Protocol and Statistical Analysis Plan

Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: A Randomized Clinical Trial.

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Contents

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-34712

REVISED CLINICAL PROTOCOL

A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-14-213
IND No. 115960
EudraCT No. 2017-003940-19

CONFIDENTIAL – PROPRIETARY INFORMATION

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Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-14-213 IND No.: 115960 EudraCT No.: 2017-003940-19
Protocol Title:	A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type
Clinical Phase/Trial Type:	3/Therapeutic confirmatory
Treatment Indication:	Agitation associated with dementia of the Alzheimer's type
Objective(s):	Primary: To confirm the efficacy of brexpiprazole compared with placebo in subjects with agitation in Alzheimer's dementia (AAD) Secondary: To evaluate the safety and tolerability of brexpiprazole compared with placebo in subjects with AAD
Trial Design:	This is a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole compared with placebo. Subjects will be randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo. The randomization will be stratified by site. Currently, there are no approved treatments in the United States for the management of agitation in patients with Alzheimer's disease. In other countries, treatment for the indication is restricted to the treatment of persistent aggression for a short period of time (6 weeks). Proven effective, tolerable, and safe treatment is essential in addressing this serious unmet need. The trial consists of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment safety follow-up period. In addition, for all subjects who terminate early from the trial, attempts will be made to collect

	data on mortality status by telephone contact with the subject's caregiver at Week 16. This trial will be monitored by an independent Data Monitoring Committee (DMC). The DMC will periodically monitor safety based on a predetermined schedule. In addition, an interim analysis of efficacy data is planned during the course of the trial, and will be performed by the independent DMC. The sponsor will remain blinded to the observed results of the interim analysis, and will only receive recommendations as per the interim analysis plan and DMC Charter. The trial is organized as follows: *Screening Period* The screening period will range from 2 days up to 42 days, with the goal of completing all screening activities within 30 days, if possible, and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. The screening period may be extended after discussion with and approval by the medical monitor. An eSource method will be used to obtain an identification number for each subject with documented consent. The purpose of the screening period is to determine the subject's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization. External quality oversight methods will be used by Clinical Surveillance & Training (CST) and the Independent Adjudication Panel to promote appropriate subject enrollment. In addition, starting at screening and continuing throughout the 12-week double-blind treatment period, the subject's behavior will be logged into a diary by the caregiver or facility staff. This diary will be sent to CST on a routine basis in order to corroborate information recorded on the Cohen-Mansfield Agitation Inventory (CMAI).

12-Week, Double-blind Treatment Period

Based on a randomization scheme, eligible subjects will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

- Brexpiprazole (further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day)
- Placebo

Subjects will follow a titration schedule, depending upon their assigned treatment group, to gradually increase their dose of the investigational medicinal product (IMP) to their assigned target dose as follows:

Dose	Day After the Baseline Visit (Days 1-7)	Days 8-14	Day After the Week 2 Visit (Days 15-28) (±2 days)	Day After the Week 4 Visit (Days 29-Week 12) (±2 days)
Brexpiprazole (2 mg/day)	0.5 mg	1 mg	2 mg	2 mg
Brexpiprazole (3 mg/day)	0.5 mg	1 mg	2 mg	3 mg
Placebo	Placebo	Placebo	Placebo	Placebo

The first dose of IMP (brexpiprazole or placebo) will be administered on the day after the baseline visit (ie, Day 1) and ending on Week 12 or early termination (ET; the last day of the treatment period).

Subjects unable to tolerate their assigned dose of brexpiprazole (or matching placebo) will be withdrawn from the trial. Down-titration is not allowed at any time during the trial. If a subject is withdrawn or discontinues prematurely before Week 12, every effort will be made to complete all of the Week 12 or ET evaluations prior to administering any additional medications for the treatment of agitation or other prohibited medications.

Subjects will be evaluated at baseline and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments.

Subjects who complete the 12-week double-blind treatment period of Trial 331-14-213 may be eligible to enter a 12-week open-label extension trial.

	If this trial is terminated early due to overwhelming efficacy from the interim analysis, subjects in this trial at the time may be offered entry into the open-label extension trial (Trial 331-201-00182) if they choose to participate. *Follow-up Period* All subjects, with the exception of those entering the optional open-label extension trial, 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.
Subject Population:	The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting, or in a non-institutionalized setting where they are not living alone. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with them in order to assess changes in the condition of the subject. All subjects must have a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, have a Mini-Mental State Examination (MMSE) score between 5 and 22 (inclusive), meet the criteria for the provisional International Psychogeriatric Association (IPA) consensus definition of agitation in patients with cognitive disorders, and meet additional predetermined blinded eligibility criteria to which the site clinical investigators will remain blinded (described in a separate blinded protocol addendum that will not be accessible to the site clinical investigators). (The provisional IPA definition is limited to patients with cognitive impairment and requires: (a) evidence of emotional distress; (b) one of 3 observable types of behaviors-excessive motor activity, verbal aggression, or physical aggression; (c) that the behavior causes excess disability; and (d) that the behaviors cannot be solely attributable to a suboptimal care environment or other disorder such as a psychiatric illness, a medical illness, or effects of a substance.)

	All trial visits will take place as a clinic visit at either the investigator's site or residential facility, as applicable. All attempts should be made to maintain the subject's normal routine with regard to physician appointments and overnight accommodations. Subjects who at any point during the double-blind treatment period transfer from an institutionalized setting to a non-institutionalized setting, or vice versa, will be withdrawn from the trial. Individual circumstances that fall outside this general convention (eg, short-term hospitalization) should be discussed with the medical monitor in order to determine appropriateness to proceed. In case of a short-term hospitalization, a determination of the subject's eligibility to stay in the trial must be made based on the subject's safety by the investigator and medical monitor. A subject in an institutionalized setting may receive supervised day passes at the discretion of the investigator and may also receive supervised overnight passes at the discretion of the investigator as long as such overnight stays are part of the subject's normal routine.
Inclusion/Exclusion Criteria:	Key inclusion criteria are described under Subject Population in this synopsis. Subjects must meet the inclusion criteria at both screening and baseline. Key exclusion criteria include the following: • Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, human immunodeficiency virus-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome. • Subjects with a previous magnetic resonance imaging (MRI)/computed tomography (CT) scan of the brain, which was performed after the onset of the symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (eg, cortical stroke, multiple infarcts), space-occupying lesion (eg, tumor), or other major structural brain disease. • Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism. • Subjects with delirium or history of delirium within the

	30 days prior to the screening visit. • Subjects who have received high-dose antipsychotics exceeding the equivalent of ≥ 3 mg of risperidone (eg, ≥ 5 mg of haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent) within 90 days prior to screening. • Subjects who have received multiple antipsychotic medications simultaneously for a period of > 7 days within 90 days prior to screening. • Subjects with evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (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. • Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.
Trial Site(s):	The trial is expected to enroll subjects at approximately 80 sites worldwide.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The IMP will be supplied as brexpiprazole tablets or matching placebo tablets. Each dose will be supplied as blister cards containing sufficient tablets for 7 (+2) days. When accessed by the site, the eSource method will assign specific blister card number(s) to be dispensed to a subject. After a 2- to 42-day screening period, eligible subjects will be randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day. The total duration of double-blind treatment will be 12 weeks for all randomized subjects. Neither the investigator nor the subject will be aware of the treatment assignment. All doses of brexpiprazole and matching placebo will be taken orally once daily, preferably in the morning, and will be administered without regard to meals. Brexpiprazole (or matching placebo) should be taken at approximately the same time each day.

Trial Assessments:	Efficacy: CMAI, Clinical Global Impression Severity of Illness (CGI-S) scale, Clinical Global Impression Improvement of Illness (CGI-I) scale [redacted] Pharmacokinetic (PK) [redacted] The PK samples for determination of brexpiprazole will be collected at the baseline visit and at the Week 8 and Week 12 or ET trial visits, at the same time as the sample collection for the clinical laboratory tests. [redacted] Safety: Adverse event (AE) reporting, clinical laboratory tests, electrocardiograms (ECGs), vital signs, physical and neurological examinations, body weight, body mass index, MMSE, Simpson Angus Scale (SAS) total score, Abnormal Involuntary Movement Scale (AIMS) Movement Rating Score, and Barnes Akathisia Rating Scale (BARS) Global Score, and Sheehan-STS. Screening/Other: Hachinski Ischemic Scale and NINCDS-ADRDA.

Criteria for Evaluation:	**Primary Efficacy Endpoint**: The primary efficacy endpoint is the change from baseline to Week 12 in the CMAI total score. **Key Secondary Efficacy Endpoint**: The key secondary efficacy endpoint is the change from baseline to Week 12 in the CGI-S score, as related to agitation. **Secondary Efficacy Endpoints**: • Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, verbally agitated behavior) • Change from baseline in CMAI total score for each trial visit during the double-blind treatment period • Change from baseline in CGI-S for each trial visit during the double-blind treatment period • CGI-I score at each trial visit during the double-blind treatment period • CMAI-based responder analysis as described in the statistical analysis plan (SAP) • CGI-I responder analysis as described in the SAP [redacted]

	Safety Endpoints: Safety and tolerability will be evaluated by reports of AEs, clinically significant changes in: physical examinations, neurological examinations, vital signs, body weight, waist circumference, clinical laboratory tests, and ECGs. Change from baseline in body mass index (derived programmatically from body weight and height measurements) will be summarized. Other safety variables will include the MMSE score and assessments of suicidality (Sheehan-STS), and extrapyramidal symptoms (SAS, AIMS, and BARS). **Pharmacokinetic/Pharmacodynamic Endpoints**: Plasma concentrations will be determined for brexpiprazole and descriptive statistics will be calculated. Concentrations of metabolites of brexpiprazole that are not identified in the protocol may also be determined, if needed. No formal statistical comparisons are planned. Additional population or PK or pharmacodynamic modeling may be performed as a separate analysis by combining data from this trial with data from all other trials.
Statistical Methods:	Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation. Tabulations of frequency distributions will be provided for categorical variables. The primary endpoint will be analyzed using a mixed-effect model repeated measures (MMRM) model. The model will include fixed-class effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CMAI total score by visit week as a covariate. The primary efficacy outcome measure is the mean change from baseline to Week 12 in the CMAI total score. The primary statistical comparison of interest is brexpiprazole versus placebo. The null hypothesis of this comparison is that there is no difference between the brexpiprazole treatment group and placebo in change from baseline to Week 12 in CMAI total score. Details of sensitivity analyses under the assumption of missing not at random will be provided in the SAP. The key secondary efficacy variable is the change from baseline to Week 12 in the CGI-S score, as related to agitation. It will be analyzed by the same statistical methodology specified for the analysis of the primary efficacy variable.

Trial Duration:	The trial is planned to randomize approximately 330 subjects at maximum. There will be one interim analysis when approximately the first 255 subjects have completed the 12-week trial or discontinued early. Depending on the result of the interim analysis, the trial may stop at the conclusion of the interim analysis, or proceed to the final analysis at the maximum sample size of approximately 330 subjects. The time from enrollment of the first subject to the last (330th) subject's last trial visit will be approximately 4.0 years, of which approximately 3.75 years are allotted for recruitment of subjects. Enrollment timelines could be shortened, as the trial may stop at the interim analysis based on the interim analysis result. If this trial is terminated early due to overwhelming efficacy from the interim analysis, subjects in this trial at the time may be offered entry into the open-label extension trial (Trial 331-201-00182) if they choose to participate. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects, with the exception of those entering the optional open-label extension trial, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP. In addition, 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.

Table of Contents

List of In-text Tables

List of In-text Figures

List of In-text Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin
5-HT_{1A}	Serotonin type 1A receptor
5-HT_{2A}	Serotonin type 2A receptor
AAD	Agitation in Alzheimer's dementia
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT (SGPT)	Alanine transaminase (serum glutamic-pyruvic transaminase)
Anti-HCV	Hepatitis C antibodies
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)
BARS	Barnes Akathisia Rating Scale
bpm	Beats per minute
CGI-I	Clinical Global Impression Improvement of Illness
CGI-S	Clinical Global Impression Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
CST	Clinical Surveillance & Training
CT	Computed tomography
CYP	Cytochrome P450
D	Dopamine
D_2	Dopamine type 2
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
ECG	Electrocardiogram
eICF	Electronic informed consent form
EPS	Extrapyramidal symptoms
ET	Early termination
EudraCT	European Clinical Trial Data Base
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High-density lipoprotein
IAP	Independent Adjudication Panel
IB	Investigator's Brochure

Abbreviation	Definition
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IPA	International Psychogeriatric Association
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LOCF	Last-observation-carried-forward
MDD	Major depressive disorder
MMRM	Mixed-effect model repeated measures
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
[redacted]	[redacted]
OC	Observed-case
OPC	Otsuka Pharmaceutical Company, Ltd.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
OTC	Over-the-counter
PK	Pharmacokinetic
PT	Prothrombin time
PTSD	Post-traumatic stress disorder
PQC	Product Quality Complaint
QTc	Corrected QT interval
QTcB	QT interval as corrected for heart rate by Bazett's formula
QTcF	QT interval as corrected for heart rate by Fridericia's formula
QTcN	QT interval as corrected for heart rate by the FDA Neuropharm Division formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure

Abbreviation	Definition
Sheehan-STS	Sheehan Suicidality Tracking Scale
T_4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UN	Un-structured
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

Term	Definition
Investigational medicinal product (IMP)	For the purposes of this protocol, IMP refers to all trial medication supplied to the sites by the sponsor (or designated agent) and includes blister cards containing brexpiprazole or matching placebo.

1 Introduction

It is currently estimated that 5.4 million Americans have Alzheimer's disease, and future projections estimate that, due to an increase in the aging population, there will be approximately 13.8 million Americans with Alzheimer's disease by 2050.[1,2] Fourteen percent of people aged 71 and older in the United States (US) have dementia and Alzheimer's disease accounts for an estimated 60% to 80% of cases.[1,3]

Neuropsychiatric symptoms, including agitation, are common features of Alzheimer's disease and related dementias. Over the course of the disease, nearly all patients with Alzheimer's dementia will likely experience neuropsychiatric symptoms.[4] Although agitation has a long history of being recognized as an important clinical feature of Alzheimer's disease, a widely recognized definition has been lacking in literature until recently. In 2015, the provisional International Psychogeriatric Association (IPA) definition of agitation limited to patients with cognitive impairment was developed and requires: a) evidence of emotional distress; (b) one of 3 observable types of behaviors-excessive motor activity, verbal aggression, or physical aggression; (c) that the behavior causes excess disability; and (d) that the behaviors cannot be solely attributable to a suboptimal care environment or other disorder such as a psychiatric illness, a medical illness, or effects of a substance.[5]

Agitation can be present from the early stages and throughout the course of Alzheimer's disease, and symptoms usually become more consequential as the disease progresses. Agitation in Alzheimer's dementia (AAD) has been associated with more rapid cognitive decline and progression to severe dementia, loss of independence, and earlier death.[6,7] Agitation is a leading cause of institutionalization for patients with Alzheimer's dementia; within care facilities, 40% to 60% of patients with Alzheimer's disease exhibit symptoms of agitation with and without aggression.[8] The presence of agitation in subjects with Alzheimer's dementia places a significant burden not only on subjects and their caregivers but also on the healthcare system. Additionally, aggressive behaviors such as combativeness, destroying property, and being a danger to oneself and others are significant predictors of time to nursing home placement.[9]

Currently, there are no approved treatments in the US for the management of agitation in patients with Alzheimer's disease. In other countries, treatment for the indication is restricted to the treatment of persistent aggression for a short period of time (6 weeks). Without approved labeling, at best in current clinical practice, clinicians rely on

guidelines when prescribing pharmaceutical treatments for patients with AAD.[10,11,12] Proven effective, tolerable, and safe treatment is essential in addressing this serious unmet need.

Brexpiprazole (OPC-34712, and Lu AF41156) was discovered by Otsuka Pharmaceutical Company, Ltd. (OPC) and is being codeveloped by Otsuka and H. Lundbeck A/S (Lundbeck). While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the efficacy of brexpiprazole is believed to be mediated by a combination of high affinity interactions with multiple monoaminergic receptors. Brexpiprazole is a serotonin (5-HT)-dopamine (D) activity modulator that is a partial agonist at 5-HT_{1A} and D_2 receptors, and an antagonist at serotonin 5-HT_{2A} and noradrenaline $\alpha_{1B/2C}$ receptors, all with similar subnanomolar potencies. The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptor antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy, reduced impulsive behavior, and cognitive improvement. Additionally, it is hypothesized that the partial agonist and antagonist activities of brexpiprazole at multiple serotonergic, dopaminergic and noradrenergic receptor systems may have a therapeutic benefit in the treatment of AAD.

Refer to the Investigator's Brochure (IB) for more detailed information about the investigational medicinal product (IMP).[13]

1.1 Nonclinical Data

A complete description of the available efficacy and safety pharmacology data from nonclinical studies, including pharmacokinetic (PK) and toxicology studies in different animal species can be found in the current IB.[13]

1.2 Clinical Data

Currently, brexpiprazole is approved in the US for use in adult patients for the treatment of schizophrenia, and for the use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD), and in Canada and Australia in adult patients for the treatment of schizophrenia. Additionally, the current clinical development program is designed to show safety and efficacy of brexpiprazole for the treatment of the following indications: treatment of adult post-traumatic stress disorder (PTSD), bipolar mania, adolescent schizophrenia, and the treatment of AAD.[13]

As of [redacted], the brexpiprazole clinical development program consisted of a total of 68 clinical trials conducted in North America, Latin America, Europe, and Asia (60 completed and 8 ongoing). This includes 61 trials conducted under US Investigational New Drug (IND) Applications (54 completed and 7 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of Attention-deficit/hyperactivity disorder (ADHD), AAD, or PTSD; and 7 non-US IND trials (6 completed and 1 ongoing) in either South Korea or Japan conducted in healthy subjects and subjects with schizophrenia.[13]

Please refer to the IB for a detailed summary of available clinical data.[13]

1.3 Known and Potential Risks and Benefits

As of [redacted], at least 8978 subjects have been exposed to a dose of brexpiprazole across the phase 2/3 completed trials for AAD, schizophrenia, MDD, ADHD, and PTSD, including 3249 subjects who have been exposed to brexpiprazole for at least 6 months and 1809 subjects who have been exposed for at least 1 year.

Data from clinical trials completed to date indicate that the maximum tolerated dose (MTD) of brexpiprazole in healthy adult subjects is 6 mg after single-dose administration and 2 mg after once-daily, multiple-dose (14 days) administration. The MTD of brexpiprazole in subjects with schizophrenia, MDD, or ADHD has not been established. Within the 3 indications with completed trials, data from completed multiple-dose phase 1 clinical trials indicate brexpiprazole is tolerated at multiple oral doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder, up to 4 mg/day as adjunctive therapy in adult subjects with MDD or ADHD, and up to 3 mg/day as adjunctive therapy in elderly subjects (70 to 85 years of age) with MDD.

Preliminary data from the 2 completed phase 3 trials (Trials 331-12-283 and 331-12-284) in subjects with AAD indicate brexpiprazole is safe and well tolerated, with no new safety signals identified in this elderly population.[14,15] There was a low incidence of treatment-emergent adverse events (TEAEs) associated with extrapyramidal symptoms (EPS) (5.8% brexpiprazole versus 4.0% placebo), weight increased (1.4% brexpiprazole versus 0.7% placebo), somnolence/sedation (3.7% brexpiprazole versus 2.2% placebo), falls (1.6% brexpiprazole versus 2.9% placebo), cardiovascular events (5.1% brexpiprazole versus 2.9% placebo), cerebrovascular events (0.7% brexpiprazole versus 0.4% placebo), and mortality (1.4% brexpiprazole versus 0.4% placebo). Overall, the TEAEs associated with mortality do not appear to support a relationship with the IMP. Results from the 2 completed phase 3 trials in subjects with AAD (Trial 331-12-283 and

Trial 331-12-284) showed that brexpiprazole doses up to 2 mg/day are safe and well-tolerated in this population.

Please refer to the IB for a summary of available nonclinical and clinical safety data.[13]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Preliminary data from the 2 completed phase 3 trials (Trials 331-12-283 and 331-12-284) indicate efficacy of brexpiprazole 2 mg/day in the treatment of subjects with AAD. The primary endpoint of mean change in Cohen-Mansfield Agitation Inventory (CMAI) total score from baseline to Week 12 in the fixed-dose trial (Trial 331-12-283) showed brexpiprazole 2 mg/day was statistically superior to placebo ($p < 0.05$). The lower dose group, 1 mg/day brexpiprazole, did not show any meaningful separation relative to placebo ($p > 0.05$). In the flexible-dose trial (Trial 331-12-284), the brexpiprazole 0.5 to 2 mg/day group (mean dose 1.54 mg/day) did not show statistical superiority relative to placebo on the CMAI total score at Week 12 ($p > 0.05$), but showed numerical improvement at each visit starting at Week 6, the first time point at which subjects could receive the 2 mg/day dose. Additionally, post-hoc analyses of subjects who were titrated to 2 mg/day brexpiprazole or similar placebo in the flexible-dose trial (Trial 331-12-284) supported the efficacy of brexpiprazole 2 mg/day (change in CMAI total score from baseline to Week 12, $p < 0.05$).

The sponsors met with the Food and Drug Administration (FDA) to discuss results of the 2 completed phase 3 trials of brexpiprazole for the treatment AAD (Trials 331-12-283 and 331-12-284). During this meeting, the FDA recommended exploring a higher dose (3 mg), measures to reduce placebo response, and potential enrichment strategies.

Based on the collective data from the 2 completed phase 3 trials, and the positive benefit/risk profile associated with brexpiprazole 2 mg/day, the proposed trial (Trial 331-14-213) is designed to confirm the efficacy, safety, and tolerability of brexpiprazole 2 mg/day compared with placebo as well as provide information about the efficacy, safety, and tolerability of brexpiprazole at 3 mg/day.

2.2 Dosing Rationale

The 2 mg/day dose of brexpiprazole to be used in Trial 331-14-213 is included based on its separation from placebo on the primary endpoint, change from baseline in CMAI total score, in Trial 331-12-283, and its demonstrated safety and tolerability, and is therefore

considered the minimum effective dose. The 3 mg/day dose is included to explore the efficacy, safety, and tolerability of a higher dose of brexpiprazole, as recommended by the FDA.

