CLINICAL STUDY PROTOCOL

A multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison trial to evaluate the efficacy and safety of brexpiprazole (OPC-34712) in the treatment of patients with agitation associated with dementia of the Alzheimer's type

NCT Number: NCT03620981
Protocol No. 331-102-00088
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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

CLINICAL PROTOCOL

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Protocol No. 331-102-00088

CONFIDENTIAL – PROPRIETARY INFORMATION

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Sponsor:	Otsuka Pharmaceutical Co., Ltd.
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-102-00088
Protocol title:	A multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison trial to evaluate the efficacy and safety of brexpiprazole (OPC-34712) in the treatment of patients with agitation associated with dementia of the Alzheimer's type
Clinical phase/ type of trial:	Phase 2/3 Confirmatory study
Treatment indication:	Agitation associated with dementia of the Alzheimer's type
Objectives:	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 patients who require medication, to investigate the safety of brexpiprazole, and to identify the optimum dose of brexpiprazole
Trial design:	Multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison
Subject population:	A total of 407 male or female patients aged ≥ 55 to ≤ 90 years old with a diagnosis of dementia of the Alzheimer's type according to 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) who require medication, who have symptoms of agitation that have persisted or shown frequent recurrence during each 2-week period before the screening examination and baseline evaluation, respectively, 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 meet both of the following diagnostic criteria: – Diagnosis of "Dementia due to Alzheimer's Disease" according to DSM-5. – Diagnosis of "Probable Alzheimer's Disease" according to NINCDS-ADRDA. • Patients who are ≥ 55 and ≤ 90 years of age at the time of obtaining informed consent. • Patients who can be followed in the same environment (as described below) from at least 3 weeks before baseline evaluation up to the completion of the examinations scheduled at the completion or discontinuation of investigational medicinal product (IMP) administration

- Patients who will be hospitalized in the same medical facility.
- Patients who will be institutionalized in the same care facility.
- Patients who will continue to receive care at home.

  For patients receiving day care or day service, those patients who will visit the same care facility at the same frequency during the above-mentioned period will be included.

- 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 have agitation that interferes with daily activities and is persistent/recurs frequently during the 2 weeks each before the screening examination and baseline evaluation. Agitation is defined according to the "Consensus provisional definition of agitation in cognitive disorders" from the International Psychogeriatric Association (IPA).[a]
- Patients who have shown verbal aggression or physical aggression for 3 times or more during the 2 weeks before baseline evaluation. Examples of verbal aggression and physical aggression include the following symptoms in the "Consensus provisional definition of agitation in cognitive disorders" of IPA.[a]
  - Verbal aggression: yelling, speaking in an excessively loud voice, using profanity, screaming, shouting, etc.
  - Physical aggression: grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, self-hitting, slamming doors, tearing things, destroying property, etc.

The main exclusion criteria are as follows:

- Patients who have dementia or memory impairment other than dementia of the Alzheimer's type, such as the following: Frontotemporal dementia, Lewy body dementia, vascular dementia, dementia secondary to head trauma, substance-induced persistent dementia, dementia due to human immunodeficiency virus infection, dementia due to prion disease, dementia due to Parkinson's disease (including Parkinsonian diseases such as progressive supranuclear palsy and basal ganglion degeneration), dementia due to Huntington's disease, dementia due to other general medical conditions (eg, subdural hematoma, normal pressure hydrocephalus, brain tumor, endocrine disorders,

[a] Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*. 2015;27:7–17.

<table>
<tr><td></td><td>nutritional disorders, or infections), dementia due to multiple diseases, and dementia not otherwise specified.
• Patients diagnosed with delirium between 30 days before the screening examination and baseline evaluation according to DSM-5.
• Patients diagnosed with any of the following disorders according to DSM-5:
– Schizophrenia spectrum and other psychotic disorders
– Bipolar and related disorders
– Major depressive disorder
However, patients who have major depressive disorder but whose condition is stable and asymptomatic within 30 days before the screening examination may be included. In regard to patients whose condition has been stabilized by medication, it should be noted that the use of antidepressants is prohibited from 7 days before baseline evaluation up to the completion of the examinations scheduled at the completion or discontinuation of IMP administration.</td></tr>
<tr><td>Trial sites:</td><td>Approximately 120 sites in Japan</td></tr>
<tr><td>Investigational medicinal products, dose, dosage regimen, treatment period, formulation, mode of administration:</td><td>The IMP will be administered orally as one tablet once a day for 10 weeks. The doses of brexpiprazole for each group are as follows:
<table>
<tr><th>Group</th><th>Day 1–7</th><th>Day 8–14</th><th>Day 15–70</th></tr>
<tr><td>Brexpiprazole 2 mg group</td><td>0.5 mg</td><td>1 mg</td><td>2 mg</td></tr>
<tr><td>Brexpiprazole 1 mg group</td><td>0.5 mg</td><td>1 mg</td><td>1 mg</td></tr>
<tr><td>Placebo group</td><td>0 mg</td><td>0 mg</td><td>0 mg</td></tr>
</table>
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).</td></tr>
<tr><td>Trial assessments:</td><td>Efficacy: Cohen-Mansfield Agitation Inventory (CMAI), [redacted] Clinical Global Impression–Severity of Illness (CGI-S), and CGI-Global Improvement (CGI-I)
Safety: Adverse events, laboratory tests, 12-lead electrocardiogram, vital signs, body weight, physical examination, pregnancy test, Drug-Induced Extrapyramidal Symptoms Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Sheehan Suicidality Tracking Scale
Pharmacokinetics: Blood sampling for the measurement of the plasma drug concentration
Screening and other tests: Mini-Mental State Examination, height, medications and therapies, blood sampling for the evaluation of pharmacogenomics, blood sampling for DNA storage, blood sampling for biomarker exploration samples storage, Alzheimer’s Disease Cooperative Study–Activities of Daily Living, and EuroQol 5-dimension 5-level health questionnaire</td></tr>
</table>

Criteria for evaluation	**Primary endpoint:** Change in CMAI total score from baseline to Week 10 **Secondary endpoints:** • Changes in CMAI subscales (Aggressive Behavior, Physically Non-aggressive Behavior, and CMAI Verbally Agitated Behavior) from baseline to Week 10 • Change in CGI-S from baseline to Week 10 • CGI-I at Week 10
Statistical methods:	**Primary endpoint:** The primary analysis will be conducted on the full analysis set by using mixed models for repeated measures analysis on the basis of the observed cases data set. For the analysis model, the treatment group (brexpiprazole 1 mg group, brexpiprazole 2 mg group, or placebo group), time point (Weeks 2, 4, 6, 8, or 10), medical care category (hospitalized or outpatient), prior use of antipsychotics (yes or no), and interaction between treatment group and time point will be included as factors, the baseline and interaction between the baseline and time point will be included as covariates, and the error variance and covariance structure will be unstructured. The Kenward–Roger method will be used to determine the degrees of freedom. Between-group comparison will be performed by calculating the difference of the least squares mean between each of the brexpiprazole groups and the placebo group at Week 10. The fixed sequence procedure will be used to adjust the multiplicity of testing due to the performance of two comparisons (ie, the brexpiprazole 1 mg group versus the placebo group and the brexpiprazole 2 mg group versus the placebo group) to control the overall type I error rate. Initially, the brexpiprazole 2 mg group will be compared with the placebo group. Only if the difference is statistically significant at a significance level of 5% (two sided), the brexpiprazole 1 mg group will be compared with the placebo group at a significance level of 5% (two sided). The least squares mean for each treatment group and the difference of the least squares mean between each brexpiprazole group and the placebo group, as well as their two-sided 95% confidence intervals, will be calculated at each time point. **Rationale for setting the target sample size:** In Trial 331-12-283, which was performed outside Japan, the 2 mg fixed-dose group showed superiority over the placebo group in patients with aggressive behavior at baseline, thus suggesting that it may also be the optimum dose for Japanese patients. Efficacy was not observed in the 1 mg fixed-dose group, but in Trial 331-12-284, the efficacy of a dose less than 2 mg was suggested by the results

	obtained in patients from the flexible-dose (0.5 to 2 mg) group, who had aggressive behavior at baseline. In this trial, a power of detection ≥ 80% will be achieved for comparison between the placebo group and the 1 mg group to allow evaluation of superiority over the placebo group if equivalent efficacy is demonstrated in the 1 and 2 mg groups. For comparison between the 2 mg group (possible optimum dose) and the placebo group, a more sufficient power of detection will be obtained by changing the randomization ratio. In this trial, it is assumed that the difference between the 2 mg group and the placebo group in the change in the CMAI total score from baseline to Week 10 is −5.35, and the standard deviation (calculated from the standard error of the difference between the 2 mg and placebo groups and the number of subjects at baseline) is 15.06 on the basis of the results of Trial 331-12-283. By setting the number of subjects in the 2 mg group, 1 mg group, and placebo group as 148, 111, and 148, respectively (randomization ratio of 4:3:4), the power of detection is 86.1% for the comparison between the 2 mg group and the placebo group and is 80.5% for the comparison between the 1 mg group and the placebo group in a test with a significance level of 5% (two sided). On the basis of the above considerations, the number of subjects will be set at 148 in the 2 mg group, 111 in the 1 mg group, and 148 in the placebo group (randomization ratio of 4:3:4).
Trial duration:	August 2018 to June 2023 (planned) The duration of participation in the trial by each subject will be up to 20 weeks.

