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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| Clinical Development Phase: | 3 |
| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>2440 Research Boulevard<br>Rockville, Maryland 20850, United States |
| Immediately Reportable Event | Syneos Health Pharmacovigilance & Drug Safety<br>[redacted] |
| Issue Date: | 23 Feb 2018 |
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| Version No.: | 4.0 |

## 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

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| Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712) | Protocol No.: 331-14-213<br>IND No.: 115960<br>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)<br><br>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.<br><br>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.<br><br>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:

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.

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| | 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.<br><br>*Follow-up Period*<br><br>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.) |

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| | 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.<br><br>Key exclusion criteria include the following:<br>• 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.<br>• 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.<br>• Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.<br>• Subjects with delirium or history of delirium within the |

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| | 30 days prior to the screening visit.<br>• 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.<br>• Subjects who have received multiple antipsychotic medications simultaneously for a period of > 7 days within 90 days prior to screening.<br>• 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.<br>• 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.<br>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.<br>The total duration of double-blind treatment will be 12 weeks for all randomized subjects.<br>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. |

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| Trial Assessments: | Efficacy: CMAI, Clinical Global Impression Severity of Illness (CGI-S) scale, Clinical Global Impression Improvement of Illness (CGI-I) scale, [redacted].<br><br>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]<br><br>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.<br><br>Screening/Other: Hachinski Ischemic Scale and NINCDS-ADRDA. |

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

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| | **Safety Endpoints**:<br><br>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).<br><br>**Pharmacokinetic/Pharmacodynamic Endpoints**:<br><br>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.<br><br>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. |

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| 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.<br><br>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.<br><br>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. |

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# List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| 5-HT | Serotonin |
| $5\text{-HT}_{1A}$ | Serotonin type 1A receptor |
| $5\text{-HT}_{2A}$ | 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 |
| FBR | Future biospecimen research |
| 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 17 Apr 2017, 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 30 Apr 2017, 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 [redacted]

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.