2.3 Trial Objectives

Primary: To confirm the efficacy of brexpiprazole compared with placebo in subjects with AAD

Secondary: To evaluate the safety and tolerability of brexpiprazole compared with placebo in subjects with AAD

3 Trial Design

3.1 Type/Design of Trial

This is a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole compared with placebo. Subjects will be randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo.

The trial consists of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment safety follow-up period. In addition, for all subjects who terminate early from the trial, attempts will be made to collect data on mortality status by telephone contact with the subject's caregiver at Week 16. See Figure 3.1-1 for a schematic of the trial design and Table 3.7-1 for the Schedule of Assessments.

This trial will be monitored by an independent Data Monitoring Committee (DMC) (Section 3.7.8). The DMC will periodically monitor safety based on a predetermined schedule. In addition, an interim analysis of efficacy data is planned during the course of the trial, and will be performed by the independent DMC. The sponsor will remain blinded to the observed results of the interim analysis, and will only receive recommendations as per the interim analysis plan and DMC Charter. The details of the DMC structure and its roles and responsibilities will be documented in a DMC Charter.

The trial is organized as follows:

Screening Period

The screening period will range from 2 days up to 42 days, with the goal of completing all screening activities within 30 days, if possible, and will begin when the informed

consent form (ICF) is signed, prior to the initiation of any procedures. The screening period may be extended after discussion with and approval by the medical monitor. Additional requirements for obtaining informed consent from this vulnerable subject population are provided in Section 3.4.1. An eSource method will be used to obtain an identification (ID) number for each subject with documented consent.

The purpose of the screening period is to determine the subject's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization (refer to Section 4.1).

External quality oversight methods will be used by Clinical Surveillance & Training (CST) and the Independent Adjudication Panel (IAP) to promote appropriate subject enrollment. Such methods will require sites to communicate certain aspects of subject data during the screening period to CST and the IAP, as detailed in the Operations Manual. The IAP will provide an independent assessment of the subject's eligibility at time of enrollment and may request exclusion of a subject from entry into the trial. Subjects cannot be randomized until approval from CST and the IAP has been received. The investigator is responsible for ensuring that subjects are eligible for enrollment into the trial and for assessing subject safety throughout the trial.

All CMAI interviews will be recorded. Regular quality reviews of CMAI audio recordings will be performed in order to verify the quality of the CMAI interview and accuracy of scoring. The process for data oversight will be outlined in the Operations Manual.

In addition, starting at screening and continuing throughout the 12-week double-blind treatment period, the subject's behavior will be logged into a diary by the caregiver or facility staff. This diary will be sent to CST on a routine basis in order to corroborate information recorded on the CMAI. Since the diary data is a tool to assist CST in monitoring CMAI rater training, the diary data will not be statistically analyzed.

While it is preferred that diary data are collected 7 days a week, it is realized that diary use for 7 days a week may not be possible because the minimum amount of time that the caregiver is required to observe the subject is 4 days a week. Every effort should be put forth by the sites to encourage the caregivers to collect and submit as much data as possible. Caretakers, facility personnel, or family members may provide information to the caregiver to complete the diary, but this is not a requirement.

Details around this procedure can be found in the Operations Manual.

12-Week, Double-blind Treatment Period

Based on a randomization scheme, eligible subjects will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

- Brexpiprazole (further randomized 1:2 to 2 mg/day or 3 mg/day)
- Placebo

Subjects will follow a titration schedule, depending upon their assigned treatment group, to gradually increase their dose of the IMP to their assigned target dose (refer to Table 3.2-1).

Subjects unable to tolerate their assigned dose of brexpiprazole (or matching placebo) will be withdrawn from the trial. Down-titration is not allowed at any time during the trial. If a subject is withdrawn or discontinues prematurely before Week 12, every effort will be made to complete all of the Week 12 or early termination (ET) evaluations prior to administering any additional medications for the treatment of agitation or other prohibited medications.

Subjects will be evaluated at baseline and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1).

Subjects who complete the 12-week double-blind treatment period of Trial 331-14-213 may be eligible to enter a 12-week open-label extension trial.

If this trial is terminated early due to overwhelming efficacy from the interim analysis, subjects in this trial at the time may be offered entry into the open-label extension trial (Trial 331-201-00182) if they choose to participate.

Follow-up Period

All subjects, with the exception of those entering the optional open-label extension trial, 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.

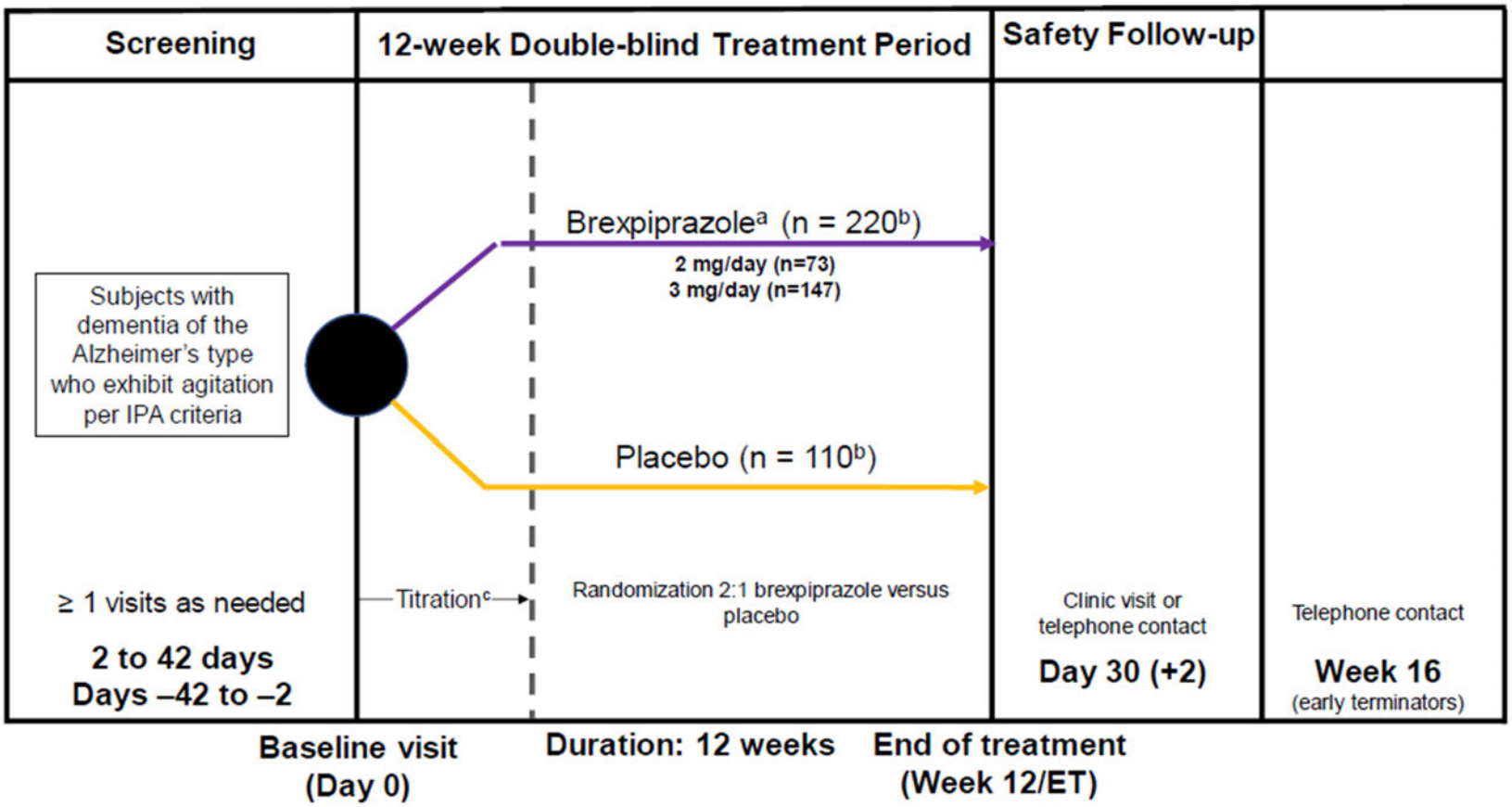

Figure 3.1-1 Trial Design Schematic

[a]Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day.

[b]The trial will have a two-stage group-sequential design with the planned maximum sample size of approximately 330 subjects for the final analysis if the trial does not stop at the interim analysis (on the first group of 255 subjects).

[c]Titration: Starting at 0.5 mg/day, and reaching 2 mg/day on Day 15, and 3 mg/day on Day 29.

3.2 Trial Treatments

Treatment assignments will be obtained by accessing eSource. Based on the fixed-block, computer-generated randomization, eligible subjects will be allocated in a 2:1 ratio at randomization to 1 of the following 2 treatment groups:

- Brexpiprazole (further randomized 1:2 to 2 mg/day or 3 mg/day)
- Placebo

Neither the investigator nor the subject will be aware of the treatment assignment. All doses of brexpiprazole and matching placebo will be taken orally once daily, preferably in the morning, and will be administered without regard to meals. Brexpiprazole (or matching placebo) should be taken at approximately the same time each day, particularly prior to visits with PK sampling.

Subjects will follow a titration schedule, depending upon their assigned treatment group, to gradually increase their dose of the IMP to their assigned target dose as described in Table 3.2-1.

Table 3.2-1 Dosing Scheme

Dose	Day after the Baseline visit (Days 1-7)	Days 8-14	Day after the Week 2 visit (Days 15-28) (±2 days)	Day after the Week 4 visit (Days 29-Week 12) (±2 days)
Brexpiprazole (2 mg/day)	0.5 mg	1 mg	2 mg	2 mg
Brexpiprazole (3 mg/day)	0.5 mg	1 mg	2 mg	3 mg
Placebo	Placebo	Placebo	Placebo	Placebo

The first dose of IMP (brexpiprazole or placebo) will be administered on the day after the baseline visit (ie, Day 1), and ending on Week 12 or ET (the last day of the treatment period).

For subjects randomly assigned to the brexpiprazole treatment group:

- The dose of IMP will be increased from 0.5 mg/day to 1.0 mg/day on Day 8.
- The dose will then be increased to 2 mg/day on the day after the Week 2 visit (Day 15).
- For applicable subjects, the dose will be increased to 3 mg/day on the day after the Week 4 visit (Day 29).
- Subjects will remain on their assigned dose until Week 12 or ET (the last day of the treatment period).

Down-titration will not be allowed at any time during the trial. Subjects unable to tolerate brexpiprazole (or matching placebo) will be discontinued from the trial (Section 3.1).

3.3 Trial Population

The trial is expected to randomize a maximum of approximately 330 subjects at approximately 80 sites worldwide. Based on the result of the interim analysis to be conducted on the first 255 randomized subjects, the trial may stop per the recommendation of the independent DMC. The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting, or in a non-institutionalized setting where they are not living alone. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with them in order to assess changes in the condition of the subject. All subjects must have a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, have a Mini-Mental State Examination (MMSE) score between 5 and 22 (inclusive), meet the criteria for the provisional IPA[16] consensus definition of agitation in patients with cognitive disorders (Section 3.7.3.4), and meet additional predetermined blinded eligibility criteria to which the site clinical investigators will remain blinded (described in a separate blinded protocol addendum that will not be accessible to the site clinical investigators).

All trial visits will take place as a clinic visit at either the investigator's site or residential facility, as applicable. All attempts should be made to maintain the subject's normal routine with regard to physician appointments and overnight accommodations. Subjects who at any point during the double-blind treatment period transfer from an institutionalized setting to a non-institutionalized setting, or vice versa, will be withdrawn from the trial. Individual circumstances that fall outside this general convention (eg, short-term hospitalization) should be discussed with the medical monitor in order to determine appropriateness to proceed. In case of a short-term hospitalization, a determination of the subject's eligibility to stay in the trial must be made based on the subject's safety by the investigator and medical monitor. A subject in an institutionalized setting may receive supervised day passes at the discretion of the investigator and may also receive supervised overnight passes at the discretion of the investigator as long as such overnight stays are part of the subject's normal routine.

3.3.1 Caregiver/Caretaker Requirements

3.3.1.1 Non-institutionalized Subjects

In a non-institutionalized setting, the subject's caretaker is the person who lives with and cares for the subject on a regular basis. For example, caring for a subject on a regular basis may include the following activities: assisting with dispensing of IMP; observing the subject's general medical condition, including nutrition and hydration intake; reducing the chance of fall; and assisting the subject if emergency medical care is needed by contacting appropriate emergency services, the subject's primary physician, or the principal investigator, whatever is warranted or associated with providing custodial care. The caretaker may be supported in providing care to the subject by a professional(s), friend(s), or family member(s).

For purposes of this trial, the subject's caregiver is defined as the person who has sufficient contact to describe the subject's symptoms, and has direct observation of the subject's behavior in order to participate in the interview for the CMAI, [redacted] and other applicable trial assessments, including completion of the diary. A caregiver must be identified during the screening period for participation in the interview of the applicable trial assessments. At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process. The caregiver role in the non-institutionalized setting may or may not be fulfilled by the same individual who fulfills the role of caretaker depending on the circumstances of the subject. The minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week. The caregiver is the person who should accompany the subject to all visits where the CMAI [redacted] are administered unless other arrangements are made and approved by the sponsor. Starting at screening, there should be no changes in living situation (eg, room) to ensure the same pre-trial routine is maintained.

3.3.1.2 Institutionalized Subjects

In the institutionalized setting, there is only one role defined and that is the role of caregiver. A caregiver in the institutionalized setting is an individual who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, [redacted]

[redacted] and other applicable trial assessments. A caregiver must be identified during the screening period for participation in the interview of the applicable trial assessments. At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. The recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week. Starting at screening, there should be no changes in living situation (eg, room) to ensure the same pre-trial routine is maintained.

3.3.2 Number of Subjects and Description of Population

Sufficient numbers of male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone, are planned to be screened at approximately 80 sites worldwide in order to randomize a maximum of approximately 330 subjects. Based on the result of the interim analysis to be conducted on the first 255 randomized subjects, the trial may stop per the recommendation of the independent DMC.

3.3.3 Subject Selection and Numbering

See Section 3.6.1 (Randomization).

3.4 Eligibility Criteria

3.4.1 Informed Consent

3.4.1.1 Determinations of Capacity

The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. This assessment will be made in accordance with the investigator's standard practice. Once these determinations are made by the investigator, the following options for obtaining informed consent from or on behalf of the subject must be followed:

- If the subject is deemed capable by the investigator, informed consent will be obtained from the subject prior to the initiation of any trial protocol-required procedures. In such cases, acknowledgement from the subject's legally acceptable representative (an individual, or judicial or other body, authorized under applicable

law to consent to the subject's participation in the clinical trial on behalf of that prospective subject) will also be obtained, if required, in accordance with state or local regulations prior to initiation of any trial protocol-required procedures.

- If the subject is deemed incapable by the investigator of providing consent (eg, subjects with severe dementia), informed consent will be obtained from the subject's legally acceptable representative prior to initiation of any trial protocol required procedures. In such cases, assent from the subject, if possible, will be confirmed in accordance with state or local regulations prior to the initiation of any trial protocol-required procedures.
- If the subject cannot provide assent, and does not dissent, then the consent of the legally acceptable representative is sufficient unless otherwise required by the governing ethics body or applicable state or local regulations.
- If the subject dissents, then the subject is not eligible for participation in the trial.
- If the subject initially provided assent at trial entry, but subsequently dissents to participate in the trial, the subject will be early terminated from the trial.
- If the subject was initially deemed capable of providing informed consent but is no longer deemed so, informed consent must be obtained from the subject's legally acceptable representative, and assent from the subject, if possible, will be confirmed in accordance with state or local regulations prior to the initiation or continuation of any trial protocol-required procedures.

3.4.1.2 Documentation of Informed Consent

In support of the site's standard process for administering informed consent, this trial will also utilize an electronic informed consent form (eICF) as a tool within applicable regions and sites. The eICF utilizes the institutional review board(IRB)-approved, site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, sites will have subjects review and sign the eICF prior to starting any trial procedures; however if local regulations does not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper signature process.

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB or independent ethics committee (IEC) that approves this protocol.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[17] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial prior to submission to the IRB or IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial participants will be provided with controlled access to the ICF application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will sign in the ICF application and a date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB or IEC (trial site staff, witnesses, or legally authorized representative [Section 3.4.1.1]) are also required to sign and these signatures will be stored with the ICF in accordance with the ICH GCP Guideline and local regulatory requirements or guidelines. These signatures cannot be altered, removed, or copied.

If the subject or subject's legally acceptable representative is unable to read or sign due to physical limitations, an impartial witness should be present during the entire informed consent discussion. After the subject's legally acceptable representative and subject orally consent and have signed, if capable, the witness should sign and personally date the consent or assent form attesting that the information is accurate and that the subject's legally acceptable representative and subject understand and have freely given consent.

The informed consent and any other information provided to the subject and the subject's legally acceptable representative should be revised whenever important new information becomes available that is relevant to the consent, and should receive IRB or IEC approval prior to use. The investigator (or qualified designee) should fully inform the subject and the subject's legally acceptable representative of all pertinent aspects of the trial and of any new information relevant to the willingness of the subject and the subject's legally acceptable representative to continue participation in the trial. This communication should be documented.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

[redacted]

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from or on behalf of the subject must be followed as provided in Section 3.4.1.
2.	Male and female subjects between 55 and 90 years of age, inclusive, at the time of informed consent.
3.	Subjects with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria.
4.	Subjects with a diagnosis of agitation that meets the IPA provisional definition of agitation (Section 3.7.3.4).
5.	Subjects with a MMSE score of 5 to 22, inclusive, at the screening and baseline visits.
6.	Subjects with a previous MRI or CT scan of the brain, that was performed after the onset of the symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease.
7.	Subjects who are residing at their current location for at least 28 days before screening and are expected to remain at the same location for the duration of the trial.
8.	Institutionalized subjects with an identified caregiver (Section 3.3.1) who has sufficient contact (minimum of 2 hours per day for 4 days per week) to describe the subject's symptoms and has direct observation of the subject's behavior. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. Non-institutionalized subjects may not be living alone (Section 3.3.1) and must have an identified caregiver who has sufficient contact (minimum of 2 hours per day for 4 days per week) to describe the subject's symptoms and has direct observation of the subject's behavior.
9.	Subjects with a total score (frequency × severity) of ≥ 4 on the agitation/aggression item of the [redacted] at the screening and baseline visits.
10.	Subjects with onset of symptoms of agitation at least 2 weeks prior to the screening visit.
11.	Subjects must meet additional predetermined blinded eligibility criteria according to the blinded addendum.
12.	Subjects who require pharmacotherapy for the treatment of agitation per the investigator's judgment, after: • An evaluation for reversible factors (eg, pain, infection, or polypharmacy), and • A trial of nonpharmacological interventions (eg, redirecting behavior, group activities, music therapy)
13.	Subjects who are capable of self-locomotion or locomotion with an assistive device (eg, 4-point walker, wheelchair).
14.	Subjects willing and able to discontinue all prohibited concomitant medications to meet protocol required washouts prior to and during the trial period.
15.	Subjects able to satisfactorily comply with the protocol requirements.

CT = computed tomography; MRI = magnetic resonance imaging.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

Target Disease	
1.	Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.
2.	Subjects with a previous MRI or CT scan of the brain, which was performed after the onset of the symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (eg, cortical stroke, multiple infarcts), space-occupying lesion (eg, tumor), or other major structural brain disease.
3.	Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.
4.	Subjects who had an insufficient response, based on the investigator's judgment, to 2 or more previous antipsychotic medications.
5.	Subjects who have received high-dose antipsychotics exceeding the equivalent of ≥ 3 mg of risperidone (eg, ≥ 5 mg of haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent) within 90 days prior to screening.
6.	Subjects who have received multiple antipsychotic medications simultaneously for a period of > 7 days within 90 days prior to screening.
7.	Subjects with delirium or history of delirium within the 30 days prior to the screening visit.
8.	Subjects who have been diagnosed with an Axis I disorder (DSM-5 criteria) including, but not limited to: • Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia • Bipolar I or II disorder, bipolar disorder not otherwise specified • Current Major Depressive Episode. Subjects with a history of MDD, that is not currently symptomatic, are eligible. Subjects currently on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization are eligible. For those not currently on antidepressant medication(s), no medication(s) should have been taken for 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited (Section 4.1).
9.	Subjects with evidence of serious risk of suicide based on the Sheehan-Suicidality Tracking Scale, 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 question 1a, 7 through 10, or 12; or who, in the opinion of the investigator, present a serious risk of suicide.
10.	Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, gastrointestinal, or psychiatric disorders. Clinically significant cardiovascular disorders include uncontrolled atrial fibrillation, heart failure, or ischemic heart disease. Surrogates for uncontrolled cardiovascular disease would include recent (within the last 6 months) hospitalizations or procedures, such as percutaneous coronary intervention or coronary artery bypass surgery. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.