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List of Abbreviations and Definitions of Terms

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
ANCOVA	Analysis of covariance
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
CMH	Cochran Mantel Haenszel
CPK	Creatine phosphokinase
CYP	Cytochrome P450
D_2	Dopamine D_2
DBP	Diastolic blood pressure
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
EDTA	Ethylenediaminetetraacetic acid
EQ-5D-5L	EuroQol 5-dimension 5-level health questionnaire
FAS	Full analysis set
FT_4	Free thyroxine
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCV Ab	Hepatitis C virus antibodies
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
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

Abbreviation	Definition
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
MMRM	Mixed models for repeated measures
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]
[redacted]	[redacted]
[redacted]	[redacted]
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OC	Observed cases
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
SBP	Systolic blood pressure
S-STS	Sheehan Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WOCBP	Women of childbearing potential
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]

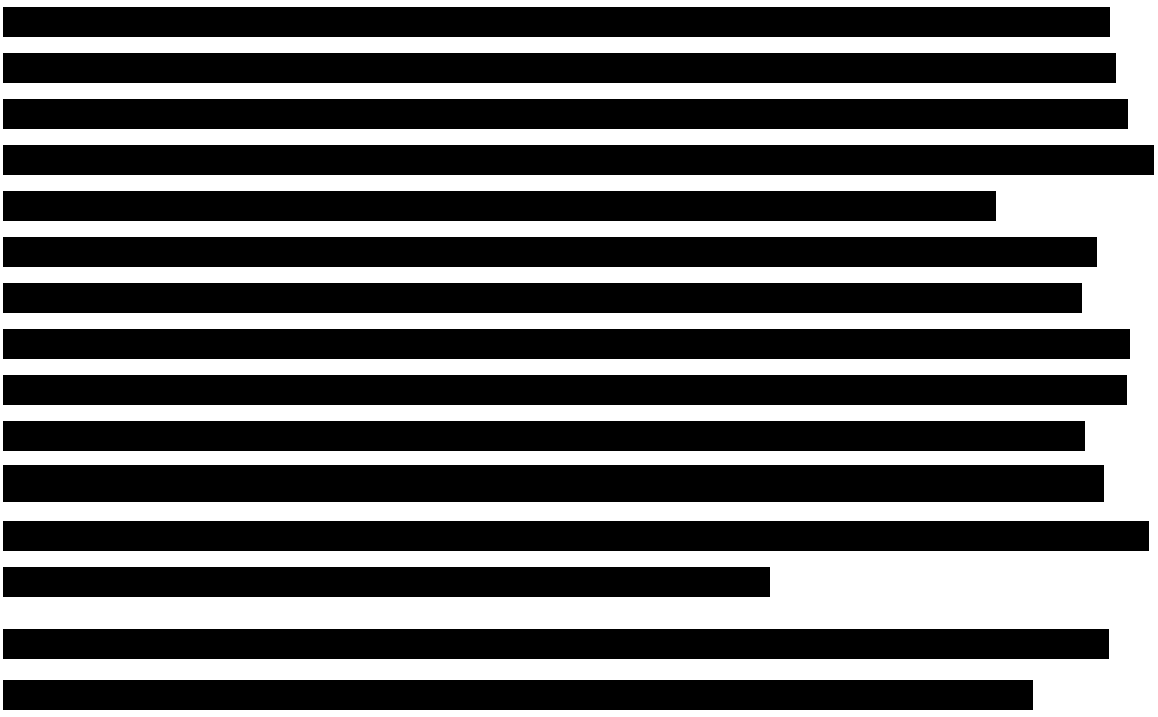
Symptoms of dementia of the Alzheimer's type are categorized into core symptoms such as memory impairment and impaired cognitive function and peripheral symptoms.[2] Peripheral symptoms are referred to as the behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms, and agitation 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 this clinical trial.

1.2 Nonclinical Data

[redacted]

1.3 Clinical Data

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Table 1.3.1.1-1 [redacted]

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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.

Based on the results of the 2 overseas confirmatory trials in agitation associated with dementia of the Alzheimer's type (Trial 331-12-283 and Trial 331-12-284), and because

the PK of brexpiprazole is not affected by ethnicity, it is considered that brexpiprazole will also show efficacy in Japanese patients with agitation associated with dementia of the Alzheimer's type.

In the overall population of Trial 331-12-284, no statistically significant differences were noted in the flexible-dose brexpiprazole group compared with the placebo group, but the results of an additional analysis showed the efficacy of brexpiprazole in patients with aggression.

On the basis of these findings, a multicenter, placebo-controlled, randomized, double-blind, parallel-group comparison trial to verify the superiority of brexpiprazole over placebo, evaluate the safety of brexpiprazole, and confirm an optimal dose in Japanese patients with aggression in agitation associated with dementia of the Alzheimer's type was planned. The doses of brexpiprazole were determined with reference to the data of the 2 overseas trials, and two doses were selected: a dose of 2 mg, which showed a statistically significant improvement compared with the placebo group in Trial 331-12-283 and might be an optimal dose in Japanese patients, and a dose of 1 mg to obtain the dose-response relationship in Japanese patients. Duration of treatment was set to 10 weeks.

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 disorder, cardiac disorder, pneumonia, and other infections, which were the causes of death associated with atypical antipsychotics, were established to minimize the risk to subjects during the trial and an Independent Data Monitoring Committee (IDMC) was established to monitor safety during the trial, as measures to ensure subject safety.

Since there are no drugs indicated for "agitation associated with dementia of the Alzheimer's type" in Japan, obtaining marketing approval for the indication through this trial would contribute to medical practice by providing another therapeutic option.

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

2.2 Rationale for CYP2D6 Genetic Testing and DNA Storage

The metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 according to in vitro metabolism studies, and CYP2D6 is known to have multiple genotypes with different enzyme activities. It has been clarified that CYP2D6 genotypes affect the pharmacokinetics of brexpiprazole. Therefore, the examination of CYP2D6 genotypes will be performed in this trial to investigate the influence of CYP2D6 genotypes on the safety and efficacy of brexpiprazole,

[redacted]

2.3 Rationale of Sample Storage for Biomarker Exploration

[redacted]

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2.4 Trial Objectives

The objective of the trial is 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 patients who require medication, to investigate the safety of brexpiprazole, and to identify the optimum dose.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison 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 a prospective subject (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 caregivers using the explanatory materials and informed consent form (ICF) and obtain written consent for

participation in the trial from the patient (or their legally acceptable representatives) and caregivers. The subject's clinical course will be followed in the same environment (see Section 3.4.2 Inclusion Criteria, 4) such as hospitalization in the same medical facility, institutionalization in the same care facility, and continued care at home from at least 3 weeks before baseline evaluation up to the completion of the examinations scheduled at the completion or discontinuation of IMP administration. After obtaining consent from the patient (or their legally acceptable representatives) and caregiver, the investigator or subinvestigator will perform the specified observations, tests, and investigations to confirm the subject's eligibility before IMP allocation. Subjects who are judged to be eligible in the screening examination and baseline evaluation will be randomized to the brexpiprazole 1 mg, brexpiprazole 2 mg, or placebo group. The IMP allocation will be performed using a dynamic allocation method to minimize bias in background factors (medical care category, prior use of antipsychotics, CMAI total score in baseline assessment) among the treatment groups. Duration of IMP treatment is 10 weeks. The subject will receive brexpiprazole or placebo for 10 weeks according to Section 3.2 Trial Treatments, and undergo periodic observations, tests, and investigations to assess efficacy and safety. 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 of each subject is from the date of informed consent to the end date of follow-up observation. If subjects have transitioned to the extension trial and commenced IMP administration, follow-up observation will not be performed. In such a case, the trial period is until the end date of evaluation at Week 10 (Day 71).

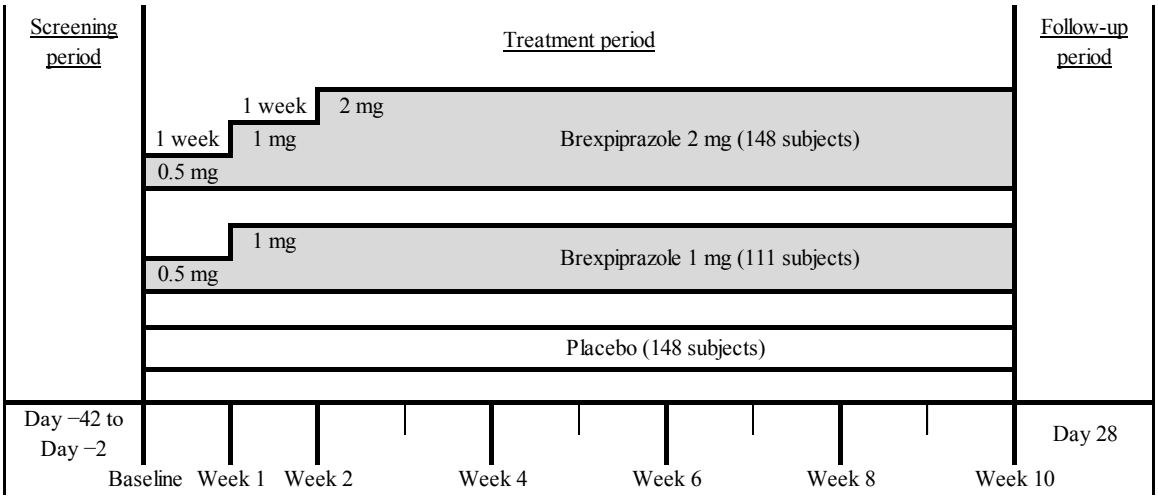

Figure 3.1-1 Trial Design

Follow-up observation will not be performed for subjects who have transitioned to the extension trial and commenced IMP administration.

3.2 Trial Treatments

3.2.1 Dosing and Regimen

The IMP will be administered orally as one tablet once a day for 10 weeks. The doses of brexpiprazole for each group is shown in Table 3.2.1-1. 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. Dose reduction is not allowed during the trial, and if there are tolerability issues, administration of the IMP will be discontinued.

Table 3.2.1-1 Doses of IMPs

Group	Day 1–7	Day 8–14	Day 15–70
Brexpiprazole 2 mg	0.5 mg	1 mg	2 mg
Brexpiprazole 1 mg	0.5 mg	1 mg	1 mg
Placebo	0 mg	0 mg	0 mg

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)

3.2.2 Rationale for Dosing and Regimen

Doses and regimen were determined on the basis of the results of the 2 overseas trials (Trial 331-12-283 and Trial 331-12-284), as no significant differences due to ethnicity have been observed in the PK of brexpiprazole.

In Trial 331-12-283, the brexpiprazole 2 mg group showed a statistically significant improvement in change from baseline in CMAI total score compared with the placebo group. In patients with aggression in the baseline evaluation in Trial 331-12-283, improvement in the 2 mg group was greater than that in the placebo group.

These findings suggested that 2 mg might be the optimal dose in Japanese patients. Therefore, 2 mg was selected to verify superiority over the placebo group.

On the other hand, although the 1 mg group in Trial 331-12-283 did not demonstrate improvement greater than that in the placebo group among either the overall population or patients with aggression, in Trial 331-12-284, which was conducted using flexible doses, the 0.5 to 2 mg group showed greater efficacy than the placebo group among patients with aggression, raising the possibility that doses lower than 2 mg might be effective. On the basis of these findings, a 1 mg group was included so that information on the dose-response relationships in Japanese patients could be obtained and superiority over the placebo group can be confirmed if the 1 mg group demonstrates efficacy similar to that in the 2 mg group.

In the 2 overseas trials, a dose titration method with a low starting dose and gradual dose increase was used in consideration of safety in elderly subjects, who were the target subjects of those trials. In the 2 overseas trials, a dose titration method in which dosing started from 0.25 mg and was increased to the maximum dose of 2 mg over 4 weeks was used, and no apparent safety problems were noted up to 2 mg. Since this trial will be conducted in patients with aggression who have a strong need for medication among patients with agitation, a dose titration method in which the dose will be started from 0.5 mg, increased to 1 mg at Week 1 (after evaluation at Week 1 [Day 8]) and to 2 mg at Week 2 (after evaluation at Week 2 [Day 15]) was selected to reach 2 mg (which may become the optimal dose) as quickly as possible. The starting dose of 0.5 mg is 1/2 of the starting dose (1 mg) of brexpiprazole in schizophrenia, and conforms to the precautions and principles for medication in elderly patients with dementia described in the Practice Guideline for Dementia 2017[26]: “depending on the type of medication, starting treatment at lower doses such as 1/2 to 1/4 of the doses recommended for younger patients should be considered.” Trial visits were set to 1 week after the start of trial treatment before a dose increase to 1 mg and 2 weeks after the start of trial treatment before a dose increase to 2 mg, and dose titration will be performed with confirmation of subject safety.

