CLINICAL STUDY PROTOCOL

A multicenter, uncontrolled, open-label trial to evaluate the safety of extended treatment with brexpiprazole (OPC-34712) in patients with agitation associated with dementia of the Alzheimer's type

NCT Number: NCT03724942

Protocol No. 331-102-00184

Version Date: 03 Feb 2021 (Version 4.0)

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

CLINICAL PROTOCOL

(Translation of Japanese Original)

A multicenter, uncontrolled, open-label trial to evaluate the safety of extended treatment with brexpiprazole (OPC-34712) in patients with agitation associated with dementia of the Alzheimer's type

Protocol No. 331-102-00184

CONFIDENTIAL – PROPRIETARY INFORMATION

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Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	[redacted]
	e-mail address: [redacted]
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-102-00184
Protocol title:	A multicenter, uncontrolled, open-label trial to evaluate the safety of extended treatment with brexpiprazole (OPC-34712) in patients with agitation associated with dementia of the Alzheimer's type
Clinical phase/ type of trial:	Phase 3 Long-term study
Treatment indication:	Agitation associated with dementia of the Alzheimer's type
Objectives:	To evaluate the safety of brexpiprazole 1 or 2 mg administered for 14 weeks in patients with agitation associated with dementia of the Alzheimer's type who have completed the treatment period of a double-blind trial (Trial 331-102-00088), and to explore the efficacy of extended treatment with brexpiprazole.
Trial design:	Multicenter, uncontrolled, open-label
Subject population:	A total of 157 male and female patients with agitation associated with dementia of the Alzheimer's type who have completed the 10-week treatment period of Trial 331-102-00088 and whose condition can be observed by a caregiver in at least 4 days per week for 4 hours or more a day.
Inclusion/exclusion criteria:	The main inclusion criteria are as follows: • Patients who have completed the 10-week treatment period of Trial 331-102-00088, as well as all observations, tests, and assessments at Week 10. • Patients whose caregiver can properly collect the necessary information (the main caregiver must observe the patient's condition in at least 4 days per week for 4 hours or more a day). Patients receiving home care must live with a specific caregiver and must not live alone. • Patients who are either capable of walking on their own or are able to move about with the use of a walking aid (a walker or wheelchair) and whose vision and hearing are sufficient to enable the required tests and observations for the trial (the use of glasses, hearing aids, etc, is acceptable). The main exclusion criteria are as follows: • Patients who experienced any serious adverse events (SAEs) that were judged to be related to the investigational medicinal product (IMP) by the investigator or subinvestigator in Trial 331-102-00088.

	• Patients who experienced episodes of delirium during Trial 331-102-00088. • Patients who had clinically significant nervous, hepatic, renal, metabolic, immunological, hematological, cardiovascular, pulmonary, or digestive abnormalities during Trial 331-102-00088.
Trial sites:	Approximately 120 sites in Japan
Investigational medicinal products, dose, dosage regimen, treatment period, formulation, mode of administration:	Brexpiprazole will be administered orally as one tablet once a day for 14 weeks. IMP administration will be initiated at 0.5 mg, and the dose will be increased to 1 mg after evaluation at Week 1 (Day 8) and to 2 mg after evaluation at Week 2 (Day 15). However, if the investigator or subinvestigator judges that dose increase is difficult for safety reasons, the dose may be maintained at 1 mg. After Week 2 (Day 15), the dose may be reduced or increased to 1 or 2 mg if the investigator or subinvestigator decides that dose adjustment is necessary.
Trial assessments:	Safety: adverse events, laboratory tests, 12-lead electrocardiogram, vital signs, body weight, physical examination, pregnancy test, Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Sheehan Suicidality Tracking Scale (S-STS) Efficacy: Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory, Clinical Global Impression–Severity of Illness (CGI-S), CGI–Global Improvement (CGI-I) Other tests: Mini-Mental State Examination and Alzheimer's Disease Cooperative Study–Activities of Daily Living
Criteria for evaluation:	Safety endpoints: adverse events, laboratory tests, 12-lead electrocardiogram, vital signs, body weight, physical examination, pregnancy test, DIEPSS, AIMS, BARS, and S-STS Efficacy endpoints: CMAI total score, CGI-S, CGI-I, [redacted]
Statistical methods:	**Safety analysis:** The incidence of adverse events occurring after initiation of IMP administration (treatment-emergent adverse events [TEAEs]) will be determined. Descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 last observation carried forward [LOCF]) will be calculated.

	Efficacy Analysis: Descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated. **Rationale for setting the target sample size:** This trial aims to include 100 completers of brexpiprazole treatment from Trial 331-102-00088 as subjects who will continue to receive brexpiprazole for more than 10 weeks. Since patients are assigned to the 1 mg group, the 2 mg group, or the placebo group at a ratio of 3:4:4 in Trial 331-102-00088, the target sample size for this trial (331-102-00184) has been determined to be 157 subjects, taking into account the fact that some of them would have received placebo in the previous trial.
Trial duration:	November 2018 to February 2022 (planned) The duration of participation in the trial by each subject will be up to 20 weeks.

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Abbreviation	Definition
5-HT	5-Hydroxytryptamine
5-HT_{1A}	5-Hydroxytryptamine 1A
5-HT_{2A}	5-Hydroxytryptamine 2A
ADCS-ADL	Alzheimer's Disease Cooperative Study–Activities of Daily Living
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BPSD	Behavioral and Psychological Symptoms of Dementia
BUN	Blood urea nitrogen
CGI-I	Clinical Global Impression–Global Improvement
CGI-S	Clinical Global Impression–Severity of Illness
CMAI	Cohen-Mansfield Agitation Inventory
CPK	Creatine phosphokinase
CYP	Cytochrome P450
D_2	Dopamine D_2
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
IB	Investigator brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent data monitoring committee
INR	International normalized ratio
IPA	International Psychogeriatric Association
IRB	Institutional review board
IRE	Immediately reportable event
IUD	Intrauterine device
IWRS	Interactive web response system
LDH	Lactate (lactic acid) dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
NGSP	The National Glycohemoglobin Standardization Program
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
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PQC	Product quality complaint
PT	Prothrombin time
PV	Pharmacovigilance
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate by Bazett's formula
QTcF	QT corrected for heart rate by Fridericia's formula
QTcN	QT corrected for heart rate by FDA Neuropharmacological Division formula
S-STS	Sheehan Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limits of normal
γ-GTP	γ-Glutamyl transpeptidase

1 Introduction

1.1 Background

Due to a recent increase in the elderly population, the number of patients with dementia is increasing. According to the Ministry of Health, Labour and Welfare (MHLW), Japanese patients with dementia account for 10% (approximately 2.42 million people) of the population aged ≥ 65 years, and the number is estimated to increase to 3.25 million people by 2020.[1] A recent epidemiology study showed that dementia of the Alzheimer's type is the most common form of dementia.[1]

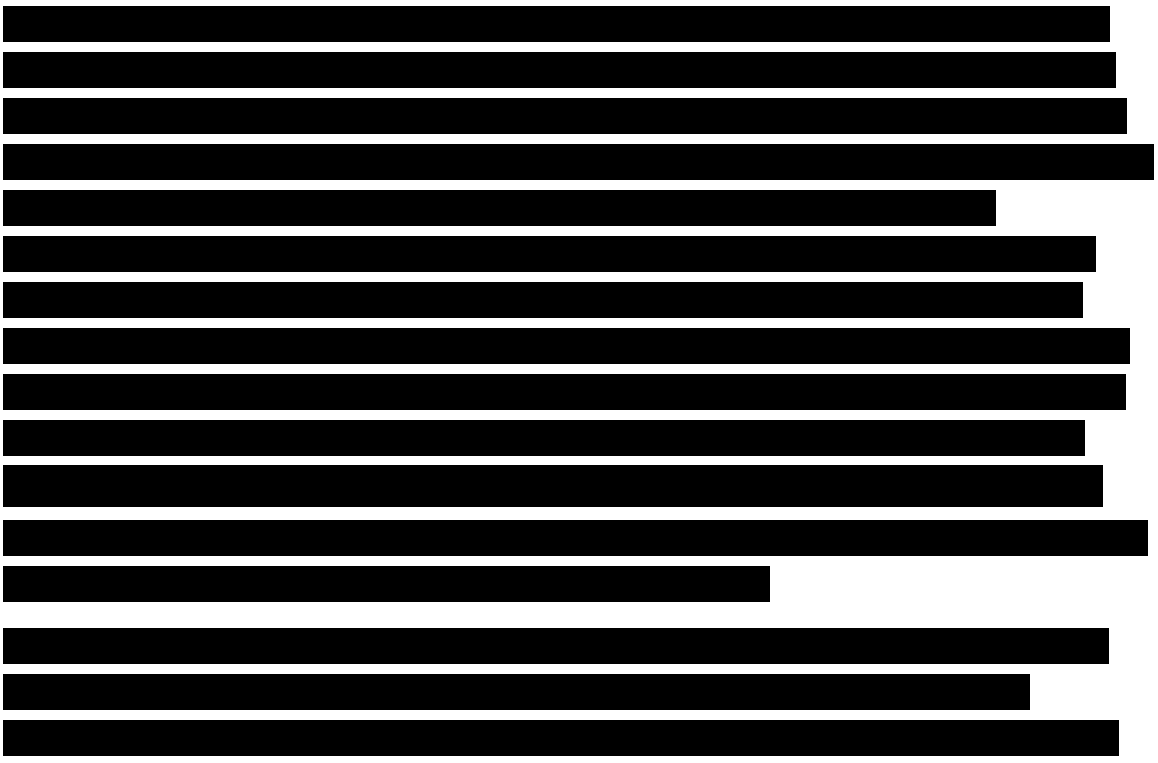
Symptoms of dementia of the Alzheimer's type are categorized into core symptoms such as memory impairment and impaired cognitive function and peripheral symptoms.[2] Peripheral symptoms are referred to as the behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms, and agitation is included in peripheral symptoms.[3,4] According to the definition given by the International Psychogeriatric Association (IPA) Working Group, agitation is a state in which the patient exhibits at least one of the symptoms of excessive motor activity, verbal aggression, and physical aggression, is not attributable solely to another psychiatric disorder or living environment, and causes impairment in the ability to perform or participate in daily living activities, other aspects of social functioning, or interpersonal relationships.[5] About 40% to 80% of patients with dementia of the Alzheimer's type present with agitation.[6,7]

Agitation has been reported to be related to cognitive decline,[8] decline in activities[9] and function[8] of daily living, progression to severe dementia of the Alzheimer's type,[10] and death.[10] Moreover, agitation has been reported to be related to the burden imposed on caregivers,[11,12] increases in care time and observation time,[13] early admission to a care facility,[8,14,15] and increased healthcare costs,[16] this being an issue for patients, caregivers, and medical resources.

