- Protocol number: 331-12-284
- Document title: A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Flexible Dosing of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated with Dementia of the Alzheimer's Type
- Version number: 4.0
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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

## OPC-34712

## **REVISED CLINICAL PROTOCOL**

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

> Protocol No. 331-12-284 IND No. 115,960 EudraCT No. 2013-000503-17

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Clinical Development Phase: Sponsor: 3

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Immediately Reportable Event:	INC Research (see Appendix 2)

PPD

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10 Sep 2015

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# **Protocol Synopsis**

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: Brexpiprazole (OPC-34712)		Protocol #331-12-284 IND #115,960 EudraCT #2013-000503-17
Protocol Title:	A Phase 3, 12-week, Multice Placebo-controlled Trial to E Tolerability of Flexible Dosin in the Treatment of Subjects Dementia of the Alzheimer's	nter, Randomized, Double-blind, valuate the Efficacy, Safety, and ng of Brexpiprazole (OPC-34712) with Agitation Associated with Type
Clinical Phase:	3	
Treatment Indication:	Agitation associated with der	nentia of the Alzheimer's type
Objective(s):	<i>Primary:</i> To compare the eff brexpiprazole (dose range of subjects with agitation associ Alzheimer's type, as assessed Agitation Inventory (CMAI) <i>Secondary:</i> To evaluate the s	ficacy of flexible dosing of 0.5 to 2 mg/day) with placebo in fated with dementia of the d by the Cohen-Mansfield after 12 weeks of treatment. safety and tolerability of flexible e range of 0.5 to 2 mg/day)
	compared with placebo in sul with dementia of the Alzhein treatment.	bjects with agitation associated her's type after 12 weeks of
Trial Design:	This is a phase 3, 12-week, m double-blind, placebo-contro designed to assess the efficace brexpiprazole (dose range of of subjects with agitation asse Alzheimer's type. The trial p female subjects between 55 a who are living in either an in- non-institutionalized setting v alone. In both the institution settings, the subject must hav minimum of 2 hours per day subject in order to assess char All subjects must have a diag disease according to the Natic Communicative Disorders an Disease and Related Disorder (NINCDS-ADRDA) criteria.	nulticenter, randomized, lled, 2-arm, flexible-dose trial ey, safety, and tolerability of 0.5 to 2 mg/day) in the treatment ociated with dementia of the population will include male and and 90 years of age (inclusive), stitutionalized setting or in a where the subject is not living alized and non-institutionalized ve a caregiver who can spend a for 4 days per week with the nges in the subject's condition. gnosis of probable Alzheimer's onal Institute of Neurological and d Stroke and the Alzheimer's rs Association

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12-week, Double-blind Treatment Period:

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

- Brexpiprazole
- Placebo

Subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule, as follows:

	D	osing Scheme		
	Recom	mended Daily	v Dose Admini	stered
Treatment Group	Day after the Baseline visit (Day 1)	Day after the Day 3 visit (Day 4 [+2 days])	Day after the Week 2 visit (Day 15 [± 2 days])	Day after the Week 4 visit (Day 29 [±2 days])
Brexpiprazole 0.5-2 mg/day	0.25 mg/day	0.5 mg/day	1 mg/day <sup>a</sup>	2 mg/day b
Placebo	<			>

<sup>a</sup>After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).

<sup>b</sup>The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (ie, Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability. Allowable IMP doses that may be given starting the day after the Week 4 visit (ie, Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

The first dose of investigational medicinal product (IMP) will be administered on the day after the Baseline visit (ie, Day 1). All subjects randomly assigned to receive brexpiprazole will receive 0.25 mg/day as a starting dose.

5

<ul> <li>The dose of IMP will be increased from 0.25 mg/day to 0.5 mg/day starting on the day after the Day 3 visit (ie, Day 4 [+2 days]).</li> <li>The dose will then be increased to 1 mg/day starting on the day after the Week 2 visit (ie, Day 15 [±2 days]). After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).</li> <li>The dose of IMP can be further increased from 1 mg/day to 2 mg/day starting on the day after the Week 4 visit (ie, Day 29 [±2 days]). Note: The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (ie, Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability.</li> <li>Allowable IMP doses that may be given starting the day after the Week 4 visit (ie, Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day. Dose decreases and increases must occur in a stepwise manner and can occur at any time (scheduled or unscheduled visits).</li> <li>For subjects randomly assigned to receive placebo, their dose of IMP will be administered daily starting on the day after the Baseline visit (ie, Day 1) and ending on Week 12/ Early Termination (ET) (the last day of the IMP (or matching placebo) will be discontinued from the trial.</li> <li>If a subject is discontinued from the trial.</li> </ul>
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Subjects unable to tolerate 0.5 mg/day of the IMP (or matching placebo) will be discontinued from the trial. If a subject is discontinued from the trial, every effort will be made to complete all of the Week 12/ET evaluations prior to
If a subject is discontinued from the trial, every effort will be made to complete all of the Week 12/ET evaluations prior to
administering any additional medications for the treatment of agitation or other prohibited medications.
Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. All trial visits will take place as a clinic visit at either the investigator's site or residential facility, if applicable. All attempts should be made to maintain the subjects' normal routine with regard to physician appointments. Individual circumstances that fall outside this general convention should be discussed with the medical monitor in order to determine appropriateness to proceed. In addition, the subject's

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	5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments.
	Follow-up Period:
	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver.
	Subjects who complete both the 12-week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-13-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at either the investigator's site or residential facility, if applicable.
Subject Population:	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition. All subjects must have a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease. If a previous MRI or CT scan of the brain performed after the onset of the symptoms of dementia is not available, then an MRI/CT scan should be performed during screening. Additionally, at both the screening and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a

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total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the Neuropsychiatric Inventory— Nursing Home (NPI-NH) or the Neuropsychiatric Assessment for Non-institutionalized Patients based on the NPI/NPI-NH (hereafter referred to as "NPI/NPI-NH"). The NPI-NH will be used for institutionalized subjects and the NPI/NPI-NH will be used for non-institutionalized subjects. The onset of the subject's symptoms of agitation must be at least 2 weeks prior to the screening visit. Subjects must require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (eg, pain, infection, polypharmacy) and a trial of nonpharmacological interventions.
Subjects must have been residing at their current location for at least 14 days before screening and be expected to remain at the same location for the duration of the trial. Subjects who at any point during the double-blind treatment phase transfer from an institutionalized setting to a non-institutionalized setting, or vice versa, will be withdrawn from the trial. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and medical monitor. All attempts should be made to maintain the subjects' normal routine with regard to appointments with physicians and overnight accommodations. Subjects in an institutionalized setting may receive supervised day passes at the discretion of the investigator and may also receive supervised overnight passes at the discretion of the investigator as long as such overnight stays are part of the subjects' normal routine.
Subjects in a non-institutionalized setting may have a caretaker as well as a caregiver. The subject's caretaker is the person who lives with and cares for the subject on a regular basis. The caretaker may be supported in providing care to the subject by a professional(s), friend(s), or family member(s). For purposes of this trial, the subject's caregiver is the person who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI/NPI-NH, and other applicable trial assessments.
For subjects in an institutionalized setting, there is only one role defined and that is the role of caregiver. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who has sufficient contact to describe the subject's symptoms and who has direct observation of the

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	subject's behavior in order to participate in the interview for the CMAI, NPI-NH, and other applicable trial assessments.
	The recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week in both the institutionalized and non-institutionalized settings.
	CCI
Inclusion/Exclusion Criteria:	Key inclusion criteria are described under Subject Population in this synopsis. Subjects must meet the inclusion criteria at both screening and baseline.
	Key exclusion criteria include the following:
	• Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.
	• Subjects with a previous MRI/CT scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (eg, cortical stroke, multiple infarcts), space-occupying lesion (eg, tumor), or other major structural brain disease.
	• Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.
	• Subjects with delirium or history of delirium within the 30 days prior to the screening visit.
	• Subjects with evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (Sheehan-STS); ie, a score of 3 or 4 on any one question 2 through 6 or 11, or a score of 2 or higher on any one questions 1a, 7 through 10, or 12, or who, in the opinion of the investigator, present a serious risk of suicide.

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	• Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.
Trial Sites:	It is planned that approximately 520 subjects will be screened at approximately 65 trial sites worldwide so that 260 subjects will be randomized to treatment.
Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	The IMP will consist of brexpiprazole tablets (identical 0.25-mg, 0.5-mg, 1-mg, and 2-mg tablets) and matching placebo tablets. The 0.25 mg/day dose will be supplied as a blister card containing sufficient tablets for 3 (+2) days; the 0.5 mg/day, 1 mg/day, and 2 mg/day doses will be supplied as a weekly blister card containing sufficient tablets for 7 (+2) days. An IVRS or IWRS will be used at each trial site to assign the specific blister-card number to be dispensed to each subject at each visit.
	After a 2- to 42-day screening period, eligible subjects will be randomly assigned to 1 of 2 treatment groups (brexpiprazole group or placebo group). Subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule.
	The total duration of double-blind treatment will be 12 weeks for all randomized subjects.
	All doses of brexpiprazole and matching placebo will be taken orally once daily, preferably in the morning, and can be administered without regard to meals. Brexpiprazole should be taken at approximately the same time each day, particularly prior to visits with pharmacokinetic sampling.

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	Safety Variables:
	Standard safety variables to be examined will include adverse events, physical examinations, neurological examinations, vital signs, body weight, waist circumference, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and electrocardiograms (ECGs). In general, summarized statistics of changes from baseline will be provided for safety variables based on all available data. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Change from baseline in body mass index (BMI) (derived programmatically from body weight and height measurements) will be summarized. Other safety variables will include the MMSE score
	Pharmacokinetic samples for determination of brexpiprazole and its metabolite(s) will be collected at the baseline visit and at the Week 8 and Week 12/ET trial visits, at the same time as the sample collection for the clinical laboratory tests.
Statistical Methods:	Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. The primary endpoint will be analyzed using a mixed-effect model repeated measure (MMRM) methodology. The model will include fixed class-effect terms for treatment, trial center, visit week, and an interaction term of treatment by visit week as a covariate. The

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	primary efficacy outcome measure is the mean change from baseline (Day 0 Visit) to the end of the double-blind treatment period (Week 12 visit) in the CMAI total score.
	The sample size was calculated based on the treatment effect of 6.5 points with a standard deviation of 16.5 in the change from baseline to the endpoint in the CMAI total score, to achieve 85% power at a 2-sided alpha level of 0.05. The resulting sample size is 117 subjects/arm. After allowance of 10% non-evaluable subjects, it results in a sample size of 130 subjects/arm, which means the total sample size is 260 subjects. The sample size was estimated based on a 1:1 randomization ratio (brexpiprazole:placebo). The randomization will be stratified by center.
Trial Duration:	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4.5 years, of which approximately 4 years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP.

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# List of Abbreviations and Definitions of Terms

<b>Abbreviation</b>	<b>Definition</b>		
5-HT <sub>1A</sub>	Serotonin type 1A receptor		
5-HT2A	Serotonin type 2A receptor		
ACR	Albumin-to-creatinine ratio		
ACTH	Adrenocorticotropic hormone		
ADHD	Attention-deficit/hyperactivity disorder		
ADL	Activities of daily living		
ADT	Antidepressant therapy		
AE	Adverse event		
CCI			
ALP	Alkaline phosphatase		
ALT (SGPT)	Alanine transaminase (serum glutamic-pyruvic transaminase)		
AMP	Adenosine monophosphate		
ANCOVA	Analysis of covariance		
APO	Apomorphine		
Anti-HCV	Antibodies to hepatitis C		
aPTT	Activated partial thromboplastin time		
AST (SGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)		
AUCt	Area under the concentration-time curve calculated to the last		
	observable concentration at time t		
CCI			
BMI	Body mass index		
BUN	Blood urea nitrogen		
Ca <sup>2+</sup>	Calcium		
CAARS-O:SV	Conners' Adult ADHD Rating Scale-Observer: Screening Version		
CCI			
CCI			
CGI-S	Clinical Global Impression-Severity of Illness scale		
CHO-K1	Chinese hamster ovary cells		
CMAI	Cohen-Mansfield Agitation Inventory		
СМН	Cochran-Mantel-Haenszel		
C <sub>max</sub>	Maximum (peak) plasma concentration		
CNS	Central nervous system		
СРК	Creatine phosphokinase		
CRO	Clinical Research Organization		
C-SSRS	Columbia-Suicide Severity Rating Scale		
CST	Clinical Surveillance Team		
CT	Computed tomography		
CVAE	Cardiovascular Adverse Events		
CYP2D6	Cytochrome P450 2D6 isozyme		
CYP3A4	Cytochrome P450 3A4 isozyme		
D2	Dopamine type 2 receptor		

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<u>Abbreviation</u>	<b>Definition</b>
D2L	Dopamine type 2 long receptor
D3	Dopamine type 3 receptor
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth
	Edition, Text Revision
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EPS	Extrapyramidal symptoms
ET	Early termination
EU	European Union
EudraCT	European Clinical Trial Data Base
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA <sub>1c</sub>	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
HEENT	Head, eyes, ears, nose, and throat
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus
IADL	Instrumental activities of daily living
IAP	Independent Adjudication Panel
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification/identifier
IDDM	Insulin-dependent diabetes mellitus
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional review board
IRE	Immediately reportable event
ISI	Insomnia Severity Index
ITT	Intent-to-treat
IUD	Intrauterine device
IVRS	Interactive voice response system
IWRS	Interactive web response system
K <sub>2</sub> EDTA	Potassium ethylenediaminetetraacetic acid
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LOCF	Last-observation-carried-forward

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<b>Abbreviation</b>	<b>Definition</b>
LS	Least squares
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
CCI	
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders
	and Stroke and the Alzheimer's Disease and Related Disorders
	Association
NMS	Neuroleptic malignant syndrome
CCI	
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory—Nursing Home
NPI/NPI-NH	Neuropsychiatric Assessment for Non-Institutionalized Patients
	based on the NPI/NPI-NH
OAPI-EQC	Otsuka America Pharmaceutical, Inc. Ethics, Quality and
Č.	Compliance
OC	Observed case
OPC	Otsuka Pharmaceutical Co.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography
PT	Prothrombin time
PQC	Product quality complaint
QoL	Quality of life
CCI	
QTc	Corrected QT interval
QTcB	QT interval as corrected by Bazett's formula
QTcF	QT interval as corrected by Fridericia's formula
QTcN	QT interval as corrected by the FDA Neuropharm Division
	formula
<u>RBC</u>	Red blood cell
CCI	
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SD	Standard deviation
CCI	

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<b>Abbreviation</b>	Definition
$T_4$	Thyroxine
TEAE	Treatment-emergent adverse event
t <sub>max</sub>	Time to maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WRAADDS	Wender-Reimherr Adult Attention Deficit Disorder Scale

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

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## 1. Introduction

Dementia is a term that describes disorders that cause cognitive decline. The most common type of dementia is Alzheimer's disease.<sup>1</sup> It is currently estimated that 5.3 million Americans have Alzheimer's disease, and future projections estimate that, due to an increase in the aging population, there will be between 11 million and 16 million Americans with Alzheimer's disease by 2050.<sup>1</sup> In the United States, among adults older than age 65, prevalence estimates of dementia.<sup>2,3,4</sup> Dementia is the most frequent contributing factor to the transition from home-based care to a long-term care facility, such as a nursing home, assisted living facility, or group home. Across numerous studies, it has been consistently demonstrated that cognitive decline, behavioral disturbances, and depression associated with Alzheimer's disease are strong predictors of nursing home admission.<sup>5</sup>

Neuropsychiatric symptoms, including agitation and aggression, are core features of Alzheimer's disease and related dementias. Alzheimer's disease-associated behavioral disturbances cause frequent emergency room visits and can lead to mismanagement of other medical conditions. These behavioral disturbances also are associated with major adverse effects on quality of life (QoL) and reduced time to institutionalization. Neuropsychiatric symptoms also have a major adverse effect on caregivers.<sup>5</sup> These neuropsychiatric symptoms contribute to subject and caregiver distress<sup>6</sup> and increased healthcare costs<sup>7</sup> and even may lead to institutionalization.<sup>8</sup>

Currently, there is no cure for Alzheimer's disease and no treatment approved in the United States for the management of behavioral disturbances, including agitation, in patients with Alzheimer's disease. In some countries of the European Union (EU), risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in subjects with moderate to severe Alzheimer's dementia unresponsive to nonpharmacological approaches and when there is a risk of harm to self or others.<sup>9</sup> Adequate treatment of behavioral disturbances is essential to increasing the comfort and safety of subjects and easing the burden of provision of care placed on families and other caregivers; it remains an ongoing and serious unmet medical need in this subject population.

In the literature, agitation has been defined as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the agitated individual." Agitation is a term used by clinicians for a group of symptoms that may reflect an underlying disorder.<sup>10,11</sup> Agitated behavior is considered to be socially inappropriate and may be:

- Abusive or aggressive toward self or others, such as hitting or kicking
- An appropriate behavior that is performed with an inappropriate frequency, such as constantly asking questions
- Considered inappropriate according to social standards, such as putting on too many layers of clothes<sup>11</sup>

Brexpiprazole (also referred to as OPC-34712 or Lu AF41156) is an organic compound synthesized by Otsuka Pharmaceutical Co, Ltd, that is a partial agonist at dopamine type 2 (D2), dopamine type 3 (D3), and serotonin type 1A (5- $HT_{1A}$ ) receptors and an antagonist at serotonin type 2A (5-HT<sub>2A</sub>) receptors; and has a low binding affinity for histamine and muscarinic receptors. Details of the receptor affinity profile of brexpiprazole are summarized in Section 1.1.1. Activity at dopamine and serotonin receptors has been shown to be useful in the treatment of psychiatric disorders, eg, schizophrenia and bipolar mania. Hence, brexpiprazole is expected to be a promising antipsychotic agent. As the relative activity at these and other receptors appears to be related to the side-effect profiles of antipsychotic drugs,<sup>12,13,14,15</sup> brexpiprazole may have the potential to exhibit improved safety compared with other agents. The more potent antagonism at 5-HT<sub>2A</sub> receptors for brexpiprazole relative to aripiprazole, another D2 partial agonist, may afford a more favorable profile with respect to sleep quality; whereas the low binding affinities for histamine and muscarinic receptors suggest that brexpiprazole may have less potential to cause H<sub>1</sub>-receptor-related weight gain than olanzapine. Preclinical data also suggest that brexpiprazole will have lower potential for hyperprolactinemia than risperidone. Results from initial phase 2 trials showed brexpiprazole to be well tolerated by subjects with major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia (see Section 1.2 and Section 1.3).

Refer to the Investigator's Brochure for more detailed information about the investigational medicinal product (IMP).<sup>16</sup>

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## 1.1. Nonclinical Data

Efficacy and safety pharmacology are summarized in Section 1.1.1 and Section 1.1.2, respectively. A complete description of the available data from nonclinical studies, including pharmacokinetic and toxicology studies in different animal species, can be found in the Investigator's Brochure.<sup>16</sup>

## 1.1.1. Efficacy Pharmacology

Brexpiprazole functions as a partial agonist at the D2 receptor. In in vitro assay systems, based on forskolin-induced cyclic adenosine monophosphate (AMP) accumulation and calcium (Ca<sup>2+</sup>) mobilization in human dopamine D2L receptor-expressing cells, its intrinsic activity at the D2 receptor was slightly lower than that of aripiprazole. Brexpiprazole inhibited apomorphine (APO)-induced hyperlocomotion, APO-induced stereotyped behavior, and conditioned avoidance response in rats, which are predictive animal models for antipsychotic-like efficacy. The inhibitory effects of brexpiprazole were more potent than those of aripiprazole. Moreover, in contrast to the D2 receptor antagonist risperidone, brexpiprazole did not increase plasma prolactin levels in reserpine-treated rats, thus demonstrating a D2 receptor partial agonistic profile in vivo. Despite its lower intrinsic activity at the D2 receptor, the in vivo catalepsy liability of brexpiprazole, an index of extrapyramidal symptoms (EPS), was similar to that of aripiprazole, but still lower than that of the typical antipsychotic haloperidol. Furthermore, brexpiprazole showed high binding affinity for the 5-HT<sub>2A</sub> receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT<sub>2A</sub> receptor antagonistic activity; and the effect of brexpiprazole was more potent than that of aripiprazole. In addition, brexpiprazole acted as a partial agonist, exhibiting high binding affinities for the D3 and 5-HT<sub>1A</sub> receptors.

## 1.1.2. Safety Pharmacology

In safety pharmacology studies in rats at an oral dose of 30 mg/kg or higher, brexpiprazole induced pharmacologically mediated clinical signs considered to be due to depression of the central nervous system (CNS) and dose-dependent decreases in body temperature. When orally administered at up to 30 mg/kg in conscious male beagle dogs, brexpiprazole showed no effect on respiratory parameters or heart rate at any dose tested. Brexpiprazole decreased blood pressure at doses of 3 mg/kg or higher and prolonged both the QT interval and the corrected QT interval (QTc) by Van de Water's formula at

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30 mg/kg. Brexpiprazole inhibited human *ether-a-go-go* related gene (hERG) current in Chinese hamster ovary cells (CHO-K1) at concentrations of  $10^{-8}$  mol/L or higher, with a 50% inhibitory concentration of  $1.17 \times 10^{-7}$  mol/L. The mechanism for the blood pressure decreasing effect of brexpiprazole was suggested to result from a blockade of the  $\alpha_1$ -adrenoceptor in peripheral blood vessels, which is a part of the compound's pharmacological profile. Proarrhythmic risk was also evaluated by examining the effects of brexpiprazole on monophasic action potential parameters in halothane-anesthetized dogs. Brexpiprazole did not affect the terminal repolarization period even at an intravenous dose of 3 mg/kg, suggesting a low potential for proarrhythmic effects. In general, the changes in the CNS and respiratory and cardiovascular systems observed with brexpiprazole occurred at doses or exposure levels higher than those at which efficacy was confirmed in rats (3 mg/kg), and similar changes were shown to occur after administration of risperidone at similar or lower doses.

## 1.2. Clinical Data

## 1.2.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of single and multiple doses of brexpiprazole were studied in healthy subjects and in subjects with MDD, ADHD, and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, brexpiprazole and the metabolite DM-3411 were identified as the major analytes that are present in human plasma. In vitro, the activity of DM-3411 is 17 times lower than that of brexpiprazole; thus, it is considered an inactive metabolite. The pharmacokinetics of both brexpiprazole and its major metabolite, DM-3411, were linear following administration of single doses (0.2 to 8 mg) and multiple daily doses (0.5 to 2 mg in healthy subjects and 1 to 12 mg in schizophrenic subjects). At steady state, the brexpiprazole and DM-3411 mean terminal elimination half-life was 95.4 and 89.3 hours, respectively. The median time to maximum (peak) plasma concentration ( $t_{max}$ ) occurred at approximately 2 to 6 hours postdose for brexpiprazole and at approximately 10 to 24 hours postdose for DM-3411. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Steady-state pharmacokinetics also appeared to be linear following multiple daily doses of brexpiprazole in the range of 0.5 to 2 mg when administered to healthy subjects. The accumulation ratio, based on the maximum (peak) plasma concentration ( $C_{max}$ ) and area under the concentration-time curve calculated to the last observable concentration at time

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t (AUC<sub>t</sub>), was approximately 4 times. After multiple-dose administration of brexpiprazole (1-12 mg/day) to subjects with schizophrenia or schizoaffective disorder, the mean terminal elimination half-life of brexpiprazole and DM-3411 at steady state was 95.4 and 89.3 hours, respectively; and the median  $t_{max}$  was 3.0 and 8.0 hours, respectively.

In drug interaction trials in healthy subjects, brexpiprazole was shown to be metabolized by the cytochrome P450 3A4 (CYP3A4) and 2D6 (CYP2D6) isozymes and was not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein. Coadministration of potent CYP3A4 or CYP2D6 inhibitors with brexpiprazole resulted in about a 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half-life of brexpiprazole.

In a single-dose trial in healthy subjects, approximately 46.0% and 24.6% of administered radioactivity following an oral dose of <sup>14</sup>C-brexpiprazole was excreted in feces and urine, respectively. In this same trial, brexpiprazole did not preferentially bind to red blood cells (RBCs). Brexpiprazole showed high protein binding in human serum ( $\geq$  99.8%) in vitro.

The binding of brexpiprazole to dopamine receptors was assessed using positron emission tomography (PET). The mean D2/D3 receptor occupancies at 4 and 24 hours postdose after single-dose administration of 0.25, 0.5, 1, 2, 4, 5, and 6 mg of brexpiprazole to healthy subjects were 11.4% to 17.4%, 36.5% to 46.3%, 45.6% to 60.2%, 52.7% to 68.6%, 67.9% to 79.5%, 71.9% to 88.2%, and 69.5% to 92.6%, respectively (Trial 331-07-202). Based on the single-dose D2/D3 receptor occupancy data and steady-state pharmacokinetic and pharmacodynamic modeling, it was predicted that the D2/D3 receptor occupancy after multiple daily dose administration of 1 to 2 mg and higher doses of brexpiprazole will result in at least 80% to 90% D2/D3 receptor occupancy occupancy.

Trials have investigated the pharmacokinetics of brexpiprazole in special populations (subjects with hepatic impairment and renal impairment); one studying the effects of age and sex on brexpiprazole pharmacokinetics has been completed. Based on the results of the special population trials, no dose adjustment is needed when brexpiprazole is administered to elderly subjects or subjects with renal or hepatic insufficiency.

Additional information on the pharmacokinetics and pharmacodynamics of brexpiprazole and its metabolites in humans can be found in the Investigator's Brochure.<sup>16</sup>

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## 1.2.2. Phase 2 and Phase 3 Studies Conducted Under a US IND

## 1.2.2.1. Major Depressive Disorder (MDD)

The use of brexpiprazole as adjunctive therapy for the treatment of MDD has been studied in 2 completed, phase 2, double-blind, placebo-controlled trials (Trials 331-08-211 and 331-09-222). Additionally, 6 studies are ongoing: 2 United States (US) trials (1 phase 1, randomized, double-blind, placebo-controlled trial in elderly adults [aged 70-80 years] with MDD [Trial 331-12-291]; 1 long-term, open-label safety trial [Trial 331-08-212]); and 4 multinational trials (2 randomized, double-blind, placebo-controlled trials [Trials 331-10-227 and 331-10-228]; 1 randomized, double-blind, placebo- and active comparator-controlled trial of flexible-dose brexpiprazole as adjunctive therapy in the treatment of adults with MDD [Trial 331-12-282]; and 1 open-label, 52-week safety trial [Trial 331-10-238]).

Trial 331-08-211 was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of brexpiprazole (0.15 to 2 mg daily) as adjunctive treatment to an assigned open-label antidepressant therapy (ADT) in subjects with MDD. Subjects received brexpiprazole 0.15 mg/day,  $0.50 \pm 0.25$  mg/day,  $1.5 \pm 0.50$  mg/day, or matching placebo. In this trial, adjunctive brexpiprazole dosed at  $1.5 \pm 0.50$  mg/day was superior to adjunctive placebo with respect to the primary endpoint (change in Montgomery Asberg Depression Rating Scale [MADRS] Total Score) and several secondary efficacy endpoints. The  $1.5 \pm 0.50$  mg/day brexpiprazole dose group also demonstrated a favorable safety profile. Few subjects experienced serious treatment-emergent adverse events (TEAEs) or discontinued due to TEAEs. The analysis of laboratory data, electrocardiogram (ECG) parameters, and EPS scales did not indicate any concerns of clinical significance.

In Trial 331-09-222, randomized subjects received a flexible dose of brexpiprazole 1 to 3 mg/day (average dose 2.2 mg/day) or placebo as adjunctive treatment to an assigned open-label ADT. In this trial, the MADRS Total Score decreased at each visit for both brexpiprazole and placebo groups; however, the decrease observed in the brexpiprazole group was statistically significant from baseline at all visits except the primary endpoint visit. The MADRS response rate ( $\geq$  50% decrease MADRS Total Score) and remission rate (MADRS Total Score  $\leq$  10) were statistically significant at endpoint. Brexpiprazole at doses up to 3 mg/day was well tolerated when administered as adjunctive therapy to a marketed ADT in subjects with MDD. During the double-blind treatment phase, TEAEs were reported in 76.2% of subjects in the brexpiprazole group and 63.6% of subjects in

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the placebo group. The most frequently reported TEAEs were akathisia (11.9%), increased weight (11.4%), and insomnia (9.2%). The Columbia-Suicide Severity Rating Scale (C-SSRS) and adverse event (AE) data showed no suicidal behavior during double-blind treatment. No serious adverse events (SAEs) were reported for subjects in the brexpiprazole group, and 3 subjects (1.6%) in the placebo group experienced an SAE; 4.9% of subjects who received adjunctive brexpiprazole and 1.1% of subjects who received adjunctive placebo discontinued treatment due to TEAEs. There were no clinically relevant changes in laboratory values, ECG parameters, or vital sign measurements, except body weight (mean increase of 1.92 kg in the brexpiprazole group versus 0.13 kg in the placebo group), in brexpiprazole-treated subjects. The minimal changes in scores for EPS scales during double-blind treatment were not clinically relevant. An EPS-related AE was observed in 21.6% of subjects in the brexpiprazole group.

Trial 331-08-212 is an ongoing, 52-week, open-label trial examining the long-term safety and tolerability of brexpiprazole in adults with MDD. Subjects who complete trials 331-08-211 or 331-09-222 are eligible to enter this trial.

Ongoing Trials 331-10-227 and 331-10-228 are phase 3, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trials designed to assess the safety and efficacy of brexpiprazole as adjunctive therapy to an assigned open-label marketed ADT in depressed subjects who have demonstrated an incomplete response to prospective treatment with the same ADT. Brexpiprazole doses evaluated in these trials include 1 and 3 mg/day in Trial 331-10-227 and 2 mg/day in Trial 331-10-228. Subjects who complete Trial 331-10-227 or Trial 331-10-228 are eligible to be enrolled into a multicenter, 52-week, open-label trial (Trial 331-10-238). The ongoing trial 331-12-282 is a phase 3, multicenter, randomized, double-blind, placebo- and active comparator (Seroquel XR<sup>®</sup>)-controlled trial designed to assess the safety and efficacy of flexible-dose brexpiprazole as adjunctive therapy to an assigned open-label ADT in depressed adults, aged 18 to 65 years. The ongoing trial 331-12-291 is a phase 1, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of multiple ascending oral doses of brexpiprazole as adjunctive therapy in the treatment of elderly subjects (70 to 85 years) with MDD.

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### 1.2.2.2. Schizophrenia

The use of brexpiprazole monotherapy for the treatment of schizophrenia has been studied in 2 completed, multinational, phase 2, double-blind, placebo-controlled trials (Trials 331- 07-203 and 331-08-210). In addition, 4 multinational, phase 3 trials are ongoing: 3 randomized, double-blind, placebo-controlled trials (Trials 331-10-230, 331-10-231, and 331-10-232) and 1 open-label, 52-week safety trial (Trial 331-10-237).

Trial 331-07-203 was a dose-ranging, placebo-controlled trial (with aripiprazole as a positive control to confirm the assay sensitivity of the trial) in subjects experiencing an acute exacerbation of schizophrenia. Although the results showed that neither brexpiprazole (dose range, 0.25-6 mg/day) nor aripiprazole was significantly different from placebo for the primary and secondary efficacy endpoints at Week 6 (last-observation-carried-forward [LOCF]), numeric improvements in efficacy scale scores were similar between the low, mid, and high flexible-dose groups of brexpiprazole and aripiprazole for several endpoints, including the primary endpoint (the Positive and Negative Syndrome Scale [PANSS] total score, which measures the severity of symptoms of schizophrenia). Factors such as sex, age, and race did not appear to have a consistent influence on efficacy outcomes; however, the small sample size in many of the subgroup categories precluded definitive conclusions. The collective efficacy data from this trial suggest an active dose range of 1 to 6 mg/day of brexpiprazole for the treatment of schizophrenia. The frequency of TEAEs was similar in the brexpiprazole (69.7%). placebo (70.5%), and aripiprazole (70.0%) groups. The frequency of SAEs was similar between the brexpiprazole (3.8%) and placebo (3.2%) groups. The C-SSRS and AE data showed no suicidal behavior during double-blind or open-label treatment. Brexpiprazole did not result in any consistent, clinically relevant changes in laboratory values, vital signs, or ECG parameters. Statistically significant increases in weight, body mass index (BMI), and waist circumference were observed in the  $2.5 \pm 0.5$  mg/day and  $5.0 \pm 1.0$  mg/day brexpiprazole groups compared with the placebo group.

