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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-34712

CLINICAL PROTOCOL

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

Protocol No. 331-201-00182
IND No. 115960
EudraCT No. 2018-002783-88

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety
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Amendment 2:	06 Aug 2020
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Version No.:	4.0

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Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the site, investigator(s), and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to coronavirus disease 2019 (COVID-19). If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits (phone or video) as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-201-00182 IND No.: 115960 EudraCT No.: 2018-002783-88
Protocol Title:	A 12-week, Multicenter, Active-treatment Extension Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type
Clinical Phase/Trial Type:	3/Safety extension
Treatment Indication:	Agitation associated with dementia of the Alzheimer's type (AAD)
Objectives:	Primary: To assess the long-term safety and tolerability of oral brexpiprazole as treatment in adult subjects with AAD.
Trial Design:	This is a multicenter, active-treatment extension trial designed to assess the long-term safety and tolerability of oral brexpiprazole (2 and 3 mg/day) as treatment in adults with AAD. Enrollment into the trial will consist of eligible subjects who completed the 12-week treatment in the double blind, phase 3 efficacy Trial 331-14-213. In addition, subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. The trial will be organized as follows: Screening/baseline: Subjects who completed Week 12 of the double-blind trial and had no substantial protocol deviations will be screened for eligibility at the last visit of the double-blind trial (ie, Week 12 or ET, if the trial is terminated, visit of Trial 331-14-213). Subjects will sign a separate informed consent form (ICF) for participation in Trial 331-201-00182 before any procedures specific to the extension trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-201-00182 for any assessment that is not unique to the extension trial. Medical history will be updated, if necessary.

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Trial Design (continued):	Active Extension Treatment: Eligible subjects from Trial 331-14-213 will receive 12 weeks of daily treatment with brexpiprazole (target doses of 2 or 3 mg/day) in Trial 331-201-00182. Visits will occur at the end of Weeks 1, 2, 6, and 12. Follow-up: All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of investigational medicinal product (IMP) during a clinic visit at either the investigator's site or residential facility, as applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver. For all subjects who terminate early from the trial, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 (relative to baseline visit).
Subject Population:	The trial population for Trial 331-201-00182 will include rollover subjects who have completed 12 weeks of post-randomization treatment in the double-blind, phase 3 efficacy Trial 331-14-213, and 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. In addition, subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.

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Inclusion/Exclusion Criteria:	Key inclusion criteria are described under Subject Population in this synopsis. Subjects must meet the inclusion criteria at the screening/baseline visit, which is also the last visit in Trial 331-14-213. Key exclusion criteria include the following: • Subjects who, in the opinion of the investigator, medical monitor, or sponsor, should not participate in the trial. • Subjects with a substantial protocol violation during the course of their participation in the double-blind Trial 331-14-213. Lesser violations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-201-00182; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the prior double-blind trial would be considered a substantial violation that would result in exclusion from Trial 331-201-00182. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
Trial Sites:	All trial centers will have participated as sites in Trial 331-14-213.

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Investigational Medicinal Product, Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The IMP will be supplied as brexpiprazole tablets. Each dose will be supplied in 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. All subjects will receive brexpiprazole at target doses of either 2 or 3 mg/day. To preserve the blind in Trial 331-14-213, all doses in Trial 331-201-00182 will remain blinded. Subjects randomized to the 2 mg/day and 3 mg/day doses of brexpiprazole in Trial 331-14-213 will begin treatment on these same doses in the active-treatment extension Trial 331-201-00182. All subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. For subjects who may be offered entry into this trial as a result of early termination of Trial 331-14-213 due to overwhelming efficacy from the interim analysis, treatment in Trial 331-201-00182 will begin based on randomization and last visit completed in Trial 331-14-213. Subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. Subjects randomized to brexpiprazole and who completed the titration schedule in Trial 331-14-213 (ie, completed Week 4 visit in 331-14-213) will begin treatment on the same dose in this trial. Subjects randomized to brexpiprazole and who have not completed the titration schedule will restart drug in Trial 331-201-00182 dependent on the point in the titration scheme for Trial 331-14-213 that early termination occurred. All doses of brexpiprazole will be taken orally once daily, preferably in the morning, and will be administered without regard to meals. Brexpiprazole should be taken at approximately the same time each day.
Trial Assessments:	Safety: Adverse event (AE) reporting, clinical laboratory tests, electrocardiograms (ECGs), vital signs, physical and neurological examinations, body weight, body mass index, Mini-Mental State Examination (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 Suicidality Tracking Scale (Sheehan-STS).

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Criteria for Evaluation:	**Primary outcome variable:** The primary outcome variable is the frequency and severity of AEs (safety and tolerability of brexpiprazole).
Statistical Methods:	The primary safety analysis is the frequency and severity of AEs. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized descriptively: • Treatment-emergent AEs (TEAEs) • TEAEs by severity • Potentially drug-related TEAEs (per investigator) • TEAEs with an outcome of death • Serious TEAEs • TEAEs leading to discontinuation of the IMP Safety and tolerability will be also evaluated by clinically significant changes in: physical examinations, neurological examinations, vital sign measurements, body weight, clinical laboratory tests, and electrocardiograms. Other safety variables will include the Mini Mental State Examination (MMSE) score and assessments of suicidality and extrapyramidal symptoms. Descriptive statistics will be provided for each endpoint, and will be summarized at each trial visit using the observed cases (OC) dataset. Baseline is defined as the last available measurement prior to the first dose of IMP in the active-treatment extension trial.

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Trial Duration:	Individual participation for subjects who complete the trial will consist of a 12-week treatment period and a 30-day follow-up period. All subjects 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 (relative to baseline visit).