Table 3.4.3-1	Exclusion Criteria
11.	Subjects with uncontrolled hypertension (DBP > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension, which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure, OR development of symptoms. Abnormal vital signs results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
12.	Subjects with diabetes mellitus (IDDM and non-IDDM) may be eligible for the trial if their condition is stable and well-controlled as determined by satisfying ALL of the following criteria at screening and baseline: • Screening HbA_{1c} < 8.0%, AND • Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND • Subject has not had any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes. Subjects with non-IDDM (ie, any subjects not using insulin) must also satisfy the below criterion: • Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening. Subjects with newly diagnosed diabetes during screening will be excluded.
13.	Subjects with a history of hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days) or an abnormal result for free T_4 at screening. Eligibility of subjects excluded based on an abnormal free T_4 result can be discussed with the medical monitor if, in the investigator's judgment, the subject is a suitable candidate for the trial.
14.	Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post-traumatic seizure, alcohol withdrawal seizure.
15.	Subjects with seropositive status for hepatitis B (ie, HBsAg positive) or hepatitis C (ie, anti-HCV positive).
16.	Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.
17.	Subjects with a body mass index < 18.5 kg/m^2 at screening and baseline.
18.	Subjects who have met DSM-5 criteria for substance abuse or dependence within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
19.	Subjects with a positive drug screen for cocaine, marijuana (whether medically prescribed or not), or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive blood alcohol test or urine drug screen resulting from use of prescription or over-the-counter medications or products that in the investigator's opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.
20.	Subjects with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subject or the interpretation of the trial results and the results have been discussed with and approved as acceptable for trial eligibility by the trial medical monitor. Criteria will be provided in a protocol appendix to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

Table 3.4.3-1 Exclusion Criteria	
	In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: • Platelets ≤ 75000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 • AST > 2 × ULN • ALT > 2 × ULN • CPK > 3 × ULN, unless discussed with and approved by the medical monitor • Albumin < 3 g/dL • HbA_{1c} ≥ 8% • Abnormal T_4, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if the result for TSH is abnormal.) • QTcF ≥ 450 msec in men and ≥ 470 msec in women (detailed further in the protocol), unless due to ventricular pacing Tests with exclusionary results should be repeated (if ECG, 3 consecutive recordings) to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
21.	Sexually active women of childbearing potential (detailed further in Section 5.5) and male subjects who are not practicing 2 different methods of birth control with their partner during the trial and for 30 days after the last dose of IMP or who will not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use 2 of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control patch, birth control depot injections, condom with spermicide, or sponge with spermicide.
22.	Women who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP in Trial 331-14-213.
23.	Subjects who have a current medical condition that requires treatment with an anticoagulant, although antiplatelet medications are not prohibited.
24.	Subjects who have received immunotherapy, such as vaccines, for the treatment of Alzheimer's disease (through clinical trial or compassionate use program) in the 6 months preceding randomization.
25.	Subjects who would be likely to require prohibited concomitant therapy during the trial.
26.	Subjects who received commercially available brexpiprazole (REXULTI) or participated in any brexpiprazole clinical trial.
27.	Subjects with a history of neuroleptic malignant syndrome.
28.	Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
29.	Subjects who participated in a clinical trial within the last 30 days prior to screening.
30.	Subjects who, in the opinion of the investigator, medical monitor, sponsor, IAP, or CST, should not participate in the trial.

ALT (SGPT) = alanine transaminase (serum glutamic-pyruvic transaminase); anti-HCV = hepatitis C antibodies; AST (SGOT) = aspartate transaminase (serum glutamic-oxaloacetic transaminase); CPK = creatine phosphokinase; CYP = cytochrome P450; DBP = diastolic blood pressure; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition;

ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; QTcF = QT interval as corrected for heart rate by Frederica's formula; SBP = systolic blood pressure;

T_4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Screen failures (Section 3.9) previously excluded for a positive drug screen for cocaine, marijuana, or other illicit drugs are not eligible to be retested or rescreened. Screen failures previously excluded for a positive blood alcohol test or a positive urine drug screen due to use of prescription or over-the-counter (OTC) medications or products may be retested or rescreened once for participation in the trial with consent of the medical monitor. Screen failures excluded for any other reasons may be retested (the evaluation may be repeated within the screening period) or rescreened at any time if the exclusion characteristic has changed. A subject may be rescreened more than once after discussion with and approval by the medical monitor. In the event that a screen failure is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects must agree to restrictions to medications and lifestyle as described in Section 4.

3.5 Endpoints

3.5.1 Primary Endpoint

3.5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in the CMAI total score.

3.5.2 Secondary Endpoints

3.5.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the change from baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) score, as related to agitation.

3.5.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, verbally agitated behavior)
- Change from baseline in CMAI total score for each trial visit during the double-blind treatment period

- Change from baseline in CGI-S for each trial visit during the double-blind treatment period
- Clinical Global Impression Improvement of Illness (CGI-I) score at each trial visit during the double-blind treatment period
- CMAI-based responder analysis as described in the statistical analysis plan (SAP)
- CGI-I responder analysis as described in the SAP

[redacted]

3.5.4 Safety Endpoints

Safety and tolerability will be evaluated by reports of adverse events (AEs), clinically significant changes in: physical examinations, neurological examinations, vital signs, body weight, waist circumference, clinical laboratory tests, and 12-lead electrocardiograms (ECGs). Other safety variables will include body mass index (BMI), the MMSE score and assessments of suicidality (Sheehan Suicidality Tracking Scale [Sheehan-STS]), EPS (the Simpson Angus Scale [SAS], the Abnormal Involuntary Movement Scale [AIMS], and the Barnes Akathisia Rating Scale [BARS]).

Adverse events will be examined by frequency, severity, seriousness, discontinuation, and relationship to treatment. Mean change from baseline and the incidence of potentially clinically relevant abnormal values will be calculated for vital signs, body weight, routine laboratory tests (including prolactin), and ECG parameters. Mean change from baseline will be calculated for glycosylated hemoglobin (HbA_{1c}), waist circumference, and BMI (derived programmatically from body weight and height measurements). A central ECG service will be used to review all ECGs to standardize interpretations for the safety analysis. Extrapyramidal symptoms (EPS) will be evaluated by calculating mean change from baseline on the SAS, AIMS, and BARS. The Sheehan-STS will be used to assess and classify reported suicidal behavior. By-subject

listings of physical and neurological examination findings will be reviewed as a further assessment of safety.

3.5.5 Pharmacokinetic/Pharmacodynamic Endpoints

Plasma concentrations will be determined for brexpiprazole and descriptive statistics will be calculated [redacted]. No formal statistical comparisons are planned. [redacted]

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

During the trial, administration of the IMP will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (ie, placebo or brexpiprazole). Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) Biometrics Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, operating eSource, and reporting serious adverse events (SAEs) to regulatory agencies. The randomization will be stratified by site. Subjects will be randomized to brexpiprazole or placebo in a 2:1 ratio within each stratum. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day.

3.7 Trial Procedures

The time from enrollment of the first subject to the last (330th) subject's last trial visit will be approximately 4.0 years, of which approximately 3.75 years are allotted for recruitment of subjects. Enrollment timelines could be shortened, as the trial may stop at the interim analysis based on the interim analysis result. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects, with the exception of those entering the optional open-label extension trial, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP. In addition, 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.

The Schedule of Assessments is summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments											
	Visit										
Assessment	Screening[a]	Baseline (Day 0)	Week 2 (±2 days)	Week 4 (±2 days)	Week 6 (±2 days)	Week 8 (±2 days)	Week 10 (±2 days)	Week 12 or ET[b] (±2 days)	Follow-up[c] (+2 days)	Week 16[d]	Notes
ENTRANCE and HISTORY											
Informed consent	X										Section 3.4.1.1
Inclusion and exclusion criteria	X	X									Section 3.4
Demography	X										
Medical history	X										
Psychiatric history	X										
Neurological history	X										Section 3.7.3.3 Section 3.7.5.3.2
Prior medication washout	X										Section 4.1
HBsAg and anti-HCV	X										
Eligibility assessment by CST and IAP	X										Section 3.1
MRI or CT scan[e]	X										Section 3.7.3.3
Randomization		X									
EFFICACY											
CMAI	X	X	X	X	X	X	X	X			
CGI-S	X	X	X	X	X	X	X	X			
CGI-I			X	X	X	X	X	X			
[redacted])	X	X			X			X			
SAFETY											
Physical examination	X							X			Section 3.7.5.3.1
Neurological examination	X							X			Section 3.7.5.3.2
Vital signs	X	X	X	X	X	X	X	X			Section 3.7.5.3.3
Body weight	X	X						X			Section 3.7.5.3.3
Clinical laboratory tests (hematology, serum chemistry, urinalysis)	X	X[f]				X		X			Section 3.7.5.2

Table 3.7-1 Schedule of Assessments

Assessment	Visit										Notes
	Screening[a]	Baseline (Day 0)	Week 2 (±2 days)	Week 4 (±2 days)	Week 6 (±2 days)	Week 8 (±2 days)	Week 10 (±2 days)	Week 12 or ET[b] (±2 days)	Follow-up[c] (+2 days)	Week 16[d]	
Prolactin (blinded)	X							X			Section 3.7.5.2
TSH with reflex to free T_4 if abnormal	X										Section 3.7.5.2
HbA_{1c}	X							X			Section 3.7.5.2
PT, aPTT, and INR	X										Section 3.7.5.2
Urine pregnancy test (women of childbearing potential) only	X							X			Section 3.7.5.2
ECG	X	X				X		X			Section 3.7.5.4
Urine drug screen and blood alcohol test	X										Section 3.7.5.2 Section 4.2
MMSE	X	X						X			
Sheehan-STS	X	X						X			Section 3.7.5.5.4
Extrapyramidal symptoms scales (SAS, AIMS, BARS)		X						X			
Adverse events	X	X	X	X	X	X	X	X	X		Section 5
Pharmacokinetic sampling		X				X		X			Section 3.7.6.1.1
[redacted]		X									Section 3.7.6.2
Concomitant medications	X	X	X	X	X	X	X	X	X		Section 3.7.4
Mortality status assessment										X	Section 3.7.1.5
OTHER PROCEDURES											
IMP dispensing		X	X	X	X	X	X				Section 8.4
IMP accountability		X	X	X	X	X	X	X			

aPTT = activated partial thromboplastin time; INR = International Normalized Ratio; PT = prothrombin time.

[a]See Section 3.7.1.1.

[b]See Section 3.1.

[c]See Section 3.8.3.2.

[d]Note that this visit is 16 weeks postbaseline and only for subjects who terminate early from the trial.

[e]If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed by CST or the IAP in order to confirm eligibility.

[f]If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit.

3.7.1 Schedule of Assessments

3.7.1.1 Screening

The screening period begins after informed consent has been obtained. All required assessments will be performed as described in the Schedule of Assessments (Table 3.7-1). Subjects will participate in screening activities from 2 days up to 42 days, with the goal of completing all screening activities within 30 days, if possible. The screening period maximum of 42 days may be extended after discussion with and approval by the medical monitor. After a subject has provided consent, sites will obtain a subject ID number for the subject by accessing eSource. Completion of screening activities may require more than one visit.

Sites are required to communicate certain aspects of subject data during the screening period to CST and the IAP, as detailed in the Operations Manual. The CST and IAP must approve subject eligibility in order for the subject to be randomized. The following should also be noted:

- At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities and their role in this trial. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.
- The investigator must assess the capacity of the subject to provide informed consent during the screening period. Once this determination is made by the investigator, the options for obtaining informed consent from or on behalf of the subject must be followed as provided in Section 3.4.1.
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years that is considered to be clinically relevant per the investigator's judgment.
- Washout from prohibited concomitant medications, if applicable, will begin after consent has been obtained (see Section 4.1).
- The eligibility review for each subject will be completed and submitted to CST and the IAP per the Operations Manual.
- The subject's caregiver or facility staff will complete a diary daily (if possible) after the ICF is signed, continuing through Week 12 or ET.

3.7.1.2 Baseline (Day 0)

If the subject is found to be eligible for the trial during the screening period, all required baseline assessments will be performed according to the Schedule of Assessments (Table 3.7-1). The following should also be noted:

- Approval from CST and the IAP for randomization of subject will be verified.
- Inclusion and exclusion criteria will be verified.
- The investigator must determine if there have been any changes to the prior assessment of the subject's capacity to provide informed consent. If changes have been made, refer to the instructions detailed in Section 3.4.1.1.
- Diary recording will continue.
- The subject will take the first dose of the IMP from the assigned blister card on Day 1 (ie, the day after the baseline visit). The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.

3.7.1.3 Double-blind Treatment Period

3.7.1.3.1 Weeks 2, 4, 6, 8, and 10

All subjects will be evaluated at Weeks 2, 4, 6, 8, and 10. Visits are to occur within ± 2 days of the target visit date. All required evaluations will be performed as described in the Schedule of Assessments (Table 3.7-1). The following should also be noted:

- The investigator must determine if there have been any changes to the prior assessment of the subject's capacity to provide informed consent. If changes have been made, refer to the instructions detailed in Section 3.4.1.1.
- Diary recording will continue.
- IMP accountability will be performed.
- The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.

3.7.1.4 End of Treatment (Week 12)

All required evaluations will be performed as described in the Schedule of Assessments (Table 3.7-1). The Week 12 visit signifies the end of treatment for all subjects. Therefore, all subjects will undergo a complete evaluation at Week 12 (± 2 days). In addition, Week 12 or ET evaluations are to be completed for any subject withdrawn from the trial at any time, if possible. If a subject is withdrawn, every effort will be made to complete all of the Week 12 or ET evaluations prior to administering any additional

medications for the treatment of agitation or other prohibited medications. The following should be noted:

- Diary recording will be stopped.
- Final IMP accountability will be performed.

Subjects who complete the 12-week double-blind treatment period of Trial 331-14-213 may be eligible to enter a 12-week open-label extension trial.

If this trial is terminated early due to overwhelming efficacy from the interim analysis, subjects in this trial at the time may be offered entry into the open-label extension trial (Trial 331-201-00182) if they choose to participate.

3.7.1.5 Follow-up

All required assessments will be performed as described in the Schedule of Assessments (Table 3.7-1). All subjects, with the exception of those entering the optional open-label extension trial, 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 with the subject and a caregiver. All AEs and concomitant medications will be recorded.

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.

3.7.2 Efficacy Assessments

It is required that adequately trained and experienced clinicians administer the CMAI, [redacted], CGI-S, and CGI-I. In addition, the raters must be certified for this trial to administer the CMAI. Notations in the subject's trial records should substantiate the ratings. Training, certification, and materials for rating will be provided by a rater training group.

A caregiver must be identified during the screening period for participation in the interview for the CMAI, [redacted] and other applicable trial assessments. In addition to providing responses to trial questionnaires, the identified caregiver will be interviewed by the trial personnel regarding the subject's general medical condition, behavioral symptoms, and activities of daily living. If the subject is in an institutionalized setting, the identified caregiver will gather information from several informants, including staff from the day, afternoon, and night shifts, as well as from reliable family members or friends, in order to provide an accurate and comprehensive

overview of the subject's behavioral symptoms and condition. If the subject is in a non-institutionalized setting, the identified caregiver can gather information from the caretaker (if different than the identified caregiver) or from other informants who are in a position to observe the subject and provide information regarding behavioral symptoms and activities of daily living. Details on the caregiver requirements can be found in Section 3.3.1.

3.7.2.1 Cohen-Mansfield Agitation Inventory

The CMAI was developed to assess the frequency of agitated behaviors in elderly persons and was originally used in nursing home residents. It consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation.[18] As initially described by Cohen-Mansfield[18] and outlined in the Instruction Manual for the CMAI[19] these distinct agitation syndromes include: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior.

All CMAI interviews will be recorded. Regular quality reviews of CMAI audio recordings will be performed in order to verify the quality of the CMAI interview and accuracy of scoring. The process for data oversight will be outlined in the Operations Manual.

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

The severity of agitation for each subject will be rated using the CGI-S.[20] 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.

3.7.2.3 Clinical Global Impression Improvement of Illness (CGI-I)

The efficacy of brexpiprazole in the treatment of agitation will be rated for each subject using the CGI-I.[20] The investigator (or designee) will rate the subject's total improvement (as related to agitation) compared to baseline whether or not it is due entirely to drug treatment. Response choices are 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

[redacted]

[redacted]

3.7.3 Other Assessments

3.7.3.1 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

The NINCDS-ADRDA, which has shown good reliability and validity, provides criteria for the possible and probable diagnosis of Alzheimer's disease.[25] These criteria require that cognitive impairment and a suspected dementia syndrome be confirmed by neuropsychological testing for a clinical diagnosis of Alzheimer's disease. The NINCDS-ADRDA criteria specify 8 cognitive domains that may be impaired in Alzheimer's disease: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving, and functional abilities.

3.7.3.2 Hachinski Ischemic Scale (Rosen Modification)

The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms.[26] The Rosen modified Hachinski Ischemic Scale will be completed to assess eligibility for the trial by the same physician who performs the neurological examination (see Section 3.7.5.3.2).

3.7.3.3 Magnetic Resonance Imaging/Computed Tomography Scan of the Brain

If a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain performed after the onset of the symptoms of dementia is not available, then an MRI or CT scan should be performed during screening. In addition, a repeat MRI or CT scan of the brain may be requested to be performed by CST or the IAP in order to confirm eligibility.

3.7.3.4 International Psychogeriatric Association

The IPA developed a provisional consensus definition of agitation utilizing *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-5) terminology. The definition is intended to advance further research in agitated patients with cognitive impairment. The IPA provisional consensus definition of agitation[16] is described in Table 3.7.3.4-1.

Table 3.7.3.4-1 Consensus Provisional Definition of Agitation in Cognitive Disorders	
Item	**Definition**
A.	The patient meets criteria for a cognitive impairment or dementia syndrome (eg, Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder). Note: Only subjects who meet the NINCDS-ADRDA criteria for Alzheimer's Disease as noted in Inclusion Criterion #3 (Section 3.4.2) are eligible for this trial.
B.	The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (eg, rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of 2 weeks' and represents a change from the patient's usual behavior. (a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms). (b) Verbal aggression (eg, yelling, speaking in an excessively loud voice, using profanity, screaming, shouting). (c) Physical aggression (eg, grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property).
C.	Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following: (a) Significant impairment in interpersonal relationships. (b) Significant impairment in other aspects of social functioning. (c) Significant impairment in ability to perform or participate in daily living activities.
D.	While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary or secondary objectives) on the eSource. Details of prohibited and restricted medications are provided in Section 4.1. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eSource.

3.7.5 Safety Assessments

3.7.5.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.5.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Urine will be collected and blood will be drawn from each subject during screening prior to treatment with the IMP. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. Clinical laboratory tests at other visits should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 12 or ET. Vital sign measurements and ECG assessments should be completed before any blood samples are collected. See exclusion criteria (Section 3.4.3) based on screening laboratory tests. If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit. The results of these tests must be reviewed by the investigator prior to initiation of the administration of the IMP. Urinalysis is not required at Week 8. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory will be retained electronically within the lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eSource.

The clinical laboratory assessments are described in Table 3.7.5.2-1.

Table 3.7.5.2-1 Clinical Laboratory Assessments

Hematology WBC count with differential RBC count Hematocrit Hemoglobin Platelet count Urinalysis pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (performed only if any part of the urinalysis is not negative) Urine Drug Screen Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Opiates Phencyclidine Propoxyphene Other Blood alcohol Additional Tests (Screening Only) HBsAg Anti-HCV	Serum Chemistry ALP ALT (SGPT) AST (SGOT) BUN CPK Creatinine Total bilirubin Triglycerides Cholesterol (total, LDL, and HDL) Calcium Chloride Glucose Insulin Sodium Potassium Total protein Uric acid GGT Prolactin (blinded) Albumin Additional Tests Urine pregnancy (women of childbearing potential)[a] TSH, with reflex to free T_4 if TSH is abnormal PT, aPTT, and INR (screening only) HbA_{1c}

ALP = alkaline phosphatase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cell; WBC = white blood cell.

[a]All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

The total volume of blood to be collected during the trial will be documented in the ICF.

A pregnancy test will be conducted in women of childbearing potential (WOCBP; Section 5.5) prior to trial intervention; results must be available prior to the administration of the IMP. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected. An additional pregnancy test will be conducted in WOCBP at the Week 12 or ET visit.

Any value outside the normal range will be flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 2 for criteria for identifying values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets $\leq 75{,}000/mm^3$
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute $\leq 1000/mm^3$
- Aspartate transaminase (AST) > 2 × upper limit of normal (ULN)
- Alanine transaminase (ALT) > 2 × ULN
- Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
- Albumin < 3 g/dL
- $HbA_{1c} \geq 8\%$
- Abnormal free thyroxine (T_4), unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if the result for thyroid-stimulating hormone [TSH] is abnormal.)

3.7.5.3 Physical and Neurological Examination and Vital Signs

3.7.5.3.1 Physical Examinations

A complete physical examination will be performed at screening and will consist of measurement of height and waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; urogenital; extremities; neurological (see Section 3.7.5.3.2); and skin and mucosa. At screening, height will be measured with a stadiometer, measuring stick or tape. Repeat measurement of height is not required at the physical examinations scheduled for the Week 12 or ET visit. Waist circumference will be measured at each physical examination (screening and Week 12 or

ET), using the provided measuring tape. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- Measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[27]

The investigator (or designee) is responsible for performing the physical examination. If the appointed designee is to perform the physical examination, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

3.7.5.3.2 Neurological Examinations

A detailed neurological examination will be performed by a physician at screening, Week 12 or ET, and as needed during the trial for new onset neurological symptoms. The neurological examination will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system.

The physician is responsible for performing the neurological examination and must be included on the delegation of authority log. Whenever possible, the same physician should perform all neurological examinations. Any condition present at the post-treatment neurological examination that was not present at the baseline examination and that is determined to be an AE should be documented as an AE and followed to a satisfactory conclusion. If new potentially clinically relevant neurological signs or symptoms are identified, referral to a neurologist is recommended.

3.7.5.3.3 Vital Signs

Vital sign measurements will include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. The following guidelines will aid in the standardization of body weight measurements:

- The same scale should be used to weigh a given subject each time, if possible.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit (screening, baseline, Week 12 or ET).

Blood pressure and heart rate measurements will be made in the supine, sitting, and standing positions. The supine measurements will be performed first, followed by sitting, and finally standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

Subjects with uncontrolled hypertension (screening DBP > 95 mmHg in any position) or symptomatic hypotension at screening or baseline are excluded from the trial as are subjects with orthostatic hypotension, which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure or development of symptoms (see Table 3.7-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening or baseline that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening or baseline vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Refer to Appendix 3 for a list of potentially clinically significant vital signs.

3.7.5.4 Electrocardiogram Assessments

Standard 12-lead ECGs will be recorded at screening and at the visits specified in Table 3.7-1. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn. Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained if the subject is terminated early. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting

whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis.

If during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject or the interpretation of the trial results) or meets an exclusion criterion (see Table 3.4.3-1), the subject should be excluded from the trial. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each time point). The central ECG service will provide the corrections for the 3 ECGs performed. Based on the QT interval as corrected for heart rate by Fridericia's formula (QTcF) reported by the central service, a subject will be excluded if the corrections are ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing. If only 1 ECG time point has a QTcF of ≥ 450 msec in men and ≥ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the trial.

Refer to Appendix 4 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical significance postrandomization. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. Please consult the medical monitor in case of questions.

3.7.5.5 Other Safety Assessments

3.7.5.5.1 Simpson Angus Scale

The SAS[28] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items. Propranolol is not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until the required time frame has elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the SAS should still be

administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

3.7.5.5.2 Abnormal Involuntary Movement Scale

The AIMS[20] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4, indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes or no questions that address the subject's dental status. Propranolol is not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until the required time frame has elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource. The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

3.7.5.5.3 Barnes Akathisia Rating Scale

The BARS[29] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning. Propranolol is not permitted within 12 hours of scale administration (see Section 4.1). Investigators are encouraged to delay scale administration until the required time frame has elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on

the eSource. The BARS global score is defined as the global clinical assessment of akathisia.