The dosing regimen is oral administration once daily based on the PK and the 2 overseas trials.

3.2.3 Rationale for Duration of Treatment

Duration of treatment was determined on the basis of the clinical position of brexpiprazole therapy and taking the results of the 2 overseas trials into consideration.

Brexpiprazole is positioned as symptomatic treatment for patients who require medication. The Practice Guideline for Dementia 2017[17] states that atypical antipsychotics including brexpiprazole "should not be continued without a compelling reason even if their efficacy is recognized." Therefore, long-term administration as maintenance therapy after improvement of symptoms is not considered.

However, in a repeated-dose trial in Japanese patients with schizophrenia, steady-state was reached from Day 10 onward, and thus a certain period is necessary to confirm if efficacy is sufficient after increasing the dose to 2 mg.

In the 2 overseas trials, after the brexpiprazole dose had been increased to 2 mg (maximum dose), brexpiprazole was continued for 8 weeks (12 weeks in total, including the 4-week dose titration period) until sufficient efficacy was confirmed, and the efficacy of brexpiprazole 2 mg had been demonstrated. Therefore, as in the 2 overseas trials, it was decided that for this trial administration would be continued for 8 weeks after reaching the maximum dose of 2 mg. As described in Section 3.2.2 Rationale for Dosing and Regimen, as administration of brexpiprazole will reach the maximum dose of 2 mg at 2 weeks, a total of 10 weeks was set as the duration of treatment.

3.3 Trial Population

3.3.1 Number of Subjects and Trial Population

A total of 407 male and female patients (brexpiprazole 2 mg, 148 subjects; brexpiprazole 1 mg, 111 subjects; placebo 148 subjects) with agitation associated with dementia of the Alzheimer's type who require medication will be enrolled in the trial.

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 informed consent form (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[27] 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).

For CYP2D6 genetic testing, DNA storage, and biomarker sample storage, a separate ICF will be used for explanation, and written informed consent will be obtained from subjects (or their legally acceptable representatives) on their voluntary decision in a similar manner. CYP2D6 genetic testing is mandatory, and if subjects (or their legally acceptable representatives) have not consented to CYP2D6 genetic testing, they cannot participate in the trial. On the other hand, DNA storage and biomarker sample storage are optional, and the refusal of subjects (or their legally acceptable representatives) to allow DNA storage and/or biomarker sample storage will not affect trial participation.

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 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 meet both of the following diagnostic criteria: • Diagnosis of "Dementia due to Alzheimer's Disease" according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). • Diagnosis of "Probable Alzheimer's Disease" according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).
3	Patients who are ≥ 55 and ≤ 90 years of age at the time of obtaining informed consent.
4	Patients who can be followed in the same environment (as described below) from at least 3 weeks before baseline evaluation up to the completion of the examinations scheduled at the completion or discontinuation of investigational medicinal product (IMP) administration. • Patients who will be hospitalized in the same medical facility. • Patients who will be institutionalized in the same care facility. • Patients who will continue to receive care at home. For patients receiving day care or day service, those patients who will visit the same care facility at the same frequency during the above-mentioned period will be included.
5	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.

Table 3.4.2-1 Inclusion Criteria	
6	Patients with a Mini-Mental State Examination (MMSE) total score of ≥ 1 to ≤ 22 at screening.
7	[redacted]
8	Patients who have agitation that interferes with daily activities and is persistent/recurs frequently during the 2 weeks each before the screening examination and baseline evaluation. Agitation is defined according to the "Consensus provisional definition of agitation in cognitive disorders" from the International Psychogeriatric Association (IPA).[a]
9	Patients who have shown verbal aggression or physical aggression for 3 times or more during the 2 weeks before baseline evaluation. Examples of verbal aggression and physical aggression include the following symptoms in the "Consensus provisional definition of agitation in cognitive disorders" of IPA.[a] • Verbal aggression: yelling, speaking in an excessively loud voice, using profanity, screaming, shouting, etc. • Physical aggression: grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, self-hitting, slamming doors, tearing things, destroying property, etc.
10	Patients who show significant improvement (of two grades or more) in CGI-S from screening to baseline evaluation.
11	Patients who show inadequate response to nonpharmacological therapy for agitation associated with dementia of the Alzheimer's type or who are otherwise judged to be in need of pharmacological therapy.
12	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).

[a] Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*. 2015;27:7–17.

[Rationale for inclusion criteria]

1. This criterion is specified for ethical considerations.
2. This criterion is specified because DSM-5 is recommended in the Practice Guideline for Dementia 2017, and NINCDS-ADRDA is widely used in clinical trials for dementia of the Alzheimer's type. These standards have been established as the diagnostic standards for dementia of the Alzheimer's type.
3. Although it is known that most patients with dementia of the Alzheimer's type are above the age of 65, there is a small number of patients below the age of 65. Past trials have suggested that patients of ages 55 and above may be suitable for such trials. Thus, the lower age limit was set at 55. On the other hand, given that patients aged over 90 could interfere with the evaluations set for this trial and in consideration of safety, [20] the upper age limit was set at 90.
4. These patients were included because the target subjects of this trial, namely, patients with agitation associated with dementia of the Alzheimer's type, may not necessarily be hospitalized patients but may be receiving care at nursing homes or at home. This criterion was also set for the appropriate assessment of the safety and efficacy of brexpiprazole.

5 to 12. These criteria are specified for the appropriate assessment of the safety and efficacy of brexpiprazole in the treatment of agitation associated with dementia of the Alzheimer's type.

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 have dementia or memory impairment other than dementia of the Alzheimer's type, such as the following: • Frontotemporal dementia • Lewy body dementia • Vascular dementia • Dementia secondary to head trauma • Substance-induced persistent dementia • Dementia due to human immunodeficiency virus infection • Dementia due to prion disease • Dementia due to Parkinson's disease (including Parkinsonian diseases such as progressive supranuclear palsy and basal ganglion degeneration) • Dementia due to Huntington's disease • Dementia due to other general medical conditions (eg, subdural hematoma, normal pressure hydrocephalus, brain tumor, endocrine disorders, nutritional disorders, or infections) • Dementia due to multiple diseases • Dementia not otherwise specified
2	Patients diagnosed with delirium between 30 days before the screening examination and baseline evaluation according to DSM-5.
3	Patients diagnosed with any of the following disorders according to DSM-5: • Schizophrenia spectrum and other psychotic disorders • Bipolar and related disorders • Major depressive disorder However, patients who have major depressive disorder but whose condition is stable and asymptomatic within 30 days before the screening examination may be included. In regard to patients whose condition has been stabilized by medication, it should be noted that the use of antidepressants is prohibited from 7 days before baseline evaluation up to the completion of the examinations scheduled at the completion or discontinuation of IMP administration (see Section 4.1 Prohibited Medications).
4	Patients with psychological symptoms or behavioral problems clearly due to other diseases or a drug substance.
5	• Patients with a complication or history of stroke or transient ischemic attack. • Patients with a complication of pulmonary embolism. However, patients with asymptomatic cerebral infarction or uncertain transient ischemic attack may be included. In regard to history of stroke or transient ischemic attack, a patient may be included if a medical monitor checks the patient's symptoms and judges that they will have no influence on the efficacy and safety of the IMP.
6	Patients with a complication or history of convulsive disorders, such as epilepsy, not including patients with febrile seizures, posttraumatic seizures, alcohol withdrawal seizures, or other seizures.
7	Patients with clinically significant nervous, hepatic, renal, metabolic, immunological, hematological, cardiovascular, pulmonary, or digestive abnormality.
8	Patients with heart failure of New York Heart Association Class III or higher.

Table 3.4.3-1 Exclusion Criteria	
9	Patients who require pharmacological therapy for arrhythmia or ischemic heart disease, not including patients for whom the investigator or subinvestigator judges pharmacological therapy to be the primary prevention of ischemic heart disease.
10	Patients who test positive for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibodies (HCV Ab).
11	Patients with a diagnosis of substance use disorder according to DSM-5, constituting substance abuse or substance dependence, including alcohol and benzodiazepines (but not including caffeine or nicotine), within 6 months prior to the acquisition of informed consent
12	Patients with a complication or history of neuroleptic malignant syndrome, tardive dyskinesia, paralytic ileus, or rhabdomyolysis
13	Patients who are unable to take oral medication due to severe dysphagia
14	Patients meeting any of the following criteria: • Patients with type 1 diabetes mellitus or patients with type 2 diabetes mellitus being treated with insulin • Patients with type 2 diabetes mellitus who have not been maintained on a stable regimen of antidiabetic medication(s) or have not undergone diet/exercise therapy for at least 28 days prior to screening • Patients meeting either of the following criteria for poor blood glucose control at screening (assessed on the basis of the results from the central 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
15	Patients whose QTcF values based on the results from the central ECG laboratory at screening match the following criteria (if the criteria are matched in 2 out of 3 measurements), not including ventricular pacing: • Men: ≥ 450 ms; women: ≥ 470 ms
16	Patients whose (supine or sitting) blood pressure values at screening match the following criteria: • Poorly controlled hypertension (diastolic blood pressure [DBP] > 95 mmHg)
17	Patients meeting any of the following criteria at screening: • Hypotension with symptoms • Orthostatic hypotension in which blood pressure after at least 3 minutes of standing is ≥ 30 mmHg lower for systolic blood pressure (SBP) or ≥20 mmHg lower for DBP compared with pressures in the supine position before standing
18	Patients with the following abnormal laboratory test values at screening (assessed on the basis of the results from the central 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
19	Patients whose body weight at screening or baseline evaluation is < 30 kg

Table 3.4.3-1 Exclusion Criteria	
20	Patients whose Sheehan Suicidality Tracking Scale (S-STS) score at screening or baseline evaluation matches 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
21	The following patients falling under the contraindications in the package insert for REXULTI®: • 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®
22	Patients with thyroid disease (not including patients whose condition has been kept stable via drug therapy for at least 3 months prior to the acquisition of informed consent) or patients who show abnormal values for thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in the screening examination
23	Patients who are likely to require any prohibited medications during the trial period
24	Patients who have previously taken brexpiprazole
25	Patients who have previously received antipsychotic medication for agitation associated with dementia of the Alzheimer's type and whose condition has been judged to be treatment resistant. Cases in which treatment has to be stopped owing to adverse events are not counted as treatment resistant.
26	Patients who have undergone disease-modifying treatment for dementia of Alzheimer's type (eg, amyloid β vaccine) within 6 months before the start of IMP administration
27	Patients who have taken any investigational drug within 30 days prior to informed consent
28	Patients who are bedridden and require assistance for excretion, eating, and changing clothes
29	Women who are nursing before the administration of IMP or have a positive pregnancy test result at screening
30	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.
31	Patients who otherwise were judged by the investigator or subinvestigator to be unsuitable for participation in the trial

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 4 These criteria are specified to exclude patients who would be inappropriate for this trial.
5 to 21 These criteria are specified in view of safety.
22 to 27, 31 These criteria are specified for the appropriate assessment of safety and efficacy.
28 This criterion is specified for the appropriate assessment of efficacy and in view of safety.[20]
29, 30 These criteria are specified in consideration of safety, as the safety of brexpiprazole during pregnancy or while breastfeeding has not yet been established.