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT	Serotonin
5-HT_{1A}	Serotonin type 1A receptor
5-HT_{2A}	Serotonin type 2A receptor
AAD	Agitation in Alzheimer's dementia
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
bpm	Beats per minute
CGI-S	Clinical Global Impression Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRF	Case report form
CYP	Cytochrome P450
D	Dopamine
D_2	Dopamine type 2
ECG	Electrocardiogram
eICF	Electronic informed consent form
EPS	Extrapyramidal symptoms
ET	Early termination
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
HbA_{1c}	Glycosylated hemoglobin
IB	Investigator's Brochure
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
IPA	International Psychogeriatric Association
IRB	Institutional review board
IRE	Immediately reportable event
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities

MMSE	Mini-Mental State Examination
MTD	Maximum tolerated dose
OC	Observed-case
OPC	Otsuka Pharmaceutical Company, Ltd.
PK	Pharmacokinetic
PTSD	Post-traumatic stress disorder
PQC	Product Quality Complaint
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcN	QT interval corrected for heart rate by the FDA Neuropharm Division formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson Angus Scale
Sheehan-STS	Sheehan Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal range
US	United States
WOCBP	Women of childbearing potential

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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 the 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. 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. 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

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 significantly 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 statistically significant 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 who received the 2 mg/day dose could be evaluated. Additionally, post-hoc analyses of subjects who had their dose titrated to 2 mg/day brexpiprazole (or equivalent placebo) in the flexible dose trial (Trial 331-12-284) supported the efficacy of brexpiprazole 2 mg/day.

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).

Trial 331-14-213 was designed to confirm the , safety, and tolerability of brexpiprazole 2 mg/day compared with placebo, as well as to provide information about the , safety, and tolerability of brexpiprazole at 3 mg/day. In a subsequent meeting with the FDA to discuss the proposed design for Trial 331-14-213, the FDA also recommended conducting an extension trial to investigate the long-term safety of brexpiprazole in subjects with AAD.

The proposed, 12-week, multicenter, active-treatment extension trial will be conducted to evaluate the long-term safety and tolerability of brexpiprazole for the treatment of subjects with AAD. This would result in 24 weeks (6 months) of continuous exposure for subjects who had received brexpiprazole in the double-blind, placebo-controlled Trial 331-14-213.

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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 , safety, and tolerability of a higher dose of brexpiprazole, as recommended by the FDA.

2.3 Trial Objectives

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

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, active-treatment extension trial designed to assess the long-term safety and tolerability of oral brexpiprazole (2 and 3 mg/day) as treatment in adults with AAD. Enrollment into the trial will consist of eligible subjects who completed the 12-week treatment in the double-blind, phase 3 efficacy Trial 331-14-213. In addition, subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.

The trial will be organized as follows:

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

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

Follow-up: All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, as applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver. For all subjects who terminate early from the trial, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 (relative to baseline visit).

See Figure 3.1-1 for a schematic of the trial design. See Table 3.6-1 for the Schedule of Assessments.

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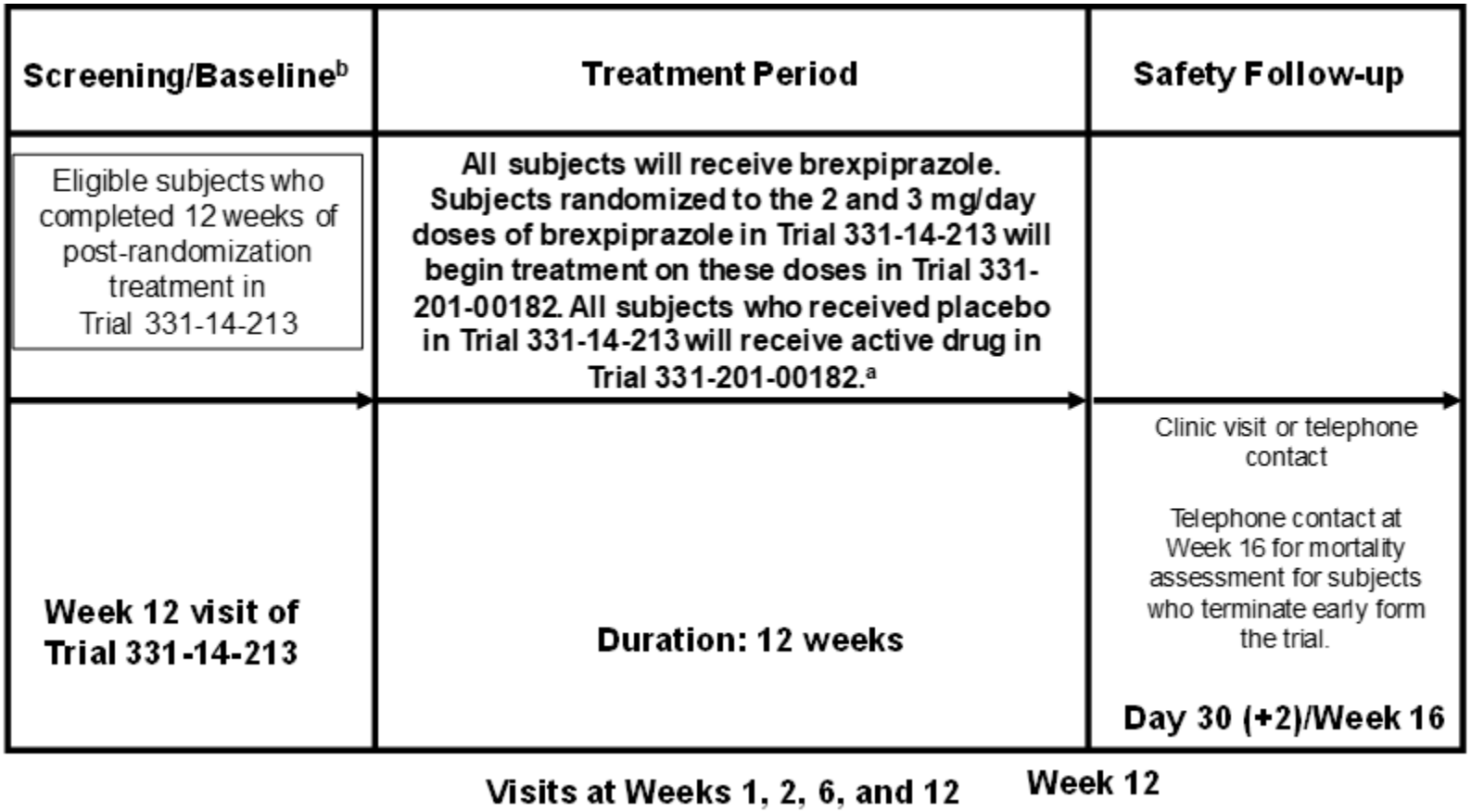