3.7.5.5.4 Sheehan Suicidality Tracking Scale

Suicidality will be monitored during the trial using the Sheehan-STS.[30] 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" versions 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 (see Table 3.4.3-1). 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.

3.7.5.5.5 Mini-Mental State Examination

The MMSE[31] 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 (refer to Table 3.4.2-1) and is also to be completed at baseline and Week 12 or ET.

3.7.6 Pharmacokinetic [redacted] Assessments

3.7.6.1 Pharmacokinetic Assessments

3.7.6.1.1 Pharmacokinetic Blood Samples

The PK samples will be collected at baseline and during Week 8 and Week 12 or ET visits. The samples will be collected at the same time as clinical laboratory sample collection for the designated trial visits, as applicable. Every possible effort should be made to collect PK samples at the same time at each visit. Furthermore, the subject should be advised to take the IMP at approximately the same time each day throughout the trial, but most importantly, prior to each PK sampling. The date and time of the last 2 doses of IMP prior to each sample draw, and the date and time of the actual blood draw

will be recorded on the eSource. Vital sign and ECG assessments should be completed before any blood samples are collected. All blood samples will be shipped to the testing facility for analysis. Detailed handling and shipping instructions are provided in Appendix 1.

[redacted]

[redacted]

3.7.7 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up eSource page for the last subject completing or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

This trial will be monitored by an independent DMC. The DMC will periodically monitor safety based on a predetermined schedule. In addition, an interim analysis of efficacy data is planned during the course of the trial, and will be performed by the independent DMC. The sponsor will remain blinded to the observed results of the interim analysis, and will only receive recommendations as per the interim analysis plan and DMC Charter. The DMC meetings will occur as outlined in the DMC Charter, but can be convened at any time at the discretion of the DMC chair or the trial medical officer. The details of the DMC structure and its roles and responsibilities will be documented in a DMC Charter.

3.7.9 Independent Adjudication Panel and Clinical Surveillance Team

The IAP will consist of medical experts from different specialties, independent from the sponsor or designee, who in collaboration with the CST at Syneos Health™ will use external quality oversight methods to promote appropriate subject enrollment. Such methods will require sites to communicate certain aspects of subject data during the screening period to CST and the IAP, as detailed in the Operations Manual. Eligibility review must be completed for each subject and submitted to CST and the IAP per the Operations Manual. Subjects cannot be randomized until approval from CST and the IAP has been received. The investigator is responsible for ensuring that subjects are eligible for enrollment into the trial and for assessing subject safety throughout the trial. The IAP will provide an independent assessment of the subject's eligibility at time of enrollment and may request exclusion of a subject from entry into the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs or IECs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

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

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4. Refer to the Schedule of Assessments (Table 3.7-1) for a description of follow-up procedures.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

If a subject discontinues the trial prematurely, the reason must be fully evaluated and recorded appropriately in eSource. If the subject is being withdrawn because of an AE, the AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw at any time during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting any of the following criteria must be withdrawn from the trial:

- Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment that, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial

- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator, unless allowed after discussion with and approval by the medical monitor
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12, Subject Compliance)
- At the request of the subject, caregiver, legally acceptable representative, investigator, sponsor, or regulatory authority
- Subject becomes pregnant (see Section 5.5)
- Subject cannot tolerate the assigned dose of brexpiprazole (or matching placebo)
- Subject develops clinically significant agitation per investigator's judgment that cannot be adequately treated with allowed medications and poses a potential safety risk to the subject or others
- Subject is lost to follow-up
- Subject transfers from an institutionalized setting to a non-institutionalized setting, or vice versa. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and medical monitor.

The medical monitor should be contacted if the Sheehan-STS score is 3 or 4 on any one question 3 through 6 or 11 or if the Sheehan-STS score is 2 or higher on any one questions 1a, 7 through 10, or 12, or 18, or if suicide results in death.

Subjects withdrawn prior to Week 12 must complete the Week 12 or ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+ 2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at 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. In addition, 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. Three attempts will be made to contact the subject's caregiver by telephone; in the event the site is unable to reach the subject's caregiver by telephone, the site will attempt to contact the subject's caregiver via certified mail or an alternative similar method where appropriate.

Meeting a screening exclusion criterion postrandomization does not require an automatic discontinuation of the subject. The investigator should assess the change for clinical significance, determine if an AE should be reported, and make a determination of subject continuation based on subject safety. The investigator will consult with the medical monitor to determine subject continuation in the trial.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital or clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.2 to determine if the subject can continue participation in the trial if modifications to his or her treatment or Schedule of Assessments can be accommodated. Only subjects who withdraw their permission for all

of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on treatment, whether through randomization or open assignment. For this trial, treatment begins with the first dose of the IMP. If a subject fails to qualify for the trial during the 42-day screening period for a reason other than a positive screen for cocaine, marijuana, or other illicit drugs, the subject is permitted to be rescreened at a later date. A subject may be rescreened more than once after discussion with and approval by the medical monitor. The medical monitor must be contacted before rescreening any subjects who initially failed screening due to a positive drug screens resulting from use of prescription or OTC medications or products. In the event that the subject is rescreened for trial participation, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete Week 12 visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Week 12 visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family

member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP (ie, brexpiprazole or matching placebo) according to the visits outlined in the Schedule of Assessments (Table 3.7-1). Accountability and compliance verification should be documented in the subject's trial records.

The importance of taking the IMP as directed should be emphasized at all trial visits. If poor compliance continues (eg, dosing errors resulting in overall compliance less than 80% or greater than 120%), discontinuation of the subject from the trial should be considered in consultation with the medical monitor.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor's designee (medical monitor) at the earliest possible time. The investigator and sponsor's designee will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor's designee, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

All subjects must discontinue all prohibited medications after signing the ICF during the screening period to meet the protocol-specified washout periods. The required duration of washout for selected prohibited medications is provided in Table 4.1-1. All other psychotropic agents not listed in Table 4.1-1 are prohibited and must be discontinued at least 24 hours before the first dose of IMP. Select CYP2D6 inhibitors and CYP3A4

inhibitors and inducers are listed in Table 4.1-2. The oral benzodiazepine therapy permitted during the trial is summarized in Table 4.1-3.

Table 4.1-1 List of Restricted and Prohibited Medications

All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.

	Medication	Prior to Randomization	During Double-Blind Treatment Period
1.	Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, or other cognitive enhancers)	Allowed provided that the dose has been stable for 90 days prior to randomization, and there is no decrease or discontinuation within 30 days prior to randomization.	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.
2.	Antipsychotics	7-day washout	Prohibited
	High-dose antipsychotics exceeding the equivalent of ≥ 3 mg of risperidone (eg ≥ 5 mg of haloperidol, ≥ 375 mg quetiapine, ≥ 10 mg olanzapine, or local equivalent)	Not allowed within 90 days prior to **screening**.	Prohibited
	Clozapine	Not allowed within 30 days prior to randomization.	Prohibited
	Depot or long-acting injectable antipsychotic drugs	Washout of 1.5 times the dosing interval (according to the prescribing information) prior to randomization.	Prohibited
3.	Antidepressants	Allowed provided that the dose has been stable for 30 days prior to randomization. Antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited and require a 7-day washout; fluoxetine requires a 28-day washout (see Table 4.1-2 for prohibited antidepressant medications). If a medication is discontinued, the subject must be stable off the drug for 30 days prior to randomization.	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition. Antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited.
4.	Mood stabilizers (such as lithium, valproate, carbamazepine)	7-day washout	Prohibited
5.	Anticonvulsants	7-day washout	Prohibited

Table 4.1-1 List of Restricted and Prohibited Medications			
All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.			
	Medication	**Prior to Randomization**	**During Double-Blind Treatment Period**
6.	Benzodiazepines (short-acting)[a]	Allowed but limited to 4 days/week between screening and randomization with a maximum dose of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects.	During the first 4 weeks of the randomized period (baseline to Week 4 visit): allowed but limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) depending on dose-limiting side effects. Prohibited after the Week 4 visit.
7.	Non-benzodiazepine sleep agents[b]	If a bedtime dose of a sleep agent for insomnia was taken prior to randomization on a regular basis, a stable pretrial dose of the sleep agent may be continued as needed during the trial. If a sleep agent was not previously taken prior to randomization and needs to be initiated, medication should be limited to a maximum dose of 5 mg/day of zolpidem (or equivalent).	If a bedtime dose of a sleep agent for insomnia was taken prior to randomization on a regular basis, a stable pretrial dose of the sleep agent may be continued as needed during the trial. If a sleep agent was not previously taken prior to randomization and needs to be initiated, medication should be limited to a maximum dose of 5 mg/day of zolpidem (or equivalent).
8.	Opioid analgesics	Prohibited unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency.	Prohibited unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency.
9.	Anticholinergics for treatment of extrapyramidal symptoms[c]	7-day washout	Prohibited
10.	Propranolol[d]	For treatment of akathisia or tremor: 7-day washout For treatment of heart disease: allowed provided that the dose has been stable for 30 days prior to randomization and total dose does not exceed 60 mg/day	For treatment of akathisia or tremor: maximum dose of 20 mg, 3 times daily (total of 60 mg/day). For treatment of heart disease: may remain on stable pretrial doses as needed throughout the trial, as long as the total dose does not exceed 60 mg/day. Propranolol must not be administered within 12 hours prior to the efficacy and safety scales.

Table 4.1-1 List of Restricted and Prohibited Medications			
All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.			
	Medication	**Prior to Randomization**	**During Double-Blind Treatment Period**
11.	Varenicline	7-day washout	Prohibited
12.	Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and anti-platelet agents	Allowed provided that the dose has been stable for 30 days prior to randomization	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition. Initiation of a new medication treatment for a medical condition may be allowed throughout the duration of the trial if medically indicated due to a change in the subject's underlying medical condition and not otherwise prohibited (ie, CYP interaction). Consultation with the medical monitor is encouraged in this case.
13.	Nutritional supplements and nonprescription herbal preparations with CNS effects (eg, St. John's wort, omega-3 fatty acids, kava extracts, GABA supplements, etc)	7-day washout	Prohibited
14.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers (see Table 4.1-2)	7-day washout	Prohibited

CNS = central nervous system; GABA = gamma-aminobutyric acid.

[a]Use of intramuscular benzodiazepines are prohibited throughout the trial. However, limited use of specific oral benzodiazepines is permitted during screening and during the first 4 weeks of the randomization period (baseline to Week 4 visit) to treat agitation or insomnia (see Table 4.1-3).

[b]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize one of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia.

[c]Anticholinergic treatment of extrapyramidal symptoms (eg, benztropine) is not permitted within the 7 days prior to randomization and for the duration of the trial.

[d]Propranolol must not be administered within 12 hours prior to scheduled efficacy and safety scales, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of propranolol documented, including a notation of the drug name, dose, and time of administration on the eSource.

Table 4.1-2	Selected CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers
Type	**Examples (Generic Names)**
CYP2D6 Inhibitors	Celecoxib, chloroquine, chlorpheniramine, clemastine, clomipramine, diphenhydramine, duloxetine, fluoxetine[a], halofantrine, hydroxyzine, methadone, moclobemide, paroxetine, pyrilamine, quinidine, terbinafine, tripelennamine
CYP3A4 Inhibitors	Amiodarone, amprenavir, aprepitant, chloramphenicol, cimetidine, clarithromycin, clotrimazole (if used orally), delavirdine, diltiazem, erythromycin, fluconazole, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, quinupristin/dalfopristin, ritonavir, saquinavir, troleandomycin, verapamil
CYP3A4 Inducers	Carbamazepine, dexamethasone, efavirenz, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifampin, St. John's wort, troglitazone

[a]Fluoxetine requires a 28-day washout prior to randomization.

Table 4.1-3	Oral Benzodiazepine (or Equivalent) Therapy During the Trial	
	Maximum Allowable Daily Dose (mg/day)	
Oral Benzodiazepine (or equivalent)[a]	**Screening (limited to 4 days/week)**	**Baseline to Week 4 Visit (limited to 4 days/week)**
Lorazepam	2	2
Oxazepam	30	30

[a]In countries where no short-acting benzodiazepines are commercially available, use of oral diazepam (maximum allowable daily dose of 10 mg/day) or oral clonazepam (maximum allowable daily dose of 1 mg/day) may be acceptable if prior authorization is obtained from the medical monitor.

4.2 Other Restrictions

The following restrictions apply:

- Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.
- Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to the first dose of IMP and during the trial is prohibited.
- Subjects should refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial.
- The investigator may request a blood or urine drug screen or blood alcohol test at any time during the trial if there is a suspicion of illicit drug use.

Treatment with other investigational agents is not permitted during the trial.

New onset nonpharmacological interventions for the treatment of agitation are not permitted during the double-blind treatment period. Subjects who have been treated with nonpharmacological interventions prior to trial entry may continue these therapies during the double-blind treatment period.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

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

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly or birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions

that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eSource. The intensity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

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

5.2 Eliciting and Reporting Adverse Events

Adverse events will be recorded, starting after the ICF has been signed. The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eSource provided by the sponsor. All AE (including SAEs) collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent per the instructions in the Operations Manual. (Please note that the IRE form is NOT the AE eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eSource.

5.5 Pregnancy

Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- ICF
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the subject will be withdrawn from the trial.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor and Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor or CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor or CRO medical advisor). The investigator must contact the sponsor and CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved or recovered) noted. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs up to 30 days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are identified or ongoing at the last scheduled contact must be recorded as such on the AE eSource page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eSource page, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

Any new SAEs or IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.4 Follow-up Mortality Assessment

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. Three attempts will be made to contact the subject's caregiver by telephone; in the event the site is unable to reach the subject's caregiver by telephone, the site will attempt to contact the subject's caregiver via certified mail or an alternative similar method where appropriate.

6 Pharmacokinetic [redacted] Analysis

The PK samples will be analyzed for brexpiprazole (OPC-34712) and descriptive statistics will be calculated [redacted] No formal statistical comparisons are planned. A separate population or PK [redacted] modeling may be performed using the data from this trial and other trials.

7 Statistical Analysis

7.1 Sample Size

The planned maximum sample size for this trial is approximately 330 randomized subjects. The sample size will be approximately 255 subjects if the trial stops at the interim analysis. Statistical assumptions and additional details are provided in the blinded addendum to the protocol.

7.2 Datasets for Analysis

The following samples are defined for this trial:

- Randomized: consists of all subjects who were randomized into this trial
- Safety: consists of all subjects who were administered at least 1 dose of IMP
- Efficacy: The intent-to-treat (ITT) population consists of all subjects in the randomized sample who took at least 1 dose of IMP (brexpiprazole or placebo), have a baseline, and at least 1 postbaseline evaluation for the CMAI total score.

In general, baseline of an efficacy endpoint is defined as the last observation of the endpoint before the subject is randomized.

The core dataset for all efficacy analyses is based on the ITT population, which is defined in the efficacy sample above. As will be described below, in order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets derived from the ITT population will be used for the efficacy analysis.

7.3 Handling of Missing Data

In general, missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed-case (OC) data from protocol specified visits in the ITT population under the assumption of missing at random. Details of sensitivity analyses under the assumption of missing data being missing not at random (MNAR) will be provided in the SAP as well as additional sensitivity analyses, as applicable.

The OC dataset consists of actual observations recorded at each visit during the double-blind treatment period, and no missing data will be imputed.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Efficacy Endpoint Analysis

The primary endpoint will be analyzed using an MMRM model. The primary efficacy outcome measure is the mean change from baseline to Week 12 in the CMAI total score. The primary statistical comparison of interest is brexpiprazole versus placebo. The null hypothesis of this comparison is that there is no difference between the brexpiprazole treatment group and placebo in change from baseline to Week 12 in CMAI total score.

The statistical comparison will be performed by the MMRM analysis with an unstructured (UN) variance covariance matrix for the repeated measures in which the change from baseline in CMAI total score (at Weeks 2, 4, 6, 8, 10, and 12) will be the dependent variable based on the OC dataset. The model will include fixed class-effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline values of CMAI total score by visit week as a covariate. The primary comparison between brexpiprazole and the placebo arm at Week 12 will be estimated as the difference between least squares (LS) means from the interaction term of treatment by visit week utilizing the computing software SAS procedure PROC MIXED.

Details of sensitivity analyses for MNAR, as well as additional sensitivity analyses will be prespecified in the SAP.

7.4.2 Key Secondary Efficacy Endpoint Analysis

The key secondary efficacy variable is the change from baseline to Week 12 in the CGI-S score, as related to agitation. It will be analyzed by the same statistical methodology specified for the analysis of the primary efficacy variable. In order to control the overall

type I error rate for this key secondary efficacy analysis, a hierarchical testing procedure will be used so that the overall experiment-wise type I error rate is maintained. Thus, if the primary efficacy analysis for the CMAI total score (as described in Section 7.4.1) yields a statistically significant result for the comparison of brexpiprazole versus placebo, then the corresponding comparison for this key secondary efficacy variable (CGI-S score) will be tested.

7.4.3 Secondary Efficacy Endpoint Analysis

Secondary efficacy variables include the following:

- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, verbally agitated behavior)
- Change from baseline in CMAI total score for each trial visit during the double-blind treatment period
- Change from baseline in CGI-S for each trial visit during the double-blind treatment period
- CGI-I score at each trial visit during the double-blind treatment period
- CMAI-based responder analysis as described in the SAP
- CGI-I responder analysis as described in the SAP

Change from baseline will be evaluated using the same MMRM model described in the primary analysis. The CGI-I score will be evaluated by the Cochran–Mantel–Haenszel row mean score differ test (van Eltern) controlling for trial site in last-observation-carried-forward (LOCF) analysis.

Further details and analysis methods will be described in the SAP.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

7.4.5 Interim Analysis

Details of the interim analysis will be provided in a blinded addendum to the protocol.

7.5 Analysis of Demographic and Baseline Characteristics

Demographic characteristics and disease severity at baseline will be summarized by descriptive statistics, eg, proportion, mean, median, standard deviation, and minimum and maximum values.

7.6 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical examination. In addition, data from the following safety scales will be evaluated: MMSE score, assessments of suicidality (eg, Sheehan-STS), and EPS (eg, the SAS, AIMS, and BARS). Safety analysis will be conducted based on the Safety Sample defined in Section 7.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, body weight, and BMI. Details of safety analysis will be provided in the SAP.

7.6.1 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, and prolactin concentrations will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined criteria for laboratory tests will be summarized.

7.6.3 Physical and Neurological Examination and Vital Signs Data

Physical and neurological examination findings will be listed by subject. Potentially clinically relevant results in vital signs and body weight will also be summarized. Summary statistics for change from baseline in vital signs, body weight, and waist circumference will be provided.

7.6.4 Electrocardiogram Data

Mean change from baseline will be summarized by treatment group and by visit. Incidence of clinically relevant changes will be calculated for ECG parameters and summarized by treatment group and by visit.

The analysis of QT and corrected QT interval (QTc) data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

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

Results will be summarized by visit.

7.6.5 Other Safety Data

Change from baseline in scores for the MMSE score will be evaluated using ANCOVA with baseline value as a covariate and treatment as main factors. The analyses will be based on the OC and LOCF datasets of the Safety Sample.

The suicidality (eg, Sheehan-STS) will be summarized by treatment group based on the OC dataset of the Safety Sample. Details will be described in SAP.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPC-34712 IB.[13]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as active brexpiprazole tablets or matching placebo tablets. Each dose will be supplied as blister cards containing sufficient tablets for 7 (+2) days. When accessed by the site, the eSource method will assign specific blister card number(s) to be dispensed to a subject.

Each blister card of brexpiprazole or matching placebo used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, site number (to be filled in by the site staff or investigator), subject ID (to be filled in by the site staff or investigator), subject's initials or other unique identifier (to be filled in by the site staff or investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements. Once a blister card has been assigned to a subject, it cannot be dispensed to another subject.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored at ambient conditions as per the clinical label on the IMP. The clinical site staff will ensure that the temperature log is maintained in the drug storage area and that the temperature is recorded at least once each working day. The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Previously dispensed blister cards are to be returned at each visit and subjects will start taking the IMP from the new blister card the day after the clinic visit. Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial site(s). The IMP may only be destroyed by the trial site(s), if approved by the sponsor and if the IMP destruction meets all local regulations.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction of used IMP containers, unused IMP, and partially-used IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure or malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online: Send information required for reporting purposes (listed below) to OAPI-EQCProductComplaints@Otsuka-us.com
- Phone: Rocky Mountain Call Center at 1-800-438-6055.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter ID (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product and compound name, coding)
- Clinical protocol reference (number or trial name)
- Dosage form and strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

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

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s) and institution(s) will permit trial-related monitoring, audits, IRB and IEC review, and regulatory inspection(s) by providing direct access to source data and

documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion and exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

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

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application – rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory or central ECG data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator and institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

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

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR

- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eSource with source documents. The investigator agrees to participate with audits.

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

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eSource, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eSource. If further subject ID is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

Per country regulations, if subject initials cannot be collected, another unique identifier will be used. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial

site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

14 Publication Authorship Requirements

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

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

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

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the

trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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Appendix 1 Handling and Shipment of Bioanalytical Samples Pharmacokinetic Sample Collection

Pharmacokinetic Sample Collection

A 4 mL sample of blood for PK testing will be collected into 4-mL Vacutainer tubes containing sodium heparin. Each tube should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from the tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. All tubes must be labeled using the central lab's barcode labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the PK sample information. It is important to note the exact date and time of the blood collection, the date and time of the last dose of brexpiprazole/placebo prior to each blood draw, and the time of the meal closest to the last dose.

The sample must be stored at −70°C, if available, or −20°C or below. If only a −20°C freezer is available, samples must be shipped within 30 days of collection and primary and backup samples may be shipped together. If samples are stored in a −70°C freezer, then one tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab. If neither a −70°C nor −20°C freezer is available, the primary and backup PK samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.

[redacted]

Pharmacokinetic, [redacted] Sample Shipment

Plasma or whole blood samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container. Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. When possible, samples should be shipped together to reduce the number of shipments.