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, starting from 14 days before the day of baseline evaluations to 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.

To the extent possible, the same main caregiver will respond to queries on the trial evaluation items from 14 days before the day of baseline evaluations to the completion of examinations scheduled at the completion or discontinuation of IMP administration. If the main caregiver is unable to respond to queries, a substitute caregiver is allowed to respond to queries on the trial evaluation items. However, to the extent possible, queries on the trial evaluation items at the time of baseline evaluation and at the completion or discontinuation of IMP administration should be answered by the person who was designated as the main caregiver at the start of the trial. A substitute caregiver should be able to obtain 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. Queries at the conclusion of follow-up observation to be performed 28 days after the completion or discontinuation of IMP administration will also be answered by a caregiver who is in charge of the patient's care and is able to provide patient information required for evaluations.

3.6 Endpoints

3.6.1 Primary Endpoint

The primary endpoint is change in CMAI total score from baseline to Week 10.

The CMAI is a scale to assess the frequency of specific agitation symptoms. The Practice Guideline for Dementia 2017 recommends the NPI, Behavioral Pathology in Alzheimer's Disease, and CMAI for assessment of BPSD. The CMAI evaluates the frequency of occurrence of specific agitation for the preceding 2 weeks and is used globally for assessment of agitation.[22,28] Therefore, the CMAI is the most appropriate scale for evaluating the efficacy of brexpiprazole for agitation associated with dementia of the Alzheimer's type, which is the primary objective of the trial. Furthermore, the CMAI was adopted as the primary endpoint in the 2 overseas trials (Trial 331-12-283 and Trial 331-12-284).

3.6.2 Secondary Endpoints

- Changes in CMAI subscales (Aggressive Behavior, Physically Non-aggressive Behavior, and CMAI Verbally Agitated Behavior) from baseline to Week 10
- Change in Clinical Global Impression–Severity of Illness (CGI-S) from baseline to Week 10
- Clinical Global Impression–Global Improvement (CGI-I) at Week 10

3.6.3 Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.6.4 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)

3.6.5 Pharmacokinetic Endpoint

Plasma concentrations of OPC-34712 at Week 10 of brexpiprazole administration

3.6.6 Pharmacogenomic Endpoint

CYP2D6 genotype

3.6.7 Other Endpoints

- Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)
- MMSE
- EuroQol 5-dimension 5-level health questionnaire (EQ-5D-5L)

3.7 Measures to Minimize/Avoid Bias

Subjects who meet all the inclusion criteria and do not fall under any of the exclusion criteria will be randomly assigned to the brexpiprazole 1 mg/day group, the brexpiprazole 2 mg/day group, or placebo group at a randomization ratio of 3:4:4. The IMP allocation will be performed using a dynamic allocation method. The details of the randomization method will be described in a separately produced procedural guide for dynamic allocation.

This is a double-blind trial. The IMP allocation manager will prepare a “Table of randomization scheme and codes” (hereinafter randomization table) and conduct IMP coding according to the operating procedures for randomization. The IMP allocation manager will prepare an emergency code list for emergencies, such as when an SAE occurs.

The treatment assignment code will be revealed to neither the subject (including any representatives or caregivers) nor the investigator. The sponsor’s staff involved in the

trial (except for those of the Department of Pharmacovigilance [PV department]), including contract research organizations (excluding the bioanalytical laboratory, genetic analysis laboratory, and IDMC), will also remain blind to the treatment assignment codes for the duration of the trial. Prior to the start of the trial, those who are involved in packaging the IMP and the sponsor will confirm that the IMP is not identifiable. The randomization table will be strictly retained until unblinding is performed after finalization of all the case report forms (CRFs) and database.

The emergency code break information will be managed by the IWRS until the completion of the trial. In the event that a subject has a medical emergency and the knowledge of the treatment assignment code is necessary for treatment, the emergency key may be opened for the subject in question (see Section 5.6 Procedure for Breaking the Blind).

The results of CYP2D6 genotyping and plasma drug concentration measurements should not be disclosed until unblinding at the end of the trial. The CYP2D6 genotyping and plasma drug concentration measurements should be performed at the designated laboratories and not at the clinical laboratories of the trial sites.

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[a]
	Day -42 to Day -2	Baseline evaluation (Day 1)[b]	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 10 (Day 71) At discontinu-ation	28 days after completion/ discontinu-ation
Same environment	Before Day -21 ←----------→								
Informed consent	•								
Subject background information	•								
Subject diary	From Day -14 ←----------→								
Inclusion/exclusion criteria	•	•							
Compliance status			•	•	•	•	•	•	
Efficacy endpoints									
CMAI		•		•	•	•	•	•	
CGI-S	•	•		•	•	•	•	•	
CGI-I				•	•	•	•	•	
[redacted][c]	•[d]	•			•			•	
[redacted][e]		•			•			•	
Safety endpoints									
Adverse events	←----------→								
Confirmation of medications and therapies	←----------→								
Height	•								
Body weight	•	•						•	
Physical examination	•	•	•	•	•	•	•	•	
Laboratory tests	•	•[f]			•			•	
Vital signs	•[g]	•	•	•	•	•	•	•	
12-lead ECG	•[h]	•		•	•			•	
Pregnancy test[i]	•							•	
DIEPSS		•	•	•	•	•	•	•	•
AIMS		•						•	•
BARS		•						•	•
S-STS	•	•			•			•	
Other endpoints									
ADCS-ADL		•						•	•
MMSE	•							•	•
EQ-5D-5L (subject and caregiver)		•						•	

Table 3.8-1 Schedule of Assessments

Item	Screening Period	Treatment Period							Follow-up Period[a]
	Day -42 to Day -2	Baseline evaluation (Day 1)[b]	Week 1 (Day 8)	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 10 (Day 71) At discontinu-ation	28 days after completion/ discontinu-ation
Blood sampling for measurement of plasma drug concentration								•[j]	
Blood sampling for CYP2D6 genotyping		•[k]							
Blood sampling for DNA storage					•[l, m]				
Blood sampling for biomarker sample storage		•[l]							

[a]Follow-up observation will not be performed for subjects who have transitioned to the extension trial and commenced IMP administration.

[b]All baseline observations, tests, and evaluations will be performed on the day before the start of IMP administration (Day -1) and the day of starting IMP administration (Day 1). CMAI, CGI-S, [redacted], and [redacted] must be performed on the same day.

[c][redacted].

[d][redacted].

[e][redacted]

[f]Performing laboratory tests at baseline is not necessary if fasting blood sample collection was performed at screening and within 14 days before baseline evaluation.

[g]Blood pressure and pulse rate will be measured in the order of supine, sitting, and standing positions.

[h]Eligibility will be assessed based on consecutive triplicate ECG measurements (central reading). The third measurement can be omitted if neither the first nor second measurement (central reading) meets the exclusion criteria.

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

[j]Blood sampling will be performed before IMP administration if the IMP is administered in Week 10 but does not need to be performed at the time of discontinuation.

[k]If blood sampling is not performed for any other test item or for some reason cannot be performed at the time of baseline evaluation, or if blood resampling is necessary, blood sampling will be performed during the trial period.

[l]Optional

[m]If for some reason it is not possible to perform blood sampling at this time or if blood resampling is necessary, blood sampling will be performed during the trial period.

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

Test Point	Base Date	Allowable Time Window From the Base Date
Screening period	At the start of screening	Day -42 to Day -2
Baseline evaluation date	Day 1	Day -1 or 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 78
Follow-up period[a]	28 days after the final administration of IMP	23 to 35 days after the final administration of IMP

[a]Follow-up observation will not be performed for subjects who have transitioned to the extension trial and commenced IMP administration.
The date of starting IMP administration is designated as Day 1.
All baseline observations, tests, and evaluations will be performed on the day before the start of IMP administration (Day -1) and the day of starting IMP administration (Day 1). CMAI, CGI-S, [redacted], and [redacted] must be performed on the same day.

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 (eg, physical restraint [including isolation] and transfer to a different ward or room, staying out overnight, and outings during hospitalization/institutionalization) 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 Efficacy Assessments to Section 3.8.5 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 Screening Period

To confirm that the subject meets the inclusion criteria and does not fall under the exclusion criteria, observations, tests, and assessments will be performed, and the results will be recorded after the date of informed consent but before the baseline assessment.

The caregivers will be provided with the subject diary for the period up to the baseline evaluation and be given an explanation on how to complete the subject diary, and instructed to record the required information in the subject diary from 14 days before the baseline evaluation until the baseline evaluation. 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).

The investigator or subinvestigator will record subject information related to the enrollment criteria, which had been collected during screening, in the eligibility form specified by the sponsor and submit to the medical monitor for confirmation of the subject's eligibility. The medical monitor will confirm the content of the eligibility form, and if there is any doubt regarding the subject's eligibility, he/she will consult with the investigator or subinvestigator to determine the subject's eligibility before the baseline examination.

The investigator or subinvestigator will investigate subject background and other information as follows and record it in the source document and CRF.

- Date of visit
- Date of informed consent by the subject (or their legally acceptable representatives) and caregivers
- Subject background information
  - Sex, date of birth, race, ethnicity, and trial country
  - Possibility of getting pregnant in women of childbearing potential (WOCBP) (see Section 5.5 Pregnancy) (if there is no childbearing potential, record the reason)
  - Diagnosis of dementia of the Alzheimer's type (diagnostic criteria of DSM-5 and NINCDS-ADRDA)
  - Timepoint of onset of dementia of the Alzheimer's type
  - Timepoint of diagnosis of dementia of the Alzheimer's type
  - Timepoint of onset of agitation associated with dementia of the Alzheimer's type
  - Complications
  - Medical history (for the 2 years preceding informed consent; however, medical history related to the inclusion/exclusion criteria is not limited to the preceding 2 years.)
  - 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)
  - Prior medications and therapies

- Confirmation of eligibility

3.8.1.2 Day of Baseline Examination

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 perform the observations, tests, and assessments shown in Table 3.8-1 and the investigation of the following items and record the results.

- Date of visit
- Confirmation of eligibility

3.8.1.3 Randomization

The investigator or subinvestigator will select subjects who meet the inclusion criteria and do not fall under the exclusion criteria on the basis of the results of the screening examination and baseline evaluation. For the clinical laboratory test and 12-lead ECG, the subject's eligibility will be judged on the basis of the results obtained by the central laboratory and central ECG laboratory at the time of screening.

The investigator or subinvestigator will enter information on eligible subjects in the IWRS. Subjects whose registration was confirmed in the IWRS will be randomized to the brexpiprazole 1 mg, brexpiprazole 2 mg, or placebo group using a dynamic randomization method to minimize bias between the treatment groups regarding the following background factors. The date of randomization and randomization number will be recorded in the CRF.