Eligible subjects from Trial 331-07-203 could have continued into the multicenter, 52-week, open-label trial (Trial 331-08-210) designed to assess the safety and tolerability of 1 to 6 mg of oral brexpiprazole in adult subjects with schizophrenia. Twenty-eight subjects were included in the 52-week trial: 20 subjects who had received prior brexpiprazole, 6 who had received prior placebo, and 2 who had received prior aripiprazole. Assessment of efficacy as a secondary objective showed improvement from baseline for each of the efficacy endpoints. The response rate (reduction of  $\geq$  30% from baseline in PANSS total score or CGI-I score of 1 [very much improved] or 2 [much

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improved] at the last visit) was 35.2% (86 of 244 subjects). Further, discontinuation for lack of efficacy was infrequent (2.0% [5 of 244 subjects]). Brexpiprazole (1-6 mg/day) was well tolerated when administered for up to 52 weeks. During the trial, 75.0% (21 of 28) of subjects enrolled for 52 weeks reported at least 1 TEAE. Most TEAEs were mild or moderate in intensity. The most frequently reported TEAEs (ie, those reported in > 10% of subjects) were viral respiratory tract infection and increased weight (14.3% each) and nasopharyngitis and somnolence (10.7% each). Although there were isolated, potentially clinically relevant results for individual subjects in clinical laboratory, vital signs, and/or ECG assessments, there were no clinically relevant mean changes overall for these assessments. Brexpiprazole was associated with slight mean increases from baseline in body weight, BMI, and waist circumference. Overall, the long-term safety and tolerability of brexpiprazole appeared to be similar to that observed after short-term exposure (up to 6 weeks); however, this could not be fully characterized in this trial due to the small number of subjects exposed for 52 weeks.

Currently, ongoing Trials 331-10-230 and 331-10-231 are designed to assess the safety and efficacy of fixed doses of 1, 2, or 4 mg/day of brexpiprazole and 0.2, 2, and 4 mg/day of brexpiprazole, respectively, in adults with acute schizophrenia; and Trial 331-10-232 will evaluate the use of brexpiprazole (1-4 mg/day) as maintenance treatment in subjects with schizophrenia. Subjects who complete Trial 331-10-230, Trial 331-10-231, or Trial 331-10-232 are eligible to be enrolled into a multicenter, 52-week, open-label trial (Trial 331-10-237), along with de novo subjects from select sites.

## 1.2.2.3. Attention-Deficit/Hyperactivity Disorder (ADHD)

For ADHD, 1 phase 2 trial (Trial 331-08-213) has been completed. Trial 331-08-213 was a proof-of-concept, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial in which adults with ADHD who had an incomplete/partial response to stimulant therapy in a prospective treatment phase were randomized to double-blind treatment with either brexpiprazole-plus-stimulant or placebo-plus-stimulant. Results showed no statistically significant improvement in the brexpiprazole group compared with the placebo group with regard to the primary efficacy endpoint (ie, the Conners' Adult ADHD Rating Scale-Observer: Screening Version [CAARS-O:SV]), the key secondary efficacy endpoints (ie, Wender-Reimherr Adult Attention Deficit Disorder Scale [WRAADDS] total score and sleep improvement as measured by the Insomnia Severity Index [ISI] total score and the ISI Item 2) or other efficacy endpoints. During the double-blind treatment phase (Phase B), a similar percentage of subjects in the brexpiprazole group (95 of 155 [61.3%]) and the placebo group (48 of 80 [60.0%])

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reported at least 1 TEAE. Only insomnia (in 13 of 155 [8.4%] subjects) and headache (in 11 of 155 [7.1%] subjects) were reported in greater than 5% of subjects in the brexpiprazole group. Most TEAEs were mild or moderate in intensity. During the double-blind treatment phase, 2 subjects reported SAEs (pneumonia and urinary tract infection), both of whom were in the placebo group. There were no unexpected or clinically relevant findings related to assessments of movement disorders, metabolic syndrome, EPS rating scales, or suicidality (based on the C-SSRS) during the double-blind phase.

### 1.3. Known and Potential Risks and Benefits

Based on the Investigator's Brochure,<sup>16</sup> combined data from the completed phase 1 clinical trials indicate that brexpiprazole is safe and well tolerated in healthy subjects at single oral doses of 0.2 to 6 mg and at multiple oral doses up to 2 mg/day. Data from the completed multiple-dose clinical trials indicate brexpiprazole is well tolerated at multiple oral doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder; up to 4 mg/day when coadministered with marketed ADT in subjects with MDD; and up to 4 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD.

Based on data from the 18 completed phase 1 clinical trials in healthy subjects or special populations (including healthy subjects from 2 phase 1 trials conducted in special populations) (15 in the US, 2 in Japan, and 1 in Korea), the most frequently reported TEAEs (incidence  $\geq$  5% or more of all healthy subjects who received brexpiprazole and more than placebo, administered either alone or with another marketed drug) were:

- Healthy subjects (N = 15 trials conducted in the US): dizziness, headache, postural dizziness, nausea, somnolence, constipation, and diarrhoea
- Healthy subjects (N = 3 trials conducted in Japan and Korea): nausea, orthostatic hypotension, somnolence, and dizziness

By indication, the most frequently reported TEAEs (incidence  $\geq$  5% or more of all subjects who received brexpiprazole and more than placebo, administered either alone or with another marketed therapy or drug (ie, ADT, stimulant therapy, or antibiotic) in completed phase 1, phase 1b, and/or phase 2 double-blind patient trials (excluding subjects enrolled in phase 2 open-label extension trials) conducted under US Investigation New Drug Applications (INDs) were:

• Schizophrenia or schizoaffective disorder (N = 4 trials): headache, anxiety, akathisia, nausea, increased weight, and dizziness

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- MDD (N = 3 trials): akathisia, increased weight, insomnia, upper respiratory tract infection, and nasopharyngitis
- ADHD (N = 2 trials): insomnia

In the single completed phase 1 trial in subjects with schizophrenia conducted in Japan, TEAEs reported in 3 or more subjects who received brexpiprazole (of 21 total subjects) were:

• Schizophrenia (N = 1 trial): increased serum prolactin and increased serum creatine phosphokinase

Brexpiprazole did not result in any consistent, clinically relevant changes in laboratory values, vital signs (blood pressure or heart rate), or ECG parameters in the completed phase 1 and 2 clinical trials in subjects with MDD or schizophrenia. Statistically significant increases in weight were observed with brexpiprazole relative to placebo in both sample populations. Brexpiprazole exhibited a favorable profile with respect to movement disorders in subjects with MDD at doses up to 3 mg/day (Trial 331-09-221) and in subjects with schizophrenia at doses up to 12 mg/day (Trial 331-08-205). In the dose-ranging trial that enrolled subjects who were experiencing an acute exacerbation of schizophrenia (Trial 331-07-203), an increase in the incidence of EPS was observed at the highest dose (ie, brexpiprazole  $5 \pm 1$  mg/day).

Two deaths have been reported in the 30 completed clinical trials. One death was reported in the completed phase 2 double-blind trial in adult subjects with acute schizophrenia (Trial 331-07-203). The second death was reported in the completed phase 2 open-label MDD trial (Trial 331-08-212). None of these subjects were taking IMP at the time of death and none of these fatal events were considered by the investigator to be related to IMP. Additionally, 4 deaths have been reported in 2 ongoing phase 3 open-label trials of brexpiprazole. One death was reported in an ongoing schizophrenia trial (331-10-237) and 3 deaths were reported in an ongoing MDD trial (331-10-238). One of the deaths (completed suicide in Trial 331-10-238) was considered by the investigator to be possibly related to IMP.

Serious TEAEs have been reported for 64 subjects who received brexpiprazole in the 30 completed trials. In ongoing trials of brexpiprazole, 120 subjects receiving brexpiprazole had reported serious TEAEs.

Refer to the current Investigator's Brochure for a summary of available nonclinical and clinical safety data.<sup>16</sup>

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# 2. Trial Rationale and Objectives

## 2.1. Trial Rationale

Behavioral symptoms, such as agitation, are core features in subjects with Alzheimer's disease and related dementias and develop in the majority of dementia subjects. The presence of agitation in subjects with Alzheimer's disease places a significant burden not only on subjects and their caregivers but also on the healthcare system.

Based on the data available from atypical antipsychotics in the treatment of agitation or aggression in Alzheimer's disease, brexpiprazole is an appropriate candidate to evaluate the benefit-risk ratio of this class of drugs in this subject population in today's clinical setting. In addition to potential treatment effects, the receptor binding profile of brexpiprazole may confer additional benefits in terms of the safety profile, particularly with respect to hyperprolactinemia, sleep quality, and weight gain.

In light of the Food and Drug Administration (FDA) boxed warning of increased mortality with the use of antipsychotics in elderly subjects with dementia-related psychosis and similar caution advised by other regulatory authorities, the clinical trial will be conducted in an environment that allows for close safety monitoring, in subjects who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone and has a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition. Furthermore, a slow titration schedule will be implemented with brexpiprazole being titrated to the highest assigned dose (2 mg/day) over a 4-week period.

## 2.2. Dosing Rationale

Brexpiprazole in a dose range of 0.5 mg/day to 2 mg/day will be studied in this flexible-dose trial. Doses will be increased slowly so that the highest dose will be reached at end of the fourth week of treatment (ie, at the Week 4 visit).

The doses to be used in this indication have been determined based on results from completed phase 1 safety and tolerability trials; from a PET trial of dopamine receptor occupancy; from phase 2 and phase 3 trials in subjects with schizophrenia, MDD, or ADHD; and from review of data from trials of similar medications in subjects with

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dementia. The following doses of brexpiprazole have been well tolerated in completed phase 1 single- and multiple-ascending-dose clinical trials:

- Up to 6 mg from single-dose trials and up to 2 mg/day from multiple-dose trials in healthy subjects
- Up to 12 mg/day from multiple-dose trials in subjects with schizophrenia or schizoaffective disorder (the maximum tolerated dose [MTD] was not reached)
- Up to 4 mg/day from a multiple-dose trial in subjects with MDD when coadministered with marketed ADT (the MTD was not reached)
- Up to 4 mg/day from a multiple-dose trial in subjects with ADHD when coadministered with marketed stimulant therapy (the MTD was not reached)

In the multiple-ascending-dose studies of subjects with schizophrenia, MDD, and ADHD, the studies ended when a prospectively chosen daily dose was reached. In all 3 studies, the MTD was not reached. The MTD of brexpiprazole in subjects with schizophrenia is greater than 12 mg/day. The MTD in subjects with MDD and ADHD, when coadministered with ADT and stimulant therapy, respectively, is greater than 4 mg/day. These data indicate that doses of at least 4 mg/day are well tolerated in nonpsychotic adult psychiatric subjects.

Efficacy in treating schizophrenia by dopamine D2 antagonists has been associated with occupancy of greater than 65% of the dopamine receptors.<sup>17,18,19</sup> However, the occupancy associated with effective doses of another partial dopamine agonist, aripiprazole, are greater than 80%<sup>20,21</sup> and the occupancy associated with therapeutic benefit of the brexpiprazole would be expected to be in the same range. To further define the proper dose range for brexpiprazole, the binding of brexpiprazole to dopamine D2/D3 receptors was investigated in a PET trial in healthy subjects (Trial 331-07-202). Single doses of up to 6 mg of brexpiprazole were administered to 15 subjects. Results from the trial predicted steady-state receptor occupancies of 80% to 90% at brexpiprazole doses of 1 to 2 mg (79.3% predicted occupancy at 1 mg brexpiprazole, 88.8% at 2 mg brexpiprazole, and 95.1% at 4 mg brexpiprazole). Based on the single-dose D2/D3 receptor occupancy data and steady-state pharmacokinetic/pharmacodynamic modeling, it was predicted that the D2/D3 receptor occupancy after multiple daily dose administration of 1 mg to 2 mg doses would result in 80% to 90% D2/D3 receptor occupancy.



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Since 4 mg/day has been well tolerated and to ensure that D2 occupancy levels at and above 80% are achieved, doses up to 4 mg/day are being studied in the phase 3 trials in schizophrenia and up to 3 mg/day in adjunctive treatment of MDD. In the phase 2 trial of adults with ADHD, the highest dose was 3 mg/day.

Three studies of another compound discovered by Otsuka, aripiprazole (Abilify<sup>®</sup>), have been conducted to investigate its benefit in the treatment of psychosis in subjects with Alzheimer's dementia.<sup>21,22,23</sup> In the 2 of the 3 aripiprazole trials that were conducted in subjects in institutional settings such as nursing homes, benefit in the treatment of agitation in that subject population was suggested by the finding of statistically significant differences between the aripiprazole treatment groups and the placebo treatment groups on 2 secondary endpoints, the Cohen-Mansfield Agitation Inventory (CMAI) and the agitation item of the Neuropsychiatric Inventory-Nursing Home (NPI-NH). In the fixed dose trial, which included 2 mg/day, 5 mg/day, and 10 mg/day dose arms, there were significant differences found on both measures for the 5 mg/day and 10 mg/day groups. Significant differences compared with placebo on both measures were also observed in the second flexible-dose trial of the 2 mg/day to 15 mg/day dose range.

Because of concerns about tolerability and safety in subjects, the doses of antipsychotics used in clinical trials in subjects with dementia have generally been lower than the doses recommended for subjects with schizophrenia.<sup>21,22,24</sup> While the dose range for brexpiprazole in schizophrenia studies is 1 mg/day to 4 mg/day, the selected dose range in the Alzheimer's population is 0.5 mg/day to 2 mg/day, to maximize tolerability while investigating doses that should achieve the occupancy of the D2 receptor associated with benefit in the alleviation of target symptoms by a D2 partial agonist. Slow titration of the dosing also will be employed to maximize tolerability.

#### 2.3. Trial Objectives

Primary: To compare the efficacy of flexible dosing of brexpiprazole (dose range of 0.5 to 2 mg/day) with placebo in subjects with agitation associated with dementia of the Alzheimer's type, as assessed by the CMAI after 12 weeks of treatment.

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Secondary: To evaluate the safety and tolerability of flexible dosing of brexpiprazole (dose range of 0.5 to 2 mg/day) compared with placebo in subjects with agitation associated with dementia of the Alzheimer's type after 12 weeks of treatment.

## 3. Trial Design

## 3.1. Type/Design of Trial

This is a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, 2-arm, flexible-dose trial designed to assess the efficacy, safety, and tolerability of brexpiprazole (dose range of 0.5 mg/day to 2 mg/day) in the treatment of subjects with agitation associated with dementia of the Alzheimer's type. The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition. All subjects must have a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period.

This trial will be monitored under the supervision of an independent Data Monitoring Committee (DMC). The DMC will monitor safety periodically, based on a predetermined schedule. The details of the DMC structure and its roles and responsibilities will be documented in a DMC charter (refer to Section 3.7.8).

The trial is organized as follows (refer to Figure 3.1-1 for a schematic of the trial design):

#### Screening Period

The screening period will range from 2 days to 42 days and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. The screening period may be extended after discussion with and approval by the medical monitor. Additional requirements for obtaining informed consent from this vulnerable subject population are provided in Section 3.4.1. An interactive voice response system (IVRS) or

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interactive web response system (IWRS) will be used to obtain the subject trial identification number for each subject with a signed ICF.

The purpose of the screening period is to determine the subject's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization (refer to Section 4.1). The subject should be randomized into the double-blind treatment period as soon as all the screening assessments are completed, the screening and baseline eligibility criteria have been met, and the required washout period has occurred.



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

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

Details around this procedure can be found in the operations manual.

### 12-week, Double-blind Treatment Period

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

- Brexpiprazole
- Placebo

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Subjects will follow a titration schedule to gradually increase their dose of the IMP to the target dose (refer to Table 3.2-1).

Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. All trial visits will take place as a clinic visit at either the investigator's site or residential facility, if applicable. All attempts should be made to maintain the subjects' normal routine with regard to physician appointments. Individual circumstances that fall outside this general convention should be discussed with the medical monitor in order to determine appropriateness to proceed. In addition, the subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1).

If a subject discontinues the trial prematurely, every effort will be made to complete the Week 12/Early Termination (ET) evaluations prior to administering additional medications for the treatment of agitation or other prohibited medications.

### Follow-up Period

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

Subjects who complete both the 12-week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-13-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit either at the investigator's site or the residential facility, if applicable.

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### 3.2. Treatments

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

- Brexpiprazole
- Placebo

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

Subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period using the recommended titration schedule as follows:

Table 3.2-1	Dosing Scher	me						
	Recommended Daily Dose Administered							
Treatment Group	Day after the Baseline visit (Day 1)	Day after the Day 3 visit (Day 4[+2 days])	Day after the Week 2 visit (Day 15[±2 days])	Day after the Week 4 visit (Day 29[±2 days])				
Brexpiprazole 0.5-2 mg/day	0.25 mg/day	0.5 mg/day	1 mg/day <sup>a</sup>	2 mg/day <sup>b</sup>				
Placebo	<			>				

<sup>a</sup>After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).

<sup>b</sup>The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (ie, Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability. Allowable IMP doses that may be given starting the day after the Week 4 visit (ie, Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

The first dose of IMP will be administered on the day after the Baseline visit (ie, Day 1). All subjects randomly assigned to receive brexpiprazole will receive 0.25 mg/day as a starting dose.

The dose of IMP will be increased from 0.25 mg/day to 0.5 mg/day starting on the day after the Day 3 visit (ie, Day 4 [+2 days]).

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The dose will then be increased to 1 mg/day starting on the day after the Week 2 visit (ie, Day 15  $[\pm 2 \text{ days}]$ ). After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).

The dose of IMP can be further increased from 1 mg/day to 2 mg/day starting on the day after the Week 4 visit (ie, Day 29 [ $\pm$ 2 days]). Note: the earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (ie, Day 29 [ $\pm$ 2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability.

Allowable IMP doses that may be given starting the day after the Week 4 visit (ie, Day 29 [ $\pm 2$  days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day. Dose decreases and increases must occur in a stepwise manner and can occur at any time (scheduled or unscheduled visits).

For subjects randomly assigned to receive placebo, their dose of IMP will be administered daily starting on the day after the Baseline visit (ie, Day 1) and ending on Week 12/ET (the last day of the Treatment Period).

Subjects unable to tolerate 0.5 mg/day of the IMP (or matching placebo) will be discontinued from the trial.

## 3.3. Trial Population

The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition. All subjects must have a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease. If a previous MRI or CT scan of the brain performed after the onset of the symptoms of dementia is not available, then an MRI/CT scan should be performed during screening. Additionally, at both the screening

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and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency x severity) of  $\geq$  4 on the agitation/aggression item of the NPI-NH or the Neuropsychiatric Assessment for Non-institutionalized Patients based on the NPI/NPI-NH (hereafter referred to as "NPI/NPI-NH"). The NPI-NH will be used for institutionalized subjects and the NPI/NPI-NH will be used for non-institutionalized subjects. The onset of the subject's symptoms of agitation must be at least 2 weeks prior to the screening visit. Subjects must require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (eg, pain, infection, polypharmacy) and a trial of nonpharmacological interventions.

Subjects must have been residing at their current location for at least 14 days before screening and be expected to remain at the same location for the duration of the trial. Subjects who at any point during the double-blind treatment phase transfer from an institutionalized setting to a non-institutionalized setting, or vice versa, will be withdrawn from the trial. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and medical monitor. All attempts should be made to maintain the subjects' normal routine with regard to appointments with physicians and overnight accommodations. Subjects in an institutionalized setting may receive supervised day passes at the discretion of the investigator and may also receive supervised overnight passes at the discretion of the investigator as long as such overnight stays are part of the subjects' normal routine.

It is planned that approximately 520 subjects will be screened at approximately 65 trial sites worldwide in order to randomize 260 subjects.

## 3.3.1. Caregiver/Caretaker Requirements

## 3.3.1.1. Non-institutionalized Subjects

In a non-institutionalized setting, the subject's caretaker is the person who lives with and cares for the subject on a regular basis. For example, caring for a subject on a regular basis may include the following activities: assisting with dispensing of IMP; observing the subject's general medical condition, including nutrition and hydration intake; reducing the chance of fall; and assisting the subject if emergency medical care is needed

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by contacting appropriate emergency services, the subject's primary physician, or the principal investigator, whatever is warranted. The caretaker may be supported in providing care to the subject by a professional(s), friend(s), or family member(s).

For purposes of this trial, the subject's caregiver is defined as the person who has sufficient contact to describe the subject's symptoms, and has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI/NPI-NH, and other applicable trial assessments, including completion of the diary. A caregiver must be identified during the screening period for participation in the interview of the applicable trial assessments. At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process. The caregiver role in the non-institutionalized setting may or may not be the same individual who fulfills the role of caretaker depending on the circumstances of the subject. The recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week. The caregiver is the person who should accompany the subject to all visits where the CMAI and NPI/NPI-NH are administered unless other arrangements are made and approved by the sponsor.

### 3.3.1.2. Institutionalized Subjects

In the institutionalized setting, there is only one role defined and that is the role of caregiver. A caregiver in the institutionalized setting is an individual who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, and other applicable trial assessments. A caregiver must be identified during the screening period for participation in the interview of the applicable trial assessments. At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. The recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week.

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## 3.4. Eligibility Criteria

## 3.4.1. Informed Consent

## 3.4.1.1. Determinations of Capacity

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

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

### 3.4.1.2. Documentation of Informed Consent

Consent will be documented on a written ICF. The ICF will be approved by the same institutional review board (IRB)/independent ethics committee (IEC) that approves this protocol. Each ICF will comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline<sup>25</sup> and local regulatory requirements. The investigator agrees to obtain sponsor approval of any written ICF used in the trial prior to submission to the IRB/IEC.

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

The subject must be informed about the trial to the extent compatible with the subject's understanding and, if capable, personally sign and date the consent or assent form, depending on local regulations.

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

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

Once appropriate essential information has been provided and fully explained in layman's language to the subject and the subject's legally acceptable representative by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by the subject, if capable, or the subject's legally acceptable

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representative, and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject and the subject's legally acceptable representative will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject and the subject's legally acceptable representative.



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## 3.4.2. Inclusion Criteria

Subjects are required to meet the following inclusion criteria:

Table	e 3.4.2-1 Inclusion Criteria
1.	The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.
2.	Male and female subjects between 55 and 90 years of age, inclusive, at the time of informed consent.
3.	Subjects with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria.
4.	Subjects with a MMSE score of 5 to 22, inclusive, at the screening and baseline visits.
5.	Subjects must have a previous MRI or CT scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease.
6.	Subjects who are residing at their current location for at least 14 days before screening and are expected to remain at the same location for the duration of the trial.
7.	Institutionalized subjects with an identified caregiver who has sufficient contact to describe the subject's symptoms and has direct observation of the subject's behavior. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. Non-institutionalized subjects may not be living alone (see Section 3.3.1.1 for caretaker definition) and must have an identified caregiver who has sufficient contact to describe the subject's symptoms and has direct observation of the subject's behavior.
8.	Subjects with a total score (frequency x severity) of $\geq 4$ on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at the screening and baseline visits.
9.	Subjects with onset of symptoms of agitation at least 2 weeks prior to the screening visit.
10.	Subjects who require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (eg, pain, infection, polypharmacy) and a trial of nonpharmacological interventions.
11.	Subjects who are capable of self-locomotion or locomotion with an assistive device (eg, 4-point walker, wheelchair).
12.	Subjects willing and able to discontinue all prohibited concomitant medications to meet protocol-required washouts prior to and during the trial period.
13.	Subjects able to satisfactorily comply with the protocol requirements.
7. 8. 9. 10. 11. 12. 13.	Institutionalized subjects with an identified caregiver who has sufficient contact to describe the subject's symptoms and has direct observation of the subject's behavior. The identified caregive can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who meets the caregiver requirements. Non-institutionalized subjects may not be living alone (see Section 3.3.1.1 for caretaker definitio and must have an identified caregiver who has sufficient contact to describe the subject's symptoms and has direct observation of the subject's behavior. Subjects with a total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at the screening and baseline visits. Subjects with onset of symptoms of agitation at least 2 weeks prior to the screening visit. Subjects who require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (eg, pain, infection, polypharmacy) and a tria of nonpharmacological interventions. Subjects who are capable of self-locomotion or locomotion with an assistive device (eg, 4-point walker, wheelchair).

CT = computed tomography; MRI = magnetic resonance imaging; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI-NH = Neuropsychiatric Inventory-Nursing Home; NPI/NPI-NH = Neuropsychiatric Assessment for Non-Institutionalized Patients based on the NPI/NPI-NH.

## 3.4.3. Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria prior to randomization:

Tab	le 3.4.3-1 Exclusion Criteria
Targ	et Disease
1.	Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.
2.	Subjects with a previous MRI or CT scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (eg, cortical stroke, multiple infarcts), space-occupying lesion (eg, tumor), or other major structural brain disease.
3.	Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.
4.	Subjects who have an insufficient response, based on the investigator's judgment, to 2 or more previous antipsychotic medications for the treatment of agitation associated with Alzheimer's disease.
5.	Subjects with delirium or history of delirium within the 30 days prior to the screening visit.
6.	Subjects who have been diagnosed with an Axis I disorder (DSM-IV-TR criteria) including, but not limited to:
	• Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia
	Bipolar I or II disorder, bipolar disorder not otherwise specified
	• Current major depressive episode. Subjects with major depressive disorder are eligible provided that they have been on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).
7.	Subjects with evidence of serious risk of suicide based on the Sheehan Suicidality Tracking Scale (Sheehan-STS), ie, a score of 3 or 4 on any one question 2 through 6 or 11 or a score of 2 or higher on any one questions 1a, 7 through 10, or 12, or who, in the opinion of the investigator, present a serious risk of suicide.
Med	ical History and Concurrent Diseases
8.	Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, gastrointestinal, or psychiatric disorders. Clinically significant cardiovascular disorders include uncontrolled atrial fibrillation, heart failure, or ischemic heart disease. Surrogates for uncontrolled cardiovascular disease would include recent (within the last 6 months) hospitalizations or procedures, such as percutaneous coronary intervention, coronary bypass surgery.
	Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.

Tab	le 3.4.3-1 Exclusion Criteria
9.	Subjects with uncontrolled hypertension (DBP > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension, which is defined as a decrease of $\ge 30$ mmHg in SBP and/or a decrease of $\ge 20$ mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure, OR development of symptoms. Abnormal vital signs results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
10.	Subjects with diabetes mellitus may be eligible for the trial if their condition is stable and well-controlled as determined by satisfying ALL of the following criteria:
	• $HbA_{1c} < 8.0\%$ , AND
	• Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (nonfasting). If the nonfasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND
	• Subject has not had any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes.
	Subjects with non-IDDM (ie, any subjects not using insulin) must also satisfy the below criterion:
	• Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening.
	Subjects with IDDM (ie, any subjects using insulin) must also satisfy the below criterion:
	• No current microalbuminuria; ie, urine ACR must be < 30 mg/g (calculated).
	Subjects with newly diagnosed diabetes during screening are excluded.
11.	Subjects with hypothyroidism or hyperthyroidism (unless condition has been stabilized with
	medications for at least the past 90 days) and/or an abnormal result for free T <sub>4</sub> at screening.
	Eligibility of subjects excluded based on an abnormal free T <sub>4</sub> result can be discussed with the medical monitor if, in the investigator's judgment, the subject is a suitable candidate for the trial.
12.	Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc.
13.	Subjects with seropositive status for hepatitis B (ie, HBsAg positive) or hepatitis C (ie, anti-HCV positive).
14.	Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.
15.	Subjects with a BMI $< 18.5 \text{ kg/m}^2$ .
16.	Subjects who have met <i>Diagnostic and Statistical Manual of Mental Disorders</i> , Fourth Edition, Text Revision (DSM-IV-TR) criteria for substance abuse or dependence within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
Phys	ical and Laboratory Results
17.	Subjects with a positive drug screen for cocaine, marijuana (whether medically prescribed or not), or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or over-the-counter (OTC) medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial
	following consultation and approval by the medical monitor.

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Tab	e 3.4.3-1 Exclusion Criteria
18.	Subjects with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subject or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Criteria are provided in Appendix 3, Appendix 4, and Appendix 5 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial:
	• Platelets $\leq$ 75,000/mm <sup>3</sup>
	• Hemoglobin $\leq 9 \text{ g/dL}$
	• Neutrophils, absolute $\leq 1000/\text{mm}^3$
	• Aspartate transaminase (AST) > 2 x ULN
	• Alanine transaminase (ALT) $> 2 \times ULN$
	• Creatine phosphokinase (CPK) > 3 x ULN, unless discussed with and approved by the medical monitor
	• Albumin $< 3 \text{ g/dL}$
	• $HbA_{1c} \ge 8\%$
	• Abnormal T <sub>4</sub> , unless discussed with and approved by the medical monitor. (Note: Free T <sub>4</sub> is measured only if the result for thyroid-stimulating hormone [TSH] is abnormal.)
	• QTcF $\ge$ 450 msec in men and $\ge$ 470 msec in women (see Section 3.7.4.4 for further details), unless due to ventricular pacing
	Tests with exclusionary results should be repeated (if ECG, 3 consecutive recordings) to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
Sex a	id Reproductive Status
19.	Sexually active females of childbearing potential (see Section 5.5) and male subjects who are not practicing 2 different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who will not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use 2 of the following precautions: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, birth control depot injections, condom with spermicide, or sponge with spermicide.
20.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial drug in Trial 331-12-284.
Proh	bited Therapies or Medications
21.	Subjects who have a current medical condition that requires treatment with an anticoagulant.
22.	Subjects who have received bapineuzumab, solanezumab, or other immunotherapy, such as vaccines, for the treatment of Alzheimer's disease (through clinical trial or compassionate use program) in the 6 months preceding randomization.
23.	Subjects who would be likely to require prohibited concomitant therapy during the trial (see Table 4.1-1).
24.	Subjects who received brexpiprazole in any prior clinical trial or commercially available brexpiprazole (Rexulti®).
Aller	ies and Adverse Drug Reactions
25.	Subjects with a history of neuroleptic malignant syndrome (NMS).
26.	Subjects with a history of true allergic response (ie, not intolerance) to more than 1 class of medications
I	mousuum.

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Tabl	e 3.4.3-1 Exclusion Criteria
Other	
27.	Subjects who participated in a clinical trial within the last 30 days.
28.	Any subject who, in the opinion of the investigator, medical monitor, or sponsor should not
	participate in the trial.

ACR = albumin-to-creatinine ratio; anti-HCV = hepatitis C antibodies; BMI = body mass index; CT = computed tomography; CYP2D6 = cytochrome P450 2D6 isozyme; DBP = diastolic blood pressure; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision;

ECG = electrocardiogram; HbA<sub>1c</sub> = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; MRI = magnetic resonance imaging; QTcF = QT interval as corrected for heart rate by Frederica's formula; SBP = systolic blood pressure; T<sub>4</sub> = thyroxine; ULN = upper limit of normal.

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

## 3.5. Outcome Variables

## 3.5.1. Primary Efficacy Variable

The primary efficacy variable is the change from baseline to Week 12/ET in the CMAI total score. The primary analysis will use a mixed-effect model repeated measure (MMRM) approach.