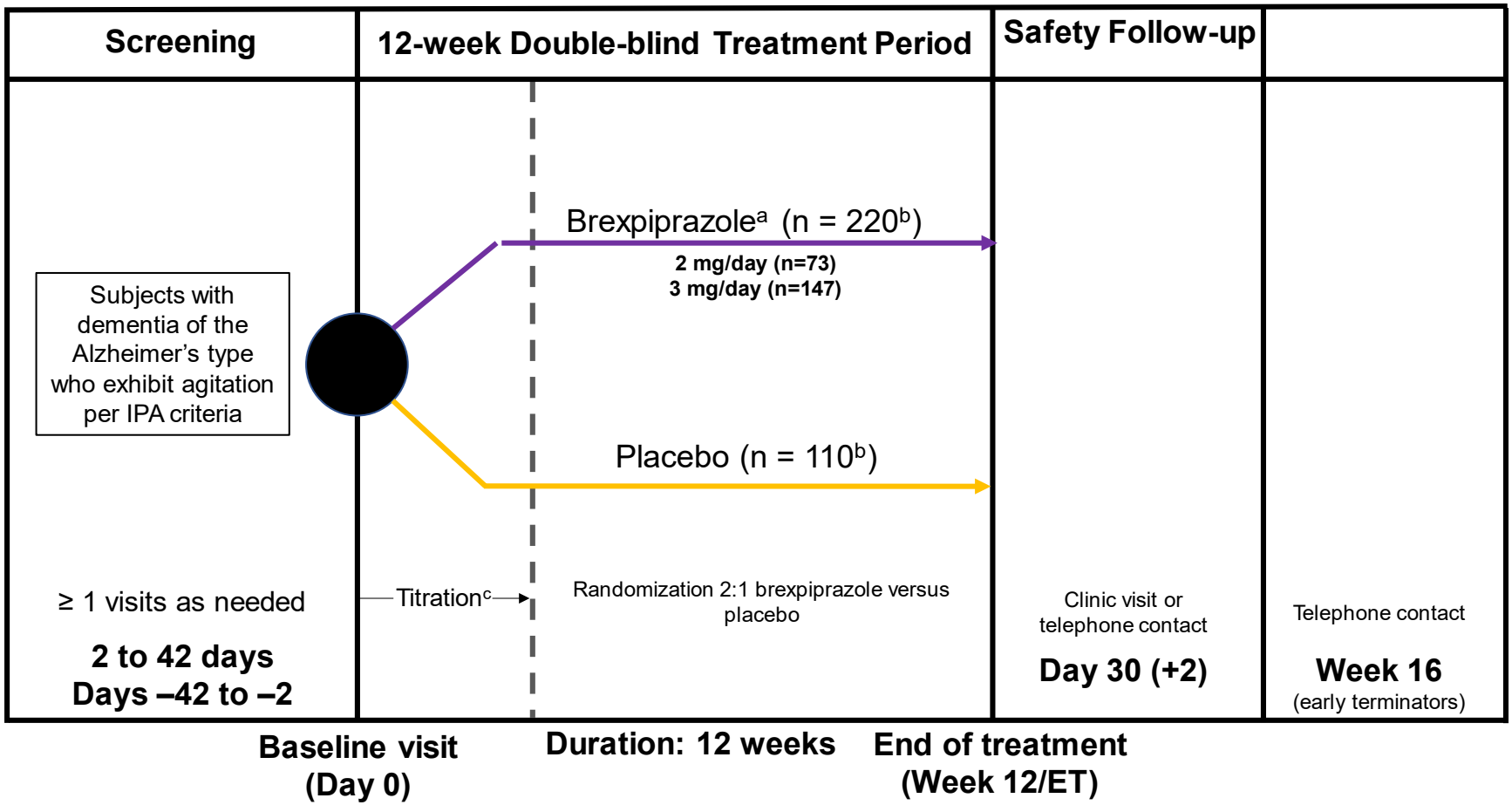


**Figure 3.1-1 Trial Design Schematic**

[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).

[redacted]

## 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 [redacted]

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:

- [redacted]
- 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.<br>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:<br>• An evaluation for reversible factors (eg, pain, infection, or polypharmacy), and<br>• 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:<br>• Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia<br>• Bipolar I or II disorder, bipolar disorder not otherwise specified<br>• 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.<br>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:<br>• Screening $HbA_{1c}$ < 8.0%, AND<br>• 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<br>• Subject has not had any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes.<br>Subjects with non-IDDM (ie, any subjects not using insulin) must also satisfy the below criterion:<br>• 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.<br>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:<br>• Platelets ≤ 75000/mm$^3$<br>• Hemoglobin ≤ 9 g/dL<br>• Neutrophils, absolute ≤ 1000/mm$^3$<br>• AST > 2 × ULN<br>• ALT > 2 × ULN<br>• CPK > 3 × ULN, unless discussed with and approved by the medical monitor<br>• Albumin < 3 g/dL<br>• $HbA_{1c}$ ≥ 8%<br>• 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.)<br>• QTcF ≥ 450 msec in men and ≥ 470 msec in women (detailed further in the protocol), unless due to ventricular pacing<br>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

### 3.5.3 Exploratory Endpoints

[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. 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.

## 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<br>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] | [redacted] | | | | | | | | | | |
| **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** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **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** |
| 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] | [redacted] | | | | | | | | | | [redacted] |
| 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].

### 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).<br>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.<br>(a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms).<br>(b) Verbal aggression (eg, yelling, speaking in an excessively loud voice, using profanity, screaming, shouting).<br>(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:<br>(a) Significant impairment in interpersonal relationships.<br>(b) Significant impairment in other aspects of social functioning.<br>(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<br>WBC count with differential<br>RBC count<br>Hematocrit<br>Hemoglobin<br>Platelet count<br><br>Urinalysis<br>pH<br>Specific gravity<br>Protein<br>Ketones<br>Glucose<br>Blood<br>Microscopic exam (performed only if any part of the urinalysis is not negative)<br><br>Urine Drug Screen<br>Amphetamines<br>Barbiturates<br>Benzodiazepines<br>Cannabinoids<br>Cocaine<br>Marijuana<br>Methadone<br>Opiates<br>Phencyclidine<br>Propoxyphene<br><br>Other<br>Blood alcohol<br><br>Additional Tests (Screening Only)<br>HBsAg<br>Anti-HCV | Serum Chemistry<br>ALP<br>ALT (SGPT)<br>AST (SGOT)<br>BUN<br>CPK<br>Creatinine<br>Total bilirubin<br>Triglycerides<br>Cholesterol (total, LDL, and HDL)<br>Calcium<br>Chloride<br>Glucose<br>Insulin<br>Sodium<br>Potassium<br>Total protein<br>Uric acid<br>GGT<br>Prolactin (blinded)<br>Albumin<br><br>Additional Tests<br>Urine pregnancy (women of childbearing potential)[a]<br>TSH, with reflex to free $T_4$ if TSH is abnormal<br>PT, aPTT, and INR (screening only)<br>$HbA_{1c}$ |

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 $\leq 9$ 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<br>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).<br>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.<br>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. [redacted]