The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 × ULN
ALT (SGPT)	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
Lactate dehydrogenase	≥ 3 × ULN
Blood urea nitrogen	≥ 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	> 3 × 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
WBC count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,500/mm^3
Platelet count	≤ 75,000/mm^3 or ≥ 700,000/mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Nonfasting	≥ 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 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

bpm = beats per minute

[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 New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 4 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

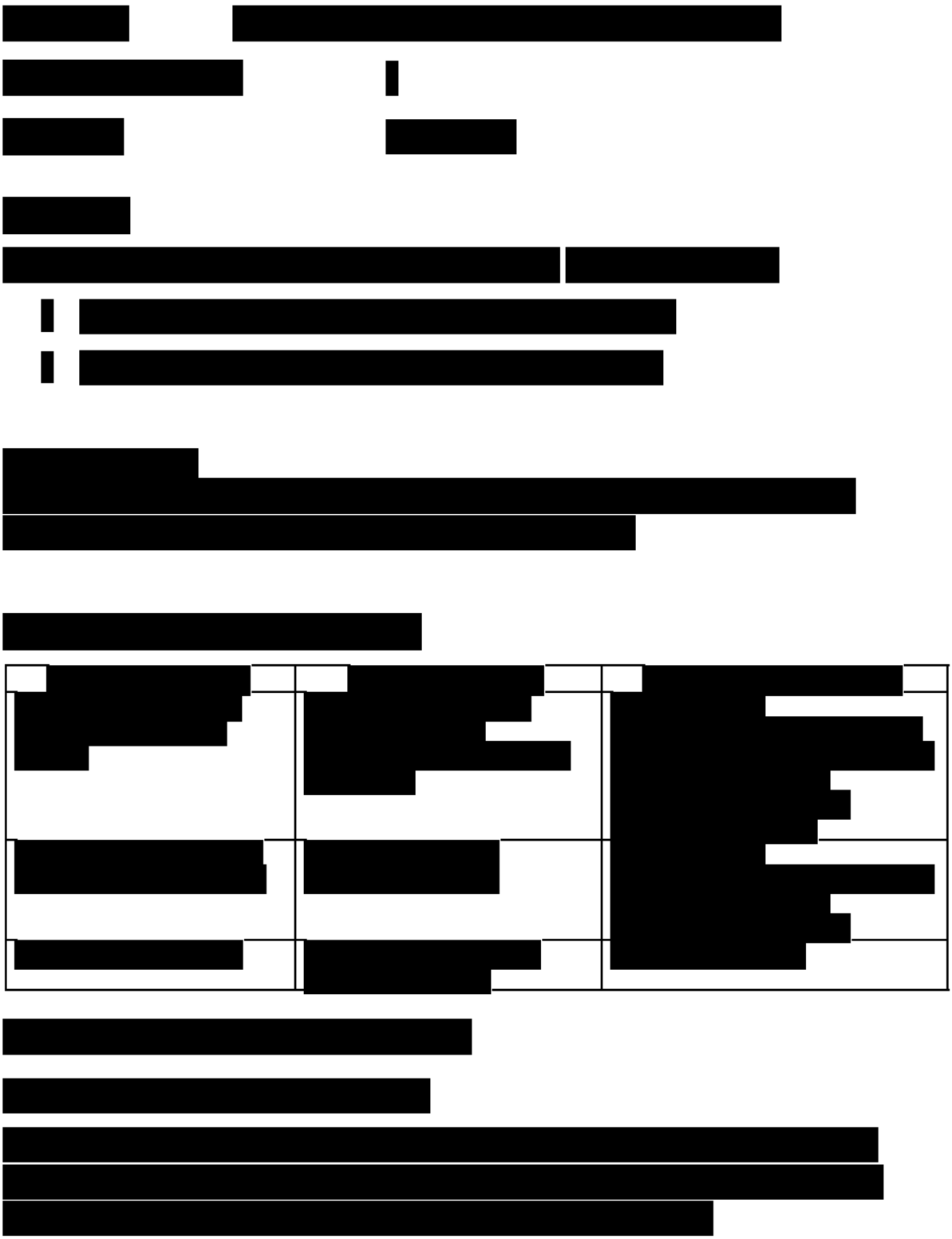
Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not 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 trial 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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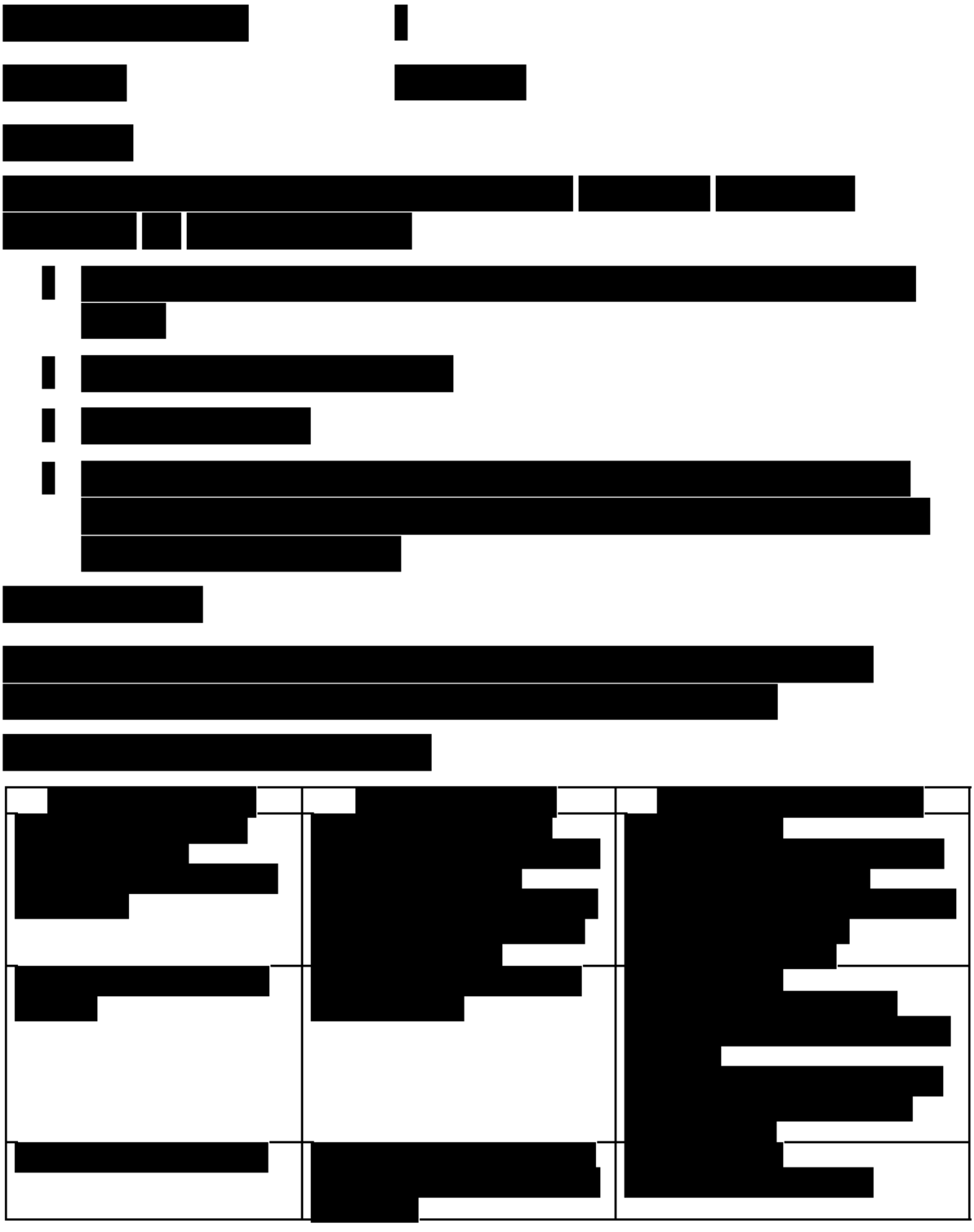

Description of Change	Rationale for Change	Sections Affected by Change
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-34712, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where OPC-34712 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

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

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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[redacted]	Approved for Clinical Pharmacology and Nonclinical	[redacted]

Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-34712

REVISED BLINDED ADDENDUM FOR CLINICAL PROTOCOL
for TRIAL 331-14-213

A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-14-213
IND No. 115960
EudraCT No. 2017-003940-19

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. [redacted]
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety [redacted]
Issue Date: Amendment 1: Amendment 2:	[redacted]
Version No.:	3.0

BLINDING & CONFIDENTIALITY

This blinded addendum is a separate entity from the associated clinical protocol for Trial 331-14-213 and provides the details of procedures and statistical methods that are blinded in the protocol, namely, the inclusion criterion and description of certain aspects of the trial design. This document is intended for use only by Otsuka personnel or their designated agents or for review only by Institutional Review Boards, Independent Ethics Committees, regulatory authorities, or any other entity considered suitable by Otsuka. The information contained herein is unblinded and confidential; therefore, it must NOT be shared with or communicated to any individual at an investigational site without written authorization from Otsuka Pharmaceutical Development & Commercialization, Inc.

Table of Contents

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAD	Agitation in Alzheimer's dementia
CMAI	Cohen Mansfield Agitation Inventory
DMC	Data Monitoring Committee

1 Background

This is a phase 3, 12-week, global, multicenter, randomized, double-blind, placebo-controlled, 2-arm, fixed-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole compared with placebo in the treatment of subjects with agitation associated with dementia of the Alzheimer's type. Subjects will be randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo.

In order to reduce potential bias, trial site personnel will be blinded to the addition of a Cohen Mansfield Agitation Inventory (CMAI) Factor 1 inclusion criterion, and the statistical analysis information for re-estimating sample size at the interim analysis.

2 Objectives

The objective of the addendum is to present the blinded procedures separately from the main protocol, namely, the additional inclusion criterion and statistical analysis details for the adaptive design.

3 Trial Design

3.1 Inclusion Criteria

In addition to the inclusion criteria described in the protocol, an additional criterion for trial eligibility that site investigators will not have knowledge of (ie, that they will be blinded to) is as follows:

Subjects must meet the criteria for CMAI Factor 1 agitation at screening and baseline.[1,2] The CMAI Factor 1 aggressive behaviors include: hitting (including self), kicking, scratching, grabbing, pushing, hurting self or others, throwing things, cursing or verbal aggression, spitting, tearing things or destroying property, screaming and biting.

In order to meet this criterion, one of the following must be displayed:

1) ≥ 1 aggressive behaviors occurring several times per week, or
2) ≥ 2 aggressive behaviors occurring once or twice per week, or
3) ≥ 3 aggressive behaviors occurring less than once per week

4 Statistical Analysis

4.1 Sample Size Estimation

Based on a 2-arm, parallel trial design with a randomization ratio of 2:1 for brexpiprazole: placebo, a sample of 300 subjects is needed to achieve 89% power at a 2-sided alpha level of 0.05 for detecting a treatment effect of 6.5 points (standard deviation = 16.5) in change-from-baseline CMAI total score at the primary endpoint Week 12. To account for early dropouts (observed as 12% - 13% in the 2 completed phase 3 trials) before Week 12 and a lack of full compliance observed at one clinical site, at least 30 additional subjects are needed to maintain the target power. The resulting total sample size is 330 subjects. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo.

The trial will use a two-stage group sequential design with one interim and one final analysis. One interim look will be conducted when approximately the first 255 subjects have had an opportunity to complete the 12-week trial. The power of the group sequential test is 87%.

The statistical assumption of the treatment effect of 6.5 points separation (for brexpiprazole versus placebo) was the same as that used for the two completed phase 3 agitation in Alzheimer's dementia (AAD) Trials 331-12-283 and 331-12-284.

4.2 Interim Analysis

An unblinded interim analysis of efficacy data is planned during the course of the trial, and will be performed by an independent DMC on approximately the first 255 randomized subjects who have either completed the Week 12 visit or discontinued the trial. Depending on the result of the interim analysis, the trial will either stop at the conclusion of the interim analysis or continue to the final analysis at the planned maximum sample size of approximately N=330. A significance level of 0.015 (2-tailed) is allocated to the interim analysis, and the significance level for the final analysis is 0.035 (two-tailed).

All the detailed calculations and analyses will be pre-specified and included in the statistical analysis plan, the interim analysis plan, and the DMC Charter which will be single-blind to investigators, patients, and trial personnel but not to the sponsor, the Institutional Review Board/Independent Ethics Committee, and the Food and Drug Administration.

The DMC will provide one recommendation based on the IA result as follows.

IA result	DMC Recommendation	Outcome
Two-sided *p*-value ≤ 0.015	Stop the trial for superiority in efficacy	The trial will be terminated at IA
Observed Effect Size ≤ 0.10	Stop the trial for futility	The trial may be terminated at IA subject to Sponsors' final decision
Otherwise (None of the above)	Continue the trial to the final analysis	The trial will proceed to its planned maximum sample size of approximately N=330

5 References

1 Instruction Manual for the Cohen Mansfield Agitation Inventory (CMAI). Rockville, MD. The Research Institute of the Hebrew Home of Greater Washington; 1991.

2 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):991-998.

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[redacted]	Biostatistics Approval	[redacted]

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

OPC-34712

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 331-14-213

A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-14-213
IND No. 115960
EudraCT No. 2017-003940-19

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc [redacted]
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety [redacted]
Issue Date:	[redacted]
Version No.:	1.0

Trial Conduct for COVID-19

All procedures and assessments in Protocol 331-14-213 are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to future COVID-19 considerations, the appropriate measures to be followed are provided in this document.

Table of Contents

List of In-text Tables

List of In-text Figures

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
anti-HCV	Hepatitis C antibodies
aPTT	Activated partial thromboplastin time
BARS	Barnes Akathisia Rating Scale
CGI-I	Clinical Global Impression Improvement of Illness
CGI-S	Clinical Global Impression Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
CST	Clinical Surveillance & Training
CT	Computed tomography
ECG	Electrocardiogram
ET	Early termination
EudraCT	European Clinical Trial Data Base
[redacted]	[redacted]
IAP	Independent Adjudication Panel
IMP	Investigational medicinal product
INR	International Normalized Ratio
IPA	International Psychogeriatric Association
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NPI	Neuropsychiatric Inventory
[redacted]	[redacted]
OPC	Otsuka Pharmaceutical Company, Ltd.
SAE	Serious adverse event
SAS	Simpson Angus Scale
Sheehan-STS	Sheehan Suicidality Tracking Scale
T_4	Thyroxine

1 Trial 331-14-213 COVID-19 Protocol Summary

1.1 Trial Design Schematic

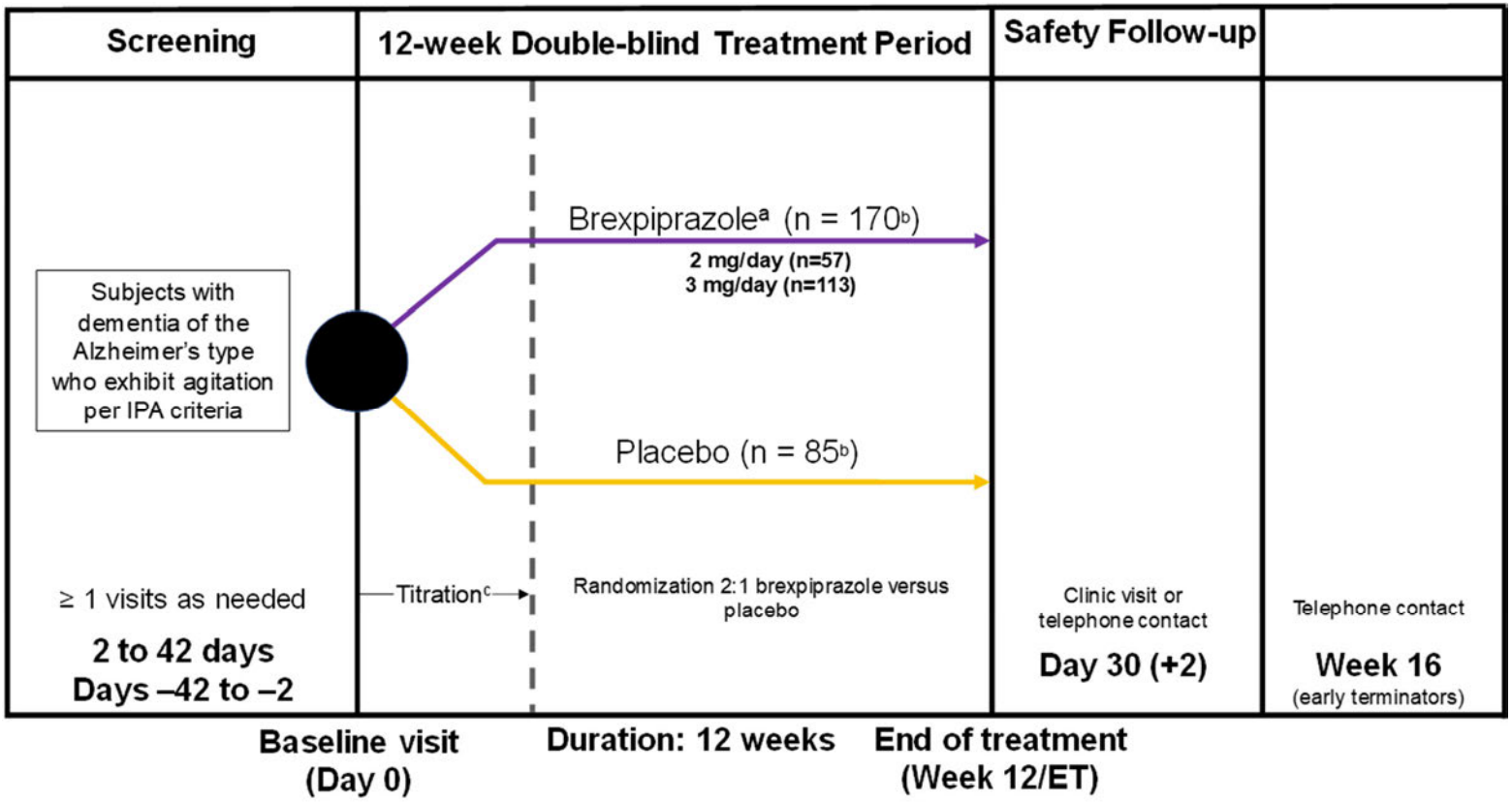

Figure 1.1-1 COVID-19 Impact Trial Design Schematic

ET = early termination; IPA = International Psychogeriatric Association.

[a]Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day.

[b]The trial will have an adaptive design and the sample size could increase based on a scheduled interim analysis. The final number of subjects to be included in the trial will be determined at the time of a blinded interim analysis conducted by the independent data monitoring committee.

[c]Titration: Starting at 0.5 mg/day, and reaching 2 mg/day on Day 15, and 3 mg/day on Day 29.

[redacted]

1.2 Schedule of Assessments

Table 1.2-1 COVID-19 Impact Schedule of Assessments

Assessment	Visit[a]										Notes
	Screening	Baseline (Day 0)	Week 2 (±2 days)	Week 4 (±2 days)	Week 6 (±2 days)	Week 8 (±2 days)	Week 10 (±2 days)	Week 12 or ET[b] (±2 days)	Follow-up (+2 days)	Week 16[c]	
ENTRANCE and HISTORY											
Informed consent	X										Section 2.2
Inclusion and exclusion criteria	X	X									Section 3
Demography	X										
Medical history	X										
Psychiatric history	X										
Neurological history	X										
Prior medication washout	X										
HBsAg and anti-HCV	X										
Eligibility assessment by CST and IAP	X										
MRI or CT scan[d]	X										
Randomization		X									
EFFICACY											
CMAI	X	X	X	X	X	X	X	X			Section 2.6
CGI-S	X	X	X	X	X	X	X	X			Section 2.6
CGI-I			X	X	X	X	X	X			Section 2.6
[redacted]	X	X			X			X			Section 2.6
SAFETY											
Physical examination	X							X[e]			
Neurological examination	X							X[e]			
Vital signs	X	X	X	X	X	X	X	X			Section 4.1.1
Body weight	X	X						X			

Table 1.2-1 COVID-19 Impact Schedule of Assessments

Assessment	Visit[a]										Notes
	Screening	Baseline (Day 0)	Week 2 (±2 days)	Week 4 (±2 days)	Week 6 (±2 days)	Week 8 (±2 days)	Week 10 (±2 days)	Week 12 or ET[b] (±2 days)	Follow-up (+2 days)	Week 16[c]	
Clinical laboratory tests (hematology, serum chemistry, urinalysis)	X	X[f]				X[e]		X[e]			
Prolactin (blinded)	X							X[e]			
TSH with reflex to free T_4 if abnormal	X										
HbA_{1c}	X							X[e]			
PT, aPTT, and INR	X										
Urine pregnancy test (women of childbearing potential) only	X							X			Section 4.1.2
ECG	X	X				X[e]		X[e]			
Urine drug screen and blood alcohol test	X										
MMSE	X	X						X			Section 2.6
Sheehan-STS	X	X						X			Section 2.6
Extrapyramidal symptoms scales (SAS, AIMS, BARS)		X						X[g]			Section 2.6
Adverse events	X	X	X	X	X	X	X	X	X		
Pharmacokinetic sampling		X				X[e]		X[e]			
[redacted]		X									
Concomitant medications	X	X	X	X	X	X	X	X	X		
Mortality status assessment										X	
OTHER PROCEDURES											
IMP dispensing[h]		X	X	X	X	X	X				Section 5
IMP accountability		X	X	X	X	X	X	X			

AIMS = abnormal involuntary movement scale; aPTT = activated partial thromboplastin time; BARS = Barnes Akathisia Scale; CGI-I = Clinical Global Impression Improvement of Illness; CGI-S = Clinical Global Impression Severity of Illness; CMAI = Cohen-Mansfield Agitation Inventory; CST = Clinical Surveillance & Training; CT = computed tomography; ECG = electrocardiogram; FBR = future biomedical research; IAP = Independent Adjudication Panel; IMP = investigational medicinal product; INR = International Normalized Ratio; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; [redacted] PT = prothrombin time; SAS = Simpson Angus Scale; TSH = thyroid stimulating hormone; T_4 = thyroxine.

[a]The screening and baseline visit(s) must occur in the clinic. All other visits may be completed virtually if site, subject, or caregiver requests a virtual visit due to COVID-19 conditions (see footnote b for exception related to Week 12 completion visit for rollover into Trial 331-201-00182).