## 3.5.2. Key Secondary Efficacy Variable

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



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## 3.5.6. Safety Variables

Safety variables to be examined in this trial will include AEs, physical and neurological examinations, vital signs, body weight, waist circumference, clinical laboratory tests (hematology, serum chemistry, and urinalysis), ECGs, <sup>CCI</sup>

Adverse events will be examined by frequency, severity, seriousness, discontinuation, and relationship to treatment. Mean change from baseline and the incidence of potentially clinically relevant abnormal values will be calculated for vital signs, body weight, routine laboratory tests (including prolactin), and ECG parameters. Mean change from baseline will be calculated for coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], and International Normalized Ratio [INR]), glycosylated hemoglobin (HbA<sub>1c</sub>), cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), waist circumference, and BMI (derived programmatically from body weight and height measurements). A central ECG service will be used to review all ECGs to standardize interpretations for the safety analysis. EPS will be evaluated by calculating mean change from baseline on the SAS, AIMS, and BARS. The Sheehan-STS will be used to assess and classify reported suicidal behavior. By-subject listings of physical and neurological examination findings will be reviewed as a further assessment of safety.

# 3.5.7. Pharmacokinetic/Pharmacodynamic Variables

Plasma concentrations will be determined for brexpiprazole and its metabolite(s) and descriptive statistics will be calculated. No formal statistical comparisons are planned. Additional population or pharmacokinetic or pharmacodynamic modeling may be performed as a separate analysis by combining data from this trial with data from all other trials.

## 3.6. Measures to Minimize/Avoid Bias

## 3.6.1. Randomization

During the trial, administration of the IMP will be double-blind. In other words, neither the investigator nor the subject will have knowledge of the treatment assignment (ie, placebo or brexpiprazole). Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical

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Development & Commercialization, Inc (OPDC) Biometrics Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, operating the IVRS/IWRS, and reporting SAEs to regulatory agencies. The randomization will be stratified by center. Subjects will be randomized to brexpiprazole or placebo in a 1:1 ratio within each stratum.

## 3.7. Trial Procedures

The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4.5 years, of which approximately 4 years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+2) days after the last dose of the IMP.



All trial visits will take place as a clinic visit at either the investigator's site or residential facility, if applicable. All attempts should be made to maintain the subjects' normal routine with regard to physician appointments. Individual circumstances that fall outside this general convention should be discussed with the medical monitor in order to determine appropriateness to proceed. Trial assessment time points are summarized in Table 3.7-1.

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Table 3.7-1 Schedule of Assessments											
	Visit										
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	CC:
ENTRANCE/HISTORY											
Informed consent <sup>e</sup>	Х										
Inclusion/exclusion criteria <sup>f</sup>	X	Х									
Demography	Х										
Medical history	Х										
Psychiatric history	Х										
Neurological history <sup>g</sup>	Х										
Prior medication washout <sup>h</sup>	Х										
NINCDS-ADRDA	Х										
Hachinski Ischemic Scale (Rosen	x										-
Modification) <sup>g</sup>											
HBsAg and anti-HCV	Х										
EFFICACY				•		•	•				•
CMAI	Х	Х		Х	Х	Х	Х	Х	Х		
CGI-S <sup>j</sup>	Х	X		Х	X	Х	Х	Х	Х		
ССІ				Х	Х	Х	Х	Х	Х		
NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects)	X	Х		Х	Х	Х	Х	Х	Х		

Table 3.7-1Schedule of Assessments											
Visit											
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	
OTHER											
CCI											
-											
	1					T	1			1	<u>т</u>
Physical examination <sup>K</sup>	Х								Х		
Neurological examination <sup>1</sup>	Х								Х		
Vital signs <sup>m</sup>	Х	Х	Х	Х	Х	X	Х	X	Х		
Clinical laboratory tests (hematology, serum	v	<sup>0</sup>			, p		p		V		
chemistry, urinalysis) <sup>n</sup>	Λ	Х			X		X		А		
Prolactin (blinded) <sup>n</sup>	Х								Х		
TSH with reflex to free T <sub>4</sub> if abnormal <sup>n</sup>	Х								Х		
HbA <sub>1c</sub> <sup>n</sup>	X								Х		
PT, aPTT, and INR <sup>n</sup>	X								Х		
ACTH and cortisol <sup>n</sup>	X								Х		
Urine pregnancy test (women of childbearing	v								v		
potential) only <sup>q</sup>	Λ								Λ		
ECG <sup>r</sup>	Х	Х			Х		Х		Х		
Blood alcohol <sup>s,t</sup>	X										
Urine drug screen <sup>s,t</sup>	X										
MMSE	Х	Х							Х		

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Visit											
ssessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	
V											
dverse events	X	Х	Х	X	X	X	X	Х	Х	X	
armacokinetic sampling <sup>W</sup>		Х					Х		Х		
oncomitant medications <sup>y</sup>	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
											I
THER PROCEDURES				L	I	L	I			l I	
gister trial visit in IVRS/IWRS	X	Х	Х	Х	Х	Х	Х	Х	Х		
ndomize eligible subjects via IVRS/IWRS		Х									
IP dispensing		Х	Х	Х	Х	Х	Х	Х			
IP accountability			Х	Х	Х	Х	Х	Х	Х		
bb elephone contact											
DDITIONAL ENTRANCE/HISTORY	•										
RI/CT scan <sup>cc</sup>	x <sup>cc</sup>										
CTH = adrenocorticotropic hormone; AIMS     thromboplastin time   CGI-S = Clinical     CGI-S = Clinical     CT = computed tomograp     HBsAg = hepatitis B surface antigen; IAP =     INR = International Normalized Ratio; IVR     Examination;     CCI     Neurological and Communicative Disorders     ;   NPI-NH = Neuron     Non-Institutionalized Patients based on the Disorders	= Abnormal In Global Impres ohy; ECG = ele Independent A S = interactive and Stroke and ropsychiatric Ir NPI/NPI-NH; F	voluntary M ; CO sion-Severity ectrocardiogradjudication voice respor (), M d the Alzhein ventory-Nur PT = prothro	y of Illne: ram; ET = Panel; IC nse syster IRI = mag mer's Dis rsing Hor mbin tim	Scale; ar ss; CMA = early ter CF = infor n; IWRS gnetic res sease and ne rating e; CC	I = Coher rmination med con = interac conance in Related scale; NI	= hepatiti n-Mansfid ; FU = fo sent form tive web maging; 1 Disorders PI/NPI-N	s C antib eld Agita ollow up; response NINCDS s Associa H = Neu	odies; aP tion Inver HbA <sub>1c</sub> = investigat system; 1 -ADRDA tion; CCI ropsychia	TT = activated p ntory; CCI glycosylated h cional medicinal MMSE = Mini- = National Inst tric Assessment ; CCI	emoglob product Mental S titute of t for	in; ;; State

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;  $T_4$  = thyroxine; TSH = thyroid-stimulating

#### hormone.

<sup>a</sup>Screening begins when the ICF is signed. Screening procedures must be initiated between Day -42 and Day -2. The screening period may be extended after discussion with and approval by the medical monitor. At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.

<sup>b</sup>If a subject discontinues prematurely before Week 12, every effort should be made to complete the Week 12/ET evaluations prior to administering additional medications for the treatment of agitation or other prohibited medications.

All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver. Subjects who complete both the 12-week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-13-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at either the investigator's site or residential facility, if applicable.

<sup>e</sup>The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.

The investigator is responsible for ensuring that subjects are eligible for enrollment into the trial and for assessing subject safety throughout the trial.

<sup>g</sup>The neurological history and Hachinski Ischemic Scale (Rosen Modification) will be completed to assess eligibility for the trial by the same physician who performs the neurological examinations (refer to Section 3.7.4.3.2). The neurological history will include an MRI/CT scan as described in Section 3.7.3.7 and as scheduled in the ADDITIONAL ENTRANCE/HISTORY.

<sup>h</sup>Washout of prohibited medications begins after signing the ICF and must comply with the required washout periods (refer to Section 4.1).

CGI-S, CCI are based on agitation.

<sup>k</sup>Physical examination includes measurement of height and waist circumference at screening and waist circumference at Week 12/ET.

<sup>1</sup>A detailed neurological examination will be performed by a physician at screening, Week 12/ET, and as needed during the trial for new onset neurological symptoms. The neurological examination will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system.

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<sup>m</sup>Vital signs include body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Blood pressure and heart rate will be measured in the supine (performed first), sitting, and standing positions. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital sign measurements scheduled for the same visit as blood samples are to be completed before blood is drawn.

<sup>n</sup>Subjects should be fasting for a minimum of 8 hours prior to blood draws for screening laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. Clinical laboratory tests at other visits should be drawn fasting, if possible, but must be drawn after a minimum 8-hour fast at Week 12/ET. Vital sign measurements and ECG assessments should be completed before any blood samples are collected. See Table 3.4.3-1 for exclusion criteria based on screening laboratory tests.

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

<sup>p</sup>Urinalysis is not required at Week 4 or Week 8.

<sup>q</sup>All positive urine pregnancy test results must be confirmed by a serum test. Subjects with a positive serum pregnancy test result at screening must not be enrolled, and subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

<sup>r</sup>Standard 12-lead ECGs will be performed after the subject has been supine and at rest for ≥ 5 minutes prior to the ECG. The ECGs will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated (with 3 consecutive ECG recordings) to confirm the finding(s) before excluding the subject from the trial. A central ECG service will review all ECGs to standardize interpretations for the safety analysis. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

<sup>s</sup>A urine drug screen and a blood alcohol test are required at screening, but either or both can be conducted at any time during the trial at the discretion of the investigator.

Eligibility for randomization is based on the screening urine drug screen results. Subjects whose urine drug screen is positive for cocaine, marijuana, or other illicit drugs at screening are not eligible for participation in the trial. Subjects with a positive blood alcohol test or a positive urine drug screen due to use of prescription or OTC medications or products may be retested (the evaluation may be repeated within the screening period) or rescreened once for participation in the trial with consent of the medical monitor.

<sup>v</sup>Adverse events will be recorded, starting after the ICF has been signed.

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<sup>A</sup>Pharmacokinetic samples will be obtained at baseline and at any time during the Week 8 and Week 12/ET visits. If blood samples for clinical laboratory tests are not collected at the baseline visit, pharmacokinetic samples do not need to be obtained at baseline. Every possible effort should be made to collect samples at the same time at each visit. The subject should be advised to take the IMP at approximately the same time each day throughout the trial, but most importantly, prior to each pharmacokinetic sampling. The date and time of the last 2 doses prior to each pharmacokinetic blood draw will be recorded on the electronic case report form (eCRF). Vital sign and ECG assessments should be completed before any blood samples are collected.

<sup>y</sup>All medications taken within 30 days of screening (signing of ICF/assent) will be recorded. In addition, all prescription and nonprescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in the protocol (refer to Section 4.1). During the first 4 weeks of the randomized phase (baseline to Week 4 visit), benzodiazepines are allowed but limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects. Benzodiazepines must not be administered within 12 hours prior to the efficacy and safety scales. After the Week 4 visit, benzodiazepines are prohibited.

<sup>aa</sup>Subjects will start taking IMP from the new blister card the day after the clinic visit.

<sup>bb</sup>The subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.

<sup>cc</sup> If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed **CC** in order to confirm eligibility.

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## 3.7.1. Schedule of Assessments

## 3.7.1.1. Screening

The screening period begins after written informed consent has been obtained. Subjects will participate in screening activities for 2 days to 42 days. The screening period may be extended after discussion with and approval by the medical monitor. After the ICF has been signed, the site will obtain a Subject identification/identifier (ID) by accessing the IVRS or IWRS. Completion of screening activities may require more than 1 visit; however, only the initial visit will be registered in the IVRS or IWRS.

Screening evaluations will include the following:

- At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities and their role in this trial. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.
- Trial personnel will call the IVRS or access the IWRS to register the visit (initial screening visit only).
- The investigator must assess the capacity of the subject to provide informed consent during the screening period. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years that is considered to be clinically relevant per the investigator's judgment.
- Psychiatric and neurological history will be recorded.
- If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed **CC** in order to confirm eligibility.
- Medications taken within 30 days of screening (signing of ICF/assent) will be recorded.
- Washout from prohibited concomitant medications will begin, if applicable (see Section 4.1).
- A complete physical examination (including height and waist circumference) will be performed.

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- A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a physician.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. See Section 3.4.3 for exclusions based on outcome of screening vital sign measurements. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Subjects with screening QTcF ≥ 450 msec (males) or ≥ 470 msec (females) will be excluded from the trial, unless due to ventricular pacing (see Section 3.7.4.4). Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject. The ECG is to be completed before any blood is drawn.
- Blood samples will be drawn for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C (anti-HCV). Subjects with a positive result for any of these tests will be excluded from the trial. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Blood samples will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR, and serum chemistry, including prolactin [blinded], HbA<sub>1c</sub>, ACTH, cortisol, and TSH with reflex to free T<sub>4</sub> if the result for TSH is abnormal) and should be obtained after a minimum 8-hour fast, if possible. See Section 3.7.4.2 for exclusions based on outcome of screening clinical laboratory tests. Vital signs and ECG assessments should be completed before any blood samples are collected.
- Samples will be obtained for blood alcohol testing. Subjects with a positive blood alcohol test at screening may be retested or rescreened once for participation in the trial with consent of the medical monitor.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. Subjects positive for cocaine, marijuana, or other illicit drugs are not eligible to be retested or rescreened. Subjects with a positive drug screen resulting from use of prescription or OTC medications or products may be retested (the evaluation may be repeated within the screening period) or rescreened once for participation in the trial after consent of the medical monitor.
- Urine albumin-to-creatinine ratio (ACR) will be determined only for subjects with insulin-dependent diabetes mellitus (IDDM) (must be < 30 mg/g; calculated as urine albumin [mg/dL]/urine creatinine [g/dL]).

- A urine pregnancy test will be performed for all women of childbearing potential. All positive results must be confirmed by a serum pregnancy test. Subjects with positive urine and serum test results will be excluded from the trial.
- An adequately trained and experienced clinician will confirm the diagnosis of probable Alzheimer's disease using the NINCDS-ADRDA criteria.
- An adequately trained and experienced physician who performs the neurological examination will complete the Hachinski Ischemic Scale (Rosen Modification).
- A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.
- An adequately trained and experienced clinician will administer the CGI-S.
- An adequately trained and experienced clinician will administer the MMSE.
- AEs will be recorded, beginning with the signing of the ICF.
- Concomitant medications will be recorded.
- • •
- The subject's caregiver and/or facility staff will complete a paper diary daily (if possible) after the ICF is signed, continuing through Week 12/ET.

# 3.7.1.2. Baseline (Day 0)

If the subject is found to be eligible for the trial during the screening period, the following procedures will be performed at the baseline visit:

- CCI
- Inclusion and exclusion criteria will be verified.
- The investigator must assess the capacity of the subject to provide informed consent throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.
- A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.
- An adequately trained and experienced clinician will administer the CGI-S.

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- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital signs are to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry) and should be obtained after a minimum 8-hour fast, if possible. Urine will be collected for urinalysis. If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit. Vital signs and ECG assessments should be completed before any blood samples are collected.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Blood samples will be obtained for pharmacokinetic analysis. If blood samples for clinical laboratory tests are not collected at the baseline visit, pharmacokinetic samples do not need to be obtained at baseline. Vital sign and ECG assessments should be completed before any blood samples are collected.

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• AEs and concomitant medications will be recorded.

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- Trial personnel will call the IVRS or access the IWRS to randomize the subject and obtain a blister card assignment.
- Diary recording will continue.
- The subject will take the first dose of the IMP from the assigned blister card on Day 1 (ie, the day after the baseline visit). The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.

## 3.7.1.3. Double-blind Treatment Period

#### 3.7.1.3.1. Day 3

This visit is to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be performed:

- The investigator must assess the capacity of the subject to provide informed consent throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital sign measurements are to be completed before any blood is drawn.
- AEs and concomitant medications will be recorded.
- IMP accountability will be performed.
- Trial personnel will call the IVRS or access the IWRS to register the visit and obtain the blister card assignments for the IMP.
- The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.
- Diary recording will continue.

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## 3.7.1.3.2. Weeks 2, 4, 6, 8, and 10

All subjects will be evaluated at Weeks 2, 4, 6, 8, and 10. Visits are to occur within  $\pm 2$  days of the target visit date. The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.

- The investigator must assess the capacity of the subject to provide informed consent throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.
- A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.
- An adequately trained and experienced clinician will administer the CGI-S, CCI
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital sign measurements are to be completed before any blood is drawn.



- AEs and concomitant medications will be recorded.
- Diary recording will continue.
- IMP accountability will be performed.
- Trial personnel will call the IVRS or access the IWRS to register the visit and to obtain their blister card assignments for the IMP.
- The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.

The following additional evaluations will be performed at the designated visits:

- A fasting blood draw for clinical laboratory tests (hematology and serum chemistry) will be obtained at *Weeks 4 and 8 only*. Vital sign and ECG assessments should be completed before any blood samples are collected.

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- Blood samples will be obtained for pharmacokinetic analysis at *Week 8 only*. The date and time of the blood draw and the date and time of the last 2 doses of IMP prior to the blood draw will be recorded on the electronic case report form (eCRF). Vital sign and ECG assessments should be completed before any blood samples are collected.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes at *Weeks 4 and 8 only*. The ECG is to be completed before any blood is drawn.

In addition, the subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.

# 3.7.1.4. End of Treatment (Week 12/ET)

The Week 12 visit signifies the end of treatment for all subjects. Therefore, all subjects will undergo a complete evaluation at Week 12 ( $\pm$  2 days). In addition, Week 12/ET evaluations are to be completed for any subject withdrawn from the trial at any time, if possible. If a subject is withdrawn, every effort will be made to complete all of the Week 12/ET evaluations prior to administering any additional medications for the treatment of agitation or other prohibited medications.

The following activities and assessments will occur at Week 12 (or at the ET visit, if applicable):

- A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.
- An adequately trained and experienced clinician will administer the CGI-S, CCI

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- An adequately trained and experienced clinician will administer the MMSE.
- CCI
- A complete physical examination (including waist circumference) will be performed.
- A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a physician.
- Vital sign measurements (body weight, body temperature, blood pressure, and heart rate) will be recorded. Blood pressure and heart rate are to be measured in the following order: supine, sitting, and standing. Blood pressure and heart rate measurements in the supine position should be taken after the subject has been lying for at least 5 minutes. The sitting and standing measurements should be taken within 1 to 3 minutes of changing positions. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- A fasting blood draw will be collected for clinical laboratory tests (hematology, including PT, aPTT, and INR; and serum chemistry, including prolactin [blinded] HbA<sub>1c</sub>, ACTH, cortisol, and TSH with reflex to free T<sub>4</sub> if the result for TSH is abnormal) and urine will be collected for urinalysis. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A blood sample will be obtained for pharmacokinetic analysis. The date and time of the blood draw and the date and time of the last 2 doses of IMP prior to the blood draw will be recorded on the eCRF. Vital sign and ECG assessments should be completed before any blood samples are collected.
- Women of childbearing potential will be given a urine pregnancy test. Any positive result must be confirmed by a serum pregnancy test.
- AEs and concomitant medications will be recorded.
- Diary recording will be stopped.
- Final IMP accountability will be performed.

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• Trial personnel will call the IVRS or access the IWRS to register completion or discontinuation from the trial.

#### 3.7.1.5. Follow-up

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

Subjects who complete both the 12-week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-13-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at either the investigator's site or residential facility, if applicable.

#### 3.7.2. Efficacy Assessments

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

A caregiver must be identified during the screening period for participation in the interview for the CMAI, NPI-NH, NPI/NPI-NH, and other applicable trial assessments. In addition to providing responses to trial questionnaires, the identified caregiver will be interviewed by the trial personnel regarding the subject's general medical condition, behavioral symptoms, and activities of daily living. If the subject is in an institutionalized setting, the identified caregiver will gather information from several informants, including staff from the day, afternoon, and night shifts, as well as from reliable family members or friends, in order to provide an accurate and comprehensive overview of the subject's behavioral symptoms and condition. If the subject is in a non-institutionalized setting, the identified caregiver can gather information from the caretaker (if different than the identified caregiver) or from other informants who are in a

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The CMAI

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position to observe the subject and provide information regarding behavioral symptoms and activities of daily living. Details on the caregiver requirements can be found in Section 3.3.1.

#### 3.7.2.1. Cohen-Mansfield Agitation Inventory (CMAI)

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

was developed to assess the frequency of agitated behaviors in elderly persons and was originally used in nursing home residents. It consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation.<sup>11</sup> As initially described by Cohen-Mansfield<sup>11</sup> and outlined in the Instruction Manual for the CMAI,<sup>26</sup> these distinct agitation syndromes include: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior. A sample of the CMAI is provided in Appendix 6.

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

The severity of agitation for each subject will be rated using the CGI-S.<sup>27</sup> To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the subject at this time?" Response choices are 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; <math>3 = mildly ill;4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects. A sample of the CGI-S is provided in Appendix 7.



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# 3.7.2.5. Neuropsychiatric Inventory-Nursing Home (NPI-NH)

The NPI-NH questionnaire is used to interview the identified caregiver about the institutionalized subject's possible neuropsychiatric symptoms (ie, delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behaviors, and appetite/eating behaviors). The NPI-NH gives an insight into the frequency (on a scale of 1 to 4), severity (on a scale of 1 to 3), and occupational disruption (on a scale of 0 to 5) of each of the 12 separate behavioral domains.<sup>28,29</sup> Therefore, for each behavioral domain, there are 4 scores: frequency, severity, total (frequency x severity), and occupational disruptiveness. A total NPI-NH score can be calculated by adding the first 10 domain total scores (frequency x severity scores) together. All 12 domain total scores can be summed in special circumstances where the neurovegetative symptoms are of particular importance.<sup>29</sup> Administering the questionnaire generally takes about 15 minutes. The psychometric properties and factor structure of the NPI-NH have been shown to have internal consistency, reliability, convergent validity, and discriminant validity.<sup>30</sup>

A sample of the NPI-NH is provided in Appendix 8.

#### 3.7.2.6. Neuropsychiatric Assessment for Non-institutionalized Patients Based on the NPI/NPI-NH (NPI/NPI-NH)

The NPI/NPI-NH is a structured caregiver interview designed to obtain information on the presence of psychopathology in non-institutionalized subjects with brain disorders, including Alzheimer's disease and other dementias.<sup>31</sup> The NPI/NPI-NH differs from the NPI-NH in that questions referring to "Occupational Disruptiveness" from the NPI-NH

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have been replaced with questions referring to "Distress" from the Neuropsychiatric Inventory (NPI). Item domains are identical between the NPI/NPI-NH and NPI-NH. Ten behavioral and two neurovegetative symptom domains comprise the NPI/NPI-NH (ie, delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behavior disorders, and appetite/eating disorders). The identified caregivers are instructed to indicate the frequency (on a scale of 1 to 4), severity (on a scale of 1 to 3), and distress (on a scale of 0 to 5) of each of the 12 separate behavioral domains. Therefore, for each behavioral domain, there are 4 scores: frequency, severity, total (frequency x severity), and distress. A total NPI/NPI-NH score is calculated by adding the first 10 domain total scores (frequency x severity scores) together. All 12 domain total scores can be summed in special circumstances where the neurovegetative symptoms are of particular importance. Administering the NPI/NPI-NH generally takes about 15 minutes.

A sample of the NPI/NPI-NH is provided in Appendix 9.



#### 3.7.3. Other Assessments

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3.7.3.2.	CCI		
2722	CCI		
5.7.5.5.			
3.7.3.4.	CCI		

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#### 3.7.3.5. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)

The NINCDS-ADRDA, which has shown good reliability and validity, provides criteria for the possible and probable diagnosis of Alzheimer's disease.<sup>37</sup> These criteria require that cognitive impairment and a suspected dementia syndrome be confirmed by neuropsychological testing for a clinical diagnosis of Alzheimer's disease. The NINCDS-ADRDA criteria specify 8 cognitive domains that may be impaired in Alzheimer's disease: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving, and functional abilities.

A sample of the NINCDS-ADRDA is provided in Appendix 14.

#### 3.7.3.6. Hachinski Ischemic Scale (Rosen Modification)

The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms.<sup>38</sup> The Rosen-modified Hachinski Ischemic Scale will be completed to assess eligibility for the trial by the same physician who performs the neurological examinations (see Section 3.7.4.3.2).

A sample of the Hachinski Ischemic Scale (Rosen Modification) is provided in Appendix 15.

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# 3.7.3.7. Magnetic Resonance Imaging/Computed Tomography Scan of the Brain

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

#### 3.7.4. Safety Assessments

#### 3.7.4.1. Adverse Events

Refer to Section 5, Reporting of Adverse Events.

#### 3.7.4.2. Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Urine will be collected and blood will be drawn from each subject during screening prior to treatment with the IMP. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. A fasting blood sample is required at baseline prior to dosing. If a fasting blood sample was obtained at the screening visit and less than 14 days have elapsed since the screening visit, clinical laboratory tests (hematology, serum chemistry, and urinalysis) do not need to be repeated at the baseline visit. The results of these tests must be reviewed by the investigator prior to initiation of the administration of the IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically.

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Table 3.7.4.2-1Clinical Laboratory Assessments				
Hematology	Serum Chemistry			
WBC count with differential	ALP			
RBC count	ALT (SGPT)			
Hematocrit	AST (SGOT)			
Hemoglobin	BUN			
Platelet count	СРК			
	Creatinine			
<u>Urinalysis</u>	LDH			
pH	Total bilirubin			
Specific gravity	Triglycerides			
Protein	Cholesterol (total, LDL, and HDL)			
Ketones	Calcium			
Glucose	Chloride			
Blood	Glucose			
Microscopic exam (performed only if any part of	Insulin			
the urinalysis is not negative)	Magnesium			
	Bicarbonate			
Urine Drug Screen	Inorganic phosphorous			
Amphetamines	Sodium			
Barbiturates	Potassium			
Benzodiazepines	Total protein			
Cannabinoids	Uric acid			
Cocaine	GGT			
Marijuana	Prolactin (blinded)			
Methadone	Albumin			
Opiates	eGFR			
Phencyclidine				
Propoxyphene	Additional Tests			
Other	Urine pregnancy (women of childbearing potential) <sup>a</sup>			
<u>Other</u> Plaad alaahal	TSH, with reflex to free $T_A$ if TSH is abnormal			
	PT aPTT and INR			
Additional Tests (Sereening Only)	ACTH			
HDada	Cortisol			
ndsAg				
Iring albumin (only for subjects with IDDM)	HDA <sub>1c</sub>			
Urine arounnin (only for subjects with IDDM)				
ACTH = adrenocorticotronic hormone: ALD = alkalir	l na phosphatasa: ALT (SCPT) — alanina transaminasa			

ACTH = adrenocorticotropic hormone; ALP = alkaline phosphatase; ALT (SGPT) = alanine transaminase (serum glutamic-pyruvic transaminase); anti-HCV = hepatitis C antibodies; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate transaminase (serum glutamic-oxaloacetic transaminase); BUN = blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; HbA<sub>1c</sub> = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HDL = high density lipoprotein; IDDM = insulin-dependent diabetes mellitus; INR = International Normalized Ratio; LDH = lactic dehydrogenase; LDL = low density lipoprotein; PT = prothrombin time; RBC = red blood cell; T<sub>4</sub> = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

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

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Any value outside the normal range will be flagged for the attention of the investigator, who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed if clinically significant abnormalities are observed. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care. Refer to Appendix 3 for criteria for identifying values of potential clinical relevance.

The following laboratory test results at screening are exclusionary:

- Platelets  $\leq 75,000/\text{mm}^3$
- Hemoglobin  $\leq 9 \text{ g/dL}$
- Neutrophils, absolute  $\leq 1000/\text{mm}^3$
- Aspartate transaminase (AST) > 2 x upper limit of normal (ULN)
- Alanine transaminase (ALT) > 2 x ULN
- Creatine phosphokinase (CPK) > 3 x ULN, unless discussed with and approved by the medical monitor
- Albumin < 3 g/dL
- (HbA<sub>1c</sub>  $\geq$  8%
- Abnormal free thyroxine (T<sub>4</sub>), unless discussed with and approved by the medical monitor. (Note: Free T<sub>4</sub> is measured only if the result for TSH is abnormal.)
- Subjects with IDDM (ie, any subjects using insulin) must also satisfy the following criterion: no current microalbuminuria; ie, urine ACR must be < 30 mg/g (calculated).

# 3.7.4.3. Physical and Neurological Examination and Vital Signs

# 3.7.4.3.1. Physical Examination

A complete physical examination will be performed at screening and will consist of measurement of height and waist circumference and a review of the following body systems: head, eyes, ears, nose, and throat (HEENT); thorax; abdomen; urogenital; extremities; neurological (see Section 3.7.4.3.2); and skin and mucosa. At screening, height will be measured with a stadiometer, measuring stick or tape. Repeat measurement of height is not required at the physical examinations scheduled for the Week 12/ET visits. Waist circumference will be measured at each physical examination (screening and Week 12/ET), using the provided measuring tape.

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The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- Measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.<sup>39</sup>

The investigator (or designee) is responsible for performing the physical examination. If the appointed designee is to perform the physical examination, he or she must be permitted by local regulations and his/her name must be included on the Form FDA1572. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

#### 3.7.4.3.2. Neurological Examination

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

The physician is responsible for performing the neurological examination and must be included on the Form FDA 1572. Whenever possible, the same physician should perform all neurological examinations. Any condition present at the post-treatment neurological examination that was not present at the baseline examination and that is determined to be an AE should be documented as an AE and followed to a satisfactory conclusion. If new potentially clinically relevant neurological signs or symptoms are identified, referral to a neurologist is recommended.

#### 3.7.4.3.3. Vital Signs

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

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

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

Subjects with uncontrolled hypertension (screening DBP > 95 mmHg in any position) or symptomatic hypotension are excluded from the trial as are subjects with orthostatic hypotension, which is defined as a decrease of  $\geq$  30 mmHg in SBP and/or a decrease of  $\geq$  20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure or development of symptoms (see Table 3.7-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening vital sign result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. Refer to Appendix 4 for a list of potentially clinically significant vital signs.

#### 3.7.4.4. ECG Assessments

Standard 12-lead ECGs will be recorded at screening and at the visits specified in Table 3.7-1. Any ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn. ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained if the subject is terminated early. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis.

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

Refer to Appendix 5 for a list of potentially clinically relevant ECG abnormalities to guide investigators for the assessment of potential ECG abnormalities for clinical significance postrandomization. Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. Please consult the medical monitor in case of questions.

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3.7.4.5.	CCI	
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3.7.4.5.2.	CCI	

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3.7.4.5.4.	CCI	

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### 3.7.4.5.5. Mini-Mental State Examination (MMSE)

The MMSE<sup>43</sup> is a brief practical test for assessing cognitive dysfunction. The test consists of 5 sections (orientation, registration, attention and calculation, recall, and language) and has a total possible score of 30. The MMSE is used for screening subjects (refer to Table 3.4.3-1) and is also to be completed at Week 12/ET. A sample of the MMSE is provided in Appendix 20.

#### 3.7.5. Pharmacokinetic Assessments

# 3.7.5.1. Blood Collection Times

Pharmacokinetic samples will be collected at baseline and at any time during Week 8 and Week 12/ET. If blood samples for clinical laboratory tests are not collected at the baseline visit, pharmacokinetic samples do not need to be obtained at baseline. The samples will be collected at the same time as clinical laboratory sample collection for the designated trial visits, if applicable. Every possible effort should be made to collect pharmacokinetic samples at the same time at each visit. Furthermore, the subject should be advised to take the IMP at approximately the same time each day throughout the trial, but most importantly, prior to each pharmacokinetic sampling. The date and time of the last 2 doses of IMP prior to each sample draw, and the date and time of the actual blood draw will be recorded on the eCRF.

#### 3.7.5.2. Sample Handling and Processing

Details for drawing and processing pharmacokinetic samples are provided in Appendix 21.



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5.7.6.1.

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# 3.7.7. End of Trial

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

#### 3.7.8. Independent Data Monitoring Committee

The DMC will monitor safety in subjects who participate in the trial. The DMC meetings will occur as outlined in the DMC Charter, but can be convened at any time at the discretion of the DMC chair or the trial medical officer. The chair will be notified by the trial medical officer of all SAEs and will receive summaries of other safety data as available.