[a]Starting at week 4, 1 dose decrease can occur at any time (scheduled or unscheduled visits) until the end of the trial. In addition, one dose increase can occur but only at the Week 6 scheduled visit. For subjects who may be offered entry into this trial as a result of early termination due to overwhelming efficacy from the 331-14-213 interim analysis, treatment in Trial 331-201-00182 will begin based on randomization and last visit completed in Trial 331-14-213. Subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. Subjects randomized to brexpiprazole and who completed the titration schedule in Trial 331-14-213 (ie, completed Week 4 visit in 331-14-213) will begin treatment on the same dose in this trial. Subjects

randomized to brexpiprazole and who have not completed the titration schedule will restart drug in Trial 331-201-00182 dependent on the point in the titration scheme for Trial 331-14-213 that early termination occurred.

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

Figure 3.1-1 Trial Design Schematic

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3.2 Trial Treatments

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

To preserve the blind in Trial 331-14-213, all doses in Trial 331-201-00182 will remain blinded. The first dose taken in Trial 331-201-00182 should be taken one day after the Week 12 or ET, if the trial is terminated due to overwhelming efficacy from the interim analysis, visit of Trial 331-14-213 so that treatment continues without interruption.

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

For subjects who may be offered entry into this trial as a result of early termination of Trial 331-14-213 due to overwhelming efficacy from the interim analysis, treatment in Trial 331-201-00182 will begin based on randomization and last visit completed in Trial 331-14-213. Subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. Subjects randomized to brexpiprazole and who completed the titration schedule in Trial 331-14-213 (ie, completed Week 4 visit in 331-14-213) will begin treatment on the same dose in this trial. Subjects randomized to brexpiprazole and who have not completed the titration schedule will restart drug in Trial 331-201-00182 dependent on the point in the titration scheme for Trial 331-14-213 that early termination occurred.

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

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

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

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

3.3 Trial Population

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 and other applicable trial assessments. The caregiver identified during the screening period for Trial-331-14-213 can continue to function as the caregiver for the extension 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 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 is administered unless other arrangements are made and approved by the sponsor. Starting at screening/baseline, 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 and other applicable trial assessments. The caregiver identified during the screening period for Trial-331-14-213 can continue to function as the caregiver for the extension 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 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 Description of Population

The trial population for Trial 331-201-00182 will include rollover subjects who have completed 12 weeks of post-randomization treatment in the double-blind, phase 3 efficacy Trial 331-14-213, and 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.

In addition, subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.

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[14] 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.

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 prior to enrollment. 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 the protocol.
2.	Subjects who completed 12 weeks of post-randomization treatment in Trial 331-14-213. In addition, subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.
3.	Institutionalized subjects with 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. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. Non-institutionalized subjects may not be living alone 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.
4.	Subjects who are able to satisfactorily comply with the protocol requirements.

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	
1.	Subjects who, in the opinion of the investigator, medical monitor, or sponsor, should not participate in the trial.
2.	Subjects with a substantial protocol violation during the course of their participation in the double-blind Trial 331-14-213. Lesser violations such as occasional visits outside of the acceptable window or a missing blood draw will not exclude a subject from participation in Trial 331-201-00182; however, continual lack of compliance with the visit schedule, trial assessments, or treatment regimen in the prior double-blind trial would be considered a substantial violation that would result in exclusion from Trial 331-201-00182. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.

3.5 Outcome Variables

3.5.1 Primary Outcome Variable

The primary outcome variable is the frequency and severity of adverse events (AEs; safety and tolerability of brexpiprazole).

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3.5.3 Safety Outcomes

In addition to AEs, safety variables to be examined in this trial will include physical/neurological examinations, vital sign measurements, body weight, waist circumference, clinical laboratory tests (hematology, serum chemistry [including prolactin], urinalysis, and pregnancy tests), electrocardiograms (ECGs), the Simpson Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Sheehan Suicidality Tracking Scale (Sheehan-STS).

Mean change from baseline and the incidence of potentially clinically relevant abnormal values will be calculated for vital sign measurements, 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 body mass index (BMI; derived programmatically from body weight and height measurements [height values will be obtained in Trial 331-14-213]). A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. 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-patient listings of physical examination findings will be reviewed as a further assessment of safety.

3.6 Trial Procedures

The time from enrollment of the first subject to the last subject's last trial visit will be approximately 3 years, of which approximately 2.5 years are allotted for rollover of subjects from Trial 331-14-213. Individual participation for subjects who complete the trial will consist of a 12-week treatment period and a 30-day follow-up period. All subjects 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 (relative to baseline visit).

Trial assessment time points are summarized in Table 3.6-1.