The Practice Guideline for Dementia 2017 instructs as follows for agitation: "Person-centered-care is the basis. The reason(s) and cause(s) of symptoms should be considered and measures to resolve them should be sought. Another effective approach is for caregivers to learn appropriate skills for conversing with patients with dementia and to exercise these skills. As nonmedication therapies, the efficacy of group activities, music therapy, tactile care, and massage has been demonstrated, and use of these therapies should also be considered" and "if the patient does not respond adequately to nonmedication therapies, medication should be considered."[17] This clearly implies that if

agitation does not respond adequately to nonmedication therapies, medication needs to be considered. While the guideline states that "medication should be introduced only after sufficient efforts have been made to reduce BPSD with nonmedication therapies," it lists "aggression that endangers self or others" as one of the "exceptions to preferentially introduce medication."[18] According to the guideline, immediate consideration of medication cannot be avoided in some patients with aggressive agitation associated with dementia of the Alzheimer's type.

However, in Japan there are no drugs indicated for agitation and all drugs are administered as off-label use. Although it is off-label use, the Practice Guideline for Dementia 2017 states the following regarding medication: "The efficacy of atypical antipsychotics such as risperidone and aripiprazole has been demonstrated. Use of Yokukansan, tiapride, carbamazepine, sertraline, escitalopram and trazodone should also be considered."[17] The results of a meta-analysis of dementia patients in clinical trials of atypical antipsychotics, for which efficacy has been demonstrated according to the guideline, showed a mortality rate 1.54-fold higher in the atypical antipsychotic group compared with the rate in the placebo group,[19] showing a risk of death. These findings show that sufficient evidence is lacking for all medications indicated for agitation and the use of atypical antipsychotics needs to be considered despite the reported safety risk. Due to these circumstances, there are unmet needs for a drug-based approach to the treatment of agitation.



[redacted]

On the basis of these background factors, Otsuka considered that the development of brexpiprazole could make a significant contribution to the treatment of agitation associated with dementia of the Alzheimer's type and accordingly planned a double-blind trial (331-102-00088) in Japan ahead of this trial. Trial 331-102-00088 is intended to evaluate the superiority of brexpiprazole 1 or 2 mg over placebo after a 10-week treatment regimen for agitation associated with dementia of the Alzheimer's type in Japanese patients, to investigate the safety of brexpiprazole, and to identify the optimum dose. In real-world clinical settings, however, a certain proportion of patients with dementia of the Alzheimer's type are receiving antipsychotics for more than 10 weeks,[20] which is the treatment duration in Trial 331-102-00088. Given this fact, Otsuka considered it necessary to provide safety data on brexpiprazole when administered for more than 10 weeks and planned this clinical trial to evaluate the safety and efficacy of brexpiprazole when given for more than 10 weeks.

1.2 Nonclinical Data

[redacted]

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1.3 Clinical Data

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1.4 Known and Potential Risks and Benefits

[redacted]

[redacted]

2 Trial Rationale and Objectives

2.1 Trial Rationale

It is considered that neurotransmitters such as serotonin, dopamine and noradrenaline are involved in agitation. Brexpiprazole, which regulates the serotonin-dopaminergic system,

is expected to improve agitation in patients with dementia of the Alzheimer's type while suppressing expression of extrapyramidal symptoms.

In Trial 331-102-00088 in Japanese patients with agitation associated with dementia of the Alzheimer's type, which is scheduled to be conducted ahead of this trial, the superiority of brexpiprazole 1 or 2 mg over placebo after a 10-week treatment regimen will be evaluated, the safety of brexpiprazole will be investigated, and the optimum dose will be determined. Given that the Practice Guideline for Dementia 2017 states[17] that atypical antipsychotics "should not be continued without a compelling reason even if their efficacy is recognized, and appropriate dose reduction or temporary cessation in response to symptom improvement should be considered to reduce the incidence of adverse drug reactions," it is considered that brexpiprazole will not be used for long-term maintenance therapy after improvement of symptoms. Therefore, brexpiprazole does not fall under the group of drugs that need to be evaluated for long-term administration as specified in "Regarding the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (*Yakushin* Notification No. 592 dated 24 May 1995). In real-world clinical settings, however, a certain proportion of patients with dementia of the Alzheimer's type are receiving antipsychotics for more than 3 months.[20] When an additional indication of brexpiprazole is approved, the drug may possibly be administered to patients for longer than the treatment period of 10 weeks used in Trial 331-102-00088. Otsuka therefore decided to provide safety data on brexpiprazole when administered for longer than 10 weeks. This trial will enroll subjects rolled over from Trial 331-102-00088, and the safety of brexpiprazole when administered for a maximum of 24 weeks (including the treatment period of Trial 331-102-00088) will be evaluated. The trial will also explore the efficacy of brexpiprazole. The dose level of brexpiprazole in the trial will be up to 2 mg, the maximum dose used in Trial 331-102-00088, and may be reduced or increased to 1 or 2 mg, both of which are doses used in Trial 331-102-00088, depending on the subject's condition.

Furthermore, on the basis of the report[19] of the risk of death associated with atypical antipsychotics, criteria to exclude patients at high risk of cerebrovascular disorders, cardiac disorders, pneumonia, and other infections, which were the causes of death associated with atypical antipsychotics, are in place to minimize the risk to subjects during the trial. In addition, to ensure subject safety, the Independent Data Monitoring Committee (IDMC) established in Trial 331-102-00088 will monitor subject safety during this trial (331-102-00184) as well.

On the basis of what has been described above, the conduct of this trial was judged to be scientifically and ethically justifiable.

2.2 Trial Objectives

The objective of the trial is to evaluate the safety of brexpiprazole 1 or 2 mg administered for 14 weeks in patients with agitation associated with dementia of Alzheimer's type who have completed the treatment period of a double-blind trial (Trial 331-102-00088), and to explore the efficacy of extended treatment with brexpiprazole.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, uncontrolled, open-label trial to evaluate the efficacy and safety of brexpiprazole in patients with agitation associated with dementia of the Alzheimer's type who require medication. The overview of the trial design is shown in Figure 3.1-1.

The trial consists of a screening period, a treatment period, and a follow-up period. The investigator or subinvestigator will explain the details of the trial to prospective subjects (if the investigator or subinvestigator judges that the subject is incapable of providing informed consent, or if the subject is hospitalized for reasons related to medical protection, the subject's legally acceptable representative must provide written consent, and even when written consent is obtained from the legally acceptable representative, the subject should be given an explanation appropriate to his or her level of understanding and, if possible, should also provide written consent) and their main caregivers using the explanatory materials and informed consent form (ICF) and obtain written consent for participation in the trial from the prospective subjects (or their legally acceptable representatives) and caregivers during Trial 331-102-00088 between the dates of evaluation at Week 4 and Week 10. The investigator or subinvestigator will assess the eligibility of subjects to participate in the trial based on observations, tests, and investigations performed during the treatment period of Trial 331-102-00088. All subjects judged to be eligible based on the results of observations, tests, and investigations in Trial 331-102-00088 will skip the follow-up observation of Trial 331-102-00088 and be rolled over into the treatment period of this trial (331-102-00084). Subjects will receive brexpiprazole for 14 weeks, starting at 0.5 mg, followed by dose titration, and then at either 1 or 2 mg, according to Section 3.2 Trial Treatments, and will undergo periodic observation, tests, and investigations to assess efficacy and safety. IMP administration will begin no later than 10 days after the date of evaluation at Week 10 of Trial 331-102-00088. The subject will return to the trial site 28 days after the completion

of IMP administration for follow-up observation. Discontinued subjects will also undergo follow-up observation.

For subjects who discontinued the trial during the treatment period, the examination at discontinuation will be performed.

The trial period for each subject is from completion of evaluation at Week 10 of Trial 331-102-0008 to the end of follow-up observation.

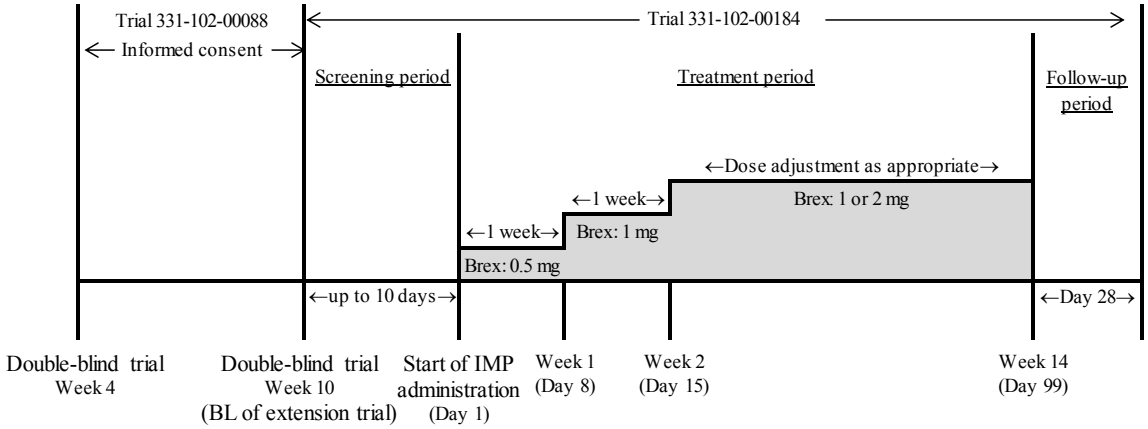

Figure 3.1-1 Trial Design

Double-blind trial = Trial 331-102-00088, Extension trial = Trial 331-102-00184, Brex = brexpiprazole, BL = baseline

3.2 Trial Treatments

3.2.1 Dosing, Regimen, and Duration of Treatment

Brexpiprazole will be administered orally as one tablet once a day for 14 weeks. Although the temporal relationship between IMP administration and meals will not be considered, subjects should take the IMP at the specified time in so far as possible. The IMP doses are shown in Table 3.2.1-1. IMP administration will be initiated at 0.5 mg and the dose will be increased to 1 mg after evaluation at Week 1 (Day 8) and to 2 mg after evaluation at Week 2 (Day 15). If the investigator or subinvestigator judges that dose increase to 2 mg is difficult for safety reasons based on the subject's condition after evaluation at Week 2 (Day 15), the dose may be maintained at 1 mg (see Section 3.2.1 1) Dose Maintenance at 1 mg). From Week 2 (Day 15), the dose may be reduced or increased to 1 or 2 mg if the investigator or subinvestigator decides that dose adjustment is necessary (see Section 3.2.1 2) Dose Change). In cases where dose reduction to lower than 1 mg is required, the trial should be discontinued.