[b]Week 12/ET visit may be completed virtually, but those subjects rolling over into Trial 331-201-00182 must have their Week 12 visit in the clinic. Subjects must be early terminated if 1. the subject tests positive for COVID-19 or 2. is presumed positive with COVID-19 or 3. the caregiver tests positive for COVID-19 and another caregiver cannot be identified. Subjects who miss an assessment due to a visit performed virtually (eg clinical laboratory tests, ECGs) may continue in the trial based on the investigator's clinical assessment and judgement.

[c]Note that this visit is 16 weeks postbaseline and only for subjects who terminate early from the trial.

[d]If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed by CST or the IAP in order to confirm eligibility.

[e]Assessment is not obligatory if the visit is virtual.

[f]If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit.

[g]If the visit is performed virtually, the BARS and AIMS can be performed using videoconference. The SAS cannot be completed remotely.

[h]For the weeks 2 to 10 visits, if the visit is performed virtually, alternative methods for dispensing IMP to the subject can be performed, if allowed by country guidances and regulations, eg, use of courier or curbside pickup.

2 General Considerations

2.1 Telemedicine

All procedures and assessments in the protocol should be followed to the fullest extent possible. However, telemedicine can be used in cases where the site, subject and/or caregiver requests a virtual visit be performed due to COVID-19 conditions. Guidance will be provided to sites on whether use of the phone is acceptable, or if video is required. Sites will be instructed to attempt to standardize collection via phone or video depending on the requirements of the trial to minimize confusion and risk of errors of utilizing varying collection strategies. All applicable country-by-country guidances and local regulations will be followed when implementing telemedicine options.

Although a visit may be completed virtually, site staff should consider using the trial tablet to collect the data directly within eSource.

Note: If a study-wide virtual visit mandate is declared due to COVID-19, hospitalized subjects where the investigator is also the subject's physician can continue in-person visits.

2.2 Reconsent

In cases where there is an immediate need to reconsent subjects and the subject and/or caregiver are unable to attend an in-clinic visit due to COVID-19 conditions, either paper reconsent or remote eConsent, in regions where remote capacity exists, are acceptable. Sites are to contact the clinical research organization to discuss the options and agree to the best approach for the site.

The investigator must continue to determine if there have been any changes to the prior assessment of the subject's capacity to provide informed consent. If changes have been made, refer to the instructions in the protocol (Section 3.4.1.1).

2.3 Protocol Deviations

Protocol deviations that occurred as a direct result of the COVID-19 pandemic and prior to a site's local regulatory agency and IRB/EC approval of this addendum, must be recorded in eSource. A "direct result" is defined as being due to actual COVID-19 illness, or as a result of quarantine, social distancing, or site closures. The flexibility in procedures due to COVID-19 conditions allowed per this addendum (eg virtual visits, missed assessments due to virtual visit, alternative IMP dispensation to subject), will not be considered protocol deviations following IRB/EC approval of this addendum. All

other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

2.4 Guidance to Record Adverse Events and Discontinuations Due to COVID-19

If a subject tests positive OR is presumed positive with COVID-19, the subject must be discontinued from the trial, and an adverse event (AE) of "Coronavirus Infection" OR "Coronavirus Positive Test Result" will be entered on the AE page of eSource. A positive test result or a presumed positive subject is not automatically a serious adverse event (SAE), unless an SAE criterion is met (eg, hospitalization).

If a subject discontinues due to COVID-19 either because they test positive OR are presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Adverse Event" and indicate the AE number in the "Specify the reason for discontinuation" space that corresponds with the AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result."

If a subject discontinues due to COVID-19 for reasons other than the subject testing positive OR being presumed positive with COVID-19 (eg, quarantine, fear of infection), then the primary reason for discontinuation should be reported as "Other." Be sure to specify the reason as "COVID-19" followed by the reason ensuring that the prefix of the description includes "COVID-19." Do note that the reason "Other" should be selected even if the subject decides to withdraw consent or if the investigator decides to withdraw the subject due to COVID-19 concerns.

In case the caregiver is COVID-19 positive and another caregiver is available to continue the trial, the situation should be discussed with the medical monitor to determine continuation in the trial on a case-by-case basis. If there is no other caregiver, the subject needs to be early terminated from the trial.

2.5 Statistical Analyses

Any impact of COVID-19 on the planned statistical analyses for the trial will be described in the final statistical analysis plan.

2.6 Clinical Outcomes

To decrease variability, sites should attempt to standardize the method of administration for a scale for an individual subject and across all subjects in the trial. Assessments should be administered by the same qualified/trained rater who rated the subject previously; if this is not possible due to staff availability and/or technological limitations,

discuss relevant information with previous raters to obtain clinical context (note that per protocol raters must be trained/qualified to conduct assessments in all cases). Raters should conduct all assessments for that visit during the same remote session, where possible.

The Cohen-Mansfield Agitation Inventory (CMAI) diary should continue to be completed by the caregiver to collect the subject's behaviour. If a virtual visit is performed, caregivers will not be required to send copies of the diary to the site. If possible, the diary can be provided to the site at a later time.

Please refer to the *Virtual and Remote Visit Overview* and *Virtual Visit Instructions for Clinical Sites* for modification of administration methods for remote visits.

3 Trial Population

3.1 Inclusion Criteria

No changes are required to the inclusion criteria due to COVID-19.

3.2 Exclusion Criteria

No changes are required to the exclusion criteria due to COVID-19.

4 Trial Procedures

If a virtual visit is conducted due to COVID-19 conditions, there are some assessments that can not be performed (eg laboratory collections, ECG, SAS). Please refer to the *Virtual and Remote Visit Overview* and *Virtual Visit Instructions for Clinical Sites* for modification of administration methods for remote visits.

4.1 Safety Assessments

4.1.1 Vital Signs

Blood pressure, heart rate, weight, and temperature will all be measured as described in the protocol at the time points defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following considerations:

- If blood pressure measurements cannot be collected for 2 consecutive visits, the medical monitor should be contacted for guidance.
- Subjects and caregivers will be asked to use their own collection device, if available, until devices can be provided.;

- Where possible, site staff will remotely supervise the collection of measurements via video or guide by telephone, if video is not possible, on the appropriate visits.
- Subjects and caregivers will be instructed to be as consistent as possible regarding the time of day the measurement is taken, and to notify the site staff of the measurement results via telephone, or other means, on the appropriate visits.
- Site staff will be instructed to record the measurement in eSource, and if there are believed to be any errors, inconsistencies, or safety concerns with the reported home measurement, the medical monitor should be notified.
- Site staff will instruct the subjects to follow the procedures in the protocol for blood pressure and heart rate collection, but specify that the supine and standing positions for blood pressure are necessary, while the sitting position is less important. If sitting position is not collected, it should be documented as a COVID-19 protocol deviation (see Section 2.3).

4.1.2 Pregnancy

Pregnancy tests will be performed as described in the protocol at the timepoints defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- For planned visits that require a pregnancy test for women of childbearing potential, the site will provide the necessary tests and instructions so the test may be performed at home;
- Applicable subjects will perform a pregnancy test at the timepoint defined in Table 1.2-1, ensuring a date and time-stamped picture or video of the result is taken, followed by notification to the site staff of the results via telephone, or other means, on the appropriate visits. Subjects will also provide the site staff with the date- and time-stamped picture/video.
  - If negative, site to inform the subject to proceed with dosing (if applicable).
  - If positive, the site must instruct the subject to immediately stop taking IMP (if applicable), and the site will refer to the Pregnancy section of the protocol for appropriate immediately reportable event reporting.

5 IMP

Given the ongoing COVID-19 restrictions, clinical sites are permitted to transport IMP directly to subjects via courier, if allowed by country guidances and regulations. Alternately, curbside pick-up by the caregiver is permitted.

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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

STATISTICAL ANALYSIS PLAN

A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-14-213
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Table of Contents

List of In-text Tables

List of Appendices

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AAD	Agitation in Alzheimer's dementia
AIM	Abnormal involuntary movement
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARH1	Heterogeneous autoregressive of order 1
AST	Aspartate transaminase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression Improvement Scale
CGI-S	Clinical Global Impression Severity of Illness Scale
CMAI	Cohen-Mansfield Agitation Inventory
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CSH	Heterogenous compound symmetry
CST	Clinical Surveillance & Training
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ET	Early termination
FDA	Food and Drug Administration
HDL	high-density lipoprotein
IA	Interim Analysis
IAP	Interim Analysis Plan
ICF	Informed consent form
IMP	Investigational medicinal product
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LOCF	Last-observation-carried-forward
LS	Least squares
MAR	Missing at Random
MCAR	Missing Completely at Random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect model repeat measurement
MMSE	Mini Mental State Examination
MNAR	Missing Not at Random

Abbreviation	Definition
[redacted]	[redacted]
OC	Observed Case
OTC	Opportunity to Complete
PCR	Potentially clinically relevant
SAP	Statistical analysis plan
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
Sheehan-STS	Sheehan- Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
TOEPH	Heterogeneous Toeplitz
ULN	Upper limit of normal
UN	Unstructured

1 Introduction

This statistical analysis plan (SAP) expands the statistical section of the protocol 331-14-213 Amendment 3 and documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy, safety and tolerability data of the study. All amendments to the protocol and the addendums to protocol amendment are taken into consideration in developing this SAP.

2 Trial Objectives

Primary: To confirm the efficacy of brexpiprazole compared with placebo in subjects with Agitation in Alzheimer's dementia (AAD)

Secondary: To evaluate the safety and tolerability of brexpiprazole compared with placebo in subjects with AAD

3 Trial Design

This is a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole compared with placebo. Subjects will be randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo. The randomization will be stratified by site.

The trial consists of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment safety follow-up period. In addition, for all subjects who terminate early from the trial, attempts will be made to collect data on mortality status by telephone contact with the subject's caregiver at Week 16.

This trial will utilize a two-stage group sequential design with one interim analysis (IA) and one final analysis. One unblinded interim analysis of efficacy data will be performed by an independent Data Monitoring Committee (DMC) on approximately the first 255 randomized subjects who have either completed the Week 12 visit or discontinued early from the trial. The trial may stop for efficacy or futility at the conclusion of the IA or may continue to the final analysis when reaching the maximum planned sample size of about 330 randomized subjects. The sponsor will remain blinded to the observed results of the IA, and will only receive recommendation regarding whether to stop or continue the trial as per the interim analysis plan (IAP) and the DMC Charter.

The trial is organized as follows:

Screening Period

The screening period will range from 2 days up to 42 days, with the goal of completing all screening activities within 30 days, if possible, and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. The screening period may be extended after discussion with and approval by the medical monitor. An eSource method will be used to obtain an identification number for each subject with documented consent.

The purpose of the screening period is to determine the subject's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization.

External quality oversight methods will be used by Clinical Surveillance & Training (CST) and the Independent Adjudication Panel to promote appropriate subject enrollment.

In addition, starting at screening and continuing throughout the 12-week double-blind treatment period, the subject's behavior will be logged into a diary by the caregiver or facility staff. This diary will be sent to CST on a routine basis in order to corroborate information recorded on the Cohen-Mansfield Agitation Inventory (CMAI).

12-week, Double-blind Treatment Period

Based on a randomization scheme, eligible subjects will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

- Brexpiprazole (further randomized in a 1:2 ratio to 2 mg/day or 3 mg/day)
- Placebo

Subjects will follow a titration schedule, depending upon their assigned treatment group, to gradually increase their dose of the investigational medicinal product (IMP) to their assigned target dose as follows:

Table 3-1 Titration Schedule

Dose	Day After the Baseline Visit (Days 1-7)	Days 8-14	Day After the Week 2 Visit (Days 15-28) (±2 days)	Day After the Week 4 Visit (Days 29-Week 12) (±2 days)
Brexpiprazole (2 mg/day)	0.5 mg	1 mg	2 mg	2 mg
Brexpiprazole (3 mg/day)	0.5 mg	1 mg	2 mg	3 mg
Placebo	Placebo	Placebo	Placebo	Placebo

The first dose of IMP (brexpiprazole or placebo) will be administered on the day after the baseline visit (ie, Day 1) and ending on Week 12 or early termination (ET; the last day of the treatment period).

Subjects unable to tolerate their assigned dose of brexpiprazole (or matching placebo) will be withdrawn from the trial. Down titration is not allowed at any time during the trial. If a subject is withdrawn or discontinues prematurely before Week 12, every effort will be made to complete all of the Week 12 or ET evaluations prior to administering any additional medications for the treatment of agitation or other prohibited medications.

Subjects will be evaluated at baseline and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments.

Subjects who complete the 12-week double-blind treatment period of Trial 331-14-213 may be eligible to enter a 12-week open-label extension trial. If this trial is terminated due to overwhelming efficacy from the IA, subjects in this trial at the time may be offered entry into the open-label extension trial if they choose to participate.

Follow-up Period

All subjects with the exception of those entering the optional open-label extension trial, 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.

4 Sample Size and Power Justification

The initial sample size was calculated based on the treatment effect of 6.5 points with a standard deviation of 16.5 in the change from baseline to Week 12 in the CMAI total score, to achieve 89% power at a 2-sided alpha level of 0.05. The initial sample size was 300 total subjects randomized in a 2:1 ratio to brexpiprazole or placebo. The statistical assumption of the treatment effect of 6.5 points separation (for brexpiprazole versus placebo) is the same as that used for the two completed phase 3 AAD Trials 331-12-283 and 331-12-284.

To account for an empirical dropout rate of 12-13% (based on the two completed phase 3 AAD Trials 331-12-283 and 331-12-284) and a lack of compliance at one identified clinical site, an increment of at least 30 additional subjects will be needed to maintain the target power. The resulting sample size is about 330 total subjects randomized in a 2:1 ratio to brexpiprazole or placebo. Within the brexpiprazole arm, subjects will be further

randomized in a 1:2 ratio to 2 mg/day or 3 mg/day, to explore the efficacy, safety, and tolerability of 2 mg/day and 3 mg/day brexpiprazole versus placebo.

One IA will be conducted when approximately the first 255 subjects had an opportunity to complete (OTC) the 12-week trial. The conservative Bonferroni critical boundary will be used for the two-stage group sequential analysis. Specifically, the alpha allocated to the IA is 0.015 and the alpha left for the final analysis is 0.035, both two-sided. The two-stage group sequential test will attain a power of 87%.

5 Data Sets and Missing Data

5.1 Data Sets for analysis

The following analysis samples are defined for this trial:

Randomized Sample: Consists of all subjects who were randomized into this trial. Subjects are considered randomized when they are assigned a treatment number by the eSource method at the end of Screening Period. A subject receiving trial treatment outside of the eSource will not be considered randomized, but safety will be reported.

Safety Sample: Consists of all subjects who were administered at least one dose of IMP. Subjects will be excluded from this population only if there is documented evidence (ie, number of tablets dispensed = number of tablets returned or no trial drug dispensed) that the subject did not take trial drug. If a subject is dispensed investigational medicinal product (IMP) and is lost to follow-up, he/she will be considered exposed.

Efficacy Sample: The intent-to-treat (ITT) population consists of all subjects in the randomized sample, who took at least 1 dose of IMP and have a baseline and at least one post-baseline evaluation for the CMAI total score.

5.2 Handling of Missing Data

The CMAI is utilized as the primary efficacy assessment of a subject's level of agitated behaviors. 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.

In addition, CMAI subscale scores for distinct agitation syndromes, also known as CMAI factors of agitation, will be calculated. The three factors include: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior. Each CMAI factor will be calculated only when all items for the factor are recorded and non-missing. CMAI factors will be derived based on a subset of CMAI items[8] as described in Section 10.3.1.

6 Trial Conduct

6.1 Subject Disposition and Reasons for Discontinuations

Subject disposition is summarized for the randomized sample. Disposition is summarized by treatment group and by subgroup of gender, age (< 65; ≥ 65 and < 75; or ≥ 75), race, and region (North America or Other).

Reasons for discontinuation will be summarized for the randomized sample by treatment group and by subgroup of gender, age, race, and region.

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%, ≥ 70% and < 80%, ≥ 80% and < 90%, ≥ 90%) will be summarized by treatment group.

6.3 Protocol Deviation

Protocol deviations are summarized by center and type of deviation for randomized subjects by treatment group. A listing of protocol deviations will also be generated.

7 Baseline Characteristics

7.1 Baseline Definition

For analyses of the double-blind treatment period data, the baseline is the Baseline measurement (expected to be at Day 0). Baseline measurement is defined as the last available measurement prior to the start of double-blind IMP.

7.2 Demographic Characteristics

Baseline demographic characteristics including age, gender, race, ethnicity, height, weight, waist circumference, and body mass index (BMI) will be tabulated by treatment group for all randomized subjects. Additional summaries by the following subgroups will be also generated: by gender, by age group (< 65; ≥ 65 and < 75; or ≥ 75), by race, and by region (North America or Other).

Mean, range and standard deviation will be used to describe continuous variables such as age. Frequency distributions will be tabulated for categorical variables such as race.

7.3 Disease History

A summary of medical, psychiatric, neurological (excluding Alzheimer's), and Alzheimer's disease history will be presented for the Randomized Sample (by treatment group and overall).

7.4 Baseline Disease Characteristics

For the Randomized Sample, baseline and baseline disease characteristics will be summarized by treatment group and overall. The following baseline characteristics will be summarized at baseline: number (%) of institutionalized / non institutionalized subjects; 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, Neuropsychiatric Inventory (NPI) total score; NPI-AA item score; Mini Mental State Examination (MMSE) score; Sheehan Suicidality Tracking Scale (Sheehan-STS) score.

Number of subjects with presence of psychotic symptoms will be summarized at baseline using NPI Delusion and Hallucination score. The counts will be provided for the following categories: NPI item score ≥ 4, ≥ 5, ≥ 6 on either the hallucination or delusion score.

8 Efficacy Analysis

All efficacy analyses pertaining to the double-blind treatment period will be performed on the Efficacy Sample, and subjects will be included in the treatment group as randomized.

[redacted]

[redacted].

8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from the baseline (Day 0 visit) to the end of the double-blind treatment period (Week 12 visit) in CMAI total score. The null hypothesis is that there is no difference in the mean change from baseline to Week 12 in CMAI total score between the two treatments brexpiprazole and placebo.

The primary analysis will be performed on the Efficacy Sample which includes all randomized subjects who took at least one dose of IMP in the double-blind treatment period and who have both a baseline and at least one post-randomization CMAI total score during the double-blind treatment period.

8.1.1 Primary Estimand

In order to support the primary objective of the trial, treatment effect will be estimated under hypothetical situation had no subjects discontinued early from treatment. Due to this strategy, the last collected efficacy assessment after premature trial discontinuation will be done only once at the Early Termination (ET) Visit. Every effort will be made to complete all the ET evaluations prior to administering any additional medications for the treatment of agitation or any other prohibited medications. In the case of terminal or lost to follow-up event, no ET evaluations would be expected, and only scheduled assessments performed before such an event would be used for the primary efficacy analysis. All collected efficacy assessments will be slotted as per the Visit Window Definition, and only one assessment per visit window will be used for the primary efficacy analysis. If there are multiple assessments available in the same window, the latest one will be used.

This trial seeks to clarify the efficacy of brexpiprazole in improving the CMAI total score in the idealistic scenario of full adherence to the assigned treatment in all subjects. In clinical trial practice, however, instances of non-adherence such as treatment discontinuation are likely to occur before the study endpoint (i.e., the Week 12 Visit for this trial). Given this consideration, the hypothetical estimand is the most appropriate for achieving the primary objective of the trial. The primary estimand is described by five attributes as follows.

- Target Population: Subjects with agitation associated with dementia of the Alzheimer's type who have met protocol inclusion/exclusion criteria

- Endpoint: Change from Baseline to Week 12 in the CMAI total score
- Intercurrent Events: Intercurrent events refer to premature treatment discontinuation (i.e., early dropout) prior to Week 12 attributable to adverse events or lack of efficacy or withdrawal of consent/assent or any other causes.
- Measure of Intervention effect: Difference in endpoint means between the brexpiprazole and placebo treatment arm.
- Treatment regimen: 2 or 3 mg daily for 12 weeks.

During the course of this trial, the COVID-19 pandemic broke out. The pandemic had a significant impact on many aspects of clinical trials. There are occasionally virtual visits (i.e., remote assessments) and possibly early discontinuation of treatment directly or indirectly related to the pandemic. However, subjects were required to attend the screening, Day 1 and the end of trial visits in person (i.e., face-to-face). Note that virtual visits in the pandemic environment will not be treated as an intercurrent event for the primary analysis. Subjects who drop out with a reason relating to the COVID-19 pandemic will be handled as they would have dropped out for another reason if the pandemic had not happened.

The hypothetical strategy of handling intercurrent events will be used to clarify the efficacy of the brexipiprazole had there be no occurrence of intercurrent events, regardless of being COVID-19 related or not. In other words, the estimand as described above will use the hypothetical strategy to address the treatment effect of interest that would be envisioned under the hypothetical setting of no occurrence of intercurrent events in the planned 12-week treatment period.

The estimator will be the Mixed Model Repeated Measurements (MMRM) estimate for treatment difference at Week 12, based on all observed case (OC) data until discontinuation from the trial. This reflects the chosen strategies for the identified intercurrent events. Details of the model is provided in the next section.

The OC data consist of actual observations recorded at each visit during the double-blind treatment period. The term “OC data” means that longitudinal data, if missing, will not be imputed by applying an imputation rule (e.g., the LOCF rule). For example, if the subject had a missing CMAI total score at Week 12, then his score at Week 12 will not be imputed with his score observed at an earlier visit. Note that in this SAP the OC data will be used as input data for all the MMRM analyses, though “OC” is not explicitly mentioned.

8.1.2 Method of the Primary Analysis

Mean change from baseline in CMAI total score will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach. The analysis will be performed by fitting the MMRM model with an unstructured (UN) variance-covariance structure in which the change from the baseline in CMAI total score (Week 2, 4, 6, 8, 10, 12) will be the dependent variable based on the OC data. The analysis will include treatment (brexpiprazole and placebo), trial center, visit week, and an interaction term of treatment by visit week as the fixed, categorical effects and include the interaction term of baseline CMAI total score by visit week as covariates. In case there is a convergence problem with the MMRM model with the UN variance-covariance matrix, the following structures will be used in the order of 1) heterogeneous Toeplitz (TOEPH), 2) heterogeneous autoregressive of order 1 (ARH1), and 3) heterogeneous compound symmetry (CSH) and the first variance-covariance structure converging to the best fit will be used as the primary analysis.