# 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]

### 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.

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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<br>< 50 bpm | ≥ 15 bpm increase<br>≥ 15 bpm decrease |
| Systolic blood pressure[b] | > 180 mmHg<br>< 90 mmHg | ≥ 20 mmHg increase<br>≥ 20 mmHg decrease |
| Diastolic blood pressure[b] | > 105 mmHg<br>< 50 mmHg | ≥ 15 mmHg increase<br>≥ 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<br>≥ 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

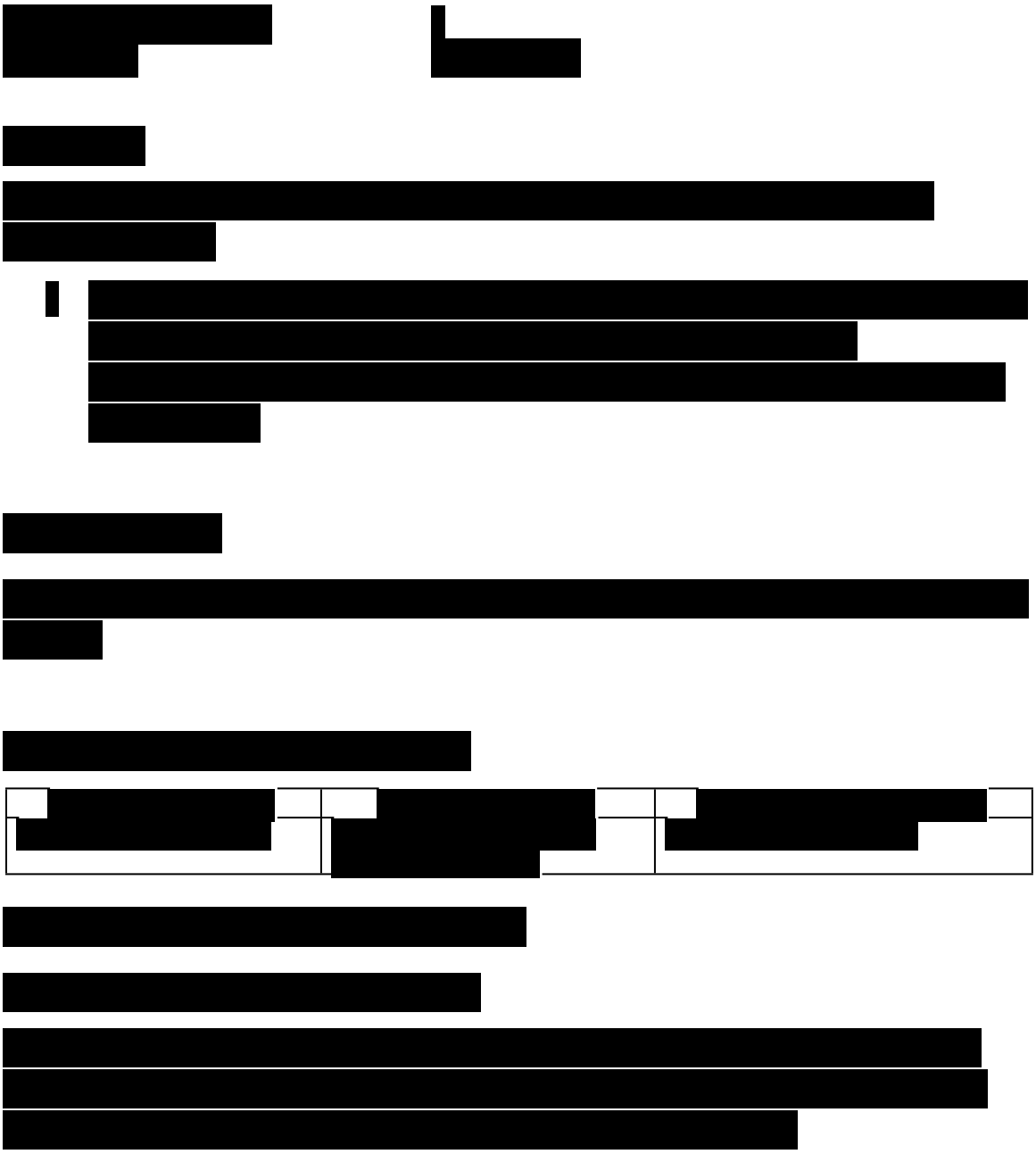
| Variable | Criterion Value[a] | Change Relative to Baseline[a] |
|---|---|---|
| **Rate** | | |
| Tachycardia | ≥ 120 bpm | increase of ≥ 15 bpm |
| Bradycardia | ≤ 50 bpm | decrease of ≥ 15 bpm |
| **Rhythm** | | |
| Sinus tachycardia[b] | ≥ 120 bpm | increase of ≥ 15 bpm |
| Sinus bradycardia[c] | ≤ 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<br>≥ 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)<br><br>QTcF ≥ 470 msec (women) | |