Table 3.2.1-1 Doses of IMP		
Day 1–7	**Day 8–14**	**Day 15–98**
0.5 mg	1 mg	1 or 2 mg

1) Dose Maintenance at 1 mg

If the investigator or subinvestigator decides that dose increase to 2 mg is difficult due to the occurrence of an AE identified from the evaluation at Week 2 (Day 15), the dose will be maintained at 1 mg. The AE for which this judgement was made will be recorded in the case report form (CRF).

2) Dose Change

If the investigator or subinvestigator decides that dose adjustment is necessary based on the subject's condition, the dose will be reduced or increased to 1 or 2 mg.

If the investigator or subinvestigator decides that the current dose is not sufficiently effective, the dose will be increased to 2 mg. If either of the following cases applies, the dose will be reduced to 1 mg and the reason for dose reduction will be recorded in the CRF. In the event that both of the following cases apply, the AE should be recorded as the reason for dose reduction. When the occurrence of an AE necessitates dose reduction, enter "dose reduction" in the CRF as the action taken for the AE in relation to IMP administration.

- The dose may be reduced to 1 mg in the following cases:
  - Dose reduction is necessary because an AE has occurred.
  - Dose reduction is necessary because symptoms have improved.

3.2.2 Rationale for Dosing and Regimen

Since this is an extension trial following Trial 331-102-00088, Otsuka considered it appropriate to administer brexpiprazole within the dose range used in Trial 331-102-00088 and selected 0.5, 1, and 2 mg for this trial.

As the subjects who were assigned to placebo in Trial 331-102-00088 were not exposed to brexpiprazole in that trial, for those subjects the dose of brexpiprazole in this trial needs to be titrated from a lower dose. Therefore, for all subjects in the current trial, the starting dose will be 0.5 mg, the same level as in Trial 331-102-00088, and the dose will be increased to 1 mg after 1 week (after evaluation at Week 1 [Day 8]) and to 2 mg after 2 weeks (after evaluation at Week 2 [Day 15]). In view of the fact that in clinical settings, pharmacotherapy for agitation is administered with caution due to the risk of AEs,[17]

maintaining the dose at 1 mg instead of increasing it to 2 mg after 2 weeks (after evaluation at Week 2 [Day 15]) will be permitted when dose increase to 2 mg is considered difficult for safety reasons. After Week 2 (Day 15), dose adjustment to either 1 or 2 mg will be permitted if the investigator or subinvestigator finds it necessary based on the subject's condition.

The regimen is oral administration once daily as in Trial 331-102-00088.

3.2.3 Rationale for Duration of Treatment

Given that the Practice Guideline for Dementia 2017 states[17] that atypical antipsychotics "should not be continued without a compelling reason even if their efficacy is recognized, and appropriate dose reduction or temporary cessation in response to symptom improvement should be considered to reduce the incidence of adverse drug reactions," it is considered that brexpiprazole will not be used for long-term maintenance therapy after improvement of symptoms. Therefore, brexpiprazole does not fall under the group of drugs that need to be evaluated for long-term administration as specified in "Regarding the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (*Yakushin* Notification No. 592 dated 24 May 1995). In real-world clinical settings, however, a certain proportion of patients with dementia of the Alzheimer's type seems to have no other choice but to stay on antipsychotics for more than 10 weeks, the treatment period used in Trial 331-102-00088. According to "Medical fee claim results for antipsychotics prescribed to patients with Alzheimer's disease during the 3 years between January 2015 and December 2017" generated by the MDV Analyzer system (Medical Data Vision Co., Ltd.), the prescription duration is 180 days or less for 85.2% of patients receiving typical antipsychotics. With all the above considered, Otsuka has decided to evaluate in this trial the safety of brexpiprazole when administered for more than 10 weeks, with a maximum of 24 weeks, in subjects who have completed the treatment period of Trial 331-102-00088.

3.3 Trial Population

3.3.1 Number of Subjects and Trial Population

A total of 157 male and female patients with agitation associated with dementia of the Alzheimer's type who have completed the treatment period of Trial 331-102-00088 and whose condition can be observed by a caregiver in at least 4 days per week for 4 hours or more a day.

3.3.2 Subject Number Assignment

[redacted]

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be obtained from all subjects (or their legally acceptable representatives) on their voluntary decision. If the investigator or subinvestigator judges that the subject is incapable of providing informed consent or is hospitalized for reasons related to medical protection, the subject does not have to provide informed consent, but the subject's legally acceptable representative must provide written consent. Even when written consent is obtained from the legally acceptable representative, the subject should be given an explanation appropriate to his or her level of understanding and, if possible, should also provide written consent. Consent will be documented on a written ICF with the subject's signature. The ICF will be approved by the same institutional review board (IRB) that approves this protocol.

The ICF for subjects and their representatives will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[23] and regional regulatory requirements.

Investigators or subinvestigators may discuss the possibility for entry with a potential subject (or their legally acceptable representative) without first obtaining consent. However, informed consent must be obtained and documented before initiating any procedure that will be performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Furthermore, to facilitate management of patient compliance with the treatment regimen and the collection of patient information during the trial via the cooperation of their caregivers, the investigator or subinvestigator will explain the details of the trial to the caregivers of potential subjects by using explanatory materials designed for caregivers and obtain their written informed consent to cooperate in the trial. Potential subjects (or their legally acceptable representatives) and caregivers are free to refuse participation in the trial or withdraw from the trial at any time, without justification, and there will be no consequences to the further care of said patients.

After the investigator or subinvestigator (or designee) has provided appropriate essential information to the subject (or their legally acceptable representative), has fully explained

the information in plain language, has provided them with the opportunity to ask questions, and has made a record indicating that these procedures were followed, the IRB-approved written ICF will be signed and dated by the subject (or their legally acceptable representative), caregiver, and person obtaining the consent (investigator, subinvestigator, or designee). If a trial collaborator has provided supplemental explanation, the IRB-approved written ICF will also be signed and dated by the trial collaborator. The subject (or their legally acceptable representative) and the subject's caregiver will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator.

Subjects (or their legally acceptable representatives) and their caregivers may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

The investigator or subinvestigator will enter information on subjects for whom informed consent has been obtained into an interactive web response system (IWRS).

3.4.2 Inclusion Criteria

Subjects must meet the inclusion criteria described in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1	Patients who, along with their caregivers, have provided written informed consent (or whose legally acceptable representative has provided written informed consent). If the investigator or subinvestigator judges that the patient is incapable of providing informed consent or is hospitalized for reasons related to medical protection, the patient's legally acceptable representative must provide written consent.
2	Patients who have completed the 10-week treatment period of Trial 331-102-00088, as well as all observations, tests, and assessments at Week 10.
3	Patients whose caregiver can properly collect the necessary information (the main caregiver must observe the patient's condition in at least 4 days per week for 4 hours or more a day). Patients receiving home care must live with a specific caregiver and must not live alone.
4	Patients who are either capable of walking on their own or are able to move about with the use of a walking aid (a walker or wheelchair) and whose vision and hearing are sufficient to enable the required tests and observations for the trial (the use of glasses, hearing aids, etc, is acceptable).

[Rationale for inclusion criteria]
1 This criterion is specified for ethical considerations.
2 This criterion is specified to identify the patients suitable for this trial.
3 and 4 These criteria are specified for the appropriate assessment of the safety of brexpiprazole.

3.4.3 Exclusion Criteria

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

Table 3.4.3-1	**Exclusion Criteria**
1	Patients who experienced SAEs that were judged to be related to the IMP by the investigator or subinvestigator in Trial 331-102-00088.
2	Patients who experienced episodes of delirium during Trial 331-102-00088.
3	Patients who had clinically significant nervous, hepatic, renal, metabolic, immunological, hematological, cardiovascular, pulmonary, or digestive abnormalities during Trial 331-102-00088.
4	Patients with psychological symptoms or behavioral problems clearly due to other diseases or a drug substance.
5	Patients who had a stroke, transient ischemic attack, or pulmonary embolism during Trial 331-102-00088.
6	Patients who had heart failure of New York Heart Association Class III or higher during Trial 331-102-00088.
7	Patients who received pharmacological therapy for arrhythmia or ischemic heart disease during Trial 331-102-00088, not including patients for whom the investigator or subinvestigator judges pharmacological therapy to be the primary prevention of ischemic heart disease.
8	Patients whose QTcF values (based on central laboratory or mechanical reading) at Week 10 of Trial 331-102-00088 meet the criteria below. If mechanically read QTcF values meet the criteria, 2 ECG examinations should be additionally performed, and at least 1 of these 2 measurements must meet the criteria. • Men: ≥ 450 msec; women: ≥ 470 msec
9	Patients with the following abnormal laboratory test values at Week 10 of Trial 331-102-00088 (assessed on the basis of the results from the central or local laboratory): • Platelet count: ≤ 75,000/mm^3 • Hemoglobin: ≤ 9 g /dL • Neutrophil count: ≤ 1000/mm^3 • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT): > 2 times the upper limit of normal (ULN) • Creatine phosphokinase (CPK): > 3 times ULN (however, this does not apply if the medical monitor judges that there will be no medically significant problems) • Albumin: < 3 g/dL
10	Patients who required insulin treatment during Trial 331-102-00088.
11	Patients whose laboratory test results at evaluation at Week 10 of Trial 331-102-00088 meet either of the following criteria for poor blood glucose control (assessed on the basis of the results from the central or local laboratory): • Glycosylated hemoglobin (HbA1c) of ≥ 8.0% according to the global standard value (NGSP value) • Fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL
12	Patients who had neuroleptic malignant syndrome, tardive dyskinesia, paralytic ileus, or rhabdomyolysis during Trial 331-102-00088.
13	Patients who had convulsive disorders (eg, epilepsy) in Trial 331-102-00088, not including patients with febrile seizure, post-traumatic seizure, or alcohol withdrawal seizure.
14	Patients who are unable to take oral medication due to severe dysphagia.