The responsibilities of the DMC include:

- Evaluating the progress of the trial, subjects' risk versus benefit, and other factors that could affect the trial outcome
- Considering relevant information that may have an impact on the safety of the participants or the ethics of the trial

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#### 3.8. Stopping Rules, Withdrawal Criteria, and Procedures

# 3.8.1. Entire Trial or Treatment Arm(s)

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

#### 3.8.2. Individual Site

A particular center may be terminated from the trial at the discretion of the investigator, sponsor, or IRB/IEC, eg, for non-enrollment of subjects or noncompliance with the protocol. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

# 3.8.3. Individual Subject

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

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

- 1) Occurrence of any AE, intercurrent illness, or abnormality in a laboratory assessment that, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial
- 2) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator
- 3) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12, Subject Compliance)
- 4) At the request of the subject, caregiver, legally acceptable representative, investigator, sponsor, or regulatory authority

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- 5) Subject becomes pregnant
- 6) Subject cannot tolerate a dose of 0.5 mg/day of brexpiprazole (or matching placebo)
- 7) Subject cannot be titrated to the target dose of 1 mg/day of brexpiprazole (or matching placebo)
- 8) Subject develops clinically significant agitation per investigator's judgment that cannot be adequately treated with allowed medications and poses a potential safety risk to the subject and/or others
- 9) Subject is lost to follow-up
- 10) Subject transfers from an institutionalized setting to a non-institutionalized setting, or vice versa. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and medical monitor.

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The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week 12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver.

Three attempts will be

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

Any subject who withdraws prematurely from the trial will not be eligible to roll-over into Trial 331-13-211.

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

#### 3.9. Screen Failures

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

#### 3.10. Definition of Completed Subjects

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

#### 3.11. Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the Week 12 visit during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as "lost to follow-up." If an institutionalized subject leaves the residential facility in which he/she was residing before completion of the trial, the site will make 3 attempts to contact the subject by telephone; in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method where appropriate. A similar procedure will be follow-up.

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#### 3.12. Subject Compliance

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

For non-institutionalized subjects, the caretaker or caregiver may administer IMP to the subject, as long as the subject is compliant with IMP dosing requirements.

For institutionalized subjects, the caregiver will be responsible for administering IMP to the subject. It may be possible that there is more than one caregiver for a subject. The caregiver(s) should be appropriately instructed to ensure that the subject is compliant with IMP dosing requirements.

#### 3.13. Protocol Deviations

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

# 4. Restrictions

#### 4.1. Prohibited Medications

All subjects must discontinue all prohibited medications during the screening period to meet the protocol-specified washout periods. The required duration of washout for selected prohibited medications is provided in Table 4.1-1. All other psychotropic agents, not listed in Table 4.1-1, are prohibited and must be discontinued at least 24 hours before the first dose of IMP. The oral benzodiazepine therapy permitted during the trial is summarized in Table 4.1-3.

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Tal	Table 4.1-1List of Restricted and Prohibited Medications				
All	All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.				
	Medication	Prior to Randomization	During Double-Blind Treatment Period		
1.	Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, and/or other cognitive enhancers)	Allowed provided that the dose has been stable for 90 days prior to randomization	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.		
2.	Antipsychotics	7-day washout	Prohibited		
	Clozapine	Not allowed within 30 days prior to randomization.	Prohibited		
	Depot or long-acting injectable antipsychotic drugs	Washout of 1.5 times the dosing interval (according to the prescribing information)	Prohibited		
3.	Antidepressants	Allowed provided that the dose has been stable for 30 days prior to randomization. Antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited and require a 7-day washout; fluoxetine requires a 28-day washout (see Table 4.1-2 for prohibited antidepressant medications).	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition. Antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited.		
4.	Mood stabilizers (such as lithium, valproate, carbamazepine)	7-day washout	Prohibited		
5.	Anticonvulsants	7-day washout	Prohibited		
6.	Benzodiazepines (short-acting) <sup>a,b</sup>	Allowed but limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects.	During the first 4 weeks of the randomized phase (baseline to Week 4 visit): allowed but limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects. Benzodiazepines must not be administered within 12 hours prior to the efficacy and safety scales. After Week 4 visit: Prohibited		

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Tał	Table 4.1-1List of Restricted and Prohibited Medications				
All	All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.				
	Medication	Prior to Randomization	During Double-Blind Treatment Period		
7.	Nonbenzodiazepine sleep agents <sup>c</sup>	If a bedtime dose of a sleep agent for insomnia was taken prior to screening on a regular basis, a stable pretrial dose of the sleep agent may be continued as needed during the trial. If a sleep agent was not previously taken prior to screening and needs to be initiated, medication should be limited to a maximum dose of 5 mg/day of zolpidem (or equivalent).	Sleep agents must not be administered within 8 hours prior to the efficacy and safety scales. Combined use of benzodiazepines and nonbenzodiazepine sleep agents for insomnia is not allowed.		
8.	Opioid analgesics	Prohibited unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency.	Prohibited unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency.		
9.	Anticholinergics for treatment of extrapyramidal symptoms <sup>d</sup>	7-day washout	Prohibited		
10.	Propranolol <sup>e</sup>	For treatment of akathisia or tremor: 7-day washout For treatment of heart disease: allowed provided that the dose has been stable for 30 days prior to randomization and total dose does not exceed 60 mg/day	For treatment of akathisia or tremor: maximum dose of 20 mg, 3 times daily (total of 60 mg/day). For treatment of heart disease: may remain on stable pretrial doses as needed throughout the trial, as long as the total dose does not exceed 60 mg/day. Propranolol must not be administered within 12 hours prior to the efficacy and safety scales.		
11.	Varenicline	7-day washout	Prohibited		
12.	Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and anti-platelet agents.	Allowed provided that the dose has been stable for 30 days prior to randomization	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.		

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Tał	Table 4.1-1List of Restricted and Prohibited Medications				
All	All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.				
	Medication	Prior to Randomization	During Double-Blind Treatment Period		
13.	Nutritional supplements and nonprescription herbal preparations with CNS effects (eg, St. John's wort, omega-3 fatty acids, kava extracts, gamma- aminobutyric acid (GABA) supplements, etc.)	7-day washout	Prohibited		
14.	Cytochrome P450 2D6 isozyme (CYP2D6) inhibitors or CYP3A4 inhibitors and inducers (see Table 4.1-2)	7-day washout	Prohibited		

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

<sup>b</sup>Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety scales, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eCRF.

- <sup>c</sup>Nonbenzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia, but not on the same day as administration of a benzodiazepine, regardless of indication. For the nonbenzodiazepine sleep aids, sites should only utilize one of the listed medications that are approved for this indication in their respective countries and the country-specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia. Nonbenzodiazepine sleep aids must not be administered within 8 hours prior to scheduled efficacy and safety scales, including EPS scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eCRF.
- <sup>u</sup>Anticholinergic treatment of extrapyramidal symptoms (eg, benztropine) is not permitted within the 7 days prior to randomization and for the duration of the trial.

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

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

<sup>a</sup>Fluoxetine requires a 28-day washout prior to randomization.

Table 4.1-3Oral Benzodiazepine Therapy During the Trial		
	Maximum Allowable Daily Dose (mg/day)	
ab	Screening	<b>Baseline to Week 4 Visit</b>
Oral Benzodiazepine	(limited to 4 days/week)	(limited to 4 days/week)
Lorazepam	2	2
Oxazepam	30	30

<sup>a</sup>Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety scales, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eCRF.

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

#### 4.2. Other Restrictions

The following restrictions apply:

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

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- The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use.
- Treatment with other investigational agents is not permitted during the trial.

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

# 5. Reporting of Adverse Events

#### 5.1. Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug 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:

- 1) Death
- 2) Life-threatening, ie, the subject was, in the opinion of the investigator, at <u>immediate</u> 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.
- 3) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 4) Requires in-patient hospitalization or prolongs hospitalization (NOTE: A prescheduled hospitalization is not considered an SAE.)
- 5) Congenital anomaly/birth defect
- 6) 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 adverse events are AEs that do not meet the criteria for an SAE.

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If a subject is experiencing an extrapyramidal symptom, the specific extrapyramidal symptom must be indicated on the AE page of the eCRF. Examples of AEs that are considered extrapyramidal symptoms include, but are not limited to: generalized rigidity, dyskinesia, hyperkinesia, bradykinesia, akinesia, dystonia, hypertonia, akathisia, tremor, flexed posture, involuntary muscle contractions, athetosis, and chorea. If a subject is experiencing two or more of these symptoms, whether or not treatment with an anticholinergic is required, this is considered as extrapyramidal syndrome and must be entered as "extrapyramidal syndrome" on the AE page of the eCRF instead of the individual symptoms.

#### **Immediately Reportable Event (IRE)**

- Any SAE
- Any AE that necessitates discontinuation of the IMP
- Potential Hy's law cases (any increase of AST or ALT ≥ 3 times the ULN with an increase in total bilirubin ≥ 2 times the ULN)

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 INC Research. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

#### **Clinical Laboratory Changes**

It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If this laboratory value is determined by the investigator to be an abnormal change from baseline for that subject, this is considered an AE.

#### **Severity**

All AEs will be graded on a 3-point scale and reported as indicated on the eCRF. The intensity of an adverse experience is defined as follows:

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

#### **IMP Causality**

The causal relationship of an AE to the use of the IMP will be assessed as follows:

Related:	There is a reasonable possibility of a causal relationship
Possibly related:	There is a reasonable causal relationship between the IMP and the AE. Dechallenge is lacking or unclear
Unlikely related:	There is a temporal relationship to the IMP administration, but there is not a reasonable causal relationship between the IMP and the AE
Not related:	There is no temporal or reasonable relationship to the IMP administration

#### 5.2. Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor or designee.

In addition, INC Research (refer to Appendix 2) must be notified immediately by telephone or fax of any **immediately reportable events** according to the procedure outlined below in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

# 5.3. Immediately Reportable Events (IRE)

The investigator must immediately report within 24 hours after either the investigator or site personnel become aware of any **SAE or potential Hy's law cases** (refer to Section 5.4) by telephone or by fax to the sponsor or designee as outlined in Appendix 2. An IRE form must be completed and sent by fax or overnight courier to the sponsor. (Note: The IRE form is NOT the AE eCRF.)

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Nonserious events that require discontinuation of the IMP (including laboratory abnormalities) should be reported to the sponsor within 3 working days. The IRE form must be completed and sent by fax or overnight courier to the sponsor.

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

#### 5.4. Potential Hy's Law Cases

For subjects that experience an elevation in AST or ALT that is  $\geq 3$  times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is  $\geq 2$  times the ULN, confirmatory repeat laboratory samples should be drawn within 48 to 72 hours of the initial draw. If these values are confirmed, trial personnel will complete an IRE form with all values listed and also report the event as an AE on the eCRF. Please note: if the subject was enrolled into the trial with non-exclusionary elevated transaminase levels at baseline, please discuss any potential drug-induced liver injury events with the medical monitor.

#### 5.5. Pregnancy

Women of childbearing potential and men who are sexually active must use an effective method of birth control during the course of the trial and for at least 30 days after the last dose in a manner such that risk of failure is minimized. Unless the subject is sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchiectomy) or remains abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom or sponge with spermicide, or any other method approved by the medical monitor. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling women of childbearing potential in this clinical trial, investigators must review guidelines about their participation in this trial. The topics should generally include:

- General information
- Informed consent
- Pregnancy prevention information

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- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

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

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

If a subject or investigator suspects that the subject may be pregnant prior to IMP administration, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking the IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy 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 withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultation as indicated in Appendix 2.

The investigator must immediately notify the sponsor (or sponsor's designee) of any pregnancy associated with IMP exposure, including at least 30 days after the last dose for female subjects and the female partner of a male subject and record the event on the IRE form and forward it to the sponsor (or sponsor's designee).

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor (or sponsor's designee), 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.

#### 5.6. Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of the IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical monitor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the clinical safety and pharmacovigilance department listed in Appendix 2 will be notified immediately. Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a given subject, that subject may not reinitiate treatment with the IMP.

#### 5.7. Follow-up of Adverse Events

#### 5.7.1. Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified on the last scheduled contact must be recorded on the AE eCRF with the current status noted. All nonserious events that are ongoing at this time will be recorded as ongoing on the eCRF.

#### 5.7.2. Follow-up of Post-Trial Serious Adverse Events

All SAEs that are identified on the last scheduled contact must be recorded on the AE eCRF page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. This may include unresolved previously reported SAEs or new SAEs. The investigator will follow SAEs until the events are resolved or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to OPDC up to the point the event has been resolved.

This trial requires that subjects be actively monitored for SAEs up to 30 days after discharge from the trial.

# 5.7.3. Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

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



subject's caregiver via certified mail or an alternative similar method where appropriate.

# 6. Pharmacokinetic Analysis

Pharmacokinetic samples will be analyzed for brexpiprazole (OPC-34712) and its metabolite(s) and descriptive statistics will be calculated. No formal statistical comparisons are planned. A separate population or pharmacokinetic/pharmacodynamic modeling may be performed using the data from this trial and other trials.

# 7. Statistical Analysis

# 7.1. Sample Size

The sample size was calculated based on the treatment effect of 6.5 points with a standard deviation of 16.5 in the change from baseline to the endpoint in the CMAI total score, to achieve 85% power at a 2-sided alpha level of 0.05. The resulting sample size is 117 subjects/arm. After allowance of 10% non-evaluable subjects, it results in a sample size of 130 subjects/arm, which means the total sample size is 260 subjects. The sample size was estimated based on 1:1 randomization ratio (brexpiprazole:placebo).

#### 7.2. Datasets for Analysis

The following samples are defined for this trial:

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

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

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



#### 7.3. Handling of Missing Data

#### 7.4. Efficacy Analyses

#### 7.4.1. Primary Efficacy Analysis

The primary endpoint will be analyzed using an MMRM model. The primary efficacy outcome measure is the mean change from baseline (Day 0 Visit) to the end of the double-blind treatment period (Week 12 visit) in the CMAI total score. Details of sensitivity analyses under the assumption of MNAR will be provided in the statistical analysis plan (SAP). The null hypothesis for the comparison of brexpiprazole flexible dose versus placebo is that there is no difference between the brexpiprazole treatment group and placebo in change from baseline to endpoint in CMAI total score. The comparison will be made at the significance level of alpha = 0.05.

The statistical comparison will be performed by fitting a MMRM analysis with an unstructured variance covariance matrix in which the change from baseline (Day 0 Visit) in CMAI total score (at Weeks 2, 4, 6, 8, 10, and 12) will be the dependent variable based on the OC dataset. The model will include fixed class-effect terms for treatment, trial center, visit week, and an interaction term of treatment by visit week. The model will also include a random effect for subject and the interaction term of baseline (Day 0 visit) by visit week as covariates. The primary comparison between the brexpiprazole and the placebo groups at Week 12 will be estimated as the difference between the least squares (LS) means utilizing the computing software SAS procedure PROC MIXED.



The primary analysis CCI will be performed on the Efficacy Sample.

### 7.4.2. Key Secondary Efficacy Analysis

The key secondary efficacy variable is the change from baseline to endpoint in the CGI-S score, as related to agitation. It will be analyzed by the same statistical methodology specified for the analysis of the primary efficacy variable, based on the ITT population. The alpha used in the analysis of this key secondary endpoint is 0.05 (2-sided), if the comparison of the brexpiprazole group versus placebo in the primary efficacy endpoint is statistically significant.

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# 7.5. Analysis of Demographic and Baseline Characteristics

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

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## 7.6. Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, body weight, waist circumference and physical examination. In addition, data from the following safety scales will be evaluated: MMSE score, <sup>CCI</sup>

Safety analysis will be conducted based on the Safety Sample defined in Section 7.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs, and body weight. Details of safety analysis will be provided in the SAP.

# 7.6.1. Adverse Events

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

- 1) TEAEs by severity
- 2) TEAEs potentially causally related to the IMP
- 3) TEAEs with an outcome of death
- 4) Serious TEAEs
- 5) Discontinuations due to TEAEs

## 7.6.2. Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, prolactin concentrations, coagulation parameters (PT, aPTT, and INR), HbA<sub>1c</sub>, cortisol, ACTH, and TSH will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined criteria for laboratory tests will be summarized.

## 7.6.3. Physical and Neurological Examination and Vital Signs Data

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

## 7.6.4. ECG Data

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

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

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

Results will be summarized by visit.

7.6.5. <sup>CCI</sup>		
7.7. <sup>CCI</sup>		
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# 8. Management of Investigational Medicinal Product

# 8.1. Packaging and Labeling

Trial medication will be provided to the investigator(s) by the sponsor or designated agent. The IMP will be supplied as active brexpiprazole tablets or matching placebo tablets. The 0.25 mg/day dose will be supplied as a blister card containing sufficient tablets for 3 (+2) days; the 0.5 mg/day, 1 mg/day, and 2 mg/day doses will be supplied as weekly blister cards, each containing sufficient tablets for 7 (+ 2) days. When accessed by the site, the IVRS or IWRS will assign specific blister card number(s) to be dispensed to a subject.

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

# 8.2. Storage

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

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

# 8.3. Accountability

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

# 8.4. Returns and Destruction

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

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

# 8.5. Reporting of Product Quality Complaints (PQC)

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

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under fill or overfill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

# 8.5.1. Eliciting and Reporting Product Quality Complaints

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

Online: Send information required for reporting purposes (listed below) to

Phone: Rocky Mountain Call Center at PPD

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

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# 8.5.2. Information Required for Reporting Purposes

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

# 8.5.3. Return Process

It should be indicated during the report of the PQC if the IMP sample is available for return. If the complaint sample is available for return, return it in the product retrieval package, which will be provided by Otsuka America Pharmaceutical, Inc. Ethics, Quality and Compliance (OAPI-EQC). It should be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to OAPI-EQC for complaint investigation.

# 8.5.4. Assessment and Evaluation

Assessment and evaluation of PQC will be handled by the OAPI EQC-QM group.

# 9. Records Management

# 9.1. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include (but are not limited) to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators. Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF.

## 9.2. Data Collection

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

- Documentation of the informed consent process, including any revisions
- The date of the visit and the corresponding visit or day in the trial schedule
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to the IMP must also be recorded.
- Any changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature (or initials or other unique identifier) and date of each clinician (or designee) who made an entry in the progress notes

In addition, any contact with the subject or caregiver via telephone or other means that provides significant clinical information also will be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be **initialed and dated on the day the change is made** by a 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, <del>wrong data</del> right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Information from the trial progress notes and other source documents will be data entered by investigative site personnel directly onto eCRFs in the sponsor's electronic data capture system.

# 9.3. File Management at the Trial Site

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

# 9.4. Records Retention at the Trial Site

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

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation).
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

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

# 10. Quality Control and Quality Assurance

# 10.1. Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial carefully in a detailed and orderly manner in accordance with established research principles, the ICH GCP guideline, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone and written communications.

## 10.2. Auditing

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

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

# 11. Ethics and Responsibility

This trial must be conducted in compliance with the protocol, the ICH GCP guideline, and applicable local laws and regulatory requirements. Each trial site will seek approval by an IRB or IEC according to regional requirements. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

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

# 12. Confidentiality

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

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

# 13. Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB/IEC approval of the

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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/IEC notification within 5 working days. The sponsor will submit protocol amendments to the applicable regulatory agencies.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained before expecting continued participation.

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Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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# 14. References

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#### Appendix 1 Names of Sponsor Personnel

Primary Medical Contacts

PPD PPD

Otsuka Pharmaceutical Development & Commercialization, Inc. 508 Carnegie Center Princeton, NJ 08540 Phone: PPD Fax: PPD

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Otsuka Pharmaceutical Development & Commercialization, Inc. 508 Carnegie Center Princeton, NJ 08540 Phone: PPD Fax: PPD

Compound Director

Otsuka Pharmaceutical Development & Commercialization, Inc. 508 Carnegie Center Princeton, NJ 08540 Phone: PPD Fax: PPD

Clinical Contact

Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Blvd Rockville, MD 20850 Phone: PPD Fax: PPD

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#### Appendix 2Institutions Concerned With the Trial

Safety Reporting

Immediately Reportable Events (serious adverse events, potential Hy's law cases, pregnancies, and adverse events requiring discontinuation of trial drug) should be reported to INC Research Pharmacovigilance & Drug Safety as follows:

Country	Safety Fax Line		
United States	PPD		
Canada			
United Kingdom			
France			
Ukraine			
Slovenia			
Finland			
Bulgaria			
Russia			

\* Please note that this is a partner CRO number, not INC.

Clinical Research Organization

INC Research, LLC 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604 USA

Medical Monitors North America: PPD PPD INC Research, LLC 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604 USA Office: PPD Mobile: PPD Fax: PPD

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*Europe:* PPD

INC Research, LLC UI. Emaus 5 30-201 Kraków, Poland Office: PPD Mobile: PPD Fax: PPD

<u>Clinical Lab - ECG Central Reader</u> eResearch Technology 1818 Market Street, Suite 1000 Philadelphia, PA 19103 USA

<u>Central Laboratory</u> Covance Central Laboratory Services 8211 SciCor Drive Indianapolis, IN 46214 USA

<u>Bioanalytical Laboratory</u> Covance Laboratories 3301 Kinsman Boulevard Madison, WI 53704 USA





Electronic Data Capture Medidata Solutions, Inc. 350 Hudson Street, 9<sup>th</sup> Floor New York, NY 10014 USA

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IVRS/IWRS S-Clinica Inc. 41 University Drive Suite 400 Newtown, PA 18940 USA

<u>Translation Agency</u> Global Language Solutions, Inc. 19800 MacArthur Boulevard, Suite 750 Irvine, CA 92612 USA

Central IRB

Rater Training and Scale Management ProPhase, LLC 3 Park Avenue, 37th Floor New York, NY 10016 USA

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Laboratory Tests	Criteria	
Chemistry		
AST (SGOT)	$> 3 \times ULN$	
ALT (SGPT)	$> 3 \times ULN$	
Alkaline phosphatase	$> 3 \times UIN$	
Lactate dehvdrogenase	$> 3 \times UIN$	
Blood urea nitrogen	$\geq 30 \text{ mg/dI}$	
Creatinine	> 2.0  mg/dL	
Uric acid	_ 2.0 mg/d2	
Men	$\geq 10.5 \text{ mg/dL}$	
Women	> 8.5  mg/dL	
Bilirubin (total)	> 2.0  mg/dL	
Creatine phosphokinase	$> 3 \times ULN$	
Prolactin	> ULN	
Hematology		
Hematocrit		
Men	$\leq$ 37 % and decrease of $\geq$ 3 percentage points from baseline	
Women	$\leq$ 32 % and decrease of $\geq$ 3 percentage points from baseline	
Hemoglobin		
Men	$\leq 11.5 \text{ g/dL}$	
Women	$\leq 9.5 \text{ g/dL}$	
WBC count	$\leq$ 2,800 mm3 or $\geq$ 16,000 mm3	
Eosinophils	≥ 10%	
Neutrophils	≤ 15%	
Absolute neutrophil count	$\leq 1,500/\text{mm}^3$	
Platelet count	$\leq$ 75,000/mm <sup>3</sup> or $\geq$ 700,000/mm <sup>3</sup>	
Urinalysis		
Protein	Increase of $\geq 2$ units	
Glucose	Increase of $\geq 2$ units	
Casts	Increase of $\geq 2$ units	
Additional Criteria		
Chloride	$\leq$ 90 mEq/L or $\geq$ 118 mEq/L	
Potassium	$\leq 2.5 \text{ mEq/L or} \geq 6.5 \text{ mEq/L}$	
Sodium	$\leq 126 \text{ mEq/L or} \geq 156 \text{ mEq/L}$	
Calcium	$\leq 8.2 \text{ mg/dL} \text{ or} \geq 12 \text{ mg/dL}$	
Glucose		
Fasting	$\geq 100 \text{ mg/dL}$	
Nonfasting	$\geq 200 \text{ mg/dL}$	
Total cholesterol, fasting	$\geq$ 240 mg/dL	
LDL cholesterol, fasting	$\geq 160 \text{ mg/dL}$	
HDL cholesterol, fasting		
Men	< 40 mg/dL	
Women	< 50 mg/dL	
Triglycerides, fasting	$\geq 150 \text{ mg/dL}$	

# Appendix 3 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

ULN = upper limit of normal

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#### Appendix 4 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value <sup>a</sup>	Change Relative to Baseline <sup>a</sup>
b b	> 120 bpm	$\geq$ 15 bpm increase
Heart rate	< 50 bpm	≥ 15 bpm decrease
b (1, 11, 1, b	>180 mmHg	$\geq$ 20 mmHg increase
Systolic blood pressure	< 90 mmHg	≥ 20 mmHg decrease
D: (1:11 1 b	>105 mmHg	$\geq$ 15 mmHg increase
Diastolic blood pressure	< 50 mmHg	$\geq$ 15 mmHg decrease
	$\geq$ 20 mmHg decrease in systolic blood	Not applicable
Orthostatic hypotension	pressure and $a \ge 25$ bpm increase in heart	(baseline status not
	rate from supine to sitting/standing	considered)
Weight	_	$\geq$ 7% increase
w eight		$\geq$ 7% decrease

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

<sup>b</sup>As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original New Drug Application Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

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Variable	Criterion Value <sup>a</sup>	Change Relative to Baseline <sup>a</sup>
Rate		
Tachycardia	$\geq 120 \text{ bpm}$	increase of $\geq 15$ bpm
Bradycardia	$\leq 50 \text{ bpm}$	decrease of $\geq 15$ bpm
Rhythm		
Sinus tachycardia <sup>b</sup>	$\geq 120 \text{ bpm}$	increase of $\geq 15$ bpm
Sinus bradycardia	$\leq 50 \text{ bpm}$	decrease of $\geq$ 15 bpm
Supraventricular premature beat	all	not present $\rightarrow$ present
Ventricular premature beat	all	not present $\rightarrow$ present
Supraventricular tachycardia	all	not present $\rightarrow$ present
Ventricular tachycardia	all	not present $\rightarrow$ present
Atrial fibrillation	all	not present $\rightarrow$ present
Atrial flutter	all	not present $\rightarrow$ present
Conduction		
1° atrioventricular block	$PR \ge 200 \text{ msec}$	increase of $\geq 50$ msec
2° atrioventricular block	all	not present $\rightarrow$ present
3° atrioventricular block	all	not present $\rightarrow$ present
Left bundle-branch block	all	not present $\rightarrow$ present
Right bundle-branch block	all	not present $\rightarrow$ present
Pre-excitation syndrome	all	not present $\rightarrow$ present
Other intraventricular conduction block <sup>d</sup>	$QRS \ge 120 \text{ msec}$	increase of $\geq 20$ msec
Infarction		
Acute or subacute	all	not present $\rightarrow$ present
Old	all	not present $\rightarrow$ present
		$\geq$ 12 weeks post trial entry
ST/T Morphological		
Myocardial ischemia	all	not present $\rightarrow$ present
Symmetrical T-wave inversion	all	not present $\rightarrow$ present
Increase in QTc	$QTcF \ge 450 \text{ msec}$	
	(men)	
	$QTcF \ge 470$ msec	
	(women)	

#### Appendix 5 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

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

<sup>b</sup>No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

<sup>c</sup>No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

<sup>d</sup>No current diagnosis of left bundle branch block or right bundle branch block.

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## Appendix 6 Cohen-Mansfield Agitation Inventory (CMAI)

#### THE COHEN-MANSFIELD AGITATION INVENTORY - Long Form

Please read each of the 29 agitated behaviors, and circle how often (from 1-7) each was manifested by the resident during the last 2 weeks:

	Never 1	Less than once a week 2	Once or twice a week 3	Several times a week 4	Once or twice a day 5	Several times a day 6	Several times an hour 7
1. Pace, aimless wandering	1	2	3	4	5	6	7
2. Inappropriate dress or disrobing	1	2	3	4	5	6	7
3. Spitting (include at meals)	1	2	3	4	5	6	7
4. Cursing or verbal aggression	1	2	3	4	5	6	7
<ol> <li>Constant unwarranted request for attention or help</li> </ol>	1	2	3	4	5	6	7
6. Repetitive sentences or questions	1	2	3	4	5	6	7
7. Hitting (including self)	1	2	3	4	5	6	7
8. Kicking	1	2	3	4	5	6	7
9. Grabbing onto people	1	2	3	4	5	6	7
10. Pushing	1	2	3	4	5	6	7
11. Throwing things	1	2	3	4	5	6	7
12. Strange noises (weird laughter or crying)	1	2	3	4	5	6	7
13. Screaming	1	2	3	4	5	6	7
14. Biting	1	2	3	4	5	6	7
15. Scratching	1	2	3	4	5	6	7

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	Never 1	Less than once a week 2	Once or twice a week 3	Several times a week 4	Once or twice a day 5	Several times a day 6	Several times an hour 7
<ol> <li>Trying to get to a different place (e.g., out of the room, building)</li> </ol>	1	2	3	4	5	6	7
17. Intentional falling	1	2	3	4	5	6	7
18. Complaining	1	2	3	4	5	6	7
19. Negativism	1	2	3	4	5	6	7
20. Eating/drinking inappropriate substances	1	2	3	4	5	6	7
21. Hurt self or other (cigarette, hot water, etc.)	1	2	3	4	5	6	7
22. Handling things inappropriately	1	2	3	4	5	6	7
23. Hiding things	1	2	3	4	5	6	7
24. Hoarding things	1	2	3	4	5	6	7
25. Tearing things or destroying property	1	2	3	4	5	6	7
26. Performing repetitious mannerisms	1	2	3	4	5	6	7
27. Making verbal sexual advances	1	2	3	4	5	6	7
28. Making physical sexual advances	1	2	3	4	5	6	7
29. General restlessness	1	2	3	4	5	6	7

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#### Clinical Study Report 331-12-284

Protocol 331-12-284



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#### Clinical Study Report 331-12-284

Protocol 331-12-284



Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976

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## Clinical Global Impression-Severity of Illness (CGI-S), as related to agitation

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

Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the subject at this time?