- Medical care category (inpatient or outpatient[a])
- Prior use of antipsychotics[b] (yes or no)
- CMAI total score (≥ 56 or < 56) in the baseline evaluation

[a]Subjects who are institutionalized or receiving care at home and visit the trial site as outpatients

[b]Receiving antipsychotics in the 6 months prior to the day of baseline evaluation will be considered as "yes."

The investigator or subinvestigator will provide the IMP and subject diary needed for the period up until the next assessment on the basis of the drug number assigned to the subject in the IWRS and give instructions to bring unused IMPs and the completed subject diary to the next assessment.

3.8.1.4 Seven Days After Administration (Week 1, Day 8) to Seventy Days After Administration (Week 10, Day 71)

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.

At visits where blood is collected for measurement of plasma drug concentrations, the date and time of last IMP administration will be recorded.

At visits from 7 days after administration (Week 1, Day 8) until 56 days after administration (Week 8, Day 57), the investigator or subinvestigator will provide the IMP and subject diary needed up until the next assessment on the basis of the drug number assigned to the subject in IWRS and give instructions to bring unused IMPs and the completed subject diary to the next assessment.

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. Follow-up observation will not be performed for subjects who have transitioned to the extension trial and commenced IMP administration.

3.8.2 Efficacy Assessments

The rater for each of the assessment items should refer to Section 3.8.9 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.

3.8.2.1 Cohen-Mansfield Agitation Inventory

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"

3.8.2.2 Clinical Global Impression–Severity of Illness

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.

3.8.2.3 Clinical Global Impression–Global Improvement

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

3.8.2.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.8.2.5 [redacted]

[redacted]

[redacted]

3.8.3 Safety Assessments

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

3.8.3.1 Adverse Events

Refer to Section 5 Reporting of Adverse Events.

3.8.3.2 Clinical Laboratory Assessments

In this trial, the clinical laboratory tests shown in Table 3.8.3.2-1 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 laboratory. For appropriate procedures for the collection, handling, and shipment

of samples, 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 3.8.3.2-1 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) Folate[a] Vitamin B_{12}[a] Endocrinology: Serum prolactin Insulin FT4[a] TSH[a] Immunology HBsAg[a] HCV Ab[a]

[a]Performed only at screening

3.8.3.3 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 screening examination, all the physical findings obtained on the evaluation day and up to the observation day will be recorded in the source document and CRF. From the baseline evaluation, only information on whether an observation occurred or not and 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.

3.8.3.4 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. In the screening examination, SBP, DBP, and pulse rate will be measured in the order of supine, sitting, and standing positions. The results, date and time of measurement will be recorded in the source document and CRF. Blood pressure and pulse rate will be measured in the order of supine, sitting, and standing positions after maintaining each position for at least 3 minutes. From the baseline evaluation, blood pressure and pulse rate will be measured in a sitting position. If the subject complained of symptoms of orthostatic hypotension before evaluation in or after the baseline evaluation, measurement should be performed in the supine and sitting positions in so far as possible in the order of the supine, sitting, and standing positions in the same manner as the screening examination.

3.8.3.5 Height and Body Weight

Height and 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 (body weight in increments of 0.1 kg, height in increments of 0.1 cm).

3.8.3.6 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. At screening, the subject's eligibility will be assessed based on consecutive triplicate ECG measurements (central reading) obtained during screening. ECG examination will be performed at appropriate intervals after the subject's resting state is confirmed. The third

measurement can be omitted if neither the first nor second measurement (central reading) meets the exclusion criteria (≥ 450 ms for men, ≥ 470 ms for women).

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/(RR interval)$^{1/2}$, QTcF = QT interval/(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.

3.8.3.7 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 screening 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.

3.8.3.8 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.

3.8.3.8.1 Drug-induced Extrapyramidal Symptoms Scale

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 subject's information from the previous assessment (baseline assessment will be based on the subject's information from the initial screening examination).

Nine items related to extrapyramidal symptoms:

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

3.8.3.8.2 Abnormal Involuntary Movement Scale

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"

3.8.3.8.3 Barnes Akathisia Rating Scale

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.

3.8.3.8.4 Sheehan Suicidality Tracking Scale

By using S-STS, the investigator or subinvestigator will assess suicidal attempt and behavior on the basis of 22 question items. At screening, assessment will cover the period spanning the previous 6 months, and for subsequent visits, the assessment will cover the period since the previous visit.

3.8.4 Pharmacokinetic Assessment, Pharmacogenomic Assessment, and Biomarker Exploration

The schedule for each of the assessment items is shown in Table 3.8-1.

3.8.4.1 Pharmacokinetic Assessment

Plasma brexpiprazole concentrations will be measured by validated high performance liquid chromatography/tandem mass spectrometry method. Metabolites that are not presented in the protocol may be measured on the basis of newly obtained information.

The bioanalytical laboratory will measure drug concentrations only for the samples collected from subjects in the brexpiprazole groups after recording the use of the randomization table. Access to the documents containing treatment assignment codes will be strictly controlled and will not be disclosed to anyone other than those who need them to perform trial-related activities in the opinion of the person responsible for drug concentration measurements. The bioanalytical laboratory will hold the results of the drug concentration measurements in strict confidence and submit an electronic file containing these results to the sponsor after unblinding. Therefore, there is no need to record the results of assessment in the source documents and CRF.

1) Timing of Blood Sampling
Blood samples will be collected before IMP administration if the IMP is administered in Week 10. The date and time of blood sampling and the date and time of the most recent IMP administration before blood sampling will be recorded in the source documents and the CRF.

2) Blood Samples for Pharmacokinetic Assessment
Details of the sample collection, handling, and shipping methods are provided in Appendix 1.

3.8.4.2 Pharmacogenomic Assessment

3.8.4.2.1 CYP2D6 Genetic Testing

CYP2D6 genotypes and phenotypes will be analyzed. CYP2D6 genetic testing is mandatory. [redacted]
The CYP2D6 genotype will be determined for each subject on the basis of the CYP2D6 genotyping table (Appendix 2). In addition, on the basis of the CYP2D6 genotype, the phenotype will be classified into the following 4 types: extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM), and unknown. In principle, the results of CYP2D6 genetic testing will not be disclosed to subjects.

The genetic analysis laboratory will extract DNA only from the blood samples of the brexpiprazole groups after recording the use of the randomization table. The blood samples collected from subjects in the placebo group will be discarded in accordance with the procedure specified by the genetic analysis laboratory. Access to the documents containing treatment assignment codes will be strictly controlled and will not be

disclosed to anyone except for those who need them to perform trial-related activities in the opinion of the person responsible for genetic testing. The genetic analysis laboratory will hold the results of CYP2D6 genetic testing in strict confidence and submit an electronic file containing these results to the sponsor after unblinding. Therefore, there is no need to record the results of the assessment in the source documents and CRF.

1) Timing of Blood Sampling

Blood samples will be collected before IMP administration on the day of baseline evaluation. If blood sampling is not performed for any other test item or for some reason cannot be performed at the time of baseline evaluation, or if blood resampling is necessary, blood sampling will be performed during the trial period. The date and time of blood sampling will be recorded in the source documents and the CRF.

2) Samples for CYP2D6 Genetic Testing

Details of the sample collection, handling, and shipping methods are provided in Appendix 1.

3.8.4.2.2 DNA Storage

[redacted]

[redacted]

[redacted]

3.8.4.3 Storage of Samples for Biomarker Exploration

[redacted]

[redacted]

[redacted]

3.8.5 Other Endpoints

The rater for each of the assessment items should refer to Section 3.8.9 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.

3.8.5.1 Alzheimer's Disease Cooperative Study–Activities of Daily Living

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 day. 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.

3.8.5.2 Mini-Mental State Examination

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"

3.8.5.3 EuroQol 5-Dimension 5-Level Health Questionnaire

The caregiver will assess the health of the subject and caregiver in relation to 5 health domains at the time of evaluation on a 5-level scale using the EQ-5D-5L. Health will be assessed using a 100 mm visual analogue scale (0 = the worst health imaginable, 100 = the best health imaginable).

In the subject assessment, the caregiver will evaluate the subject's health using the EQ-5D-5L proxy version and will record the results. In the caregiver self-evaluation, the caregiver will evaluate his/her own health using the EQ-5D-5L and record the results. The caregiver self-evaluation will be performed only when the caregiver in the baseline evaluation and the caregiver in subsequent evaluations are the same person.

[5 domains]

"Mobility," "self-care," "usual activities," "pain/discomfort," and "anxiety/depression"

3.8.6 Medications and Therapies

The investigator or subinvestigator will investigate medications and therapies administered during the periods below. 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.

- Antipsychotics: from 6 months before the date of baseline evaluation through to the trial end date
- Antidementia drugs: from 3 months before the date of baseline evaluation through to the trial end date
- Prohibited concomitant drugs other than antipsychotics and restricted concomitant drugs other than antidementia drugs: from 30 days before the date of informed consent or date of baseline evaluation, whichever is earlier, through to the trial end date
- Other medications and therapies: from the date of informed consent through to the trial end date

3.8.7 End of Trial

The end of the trial date is defined as the date of completion or discontinuation of the trial as recorded on the trial completion page or the date of last visit or contact or 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.

3.8.8 Independent Data Monitoring Committee

The IDMC will be established to avoid exposing subjects to all potential risks (including the risk of death) during the trial period and to ensure the safe conduct of the trial. The IDMC will meet regularly 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.

3.8.9 Raters

Table 3.8.9-1 shows persons who are authorized to evaluate each evaluation scale. While the [redacted], [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. For EQ-5D-5L, as described in Section 3.8.5.3 EuroQol 5-Dimension 5-Level Health Questionnaire, the caregiver will evaluate the subject and himself/herself.

For CMAI, the same rater will evaluate the same subject throughout the trial period. For CGI-S, CGI-I, DIEPSS, AIMS, BARS, S-STS, [redacted], [redacted], ADCS-ADL, and MMSE, the same rater will evaluate the same subject throughout the trial period whenever possible.

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

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

Table 3.8.9-1 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	○				
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

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with 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 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 therapies or is judged to be in need of prohibited drugs or therapies.
  - The subject requires a change in care environment[a] (for reasons other than AE occurrence) before the completion of the examinations at the end of IMP administration.
- 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

[a] A change in the environment under which the subject's condition is being followed, as specified in Inclusion Criterion 4 (see Section 3.4.2 Inclusion Criteria).

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 from whom informed consent is obtained and is documented in writing (ie, subject has signed an ICF), but who has not been randomized or has not been assigned to a treatment group. 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)
- Results of eligibility criteria assessment
- Date of assessment as screen failure
- Reason for screening failure

Subjects participating in this trial who fall under any of the exclusion criteria in the screening examination may undergo rescreening only if there is a change in the particular exclusion criterion that they met. If rescreening can be performed within the allowable time window for the screening period, there is no need to obtain reconsent, and only the tests relevant to the item that has changed need to be performed. If rescreening cannot be performed within the allowable time window for the screening period, written informed

consent must be newly obtained, and a new subject ID must be assigned prior to the screening examination.