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Table 3.6-1 Schedule of Assessments

Assessment	Visit						
	Screening/Baseline[a]	Week 1 (±2 days)	Week 2 (±2 days)	Week 6 (±2 days)	Week 12 or ET (±2 days)	Follow-up[b] (+2 days)	Week 16[c]
ENTRANCE and HISTORY							
Informed consent	X						
Inclusion and exclusion criteria	X						
SAFETY							
Physical examination	X				X		
Neurological examination	X				X		
Vital signs	X	X	X	X	X		
Body weight	X				X		
Clinical laboratory tests (hematology, serum chemistry, urinalysis)	X				X		
Prolactin	X				X		
HbA_{1c}	X				X		
Urine pregnancy test (women of childbearing potential only)	X				X		
ECG	X				X		
MMSE	X				X		
Sheehan-STS	X				X		
Extrapyramidal symptoms scales (SAS, AIMS, BARS)	X			X	X		
Adverse events	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	
Mortality assessment							X[c]
OTHER PROCEDURES							
IMP dispensing	X	X	X	X			
IMP accountability	X	X	X	X	X		

ET = early termination; MMSE = Mini-Mental State Examination.

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[a]Screening for Trial 331-201-00182 occurs simultaneously with baseline, which will be the same day as the Week 12, or ET visit if the trial is terminated due to overwhelming efficacy from the interim analysis, of Trial 331-14-213.

[b]All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver.

[c]For all subjects who terminate early from the trial, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 (relative to baseline visit).

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3.6.1 Schedule of Assessments

3.6.1.1 Screening/Baseline

Screening for rollover subjects occurs simultaneously with baseline at the Week 12 or ET, if the trial is terminated, visit of Trial 331-14-213 (see Table 3.6-1). Rollover subjects entering Trial 331-201-00182 must sign the ICF for the active-treatment trial before any procedures specific to Trial 331-201-00182 can be performed. Subjects will retain the same subject identification (ID) number assigned in the double-blind, phase 3 Trial 331-14-213. Screening/baseline values will be derived from the Week 12 or ET visit of Trial 331-14-213 for the following assessments: CMAI, CGI-S, SAS, AIMS, BARS, Sheehan-STS, physical/neurological examination, waist circumference, vital signs, ECG, and clinical laboratory tests. The only additional procedures to be performed for rollover subjects at screening/baseline of the active-treatment trial are as follows:

- Inclusion/exclusion criteria for Trial 331-201-00182 will be reviewed to ensure the subject's eligibility.
- Medical history will be updated, if necessary.
- Concomitant medications will be reviewed to ensure that the subject is not receiving any prohibited medications.
- Brexpiprazole will be dispensed to the subject.
- AE recording will begin with the signing of the ICF for Trial 331-201-00182.
- The subject will take the first dose of the IMP 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.

3.6.1.2 Weeks 1, 2, and 6

All subjects will be evaluated at Weeks 1 and 2. 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 3.6-1). 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.
- 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.

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3.6.1.3 End of Treatment (Week 12 or ET)

All required evaluations will be performed as described in the Schedule of Assessments (Table 3.6-1). The Week 12 visit signifies the end of treatment with IMP for all subjects. Therefore, all subjects will undergo a complete evaluation at Week 12 (± 2 days). In addition, Week 12 or early termination (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:

- Final IMP accountability will be performed.

3.6.1.4 Follow-up

All required assessments will be performed as described in the Schedule of Assessments (Table 3.6-1). All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, as applicable. If a clinic visit is not possible, the subject should be assessed by telephone 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.

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3.6.2.1 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.[15] As initially described by Cohen-Mansfield[15] and outlined in the Instruction Manual for the CMAI[16] 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.

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

The severity of agitation for each subject will be rated using the CGI-S.[17] 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.

3.6.3 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from the time of signing of informed consent for Trial 331-201-00182 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.

3.6.4 Safety Assessments

3.6.4.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.6.4.2 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. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. Vital sign measurements and ECG assessments should be completed before any blood samples are collected. 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 3.6.4.2-1.

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Table 3.6.4.2-1 Clinical Laboratory Assessments	
Hematology White blood cell count with differential Red blood cell count Hematocrit Hemoglobin Platelet count Urinalysis pH Specific gravity Protein Ketones Glucose Blood Microscopic exam (performed only if any part of the urinalysis is not negative)	Serum Chemistry Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Blood urea nitrogen Creatine phosphokinase Creatinine Total bilirubin Triglycerides Cholesterol (total, low-density and high-density lipoproteins) Calcium Chloride Glucose Insulin Sodium Potassium Total protein Uric acid Gamma glutamyltransferase Prolactin Albumin Additional Tests Urine pregnancy (women of childbearing potential)[a] HbA_{1c}

[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.

Pregnancy tests can be performed at any point during the trial if pregnancy is suspected. An additional pregnancy test will be conducted in women of childbearing potential (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.

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3.6.4.3 Physical and Neurological Examination and Vital Signs

3.6.4.3.1 Physical Examinations

A complete physical examination will be performed at baseline and will consist of measurement of waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat; thorax; abdomen; urogenital; extremities; neurological (see Section 3.6.4.3.2); and skin and mucosa. Waist circumference will be measured at each physical examination (baseline and Week 12/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.[18]

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.

3.6.4.3.2 Neurological Examinations

A detailed neurological examination will be performed by a physician at baseline and Week 12/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.

3.6.4.3.3 Vital Signs

Vital sign measurements will include body weight, body temperature, systolic blood pressure, diastolic blood pressure, 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.

3.6.4.4 Electrocardiogram Assessments

Standard 12-lead ECGs will be recorded at the visits specified in Table 3.6-1. 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.

Please consult the medical monitor in case of questions.

3.6.4.5 Other Safety Assessments

3.6.4.5.1 Simpson Angus Scale

The SAS[19] 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.

3.6.4.5.2 Abnormal Involuntary Movement Scale

The AIMS[17] 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).

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3.6.4.5.3 Barnes Akathisia Rating Scale

The BARS[20] 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.