Table 3.4.3-1	Exclusion Criteria
15	Patients whose Sheehan Suicidality Tracking Scale (S-STS) score in Trial 331-102-00088 meets any of the following criteria, or who are judged by the investigator or subinvestigator to be at high risk of suicide: • Patients with a score of 3 or 4 on any of S-STS Questions 2, 3, 4, 5, 6, or 11 • Patients with a score of 2 or more on any of S-STS Questions 1a, 7, 8, 9, 10, or 12
16	Patients whose body weight at evaluation at Week 10 of Trial 331-102-00088 was < 30 kg.
17	Patients whose body weight had fallen by ≥ 7% at Week 10 from baseline in Trial 331-102-00088.
18	Patients who were confirmed to meet the following contraindications in the package insert of REXULTI® during Trial 331-102-00088: • Patients in a coma • Patients under the strong influence of central nervous system depressants, including barbiturate analogs/anesthetics • Patients receiving adrenaline • Patients with a history of hypersensitivity to the components of REXULTI®
19	Patients who are bedridden and require assistance for excretion, eating, and changing clothes
20	Women who had a positive pregnancy test result at Week 10 of Trial 331-102-00088 (women of childbearing potential only)
21	Sexually active men or sexually active women of childbearing potential who will not agree to practice 2 different methods of birth control or to remain abstinent during the trial and for 30 days after the final IMP administration. For birth control, two of the following methods must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine contraceptive device (IUD), oral contraceptives, or condom with spermicide.
22	Patients who otherwise were judged by the investigator or subinvestigator to be unsuitable for extended treatment with brexpiprazole.

Men without the ability to procreate are defined as those who have had bilateral orchidectomy, and women who are incapable of pregnancy are defined as those who have had bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 months.

Subjects must agree to the restrictions described in Section 4 Restrictions.

[Rationale for the exclusion criteria]
1 to 19 These criteria are specified in view of safety.
20, 21 These criteria are specified in consideration of safety, as the safety of brexpiprazole during pregnancy or while breastfeeding has not yet been established.
22 This criterion is specified for the appropriate assessment of safety and efficacy.

3.5 Requirements for Caregivers

A caregiver who meets the following criteria will be designated as the main caregiver in the trial:

- Is able to obtain the patient information required for evaluation (24-hour information wherever possible on the patient's activities including toilet use, eating, bathing, changing, and other daily activities) during the trial period and provide this information during the inquiries on trial evaluation items; and
- Provides the patient with care and can observe the patient's condition in at least 4 days per week for 4 hours or more a day, until the completion of the examinations scheduled at the completion or discontinuation of IMP administration.

If there are multiple caregivers in charge of the patient's care, the main caregiver will not only provide patient information from his or her own observations but also obtain from the other caregivers information on the patient's condition during those periods when the patient was not under his or her observation and provide all patient information required for evaluations during the inquiries on the trial evaluation items.

If the main caregiver is unable to respond to queries, a substitute caregiver is allowed to respond to queries on the trial evaluation items. A substitute caregiver should be able to obtain basic patient information required for evaluations from other caregivers and provide the same information as would have been provided by the main caregiver during inquiries on the trial evaluation items, and should be selected from among the caregivers in charge of the patient's care. Patient information required for evaluations should be collected until the end of follow-up observation period, which is 28 days after the completion or discontinuation of IMP administration. Queries at the end of follow-up observation period will be answered not only by the main caregiver but also by caregivers who are in charge of the patient's care and able to provide the patient information required for evaluations.

In the event that replacement of the main caregiver is required during the trial period due to a change in the patient care environment or for other reasons, a caregiver who is able to provide the patient information required for evaluations in response to queries regarding the trial evaluation items will be selected as the new main caregiver. The new main caregiver must also be able to observe the patient's condition in at least 4 days per week for 4 hours or more a day.

3.6 Endpoints

3.6.1 Safety Endpoints

- Adverse events
- Physical examinations
- Laboratory tests
- Vital signs
- Body weight

- Twelve-lead electrocardiogram (ECG)
- Pregnancy test (for women of childbearing potential [WOCBP] only)
- Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Sheehan Suicidality Tracking Scale (S-STS)

3.6.2 Efficacy endpoints

- CMAI total score
- Clinical Global Impression–Severity of Illness (CGI-S)
- Clinical Global Impression–Global Improvement (CGI-I)

3.6.3 Other Endpoints

- Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)
- Mini-Mental State Examination (MMSE)

3.7 Measures to Minimize/Avoid Bias

This is an uncontrolled trial.

3.8 Trial Procedures

The schedule of assessments is shown in Table 3.8-1, and the allowable time windows for observations, tests, and assessments are shown in Table 3.8-2.

Table 3.8-1 Schedule of Assessments

Item	Screening Period	Treatment Period								Follow-up Period
	Baseline evaluation[a]	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 10 (Day 71)	Week 12 (Day 85)	Week 14 (Day 99) At discontinu-ation	28 days after completion/ discontinuation
Informed consent	From Week 4 of Trial 331-102-00088									
Subject background information	●									
Environment investigation	←	—	—	—	—	—	—	—	→	
Subject diary			←	—	→				← →	
Inclusion/exclusion criteria	●									
Compliance status		●	●	●	●	●	●	●	●	
Safety endpoints										
Adverse events	←	—	—	—	—	—	—	—	—	→
Confirmation of medications and therapies	←	—	—	—	—	—	—	—	—	→
Height	Δ									
Body weight	Δ				●				●	
Physical examination	Δ	●	●	●	●	●	●	●	●	
Laboratory tests	Δ			●			●		●	
Vital signs	Δ	●	●	●	●	●	●	●	●	
12-lead ECG	Δ		●	●			●		●	
Pregnancy test[b]	Δ								●	
DIEPSS	Δ	●	●	●	●		●		●	●
AIMS	Δ								●	●
BARS	Δ								●	●
S-STS	Δ			●					●	

Table 3.8-1 Schedule of Assessments

Item	Screening Period	Treatment Period								Follow-up Period
	Baseline evaluation[a]	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 10 (Day 71)	Week 12 (Day 85)	Week 14 (Day 99) At discontinu-ation	28 days after completion/ discontinuation
Efficacy endpoints										
CMAI	△			●					●	
CGI-S	△		●	●	●		●		●	
CGI-I			●	●	●		●		●	
[redacted]	△			●					●	
[redacted]	△			●					●	
Other endpoints										
ADCS-ADL	△								●	●
MMSE	△								●	●

The date of starting IMP administration is designated as Day 1. IMP administration will begin no later than 10 days after the date of evaluation at Week 10 of Trial 331-102-00088.

△ The results of evaluation at Week 10 of Trial 331-102-00088 will be used except for height, for which the data obtained at screening of Trial 331-102-00088 will be used.

[a]The date of evaluation at Week 10 of Trial 331-102-00088 will be the date of baseline evaluation in this trial.

[b]Pregnancy test (human chorionic gonadotropin [HCG] test) will be performed for WOCBP only. If urinary test is positive, serum test will be performed.

[c][redacted]

[d][redacted]

Table 3.8-2 Allowable Time Windows for Evaluations, Tests, and Observations

Test Point	Base Date	Allowable Time Window From the Base Date
Baseline evaluation date (at evaluation at Week 10 of Trial 331-102-00088)	Baseline evaluation date	Day −9 to Day 1
Week 1	Day 8	Day 6 to Day 10
Week 2	Day 15	Day 13 to Day 17
Week 4	Day 29	Day 27 to Day 31
Week 6	Day 43	Day 40 to Day 46
Week 8	Day 57	Day 54 to Day 60
Week 10	Day 71	Day 68 to Day 74
Week 12	Day 85	Day 82 to Day 88
Week 14	Day 99	Day 96 to Day 106
Follow-up period	28 days after the final administration of IMP	23 to 35 days after the final administration of IMP

The date of starting IMP administration is designated as Day 1, and the day before initiation of IMP treatment is designated as Day −1.

3.8.1 Schedule of Assessments

The investigator or subinvestigator will perform observations, tests, and assessments within the allowable windows shown in Table 3.8-2 according to the schedule of assessments shown in Table 3.8-1. Special consideration should be given to environmental factors that may affect assessments. The investigation of subject background information, clinical laboratory tests, and other investigation/test items that can be performed by the trial collaborator may be performed by the trial collaborator under supervision of the investigator.

The methods employed for observations, tests, and assessments are shown in Section 3.8.2 Safety Assessments to Section 3.8.4 Other Endpoints.

The date and time of observations, tests, and assessments and the results will be recorded in the source document and case report form (CRF).

3.8.1.1 Date of Informed Consent

The investigator or subinvestigator will obtain informed consent from prospective subjects (or their legally acceptable representatives) between the date of evaluation at Week 4 and the date of evaluation at Week 10 (both dates inclusive) of Trial 331-102-00088. The investigator or subinvestigator will also explain the details of the trial to the caregivers of prospective subjects by using explanatory materials designed for caregivers and obtain their written informed consent to cooperate in the trial. Following the provision of informed consent, the subject will be assigned the same subject ID as in

Trial 331-102-00088 and will be registered in the IWRS. The investigator or subinvestigator will record the following information.