3.11 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for the primary and/or secondary objectives of the trial (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 10 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 the trial 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

For this trial, subjects will receive care under the same environment from at least 3 weeks before the date of baseline evaluations to the completion of the examinations scheduled at the completion or discontinuation of IMP administration. If a change in the subject's care environment is unavoidable, the subject's participation in the trial should be discontinued. In the case of discontinuation, the necessary measures must be followed in accordance with Section 3.9 Stopping Rules, Withdrawal Criteria, and Procedures.

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, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant therapy 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 for brexpiprazole are prohibited until completion of the 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	Prohibited Period Before Baseline Evaluation	Remarks
Antipsychotics • Clozapine • Sustained release injections • Brexpiprazole • Other antipsychotics	 30 days 1.5 cycles Any past use 7 days	Brexpiprazole is prohibited until completion of follow-up observation
Antidepressants	7 days	
Mood stabilizers	7 days	
Psychostimulants	7 days	
Narcotic analgesics for agitation	7 days	
Yokukansan and other herbal medicines and supplements for treatment of BPSD	7 days	
Adrenaline	7 days	
Antiepileptic drugs	7 days	
Antiparkinson drugs	7 days	
Varenicline	7 days	
Benzodiazepines	7 days	
Belsomra	7 days	
Lemborexant	7 days	

Table 4.1-1 Prohibited Medications		
Drug Type	**Prohibited Period Before Baseline Evaluation**	**Remarks**
Drugs (β-blockers) for extrapyramidal symptoms	7 days	If administration is necessary due to AEs that occur after IMP administration, use will be permitted in accordance with the stipulations for restricted drugs.
CYP2D6 inhibitors, CYP3A4 inhibitors and inducers[a]	7 days	

[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 from the baseline evaluation to the completion of the examinations scheduled at the completion or discontinuation of IMP administration is permitted under the prescribed restrictions. If the following restrictions cannot be complied with, restricted drugs should be discontinued before the day prior to the first day of IMP administration.

Table 4.2-1 Restricted Medications		
Drug Type	**Restriction**	**Remarks**
Antidementia drugs	These drugs can be continued if the dose and regimen have not been changed for ≥3 months before the baseline evaluation. The dose and regimen should remain the same until the completion of the examinations scheduled at the completion or discontinuation of IMP administration.	

Table 4.2-1 Restricted Medications

Drug Type	Restriction	Remarks
Narcotic analgesics	If not used for agitation (eg, pain control, tooth extraction), the use of these drugs is permitted from the baseline evaluation to the completion of the examinations scheduled at the completion or discontinuation of IMP administration.	
β-Blockers	• Treatment of complications (eg, cardiovascular diseases) other than psychiatric diseases These drugs can be continued if they have been used before the acquisition of informed consent and the dose and regimen have not been changed for ≥ 30 days before the baseline evaluation. The type, dose, and regimen should remain the same until completion of the examinations scheduled at the completion or discontinuation of IMP administration (discontinuation or dose reduction are permitted only when these actions are necessary due to AEs caused by β-blockers and 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. These drugs are prohibited within 12 hours prior to efficacy and safety assessments.	
Hypnotics	• Ultra-short-acting nonbenzodiazepine hypnotics (zolpidem, zopiclone, eszopiclone), ramelteon These drugs can be continued if the dose and regimen have not been changed for ≥ 30 days before the baseline evaluation. The type, dose, and regimen should remain the same until completion of the examinations scheduled at the completion or discontinuation of IMP administration (discontinuation and dose reduction are permitted only when these actions are necessary due to AEs caused by hypnotics and for remission of the symptoms of insomnia). These drugs are prohibited within 8 hours prior to efficacy and safety assessments. • 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. These drugs are prohibited within 8 hours prior to efficacy and safety assessments.	

4.3 Restricted Therapies

Starting new cognitive function training, cognitive stimulation, cognitive rehabilitation, exercise therapy, music therapy, and reminiscence therapy, as nonmedication therapies for dementia, and other nonmedication therapies which are judged by the investigator or subinvestigator to affect the efficacy and safety assessments is prohibited from baseline evaluation until completion of the examinations scheduled at the completion or discontinuation of IMP administration.

4.4 Other Restrictions

[redacted]

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as complications at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. 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 from after a subject has signed the ICF to the date of trial completion.

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 screening. 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 the start of IMP administration, 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

Only in the event that a subject has a medical emergency and knowledge of the treatment assignment code is necessary for treatment, the investigator or subinvestigator may obtain the emergency key code for the subject in question through the IWRS, in accordance with the separately specified procedures. When emergency key code opening is performed, the sponsor will receive automatic notification from the IWRS via e-mail. If the emergency key code is opened, the PV department must be notified immediately (see the cover page of this protocol for contact information).

Documentation of emergency key code opening should be recorded in the subject's medical record with the date and time of opening and the names of the personnel involved. Once a subject's emergency key code is opened, IMP administration may not be reinitiated for that subject.

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

In Trial 331-12-283, which was performed outside Japan, the 2 mg fixed-dose group showed superiority over the placebo group in patients with aggression (patients with aggressive behavior at baseline), thus suggesting that it may also be the optimum dose for Japanese patients. Efficacy was not observed in the 1 mg fixed-dose group, but in Trial 331-12-284, the efficacy of a dose less than 2 mg was suggested by the results obtained in patients from the flexible-dose (0.5 to 2 mg) group, who had aggression.

In this trial, a power of detection ≥ 80% will be achieved for comparison between the placebo group and the 1 mg group to allow evaluation of superiority over the placebo group if equivalent efficacy is demonstrated in the 1 and 2 mg groups. For comparison between the 2 mg group (possible optimum dose) and the placebo group, a more sufficient power of detection will be obtained by changing the randomization ratio. In this trial, it is assumed that the difference between the 2 mg group and the placebo group in the change in the CMAI total score from baseline to Week 10 is −5.35, and the standard deviation (calculated from the standard error of the difference between the 2 mg and placebo groups and the number of subjects at baseline) is 15.06 on the basis of the results

of Trial 331-12-283. By setting the number of subjects in the 2 mg group, 1 mg group, and placebo group as 148, 111, and 148, respectively (randomization ratio of 4:3:4), the power of detection is 86.1% for the comparison between the 2 mg group and the placebo group and is 80.5% for the comparison between the 1 mg group and the placebo group in a test with a significance level of 5% (two sided).

On the basis of the above considerations, the number of subjects will be set at 148 in the 2 mg group, 111 in the 1 mg group, and 148 in the placebo group (randomization ratio of 4:3:4).

6.2 Datasets for Analysis

6.2.1 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will comprise subjects who have been treated with brexpiprazole and for whom plasma drug concentration data have been obtained, other than those deemed as “not analyzed” or “not determined.”

6.2.2 Full Analysis Set

The full analysis set (FAS) will comprise subjects who, after randomization, 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 the treatment.

6.2.3 Safety Analysis Set

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

6.3 Handling of Missing Data

The primary analysis of the primary endpoint will be performed in the observed cases (OC) dataset by mixed models for repeated measures (MMRM) without data imputation for missing data under the “missing at random” assumption. As a sensitivity analysis for the handling of missing data, placebo multiple imputation and tipping point analysis will be performed under the “missing not at random” assumption. Details are described in the statistical analysis plan.

For efficacy and safety analyses, the last observation carried forward (LOCF) method (in which missing post-dose data are imputed by the last observed data after initiation of IMP treatment) will be used as needed.

For pharmacokinetic analysis, no imputation will be performed for missing data.

6.4 Primary and Secondary Endpoint Analyses

6.4.1 Primary Endpoint Analyses

The primary endpoint will be change in CMAI total score from baseline to Week 10. The primary analysis will be conducted on the FAS by using MMRM analysis on the basis of the OC data set. For the analysis model, the treatment group (brexpiprazole 1 mg group, brexpiprazole 2 mg group, or placebo group), time point (Weeks 2, 4, 6, 8, or 10), medical care category (hospitalized or outpatient), prior use of antipsychotics (yes or no), and interaction between treatment group and time point will be included as factors, the baseline and interaction between the baseline and time point will be included as covariates, and the error variance and covariance structure will be unstructured. The Kenward–Roger method will be used to determine the degrees of freedom.

Between-group comparison will be performed by calculating the difference of the least squares mean between each of the brexpiprazole groups and the placebo group at Week 10. The fixed sequence procedure will be used to adjust the multiplicity of testing due to the performance of two comparisons (ie, the brexpiprazole 1 mg group versus the placebo group and the brexpiprazole 2 mg group versus the placebo group) to control the overall type I error rate. Initially, the brexpiprazole 2 mg group will be compared with the placebo group. Only if the difference is statistically significant at a significance level of 5% (two sided), the brexpiprazole 1 mg group will be compared with the placebo group at a significance level of 5% (two sided).

The least squares mean for each treatment group and the difference of the least squares mean between each brexpiprazole group and the placebo group, as well as their two-sided 95% CIs, will be calculated at each time point.

If any problems in convergence status arise in the estimation of variance components of MMRM, heterogeneous Toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry, which are error variance-covariance structures, will be applied in this order, and the first structure that achieves convergence will be used in the primary analysis. If anything other than an unstructured variance-covariance structure is selected, a sandwich estimator for standard errors will be used.

6.4.2 Secondary Endpoint Analyses

The secondary endpoint analysis will be performed on the FAS.

- Changes in CMAI subscales (Aggressive Behavior, Physically Non-aggressive Behavior, and Verbally Agitated Behavior) from baseline at Week 10
- Change in CGI-S related to agitation from baseline to Week 10

The same MMRM analysis as that for the primary endpoint will be performed using the OC dataset.

- CGI-I at Week 10

Each brexpiprazole group will be compared with the placebo group by the Cochran Mantel Haenszel (CMH) Row Mean Scores test with medical care category (inpatient or outpatient) and prior use of antipsychotics (yes or no) as strata using the LOCF dataset. Mean values in each treatment group, differences in mean values between each brexpiprazole group and the placebo group, and their two-sided 95% CIs will be calculated.

6.4.3 Exploratory Endpoint Analyses

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

6.4.4 Interim Analysis

Safety will be evaluated by the IDMC when approximately 25%, 50%, and 75% of the target number of subjects have completed or discontinued the trial.

6.4.5 Subgroup Analyses

The same MMRM analysis as that for the primary endpoint will be performed on the change in CMAI total score from baseline to Week 10 for each of the subgroup

categories within each of the following items using the OC dataset (in the subgroup analyses of medical care category and prior use of antipsychotics, those particular factors will be excluded from the respective analysis models).