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976

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# Appendix 8 Neuropsychiatric Inventory-Nursing Home Rating Scale (NPI-NH)

A. DELUSIONS		(NA)
Does the resident have beliefs that you know are not true? For example, saying that people are steal from him/her. Has he/she said that family members or staff are not who they say they ar having an affair? Has the resident had any other unusual beliefs?	trying to he e or that hi	arm him/her or s/her spouse is
☐ Yes (If yes, please proceed to subquestions)         ☐ No (if no, please proceed to next screening question)         ☐ N/A		
<ol> <li>Does the resident believe that he/her is in danger – that others are planning to hurt him/her or have been hurting him/her?</li> </ol>	□ Yes	□ No
2. Does the resident believe that others are stealing from him/her?	🗆 Yes	No No
3. Does the resident believe that his/her spouse is having an affair?	□ Yes	No No
4. Does the resident believe that his/her family, staff members or others are not who they say they are?	🗆 Yes	No No
<ol><li>Does the resident believe that television or magazine figures are actually present in the room? (Does he/she try to talk or interact with them?)</li></ol>	□ Yes	□ No
6. Does he/she believe any other unusual things that I haven't asked about?	C Yes	No No
Comments:		
If the screening question is confirmed, determine the frequency and severity of the delusions.		
Frequency:		
1. Rarely – less than once per week		
2. Sometimes – about once per week		
3. Often – several times per week but less than every day		
4. Very often – once or more per day		
Severity:		
1. Mild – delusions present but seem harmless and does not upset the resid	lent that mu	ich.
2. Moderate – delusions are stressful and upsetting to the resident and cause behavior.	se unusual o	or strange
3. Severe – delusions are very stressful and upsetting to the resident and ca unusual or strange behavior.	use a major	amount of
Occupational Disruptiveness: How much does this behavior upset you and/or create more work for	or you?	
0. Not at all		
1. Minimally (almost no change in work routine)		
2. Mildly (some change in work routine but little time rebudgeting required)	)	
3. Moderately (disrupts work routine, requires time rebudgeting)		
□ 4. Severely (disruptive, upsetting to staff and other residents, major time in	fringement)	
5. Very Severely or Extremely (very disruptive, major source of distress for s residents, requires time usually devoted to other residents or activities)	taff and oth	er
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B. HALLUCIN	IAIONS		(NA)
Does the resi	dent have hallucinations – meaning, does he/she see, hear, or experience thir	ngs that are n	ot present? (If
"Yes," ask for	an example to determine if in fact it is a hallucination). Does the resident talk to	people who are	e not there?
	es (if yes, please proceed to subquestions)		
	o (if no, please proceed to next screening question) □ N/A		
1. Does the re	sident act as if he/she hears voices or describe hearing voices?	□ Yes	No No
2. Does the re	sident talk to people who are not there?	C Yes	No No
<ol> <li>Does the re not present</li> </ol>	sident see things that are not present or act like he/she sees things that are (people, animals, lights, etc)?	□ Yes	□ No
4. Does the re	sident smell things that others cannot smell?	🗆 Yes	No No
5. Does the r	esident describe feeling things on his/her skin or act like he/she is feeling		
things craw	ling or touching him/her?	L Yes	
6. Does the re	sident say or act like he/she tastes things that are not present?	L Yes	
7. Does the re	sident describe any other unusual sensory experiences?	LI Yes	LI No
Commen	3:	-	
If the screenin	ng question is confirmed, determine the frequency and severity of the hallucinatio	ns.	
Frequency:			
	1. Rarely – less than once per week		
	2. Sometimes – about once per week		
	3. Often – several times per week but less than every day		
	□ 4. Very often – once or more per day		
Severity:			
	1. Mild – hallucinations are present but seem harmless and does not upset	et the resident	that much.
	2. Moderate – hallucinations are stressful and upsetting to the resident a behavior.	nd cause unus	ual or strange
	3. Severe – hallucinations are very stressful and upsetting to the resident of unusual or strange behavior. (PRN medications may be required to c	and cause a m control them).	ajor amount
Occupational	Disruptiveness: How much does this behavior upset you and/or create more wor	k for you?	
	O. Not at all		
	<ol> <li>Minimally (almost no change in work routine)</li> </ol>		
	2. Mildly (some change in work routine but little time rebudgeting require	ed)	
	3. Moderately (disrupts work routine, requires time rebudgeting)		
	$\Box$ 4. Severely (disruptive, upsetting to staff and other residents, major time	infringement)	
	5. Very Severely or Extremely (very disruptive, major source of distress fo residents, requires time usually devoted to other residents or activities	or staff and oth )	er
			0

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C. AGITATION/AGGRESSION	(NA)
Does the resident have periods when he/she refuses to let people help him/her? Is he/s	he hard to handle? Is he/she noisy
or uncooperativer boes the resident attempt to hurt or hit others?	
<ul> <li>☐ Yes (if yes, please proceed to subquestions)</li> <li>☐ No (if no, please proceed to next screening question)</li> <li>☐ N/A</li> </ul>	
<ol> <li>Does the resident get upset when people are trying to care for him/her or resist activities such as bathing or changing clothes?</li> </ol>	Yes No
2. Does the resident always want things his/her own way?	🗌 Yes 📃 No
3. Is the resident uncooperative, resistive to help from others?	🗌 Yes 🔹 No
4. Does the resident have any other behaviors that make him/her hard to handle?	🗆 Yes 🔷 No
5. Does the resident shout, make loud noises, or swear angrily?	Yes No
6. Does the resident slam doors, kick furniture, throw things?	Yes No
7. Does the resident attempt to hurt or hit others?	Yes No
8. Does the resident have any other aggressive or agitated behaviors?	Yes No
Comments:	
If the screening question is confirmed, determine the frequency and severity of the agitat	tion/aggression.
Frequency:	
1. Rarely – less than once per week.	
2. Sometimes – about once per week.	
3. Often – several times per week but less than every day.	
4. Very often – once or more per day.	
Severity:	
1. Mild – behavior is stressful for the resident, but can be controlled	d by the caregiver.
2. Moderate – behaviors are stressful for and upsetting to the resid	lent and are difficult to control.
3. Severe – agitation is very stressful or upsetting to the resident a to control. There is a possibility they may injure themselves and	nd is very difficult or impossible medications are often required.
Occupational Disruptiveness: How much does this behavior upset you and/or create more	e work for you?
0. Not at all	
1. Minimally (almost no change in work routine)	
2. Mildly (some change in work routine but little time rebudgeting)	required)
3. Moderately (disrupts work routine, requires time rebudgeting)	
4. Severely (disruptive, upsetting to staff and other residents, majo	r time infringement)
5. Very Severely or Extremely (very disruptive, major source of distriction residents, requires time usually devoted to other residents or activation of the severe sev	ress for staff and other tivities)
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D. DEPRESSI	ON/DYSPHORIA	(NA
Does the resi times?	dent seem sad or depressed? Does he/she say that he/she feels sad or o	depressed? Does the resident cry
	es (if yes, please proceed to subquestions) o (if no, please proceed to next screening question)	
1. Does the re	sident cry at times?	Yes No
2. Does the re	sident say, or act like he/she is depressed?	Yes No
3. Does the re	sident put him/herself down or say that he/she feels like a failure?	Yes No
4. Does the re	sident say that he/she is a bad person or deserves to be punished?	Yes No
5. Does the re	sident seem very discouraged or say that he/she has no future?	🗆 Yes 🔹 No
6. Does the re better off w	sident say he/she is a burden to the family or that the family would be /ithout him/her?	Yes No
7. Does the re	sident talk about wanting to die or about killing him/herself?	🗆 Yes 🔹 No
8. Does the re	sident show any other signs of depression or sadness?	Yes No
Commen	ts:	
If the screenin	ng question is confirmed, determine the frequency and severity of the dep	ression.
Frequency:		
	1. Rarely – less than once per week.	
	2. Sometimes – about once per week.	
	□ 3. Often – several times per week but less than daily.	
	□ 4. Very often – once or more per day.	
Severity:		
	$\square$ 1. Mild – depression is stressful for the resident but will usually ch	hange with the help of a caregiver.
	2. Moderate – depression is stressful for the resident and is difficult	ult to change by the caregiver.
	3. Severe – depression is very upsetting and stressful for the impossible to change.	he resident and is very difficult
Occupational	Disruptiveness: How much does this behavior upset you and/or create mo	ore work for you?
	0. Not at all	
	1. Minimally (almost no change in work routine)	
	2. Mildly (some change in work routine but little time rebudgeting	g required)
	□ 3. Moderately (disrupts work routine, requires time rebudgeting)	
	□ 4. Severely (disruptive, upsetting to staff and other residents, maj	or time infringement)
	5. Very Severely or Extremely (very disruptive, major source of dis residents, requires time usually devoted to other residents or a	stress for staff and other ctivities)

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E. ANXIETY				(NA)
Is the resident	t very nervous, worried, or frightened for no reason? Does he/she se	em verv tense	e or unable to	relax? is the
resident afraid	to be apart from you or from others that he/she trusts?			
□ Ye □ No	es (if yes, please proceed to subquestions) o (if no, please proceed to next screening question)	N/A		
1. Does the res appointmen	sident say that he/she is worried about planned events such as its or family visits?		□ Yes	□ No
2. Does the res	sident have periods of feeling shaky, unable to relax, or feeling very to	ense?	2 Yes	🗆 No
<ol> <li>Does the res sighing for n</li> </ol>	sident have periods of (or complain of) shortness of breath, gasping, on apparent reason other than being nervous?	or	□ Yes	□ No
4. Does the res the heart be	sident complain of butterflies in his/her stomach, or of racing or pour cause of being nervous? (Symptoms not explained by ill health)	nding of	□ Yes	□ No
5. Does the res such as mee	sident avoid certain places or situations that make him/her more new ting with friends or participating in ward activities?	vous	□ Yes	□ No
6. Does the res that he/she	sident become nervous and upset when separated from you or from o trusts? (Does he/she cling to you to keep from being separated?)	others	□ Yes	□ No
7. Does the res	sident show any other signs of anxiety?		🗆 Yes	🗆 No
Comment	5:			
If the screenin	g question is confirmed, determine the frequency and severity of the	anxiety.		
Frequency:				
	1. Rarely – less than once per week.			
	2. Sometimes – about once per week.			
	3. Often – several times per week but less than every day.			
	4. Very often – essentially continuously present.			
Severity:				
	1. Mild –anxiety is stressful for the resident but will usually ch	hange with the	help of a care	giver.
	2. Moderate – anxiety is stressful for the resident and is diffic	ult to change l	by the caregive	er.
	3. Severe – anxiety is very upsetting and stressful for the resi- change.	dent and is ve	ry difficult or i	mpossible to
Occupational [	Disruptiveness: How much does this behavior upset you and/or create	e more work fo	or you?	
	O. Not at all			
	1. Minimally (almost no change in work routine)			
	2. Mildly (some change in work routine but little time rebudge	eting required	)	
	3. Moderately (disrupts work routine, requires time rebudget	ting)		
	4. Severely (disruptive, upsetting to staff and other residents,	, major time in	fringement)	
	5. Very Severely or Extremely (very disruptive, major source or residents, requires time usually devoted to other residents	of distress for s or activities)	staff and other	
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F. ELATION	/EUPHORIA			(NA)
Does the res at things tha	ident seem too cheerful or too happy for no reason? I don't t others do not find funny?	t mean normal happin	ess but, for exa	mple, laughing
	<pre>/es (if yes, please proceed to subquestions) No (if no, please proceed to next screening question)</pre>	□ N/A		
1. Does the r	esident appear to feel too good or to be too happy?		□ Yes	No No
2. Does the r	esident find humor and laugh at things that others do not fi	ind funny?	🗆 Yes	No No
3. Does the r laugh inap	esident seem to have a childish sense of humor with a tend propriately (such as when something unfortunate happens	ency to giggle or to others)?	Ves	No No
4. Does the r him/her?	esident tell jokes or say things that are not funny to others	but seem funny to	Yes	□ No
5. Does the r	esident show any other signs of feeling too good or being to	oo happy?	C Yes	No No
Commer	nts:		_	
If the screen	ing question is confirmed, determine the frequency and sev	erity of the elation/eu	phoria.	
Frequency:				
	1. Rarely – less than once per week.			
	2. Sometimes – about once per week.			
	□ 3. Often – several times per week but less than ev	ery day.		
	4. Very often – once or more per day.			
Severity:				
	1. Mild – resident is too happy at times.			
	2. Moderate – resident is too happy at times and t	this sometimes causes	strange behavio	or.
	3. Severe – resident is almost always too happy an	d finds nearly everyth	ing to be funny.	
Occupationa	I Disruptiveness: How much does this behavior upset you ar	nd/or create more wor	k for you?	
	0. Not at all			
	1. Minimally (almost no change in work routine)			
	2. Mildly (some change in work routine but little ti	me rebudgeting requir	red)	
	3. Moderately (disrupts work routine, requires tim	e rebudgeting)		
	$\Box$ 4. Severely (disruptive, upsetting to staff and othe	r residents, major time	e infringement)	
	5. Very Severely or Extremely (very disruptive, may residents, requires time usually devoted to other	jor source of distress for er residents or activitie	or staff and oth s)	er
				12
				15

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G. APATHY/IN	DIFFERENCE		(NA)
Does the reside things or lack r activities.	nt sit quietly without paying attention to things going on around him/her? Has h notivation for participating in activities? Is it difficult to involve the resident in	e/she lost int conversation	erest in doing n or in group
□ Yes □ No	(if yes, please proceed to subquestions) (if no, please proceed to next screening question)		
1. Has the resid	ent lost interest in the world around him/her?	□ Yes	□ No
2. Does the resi	dent fail to start conversation? (score only if conversation is possible)	□ Yes	□ No
3. Does the resi the visit of a	dent fail to show emotional reactions that would be expected (happiness over friend or family member, interest in the news or sports, etc)?	🗆 Yes	□ No
4. Has the resid	ent lost interest in friends and family members?	C Yes	No No
5. Is the residen	t less enthusiastic about his/her usual interests?	C Yes	No No
6. Does the resi	dent sit quietly without paying attention to things going on around him/her?	🗆 Yes	No No
7. Does the resi	dent show any other signs that he/she doesn't care about doing new things?	C Yes	No No
Comments			
If the screening	question is confirmed, determine the frequency and severity of the apathy/indiffe	erence.	
Frequency:			
	1. Rarely – less than once per week.		
	2. Sometimes – about once per week.		
	□ 3. Often – several times per week but less than every day.		
	4. Very often – essentially continuously present.		
Severity:			
	1. Mild – resident has a loss of interest in things at times, but this cases little or participation in activities.	e change in th	eir behavior
	2. Moderate – resident has a major loss of interest in things, which can only events such as visits from close relatives or family members.	be changed	by powerful
	3. Severe – resident has completely lost interest and motivation.		
Occupational Di	sruptiveness: How much does this behavior upset you and/or create more work for	or you?	
	0. Not at all		
	1. Minimally (almost no change in work routine)		
	$\square$ 2. Mildly (some change in work routine but little time rebudgeting required	)	
	□ 3. Moderately (disrupts work routine, requires time rebudgeting)		
	$\Box$ 4. Severely (disruptive, upsetting to staff and other residents, major time in	fringement)	
	5. Very Severely or Extremely (very disruptive, major source of distress for s residents, requires time usually devoted to other residents or activities)	taff and othe	r
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	ITION		(11.0.)
H. DISINHIB	HION		(NA)
Does the resi thinking? Doe	dent do or say things that are not usually done or said in public? Does he/she see es the resident say things that are insensitive or hurt people's feelings?	m to act impu	lsively without
	es (if yes, please proceed to subquestions) Io (if no, please proceed to next screening question)		
1. Does the re	esident act impulsively without thinking of the consequences?	🗆 Yes	No No
2. Does the re	esident talk to total strangers as if he/she knew them?	🗆 Yes	No No
3. Does the re	esident say things to people that are insensitive or hurt their feelings?	□ Yes	No No
4. Does the re	esident say crude things or make inappropriate sexual remarks?	C Yes	No No
5. Does the re in public?	esident talk openly about very personal or private matters not usually discussed	🗆 Yes	No No
6. Does the re	esident fondle, touch or hug others in way that is not appropriate?	C Yes	No No
7. Does the re	esident show any other signs of loss of control of his/her impulses?	□ Yes	No No
Commen	ts:	-	
		-	
If the screeni	ng question is confirmed, determine the frequency and severity of the disinhibition	n.	
Frequency:			
	1. Rarely – less than once per week.		
	2. Sometimes – about once per week.		
	□ 3. Often – several times per week but less than every day.		
	4. Very often – nearly always present.		
Severity:			
	1. Mild – resident acts impulsively at times, but behavior is not difficult to	change by ca	regiver.
	2. Moderate – resident is very impulsive and this behavior is difficult to ch	nange by the c	aregiver.
	3. Severe – resident is almost always impulsive and this behavior is nearly	impossible to	change.
<b>Occupational</b>	Disruptiveness: How much does this behavior upset you and/or create more work	for you?	
	0. Not at all		
	1. Minimally (almost no change in work routine)		
	$\square$ 2. Mildly (some change in work routine but little time rebudgeting require	ed)	
	□ 3. Moderately (disrupts work routine, requires time rebudgeting)		
	$\Box$ 4. Severely (disruptive, upsetting to staff and other residents, major time	infringement)	
	5. Very Severely or Extremely (very disruptive, major source of distress for residents, requires time usually devoted to other residents or activities)	r staff and oth )	er
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I. IRRITABILITY/LABILITY		(NA)
Does the resident get easily irritated or disturbed? Are his/her moods very changeable? Is he/she	extremely in	mpatient?
□ Yes (if yes, please proceed to subquestions) □ No (if no, please proceed to next screening question) □ N/A		
1. Does the resident have a bad temper, flying "off the handle" easily over little things?	🗆 Yes	No No
2. Does the resident rapidly change moods from one to another, being fine one minute and angry the next?	□ Yes	No No
3. Does the resident have sudden flashes of anger?	🗆 Yes	□ No
4. Is the resident impatient, having trouble coping with delays or waiting for planned activities or other things?	□ Yes	No No
5. Is the resident easily irritated?	🗆 Yes	□ No
6. Is the resident argue or is he/she difficult to get along with?	🗆 Yes	🗆 No
7. Does the resident show any other signs of irritability?	🗌 Yes	🗆 No
Comments:		
If the screening question is confirmed, determine the frequency and severity of the irritability /la	bility.	
Frequency:		
□ 1. Rarely – less than once per week.		
□ 2. Sometimes – about once per week.		
□ 3. Often – several times per week but less than every day.		
Li 4. Very often – essentially continuously present.		
<u>Sevency</u> .	by the enco	huar
2. Moderate – resident is unreaded times but behavior is not difficult for the	caregiver to a	thange
2. Noverate – resident is very irritable and this behavior is difficult for the i	norsible to a	hange.
Occupational Discuptiveness: How much does this behavior upset you and/or create more work f	or you?	lionge.
O. Not at all		
1. Minimally (almost no change in work routine)		
2. Mildly (some change in work routine but little time rebudgeting required	)	
3. Moderately (disrupts work routine, requires time rebudgeting)	,	
4. Severely (disruptive, upsetting to staff and other residents. maior time in	fringement)	
5. Very Severely or Extremely (very disruptive, major source of distress for residents, requires time usually devoted to other residents or activities).	staff and othe	er
residents, requires time usually devoted to other residents of activities)		
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J. ABERRAN	T MOTOR BEHAVIOR		(NA)
Does the resi and forth, pic	dent have repetitive activities or "habits" that he/she performs over and over suc king at things, or winding string? (Do not include simple tremors or tongue moveme	h as pacing, ents).	wheeling bac
	es (if yes, please proceed to subquestions) o (if no, please proceed to next screening question)		
1. Does the re	sident pace or wheel around the facility with no reason?	□ Yes	No No
2. Does the re	sident open or unpack drawers or closets over and over?	C Yes	No No
3. Does the re	sident repeatedly put on and take off clothing?	🗆 Yes	🗆 No
<ol> <li>Does the re string, more</li> </ol>	sident engage in repetitive activities such as handling buttons, picking, wrapping ving bed sheets, etc.?	🗆 Yes	No No
5. Does the re	sident have repetitive activities or "habits" that he/she performs over and over?	Tes 🗆	No No
6. Is the resid	ent excessively fidgety?	🗆 Yes	No No
Commen	ts:		
If the screening	ng question is confirmed, determine the frequency and severity of the aberrant mot	or activity:	
Frequency:			
	1. Rarely – less than once per week.		
	2. Sometimes – about once per week.		
	3. Often – several times per week but less than every day.		
	4. Very often – essentially continuously present.		
Severity:			
	1. Mild – resident has repetitive behaviors at times, but this does not changed	e daily activ	ities.
	2. Moderate – repetitive behaviors of the resident are very noticeable but from the caregiver.	can be contr	olled with he
	3. Severe – repetitive behaviors are very noticeable and upsetting to the re impossible to control by the caregiver.	sident and a	re difficult or
Occupational	Disruptiveness: How much does this behavior upset you and/or create more work f	or you?	
	0. Not at all		
	1. Minimally (almost no change in work routine)		
	2. Mildly (some change in work routine but little time rebudgeting required	)	
	3. Moderately (disrupts work routine, requires time rebudgeting)		
	4. Severely (disruptive, upsetting to staff and other residents, major time in	fringement)	
	5. Very Severely or Extremely (very disruptive, major source of distress for residents, requires time usually devoted to other residents or activities)	staff and oth	ier
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K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS		(NA)	
This group of questions should be directed only to caregivers who work the night shift and observe the resident directly or have acceptable knowledge (e.g., receive regular morning report) of the resident's nighttime activities. If the caregiver is not knowledgeable about the patient's nighttime behavior, mark this category "NA".			
Does the resident have difficulty sleeping (do not count as present if the resident simply gets u only to go to the bathroom and falls back asleep immediately)? Is he/she awake at night? Does h dressed, or go into others' rooms?	ip once or tw e/she wander	rice per night r at night, get	
<ul> <li>☐ Yes (if yes, please proceed to subquestions)</li> <li>☐ No (if no, please proceed to next screening question)</li> <li>☐ N/A</li> </ul>			
1. Does the resident have difficulty falling asleep?	□ Yes	No No	
2. Does the resident get up during the night (do not count if the resident gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?	□ Yes	No No	
3. Does the resident wander, pace, or get involved in inappropriate activities at night?	Tes 1	No No	
4. Does the resident wake up at night, dress, and plan to go out, thinking that it is morning and time to start the day?	Yes	No No	
5. Does the resident wake up too early in the morning (before other residents)?	🗆 Yes	No No	
6. Does the resident have any other nighttime behaviors that we haven't talked about?	🗆 Yes	No No	
Comments:			
If the screening question is confirmed, determine the frequency and severity of the nighttime beh	avior.		
Erequency:			
1. Rarely – less than once per week.			
2. Sometimes – about once per week.			
3. Often – several times per week but less than every day.			
4. Very often – once or more per day (every night).			
<u>Severity</u> :			
1. Mild – nighttime behaviors are present but not too stressful for the reside	ent.		
2. Moderate – nighttime behaviors are present and disturb others in the numone type of nighttime behavior may be present.	rsing home; n	nore than	
3. Severe – nighttime behaviors are present and the resident is very disturbed	ed during the	night.	
Occupational Disruptiveness: How much does this behavior upset you and/or create more work for	or you?		
0. Not at all			
1. Minimally (almost no change in work routine)			
2. Mildly (some change in work routine but little time rebudgeting required)	)		
3. Moderately (disrupts work routine, requires time rebudgeting)			
4. Severely (disruptive, upsetting to staff and other residents, major time in	fringement)		
5. Very Severely or Extremely (very disruptive, major source of distress for s residents, requires time usually devoted to other residents or activities)	taff and othe	r	
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Arr resident have an extremely good or poor appetite, changes in weight, or unusual eating habits (count as "N/A" he resident is incapacitated and has to be fo()? Has there been any change in type of food he/she prefers?            \[		ID FATING CHANGES			(NA)
<pre>ise the resident have an extremely good or poor appetite, changes in weight, or unusual eating habits (count as "N/A" the resident is incapacitated and has to be fed? Has there been any change in type of food he/she prefers?</pre>	L. APPEIIIE AN	ID EATING CHANGES			(NA)
Yes (if yes, please proceed to next screening question)            N/A              Does he/she have a poor appetite?	Does the resider if the resident is	nt have an extremely good or poor appetite, changes in weig incapacitated and has to be fed)? Has there been any change	ght, or unusual eatir e in type of food he/	ng habits (cou /she prefers?	unt as "N/A"
Does he/she have a poor appetite?          ves    no         Does he/she have an unusually good appetite?          ves    no         Has he/she lost weight?          ves    no         Has he/she have unusual eating behavior such as putting too much food in his/her          ves    no         mouth at once?          ves    no         Has he/she dad change in the kind of food he/she likes such as wanting too many sweets          ves    no         or other specific types of food?          ves    no         Has he/she have any other changes in appetite or eating that I haven't asked about?          ves    no         Have there been any other changes in appetite or eating that I haven't asked about?          ves    no         Comments:          narely - less than once per week.          Sometimes - about once per week.            0. Often - several times per week but less than every day.          Nild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing.            1. Mild - changes in appetite or eating are present and cause minor changes in weight, are about once per week.          Sovere - obvious changes in appetite or eating are present and cause changes in weight, are about once per week.            2. Moderate - changes in appetite or eating are present and cause changes in weight, are about once per week.          3. Severe - obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.         cupational Discruptivenes	□ Yes ( □ No (i	(if yes, please proceed to subquestions) if no, please proceed to next screening question)	□ N/A		
Does he/she have an unusually good appetite?       Image: Im	1. Does he/she h	ave a poor appetite?		□ Yes	No No
Has he/she lost weight? Image:	2. Does he/she h	ave an unusually good appetite?		C Yes	No No
Has he/she gained weight? <pre></pre>	3. Has he/she los	st weight?		Tes 1	No No
Does he/she have unusual eating behavior such as putting too much food in his/her mouth at once?   Yes   No Has he/she had a change in the kind of food he/she likes such as wanting too many sweets or other specific types of food?   Yes   No Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?   Yes   No Have there been any other changes in appetite or eating that I haven't asked about?   Yes   No Comments:	4. Has he/she ga	ined weight?		C Yes	No No
Has he/she had a change in the kind of food he/she likes such as wanting too many sweets Ives No   Has he/she developed eating behaviors such as eating exactly the same types of food each Ives No   Has he/she developed eating behaviors such as eating exactly the same types of food each Ives No   Have there been any other changes in appetite or eating that I haven't asked about? Ives No   Comments:	5. Does he/she h mouth at once	ave unusual eating behavior such as putting too much food i ??	n his/her	□ Yes	□ No
Has he/she developed eating behaviors such as eating exactly the same types of food each   day or eating the food in exactly the same order?   Have there been any other changes in appetite or eating that I haven't asked about?   Comments:	6. Has he/she ha or other specif	d a change in the kind of food he/she likes such as wanting to fic types of food?	oo many sweets	□ Yes	No No
Have there been any other changes in appetite or eating that I haven't asked about?       Yes       No         Comments:	7. Has he/she de day or eating t	veloped eating behaviors such as eating exactly the same typ the food in exactly the same order?	oes of food each	□ Yes	No No
Comments:	8. Have there be	en any other changes in appetite or eating that I haven't ask	ed about?	🗆 Yes	□ No
the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite. equency: 	Comments:				
equency: <ul> <li>1. Rarely – less than once per week.</li> <li>2. Sometimes – about once per week.</li> <li>3. Often – several times per week but less than every day.</li> <li>4. Very often – essentially continuously present.</li> </ul> verity: <ul> <li>1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.</li> <li>2. Moderate – changes in appetite or eating are present and cause minor changes in weight, are abnormal, or upset the resident.</li> </ul> xupational Disruptiveness: How much does this behavior upset you and/or create more work for you? <ul> <li>0. Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>	If the screening of	question is confirmed, determine the frequency and severity	of the changes in ea	ating habits o	r appetite.
<ul> <li>1. Rarely - less than once per week.</li> <li>2. Sometimes - about once per week.</li> <li>3. Often - several times per week but less than every day.</li> <li>4. Very often - essentially continuously present.</li> <li>verity:</li> <li>1. Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing.</li> <li>2. Moderate - changes in appetite or eating are present and cause minor changes in weight, are abnormal, or upset the resident.</li> <li>verity:</li> <li>Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Midly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>	Frequency:				
2. Sometimes – about once per week.         3. Often – several times per week but less than every day.         4. Very often – essentially continuously present.         verity:         1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.         2. Moderate – changes in appetite or eating are present and cause minor changes in weight.         3. Severe – obvious changes in appetite or eating are present and cause minor changes in weight, are abnormal, or upset the resident.         xupational Disruptiveness: How much does this behavior upset you and/or create more work for you?         0. Not at all         1. Minimally (almost no change in work routine)         2. Mildly (some change in work routine but little time rebudgeting required)         3. Moderately (disruptive, upsetting to staff and other residents, major time infringement)         5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)		1. Rarely – less than once per week.			
3. Often - several times per week but less than every day.         4. Very often - essentially continuously present.         verity:         1. Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing.         2. Moderate - changes in appetite or eating are present and cause minor changes in weight.         3. Severe - obvious changes in appetite or eating are present and cause minor changes in weight, are abnormal, or upset the resident.         xupational Disruptiveness: How much does this behavior upset you and/or create more work for you?         0. Not at all         1. Minimally (almost no change in work routine)         2. Middly (some change in work routine but little time rebudgeting required)         3. Moderately (disrupts work routine, requires time rebudgeting)         4. Severely (disruptive, upsetting to staff and other residents, major time infringement)         5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)		2. Sometimes – about once per week.			
A. Very often – essentially continuously present.  verity:  1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.  2. Moderate – changes in appetite or eating are present and cause minor changes in weight.  3. Severe – obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.  veupational Disruptiveness: How much does this behavior upset you and/or create more work for you?  0. Not at all  2. Mildly (almost no change in work routine)  2. Mildly (some change in work routine but little time rebudgeting required)  3. Moderately (disruptive, upsetting to staff and other residents, major time infringement)  5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)		□ 3. Often – several times per week but less than every d	ay.		
verity: <ul> <li>1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.</li> <li>2. Moderate – changes in appetite or eating are present and cause minor changes in weight.</li> <li>3. Severe – obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.</li> </ul> <li>xcupational Disruptiveness: How much does this behavior upset you and/or create more work for you?         <ul> <li>0. Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, reguires time usually devoted to other residents or activities)</li> </ul> </li>		4. Very often – essentially continuously present.			
<ul> <li>1. Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing.</li> <li>2. Moderate - changes in appetite or eating are present and cause minor changes in weight.</li> <li>3. Severe - obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.</li> <li>2. Moderates: How much does this behavior upset you and/or create more work for you?</li> <li>0. Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>	Severity:				
<ul> <li>2. Moderate - changes in appetite or eating are present and cause minor changes in weight.</li> <li>3. Severe - obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.</li> <li><u>ccupational Disruptiveness</u>: How much does this behavior upset you and/or create more work for you?</li> <li>0. Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>		<ul> <li>1. Mild – changes in appetite or eating are present but disturbing.</li> </ul>	have not led to cha	nges in weigh	t and are not
3. Severe – obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.         ccupational Disruptiveness: How much does this behavior upset you and/or create more work for you?         0. Not at all         1. Minimally (almost no change in work routine)         2. Mildly (some change in work routine but little time rebudgeting required)         3. Moderately (disrupts work routine, requires time rebudgeting)         4. Severely (disruptive, upsetting to staff and other residents, major time infringement)         5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)         \$/01/09: JLC)	2. Moderate – changes in appetite or eating are present and cause minor changes in weight.				
ccupational Disruptiveness: How much does this behavior upset you and/or create more work for you?         0. Not at all         1. Minimally (almost no change in work routine)         2. Mildly (some change in work routine but little time rebudgeting required)         3. Moderately (disrupts work routine, requires time rebudgeting)         4. Severely (disruptive, upsetting to staff and other residents, major time infringement)         5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)         5/01/09: JLC)		3. Severe – obvious changes in appetite or eating an abnormal, or upset the resident.	re present and cau	se changes ir	n weight, are
<ul> <li>O. Not at all</li> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>	Occupational Dis	ruptiveness: How much does this behavior upset you and/or	create more work f	for you?	
<ul> <li>1. Minimally (almost no change in work routine)</li> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>		0. Not at all			
<ul> <li>2. Mildly (some change in work routine but little time rebudgeting required)</li> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> </ul>		1. Minimally (almost no change in work routine)			
<ul> <li>3. Moderately (disrupts work routine, requires time rebudgeting)</li> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> <li>5/01/09: JLC)</li> </ul>		2. Mildly (some change in work routine but little time r	ebudgeting required	d)	
<ul> <li>4. Severely (disruptive, upsetting to staff and other residents, major time infringement)</li> <li>5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)</li> <li>5/01/09: JLC)</li> </ul>		□ 3. Moderately (disrupts work routine, requires time reb	oudgeting)		
5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities) 5/01/09: JLC)		4. Severely (disruptive, upsetting to staff and other resi	dents, major time ir	nfringement)	
5/01/09: JLC) 19		5. Very Severely or Extremely (very disruptive, major so residents, requires time usually devoted to other residents)	ource of distress for idents or activities)	staff and oth	er
19	(06/01/09: JLC)				
					19

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# Appendix 9 Neuropsychiatric Assessment for Non-Institutionalized Patients Based on the NPI/NPI-NH

A. DELUSIONS		(NA)
Does the resident have beliefs that you know are not true? For example, saying that peopleare from him/her. Has he/she said that family members or staff are not who they say they are or the affair? Has the resident had any other unusual beliefs?	trying to harr at his/her spo	m him/her or ste a ouse is having an
Yes (If yes, please proceed to subquestions)		
No (If no, please proceed to next screening question) N/A		
1. Does the resident believe that he/she is in danger – that others are planning to hurt him/her		
or have been hurting him/her?		□ No

or have been hurting him/her?	🗆 Yes	
2. Does the resident believe that others are stealing from him/her?	🗆 Yes	🗆 No
3. Does the resident believe that his/her spouse is having an affair?	🗆 Yes	🗆 No
4. Does the resident believe that his/her family, staff members or others are not who they sa they are?	iy 🗆 Yes	🗆 No
5. Does the resident believe that television or magazine figures are actually present in the room? (Does he/she try to talk or interact with them?)	🗆 Yes	🗆 No
<ol><li>Does he/she believe any other unusual things that I have n't asked a bout? Comments:</li></ol>	🗆 Yes	🗆 No

If the screening question is confirmed, determine the frequency and severity of the delusions.