- Subject ID
- Date of informed consent by the subject (or their legally acceptable representatives) and caregivers

3.8.1.2 Day of Baseline Assessment

To confirm that the subject meets the inclusion criteria and does not fall under the exclusion criteria before starting IMP administration, the investigator or subinvestigator will review the observations, tests, and assessments performed in Trial 331-102-00088 and record the following:

- Date of visit
- Subject background information
  - Sex, date of birth, race, ethnicity, and trial country[a]
  - Possibility of getting pregnant in women of childbearing potential (WOCBP) (see Section 5.5 Pregnancy) (if there is no childbearing potential, record the reason)[a]
  - Diagnosis of dementia of the Alzheimer's type (diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA])[a]
  - Timepoint of onset of dementia of the Alzheimer's type[a]
  - Timepoint of diagnosis of dementia of the Alzheimer's type[a]
  - Timepoint of onset of agitation associated with dementia of the Alzheimer's type[a]
  - Complications[a]
  - Medical history[a]
  - Medical care category (inpatient or outpatient; if outpatient, institutionalized or care at home)
  - Classification of the main caregiver specified at the start of the trial (hospital staff, care facility staff, family, or other), care status over the 2 weeks prior to the visit (amount of care time per day and days of care in a week)
- Confirmation of eligibility
- Prior use of antipsychotics (yes or no)[a]
- Height[a]

[a]The screening results of Trial 331-102-00088 will be used.

The investigator or subinvestigator will start administration of the IMP to subjects who are judged to be eligible and for whom registration in the IWRS has been completed. The investigator or subinvestigator will provide subjects with the IMP needed for the period up until the next assessment and give them instructions to bring any unused IMPs with them to the next assessment.

3.8.1.3 Environment Investigation (Day of Baseline Evaluation to Week 14 [Day 99])

If there are any changes to the subject's environment from the time of registration, the investigator or subinvestigator will record the following.

- Date of change
- Medical care category (inpatient or outpatient; if outpatient, institutionalized or care at home)
- Type of caregiver (hospital staff, care facility staff, family, or other)

3.8.1.4 Seven Days After Administration (Week 1 [Day 8]) to 98 Days After Administration (Week 14 [Day 99])

The investigator or subinvestigator will perform the observations, tests, and assessments shown in Table 3.8-1 and record the results and date of visit.

On each assessment day, the investigator or subinvestigator will provide subjects with the IMP needed for the period up until the next assessment and give them instructions to bring any unused IMPs with them to the next assessment. At visits 14 days after administration (Week 2 [Day 15]) and 84 days after administration (Week 12 [Day 85]), the investigator or subinvestigator will provide caregivers with a subject diary and give them instructions to complete the diary for 14 days before CMAI assessment and bring it with them to the next visit. In the subject diary, occurrence of daily symptoms will be recorded to evaluate the frequency of occurrence of agitation associated with dementia of the Alzheimer’s type (CMAI).

3.8.1.5 Examination at Discontinuation

At discontinuation, the investigator or subinvestigator will perform the observations, tests, and assessments shown in Table 3.8-1 as promptly as possible, within the same day if possible, after discontinuation has been decided and will record the results along with the date of visit. If at time of discontinuation, the subject or caregiver refuses any of the tests or if the investigator or subinvestigator judges that tests cannot be performed due to an emergency, only those observations, tests, and assessments that are feasible will be performed.

3.8.1.6 Follow-up Observation (Twenty-eight Days After Completion or Discontinuation of IMP Administration)

The investigator or subinvestigator will perform the observations, tests, and assessments shown in Table 3.8-1 and record the results and date of visit. These observations, tests, and assessments will also be performed in discontinued subjects unless the subject or caregiver refuses any of the tests or the investigator or subinvestigator judges that tests cannot be performed due to an emergency.

3.8.2 Safety Assessments

Evaluation points for each item are shown in Table 3.8-1.

3.8.2.1 Adverse Events

Refer to Section 5 Reporting of Adverse Events.

3.8.2.2 Clinical Laboratory Assessments

In this trial, the clinical laboratory tests shown in Table 3.8.2.2-1 will be conducted by central analysis. Blood and urine samples will be collected from each subject, and the date and time of blood sampling, the date of urine sampling, and the verification of whether blood sampling was performed when the subject was in a fasted state (having fasted for at least 8 hours) will be recorded in the source documents and the CRF. Subject eligibility will be verified using the clinical laboratory test values determined at the central or local laboratory. If laboratory test values determined at the local laboratory are used for verification of subject eligibility, it must first be verified that quality control has been performed. If any of the test results provided by the central laboratory at a later date falls under the exclusion criteria, the subject will be withdrawn from the trial. For appropriate procedures for the collection, handling, and shipment of samples analyzed at the central laboratory, the separately prepared procedures should be followed. The total amount of blood to be collected for clinical laboratory tests during the trial period will be described in the ICF and explanatory materials.

The central laboratory will report the results of tests to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of tests and date and sign the clinical laboratory test report to make it an official document. The results of laboratory tests, which will be reported directly from the central laboratory to the sponsor as an electronic file, do not need to be recorded in the source documents or the CRF.

Table 3.8.2.2-1 Clinical Laboratory Assessments	
Hematology: Red blood cell count White blood cell count Differential count of white blood cells (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) Platelet count Hemoglobin Hematocrit Prothrombin time (PT) PT (international normalized ratio [INR]) Activated partial thromboplastin time (APTT) Urinalysis: pH Protein Glucose Occult blood Urobilinogen Specific gravity Ketone body	Serum chemistry: ALT AST Alkaline phosphatase (ALP) Lactic dehydrogenase (LDH) Gamma-glutamyl transpeptidase (γ-GTP) Total protein Total bilirubin Albumin Cholesterol (total cholesterol, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol) Triglycerides Blood urea nitrogen (BUN) Creatinine Uric acid CPK Blood electrolytes (Na, K, Cl, Mg, Ca, P,) Blood glucose (fasting or nonfasting) HbA1c (NGSP value) Endocrinology: Serum prolactin Insulin

3.8.2.3 Physical Examination

The investigator or subinvestigator will conduct a physical examination for HEENT (head, eye, ear, nose, and throat), chest, abdomen, urogenital organs, extremities, nerves, and skin/mucosa.

In the baseline evaluation, all the physical findings obtained on the evaluation day will be recorded in the source document and CRF. In subsequent evaluations, only information on whether an observation was made or not and the date and time of observation will be recorded in the source document and CRF. Clinically significant physical findings obtained in and after the baseline evaluation will be recorded as AEs in the source document and CRF.

3.8.2.4 Vital Signs (Blood Pressure and Pulse Rate)

After the subject has been rested, the investigator or subinvestigator will measure vital signs in accordance with the methods specified by the trial site. The results, date and time of measurement will be recorded in the source document and CRF. If the subject complained of symptoms of orthostatic hypotension before evaluation, measurement should also be performed in the supine and standing positions, in so far as possible, in the order of the supine, sitting, and standing positions.

3.8.2.5 Body Weight

Body weight will be measured using a standard measurement method (no shoes, with clothes on).

The date and results of measurements will be recorded in the source document and CRF (increments: 0.1 kg).

3.8.2.6 Twelve-lead Electrocardiography

After the subject has been placed in a resting position, the subject's ECG will be recorded using a 12-lead electrocardiograph supplied by the central ECG laboratory. The subject's eligibility will be determined on the basis of their centrally or mechanically read QTcF values. If eligibility judgment is based on the results of centrally read QTcF values, those subjects whose values at Week 10 of Trial 331-102-00088 meet the criteria (≥ 450 msec for men, ≥ 470 msec for women) will be excluded from the trial. If eligibility judgment is based on the results of mechanically read QTcF values, those subjects whose values at Week 10 of Trial 331-102-00088 meet the criteria (≥ 450 msec for men, ≥ 470 msec for women) will undergo 2 additional ECG examinations, and those with at least 1 of the 2 QTcF measurements meeting the criteria will be excluded from the trial. If QTcF results provided by the central ECG laboratory at a later date fall under the discontinuation criteria, the subject will be withdrawn from the trial. In triplicate ECG examinations, a subject will be withdrawn from the trial if at least 2 of 3 QTcF measurements meet the discontinuation criteria. ECG examinations will be performed at appropriate intervals after the subject's resting state is confirmed.

The investigator or subinvestigator will check the ECG and assess whether the result is normal or abnormal and will record the date and time of ECG, normal/abnormal judgment, and abnormal findings in the source documents and the CRF. The original of the 12-lead ECG chart will be kept in the medical record or the investigator's file. The central ECG laboratory will collect 12-lead ECG data and measure the heart rate, PR interval, RR interval, QRS interval, QT interval, and QT corrected for heart rate (QTc) [QTcB = QT interval/$(\text{RR interval})^{1/2}$, QTcF = QT interval/$(\text{RR interval})^{1/3}$], and the physician of the central ECG laboratory will assess the data.

The central ECG laboratory will report the results of analysis to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of analysis and date and sign the analysis result report to make it an official document. The investigator or subinvestigator will reconfirm the normal/abnormal judgment with reference to the analysis result report sent from the central ECG laboratory. As the results of analysis by the central ECG laboratory are reported directly from the central ECG

laboratory to the sponsor as an electronic file, they do not need to be recorded in the source documents or the CRF.

3.8.2.7 Pregnancy Test

A urine pregnancy test will be performed in WOCBP (see Section 5.5 Pregnancy), and the date of urine sampling and the result of the test will be recorded in the source documents and the CRF. The result of the pregnancy test performed at Week 10 of Trial 331-102-00088 must be obtained before starting IMP administration. If the urine test is positive, another pregnancy test will be performed using serum, and the date of blood sampling will be recorded in the source documents and the CRF. A serum pregnancy test will be performed by the central laboratory selected by the sponsor. For appropriate procedures for the collection, handling, and shipment of samples, separately documented procedures will be prepared and provided prior to the start of the trial. The central laboratory will report the results of tests to the investigator or subinvestigator. The investigator or subinvestigator will confirm the results of tests and date and sign the clinical laboratory test report to make it an official document. The results of serum tests, which will be reported directly from the central laboratory to the sponsor as an electronic file, do not need to be recorded in the source documents or the CRF.