- Medical care category (inpatient or outpatient)
- Prior use of antipsychotics (yes or no)
- Type of caregiver (hospital staff, care facility staff, family, or other)
- Sex (male or female)
- Age (< 80 or ≥ 80)
- CMAI total score at baseline (< 56 or ≥ 56)
- [redacted]
- Body weight (≤ median or > median)
- Body mass index (BMI) (≤ median or > median)

6.5 Analysis of Demographic and Baseline Characteristics

Descriptive statistics or frequency distribution of demographic and other baseline characteristics will be determined for each treatment group and for the overall brexpiprazole group in each analysis dataset.

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 the trial.

6.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of the following events will be summarized by treatment group and by the overall brexpiprazole group, 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 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 will be calculated for each treatment group and for the overall brexpiprazole group.

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 treatment group and for the overall brexpiprazole group.

For each qualitative laboratory parameter, a shift table from baseline will be produced for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with potentially clinically significant laboratory test values will be determined for each treatment group and for the overall brexpiprazole group.

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 will be calculated for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with potentially clinically significant vital signs will be determined for each treatment group and for the overall brexpiprazole group.

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 will be calculated for each treatment group and for the overall brexpiprazole group.

A shift table from baseline for normal/abnormal 12-lead ECG will be produced for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with actual measurements of corrected QT interval (QTcF, QTcB, and QTcN) at each time point of > 450 msec, > 480 msec, and > 500 msec will be determined for each treatment group and for the overall brexpiprazole group. Numbers and proportions of subjects with changes from baseline of > 30 msec and > 60 msec will be determined for each treatment group and for the overall brexpiprazole group.

Numbers and proportions of subjects with ECG results meeting the criteria for potentially clinically significant ECG data will be determined for each treatment group and for the overall brexpiprazole group.

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 will be calculated for each treatment group and for the overall brexpiprazole group.

In addition, using the LOCF data set, analysis will be performed by the analysis of covariance (ANCOVA) model with treatment group, medical care category (hospitalized or outpatient), and prior use of antipsychotics (yes or no) as factors and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

Numbers and proportions of subjects with results meeting the criteria for potentially clinically significant body weight gain or loss will be determined for each treatment group and for the overall brexpiprazole group.

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 will be calculated for each treatment group and for the overall brexpiprazole group.

In addition, using the LOCF data set, analysis will be performed by the ANCOVA model with treatment group, medical care category (hospitalized or outpatient), and prior use of antipsychotics (yes or no) as factors and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

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 will be calculated for each treatment group and for the overall brexpiprazole group.

In addition, using the LOCF data set, analysis will be performed by the ANCOVA model with treatment group, medical care category (hospitalized or outpatient), and prior use of antipsychotics (yes or no) as factors and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

6.7 Analysis of Pharmacokinetic Endpoints

Descriptive statistics of plasma drug concentration at the time of blood sampling (Week 10) will be calculated for each dose group.

6.8 Analysis of Pharmacogenomic Endpoints

A list of data obtained from CYP2D6 genetic assessment will be provided without summarization.

6.9 Genomic/Genetic Analysis

See Section 3.8.4.2.2 5) Genomic/Genetic Analysis for genomic/genetic analysis.

6.10 Biomarker Exploration Analysis

See Section 3.8.4.3 5) Biomarker Exploration for biomarker exploration analysis.

6.11 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 the trial.

- ADCS-ADL
- MMSE
- EQ-5D-5L

For ADCS-ADL total score, MMSE total score and each item of EQ-5D-5L, descriptive statistics of actual measurements and changes from baseline at each time point will be calculated for each treatment group and for the overall brexpiprazole group.

In addition, using the LOCF data set, analysis will be performed by the ANCOVA model with treatment group, medical care category (hospitalized or outpatient), and prior use of antipsychotics (yes or no) as factors and baseline as a covariate. Least square means of each treatment group and differences in least square means between each brexpiprazole group and the placebo group, as well as the two-sided 95% CIs will be determined.

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] 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 [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. ([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 clinician (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 documentation 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 four 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.
- Until the date on which it is decided to end DNA storage
- Until the date on which it is decided to end biomarker sample storage

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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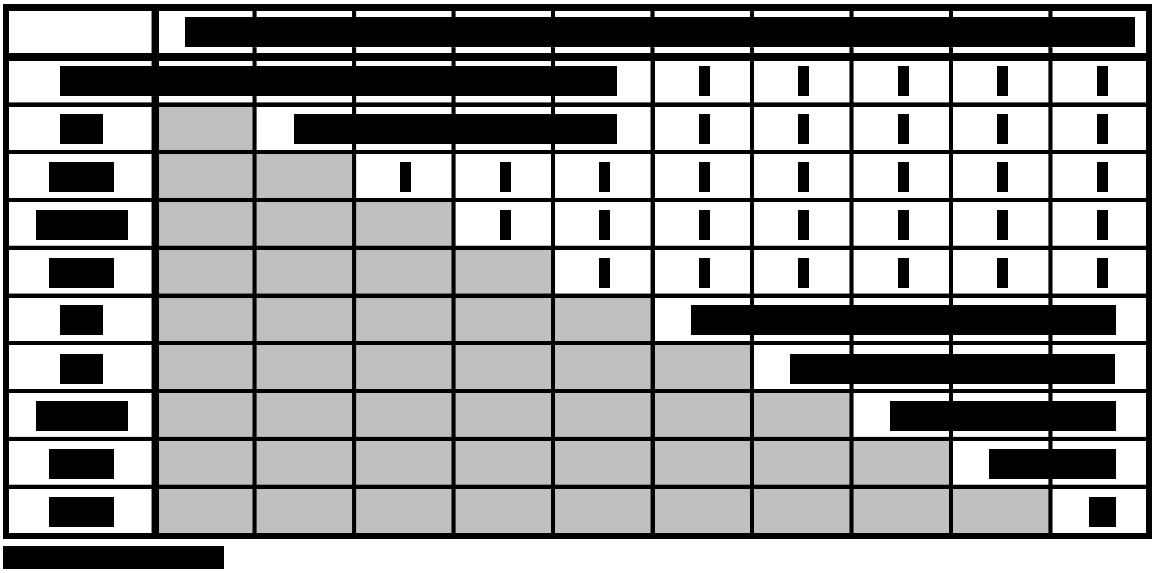
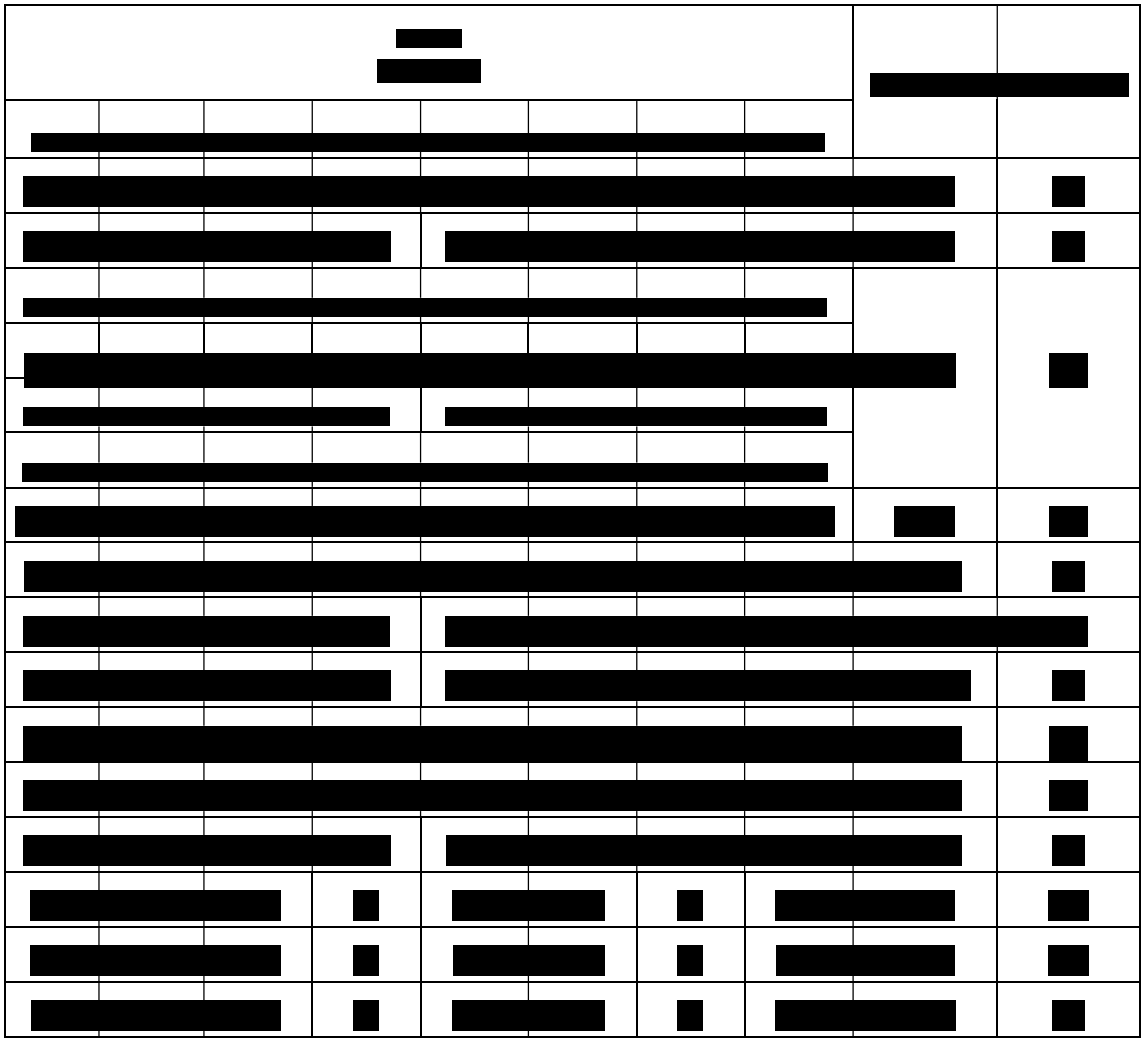
Appendix 1 [redacted]