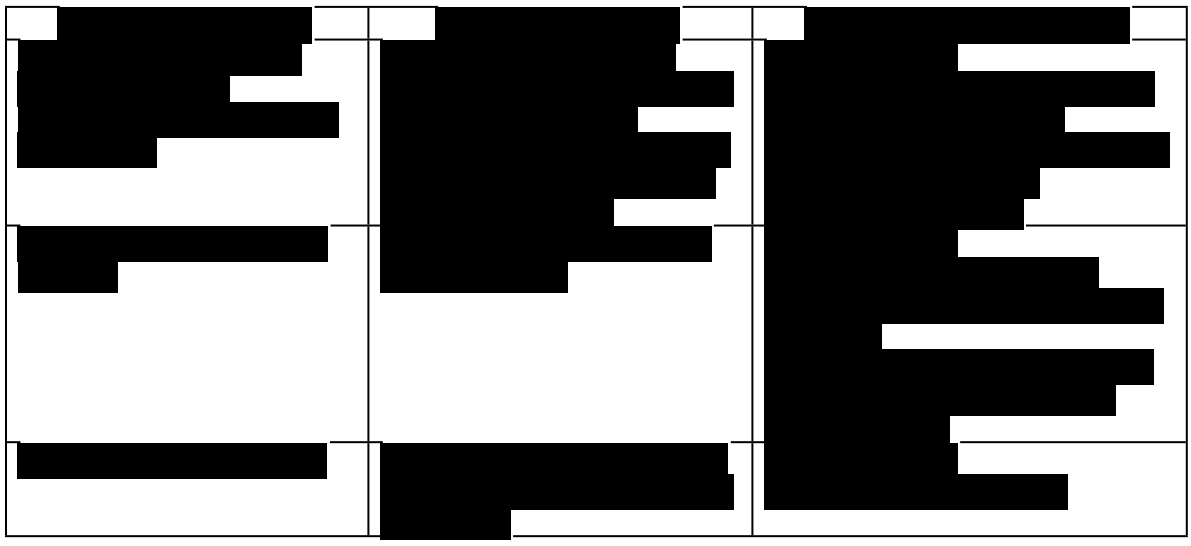
[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

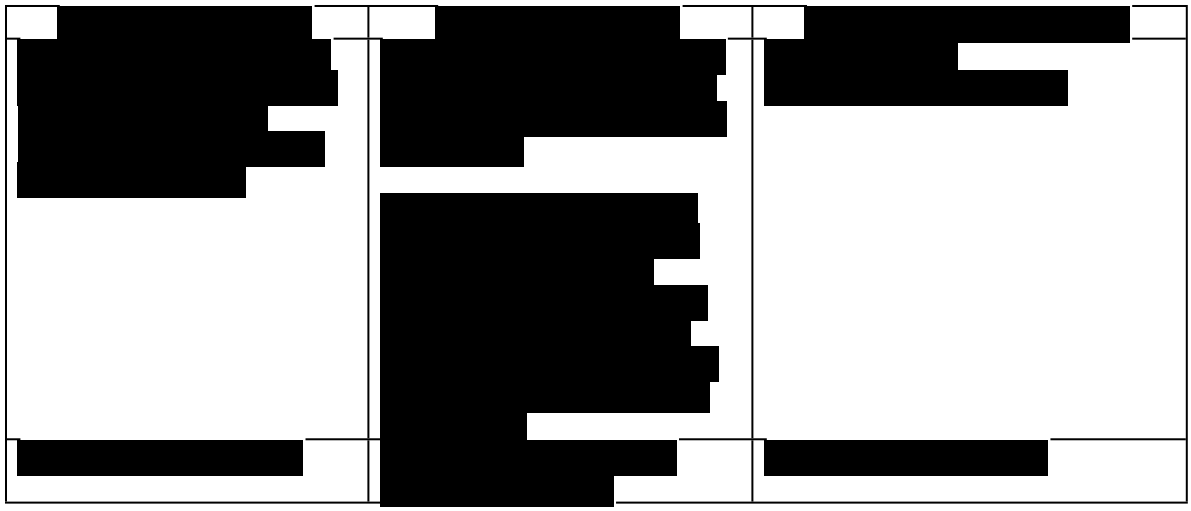
[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[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.







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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# SIGNATURE PAGE

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