3.8.2.8 Other Safety Assessments

The investigator or subinvestigator will record the results and the date and time of the assessments in the source documents and the CRF. The schedule for each of the assessment items is shown in Table 3.8-1.

3.8.2.8.1 Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)

By using DIEPSS, the investigator or subinvestigator will assess 9 items related to extrapyramidal symptoms on a 5-point scale on the basis of the information regarding the subject's condition after the previous assessment.

Nine items related to extrapyramidal symptoms:

Gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia, and overall severity

3.8.2.8.2 Abnormal Involuntary Movement Scale (AIMS)

By using AIMS, the investigator or subinvestigator will assess the severity of abnormal involuntary movement at 7 sites and 3 global judgment items on a 5-point scale and assess the dental status items “current problems with teeth and/or dentures” and “Dose patient wear dentures” as either “yes” or “no” (assessment at specified time points).

Seven sites:

"Muscles of facial expression," "lips and perioral area," "jaw," "tongue," "upper (arms, wrists, hands, fingers)," "lower (legs, knees, ankles, toes)," and "neck, shoulders, hips"

3.8.2.8.3 Barnes Akathisia Rating Scale (BARS)

By using BARS, the investigator or subinvestigator will assess the "objective," "subjective—awareness of restlessness," and "subjective—distress related to restlessness" for akathisia on a 4-point scale and a "global clinical assessment of akathisia" on a 6-point scale.

3.8.2.8.4 Sheehan Suicidality Tracking Scale (S-STS)

By using S-STS, the investigator or subinvestigator will assess suicidal attempt and behavior during the period since the previous visit on the basis of 22 question items.

3.8.3 Efficacy Assessments

The rater for each of the assessment items should refer to Section 3.8.8 Raters. The results and the date and time of assessments should be recorded in the source documents and the CRF. The schedule for each of the assessment items is shown in Table 3.8-1.

3.8.3.1 Cohen-Mansfield Agitation Inventory (CMAI)

The rater will use CMAI to determine how often each of the 29 agitated behaviors associated with dementia of the Alzheimer's type occurred with each behavior rated on a 7-point scale of frequency through an interview with the caregiver. The evaluation will be made on the basis of information on the subject from 14 days before each assessment day and the frequency of agitation will be evaluated on the basis of the information contained in the subject diary. However, records in the subject diary are supplementary data for assessment, and the investigator or subinvestigator will perform the final assessment based not only on the information contained in the subject diary but also the information collected through an interview with the caregiver.

[29 agitated behaviors]

"Pace, aimless wandering," "inappropriate dressing or disrobing," "spitting (include at meal)," "cursing or verbal aggression," "constant unwarranted request for attention or help," "repetitive sentences or questions," "hitting (including self), " "kicking," "grabbing onto people," "pushing," "throwing things," "strange noises (weird laughter or crying)," "screaming," "biting," "scratching," "trying to get to a different place (e.g., out of the room, building)," "intentional falling," "complaining," "negativism," "eating/drinking inappropriate substances," "hurt self or other (cigarette, hot water, etc.)," "handling things inappropriately," "hiding things," "hoarding things," "tearing things or

destroying property," "performing repetitious mannerisms," "making verbal sexual advances," "making physical sexual advances," and "general restlessness"

3.8.3.2 Clinical Global Impression–Severity of Illness (CGI-S)

The rater will assess (by time point evaluation) the severity of agitation associated with dementia of the Alzheimer's type on an 8-point scale using the CGI-S.

3.8.3.3 Clinical Global Impression–Global Improvement (CGI-I)

The rater will assess (by time point evaluation in comparison with the date of baseline evaluation of this trial) improvement of agitation associated with dementia of the Alzheimer's type on an 8-point scale using the CGI-I.

3.8.3.4 [redacted]

[redacted]

3.8.3.5 [redacted]

[redacted]

[redacted]

3.8.4 Other Endpoints

The rater for each of the assessment items should refer to Section 3.8.8 Raters. The results and the date and time of assessments should be recorded in the source documents and the CRF. The schedule for each of the assessment items is shown in Table 3.8-1.

3.8.4.1 Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)

The rater will review the answers to the 19 questions on the dementia patient's activities of daily living through an interview with the caregiver using the ADCS-ADL severe dementia version and will record the results. The evaluation will be made on the basis of information for the period from 28 days before each evaluation date. If the caregiver cannot come to the trial site for a compelling reason, an interview by telephone is acceptable for the follow-up observation only.

3.8.4.2 Mini-Mental State Examination (MMSE)

The rater will assess each of 11 cognitive function items for the subject at the time of evaluation using the MMSE and will record the results.

[11 cognitive function items]

"Orientation to time," "orientation to place," "registration," "attention and calculation," "recall," "naming," "repetition," "comprehension," "reading," "writing," and "drawing"

3.8.5 Concomitant Medications and Therapies

The investigator or subinvestigator will investigate medications and therapies administered during the trial. If any medication is used during the periods, the name of the drug, purpose of use, dose, frequency, route of administration, and start date and end date of treatment will be investigated. If any therapy is performed, the name of the therapy, purpose of therapy, and start date and end date of treatment will be investigated. The results of the investigation will be recorded in the source document and CRF.

3.8.6 End of Trial

The end-of-trial date is defined as the date of last visit or contact, or the date of final contact attempt as recorded on the follow-up page of the CRF prepared for the last subject completing or withdrawing from the trial.

3.8.7 Independent Data Monitoring Committee (IDMC)

In order to avoid exposing subjects to any potential risks (including the risk of death) during the trial period and to ensure the safe conduct of the trial, the IDMC established in Trial 331-102-00088 will monitor the current trial (331-102-00184) as well. The IDMC will meet either regularly as specified in the protocol of Trial 331-102-00088 and as needed to review the subject demographics and AEs and to give advice on the appropriateness of continuing the trial or the necessity of modifying the protocol.

The sponsor will designate the following as IDMC members: [redacted]

The IDMC members, their roles, and other details will be specified in a separate procedure.

3.8.8 Raters

Table 3.8.8-1 shows persons who are authorized to evaluate each evaluation scale. While the CMAI, [redacted] ADCS-ADL, and MMSE are allowed to be evaluated by persons other than the investigator or subinvestigator, the investigator or subinvestigator will check the content and decide whether the data should be adopted.

Evaluations using the CMAI, CGI-S, CGI-I, [redacted], DIEPSS, AIMS, BARS, S-STS, ADCS-ADL, and MMSE will be conducted by raters who have been trained for this trial.

The investigator or subinvestigator will check how evaluations are being conducted and their content after receiving training for the trial.

Table 3.8.8-1 Raters of Evaluation Scales

	Investigator or Subinvestigator	Clinical Psychologist (Including Clinical Psychological Technologist)	Occupational Therapist	Speech-language-Hearing Therapist	Nurse
CMAI	○	○			
[redacted]	○	○	○		
CGI-S	○				
CGI-I	○				

Table 3.8.8-1 Raters of Evaluation Scales					
	Investigator or Subinvestigator	**Clinical Psychologist (Including Clinical Psychological Technologist)**	**Occupational Therapist**	**Speech-language-Hearing Therapist**	**Nurse**
DIEPSS	○				
AIMS	○				
BARS	○				
S-STS	○				
ADCS-ADL	○	○	○		
MMSE	○	○	○	○	○

3.9 Stopping Rules, Withdrawal Criteria, and Procedures

3.9.1 Entire Trial

In the event of sponsor termination or suspension of the trial for any reason, prompt notification will be given to the heads of the trial sites and regulatory authorities in accordance with the regulatory requirements.

3.9.2 Individual Site

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

3.9.3 Individual Subject Discontinuation

3.9.3.1 Treatment Discontinuation

A subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with the 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 or subinvestigator. Regardless, each investigator or subinvestigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.9.3.4 Procedures to Encourage Continued Trial Participation.

3.9.3.2 Documenting Reasons for Discontinuation

All subjects have the right to withdraw, and the investigator or subinvestigator can discontinue a subject's participation in the trial at any time if medically necessary. In

addition, subjects meeting the following criteria must be withdrawn from the trial. Only one main reason for discontinuation will be recorded in the CRF.

- Adverse event
  - Death
  - Continuation of IMP would place the subject at undue risk, as determined by the investigator or subinvestigator (eg, there is a safety concern possibly, probably, or likely related to IMP).
    - SAE
    - The dose of brexpiprazole needs to be reduced to lower than 1 mg due to the occurrence of an AE.
  - The subject experiences worsening of agitation, and the investigator or subinvestigator judges that the subject should be withdrawn from the trial (worsening of agitation is to be reported as an AE).
  - The subject decides to discontinue the treatment because of annoyance or discomfort due to a nonserious AE that is not otherwise determined to be an undue hazard.
- Subjects becoming bedridden and requiring assistance for excretion, eating, and changing clothes
- Subject's withdrawal of informed consent
- Legally acceptable representative's withdrawal of informed consent
- Caregiver's withdrawal of informed consent
- Marked noncompliance with the IMP regimen (compliance rate of < 65% during the interval between the previous date of compliance verification and the current date of compliance verification)
- Protocol deviation (other than marked noncompliance with the IMP regimen)
  - The subject is discovered to have not met the inclusion/exclusion criteria.
  - The subject has received any prohibited concomitant drugs or is judged to be in need of prohibited drugs.
- Lost to follow-up
- Lack of efficacy
- Pregnancy (see Section 5.5 Pregnancy)
- Termination of all or part of the trial by the sponsor
- Investigator or subinvestigator's judgment (for reasons other than occurrence of AE)
- Other
  - After initiation of IMP treatment, any of the following external test results at Week 10 of Trial 331-102-00088 are obtained:
    - QTcF on the basis of ECG results from the central ECG laboratory is ≥ 450 msec in men or ≥ 470 msec in women (in triplicate ECG examinations, at least 2 measurements meet the criteria).