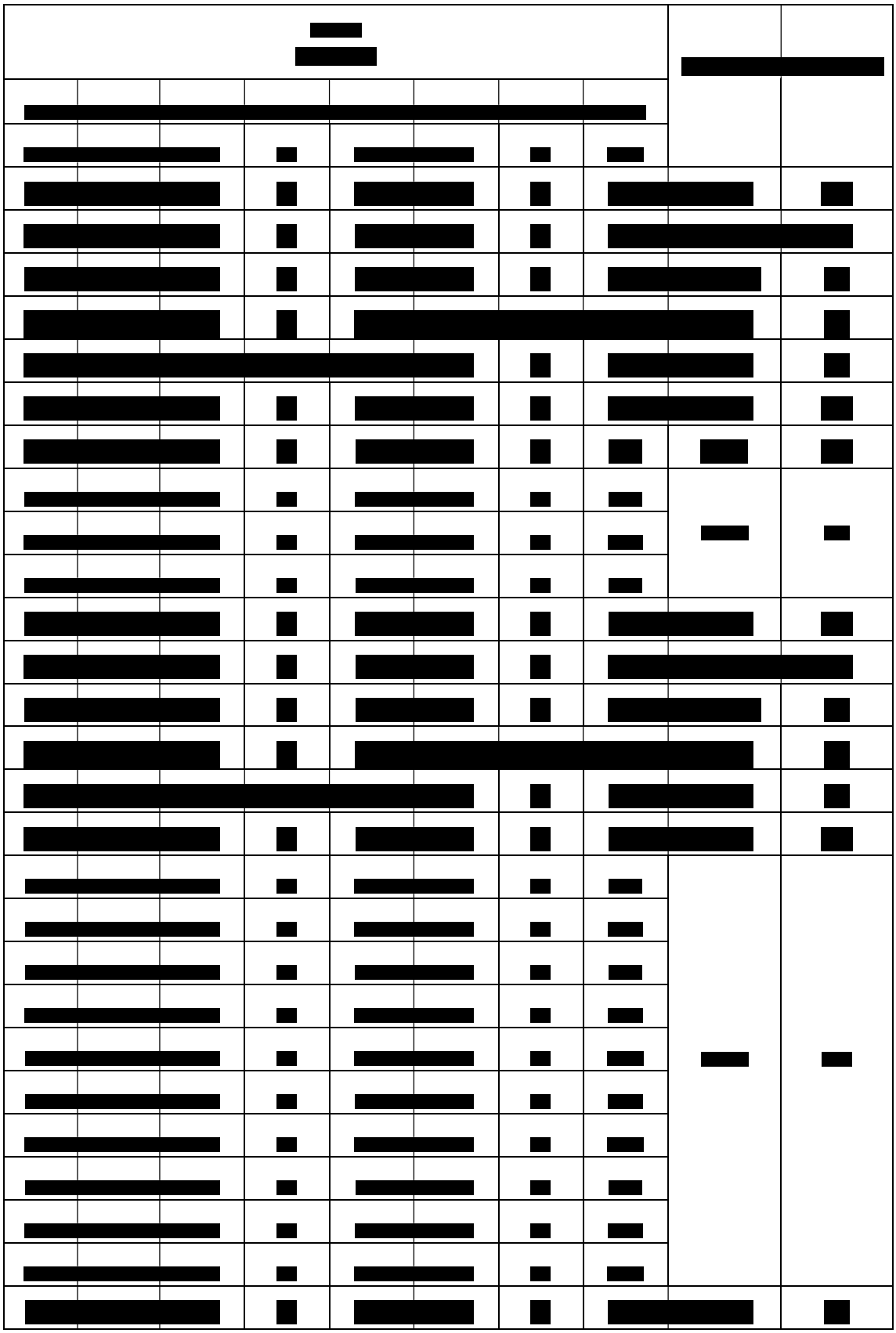
[redacted]

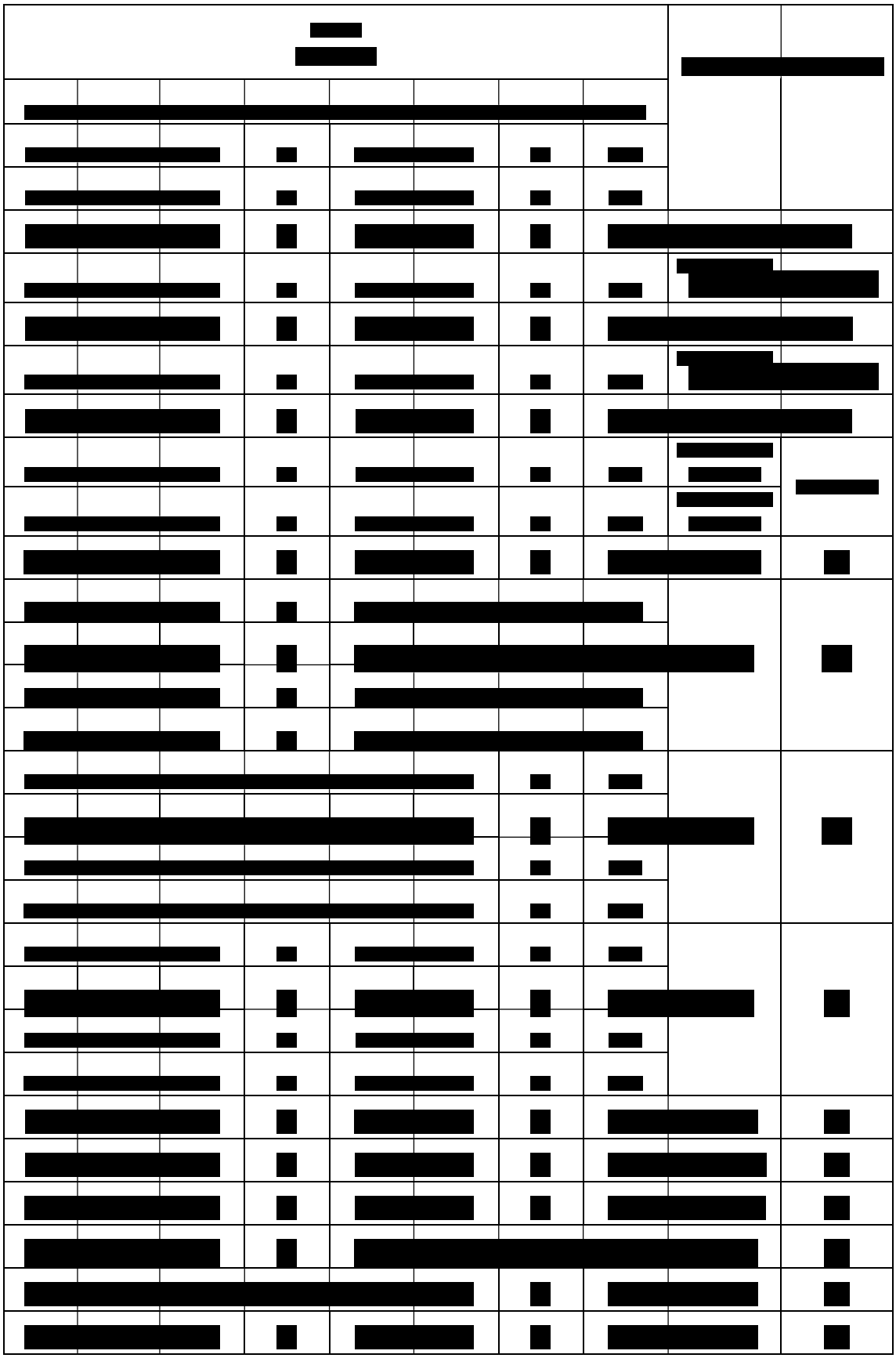
[redacted]

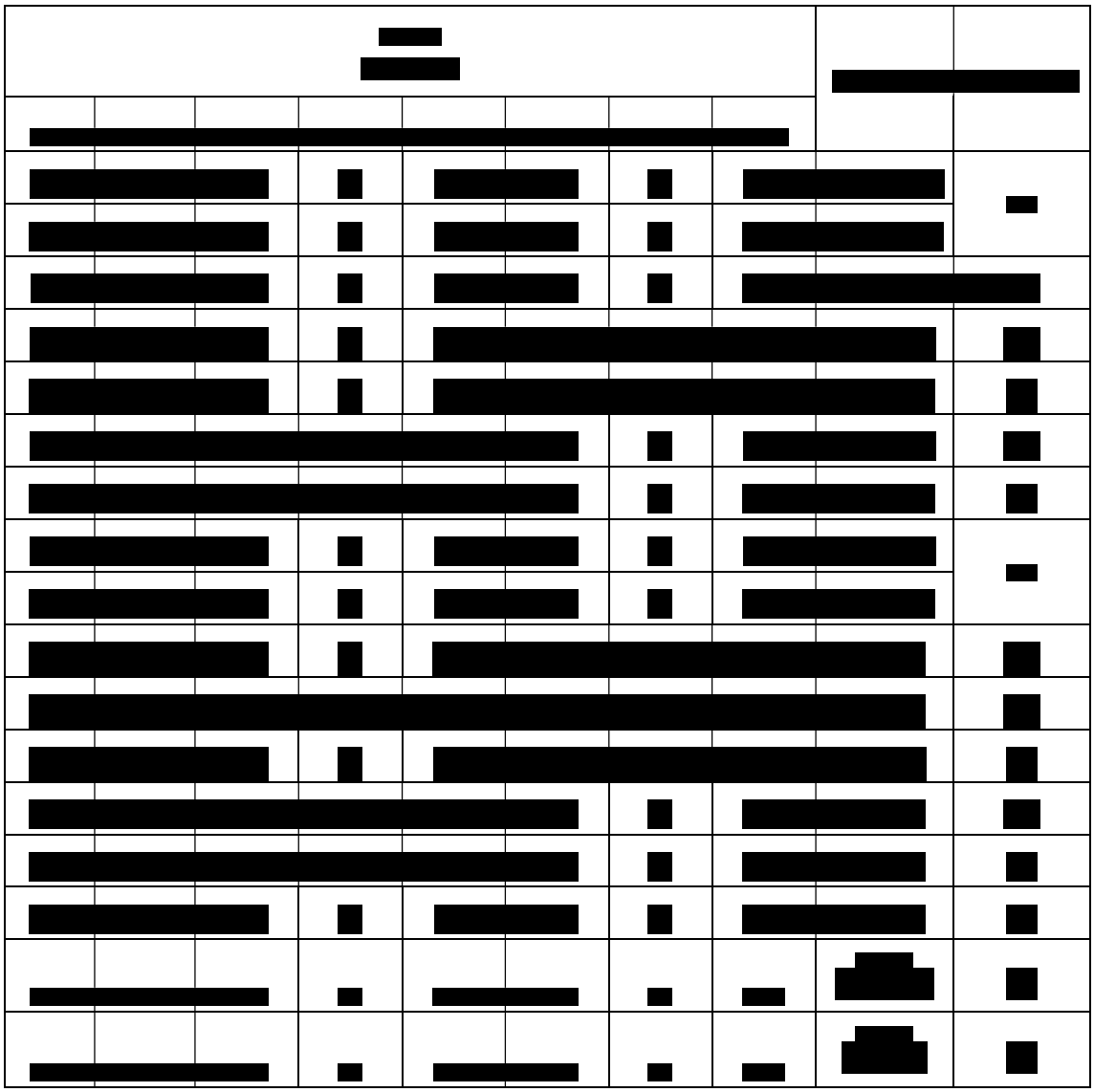
Appendix 2











Appendix 3 Protocol Amendments/Administrative Changes

Amendment: Number: 1

Issue Date: 24 Aug 2018

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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ADDITIONAL RISK TO THE SUBJECT

[redacted]

Amendment: Number: 2

Issue Date: 05 Mar 2020

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

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

Amendment: Number: 4

Issue Date: 27 Apr 2022

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

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

ADDITIONAL RISK TO THE SUBJECT

[redacted]

Amendment: Number: 5

Issue Date: 24 Nov 2022

PURPOSE:

[redacted]

BACKGROUND:

[redacted]

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Location	Before Change	After Change
[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.