia).

10.2.6 Sheehan Suicidality Tracking Scale

Suicidality will be monitored during the trial using the Sheehan-STS. The Sheehan-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors. Each item of the Sheehan-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). The Sheehan-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. The trial will use the “Screening” and “Since Last Visit” version of the scale. The “Screening” Sheehan-STS form will be completed at the screening visit to determine eligibility. Any subject with evidence of serious risk of suicide based on the Sheehan-STS, ie,

a score of 3 or 4 on any one question 2 through 6 or 11 or a score of 2 or higher on any one questions 1a, 7 through 10, or 12, or who, in the opinion of the investigator, present a serious risk of suicide should be excluded from the trial. The "Since Last Visit" Sheehan-STS form will be completed at all other visits. The medical monitor should be contacted if a score of 3 or 4 on any one question 3 through 6 or 11 or a score of 2 or higher on any one questions 1a, 7 through 10, or 12, or 18, or if suicide results in death.

10.2.7 Mini-Mental State Examination

The MMSE is a brief practical test for assessing cognitive dysfunction. The test consists of 5 sections (orientation, registration, attention and calculation, recall, and language) and has a total possible score of 30. The MMSE is used for screening subjects and is also to be completed at Week 12/ET.

The MMSE is a 19-item scale. Items 1 to 10, 15, and 17 to 19 are rated on a scale from 0 to 1, item 14 is rated on a 0 to 2 scale, items 11, 13 and 16 are rated on a scale from 0 to 3, and Item 12 is rated on a scale from 0 to 5. Low scores are the worst, high scores are the best. The MMSE total score is calculated by adding the individual item scores. The possible range for the MMSE total score is from 0 to 30. If the maximum total of the missing items could contribute more than 6 points to the total score then the total score will be set to missing. Otherwise, a mean non-missing items score will be calculated by summing the non-missing items and dividing them by the maximum score possible from the non-missing items. For missing items with possible scores from 0 to 1, the mean score will be imputed for each missing item. If item 14 is missing, two times this mean will be imputed for item 14. If items 11, 13, or 16 are missing three times this mean for will be imputed each missing item. If item 12 is missing 5 times then this mean will be imputed for item 12. After all by-item imputation has been done, the individual item scores will be added and this sum will be rounded to the first decimal place to arrive at an imputed total score. In other terms, the MMSE total score is simply the mean non-missing items score multiplied by 30, and then rounded to the first decimal place.

11 References

1 Rabinowitz J, Davidson M, Paul De Deyn P, Katz I, Brodaty H, Cohen-Mansfield J. Factor Analysis of the Cohen-Mansfield Agitation Inventory in Three Large Samples of Nursing Home Patients With Dementia and Behavioral Disturbance. Am J Geriatr Psychiatry. 2005;13(11):991-8.

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