3.6.4.5.4 Sheehan Suicidality Tracking Scale

Suicidality will be monitored during the trial using the Sheehan-STS.[21] 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 “Screening” Sheehan-STS form was completed at the screening visit of the double-blind Trial 331-14-213 to determine eligibility. The “Since Last Visit” Sheehan-STS form will be completed baseline and Week 12/ET during Trial 331-201-00182. 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.

3.6.4.5.5 Mini-Mental State Examination

The Mini-Mental State Examination (MMSE)[22] 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 completed at baseline and Week 12 or ET.

3.6.5 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 Stopping Rules, Withdrawal Criteria, and Procedures

3.7.1 Entire Trial

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

3.7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/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/IEC at the site.

3.7.3 Individual Subject Discontinuation

3.7.3.1 Treatment Discontinuation

After entry into Trial 331-201-00182, 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 3.7.3.4. Refer to the Schedule of Assessments (Table 3.6-1) for a description of follow-up procedures.

3.7.3.2 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.

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 3.11, 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
- 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

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.

3.7.3.3 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 3.7.3.1). 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 3.7.3.2 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.

3.7.3.4 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.

3.8 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. For the purposes of this trial, treatment begins with the first dose of brexpiprazole in Trial 331-201-00182. Rollover subjects who do not qualify for Trial 331-201-00182 at the last visit of Trial 331-14-213 may not be rescreened.

3.9 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/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 the Week 12 visit will be defined as trial completers.

3.10 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the 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.

3.11 Subject Compliance

Responsible trial personnel will dispense the IMP (ie, brexpiprazole) according to the visits outlined in the Schedule of Assessments (Table 3.6-1). 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.

3.12 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

Concomitant medications taken by subjects who are rolling over into Trial-331-201-00182 from Trial 331-14-213 should be reviewed for the prohibited medications listed in Table 4.1-1. Any subject taking a prohibited concomitant medication should not be enrolled in Trial 331-201-00182.

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Table 4.1-1 List of Restricted and Prohibited Medications		
All other psychotropic agents not listed in the below table are prohibited		
Medication		**During the Active Drug Treatment Period**
1.	Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, or other cognitive enhancers)	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	Prohibited
	Clozapine	Prohibited
3.	Antidepressants	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)	Prohibited
5.	Anticonvulsants	Prohibited
6.	Benzodiazepines	Prohibited
7.	Non-benzodiazepine sleep agents[a]	If a bedtime dose of a sleep agent for insomnia was taken on a regular basis during Trial 331-14-213, a stable dose of the sleep agent may be continued as needed during the trial. If a sleep agent was not previously taken 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.
9.	Anticholinergics for treatment of extrapyramidal symptoms	Prohibited
10.	Propranolol[b]	For treatment of akathisia or tremor: maximum dose of 20 mg, 3 times daily (total of 60 mg/day). For treatment of heart disease: may remain on stable pretrial doses as needed throughout the trial, as long as the total dose does not exceed 60 mg/day. Propranolol must not be administered within 12 hours prior to the efficacy and safety scales.
11.	Varenicline	Prohibited

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Table 4.1-1 List of Restricted and Prohibited Medications

All other psychotropic agents not listed in the below table are prohibited

	Medication	During the Active Drug Treatment Period
12.	Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and anti-platelet agents	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)	Prohibited
14.	CYP2D6 inhibitors or CYP3A4 inhibitors and inducers (see Table 4.1-2)	Prohibited

CNS = central nervous system; CYP = cytochrome P450; GABA = gamma-aminobutyric acid.

[a]For the non-benzodiazepine sleep aids, site personnel 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.

[b]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

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

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.

A serious AE (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 aspartate transaminase or alanine transaminase that is ≥ 3 times the upper limit of normal range (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 (WOCBP) 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 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 Follow-up of Adverse Events

5.6.1 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).

5.6.2 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.

5.6.3 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.

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5.6.4 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 Analysis

No pharmacokinetic analysis is planned.

7 Statistical Analysis

7.1 Sample Size

The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects who rollover from the double-blind phase 3 Trial 331-14-213.

7.2 Datasets for Analysis

The following datasets are defined for this trial:

Safety Sample: comprised of those subjects who sign an ICF for the trial and receive at least one dose of brexpiprazole in Trial 331-201-00182.

Efficacy Sample: comprises those subjects in the Safety Sample who have at least one postbaseline efficacy evaluation.

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

7.3 Handling of Missing Data

Since this trial is planned as an extension trial with safety as the primary objective and no reference arm is planned, there is no pre-specified primary efficacy estimand. All efficacy evaluations are exploratory and no formal sensitivity analysis is planned.

All efficacy summaries will be presented based on the OC dataset, which is defined in Section 7.2.

7.4 Primary and Secondary Outcome Analyses

7.4.1 Primary Outcome Analysis

The primary safety analysis is the frequency and severity of AEs (see Section 7.6.1).

Descriptive statistics will be provided for each endpoint, and will be summarized at each trial visit using the OC dataset. Baseline is defined as the last available measurement prior to the first dose of IMP in the active-treatment extension trial.

7.5 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height (from Trial 331-14-213), and BMI will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable). These summaries will be presented for the Safety Sample.

7.6 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and BMI. In addition, data from the following safety scales will be evaluated: SAS, AIMS, BARS, and Sheehan-STS. Safety analysis will be conducted based on the safety dataset. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of brexpiprazole during Trial 331-201-00182, unless specified otherwise. Details of safety analysis will be provided in the statistical analysis plan (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 descriptively:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP (per investigator)

- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

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

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, prolactin concentrations, and HbA_{1c} will be provided. In addition, potentially clinically significant results in laboratory tests identified using prospectively defined criteria will be summarized.

7.6.3 Physical/Neurological Examination and Vital Sign Measurements Data

By-patient listings will be provided for physical and neurological examinations. Summary statistics for changes from baseline in vital sign measurements will be provided. Potentially clinically significant results in vital sign measurements will also be summarized.