#### Frequency:

- 1. Rarely less than once per week
- 2. Sometimes a bout once per week
- 3. Often several times per week but less than every day
- 4. Very often once or more per day

### Severity:

- □ 1. Mild delusions present but seem harmless and does not upset the resident that much.
- □ 2. Moderate delusions are stressful and upsetting to the resident and cause unusual or strange behavior.
- 3. Severe delusions are very stressful and upsetting to the resident and cause a major a mount of unusual or strange behavior.

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatali
- 🗆 1. Minimally
- 🗆 2. Mildly
- 🗆 3. Moderately
- 🗆 4. Severely
- □ 5. Very severely or extremely

## B. HALLUCINATIONS

Does the resident have hallucinations – meaning, does he/she see, hear, or experience things that are not present? (If "Yes," ask for an example to determine if in fact it is a hallucination). Does the resident talk to people who are not there?

Yes (If yes, please proceed to subquestions)

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(NA)

1.

2. 3.

4.

🗆 No

🗆 No

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No (If no, please proceed to next screening question)	
Does the resident act as if he/she hears voices or describe hearing voices?	🗆 Yes
Does the resident talk to people who are not there?	🗆 Yes
Does the resident see things that are not present or act like he/she sees things that are not	
present (people, a nimals, lights, etc)?	🗆 Yes
Does the resident smell things that others cannot smell?	🗆 Yes

5.	Does the resident describe feeling things on his/her skin or act like he/she is feeling things		
	crawling or touching him/her?	🗆 Yes	🗆 No
6.	Does the resident say or act like he/she tastes things that are not present?	🗆 Yes	🗆 No
7.	Does the resident describe any other unusual sensory experiences?	🗆 Yes	🗆 No
	Comments:		

If the screening question is confirmed, determine the frequency and severity of the

hallucinations.

#### Frequency:

- 1. Rarely less than once per week
- 2. Sometimes about once per week
- 3. Often several times per week but less than every day
- 🗆 4. Very often once or more per day

## Severity:

- □ 1. Mild hallucinations are present but seem harmless and does not upset the resident that much.
- 2. Moderate hallucinations are stressful and upsetting to the resident and cause unusual or strange behavior.
- 3. Severe hallucinations are very stressful and upsetting to the resident and cause a major amount of unusual or strange behavior. (PRN medications may be required to control them).

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatall
- 1. Minimally
- 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

C. AGITATION/AGGRESSION

Does the resident have periods when he/she refuses to let people help him/her? Is he/she hard to handle? Is he/she noisy or uncooperative? Does the resident attempt to hurt or hit others?

□ Yes (If yes, please proceed to subquestions) □ No (If no, please proceed to next screening question) □ N/A

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(NA)

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1. Does the resident get upset when people are trying to care for him/her or resist activities

such as bathing or changing clothes?	🗆 Yes	🗆 No
2. Does the resident always want things his/her own way?	🗆 Yes	🗆 No
3. Is the resident uncooperative, resistive to help from others?	🗆 Yes	🗆 No
4. Does the resident have any other behaviors that make him/her hard to handle?	🗆 Yes	🗆 No
5. Does the resident shout, make loud noises, or swear angrily?	🗆 Yes	🗆 No
6. Does the resident slam doors, kick furniture, throw things?	🗆 Yes	🗆 No
7. Does the resident attempt to hurt or hit others?	🗆 Yes	🗆 No
8. Does the resident have any other aggressive or agitated behaviors? Comments:	🗆 Yes	□ No

If the screening question is confirmed, determine the frequency and severity of the agitation / Aggression.

#### Frequency:

1. Rarely–less than once per week.

2. Sometimes – a bout once per week.

□ 3. Often – several times per week but less than every day.

4. Very often – once or more per day.

#### Severity:

□ 1. Mild – behavior is stressful for the resident, but can be controlled by the caregiver.

2. Mode rate – behaviors are stressful for and upsetting to the resident and are difficult to control.

3. Severe – agitation is very stressful or upsetting to the resident and is very difficult or impossible to control. There is a possibility they may injure themselves and medications are often required.

Distress: How emotionally distressing do you find this behavior?

O. Notatall
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

## D. DEPRESSION/DYSPHORIA

Does the resident seem sad or depressed? Does he/she say that he/she feels sad or depressed? Does the resident cry at times?

<ul> <li>Yes (If yes, please proceed to subquestions)</li> <li>No (If no, please proceed to next screening question)</li> </ul>	□ N/A		
1. Does the resident cryat times?		🗆 Yes	🗆 No
2. Does the resident say, or act like he/she is depressed?		🗆 Yes	🗆 No
3. Does the resident put him/herself down or say that he/she feels li	ke a failure?	🗆 Yes	🗆 No
4. Does the resident say that he/she is a bad person or deserves to b	e punished?	🗆 Yes	🗆 No

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(NA)

5. Does the resident seem very discouraged or say that he/she has no future?	🗆 Yes	🗆 No
6. Does the resident say he/she is a burden to the family or that the family would be better off		
without him/her?	🗆 Yes	🗆 No
7. Does the resident talk about wanting to die or a bout killing him/herself?	🗆 Yes	🗆 No
<ol> <li>Does the resident show any other signs of depression or sadness?</li> <li>Comments:</li> </ol>	🗆 Yes	□ No

If the screening question is confirmed, determine the frequency and severity of the depression.

#### Frequency:

1. Rarely – less than once per week.
□ 2. Sometimes – about once per week.
□ 3. Often – several times per week but less than daily.

□ 4. Very often – once or more per day.

### Severity:

1. Mild – depression is stressful for the resident but will usually change with the help of a caregiver.

2. Moderate – depression is stressful for the resident and is difficult to change by the caregiver.

3. Severe – depression is very upsetting and stressful for the resident and is very difficult or impossible to change.

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatall
- 1. Minimally
- 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

## E. ANXIETY

(NA)

Is the resident very nervous, worried, or frightened for no reason? Does he/she seem very tense or unable to relax? Is the resident afraid to be apart from you or from others that he/she trusts?

□ Yes (If yes, please proceed to subquestions)
□ No (If no, please proceed to next screening question) □ N/A

1. Does the resident say that he/she is worried about planned events such as appointments or

family visits?	Yes	🗆 No
2. Does the resident have periods of feeling shaky, unable to relax, or feeling very tense?	🗆 Yes	🗆 No
3. Does the resident have periods of (or complain of) shortness of breath, gasping, or sighing fo	or	
no apparent reason other than being nervous?	🗆 Yes	🗆 No
<ol> <li>Does the resident complain of butterflies in his/her stomach, or of racing or pounding of the heart because of being nervous? (Symptoms not explained by ill health)</li> </ol>	🗆 Yes	□ No
5. Does the resident avoid certain places or situations that make him/hermore nervous such a	15	

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meeting with friends or participating in ward activities?	🗆 Yes	🗆 No
6. Does the resident become nervous and upset when separated from you or from others that		
he/she trusts? (Does he/she cling to you to keep from being separated?)	🗆 Yes	🗆 No
7. Does the resident show any other signs of anxiety?	🗆 Yes	🗆 No
Comments:		

If the screening question is confirmed, determine the frequency and severity of the anxiety.

## Frequency:

1. Rarely – less than once per week.
--------------------------------------

2. Sometimes – about once per week.

3. Often – several times per week but less than every day.

4. Very often – essentially continuously present.

## Severity:

□1. Mild – anxiety is stressful for the resident but will usually change with the help of a caregiver.

□2. Moderate – anxiety is stressful for the resident and is difficult to change by the caregiver.

□3. Severe – anxiety is very upsetting and stressful for the resident and is very difficult or impossible to change.

Distress: How emotionally distressing do you find this behavior?

🗆 0. Not at all
🗆 1. Minimally
🗆 2. Mildly
3. Moderately

4. Severely

5. Very severely or extremely

# F. ELATION/EUPHORIA

(NA)

Does the resident seem too cheerful or too happy for no reason? I don't mean normal happiness but, for example, laughing at things that others do not find funny?

Yes (If yes, please proceed to subquestions)		
No (If no, please proceed to next screening question)		
1. Does the resident a mean to feel too good or to be too hanny?	□ Ver	□ No
1. Does the resident appear to real too good of to be too happy:		
2. Does the resident find humor and laugh at things that others do not find funny?	🗆 Yes	🗆 No
3. Does the resident seem to have a childish sense of humor with a tendency to giggle or laugh		
in a ppropriately (such as when something unfortunate happens to others)?	🗆 Yes	🗆 No
4. Does the resident tell jokes or say things that are not funny to others but seem funny to		
him/her?	🗆 Yes	🗆 No
<ol><li>Does the resident show any other signs of feeling too good or being too happy? Comments:</li></ol>	🗆 Yes	□ No

If the screening question is confirmed, determine the frequency and severity of the

# elation/euphoria.

Frequency:

1. Rarely – less than once per week.

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- 2. Sometimes about once per week.
- 3. Often several times per week but less than every day.
- 4. Very often once or more per day.

## Severity:

- 1. Mild resident is too happy at times.
- 2. Moderate resident is too happy at times and this sometimes causes strange behavior.
- □ 3. Severe resident is almost always too happy and finds nearly everything to be funny.

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatall
- 1. Minimally
- 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

# G. APATHY/INDIFFERENCE

(NA)

Does the resident sit quietly without paying a ttention to things going on a round him/her? Has he/she lost interest in doing things or lack motivation for participating in activities? Is it difficult to involve the resident in conversation or in grou pactivities?

□ Yes (If yes, please proceed to subquestions) □ No (If no, please proceed to next screening question) □ N/A

1. Has the resident lost interest in the world a round him/her?	🗆 Yes	🗆 No
2. Does the resident fail to start conversation? (score only if conversation is po	ossible) 🗆 Yes	🗆 No
3. Does the resident fail to show emotional reactions that would be expected	(happiness over	
the visit of a friend or family member, interest in the news or sports, etc)?	🗆 Yes	🗆 No
4. Has the resident lost interest in friends and family members?	🗆 Yes	🗆 No
5. Is the resident less enthusiastic about his/her usual interests?	🗆 Yes	🗆 No
6. Does the resident sit quietly without paying attention to things going on aro	ound him/her? 🗆 Yes	🗆 No
<ol><li>Does the resident show any other signs that he/she doesn't care about doin Comments:</li></ol>	ng new things? 🗆 Yes	🗆 No

If the screening question is confirmed, determine the frequency and severity of the apathy/in difference.

#### Frequency:

- 1. Rarely-less than once per week.
- 2. Sometimes about once per week.
- 3. Often several times per week but less than every day.
- 4. Very often essentially continuously present.

### <u>Severity</u>:

I. Mild – resident has a loss of interest in things at times, but this causes little change in their behavior or participation in activities.

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2. Moderate – resident has a major loss of interest in things, which can only be changed by powerful events such as visits from close relatives or family members.

3. Severe – resident has completely lost interest and motivation.

Distress: How emotionally distressing do you find this behavior?

🗆 0. Notatali	
🗆 1. Minimally	
🗆 2. Mildly	
3. Moderately	
□ 4. Severely	
□ 5. Very severely or extremely	1

### H. DISINHIBITION

(NA)

Does the resident do or say things that are not usually done or said in public? Does he/she seem to act impulsively without thinking? Does the resident say things that are insensitive or hurt people's feelings?

	Yes (If yes, please proceed to subquestions)			
	No (If no, please proceed to next screening question)	□ N/A		
1. Does the re 2. Does the re	esi dent act impulsively without thinking of the consequences? As ident talk to total strangers as if he/she knew them?		□ Yes □ Yes	□ No □ No
3. Does the re	esident say things to people that are insensitive or hurt their fee	lings?	□ Yes	🗆 No
4. Does the re	esident say crude things or make in appropriate sexual remarks?		🗆 Yes	🗆 No
5. Does the re	esi dent talk openly a bout very personal or private matters not u	sually discussed in		
public?			🗆 Yes	🗆 No
6. Does the re	sident fondle, touch or hug others in way that is not a ppropriat	e?	🗆 Yes	🗆 No
7. Does the re Commen	esident show any other signs of loss of control of his/her impulse ts :	25?	🗆 Yes	□ No

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

#### Frequency:

1. Rarely – less than once per week.

- 2. Sometimes about once per week.
- 3. Often several times per week but less than every day.
- 4. Very often nearly always present.

### Severity:

□ 1. Mild – resident acts impulsively at times, but behavior is not difficult to change by caregiver.

- 2. Moderate resident is very impulsive and this behavior is difficult to change by the caregiver.
- 3. Severe resident is almost always impulsive and this behavior is nearly impossible to change.

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Distress: How emotionally distressing do you find this behavior?

## 🗆 0. Notatal I

- 1. Minimally
- 2. Mildly

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4. Severely
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□ 5. Very severely or extremely

## I. IRRITABILITY/LABILITY

(NA)

Does the resident get easily irritated or disturbed? Are his/her moods very changeable? Is he/she extremely impatient?

Yes (If yes, please proceed to subquestions)		
No (If no, please proceed to next screening question)		
1. Does the resident have a bad temper, flying "off the handle" easily over little things?	🗆 Yes	🗆 No
2. Does the resident rapidly change moods from one to another, being fine one minute and angry the next?	🗆 Yes	🗆 No
3. Does the resident have sudden flashes of a nger?	🗆 Yes	🗆 No
4. Is the resident impatient, having trouble coping with delays or waiting for planned activities		
or other things?	🗆 Yes	🗆 No
5. Is the resident easily irritated?	🗆 Yes	🗆 No
6. Does the resident argue or is he/she difficult to get along with?	🗆 Yes	🗆 No
7. Does the resident show any other signs of irritability? Comments:	🗆 Yes	🗆 No

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

### Frequency:

□ 1. Rarely – less than once per week.

□ 2. Sometimes - about once per week.

- 3. Often several times per week but less than every day.
- 4. Very often essentially continuously present.

### Severity:

- 1. Mild resident is irritable at times but behavior is not difficult to change by the caregiver.
- 2. Moderate resident is very irritable and this behavior is difficult for the caregiver to change.
- 3. Severe resident is almost always irritable and this behavior is nearly impossible to change.

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatall
- □ 1. Minimally
- 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

## J. ABERRANT MOTOR BEHAVIOR

(NA)

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Does the resident have repetitive activities or "habits" that he/she performs over and over such as pacing, wheeling back and forth, picking at things, or winding string? (Do not include simple tremors or tongue movements).

Yes (If yes, please proceed to subquestions)		
No (If no, please proceed to next screening question)		
1. Does the resident pace or wheel around the facility with no reason?	🗆 Yes	🗆 No
2. Does the resident open or unpack drawers or closets over and over?	🗆 Yes	🗆 No
3. Does the resident repeatedly put on and take off clothing?	□ Yes	🗆 No
4. Does the resident engage in repetitive activities such as handling buttons, picking, wrapping		
string, moving bed sheets, etc.?	🗆 Yes	🗆 No
5. Does the resident have repetitive activities or "habits" that he/she performs over and over?	🗆 Yes	🗆 No
6. Is the resident excessively fidgety?	🗆 Yes	🗆 No
Comments:		

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

#### Frequency:

- 1. Rarely less than once per week.
- 2. Sometimes about once per week.
- 3. Often several times per week but less than every day.
- 4. Very often essentially continuously present.

#### Severity:

1. Mild – resident has repetitive behaviors at times, but this does not change daily activities.

- 2. Moderate repetitive behaviors of the resident are very noticeable but can be controlled with help from the caregiver.
- 3. Severe repetitive behaviors are very noticeable and upsetting to the resident and are difficult or impossible to control by the caregiver.

Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Notatal I
- 1. Minimally
- 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

### K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS

### (NA)

This group of questions should be directed only to caregivers who work the night shift and observe the resident directly or have acceptable knowledge (e.g., receive regular morning report) of the resident's nighttime activities. If the caregiver is not knowledgeable about the resident's nighttime behavior, mark this category "NA".

Does the resident have difficulty sleeping (do not count as present if the resident simply gets up once or twice per night on ly to go to the bathroom and falls back asleep immediately)? Is he/she awake at night? Does he/she wander at night, get dressed, or go into others' rooms?

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(NA)

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□ Yes (If yes, please proceed to subquestions)
□ No (If no, please proceed to next screening question) □ N/A

1. Does the resident have difficulty falling asleep?	🗆 Yes	🗆 No
2. Does the resident get up during the night (do not count if the resident gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?	🗆 Yes	🗆 No
3. Does the resident wander, pace, or get involved in inappropriate activities at night?	🗆 Yes	🗆 No
4. Does the resident wake up at night, dress, and plan to go out, thinking that it is morning and		
time to start the day?	🗆 Yes	🗆 No
5. Does the resident wake up too early in the morning (before other residents)?	🗆 Yes	🗆 No
<ol><li>Does the resident have any other nighttime behaviors that we haven't talked about? Comments:</li></ol>	🗆 Yes	🗆 No

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior.

#### Frequency:

1. Rarely – less than once per week.

2. Sometimes – about once per week.

3. Often – several times per week but less than every day.

4. Very often – once or more per day (every night).

#### Severity:

1. Mild – nighttime behaviors are present but not too stressful for the resident.

- 2. Moderate nighttime behaviors are present and disturb others in the nursing home; more than one type of nighttime behavior may be present.
- 3. Severe nighttime behaviors are present and the resident is very disturbed during the night.

### Distress: How emotionally distressing do you find this behavior?

- 🗆 0. Not at all
- □ 1. Minimally
- 🗆 2. Mildly
- 3. Moderately
- 4. Severely
- 5. Very severely or extremely

### L. APPETITE AND EATING CHANGES

Does the resident have an extremely good or poor appetite, changes in weight, or unusual eating habits (count as "N/A" if the resident is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

□ Yes (If yes, please proceed to subquestions)
 □ No
 □ N/A

∕es □No	,
∕es □No	,
∕es □No	,
∕es □No	,
	es □No es □No es □No es □No

5. Does he/she have unusual eating behavior such as putting too much food in his/her mouth at

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once?	🗆 Yes	🗆 No
6. Has he/she had a change in the kind of food he/she likes such as wanting too many sweets or other specific types of food?	🗆 Yes	□ No
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?	🗆 Yes	□ No
8. Have there been any other changes in appetite or eating that I haven't asked about? Comments:	🗆 Yes	□ No

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

## Frequency:

Completed by:	Signature		
	LIS. Very severely or extremely		
	14. Severely		
	□3 Moderately		
	□ 2 Mildly		
	1. Minimally		
	0. Not at all		
Distress: How emotionally distressing do you find this behavior?			
	3. Severe – obvious changes in appetite or eating are present and cause changes in weight, are abnormal, or upset the resident.		
	2. Moderate – changes in appetite or eating are present and cause minor changes in weight.		
<u>seventy</u> .	1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.		
Severity	14. Very often – essentially continuously present.		
	15. Orten – severar umes per week but less tranevery day.		
	2. Often - several times nor week but less than every day.		
	2. Sometimer – about once per week		
riequency.	1 Barely – Jess than once per week		

NPI-NH - United States/English - Mapi. ID8281 / NPI-NH\_TS2.0\_eng-USori.doc

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# Appendix 14National Institute of Neurological and Communicative<br/>Disorders and Stroke and the Alzheimer's Disease and Related<br/>Disorders Association (NINCDS-ADRDA)

NINCDS-ADRDA Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

- VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
  - familial occurrence;
  - onset before age of 65;
  - presence of trisomy-21: and
  - coexistence of other relevant conditions such as Parkinson's disease.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, & Stadlan EM. (1984). Clinical diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group\* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34 (7), 939.

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## Appendix 15Hachinski Ischemic Scale (Rosen Modification)

Please complete the following scale using information obtained from the subject's history and neurological examination. Indicate if a clinical feature is present or absent by selecting the appropriate score.

Clinical Feature	Present	Absent
Abrupt onset	2	0
Stepwise deterioration	1	0
Somatic complaints	1	0
Emotional incontinence	1	0
History of hypertension	1	0
History of strokes	2	0
Focal neurological symptoms	2	0
Focal neurological signs	2	0

Total Score: \_\_\_\_\_

Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980;7:486-8. Copyright VC Hachinski, 1975.

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## Appendix 20 Mini-Mental State Examination (MMSE)

#### Mini-Mental State Examination (MMSE)

**Instructions:** Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? May I ask you some questions about your memory?

#### ORIENTATION TO TIME

	Response	Score (circle one)	
What is the year?		0	1
season?		0	1
month of the year?		0	1
day of the week?		0	1
date?		0	1

#### ORIENTATION TO PLACE\*

	Response	Score (ci	rcle one)
Where are we now? What is the state (province)?		0	1
county (or city/town)?		0	1
city/town (or part of city/ neighborhood)?		0	1
building (name or type)?		0	1
floor of the building (room number or address)?		0	1

\* Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

#### **REGISTRATION\***

Listen carefully. I am going to say three words. You say them back after I stop. Ready?

Here they are ... APPLE [pause], PENNY [pause], TABLE [pause]. Now repeat those words back to me. [Repeat up to 5 times, but score only the first trial.]

	Response	Score (ci	Score (circle one)	
APPLE		0	1	
PENNY		0	1	
TABLE		0	1	

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

\* Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

#### ATTENTION AND CALCULATION [Serial 7s]\*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

		Response	Score (ci	rcle one)
What is 100 take away 7?	[93]		0	1
If needed, say: Keep going.	[86]		0	1
If needed, say: Keep going.	[79]		0	1
If needed, say: Keep going.	[72]		0	1
If needed, say: Keep going.	[65]		0	1

\* Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task.

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

## Spell WORLD forward, then backward.

Correct forward spelling if misspelled, but score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)

#### RECALL

What were those three words I asked you to remember? [Do not offer any hints.]

	Response	Score (cire	cle one)
APPLE		0	1
PENNY		0	1
TABLE		0	1

#### NAMING\*

	Response	Score (circ	:le one)
What is this? [Point to a pencil or pen.]		0	1
What is this? [Point to a watch.]		0	1

\* Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

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#### REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

	Response	Score (cire	cle one)
NO IFS, ANDS, OR BUTS		0	1

Detach the page following this scale along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

#### COMPREHENSION

Listen carefully because I am going to ask you to do something.

Take this paper in your right hand [pause], fold it in half [pause], and put it on the floor (or table).

	Response	Score (cir	rcle one)
TAKE IN RIGHT HAND		0	1
FOLD IN HALF		0	1
PUT ON FLOOR (or TABLE)		0	1

#### READING

Please read this and do what it says. [Show examinee the words on the stimulus form.]

	Response	Score (cire	cle one)
CLOSE YOUR EYES		0	1

#### WRITING

Please write a sentence. [If examinee does not respond, say: Write about the weather.]

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

Score (circle one)

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#### DRAWING

Please copy this design. [Display the intersecting pentagons on the stimulus form.]

Score (ci	rcle one)
0	1

Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Assessment of level of consciousness.

Drowsy

Alert/ Responsive Stuporous

Comatose/ Unresponsive

Total Score =	
(Sum all item scores)	(30 points max.)

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## **CLOSE YOUR EYES**

\_\_\_\_\_

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## Appendix 21 Handling and Shipment of Bioanalytical Samples

## **Pharmacokinetic Sample Collection**

Four mL of blood for pharmacokinetic testing will be collected into 4-mL Vacutainer tubes containing sodium heparin. Each tube should be gently inverted three to four times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from the tube should then be divided equally between the 2 bar-code labeled polypropylene tubes.

All tubes must be labeled using the central lab's bar code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the pharmacokinetic sample information. It is important to note the exact date and time of the blood collection, the date and time of the last dose of brexpiprazole/placebo prior to each blood draw, and the time of the meal closest to the last dose.

The sample must be stored at  $-70^{\circ}$ C, if available, or  $-20^{\circ}$ C or below. If only a  $-20^{\circ}$ C freezer is available, samples must be shipped within 30 days of collection. Primary and backup samples may be shipped together. If samples are stored in a  $-70^{\circ}$ C freezer, then one tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab.

If neither a  $-70^{\circ}$ C nor  $-20^{\circ}$ C freezer is available, the primary and backup pharmacokinetic samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.



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## Pharmacokinetic CCI

## Sample Shipment

Plasma **Classical** samples must be neatly packed in the kits provided by the central lab and restrained in a Styrofoam container (place Styrofoam container supplied within a cardboard box). Boxes should be completely filled with dry ice to avoid air spaces that allow evaporation of the dry ice. The Styrofoam container should be sealed with tape and placed in a cardboard box. The central laboratory must be alerted of sample shipment. Packages must not be shipped on Thursdays, Fridays, Saturdays, or any day prior to a holiday without the expressed consent of OPDC. Shipments from clinical sites will be via an overnight carrier to the central laboratory.

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## Appendix 22Protocol Amendment(s)/Administrative Change(s)

1

## Amendment Number:

**Issue Date:** 

16 December 2013

## **PURPOSE:**

The sponsor has determined the need for a first formal amendment to the original protocol. This amendment serves to reflect clarifications and additions to study procedures intended to enhance subject safety and accuracy of data. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency and to correct typographical, punctuation, and formatting errors. These changes were minor and do not change the design or content of the protocol, and therefore, are not summarized in this appendix.

The purpose of amending the Protocol 331-12-284, issued 06 May 2013, was to:

- update changes to study staff.
- increase numbers of participating centers from 20 to 30; trial recruitment period from 3 to 4 years; and trial duration from 3.5 to 4.5 years.
- clarify the role and responsibility of the investigator to assess the capacity of the subject to provide informed consent at screening and throughout the study.
- add a requirement to screening assessments of an MRI/CT scan of the brain.
- clarify the process for achieving the target dose.
- clarify the definition of other efficacy variables.
- remove the requirement that subjects who cannot provide consent must provide assent, and add that if a subject cannot provide assent, but does not dissent, then consent from a legally acceptable representative is sufficient.
- modify inclusion criteria #1, #5, and #10.
- modify exclusion criteria #2, #3, #6, #8, #11, #14, #20, #22, #30, and #34.
- clarify the definition for retesting during the screening period.
- clarify that the detailed neurological examination can be performed by a physician who is not necessarily a neurologist.
- clarify the visit window of time and the dosing scheme.
- add that subjects who complete this study are eligible to enter study 331-13-211.

- update Table 4.1-1 List of Restricted and Prohibited Medications, row 3 Antidepressants, to indicate that antidepressants that are CYP3A4 inhibitors, in addition to antidepressants that are CYP2D6 inhibitors, are prohibited from use during the study and require a 7-day washout prior to randomization. Add that fluoxetine requires a 28-day washout prior to randomization.
- add footnote a to fluoxetine in Table 4.1-2 to indicate that fluoxetine requires a 28-day washout prior to randomization.
- clarified restrictions on psychotropic agent use.
- add that eDiary information can be entered by facility staff.
- clarify the frequency of DMC meetings.
- add eGFR to the list of clinical laboratory assessments.
- added definition of EPS.
- revise the definition of Hy's law cases.
- allow for unique identifiers other than the subject's initials.
- update references to the Investigator's Brochure to include the most recent version.
- update country list and fax numbers for safety reporting.
- add agitation as a criterion for the CCI and CGI-S tools.
- update the list of abbreviations and definitions of terms.

## **BACKGROUND:**

These changes to Protocol 331-12-284 were made on the basis of adjustments considered important to ensure the safety of the subjects enrolled and to facilitate appropriate study implementation and communication.

## **MODIFICATIONS TO PROTOCOL:**

- Bold and underlined text: Changed text
- Bold and strikethrough text: Deleted text
- Bold and italicized text: Added text

## **General Revisions:**

No global changes were made to Protocol 331-12-284 in this first amendment. Changes by section are provided below.

## **Sectional Revisions:**

Location	Current Text	Revised Text
Title Page Director of Clinical Management	PPD Phone: PPD Fax: PPD E-mail: PPD	PPD Phone: PPD Fax: PPD PPD PPD PPD Fax: PPD PPD
Synopsis Trial Design Screening Period	The screening period will range from a minimum of 2 days to a maximum of 42 days and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. Written informed consent will be obtained from the subject, if the subject is deemed capable by the investigator, and acknowledgement will be obtained from the subject's legally acceptable representative, in accordance with country, state, and/or local regulations, prior to initiation of any study-required procedures. Alternatively, if the subject is deemed incapable of providing consent by the investigator, written informed consent from the subject's legally acceptable representative and assent from the subject will be obtained prior to the initiation of any protocol-required procedures. Further, the investigator must assess capacity during the screening period and throughout the course of the study; if the subject no longer is deemed capable of providing informed consent, informed consent must be obtained from the legally acceptable representative, and assent must be obtained from the subject.	The screening period will range from a minimum of 2 days to a maximum of 42 days and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. Written informed consent will be obtained from the subject, if the subject is deemed capable by the investigator, and acknowledgement will be obtained from the subject's legally acceptable representative, in accordance with country, state, and/or local regulations, prior to initiation of any study-required procedures. Alternatively, if the subject is deemed incapable of providing consent by the investigator, written informed consent from the subject's legally acceptable representative and assent from the subject will be obtained prior to the initiation of any protocol-required procedures. Further, the investigator must assess capacity during the screening period and throughout the course of the study; if the subject no longer is deemed consent, informed consent must be obtained from the legally acceptable representative, and assent must be obtained from the subject. The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the study. Determinations by the investigator of the capacity of

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SynopsisStarting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose-limiting side effects, the dose may be further increased to 1 mg/day on Day 29 the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.the subject's efficacy and tolerability.the subject's efficacy and tolerability.	Location	Current Text	Revised Text
Synopsis Trial Design 12-week, Double-blind Treatment PeriodStarting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose-limiting side effects, the dose may be further increased to 2 mg/day on Day 29 the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.Starting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2 week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose may be further increased to 2 mg/day on Day 29 the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.Starting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2 week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Day 3 visit). On Day 15 (the day after the Week 4 visit), based on the investigator's clinical evaluatio			the subject to provide informed consent and the options for obtaining informed consent from and/or on behalf of the subject under each potential circumstance will be made and implemented according to strict criteria.
Subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule, as	Synopsis Trial Design 12-week, Double-blind Treatment Period	Starting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose-limiting side effects, the dose may be further increased to 2 mg/day on Day 29 the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.	Starting with 0.25 mg of brexpiprazole (or matching placebo) on Day 1 (the day after the Baseline visit), subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule (see below). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose-limiting side effects, the dose may be further increased to 2 mg/day on Day 29 the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability. Subjects will be titrated to a target dose of 1 mg/day of brexpiprazole over a 2-week period, using the recommended titration schedule, as

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Synopsis Trial Design 12-week, Double-blind Treatment Period

Dosing Scheme Titration Schedule for Brexpiprazole				
	Recommended Daily Dose Administered			
Treatment Group	Day-1(day after the Baseline visit (Day 1)Day 4 (day after the Day 3 visit 			
Brexpiprazole 0.5-2 mg/day	0.25 mg/ <i>day</i>	0.5 mg/ <b>day</b>	1 mg/ <i>day</i> <sup>a</sup>	2 mg/ <b>day</b> <sup>b</sup>
Placebo	<			>

<sup>a</sup> After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and reincreased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).