- Results from the central laboratory:
  - Platelet count: ≤ 75,000/mm^3
  - Hemoglobin: ≤ 9 g/dL
  - Neutrophil count: ≤ 1000/mm^3
  - AST and ALT: > 2 times ULN
  - CPK > 3 times ULN (however, this does not apply if the medical monitor judges that there will be no medically significant problems)
  - Albumin: < 3 g/dL
  - HbA1c (NGSP): ≥ 8.0%
  - Fasting blood glucose level of ≥ 126 mg/dL or nonfasting blood glucose level of ≥ 200 mg/dL

If the subject discontinues IMP due to an AE, the investigator, subinvestigator, or other trial personnel will make every effort to follow the event until the event is resolved or stabilized, or the subject is lost to follow-up or has died. Follow-up procedures in Section 3.9.3.1 Treatment Discontinuation must be followed.

3.9.3.3 Withdrawal of Consent

All subjects (including their legal representatives and caregivers) 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 or subinvestigator 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 or subinvestigator 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 refusal by a subject 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 to obtain necessary medical or laboratory reports relevant to the trial's objectives.

- Contact of alternative person(s) who have been designated in source documents 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/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 of a subject for an 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 3.9.3.1 Treatment Discontinuation). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 3.9.3.2 Documenting Reasons for Discontinuation to determine if the subject can continue participation in the trial if modifications to his/her treatment and/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.

3.9.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator or subinvestigator should ensure understanding and documentation of the reasons why the subject wishes to withdraw consent.

3.10 Screen Failures

A screen failure subject is one who has given informed consent to participate in the trial and has signed the informed consent form, but who was not enrolled.

For screen failures, the following information will be recorded in the CRF:

- Subject ID
- Date of informed consent
- Date of visit

- Subject demographics (date of investigation, date of birth, sex, race, ethnicity, and country where trial is performed; all of these data are derived from the screening results of Trial 331-102-00088.)
- Results of eligibility criteria assessment
- Date of assessment as screen failure
- Reason for screening failure

3.11 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for safety and efficacy (corresponding to the treatment period in this trial) irrespective of whether the subject has received 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 the purposes of this trial, subjects who are evaluated at Week 14 will be defined as trial completers.

3.12 Definition of Subjects Lost to Follow-up

Subjects who can no longer be contacted 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-trial date cannot be determined will be classified as "lost to follow-up." 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 investigator, subinvestigator, or designee will make 3 documented attempts to contact the subject by telephone and in the event that 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. When a subject is lost to follow-up, the results of the investigation (whether or not the subject could be contacted and the date and method of contact) will be recorded in the source documents and the CRF.

3.13 Subject Compliance

The investigator or subinvestigator will appropriately instruct subjects and caregivers to comply with the protocol-defined provisions.

3.14 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, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator, subinvestigator, or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. The process of the decision for trial continuation will be documented by the investigator or subinvestigator and the sponsor, and reviewed by the site monitor. For major deviations, the date on which the deviation occurred and the details of the deviation will be recorded in the CRF.

4 Restrictions

4.1 Prohibited Medications

Drugs shown in Table 4.1-1 except brexpiprazole are prohibited from the date of evaluation at Week 10 of Trial 331-102-00088 until completion of examinations scheduled at the completion or discontinuation of IMP administration. Brexpiprazole is prohibited until completion of follow-up observation.

Table 4.1-1 Prohibited Medications

Drug Type	Remarks
Antipsychotics • Clozapine • Sustained release injections • Brexpiprazole • Other antipsychotics	Brexpiprazole is prohibited until completion of follow-up observation
Antidepressants	
Mood stabilizers	
Psychostimulants	
Narcotic analgesics for agitation	
Yokukansan and other herbal medicines and supplements for treatment of BPSD	
Adrenaline	
Antiepileptic drugs	
Antiparkinson drugs	
Varenicline	
Benzodiazepines	
Belsomra	
Lemborexant	
Drugs (β-blockers) for extrapyramidal symptoms	If administration is necessary due to AEs that occur after IMP administration, use will be permitted in accordance with the stipulations for restricted drugs.

Table 4.1-1 Prohibited Medications	
Drug Type	**Remarks**
CYP2D6 inhibitors, CYP3A4 inhibitors and inducers[a]	

[a]see Table 4.1-2

Table 4.1-2 Prohibited Concomitant CYP2D6 Inhibitors, CYP3A4 Inhibitors, and CYP3A4 Inducers (Except for External Use)	
CYP2D6 inhibitors	[redacted]
CYP3A4 inhibitors	[redacted]
CYP3A4 inducers	[redacted]

4.2 Restricted Medications

Use of drugs listed in Table 4.2-1 is permitted under the prescribed restrictions from completion of evaluation at Week 10 of Trial 331-102-00088 until completion of examinations scheduled at the completion or discontinuation of IMP administration.

Table 4.2-1 Restricted Medications	
Drug Type	**Restriction**
Antidementia drugs	The continued use of these drugs from Trial 331-102-00088 is permitted if the dose and regimen have not been changed.
Narcotic analgesics	If not used for agitation (eg, pain control, tooth extraction), the use of these drugs is permitted.
β-Blockers	• Treatment of complications (eg, cardiovascular diseases) other than psychiatric diseases The continued use of these drugs from Trial 331-102-00088 is permitted if the dose and regimen have not been changed. (Discontinuation or dose reduction is permitted only when these actions are necessary due to AEs caused by β-blockers or for remission of symptoms.) • Treatment of extrapyramidal symptoms reported as AEs after IMP administration If medication is necessary, the use at a dose up to the equivalent of 60 mg/day of propranolol is permitted.

Table 4.2-1 Restricted Medications	
Drug Type	**Restriction**
Hypnotics	• Ultra-short-acting nonbenzodiazepine hypnotics (zolpidem, zopiclone, eszopiclone), ramelteon The continued use of these drugs from Trial 331-102-00088 is permitted if the dose and regimen have not been changed. (Discontinuation and dose reduction are permitted only when these actions are necessary due to AEs caused by hypnotics or after remission of symptoms of insomnia.) • Treatment of insomnia reported as an AE after IMP administration If medication is necessary, one (change of the type is permitted) ultra-short-acting nonbenzodiazepine hypnotic (zolpidem, zopiclone or eszopiclone) can be used.

4.3 Other Restrictions

[redacted] is prohibited from completion of evaluation at Week 10 of Trial 331-102-00088 until completion of examinations scheduled at the completion or discontinuation of IMP administration.

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 events recorded as complications at screening of Trial 331-102-00088 for which the underlying condition was known and no worsening occurred during this trial. In addition, events that were recorded as AEs before evaluation at Week 10 of Trial 331-102-00088 and did not worsen during this trial (331-102-00184) will not be deemed to be AEs in this trial. An adverse drug 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 Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, 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/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient 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 nonmedical need) are not considered SAEs.
- Congenital anomaly/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 drug-induced liver injury (see Section 5.4 Potential Drug-induced Liver Injury).
- 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 recorded in the AE section of the CRF if there is an abnormality or complication.

Clinical Laboratory Assessment Value Changes: It is the investigator's or subinvestigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's or subinvestigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator or subinvestigator needs to determine whether this is an abnormal (ie,

clinically relevant) 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 or subinvestigator 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 or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation or meets the criteria for an SAE, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale. The intensity of an AE 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 between an AE and the IMP:

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 reasonable relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator 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 in the source documents and CRFs provided by the sponsor. The event name, date and time of onset, date and time of recovery, seriousness, severity, causal relationship to IMP, actions taken regarding IMP administration, and outcome thereof will be recorded in the CRF. The period for AE and SAE collection is defined as the period after evaluation at Week 10 of Trial 331-102-00088 until the end-of-trial date.

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 on the basis of the course of the condition.

Worsening of severity and seriousness of reported AEs must be reported as new AEs in the CRF.

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

5.3 Immediately Reportable Events

The investigator, subinvestigator, or designee must report any and all IREs (see Section 5.1 Definitions) to the sponsor by e-mail (using the contact information on the title page of this protocol) immediately after either the investigator, subinvestigator, or designee becomes aware of the event. An IRE form must be sent by e-mail to the sponsor. Please note that the IRE form is NOT the AE section of the CRF. Due consideration must be given to the subject's privacy when an IRE form is sent by e-mail.

For subjects experiencing SAEs or IREs, such events should be followed until the events are resolved or clinically stabilized, or the subject is lost to follow-up. *Resolved* means that the subject has returned to the baseline state of health, and *stabilized* means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. It is expected that the investigator or subinvestigator 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 Drug-induced Liver Injury

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

5.5 Pregnancy

Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/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 and/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 final administration of IMP. Unless the subject or their partner is sterile (ie, women who have had a bilateral oophorectomy and/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, IUD, oral contraceptives, or condom with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

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

- General information
- Informed consent form
- 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 informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

All WOCBP must undergo a urine or serum pregnancy test (human chorionic gonadotropin [HCG] test) at evaluation at Week 10 of Trial 331-102-00088. If a urine test is performed and is positive, the investigator or subinvestigator will follow up with a confirmatory serum test.

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

If a subject is suspected to be pregnant before initiation of IMP treatment, the IMP administration must be withheld until the results of pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the serum pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after

consultations with the PV department [see the cover page of this protocol for contact information].)

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the final administration 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. The same applies to the pregnancy of a subject's partner.

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 or subinvestigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

Not applicable.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded in the AE section of the CRF, with the current status (ongoing or resolved/recovered) noted. All nonserious events (other than IREs) that are ongoing at the end-of-trial date (final day of observation) will be recorded as ongoing in the CRF. For any AE having been identified throughout the trial, during data 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). The follow-up information after the end-of-trial date (final day of observation) will be recorded in the subject's medical record.

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

This trial requires that subjects be actively monitored for SAEs and IREs up to the end-of-trial date (final day of observation).