7.6.4 Electrocardiogram Data

Mean change from baseline will be summarized by visit. Incidence of clinically relevant changes will be calculated for ECG parameters and summarized 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: $QTcB = QT/(RR)^{0.5}$
- 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.

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7.6.5 Other Safety Data

Change from baseline in scores for the MMSE score will be summarized descriptively. The analyses will be based on the OC dataset of the Safety Sample.

The suicidality (eg, Sheehan-STS) will be summarized 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 Brexpiprazole 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. 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 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.

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8.3 Accountability

The investigator or designee must maintain an inventory record of IMP 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
- Phone:

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 4 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 26 Jun 2020

PURPOSE:

The purpose of this protocol amendment is to introduce a COVID-19 Addendum for any protocol-specified activities that are 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. Wording was added to state that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. Additional minor edits were made to the protocol.

BACKGROUND:

These changes to clinical trial protocol 331-201-00182, originally issued on 18 Jun 2018, were made to introduce a COVID-19 Addendum, specify that measurements for height will be taken from Trial 331-14-213, and to specify that subjects who are early terminated from Trial 331-14-213 due to trial termination may be enrolled into this trial.

MODIFICATIONS TO PROTOCOL:

Description of Change	Rationale for Change	Sections Affected by Change
Added that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. Week 12 visit of Trial 331-14-213 was changed to Week 12 or ET, if the trial is terminated, visit of Trial 331-14-213.	Trial 331-14-213 may be ended early if overwhelming efficacy is shown in the interim analysis.	Protocol Synopsis Section 3.1 Type/Design of Trial Figure 3.1-1 Trial Design Schematic Section 3.2 Trial Treatments Section 3.3.2 Description of Population Table 3.4.2-1 Inclusion Criteria Table 3.6-1 Schedule of Assessments (footnotes) Section 3.6.1 Schedule of Assessments
Randomization for subjects from Trial 331-14-213 was specified.	To provide additional details regarding rollover subjects.	Protocol Synopsis Section 3.2 Trial Treatments
Specified that measurements for height will be taken from Trial 331-14-213.	To specify where height data will be obtained.	Section 3.5.3 Safety Outcomes Section 7.5 Analysis of Demographic and Baseline Characteristics

Protocol 331-201-00182

Description of Change	Rationale for Change	Sections Affected by Change
Minor formatting changes.	Correction of typographical errors and formatting.	Throughout document.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

Protocol 331-201-00182

Amendment Number: 2

Issue Date: 06 Aug 2020

PURPOSE:

The purpose of this protocol amendment is to remove wording that was added with amendment 1 to state that subjects who are early terminated from Trial 331-14-213, if the trial is terminated following the interim analysis, may be offered entry into this trial.

BACKGROUND:

The changes to clinical trial protocol 331-201-00182, originally issued on 18 Jun 2018, and amended 26 Jun 2020, were made to remove language stating that subjects who are early terminated from Trial 331-14-213 (the parent trial) due to trial termination may be enrolled into this trial. Due to feedback from the FDA on protocol 331-14-213, the parent trial is expected to conclude with a total enrollment of roughly 255 or roughly 330 subjects. The decision to stop at 255 or 330 subjects will be determined by the results of an interim analysis. The changes from amendment 1 of protocol 331-201-00182 did not go into effect and the amendment was not distributed to sites or IRBs. Since amendment 1 was finalized, signed, and distributed externally to vendors, the protocol is being formally amended.

Additionally, an addendum describing COVID-19-related trial procedures was included in amendment 1.

MODIFICATIONS TO PROTOCOL:

Description of Change	Rationale for Change	Sections Affected by Change
Deleted language stating that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.	Language no longer needed due to FDA feedback on the parent protocol, 331-14-213.	Protocol Synopsis Section 3.1 Type/Design of Trial Figure 3.1-1 Trial Design Schematic Section 3.2 Trial Treatments Section 3.3.2 Description of Population Table 3.4.2-1 Inclusion Criteria Table 3.6-1 Schedule of Assessments (footnotes) Section 3.6.1.1 Screening/Baseline
Deleted details regarding treatment assignment for subjects from Trial 331-14-213.	Language no longer needed.	Protocol Synopsis Figure 3.1-1 Trial Design Schematic Section 3.2 Trial Treatments

Protocol 331-201-00182

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

Protocol 331-201-00182

Amendment Number: 3

Issue Date: 22 Sep 2020

PURPOSE:

The purpose of this protocol amendment is to state that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. Additional minor edits were made to the protocol.

BACKGROUND:

These changes to clinical trial protocol 331-201-00182, originally issued on 18 Jun 2018, and amended 26 Jun 2020 and 06 Aug 2020, were made to specify that subjects who are early terminated from Trial 331-14-213 because of trial termination due to overwhelming efficacy from the interim analysis may be enrolled into this trial.

MODIFICATIONS TO PROTOCOL:

Description of Change	Rationale for Change	Sections Affected by Change
Added that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. Week 12 visit of Trial 331-14-213 was changed to Week 12 or ET, if the trial is terminated, visit of Trial 331-14-213.	Trial 331-14-213 may be ended early based on the results from the interim analysis.	Protocol Synopsis Section 3.1 Type/Design of Trial Figure 3.1-1 Trial Design Schematic Section 3.2 Trial Treatments Section 3.3.2 Description of Population Table 3.4.2-1 Inclusion Criteria Table 3.6-1 Schedule of Assessments (footnote a) Section 3.6.1.1 Screening/Baseline
Enrollment for subjects from Trial 331-14-213 was specified.	To provide additional details regarding rollover subjects.	Protocol Synopsis Figure 3.1-1 Trial Design Schematic. Section 3.2 Trial Treatments
Minor formatting changes.	Correction of typographical errors and formatting.	Throughout document.