<sup>b</sup> The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (i.e., Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability. Allowable IMP doses that may be given starting the day after the Week 4 visit (i.e., Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Location	Current Text	Revised Text
Synopsis	After achieving the target dose of 1	The first dose of IMP will be
Trial Design	mg/day, dose decreases can occur at	administered on the day after the
12-week, Double-blind	any time (scheduled or unscheduled	Baseline visit (i.e., Day 1). All
Treatment Period	visits) based on tolerability. The dose	subjects randomly assigned to receive
	may be reduced to the previously	brexpiprazole will receive 0.25
	highest tolerated dose (to a minimum	mg/day as a starting dose.
	dose of 0.5 mg/day) in a stepwise	The dose of IMP will be increased
	manner.	from 0.25 mg/day to 0.5 mg/day
		starting on the day after the Day 3
	Allowable IMP doses after the Week 4	<i>visit (i.e., Day 4 [+2 days]).</i>
	visit will be 0.5 mg/day, 1 mg/day, or	
	2 mg/day. Subjects unable to tolerate	The dose will then be increased to
	0.5 mg/day of the IMP will be	1 mg/day starting on the day after the
	discontinued from the trial. If a	<i>Week 2 visit (i.e., Day 15 [±2 days]).</i>
	subject is withdrawn, every effort will	After achieving the target dose of 1
	be made to complete all of the Week	mg/day, the dose may be decreased to
	12/ET evaluations prior to	a 0.5 mg/day and re-increased to 1
	administering any additional	mg/day based on the investigator's
	medications for the treatment of	clinical judgment. Dose decreases
	agitation or other prohibited	and increases can occur at any time
	medications.	(scheduled or unscheduled visits). The
		dose may be reduced to the
		previously highest tolerated dose (to
		a minimum dose of 0.5 md/day) in a
		stepwise manner.
		The dose of IMP can be further
		increased from 1 mg/day to 2 mg/day
		starting on the day after the Week 4

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		visit (i.e., Day 29 [ $\pm$ 2 days]). Note: The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (i.e., Day 29 [ $\pm$ 2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability.
		Allowable IMP doses-that may be given starting the day after the Week 4 visit (i.e., Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day. Dose decreases and increases must occur in a stepwise manner and can occur at any time (scheduled or unscheduled visits).
		For subjects randomly assigned to receive placebo, their dose of IMP will be administered daily starting on the day after the Baseline visit (i.e., Day 1) and ending on Week 12/ET (the last day of the Treatment Period).
		Subjects unable to tolerate 0.5 mg/day of the IMP ( <i>or matching placebo</i> ) will be discontinued from the trial.
		If a subject is <i>discontinued from the</i> <i>trial</i> withdrawn, every effort will be made to complete all of the Week 12/ <i>Early termination</i> (ET) evaluations prior to administering any additional medications for the treatment of agitation or other prohibited medications.
Synopsis Follow-up Period	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a clinic visit at the residential facility 30 (+ 2) days after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject may be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and c	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a clinic visit at the residential facility 30 (+ 2) days after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject <i>should</i> may be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by talaphone content with the subject and

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	caregiver.	a caregiver.	
	If a subject discontinues the trial prematurely, every effort will be made to complete the Week 12/ET evaluations prior to administering additional medications for the treatment of agitation or other prohibited medications.	Subjects who complete both the 12- week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331- 13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-12- 211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at the residential facility. If the subject has left the residential facility where he or she participated in the trial, the 30-day safety follow- up visit will occur as a clinic visit at the investigator's site. If a subject discontinues the trial prematurely, every effort will be made to complete the Week 12/ET evaluations prior to administering additional medications for the treatment of agitation or other	
~ .		prohibited medications.	
Synopsis Subject Population	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan, which was performed after the onset of symptoms of dementia, consistent with a diagnosis of Alzheimer's disease. Additionally, at both the screening and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the NPI-NH. Subjects must require	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan <i>of the brain</i> , which was performed after the onset of symptoms of dementia, <i>with</i> <i>findings</i> consistent with a diagnosis of Alzheimer's disease. Additionally, at both the screening and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the <i>Neuropsychiatric Inventory-Nursing</i> <i>Home</i> (NPI-NH).	

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	pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (e.g., pain, infection) and trial of nonpharmacological interventions.	Subjects must require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (e.g., pain, infection, <i>polypharmacy</i> ) and trial of nonpharmacological interventions.	
Synopsis Exclusion Criteria	• Subjects with a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan performed after the onset of symptoms of dementia with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (e.g., cortical stroke, multiple infarcts), space-occupying lesion (e.g., tumor), or other major structural brain disease.	• Subjects with a previous magnetic resonance imaging (MRI/) or computed tomography (CT) scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (e.g., cortical stroke, multiple infarcts), space-occupying lesion (e.g., tumor), or other major structural brain disease.	
	• Subjects with a history of stroke, transient ischemic attack, or embolism.	• Subjects with a history of stroke, transient ischemic attack, or <i>pulmonary or cerebral</i> embolism.	
Synopsis Trial Sites	It is planned that approximately 330 subjects will be screened at approximately 20 trial centers worldwide so that 230 subjects will be randomized to treatment.	It is planned that approximately 330 subjects will be screened at approximately <u>30</u> trial centers worldwide so that 230 subjects will be randomized to treatment.	
Synopsis Investigational Medicinal Product, Dose, Formulation, Mode of Administration	The first dose of the IMP will be administered on Day 1, i.e., the day after the Baseline visit. On Day 1, all subjects will be administered 0.25 mg/day of brexpiprazole (or matching placebo). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose-limiting side effects, the dose may be further increased to 2 mg/day on Day 29 (the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.	The first dose of the IMP will be administered on Day 1, i.e., the day after the Baseline visit. On Day 1, all subjects will be administered 0.25 mg/day of brexpiprazole (or matching placebo). The dose will be increased to 0.5 mg/day on Day 4 (the day after the Day 3 visit). On Day 15 (the day after the Week 2 visit), the dose will be increased to 1 mg/day. In the absence of clinical response and dose limiting side effects, the dose may be further increased to 2 mg/day on Day 29 (the day after the Week 4 visit), based on the investigator's clinical evaluation of the subject's efficacy and tolerability.	
	After achieving the target dose of 1 mg/day, dose decreases can occur at any time (scheduled or unscheduled visits) based on tolerability. The dose may be reduced to the previously highest tolerated dose (to a minimum	After achieving the target dose of 1 mg/day, dose decreases can occur at any time (scheduled or unscheduled visits) based on tolerability. The dose may be reduced to the	

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	dose of 0.5 mg/day) in a stepwise manner. Allowable IMP doses after the Week 4 visit will be 0.5 mg/day, 1 mg/day, or 2 mg/day. Subjects unable to tolerate 0.5 mg/day of the IMP will be discontinued from the trial.	previously highest tolerated dose (to a minimum dose of 0.5 mg/day) in a stepwise manner. Allowable IMP doses after the Week 4 visit will be 0.5 mg/day, 1 mg/day, or 2 mg/day. Subjects unable to tolerate 0.5 mg/day of the IMP will be discontinued from the trial.
Synopsis Trial Duration	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 3.5 years, of which approximately 3 years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately <b>4</b> .5 years, of which approximately <b>4</b> years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact-30 (+ 2) days after the last dose of the IMP. <b>Subjects who complete both the 12-</b> week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331- 13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-12-211, the 30- day safety follow-up visit for Trial

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		331-12-284 will occur as a clinic visit	
		at the residential facility. If the	
		subject has left the residential	
		facility where he or she participated	
		in the trial, the 30-day safety follow-	
		up visit will occur as a clinic visit at	
		the investigator's site.	
Section 1.2.1	Trials have investigated the	Trials have investigated the	
Pharmacokinetics and	pharmacokinetics of brexpiprazole in	pharmacokinetics of brexpiprazole in	
Pharmacodynamics	special populations (subjects with	special populations (subjects with	
	hepatic impairment and renal	hepatic impairment and renal	
	impairment); one studying the effects	impairment); one studying the effects	
	of age and sex on brexpiprazole	of age and sex on brexpiprazole	
	pharmacokinetics recently was	pharmacokinetics recentlywashas	
	completed. Based on the results of the	<i>been</i> completed. Based on the results	
	special population trials, no dose	of the special population trials, no	
	adjustment is needed when	dose adjustment is needed when	
	brexpiprazole is administered to	brexpiprazole is administered to	
	elderly subjects or subjects with renal	elderly subjects or subjects with renal	
	or hepatic insufficiency.	or hepatic insufficiency.	
Section 3.1	The screening period will range from a	The screening period will range from a	
Type/Design of Trial	minimum of 2 days to a maximum of	minimum of 2 days to a maximum of	
Screening Period	42 days and will begin when the	42 days and will begin when the	
	informed consent form (ICF) is	informed consent form (ICF) is	
	signed, prior to the initiation of any	signed, prior to the initiation of any	
	procedures. Written informed consent	procedures. Additional requirements	
	will be obtained from the subject, if	for obtaining informed consent from	
	the subject is deemed capable by the	this vulnerable subject population are	
	will be obtained from the subject's	provided in Section 5.4.1. Written	
	legally acceptable representative in	from the subject of the subject is	
	accordance with country state and/or	deemed canable by the investigator	
	local regulations prior to initiation of	and acknowledgement will be	
	any study-required procedures	and acknowledgement will be obtained from the subject's legally	
	Alternatively if the subject is deemed	accontable representative in	
	incapable of providing consent by the	accordance with country, state	
	investigator, written informed consent	and/or local regulations, prior to	
	from the subject's legally acceptable	initiation of any study-required	
	representative and assent from the	procedures. Alternatively, if the	
	subject will be obtained prior to the	subject is deemed incapable of	
	initiation of any protocol-required	providing consent by the	
	procedures. Further, the investigator	investigator, written informed	
	must assess the subject's capacity to	consent from the subject's legally	
	provide informed consent during the	acceptable representative and assent	
	screening period and throughout the	from the subject will be obtained	
	course of the study; if the subject is no	<del>prior to the initiation of any</del>	
	longer deemed capable of providing	protocol-required procedures.	
	informed consent, informed consent	Further, the investigator must	
	must be obtained from the legally	assess the subject's capacity to	
	acceptable representative and assent	provide informed consent during	
	must be obtained from the subject. An	the screening period and throughout	
	(IVDS) an interaction 1	the course of the study; if the	
	(IVKS) or interactive web response	subject is no longer deemed capable	

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	system (IWRS) will be used to obtain	of providing informed consent,
	the subject study identification number	informed consent must be obtained
	for each subject with a signed ICF.	from the legally acceptable
		representative and assent must be
		obtained from the subject. An
		interactive voice response system
		(IVRS) or interactive web response
		system (IWRS) will be used to obtain
		the subject study identification number
		for each subject with a signed ICF.
Section 3.1	If the subject decides not to wear the	If the subject decides not to wear the
Type/Design of Trial	actigraph at any time after the consent	actigraph at any time after the consent
Screening Period	is obtained, the assessment may be	is obtained, the assessment may be
	discontinued and study participation	discontinued and study participation
	will not be affected. The patient's	will not be affected. The patient's
	daily behavior will be logged into an	daily behavior will be logged into an
	eDiary by the caregiver.	eDiary by the caregiver and/or facility
		staff.
Section 3.1	Starting with 0.25 mg of brexpiprazole	Subjects will follow a titration
Type/Design of Trial	(or matching placebo) on Day I (the	schedule to gradually increase their
12-week, Double-blind	day after the Baseline Visit), subjects	dose of the IMP to the target dose
Treatment Period	will be titrated to a target dose of	(refer to Table 3.2-1).
	1 mg/day of brexpiprazole over a	Stanting with 0.25 may of
	2-week period, using the	Starting with 0.25 mg of
	to Table 3.2.1) The dose will be	on Day 1 (the day after the Baseline
	increased to 0.5 mg/day on Day 4 (the	visit) subjects will be titrated to a
	day after the Day 3 visit) On Day 15	target dose of 1 mg/day of
	(the day after the Week 2 visit), the	brexpinrazole over a 2-week period.
	dose will be increased to 1 mg/day. In	using the recommended titration
	the absence of clinical response and	schedule (refer to Table 3.2-1). The
	dose-limiting side effects, the dose	dose will be increased to 0.5 mg/day
	may be further increased to 2 mg/day	on Day 4 (the day after the Day 3
	on Day 29 (the day after the Week 4	visit). On Day 15 (the day after the
	visit), based on the in	Week 2 visit), the dose will be
	vestigator's clinical evaluation of the	increased to 1 mg/day. In the
	subject's efficacy and tolerability.	absence of clinical response and
		dose-limiting side effects, the dose
		may be further increased to
		<del>2 mg/day on Day 29 (the day after</del>
		the Week 4 visit), based on the
		investigator's clinical evaluation of
		the subject's efficacy and
		tolerability.

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Section 3.1	After achieving the target dose of 1	After achieving the target dose of 1
Type/Design of Trial	mg/day, dose decreases can occur at	mg/day, dose decreases can occur at
12-week, Double-blind	any time (scheduled or unscheduled	any time (scheduled or unscheduled
Treatment Period	visits) based on tolerability. The dose	visits) based on tolerability. The
	may be reduced to the previously	dose may be reduced to the
	highest tolerated dose (to a minimum	previously highest tolerated dose (to
	dose of 0.5 mg/day) in a stepwise	a minimum dose of 0.5 mg/day) in a
	manner. Allowable IMP doses after	stepwise manner. Allowable IMP
	the Week 4 visit will be 0.5 mg/day,	doses after the Week 4 visit will be
	1 mg/day, or 2 mg/day. Subjects	0.5 mg/day, 1 mg/day, or 2 mg/day.
	Unable to tolerate 0.5 mg/day of the	Subjects unable to tolerate 0.3
	trial. If a subject is with drawn avery	mg/day of the HVIF will be discontinued from the trial. If a
	offert will be made to complete all of	anscontinued from the trial. If a
	the Week 12/ET evaluations prior to	subject is withdrawn, every effort
	administering any additional	Week 12/FT evaluations prior to
	medications for the treatment of	administoring any additional
	agitation or other prohibited	modiantions for the treatment of
	medications	agitation or other prohibited
	incultations.	modications
		If a subject discontinues the trial
		nrematurely every effort will be made
		to complete the Week 12/ET
		evaluations prior to administering
		additional medications for the
		treatment of agitation or other
		prohibited medications.
Section 3.1 Type/Design of Trial	All subjects, whether they complete the trial or are withdrawn prematurely	All subjects, whether they complete the trial or are withdrawn prematurely
Follow-up Period	for any reason, will be followed up for a safety evaluation at a clinic visit at	for any reason, will be followed up for a safety evaluation at a clinic visit at
	the residential facility $30 (+2)$ days	the residential facility $30 (+2)$ days
	after the last dose of the IMP. If the	after the last dose of the IMP. If the
	subject has left the residential facility	subject has left the residential facility
	where he or she participated in the	where he or she participated in the
	trial, the subject may be seen in the	trial, the subject <b>should</b> may be seen in
	investigator's clinic or (if a clinic visit	the investigator's clinic or (if a clinic
	is not possible) assessed by telephone	visit is not possible) assessed by
	contact with the subject and a	telephone contact with the subject and
	caregiver. If a subject discontinues	a caregiver. If a subject discontinues
	the trial prematurely, every effort will	the trial prematurely, every effort
	be made to complete the Week 12/ET	will be made to complete the Week
	evaluations prior to administering	<b>12/ET evaluations prior to</b>
	additional medications for the	administering additional
	treatment of agitation or other	medications for the treatment of
	prohibited medications.	agitation or other prohibited
		medications.
		Subjects who complete both the 12-
		week aouble-blina treatment period
		ana the su-aay safety follow-up visit
		ure eligible lo enroll into 1rial 551- 13 211 which is a 2 month
		15-211, which is a 2-month, observational rollover trial to
		ooservational, rouover trait to

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		evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-12- 211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at the residential facility. If the subject has left the residential facility where he or she participated in the trial, the 30-day safety follow- up visit will occur as a clinic visit at
		the investigator's site.

## Section 3.2

Treatments Table 3.2-1 Dosing Scheme

Table 3.2-1         Dosing Scheme Titration Schedule for Brexpiprazole				
	Recommended Daily Dose Administered			
Day-1(day-after the Baseline visit (Day 1)Day 4 (day-after the Day 3 visitDay 15(day-after the Week 2 visit (Day 15)Day 15(day-after the Week 2 visit (Day 15)Treatment Group[+2 days])[±2 days])[=		Day <del>29(day after</del> the Week 4 visit (Day 29 [±2 days])		
Brexpiprazole 0.5- 2 mg/day	0.25 mg/ <b>day</b>	0.5 mg/ <b>day</b>	1 mg/ <b>day</b> <sup>a</sup>	2 mg/ <b>day</b> <sup>b</sup>
Placebo	<			>

<sup>a</sup> Subject must achieve the target dose of 1 mg/day before the dose can be decreased. After achieving the target dose of 1 mg/day, the dose may be decreased to a 0.5 mg/day and re-increased to 1 mg/day based on the investigator's clinical judgment. Dose decreases and increases can occur at any time (scheduled or unscheduled visits).

<sup>b</sup> The earliest time point that the dose can be increased to 2 mg/day is starting on the day after the Week 4 visit (i.e., Day 29 [±2 days]); however, it is not mandatory for the dose to be increased to 2 mg/day. The decision to increase the dose should be based on the investigator's clinical evaluation of the subject's response and tolerability. Allowable IMP doses that may be given starting the day after the Week 4 visit (i.e., Day 29 [±2 days]) will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Location	Current Text	<b>Revised Text</b>
Section 3.2	The first dose of the IMP will be	The first dose of IMP will be
Treatments	administered on Day 1, i.e., the day	administered on the day after the
	after the Baseline visit. On Day 4, i.e.,	Baseline visit (i.e., Day 1). All
	the day after the Day 3 visit, the dose	subjects randomly assigned to receive
	will be increased to 0.5 mg/day of	brexpiprazole will receive 0.25
	brexpiprazole (or matching placebo)	mg/day as a starting dose.
	for all subjects; and on Day 15 i.e., the	
	day after the week 2 visit, the dose	The dose of IMP will be increased
	will be increased to 1 mg/day of	from 0.25 mg/ady to 0.5 mg/ady
	for all subjects. In the absence of	starting on the day after the Day 5 visit (i.e. Day $A [\pm 2 ]$ days])
	clinical response and dose-limiting	visu (i.e., Duy 4 [+2 uuys]).
	side effects, the dose may be further	The dose will then he increased to
	increased to 2 mg/day on Day 29 (the	1 mg/day starting on the day after the
	day after the Week 4 visit) based on	Week 2 visit (i.e., Day 15 [±2 days]).
	the investigator's clinical evaluation of	After achieving the target dose of 1
	the subject's efficacy and tolerability.	mg/day, the dose may be decreased to
	· · · · · · · · · · · · · · · · · · ·	a 0.5 mg/day and re-increased to 1
	After achieving the target dose of 1	mg/day based on the investigator's
	mg/day, dose decreases can occur at	clinical judgment. Dose decreases
	any time (scheduled or unscheduled	and increases can occur at any time
	visits) based on tolerability. The dose	(scheduled or unscheduled visits).
	may be reduced to the previously	The dose of IMP can be further
	highest tolerated dose (to a minimum	increased from 1 mg/day to 2 mg/day
	dose of 0.5 mg/day) in a stepwise	starting on the day after the Week 4
	manner. Allowable IMP doses after	<i>visit (i.e., Day 29 [±2 days]). Note:</i>
	the Week 4 visit will be 0.5 mg/day, 1	The earliest time point that the dose
	mg/day, or 2 mg/day.	can be increased to 2 mg/day is
	Solt is start and the table matrix $0.5 = 1/1$	starting on the day after the Week 4
	of the IMP will be discontinued from	visit (i.e., Day 29 $(\pm 2 \text{ adys})$ ; nowever,
	the trial	it is not manuatory for the dose to be
		to increase the dose should be based
	If a subject is withdrawn every effort	on the investigator's clinical
	will be made to complete all of the	evaluation of the subject's response
	Week 12/ET evaluations prior to	and tolerability.
	administering any additional	Allowable IMP doses that may be
	medications for the treatment of	given starting the day after the Week
	agitation or other prohibited	4 visit (i.e., Day 29 [±2 days]) will be
	medications.	0.5 mg/day, 1 mg/day, or 2 mg/day.
		Dose decreases and increases must
		occur in a stepwise manner and can
		occur at any time (scheduled or
		unscheduled visits).
		For subjects randomly assigned to
		receive placebo, their dose of IMP
		will be administered daily starting on
		the day after the Baseline visit (i.e.,
		Duy 1) and ending on Week 12/EI (the last day of the Treatment
		(ine iusi auy of ine Treaimeni Period)
		- Crivuj.

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		Subjects unable to tolerate 0.5 mg/day of the IMP ( <i>or matching placebo</i> )will be discontinued from the trial.
		If a subject is <i>discontinued from the</i> <i>trial</i> withdrawn, every effort will be made to complete all of the
		Week 12/ET evaluations prior to
		administering any additional
		agitation or other prohibited
		medications.
Section 3.3 Trial Population	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan, which was performed after the onset of symptoms of dementia, consistent with a diagnosis of Alzheimer's disease. Additionally, at both the screening and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the NPI-NH. Subjects must require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan <i>of the brain</i> , which was performed after the onset of symptoms of dementia, <i>with</i> <i>findings</i> consistent with a diagnosis of Alzheimer's disease. Additionally, at both the screening and baseline visits, subjects must have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the NPI-NH. Subjects must require pharmacotherapy for the treatment of agitation per the investigator's indownet effective.
	and trial of nonpharmacological	reversible factors (e.g., pain, infection,
	interventions.	<i>polypharmacy</i> ) and trial of
Section 3.4.1	Written informed consent will be	nonpharmacological interventions.
Informed Consent	obtained from the subject, if deemed	
	capable by the investigator, and	The investigator must assess the
	acknowledgement from the subject's	capacity of the subject to provide
	accordance with state and/or local	injormea consent during the screening period and throughout the
	regulations, prior to initiation of any	course of the study. Once these
	study protocol-required procedures.	determinations are made by the
	Alternatively, if the subject is deemed	investigator, the following options for
	incapable of providing consent by the	obtaining informed consent from

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	investigator, written informed consent	and/or on behalf of the subject must
	from the subject's legally acceptable	be followed:
	representative and assent from the	
	subject will be obtained prior to the	Written informed consent will be
	initiation of any study protocol-	obtained from the subject, if If the
	required procedures. Further, the	subject is deemed capable by the
	investigator must assess capacity	investigator, written informed consent
	during the screening period and	will be obtained from the subject
	throughout the course of the study; if	prior to the initiation of any study
	the subject is no longer deemed	protocol-required procedures. In
	capable of providing informed	such cases, and acknowledgement
	consent, informed consent must be	from the subject's legally acceptable
	obtained from the legally acceptable	representative (an individual, or
	representative and assent must be	judicial or other body, authorized
	obtained from the subject.	under applicable law to consent to the
		subject's participation in the clinical
		trial on behalf of that prospective
		subject) will also be obtained, in
		accordance with state and/or local
		regulations prior to initiation of any
		study protocol-required procedures.
		Alternatively,
		Further, the investigator must
		assess capacity during the screening
		period and throughout the course of
		the study; <i>I</i> if the subject was initially
		<i>deemed capable</i> of providing
		informed consent <b>but</b> is no longer
		deemed <i>so</i> , informed consent must be
		obtained from the legally acceptable
		representative, and assent from the
		subject, if possible, willmust be
		confirmedobtained from the subject
		in accordance with state and/or local
		regulations prior to the initiation of
		any study protocol-required
		procedures.
		<b>Ii</b> f the subject is deemed incapable <b>by</b>
		the investigator of providing consent
		(e.g., <del>minors</del> , subjects with severe
		dementia) by the investigator, written
		informed consent will be obtained
		from the subject's legally acceptable
		representative prior to initiation of
		any study protocol-required
		procedures. In such cases, assent
		from the subject, <i>if possible</i> , will be
		confirmedobtained in accordance
		with state and/or local regulations
		prior to the initiation of any study
		protocol-required procedures.
		If the subject cannot provide assent,
		and does not dissent, then the consent

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		of the legally acceptable
		representative is sufficient unless
		otherwise required by the governing
		ethics body and/or applicable state
		and/or local <i>regulations</i> .
		If the subject dissents, then the
		subject is not eligible for
		participation in the trial
		If the subject initially provided assent
		at study entry, but subsequent
		assents to participate in the trial, the
		subject will be early terminated from
Section 3.4.1	Consent will be documented on a	Section 3.4.1.2 Documentation of
Informed Consent	written ICF The ICF will be	Informed Consent
informed Consent	approved by the same IRB/IEC that	ngormeu consent
	approves this protocol. Each ICF will	Consent will be documented on a
	comply with the International	written ICF. The ICF will be
	Conference on Harmonization (ICH)	approved by the same IRB/IEC that
	Good Clinical Practice (GCP)	approves this protocol. Each ICF will
	Guideline and local regulatory	comply with the International
	requirements. The investigator agrees	Conference on Harmonization (ICH)
	to obtain sponsor approval of any	Good Clinical Practice (GCP)
	written ICF used in the trial prior to	Guideline and local regulatory
	submission to the IRB/IEC.	requirements. The investigator agrees
		to obtain sponsor approval of any
	Investigators may discuss trial	written ICF used in the trial prior to
	availability and the possibility for	submission to the IRB/IEC.
	entry with a potential subject and	Investigators may discuss trial
	subject's legally acceptable	availability and the possibility for
	representative without first obtaining	entry with a potential subject and
	consent. However, informed consent	subject's legally acceptable
	must be obtained and documented	representative without first obtaining
	that are performed solely for the	must be obtained and documented
	nurnose of determining eligibility for	prior to initiation of any procedures
	this trial including withdrawal from	that are performed solely for the
	current medication(s)	nurpose of determining eligibility for
		this trial, including withdrawal from
	When a study includes subjects who	current medication(s).
	may not have the capacity to provide	
	informed consent, the investigator will	When a study includes subjects who
	be required to assess capacity. If the	may not have the capacity to
	subject is deemed capable of	provide informed consent, the
	providing informed consent, then the	investigator will be required to
	subject can be enrolled with the	assess capacity. If the subject is
	consent of the subject. If the subject is	deemed capable of providing
	deemed to not have the capacity to	informed consent, then the subject
	provide informed consent (e.g.,	can be enrolled with the consent of
	minors, subjects with severe	the subject. If the subject is deemed
	be appelled with the concent of the	to not nave the capacity to provide
	subject's legally acceptable	subjects with severe domentic) then
	subject's legally acceptable	subjects with severe dementia), then

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	representative and the subject must be	the subject can only be enrolled with
	informed about the study to the extent	the consent of the subject's legally
	compatible with the subject's	acceptable representative and Tthe
	understanding and, if capable,	subject must be informed about the
	personally sign and date the consent or	study to the extent compatible with the
	assent form, depending on local	subject's understanding and, if
	regulations.	capable, personally sign and date the
		consent or assent form, depending on
		local regulations.
Table 3.4-1	#1 Written informed consent will be	#1 Written informed consent will be
Inclusion Criteria	obtained from the subject, if deemed	obtained from the subject, if deemed
	capable by the investigator, and	capable by the investigator, and
	acknowledgement will be obtained	acknowledgement will be obtained
	from the subject's legally acceptable	from the subject's legally acceptable
	representative, in accordance with	representative, in accordance with
	country, state, and/or local regulations,	country, state, and/or local
	prior to initiation of any study-	regulations, prior to initiation of any
	required procedures. Alternatively, if	study-required procedures.
	newiding concert by the investigator	Alternatively, if the subject is
	written informed consent from the	accined incupable of providing
	subject's legally acceptable	informed consent from the subject's
	representative and assent from the	lagelly accentable representative
	subject will be obtained prior to the	and assant from the subject will be
	initiation of any protocol-required	and assent from the subject will be obtained prior to the initiation of
	procedures	any protocol required procedures
		The investigator must assess the
		canacity of the subject to provide
		informed consent during the
		screening period and throughout the
		course of the study. Once this
		determination is made by the
		investigator, the options for obtaining
		informed consent from and/or on
		behalf of the subject must be followed
		as provided in Section 3.4.1.
Table 3.4-1	#5 Subjects must have a previous	#5 Subjects must have a previous
Inclusion Criteria	MRI or CT scan, which was	MRI or CT scan of the brain, which
	performed after the onset of symptoms	was performed after the onset of
	of dementia, consistent with a	symptoms of dementia, with findings
	diagnosis of Alzheimer's disease.	consistent with a diagnosis of
		Alzheimer's disease.
Table 3.4-1	#10 Subjects who require	# 10 Subjects who require
Inclusion Criteria	pharmacotherapy for the treatment of	pharmacotherapy for the treatment of
	agitation per the investigator's	agitation per the investigator's
	judgment, after an evaluation for	judgment, after an evaluation for
	reversible factors (e.g., pain, infection)	reversible factors (e.g., pain, infection,
	and trial of nonpharmacological	<i>polypharmacy</i> ) and trial of
T 11 2 4 2	interventions.	nonpharmacological interventions.
Table $3.4-2$	#2 Subjects with a previous MRI or	#2 Subjects with a previous MRI or
Exclusion Criteria	C1 scan performed after the onset of	C1 scan of the brain, which was
	symptoms of dementia with findings	performed after the onset of symptoms
	consistent with a clinically significant	of dementia, with findings consistent

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	central nervous system disease other than Alzheimer's disease, such as vascular changes (e.g., cortical stroke, multiple infarcts), space-occupying lesion (e.g., tumor), or other major structural brain disease.	with a clinically significant central nervous system disease other than Alzheimer's disease, such as vascular changes (e.g., cortical stroke, multiple infarcts), space-occupying lesion (e.g., tumor), or other major structural brain disease.
Table 3.4-2 Exclusion Criteria	#3 Subjects with a history of stroke, transient ischemic attack, or embolism.	#3 Subjects with a history of stroke, transient ischemic attack, or <i>pulmonary or cerebral</i> embolism.
Table 3.4-2 Exclusion Criteria	#6 Subjects who have an insufficient response, based on the investigator's judgment, to previous antipsychotic medications for the treatment of agitation associated with Alzheimer's disease.	#6 Subjects who have an insufficient response, based on the investigator's judgment, to <i>two2 or more</i> previous antipsychotic medications for the treatment of agitation associated with Alzheimer's disease.
Table 3.4-2 Exclusion Criteria	<ul> <li>#8</li> <li>Bipolar I or II disorder, bipolar disorder not otherwise specified</li> <li>Current major depressive episodeunless on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).</li> <li>Eating disorder (including anorexia nervosa or bulimia)unless resolved with no symptoms for at least 1 year prior to screening</li> </ul>	<ul> <li>#8</li> <li>Bipolar I or II disorder, bipolar disorder not otherwise specified</li> <li>Current major depressive episode-unless on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).</li> <li>Eating disorder (including anorexia nervosa or bulimia)unless resolved with no symptoms for at least 1 year prior to screening</li> </ul>
Table 3.4-2 Exclusion Criteria	#11 Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders, such as atrial fibrillation, myocardial infarction, congestive heart failure, procedure for cardiovascular disease (i.e., angioplasty, stenting, coronary artery bypass surgery). Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator	<ul> <li>#11 Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular pulmonary, or gastrointestinal disorders. Clinically significant cardiovascular disorders include uncontrolled atrial fibrillation, heart failure, or ischemic heart disease. Surrogates for uncontrolled cardiovascular disease would include recent (within the last 6 months) hospitalizations or procedures, such as percutaneous coronary intervention, coronary bypass surgery.</li> <li>Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not</li> </ul>

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	is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.	expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical condition(s) and the potential impact of the condition(s) on trial participation.			
Table 3.4-2 Exclusion Criteria	#14 Subjects with stage 3 or higher renal disease.	#14 Subjects with stage 3 or higher <i>chronic</i> renalkidney disease (glomerular filtration rate < 60 mL /min/1 73 m <sup>2</sup> )			
Table 3.4-2 Exclusion Criteria	#20 Subjects with significant swallowing difficulties that would preclude taking oral medications in tablet form.	#20 Subjects with significant swallowing difficulties that would preclude taking oral medications in tablet form; <i>subjects with clinically</i> <i>relevant dysphagia</i> .			
Table 3.4-2 Exclusion Criteria	#22 Subjects with weight loss of more than 5% in the last 7 days or more than 10% in the last 30 days.	#22 Subjects with weight loss of more than 5% in the last the 7 days prior to the baseline or more than 10% between screening and baseline visitsin the last 30 days.			
Table 3.4-2 Exclusion Criteria	#30 Subjects with a positive drug screen for cocaine, marijuana, or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or over-the-counter (OTC) medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.	#30 Subjects with a positive drug screen for cocaine, marijuana (whether medically prescribed or not), or other illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of prescription or over-the-counter (OTC) medications or products that in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.			
Table 3.4-2 Exclusion Criteria	#33 Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial drug in Trial 331-12-283.	#33 Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial drug in Trial 331-12- <b>283</b> 284.			
Table 3.4-2 Exclusion Criteria	#34 Subjects who are being treated with anticoagulants.	#34 Subjects who <i>have a medical</i> <i>condition that requires treatment with</i> <i>anare being treated with</i> anticoagulants.			
Table 3.4-2 Exclusion Criteria	Screen failures previously excluded for a positive drug screen for cocaine, marijuana, or other illicit drugs are not eligible to be retested or rescreened.	Screen failures previously excluded for a positive drug screen for cocaine, marijuana, or other illicit drugs are not eligible to be retested or rescreened.			