The Kenward-Roger approximation will be used to estimate denominator degree of freedom and adjust standard errors. The contrast (i.e., difference in least-square means between brexpiprazole and placebo) at the Week 12 visit will be estimated from the interaction term of treatment by visit week and will serve as the primary treatment comparison. The point estimate and the 95% confidence interval estimate of the contrast at the Week 12 visit will be reported. Significance test will be based on the contrast estimate at the Week 12 visit by using a two-sided 0.015 level for the interim analysis and a two-sided 0.035 level for the final analysis (when the trial does not stop at the interim analysis). Analysis will be implemented using the software Statistical Analysis System® (SAS® version 9.4 or later) procedure PROC MIXED.

If a structured variance-covariance is used, the empirical sandwich estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the variance-covariance matrix.

Small centers will be defined as centers that do not have at least one evaluable subject (evaluability with regard to the primary efficacy variable) in each treatment arm in the double-blind treatment period. All small centers will be pooled within region to form “pseudo centers” for the purpose of analysis according to the following algorithm. Small centers will be ordered from the largest to the smallest based on the number of evaluable subjects. The process will start by pooling the largest of the small centers with the smallest of the small centers until a non-small center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end

of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest non-small center. The pooling of the small centers will be performed within each region (North America and Other).

The chosen MMRM analysis assumes missing data to be "missing at random" (MAR), which is a reasonable assumption in longitudinal clinical trials.[2] However, the possibility of "missing not at random" (MNAR) data can never be ruled out. In order to further evaluate robustness of the primary results to the deviations from MAR assumptions, additional sensitivity analysis will be conducted. Sensitivity analyses based on selection model[3], pattern-mixture model[4,5,6], and/or shared parameter model[7] will be performed in order to explore data missing mechanisms of MNAR and investigate the response profile of dropout reason.

In case of gross violations of the MMRM model assumptions, additional supportive analyses will be provided using the generalized version of the Cochran-Mantel-Haenszel (CMH) procedure (van Elteren test), controlling for trial site.

8.1.3 Technical Computation Details for Primary Efficacy Analysis

1) For primary analyses at Week 12 during the double-blind treatment period, the following algorithm will be used for including subjects in the 12-week analysis.
   a) All scheduled visits during the 12 weeks after randomization, regardless of compliance to trial assessment schedule, will be included in the 12-week analysis.
   b) All early terminated (ET) visits before week 12 will be included according to visit window in the 12-week analysis.
   c) All ET visits > 12 weeks after randomization and outside of visit window will not be included in 12-week analysis.
   d) The week number for an ET visit will be calculated by (date of ET visit randomization/drug start date + 1) according to visit window.
2) The SAS code for the PROC MIXED procedure to carry out the above MMRM analysis with an unstructured variance covariance structure is illustrated as follows:

```
proc mixed;
    class treatment center visit subjid;
   model change=treatment center visit treatment*visit baseline*visit  / s cl
ddfm=kr;
   repeated visit /type=un subject=subjid r rcorr;
   lsmeans treatment*visit / pdiff cl alpha=0.05 slice=visit;
   ods output diffs=diffs lsmeans=lsmeans;
```

run;

Baseline is the CMAI total score at baseline (Day 0 visit).

8.1.4 Sensitivity Analyses for the Primary Efficacy Endpoint

Traditionally the dropout mechanisms are divided into three types[4]: (1) Missing Completely at Random (MCAR), in which the probability of dropout doesn't depend on the observed data and the missing data; (2) MAR, in which the probability of dropout depends on the observed data; and (3) MNAR, where the probability of dropout depends on the missing data and possibly the observed data.

Most of MNAR methods have treated all observations with dropout as if they fall within the same dropout type[3]. In practice, we would find that different dropout reasons may be related to the outcomes in different ways, for example, detailed dropout reasons for this trial are: adverse events (AE), lost to follow-up, protocol deviation, sponsor discontinued trial, subject met (protocol-specified) withdrawal criteria, subject was withdrawn from participation by the investigator, and subject withdrew consent to participate. Dropout due to an AE may lead to MNAR dropout. Subject withdrew consent may also lead to MNAR dropout. However, it is debatable whether a dropout caused by subjects withdrew consent is MAR or MNAR. Except AE, and subject withdrew consent, all other dropout reasons may be assumed as either MCAR or MAR dropout.

As sensitivity analyses for MAR assumption, analyses for MNAR will be carried out. Pattern Mixture Models (PMM) based on Multiple Imputation (MI) with mixed missing data mechanisms will be used to investigate the response profile of dropout subjects by last dropout reason under MNAR mechanism for the following three scenarios:

- Dropout reasons due to AE as MNAR
- Dropout reasons due to either AE or subject withdrew consent as MNAR
- All dropouts as MNAR

Delta Adjustment Imputation Methods

This MNAR sensitivity analysis is to departure from MAR assumption by progressively increasing the delta until conclusion from the primary analysis is overturned. The delta is 0%, 10%, 20%, 30%, ..., 100% of the expected treatment difference of 6.5 points and/or the observed treatment difference between brexpiprazole and placebo from the primary analysis of MMRM model until conclusion of the primary analysis is overturned. When delta = 0 the missing data are assumed to be MAR. When delta > 0, the missing data are assumed to be MNAR.

1) Using Monte Carlo Markov Chain (MCMC) methodology from PROC MI to impute the intermittent missing data to a monotone missing pattern
2) Using a standard MAR-based multiple imputation approach from PROC MI to impute the monotone missingness data
3) For subjects in the treated group and with a dropout reason of AE or subject withdrew consent, a delta will be added for all the values after the dropout time
4) Using MMRM model in the primary analysis to analyze the completed data using PROC MIXED on the multiple imputed data
5) Obtaining the overall results using PROC MIANALYZE.

Placebo Based Imputation Methods

Similar to the "Standard" multiple imputations, except parameters for imputation model obtained from only the placebo (control) group. Missing data for both placebo and drug group are imputed based on the imputation model derived from placebo data. If drug improved outcomes prior to dropout, this benefit is carried into subsequent imputed values, but will diminish over time in accordance with the correlation structure.

8.1.5 Subgroup Analyses for Primary Efficacy Endpoint

Subgroup analyses of change from baseline in CMAI total score to every trial week in the double-blind treatment period will be performed for the following factors:

- Gender
- Race (White and All Other Races)
- Age group (< 65; ≥ 65 and < 75; or ≥ 75)
- Region (North America and Other)

Interaction effects of treatment-by-subgroup will be assessed at Week 12 for the subgroups identified in the previous paragraph. The same MMRM model will be used as for the primary efficacy analysis with the addition of terms for subgroup-by-week and treatment-by-subgroup-by-week. These treatment-by-subgroup interaction analyses will be presented in statistical documentation.

All subgroup analyses will be conducted using the same MMRM analysis as for the primary efficacy analysis except that the fixed class effect terms trial center will not be included in the model.

8.1.6 COVID-19 Pandemic related Sensitivity Analyses

On [redacted], the national emergence concerning the COVID-19 pandemic was announced in the US. The following analyses will be performed on the Efficacy Sample to evaluate the sensitivity of the primary analysis results to the impact of pandemic. The same model (e.g., with the same set of explanatory variables and the response variable) as

that for the primary efficacy analysis will be used for these analyses specified below. Of note, the definition of intercurrent events and the strategy for handling intercurrent events are identical to that for the primary efficacy analysis.

1) An MMRM analysis based on the pre-COVID Efficacy Sample. The pre-COVID Efficacy Sample comprises those subjects in Efficacy Sample who had completed or discontinued the trial before March 13, 2020.
2) An MMRM analysis based on the Efficacy Sample by using the subset of pre-COVID data. The pre-COVID data consist of the data collected before [redacted].
3) An MMRM analysis based on the non-COVID Efficacy Sample. The non-COVID Efficacy Sample comprises those subjects in Efficacy Sample who had no remote assessment of the primary endpoint.
4) An MMRM analysis based on the Efficacy Sample by using the subset of non-COVID data. At the subject level, the non-COVID data refer to the data that exclude his/her first remote assessment of the primary endpoint and all the assessments thereafter.
5) An MMRM analysis based on the Efficacy Sample by using the subset of data that exclude all remote assessments.

If the trial stops early for efficacy at the conclusion of IA, the above COVID-19 related sensitivity analyses will be performed on all available data including the data accrual post IA database lock. The point estimate along with the 95% confidence interval estimate of the treatment contrast will be presented for each of the above sensitivity analyses.

8.1.7 Compliance related Sensitivity Analyses

Two clinical sites were identified by audit as having had non-compliance issues. The primary analysis as described in Section 8.1.2 and the key secondary analysis as described in Section 8.2 will be repeated on all available data but with the exclusion of the data from the two identified sites.

8.1.8 Sensitivity Analyses based on the OTC Subset

The primary analysis as described in Section 8.1.2 and the key secondary analysis as described in Section 8.2 will be repeated on the data of the OTC subset of the Efficacy Sample.

8.2 Key Secondary Analysis

The key secondary efficacy variable is the change from baseline to Week 12 in the CGI-S score, as related to agitation. It will be analyzed by the same statistical methodology specified for the analysis of the primary efficacy variable. In order to control the overall

type I error rate for this key secondary efficacy analysis, a hierarchical testing procedure will be used so that the overall experiment-wise type I error rate is maintained. Thus, if the primary efficacy analysis for the CMAI total score yields a statistically significant result for the comparison of brexpiprazole versus placebo, then the corresponding comparison for this key secondary efficacy variable (CGI-S score) will be tested.

8.3 Secondary Efficacy Analyses

Secondary efficacy variables include the following:

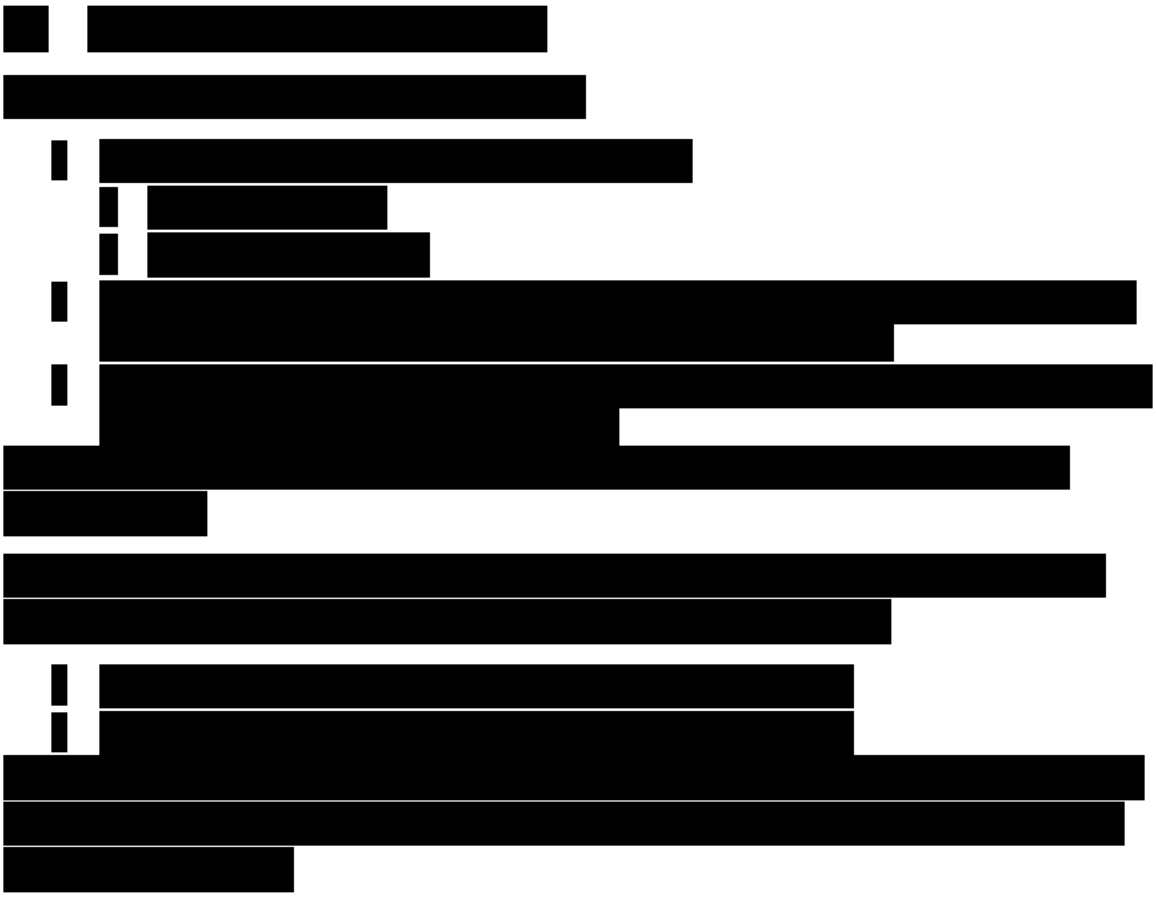
- Change from baseline to Week 12 in CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, verbally agitated behavior)
- Change from baseline in CMAI total score for each trial visit during the double-blind treatment period
- Change from baseline in CGI-S for each trial visit during the double-blind treatment period
- CGI-Improvement (CGI-I) score at each trial visit during the double-blind treatment period
- CMAI response rate at every scheduled trial visit in the double-blind treatment period, where response is defined as ≥ 40%, ≥ 30%, and ≥ 20% reduction in CMAI total score from baseline;
- CMAI Response Rate based on improvement from baseline in agitation status at every scheduled trial visit in the double blind treatment period;
- CGI-I response rate at every scheduled trial visit in the double-blind treatment period, where response is defined as a CGI-I score of 1 or 2 (very much improved or much improved);

Change from baseline will be evaluated using the same MMRM model described in the primary analysis. The CGI-I score will be evaluated by the Cochran–Mantel–Haenszel row mean score differ test (van Elteren) controlling for trial site in last-observation-carried-forward (LOCF) analysis. Response endpoints will be evaluated by the CMH General Association Test controlling for trial site in LOCF analysis.

CMAI subscale scores or factors and agitated status for the first 3 factors will be derived based on a subset of CMAI items[8] as described in Section 10.3.1.

Improvement in agitation status is defined as subject meeting agitation status criteria at baseline on at least one of the 3 subscale scores (aggressive, physically nonaggressive, verbally agitated) and changing the status to non-agitated for the same subscale, while not becoming agitated on another at each visit.

Each factor will be analyzed by the same statistical methodology specified for the analysis of the primary efficacy variable, based on the Efficacy Sample.



8.5 Interim Analysis

An IA of the efficacy data will be performed by an independent DMC when approximately 255 subjects have completed the 12-week trial or discontinued early from the trial. The sponsor will remain blinded to the IA results and will only receive DMC's recommendation as per the IAP and the DMC charter. The DMC may recommend stopping the trial for efficacy or for futility or continuing the trial to the final analysis.

To control the overall Type-I error rate at 0.05 level (two-tailed) in a strong sense, a conservative Bonferroni critical boundary will be used for this two-stage group sequential trial. Specifically, the significance level for the IA is set at 0.015 (2-sided) and the significance level for the final analysis (if the trial does not stop at the IA) is set at 0.035 (2-sided). The IA will be performed as pre-specified in the IAP.

If the DMC recommends stopping the trial for overwhelming efficacy at the conclusion of IA, the sponsor intends to halt the trial in two weeks after receiving DMC's recommendation. The MMRM analysis for the primary endpoint will be repeated on all available data including the data newly accrued after the IA database lock. A significance

level of 0.05 (two-sided) will be used for this additional analysis. All on-going subjects will be given a chance to rollover to the active treatment extension trial Trial 331-201-00182.

8.6 Multiplicity Adjustment

In this SAP, the term endpoint and hypothesis are interchangeably used. The hierarchical testing procedure[11] will be applied to this trial to strongly control the experimental-wise error rate at 5% (two-tailed), wherein the experimental-wise error rate is the probability of making at least one false rejection of the true nulls arising from repeated testing of multiple hypotheses in a group sequential trial. The testing will be conducted on 5 hypotheses of interest in the sequence specified below, respectively at the IA and at the final analysis (if the trial does not stop at the IA), by using pre-specified significance levels. The alpha-spending for the primary endpoint will be applied to the key secondary endpoint and other efficacy endpoints included in the hierarchical testing procedure.

1) The primary efficacy endpoint via the MMRM analysis with an unstructured variance covariance, based on the OC data.

2) The key secondary efficacy endpoint (i.e., Change from baseline to Week 12 in the CGI-S score) via the MMRM analysis with an unstructured variance-covariance, based on the OC data.

3) Change from baseline to Week 12 in the CMAI subscale score (aggressive behavior) via the MMRM analysis with an unstructured variance-covariance, based on the OC data.

4) Change from baseline to Week 12 in the CMAI subscale score (physically nonaggressive behavior) via the MMRM analysis with an unstructured variance-covariance, based on the OC data.

5) Change from baseline to Week 12 in the CMAI subscale score (verbally agitated behavior) via the MMRM analysis with an unstructured variance-covariance, based on the OC data.

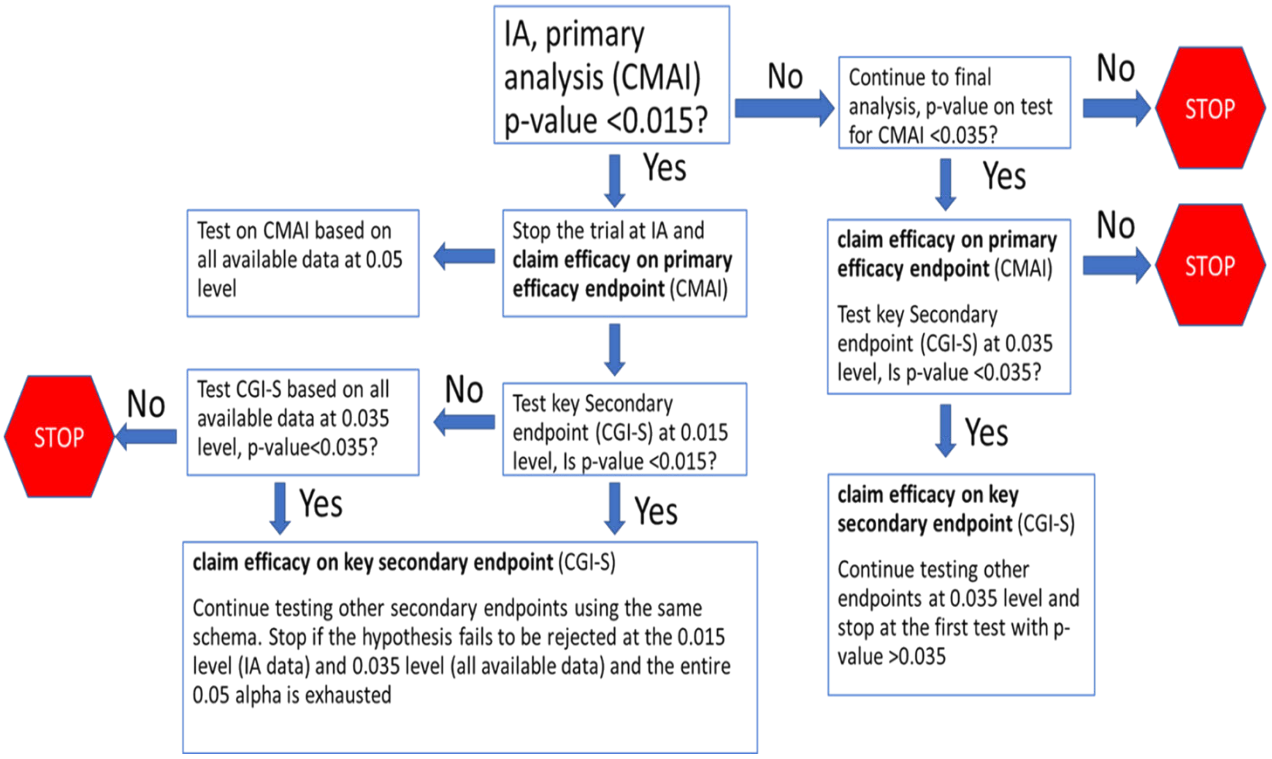
The hierarchical testing procedure is described as follows.

If the trial stops at the IA, the primary efficacy endpoint will be re-tested on all available data (including the recent data accrual post IA database lock) at a two-sided 0.05 level, as mentioned in Section 8.5. Meanwhile, the key secondary endpoint will be tested on the IA data at a two-sided 0.015 level and will also be tested on all available data (including the recent data accrual) at a two-sided 0.035 level. If either of these two tests is nominally

significant at the pre-specified level, then statistical significance on the key secondary endpoint will be claimed and the testing will proceed down to test the CMAI subscale score (aggressive behavior). If neither of these two tests is nominally significant, then statistical significance on the key secondary endpoint cannot be claimed and testing will stop. Testing for each of the other secondary endpoints in the above sequence from 3) to 5) will be conducted similarly to that of key secondary endpoint. Specifically, one test will be conducted on the IA data at a two-sided 0.015 level and the other will be on all available data at a two-sided 0.035 level. Decision rules regarding whether to claim statistical significance and whether to stop the testing will be similar as in the case of testing the key secondary endpoint.

If the trial does not stop at the IA, the above sequence of testing from 1) to 5) will be repeated for the final analysis with the use of a two-sided 0.035 level. In this scenario, the final analysis will be conducted using the data of approximately 330 subjects. There will be no data accrual after the database lock for the final analysis.

Below is the flowchart illustrating the above multiple testing procedure:



For completeness of the presentation, all unadjusted (unadjusted for multiplicity) *p*-values will be reported regardless of whether the endpoints are nominally significant or not.

8.7 Bias Estimation

The naïve point estimate of the parameter mean difference is usually biased upward in a group sequential trial with early efficacy stopping. In this trial, the bias of the estimate of mean difference in change from baseline CMAI total score at Week 12 between brexpiprazole and placebo is fairly small due to (1) the sample size is not small; (2) information fraction for the IA is large, which is 255/330 = 0.77. Regardless of the true mean difference θ, the bias of the mean difference estimate will not exceed 3.02% unit of standard deviation, per the analytic expression for bias (see the penultimate expression on Page 177 of Jennison & Turnbull (2000; Section 8.3)). As a result, the upper bound of the bias will be less than 0.5 point (in terms of the CMAI total score) assuming one unit of within-group standard deviation of 16.5 points.