Protocol 331-201-00182

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

The COVID-19 addendum to this protocol was also updated accordingly.

Protocol 331-201-00182

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, brexpiprazole, 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 brexpiprazole 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

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Protocol 331-201-00182 Amendment 3

Document Number:

Document Version: 5.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
	Clinical Approval	22-Sep-2020 13:49:15
	Biostatistics Approval	22-Sep-2020 13:36:10

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

OPC-34712

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 331-201-00182

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

IND No. 115960
EudraCT No. 2018-002783-88

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850
Immediately Reportable Event	Syneos Health Pharmacovigilance & Drug Safety
Issue Date:	26 Jun 2020
Amendment 1:	06 Aug 2020
Amendment 2:	22 Sep 2020
Version No.:	3.0

Protocol 331-201-00182

Trial Conduct for COVID-19

All procedures and assessments in Protocol 331-201-00182 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 coronavirus disease 2019 (COVID-19). If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, the appropriate measures to be followed are provided in this document.

Note: The changes from amendment 1 of protocol 331-201-00182 (including version 1 of this COVID-19 addendum) did not go into effect and the amendment and COVID-19 addendum were not distributed to sites or IRBs. Since amendment 1 and COVID-19 addendum version 1 were finalized, signed, and distributed externally to vendors, the documents were formally amended.

Protocol 331-201-00182

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List of In-text Tables

Protocol 331-201-00182

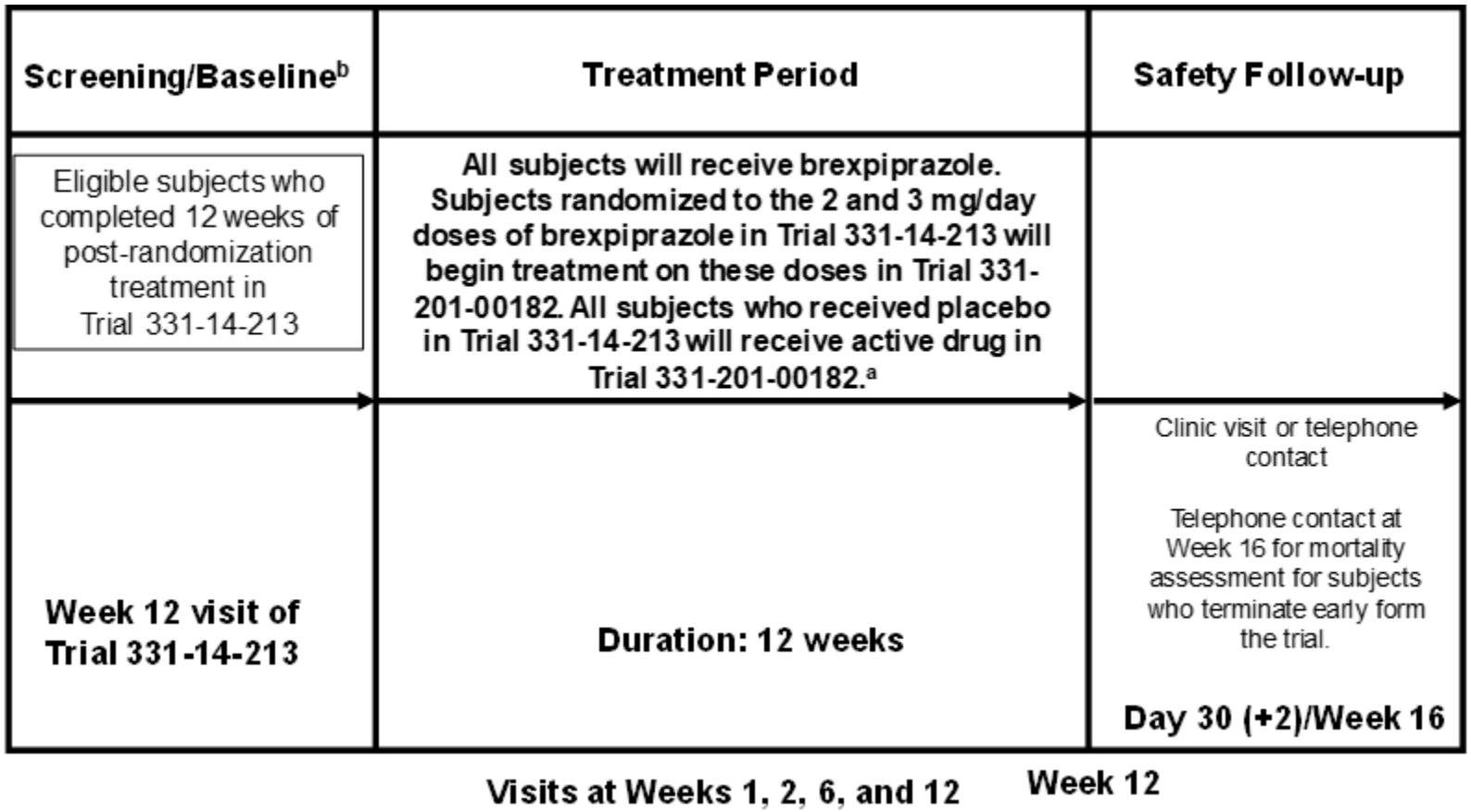
List of In-text Figures

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
CGI-S	Clinical Global Impression Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
COVID-19	Coronavirus disease 2019
CRO	Clinical research organization
EC	Ethics committee
ECG	Electrocardiogram
ET	Early termination
EudraCT	European Clinical Trial Data Base
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
MMSE	Mini-Mental State Examination
SAE	Serious adverse event
SAS	Simpson Angus Scale
Sheehan-STS	Sheehan Suicidality Tracking Scale
WOCBP	Women of childbearing potential

1 Trial 331-201-00182 COVID-19 Protocol Summary

1.1 Trial Design Schematic



[a]Starting at Week 4, one dose decrease can occur at any time (scheduled or unscheduled visits) until the end of the trial. In addition, one dose increase can occur but only at the Week 6 scheduled visit. For subjects who may be offered entry into this trial as a result of early termination due to overwhelming efficacy from the 331-14-213 interim analysis, treatment in Trial 331-201-00182 will begin based on randomization and last visit completed in Trial 331-14-213. Subjects who received placebo in Trial 331-14-213 will receive active drug in Trial 331-201-00182. Subjects randomized to brexpiprazole and who completed the titration schedule in Trial 331-14-213 (ie, completed Week 4 visit in 331-14-213) will begin treatment on the same dose in this trial. Subjects randomized to brexpiprazole and who have not completed the titration schedule will restart drug in Trial 331-201-00182 dependent on the point in the titration scheme for Trial 331-14-213 that early termination occurred.