Serious AEs and IREs that are identified or ongoing at the end-of-trial date must be recorded in the AE section of the CRF. Between the end-of-trial date for the individual

subject and the end-of-trial date for the last subject, if any new information regarding an SAE or IRE becomes available (eg, the event is resolved), this must be reported to the sponsor using the IRE form and so on, and the information must be recorded in the AE section of the CRF. The investigator or subinvestigator will follow SAEs and IREs, and will continue to report any significant information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died, using the IRE form and so on.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring After the End-of-trial Date (Final Day of Observation)

Any new SAEs or IREs reported to the investigator or subinvestigator, which occur after the end-of-trial date (final day of observation) and are determined by the investigator or subinvestigator to be associated with the use of the IMP, should be reported to the sponsor. This includes SAEs and IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator or subinvestigator will follow SAEs and 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, using the IRE form and so on.

6 Statistical Analysis

The definitions of the datasets for analysis and the analysis methods for the specified endpoints are described below. The statistical analysis plan details are described in a separate Statistical Analysis Plan. The Statistical Analysis Plan will be finalized prior to data lock.

6.1 Determination of Sample Size

This trial aims to include 100 completers of brexpiprazole treatment in Trial 331-102-00088 as subjects who will continue to receive brexpiprazole for more than 10 weeks. Since patients are assigned to the 1 mg group, the 2 mg group, or the placebo group at a ratio of 3:4:4 in Trial 331-102-00088, the target sample size for this trial (331-102-00184) has been determined to be 157 subjects, taking into account some of them have received placebo in the previous trial.

6.2 Datasets for Analysis

Analyses in this trial will be performed for each of the following groups unless otherwise specified:

- Rollover subjects from the brexpiprazole group in Trial 331-102-00088
- Rollover subjects from the placebo group in Trial 331-102-00088
- All subjects (rollover subjects from the brexpiprazole group + rollover subjects from the placebo group)

6.2.1 Efficacy Analysis Set

The efficacy analysis set will comprise subjects who have received at least 1 dose of the IMP and from whom CMAI total scores have been obtained at baseline and at least 1 time point after initiation of treatment.

6.2.2 Safety Analysis Set

The safety analysis set will comprise subjects who have received at least 1 dose of the IMP.

6.3 Handling of Missing Data

For analyses at the final assessment, the last observation carried forward (LOCF) method (in which missing Week 14 data are imputed by the data which were observed after initiation of IMP treatment and obtained immediately before Week 14) will also be used.

6.4 Efficacy Endpoint Analyses

Efficacy analyses will be performed on the efficacy analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in this trial.

- CMAI total score
- CGI-S
- CGI-I

[redacted]

For endpoints other than CGI-I, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated. For CGI-I, descriptive statistics of actual measurements at each time point and the final assessment (Week 14 LOCF) will be calculated.

[redacted].

6.4.1 Interim Analysis

In this trial, safety will also be evaluated by the IDMC, when approximately 25%, 50%, and 75% of the target number of subjects in the preceding Trial 331-102-0008 have completed or discontinued the trial. Additional evaluation by the IDMC may be performed depending on the status of subject enrollment into the current trial (331-102-00184).

6.5 Analysis of Demographic and Baseline Characteristics

Descriptive statistics or frequency distribution of demographics and other baseline characteristics will be determined for each analysis set.

6.6 Safety Analysis

Safety analysis will be performed using the safety analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in this trial.

6.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidences of the following events will be summarized according to system organ class and preferred term.

- Adverse events occurring after initiation of IMP administration (treatment-emergent adverse events [TEAEs])
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs leading to IMP dose reduction

TEAEs potentially causally related to the IMP will also be summarized in the same manner.

6.6.2 Clinical Laboratory Data

For each quantitative laboratory parameter, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

For each laboratory parameter (excluding qualitative parameters), actual measurements will be classified as "lower than the lower limit of the reference range," "within the reference range," and "higher than the upper limit of the reference range" using the reference range specified by the central laboratory, and a shift table from baseline will be produced.

For each qualitative laboratory parameter, a shift table from baseline will be produced.

Numbers and proportions of subjects with clinically significant changes in laboratory test values will be determined.

6.6.3 Physical Examination and Vital Signs Data

Physical examination data will be provided in a listing.

For each vital sign parameter, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

Numbers and proportions of subjects with clinically significant changes in vital signs will be determined.

6.6.4 Electrocardiogram Data

For heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

A shift table from baseline for normal/abnormal 12-lead ECG will be produced.

The numbers and proportions of subjects with actual measurements of corrected QT interval (QTcF, QTcB, and QTcN) at each time point and the final assessment (Week 14 LOCF) of > 450 msec, > 480 msec, and > 500 msec will be determined. Numbers and proportions of subjects with changes from baseline of > 30 msec and > 60 msec will be determined.

Numbers and proportions of subjects with clinically significant changes in ECG parameters will be determined.

6.6.5 Other Safety Data

6.6.5.1 Body Weight and Body Mass Index

For body weight and BMI, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

Numbers and proportions of subjects with results meeting the criteria for clinically significant changes will be determined.

6.6.5.2 DIEPSS, AIMS, and BARS

For DIEPSS total score (total of scores for items 1 through 8) and score for each DIEPSS item, AIMS total score (total of scores for items 1 through 7) and score for each of the 3 global judgment items (items 8 through 10), and BARS, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

6.6.5.3 S-STS

For each item of S-STS, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

6.7 Analysis of Other Endpoints

Analysis of other endpoints will be performed using the safety analysis set. Baseline is defined as the last data obtained prior to initiation of IMP treatment in this trial.

- ADCS-ADL
- MMSE

For ADCS-ADL total score and MMSE total score, descriptive statistics of actual measurements and changes from baseline at each time point and the final assessment (Week 14 LOCF) will be calculated.

7 Management of Investigational Medicinal Product

Refer to the investigator's brochure on brexpiprazole and the separately-specified manual for details regarding IMP management.

7.1 Packaging and Labeling

The IMP will be provided to the IMP manager by the sponsor or designated agent. The IMP will be supplied as [redacted]. Each [redacted] used in the dosing period will be

labeled to clearly indicate that the drug is for clinical trial use and to disclose the subject ID, compound ID, the protocol number, sponsor's name and address, route of administration, manufacturing number, expiry date, storage conditions, etc.

7.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager. The IMP manager may not provide IMP to any subject not participating in this protocol.

The IMP is to be stored at room temperature. The clinical site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

7.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, or returned.

7.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP must be returned to the sponsor or a designated agent.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original [redacted]. The assigned trial monitor will facilitate the return of unused and/or partially used IMP.

7.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) regarding the IMP 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/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- [redacted]
- Product defect (eg, odor, chipped, broken, embossing illegible)

- Loss or theft of product

7.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, 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, subinvestigator, or designee must notify the sponsor (or sponsor's designee) via e-mail immediately after becoming aware of the PQC according to the procedure outlined in Section 7.5.2 Information Required for Reporting Product Quality Complaints. (E-mail address: [redacted])

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

7.5.2 Information Required for Reporting Product Quality Complaints

- Description of complaint
- Reporter identification (eg, subject, investigator or subinvestigator, site information, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, drug number)
- Clinical protocol reference (protocol number or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Complaint sample availability for return

7.5.3 Return Process for Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide instructions for complaint sample return, when applicable.

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.

7.5.4 Assessment/Evaluation

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

8 Records Management

8.1 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, medical records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the trial site and made available for direct inspection by authorized persons. Investigator(s)/trial site(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with regional regulatory requirements.

8.2 Data Collection

During each subject's visit to the trial site, an investigator or subinvestigator will document all significant observations and findings in the medical records. At a minimum, these records will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's or subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to commencement of 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 or subinvestigator'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 investigator or subinvestigator (or designee) who made an entry in the medical records.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical records as described above. Any changes to information in the medical records and other 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 document by the investigator or subinvestigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the medical records and other source documents will be entered by trial site personnel directly onto electronic CRFs in the sponsor's electronic data capture system. Changes to the data will be captured by an automatic audit trail.

Subject diaries collected by caregivers (original documents) will be kept by the study site.

8.3 File Management at the Trial Site

The head of the trial site 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 trial site will take measures to prevent accidental or premature destruction of these documents.

8.4 Record Retention at the Trial Site

The trial site will retain all the trial-related documents and records for whichever is the longer of the two periods indicated below. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.

- Until the date 2 years after manufacturing and marketing approval date; however, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, until the date 3 years after receipt of such notification.
- Until the date 3 years after termination or completion of the trial.

The trial site must not dispose of any records relevant to this trial without either 1) written permission from the sponsor or 2) providing an opportunity for the sponsor to collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during the trial. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

9 Quality Control and Quality Assurance

9.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, ICH E6 GCP: Consolidated Guidance, and applicable regional regulatory requirements and 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 or subinvestigators and trial site clinical personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

9.2 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 CRFs with source documents. The investigator agrees to participate with audits.

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

10 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 according to the requirements of each region, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs and IRE forms, the investigator or subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number or subject ID will be used to identify each subject. Financial aspects, subject insurance, and publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

11 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 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, and 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 a unique subject ID in the CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

12 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. 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, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or subinvestigators will wait for IRB 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, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agency within local applicable timelines.

When the IRB, 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 written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written 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.

13 Publication Authorship Requirements

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

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

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

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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Appendix 1 Protocol Amendments/Administrative Changes

Amendment: Number: 1
Issue Date: 01 Oct 2018

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ADDITIONAL RISK TO THE SUBJECT

[redacted].

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Location	Before Change	After Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ADDITIONAL RISK TO THE SUBJECT

[redacted]

Amendment: Number: 3

Issue Date: 03 Feb 2021

PURPOSE:

[redacted]

BACKGROUND:

[redacted].

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ADDITIONAL RISK TO THE SUBJECT

[redacted].

Agreement

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

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

I understand that this IRB-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 trial sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the trial site for subjects screened or enrolled in the trial.

I agree to await IRB 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 within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB 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 events 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 subinvestigators 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's Name	Name of Trial Site
Signature	Date

The sponsor's signature for this Agreement is provided as an electronic signature. The electronic signature page is attached to this Agreement.