If the trial stops for efficacy at the IA, a rough bias estimate will be calculated by simply plugging the naïve estimate of mean difference θ into the following expression, which is a simplification from the bias expression mentioned above.

$$\text{bias} = 3.02\% \cdot \sigma \cdot exp\{-(b - \theta\sqrt{I_1})^2/2\}, \text{ where } I_1 = \frac{85}{1.5\sigma^2} \text{ and } b = \Phi^{-1}(1 - 0.015/2) = 2.432$$

and σ is the pooled within-group standard deviation.

The small overestimation bias inherent in the analysis of a group sequential trial is practically negligible given the attenuating circumstance as follows. Due to the enrollment challenges in the US and Western Europe, this study is expected to supplement enrollment with at least 25% of subjects from Eastern Europe and rest of the world (ROW). Based on the results observed in two completed pivotal studies, it is expected that, due to the different healthcare system and different standard of care in Eastern Europe, the effect size in that region would be reduced when compared to that of observed in US, Western Europe and potentially ROW. The oversampling of subjects from Eastern Europe is expected to result in underestimation of the true effect to such a degree that would negate any potential overestimation bias.

9 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examination. In addition, data from the following safety scales will be evaluated: MMSE score, assessments of suicidality (e.g, Sheehan-STS), and extrapyramidal symptoms (EPS; e.g, the Simpson-Angus Scale, abnormal involuntary movement scale [AIMS], and Barnes Akathisia Rating Scale [BARS]). Safety analysis will be conducted based on the Safety Sample. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant (PCR) abnormal values for clinical laboratory tests, vital signs, ECGs, body weight, and BMI.

9.1 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

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 treatment and by visit.

9.2.2 Potentially Clinically Relevant Values

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria in Appendix 1 for laboratory tests will be summarized by 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 be will summarized for subjects who met following criteria in the Short-term Controlled Trials and Long-term Open-label Trials groups. The corresponding listing will be provided as well.

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

9.2.4 Metabolic Change

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

Table 9.2.4-1 Criteria for Treatment-Emergent Significant Change in Lipids and Glucose

Lab Parameter	Baseline[a]	Anytime Post Baseline
LDL Direct, Fasting (mg/dL)	Borderline 100 < 160 Normal/Borderline < 160 Normal < 100 Any Value	High ≥ 160 High ≥ 160 Borderline/High ≥ 100 Increased ≥ 30
HDL Cholesterol, Fasting (mg/dL)	Normal ≥ 40 Any Value	Low <40 Decreased ≥ 20
Triglycerides, Fasting (mg/dL)	Normal < 150 Borderline 150 < 200 Normal/Borderline < 200 Normal < 150 Any Value	High 200 < 500 High 200 < 500 High 200 < 500 Borderline/High/Very High ≥ 150 Increased ≥ 50
Glucose Fasting, Serum(mg/dL)	Normal < 100 Impaired 100 < 126 Normal/Impaired < 126 Any Value	High ≥ 126 High ≥ 126 High ≥ 126 Increased ≥ 10

[a] Baseline is calculated from Day 0; if Day 0 is unavailable screen visit will be used

Table 9.2.4-2 Criteria for Treatment-Emergent Metabolic Syndrome		
Description	**Lab Parameter**	**Anytime Post Baseline[a]**
Central Obesity	Waist Circumference	Males: ≥ 102 cm Females: ≥ 88 cm
Dyslipidemia	Triglycerides	≥ 150 mg/dL
	HDL	Males: < 40 mg/dL Females: < 50 mg/dL
Supine Blood Pressure	Systolic	≥ 130 mmHg
	Diastolic	≥ 85 mmHg
Fasting Glucose	Glucose Fasting, Serum	≥ 100 mg/dL

[a] Baseline is calculated from Day 0; if Day 0 is unavailable screen visit will be used

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, and waist circumference will be provided by treatment group.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria in Appendix 2 for vital signs and body weight will be summarized by 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 treatment and by visit.

In addition, the incidence of treatment-emergent PCR values identified using prospectively defined criteria for ECG will be summarized by 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 double-blind treatment period will be summarized based on the criteria in Table 9.4-1.

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 Body Weight, Waist Circumference and Body Mass Index

Analyses of body weight, waist circumference and BMI will be performed for the Safety Sample. Body mass index is defined as weight in kilograms divided by the square of height in meters. The mean change from baseline to Week 12 and the last visit in the double-blind treatment period in body weight will be tabulated and analyzed using analysis of covariance (ANCOVA). The ANCOVA models will include the baseline as a covariate and the treatment group as fixed effect.

Percentages of subjects showing significant weight gain (≥ 7% increase in weight), as well as percentages of subjects showing significant weight loss (≥ 7% decrease in weight) from baseline to Week 12 (OC and LOCF) will be analyzed using CMH General Association Test.

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

The mean change from baseline to Week 12/ET in the double-blind treatment period obtained from the Simpson-Angus Scale total score, AIMS total score (total of the first 7 item scores), and BARS Global Clinical Assessment will be performed for the Safety Sample and tabulated and analyzed using ANCOVA.

The ANCOVA model will include the baseline measure and the treatment group.

The same analyses will be performed on the AIMS individual item scores 8, 9, and 10. In addition, incidence of BARS Global Clinical Assessment of Akathisia during the double-blind treatment period by severity category will be provided. Analyses of these EPS rating scales will be performed for the Safety Sample.

9.7 Mini-Mental State Examination

The mean changes from baseline to Week 12/ET visit in the double-blind treatment period in MMSE will be tabulated and analyzed by treatment group using ANCOVA. The ANCOVA model will include the baseline item score as covariate and treatment group as main effect. The analyses will be performed for Safety Sample.

9.8 Suicidality Data

The mean changes from baseline to Week 12/ET visit in the double-blind treatment period in Sheehan-STS individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score will be tabulated and analyzed by treatment group using ANCOVA. The ANCOVA model will include the baseline item score as covariate and treatment group as main effects.

Incidence of treatment emergent suicidal ideation, suicidal behavior will be summarized by treatment, and overall.

9.9 Concomitant Medications

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

9.10 Extent of Exposure

The start date of double-blind IMP with brexpiprazole or placebo will be the first day of double-blind dosing. The number and percentage of subjects who receive double-blind IMP will be presented by week and by 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 treatment group.

The mean daily dosage will be summarized by week and 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

treatment group the number of subjects receiving double-blind IMP, and the mean and range of the mean daily dose for each week.

10 Conventions

10.1 Trial 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. 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 double-blind period. The variable "target day" is defined using the number of days since the start of double-blind dosing. The first day of double-blind 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 double-blind dosing date will not be mapped into trial visit windows, and will be excluded from the analysis.

Table 10.1-1 Trial Day and Visit Window

Week	Target Day	Trial Day Interval[a]
1	7	2 - 10
2	14	11 - 17
3	21	18 - 24
4	28	25 - 31
5	35	32 - 38
6	42	39 - 45
7	49	46 - 52
8	56	53 - 59
9	63	60 - 66
10	70	67 - 73
11	77	74 - 80
12	84	81 - 91[b]

[a] Relative to the first day of IMP in the double-blind treatment period.

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

10.2 Pooling of small centers

Primary efficacy analysis will be performed on the ITT Efficacy Sample which comprises those subjects in the randomized sample who have a baseline value and at least one post-randomization value for CMAI total score in the double-blind treatment period.

Small centers will be defined as centers that do not have at least one evaluable subject (evaluable with regard to the primary efficacy variable) in each treatment arm in the double-blind treatment period. All small centers will be pooled to form "pseudo centers" for the purpose of analysis according to the following algorithm. Small centers will be ordered from the largest to the smallest based on the number of evaluable subjects (ie, subjects who have a baseline value and at least one post-randomization value for CMAI total score in the double-blind treatment period). The process will start by pooling the largest of the small centers with the smallest of the small centers until a non-small center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest non-small center. The pooling of the small centers will be performed within each region (North America and Other).

10.3 Scales: Rules for Scoring and Handling of Missing Data

10.3.1 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 behavior occurring at a frequency of at least 3; or
- at least three aggressive behavior 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[8]: Intentional Falling; Making Verbal Sexual Advances; Making Physical Sexual Advances; Strange Noises (weird laughter or crying); Eating or Drinking Inappropriate Substances.

10.3.2 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.

10.3.3 Clinical Global Impression-Improvement Scale

The efficacy of brexpiprazole in the treatment of agitation will be rated for each subject using the CGI-I. The investigator (or designee) will rate the subject's total improvement (as related to agitation) whether or not it is due entirely to IMP. Response choices are 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

This is also a 7-point scale (1 to 7), with 1 being very much improved and 7 being very much worse. The scale also includes 0: not assessed, which will be set to missing for

purposes of analysis. At each visit other than randomization, the global improvement will be judged with respect to subject's condition at randomization.

[redacted]

10.3.5 Hachinski Ischemic Scale (Rosen Modification)

The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms. The Rosen modified Hachinski Ischemic Scale will be completed to assess eligibility for the trial by the same neurologist who performs the neurological examination.

10.3.6 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.

10.3.7 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.

10.3.8 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).

10.3.9 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.

10.3.10 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.

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Appendix 1 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 × ULN
ALT (SGPT)	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
LDH	≥ 3 × 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 × 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 2 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm	≥ 15 bpm increase
	< 50 bpm	≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mmHg	≥ 20 mmHg increase
	< 90 mmHg	≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg	≥ 15 mmHg increase
	< 50 mmHg	≥ 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 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

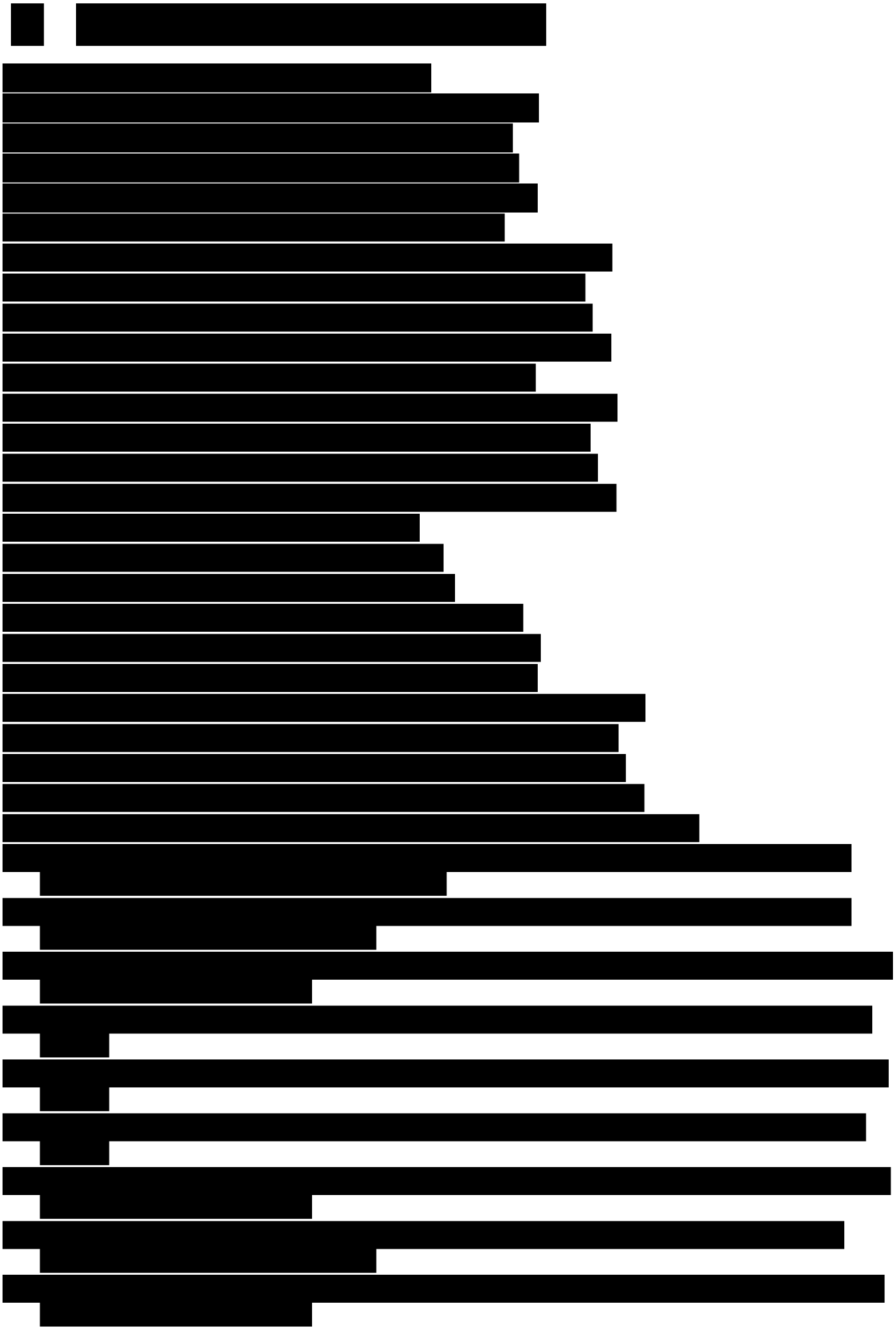
Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not 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 trial 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)	

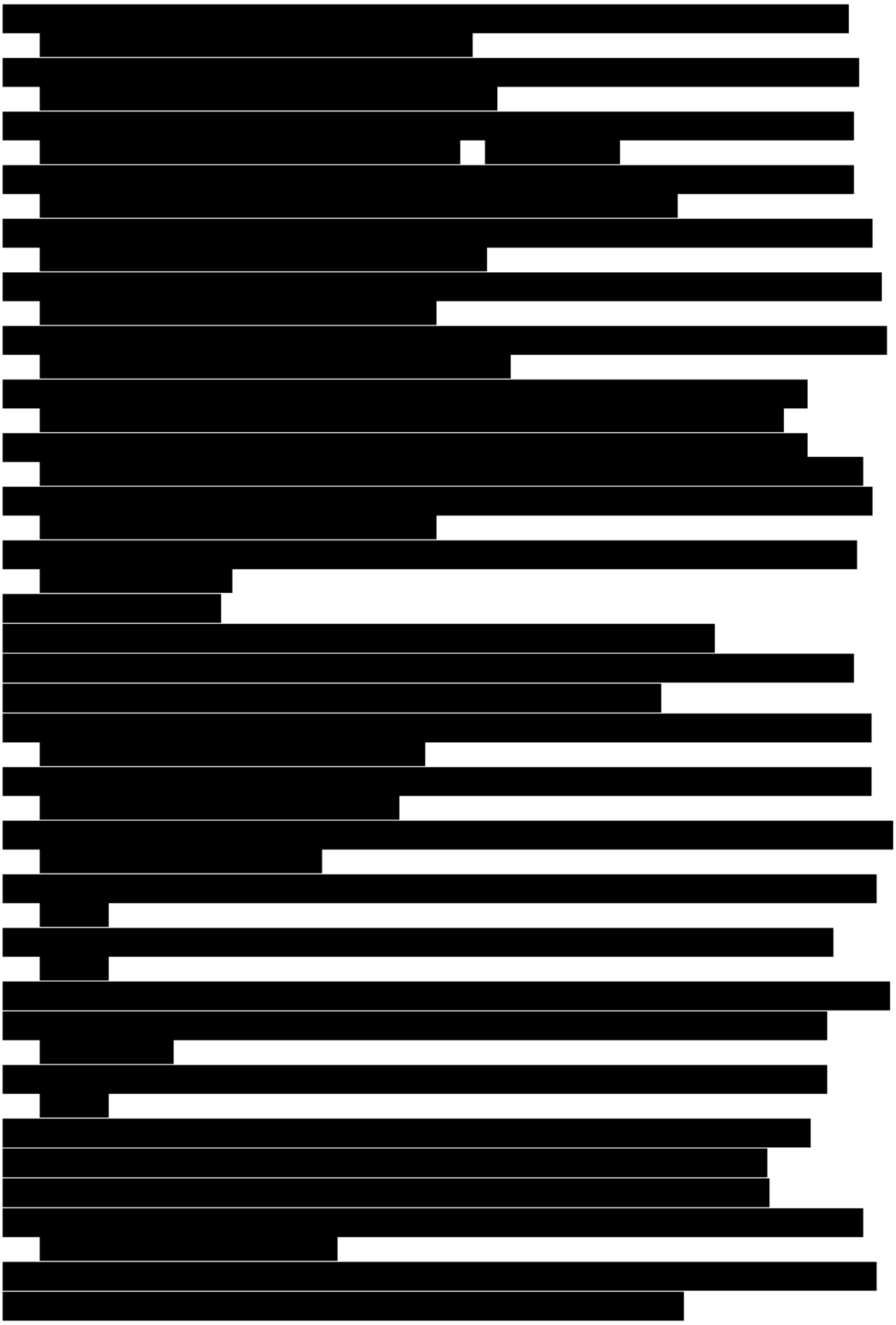
[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

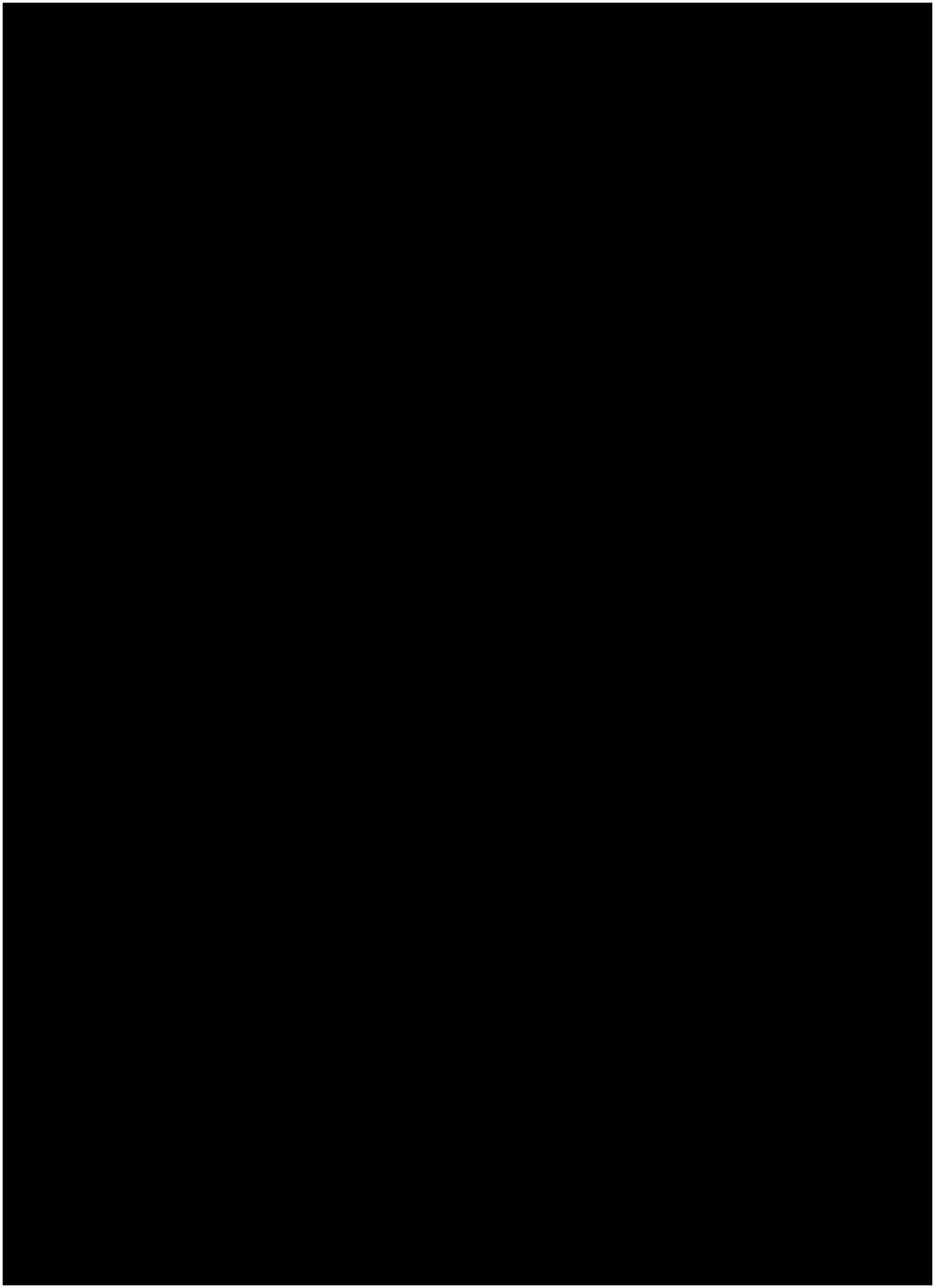
[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[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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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

Addendum to Statistical Analysis Plan Version 2.0

A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2-Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Protocol No. 331-14-213
IND No. 115,960
EudraCT No. 2017-003940-19

Version: 1.0

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CONFIDENTIAL - PROPRIETARY INFORMATION

Table of Contents

1 Introduction

This addendum to the statistical analysis plan (SAP) version 2.0 is to document a modification to the multiplicity adjustment after the approval of the original SAP (version 2.0, issued on [redacted]) and the interim analysis plan (version 4.0, issued on [redacted]), and to address FDA's feedbacks on the SAP. The modification will have no impact on the familywise Type-I error rate, which is strongly controlled at a two-sided 5% level. The statistical methodology, data analysis algorithms and conventions remain the same as those in the original SAP.

2 Modification to the Multiplicity Adjustment

The hypotheses of interest for the planned labeling will be comprised of only the primary endpoint CMAI total score and the key secondary endpoint CGI-S score. The hypotheses pertaining to all other secondary endpoints will be excluded from the hierarchical testing procedure.

The testing will be conducted on two hypotheses of interest in the order specified below:

1) The primary efficacy endpoint, change from baseline to Week 12 in the CMAI total score

2) The key secondary efficacy endpoint, change from baseline to Week 12 in the CGI-S score

After reviewing the unblinded interim analysis results, DMC recommended that the trial be continued to the planned end. As a result, at the final analysis, the primary efficacy endpoint will be tested at a two-sided 3.5% significance level, and upon achieving significance on the primary endpoint, the key secondary endpoint will be tested at the same level. The hierarchical testing procedure controls the Type-I error rate for both the primary efficacy endpoint and the key secondary efficacy endpoint.

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