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

Figure 1.1-1 COVID-19 Impact Trial Design Schematic

1.2 Schedule of Assessments

Table 1.2-1 COVID-19 Impact Schedule of Assessments

Assessment	Visit						
	Screening/Baseline[a]	Week 1[b] (±2 days)	Week 2[b] (±2 days)	Week 6[b] (±2 days)	Week 12 or ET[b,c] (±2 days)	Follow-up[d] (+2 days)	Week 16[e]
ENTRANCE and HISTORY							
Informed consent	X						
Inclusion and exclusion criteria	X						
SAFETY							
Physical examination	X				X[f]		
Neurological examination	X				X[f]		
Vital signs	X	X	X	X	X		
Body weight	X				X		
Clinical laboratory tests (hematology, serum chemistry, urinalysis)	X				X[f]		
Prolactin	X				X[f]		
HbA_{1c}	X				X[f]		
Urine pregnancy test (women of childbearing potential only)	X				X		
ECG	X				X[f]		
MMSE	X				X		
Sheehan-STS	X				X		
Extrapyramidal symptoms scales (SAS, AIMS, BARS)	X			X[g]	X[g]		
Adverse events	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	

Table 1.2-1 COVID-19 Impact Schedule of Assessments

Assessment	Visit						
	Screening/Baseline[a]	Week 1[b] (±2 days)	Week 2[b] (±2 days)	Week 6[b] (±2 days)	Week 12 or ET[b,c] (±2 days)	Follow-up[d] (+2 days)	Week 16[e]
Mortality assessment							X[e]
OTHER PROCEDURES							
IMP dispensing[h]	X	X	X	X			
IMP accountability	X	X	X	X	X		

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; ECG = electrocardiogram; ET = early termination; IMP = investigational medicinal product; MMSE = Mini-Mental State Examination; SAS = Simpson Angus Score; Sheehan-STS = Sheehan Suicidality Tracking Scale.

[a]Screening for Trial 331-201-00182 occurs simultaneously with baseline, which will be the same day as the Week 12 or ET visit if the trial is terminated due to overwhelming efficacy from the interim analysis, visit of Trial 331-14-213. The screening/baseline visit must occur in the clinic.

[b]The Week 1, 2, 6, and 12 visits may be completed virtually.

[c]Subjects must be early terminated if 1. the subject tests positive for COVID-19 or 2. is presumed positive with COVID-19 or 3. the caregiver tests positive for COVID-19 and another caregiver cannot be identified. Subjects who miss an assessment due to a visit performed virtually (eg, clinical laboratory tests, ECGs) may continue in the trial based on the investigator's clinical assessment and judgement.

[d]All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver.

[e]For all subjects who terminate early from the trial, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 (relative to baseline visit).

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

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

[h]For the Weeks 1, 2 and 6 visits, if the visit is performed virtually, alternative methods for dispensing IMP to the subject can be performed, if allowed by country guidances and regulations, eg, use of courier or curbside pickup.

Protocol 331-201-00182

2 General Considerations

2.1 Telemedicine

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

Note: If a trial-wide virtual visit mandate is declared due to COVID-19, virtual visit guidance is not applicable for hospitalized subjects where the investigator is also the subject's physician. Subjects who meet this description can continue in-person visits.

2.2 Reconsent

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

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

2.3 Protocol Deviations

Protocol deviations that occurred as a direct result of the COVID-19 pandemic and prior to a site's local regulatory agency and investigational review board/ethics commitee (IRB/EC) approval of this addendum, must be recorded in eSource. A "direct result" is defined as being due to actual COVID-19 illness, or as a result of quarantine, social distancing, or site closures. The flexibility in procedures due to COVID-19 conditions allowed per this addendum (eg, virtual visits, missed assessments due to virtual visit, alternative investigational medicinal product [IMP] dispensation to subject), will not be be considered protocol deviations following IRB/EC approval of this addendum. All other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

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

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

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

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

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

2.5 Statistical Analyses

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

2.6 Clinical Outcomes

To decrease variability, sites should attempt to standardize the method of administration for a scale for an individual subject and across all subjects in the trial. Assessments should be administered by the same qualified/trained rater who rated the subject previously; if this is not possible due to staff availability and/or technological limitations, discuss relevant information with previous raters to obtain clinical context (note that, per protocol, raters must be trained/qualified to conduct assessments in all cases). Raters

should conduct all assessments for that visit during the same remote session, where possible.

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

3 Trial Population

3.1 Inclusion Criteria

No changes are required to the inclusion criteria due to COVID-19. However, if there is a future restriction on face-to-face visits and virtual visits are mandated due to COVID-19, then hospitalized subjects who are currently enrolled in the parent Trial 331-14-213 where the investigator is also the subject's physician can rollover into the 331-201-00182 trial.

3.2 Exclusion Criteria

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

4 Trial Procedures

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

4.1 Safety Assessments

4.1.1 Vital Signs

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

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

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

4.1.2 Pregnancy

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

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

5 IMP

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

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