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	Screen failures previously excluded for a positive blood alcohol test or a positive urine drug screen due to use of prescription or over-the-counter (OTC) medications or products may be retested or rescreened once for participation in the trial with consent of the medical monitor. Screen failures excluded for any other reasons may be rescreened (or the evaluation may be repeated within the screening period) once at any time if the exclusion characteristic has changed. In the event that a screen failure is rescreened after the 42-day screening period expires, a new ICF must be signed, an ew screening number assigned, and all screening procedures repeated.	Screen failures previously excluded for a positive blood alcohol test or a positive urine drug screen due to use of prescription or over-the-counter (OTC) medications or products may be retested or rescreened once for participation in the trial with consent of the medical monitor. Screen failures excluded for any other reasons may be <i>retestedrescreened</i> (or the <i>evaluation may be repeated within</i> <i>the screening period</i> ) or rescreened once at any time if the exclusion characteristic has changed. In the event that a screen failure is rescreened after the 42-day screening period expires, a new ICF must be signed, an ew screening procedures
Section 3.7 Trial Procedures	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 3.5 years, of which approximately 3 years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately <u>4.5</u> years, of which approximately <u>4</u> years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP.

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Section 3.7

Schedule of Assessments

### Revised Text (truncated)

Table 3.7-1     Schedule of Assessments											
Assessment	Visit										
OTHER PROCEDURES											
Register trial visit in IVRS/IWRS	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Randomize eligible subjects via IVRS/IWRS		Х									
IMP dispensing <sup>aa</sup>		Х	Х	Х	Х	Х	Х	Х			
IMP accountability			Х	Х	X	Х	Х	Х	Х		
ADDITIONAL ENTRANCE/HISTORY											
MRI/CT scan <sup>bb</sup>	$X^{bb}$										
Abbreviations: ACTH = adrenocorticotrop	oic hormone;	CCI					anti-HC	CV = hepati	tis C antibodies	s; aPTT = activ	vated
partial thromboplastin time CCI	partial thromboplastin time CCI										
CGI-S = Clinical Global Impression-Severity of Illness; CMAI = Cohen-Mansfield Agitation Inventory;											
CT = computed tometers	ography; EC	CG = electro	cardiogram	m; ET = e	early term	ination; 1	FU = following for the follo	ow up; HbA	$A_{1c} = glycosyla$	ted hemoglobi	in;
HBsAg = hepatitis B surface antigen; HI	[V = human	immunodef	iciency vi	rus; <i>IAP</i> :	= Indepe	ndent Ad	<i>judication</i>	n <b>Panel;</b> IC	CF = informed c	consent form; ]	IMP
= investigational medicinal product; INF	R = Internatio	onal Norma	lized Ratio	o IVRS =	interactiv	ve voice	response s	system; IW	RS = interactiv	e web respons	e
system; MMSE = Mini-Mental State Exa	amination;	CI					- MR	I = magnet	ic resonance in	naging;	
NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders											
Association: COL											
PT = prothrombin time; CCI						1 5	CCI	- J (	, , , , , , , , , , , , , , , , , , , ,	,	
$T_4$ = thyroxine; TSH = thyroid-st	imulating ho	rmone.									

Follow-up at a clinic visit or via telephone contact for evaluation of safety will occur 30 (+ 2 days) after the last dose of IMP and applies to all subjects. All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a

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clinic visit at the residential facility 30 (+ 2) days after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject should be seen in the investigator's clinic. Eligible subjects who complete the 30-day safety follow-up after completing the 12-week treatment period will have the option to enroll into a safety study (protocol number 331-13-211) for an additional 2 months of follow-up.

Written informed consent will be obtained from the subject, if deemed capable by the investigator, and acknowledgement will be obtained from the subject's legally acceptable representative, in accordance with country, state, and/or local regulations, prior to initiation of any study-required procedures. Alternatively, if the subject is deemed incapable of providing consent by the investigator, written informed consent from the subject's legally acceptable representative and assent from the subject will be obtained prior to the initiation of any protocol-required procedures. Further, the investigator must assess capacity during the screening period and throughout the course of the study; if the subject is no longer deemed capable of providing informed consent, informed consent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the legally acceptable representative and assent must be obtained from the subject. The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the study. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.

The neurological history and Hachinski Ischemic Scale (Rosen Modification) will be completed to assess eligibility for the trial by the same neurologistphysician who performs the neurological examinations (refer to Section 3.7.4.3.2). The neurologic history will include an MRI/CT scan as described in Section 3.7.3.8 and as scheduled in the ADDITIONAL ENTRANCE/HISTORY.

Electronic diary (eDiary) information will be entered by the caregiver *and/or facility staff* after the ICF is signed.

<sup>n</sup> A detailed neurological examination will be performed by a physician at screening, Week 6, Week 12/ET, and as needed during the trial for new onset neurological symptoms by a neurologist. The neurological examination will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system.

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<sup>bb</sup> If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia, is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed **SC** in order to confirm eligibility.

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Section 3.7.1.1 Screening	Trial personnel will call the IVRS or access the IWRS to register the visit (initial screening visit only). Subject's capacity will be evaluated by the investigator during the screening period. If the subject is no longer deemed capable of providing informed consent, informed consent	Trial personnel will call the IVRS or access the IWRS to register the visit (initial screening visit only). Subject's capacity will be evaluated by the investigator during the screening period. If the subject is no longer deemed capable of providing informed consent.			
	must be obtained from the legally acceptable representative and assent must be obtained from the subject. An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.	informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject. The investigator must assess the capacity of the subject to provide informed consent during the screening period. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1. An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.			
Section 3.7.1.1 Screening	<ul> <li>Psychiatric and neurological history will be recorded.</li> <li>Medications taken within 30 days of screening (signing of ICF/assent) will be recorded.</li> </ul>	<ul> <li>Psychiatric and neurological history will be recorded.</li> <li>If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed GCI in order to confirm eligibility.</li> <li>Medications taken within 30 days of screening (signing of ICF/assent) will be recorded.</li> </ul>			
Section 3.7.1.1 Screening	A complete physical examination (including height and waist circumference) will be performed. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a neurologist. Vital sign measurements (body weight, body temperature, blood	A complete physical examination (including height and waist circumference) will be performed. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by aneurologistphysician. Vital sign measurements (body			

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Location	Current Text	Revised Text
	pressure, and heart rate) will be	weight, body temperature, blood
	recorded	pressure, and heart rate) will be recorded
Section 3.7.1.1 Screening	An adequately trained and experienced clinician will confirm the diagnosis of probable Alzheimer's disease using the NINCDS-ADRDA criteria. An adequately trained and experienced neurologist who performs the neurological examination will complete the Hachinski Ischemic Scale (Rosen Modification). A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.	An adequately trained and experienced clinician will confirm the diagnosis of probable Alzheimer's disease using the NINCDS-ADRDA criteria. An adequately trained and experienced <b>neurologistphysician</b> who performs the neurological examination will complete the Hachinski Ischemic Scale (Rosen Modification). A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.
Section 3.7.1.1 Screening	Once the download is complete, the device will be placed back on the subject. If the screening period extends beyond 4 weeks, the battery will need to be replaced once. Once the download is complete, the device will be placed back on the subject. After the ICF has been signed, the caregiver will enter daily into the electronic diary (eDiary) information regarding the subject's behavior.	Once the download is complete, the device will be placed back on the subject. If the screening period extends beyond 4 weeks, the battery will need to be replaced once. Once the download is complete, the device will be placed back on the subject. After the ICF has been signed, the caregiver <i>and/or facility staff</i> will enter daily into the electronic diary (eDiary) information regarding the subject's behavior
Section 3.7.1.2 Baseline (Day 0)	Inclusion and exclusion criteria will be verified. The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject. A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.	Inclusion and exclusion criteria will be verified. The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject. The investigator must assess the capacity of the subject to provide informed consent during the screening period. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1. A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver
Section 3.7.1.3.1 Day 3	Visits are to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be	Visits are to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be

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Location	Current Text	Revised Text			
	performed:	performed:			
	The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject.	The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject The investigator must assess the capacity of the subject to provide informed consent throughout the study. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1.			
Section 3.7.1.3.2 Weeks 2, 4, 6, 8, and 10	The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.	The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.			
	The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject. A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.	The subject's capacity to provide informed consent will be evaluated by the investigator. If the subject no longer is deemed capable of providing informed consent, then informed consent must be obtained from the legally acceptable representative and assent must be obtained from the subject The investigator must assess the capacity of the subject to provide informed consent throughout the study. Once this determination is made by the investigator, the options for obtaining informed consent from and/or on behalf of the subject must be followed as provided in Section 3.4.1. A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.			
Section 3.7.1.3.2 Weeks 2,4,6,8, and 10	The following additional evaluations will be performed at the designated visits:	The following additional evaluations will be performed at the designated visits:			
	A complete physical examination (including waist circumference) will be performed at <i>Week 6 only</i> . A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial	A complete physical examination (including waist circumference) will be performed at <i>Week 6 only</i> . A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial			

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	nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a neurologist at <i>Week</i> 6 only.	nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a <b>neurologistphysician</b> at <i>Week 6</i> only.
Section 3.7.1.4 End of Treatment	A complete physical examination (including waist circumference) will be performed. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a neurologist.	A complete physical examination (including waist circumference) will be performed. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (eg, motor strength, muscle tone, reflexes), cerebellar system (eg, coordination), gait and station, and sensory system, will be performed by a <u>neurologistphysician</u> .
Section 3.7.1.5 Follow-up	Follow-up safety information will be collected at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of IMP. AEs and concomitant medications will be recorded.	Follow-up safety information will be collected at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of IMP. AEs and concomitant medications will be recorded.All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a clinic visit at the residential facility 30 (+ 2) days after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject should be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone with the subject and a caregiver. All AEs and concomitant medications will be recorded. Subjects who complete both the 12- week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331- 13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-12- 211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at the residential facility. If the subject has left the residential

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Location	Current Text	Revised Text
		facility where he or she participated in the trial, the 30-day safety follow- up visit will occur as a clinic visit at the investigator's site.
Section 3.7.3.5 Hachinski Ischemic Scale (Rosen Modification)	The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms. The Rosen-modified Hachinski Ischemic Scale will be completed to assess eligibility for the trial by the same neurologist who performs the neurological examinations (see Section 3.7.4.3.2). A sample of the Hachinski Ischemic Scale (Rosen Modification) is	The Rosen-modified Hachinski Ischemic Scale assesses whether a subject's dementia is likely due to vascular causes by the response to 8 questions: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, history of hypertension, history of stroke, focal neurologic signs, and focal neurologic symptoms. The Rosen-modified Hachinski Ischemic Scale will be completed to assess eligibility for the trial by the same <b>neurologistphysician</b> who performs the neurological examinations (see Section 3.7.4.3.2). A sample of the Hachinski Ischemic Scale (Rosen Modification) is
Section 3.7.3.7 Electronic Diary	provided in Appendix 13. The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including daily behavior logs collected by caregivers through eDiaries (refer to Appendix 15). Caregivers will record occurrence of the 29 behaviors listed in the CMAI as they occur using an eDiary. All 29 behaviors will be listed, and the caregiver will check the box next to the behavior when it occurs; there is no free text in the eDiary. Observations recorded using the eDiary will be transmitted wirelessly to the eDiary vendor.	provided in Appendix 13. The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including daily behavior logs collected by caregivers <i>and/or facility staff</i> through eDiaries (refer to Appendix 15). Caregivers will record occurrence of the 29 behaviors listed in the CMAI as they occur using an eDiary. All 29 behaviors will be listed, and the caregiver will check the box next to the behavior when it occurs; there is no free text in the eDiary. Observations recorded using the eDiary will be transmitted wirelessly to the eDiary vendor.
Section 3.7.3.8 Magnetic Resonance Imaging/Computed Tomography Scan of the Brain	New section.	If a previous MRI or CT scan of the brain performed after the onset of symptoms of dementia is not available, then an MRI/CT scan of the brain should be performed during screening. In addition, a repeat MRI/CT scan of the brain may be requested to be performed CCI in order to confirm eligibility.
Section 3.7.4.3.1 Physical Examination	The investigator (or designee) is responsible for performing the physical examination. If the appointed designee is to perform the physical	The investigator (or designee) is responsible for performing the physical examination. If the appointed designee is to perform the physical

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Location	Current Text	Revised Text
	examination, he or she must be	examination, he or she must be
	permitted by local regulations and	permitted by local regulations and
	his/her name must be included on the	his/her name must be included on the
	FDA Form 1572. Whenever possible,	Form FDA Form1572. Whenever
	the same individual should perform all	possible, the same individual should
	physical examinations.	perform all physical examinations.
Section 3.7.4.3.2	A detailed neurological examination	A detailed neurological examination
Neurological	will be performed at screening, Week	will be performed <i>by a physician</i> at
Examination	6, Week 12/ET, and as needed during	screening, Week 6, Week 12/ET, and
	the trial for new onset neurological	as needed during the trial for new
	symptoms by a neurologist. The	onset neurological symptoms by a
	neurological examination will consist	neurologist. The neurological
	of an evaluation of the subject's	examination will consist of an
	mental status, cranial nerves, motor	evaluation of the subject's mental
	system (eg, motor strength, muscle	status, cranial nerves, motor system
	tone, reflexes), cerebellar system (eg,	(eg, motor strength, muscle tone,
	coordination), gait and station, and	reflexes), cerebellar system (eg,
	sensory system.	coordination), gait and station, and
	The neurologist is regrangible for	sensory system.
	performing the neurological	The neurologistnhusician is
	evamination and must be included on	responsible for performing the
	the FDA Form 1572 Whenever	neurological examination and must be
	nossible the same neurologist should	included on the <b>Form</b> FDA
	perform all neurological examinations	<b>Form</b> 1572 Whenever possible the
	Any condition present at the post-	same <del>neurologist<i>physician</i> should</del>
	treatment neurological examination	perform all neurological examinations.
	that was not present at the baseline	Any condition present at the post-
	examination should be documented as	treatment neurological examination
	an AE and followed to a satisfactory	that was not present at the baseline
	conclusion.	examination and that is determined to
		be an AE should be documented as an
		AE and followed to a satisfactory
		conclusion. If new potentially
		clinically relevant neurological signs
		or symptoms are newly identified,
		referral to a neurologist is
		recommended.
Section 3.7.8	The data monitoring committee	The data monitoring committee
Independent Data	(DMC) will monitor safety in subjects	(DMC) will monitor safety in subjects
Monitoring Committee	who participate in the trial. The DMC	who participate in the trial. The DMC
	meetings will occur every 6 months,	meetings will occur as outlined in the
	but can be convened at any time at the	<b>DMC Charterevery 6 months</b> , but
	discretion of the DMC chair or the	dispersion of the DMC shain on the
	notified by the trial modical afficient of	trial modical officer. The chair will he
	all SAEs and will reasing summarias	notified by the trial medical efficer of
	of other safety data as available	all SAFs and will receive summaries
	or other safety data as available.	of other safety data as available
Section 3 8 3	The investigator will notify the	The investigator will notify the
Individual Subject	sponsor promptly when a subject is	sponsor promptly when a subject is
marviadar Subject	withdrawn Subjects withdrawn prior	withdrawn Subjects withdrawn prior
	to Week 12 must complete the Week	to Week 12 must complete the Week

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Location	Current Text Revised Text	
4.1. Prohibited	12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at the residential facility. If the subject has left the residential facility where he or she participated in the trial, the subject may be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and a caregiver.	12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at the residential facility. If the subject has left the residential facility where he or she participated in the trial, the subject <i>should</i> may be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and a caregiver.
Medications	All subjects must discontinue all prohibited medications during the screening period to meet the protocol- specified washout periods. All psychotropic agents, including but not limited to those listed in Table 4.1-1, are prohibited. The required duration of washout for selected prohibited medications is provided in Table 4.1- 1. The oral benzodiazepine therapy permitted during trial is summarized in Table 4.1-3. All prohibited medications must be discontinued at least 24 hours before the first dose of IMP.	All subjects must discontinue all prohibited medications during the screening period to meet the protocol- specified washout periods. <i>The</i> <i>required duration of washout for</i> <i>selected prohibited medications is</i> <i>provided in Table 4.1-1</i> . All other psychotropic agents, <del>including but</del> not limited to those not listed in Table 4.1-1, are prohibited. The required duration of washout for selected prohibited medications is provided in Table 4.1-1. The oral benzodiazepine therapy permitted during trial is summarized in Table 4.1-3. All Prohibited medications and must be discontinued at least 24 hours before the first dose of IMP. <i>The oral benzodiazepine therapy</i> <i>permitted during the trial is</i> <i>summarized in Table 4.1-3</i> .
Top of Table 4.1-1 Prohibited Medications	Added text	All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.

Location	Current Text	Revised Text
Table 4.1-1	#3 Prior to Randomization	#3 Prior to Randomization
Prohibited Medications		
	Allowed provided that the dose has	Allowed provided that the dose has
	been stable for 30 days prior to	been stable for 30 days prior to
	randomization. Antidepressant	randomization. Antidepressant
	inhibitons and machibited (and	CVD2 44 inhibitors are mahibited and
	Table 4 1-2 for prohibited	<i>carsa</i> a 7-day washout: fluorating
	antidepressant medications)	requires a 28-day washout
	undepressunt medicutions).	requires a 20-aay washoat
		During Double-Blind Treatment
		Period
		Antidepressant medications that are
		CYP2D6 or CYP3A4 inhibitors are
		prohibited. (see Table 4.1-2 for
		prohibited antidepressant
T 11 4 1 1		medications).
Prohibited Medications	Added text	#5 Anticonvuisants, /-aay wasnout, prohibitad
Table 4 1-1	#11 Medication	#11 Medication
Prohibited Medications		
	Medications to treat other medical	Medications to treat other medical
	conditions, such as hypertension	conditions, such as hypertension,
		hypercholesterolemia, etc., and anti-
		platelet agents.
Section 5.1	Nonserious adverse events are AEs	Nonserious adverse events are AEs
Definitions	that do not meet the criteria for an	that do not meet the criteria for an
	SAE.	SAE.
		If a subject is experiencing an
		If a subject is experiencing an avtranyramidal symptom the specific
		extrapyrumidal symptom, the specific
		indicated on the AE page of the
		eCRF. Examples of AEs that are
		considered extrapyramidal symptoms
		include, but are not limited to:
		dyskinesia, generalized rigidity,
		hyperkinesia, bradykinesia, akinesia,
		dystonia, hypertonia, akathisia,
		tremor, flexed posture, involuntary
		muscle contractions, athetosis, and
		chorea. If a subject is experiencing
		whother or not treatment with an
		whether or not treatment with an anticholingraic is required this is
		considered as extranoramidal
		syndrome and must be entered as
		"extrapyramidal syndrome" on the
		AE page of the eCRF instead of the
		individual symptoms.
Section 5.1	Immediately Reportable Event	Immediately Reportable Event
Definitions	<u>(IRE)</u>	<u>(IRE)</u>

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Location	Current Text	Revised Text
Location	Any SAE	Any SAE
	Any AE that necessitates	Any AE that necessitates
	discontinuation of the IMP	discontinuation of the IMP
	Potential Hy's law cases (any increase	Potential Hy's law cases (any increase
	of AST or $ALT \ge 3$ times the ULN or	of AST or $ALT \ge 3$ times the ULN-or
	screening value with an increase in	screening value with an increase in
	total bilirubin $\geq 2$ times the ULN or	total bilirubin $\geq 2$ times the ULN <b>or</b>
	screening value)	screening value)
Section 5.4	For subjects that experience an	For subjects that experience an
Potential Hy's Law	elevation in AST or ALT that is $\geq 3$	elevation in AST or ALT that is $\geq 3$
Cases	times the ULN, a total bilirubin level	times the upper normal limit, a total
	should also be evaluated. If the total	bilirubin level should also be
	bilirubin is $\geq 2$ times the ULN,	evaluated. If the total bilirubin is
	confirmatory repeat laboratory	>2 times the upper normal limit,
	samples should be drawn within 48 to	confirmatory repeat labs should be
	72 hours of the initial draw. If these	drawn within 48 to 72 hours of the
	values are confirmed, trial personnel	initial draw. If these values are
	will complete an IRE form with all	contirmed, study personnel will
	as an AE on the aCPE. Please note: If	values listed and also report the
	the subject was enrolled into the trial	event as an AF on the aCRF Please
	with non-exclusionary elevated	note. If the subject was aprolled into
	transaminase levels at baseline, please	the study with nonexclusionary
	discuss any potential drug-induced	elevated transaminase levels at
	liver injury events with the medical	baseline, please discuss any
	monitor.	potential drug-induced liver injury
		events with the medical monitor.
		For subjects that experience an
		elevation in AST or ALT that is $\geq 3$
		times the ULN, a total bilirubin level
		should also be evaluated. If the total
		bilirubin is $\geq 2$ times the ULN,
		confirmatory repeat laboratory
		Samples should be drawn within 46 to
		72 nours of the initial araw. If these
		will complete an IRF form with all
		values listed and also report the event
		as an AE on the eCRF. Please note:
		If the subject was enrolled into the
		trial with non-exclusionary elevated
		transaminase levels at baseline,
		please discuss any potential drug-
		induced liver injury events with the
		medical monitor.
Section 5.7.3	Any new SAEs reported by the subject	Any new SAEs reported by the subject
Follow-up and	to the investigator that occur after the	to the investigator that occur after the
Reporting of Serious	last scheduled contact and are	last scheduled contact and are
Adverse Events	determined by the investigator to be	determined by the investigator to be
Scheduled Contact	the IMP should be reported to OPDC	the IMP should be reported to OPDC
Scheduled Contact	This may include SAEs that are	This may include SAEs that are
	This may include SAEs that are	This may include SAEs that are

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Location	Current Text Revised Text	
Location Section 8.1 Packaging and Labeling	Current Text captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow related SAEs identified after the last scheduled contact until the events are resolved or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to OPDC up to the point the event has been resolved. Each blister card of brexpiprazole or matching placebo used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, Site number (to be filled in by the site staff/investigator), Subject ID (to be filled in by the site staff/investigator), subject's initials (to be filled in by the site staff/investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements. Once a blister card has been assigned to a subject via the IVRS or IWRS, it	Revised Text captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow related SAEs identified after the last scheduled contact until the events are resolved or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to OPDC up to the point the event has been resolved. Each blister card of brexpiprazole or matching placebo used in the trial will be given an identifying number and will be labeled to clearly disclose the blister card number, Site number (to be filled in by the site staff/investigator), Subject ID (to be filled in by the site staff/investigator), subject's initials or other unique identifier as appropriate (to be filled in by the site staff/investigator), compound ID, protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements. Once a
Section 9.2 Data Collection	A general reference to the procedures completed The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes	A general reference to the procedures completed The signature (or initials <i>or other</i> <i>unique identifier as appropriate)</i> and date of each clinician (or designee) who made an entry in the progress poter
Section 12 Confidentiality	Subjects will be identified only by initials and unique subject numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.	Subjects will be identified only by initials and unique subject numbers in eCRFs. <i>Per country regulations, if</i> <i>subject initials cannot be collected,</i> <i>another unique identifier will be</i> <i>used.</i> Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.
Section 14 References	16 Brexpiprazole (OPC-34712) Investigator's Brochure, Otsuka Pharmaceutical Development & Commercialization, Inc. Version	16 Brexpiprazole (OPC-34712) Investigator's Brochure, Otsuka Pharmaceutical Development & Commercialization, Inc. <del>Version No.</del>

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Location	Current Text	Revised Text
	No. 7, 21 Mar 2012.	7, 21 Mar 2012 Version No. 9, 09 Sep
		2013.
Appendix 1	Compound Director	Compound Director
Names of	PPD	PPD
Sponsor Personnel	PPD	PPD
	Otsuka Pharmaceutical Development	Otsuka Pharmaceutical Development
	& Commercialization, Inc.	& Commercialization, Inc.
	2440 Research Boulevard	2440 Research Boulevard
	Rockville, MD 20850	Rockville, MD 20850
	Phone: PPD	Phone: PPD
	Fax: PPD	Fax: PPD
	Primary Clinical Contact	PPD
	PPD	PPD
	PPD	<b>Otsuka Pharmaceutical</b>
	Otsuka Pharmaceutical Development	<b>Development &amp; Commercialization</b> ,
	& Commercialization, Inc.	Inc.
	2440 Research Boulevard	2440 Research Boulevard
	Rockville MD 20850	Rockville, MD 20850
	Phone: PPD	Phone: PPD
	Mobile: PPD	Fax: PPD
	Fax: PPD	Primary Clinical Contact
	E-mail: PPD	PPD
		PPD
		<b>Otsuka Pharmaceutical</b>
		<b>Development &amp; Commercialization</b> ,
		Inc.
		2440 Research Boulevard
		Rockville MD 20850
		Phone: PPD
		Mobile: PPD
		Fax: PPD
		E-mail: PPD

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Appendix 2

Institutions Concerned With the Trial

Safety Reporting

Revised Text

Country		Safety Fax Line	
United States		PPD	
Canada			
United Kingdom			
France			
Germany			
Ukraine			
Russia			
Slovakia			
Czech Republic			
Netherlands			
Additional countries being considered for participat	on		
Slovenia			
Lithuania			
Sweden			
Austria			
Finland			
Ireland			

\* Please note that this is a partner CRO number, not INC.

Medical Monitors

North America:

INC Research, LLC 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604 USA Phone: PPD Cell: PPD Mobile: PPD

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Appendix 9

Clinical Global Impression (CGI)

Revised Text

CCI

Clinical Global Impression Improvement (CGI-S), as related to agitation

**ADDITIONAL RISK TO THE SUBJECT:** 

The addition of the requirement for performing an MRI/CT scan of the brain during screening to confirm eligibility for enrollment in the study does pose some additional risk to these subjects; however, the sponsor has determined that the benefit derived from confirming the diagnosis of Alzheimer's disease and from ruling out other causes for dementia in the subjects enrolled in this study outweighs the risks to the subjects.

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### Amendment Number: 2

Issue Date: 07 Jul 2014

# **PURPOSE:**

The sponsor has determined the need for a second formal amendment to the first amendment of the original protocol. This amendment serves to reflect clarifications and additions to study procedures intended to enhance subject safety and accuracy of data. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency, and changes to correct typographical, punctuation, and formatting errors. These changes were minor and do not change the design or content of the protocol, and therefore, are not summarized in this appendix.

The purpose of amending Protocol 331-12-284, issued 16 Dec 2013, was to:

- CCI
- Allow the inclusion of non-institutionalized subjects.
- Clarify the caregiver/caretaker requirements.
- Modify the Neuropsychiatric Inventory-Nursing Home scale (NPI-NH) by replacing the Occupational Disruptiveness NPI-NH questions with the Distress questions from the Neuropsychiatric Inventory (NPI) for subjects in a non-institutionalized setting.
- Increase the number of planned trial centers from 30 to 46.
- Modify inclusion criteria #6 and #7.
- Modify exclusion criteria #8, #13, #14, #31, #32, and #40.
- Remove exclusion criterion #27 (this resulted in renumbering of exclusion criteria #28 through #41).
- Add another primary medical contact.
- Change the medical monitor for Europe.

# **BACKGROUND:**

These changes to Protocol 331-12-284 Amendment 1 were made to address the potential issue of missing data due to subjects terminating early, as well as on the basis of adjustments considered important to ensure the safety of the subjects enrolled and to facilitate appropriate study implementation and communication.

# **MODIFICATIONS TO PROTOCOL:**

- **Bold and underlined text:** •
- **Bold and strikethrough text:** •
- Bold and italicized text: •

## **General Revisions:**

All changes by section are provided below.

# **Sectional Revisions:**

Location	Current Text	Revised Text
Title Page	Director, Global Clinical Development	Director, Global Clinical Development
	PPD	PPD
	Phone: PPD	Phone: PPD
	Fax: PPD	Fax: PPD
	E-mail: PPD	E-mail: PPD
		PPD
	Original Protocol: 06 May 2013	Phone: PPD
	Date of Amendment 1: 16 December	Fax: PPD
	2013	PPD
		Original Protocol: 06 May 2013
		Date of Amendment 1: 16 December
		2013
		Date of Amendment 2: 07 Jul 2014
Synopsis	The trial population will include	The trial population will include
Trial Design	male and female subjects between 55	male and female subjects between 55
	and 90 years of age (inclusive), who	and 90 years of age (inclusive), who
	are residing in a dementia unit,	are <u>living in either an</u>
	nursing home, assisted living facility,	institutionalized setting (e.g.,
	or any other residential care facility	<u>nursing home, dementia unit,</u>
	providing long-term care, with a	assisted living facility, or any other
	diagnosis of probable Alzheimer's	residential care facility providing
	disease according to the National	long term care) or in a non-
	Institute of Neurological and	institutionalized setting where the
	Communicative Disorders and Stroke	subject is not living alone. In both
	and the Alzheimer's Disease and	the institutionalized and non-
	Related Disorders Association	institutionalized settings, the subject
	(NINCDS-ADRDA) criteria.	must have a caregiver who can
		spend a minimum of 2 nours per
	The trial comprises a 2- to 42-day	day for 4 days per week with the
	screening period, a 12-week	subject in order to assess changes in
	double-blind treatment period, and a	demontic unit number home
	so-day post-treatment follow-up	assisted living facility on any other
	supervised day passes at the discretion	residential care facility providing
	of the investigator. Overnight passes	long term care All subjects must
	will not be allowed for this trial	have with a diagnosis of probable
		Alzheimer's disease according to the
		National Institute of Neurological and

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Deleted text

Added text

Location	Current Text	Revised Text
		Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
		The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> <i>who terminate early from the study,</i> <i>all attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> <i>16.</i> Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.
Synopsis Trial Design 12-week, Double-blind Treatment Period	The subjects' condition will be evaluated routinely, including vital signs assessments, as per the local guidelines of the facility. Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. Beginning at Week 3, the subject's identified caregiver will be contacted by telephone between the scheduled visits. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments.	The subjects' condition will be evaluated routinely, including vital signs assessments, as <i>required</i> per the local guidelines of <u>the</u> <u>institutionalized setting or</u> <u>according to the discretion of the</u> <u>principal investigator</u> the facility. Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. All study visits will take place as a clinic visit at either the investigator's site (for non- institutionalized subjects) or residential facility (for institutionalized subjects). Beginning at Week 3, the subject's identified caregiver will be contacted by telephone between the scheduled visits. In addition, the subject's identified caregiver will be contacted
		by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments.
Synopsis Trial Design Follow-up Period	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a clinic visit at the residential facility $30 (+2)$ days	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during at-a clinic

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Location	Current Text	<b>Revised Text</b>
	after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject should be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and a caregiver. Subjects who complete both the 12- week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13- 211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-12-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at the residential facility. If the subject has left the residential facility where he or she participated in the trial, the 30-day safety follow-up visit will occur as a clinic visit at the investigator's site.	visit at <i>either</i> the <i>investigator's site or</i> residential facility, <i>if institutionalized</i> <b>30</b> (+ 2) days after the last dose of the IMP. If the <i>institutionalized</i> subject has left the residential facility where he or she participated in the trial, the subject should be seen atim the investigator's <u>site-elinic or (if If</u> a clinic visit is not possible), <i>the subject</i> <i>should be</i> assessed by telephone contact with the subject and a caregiver. For all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16. Subjects who complete both the 12- week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13- 211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-284. For those subjects who plan to enroll into Trial 331-1 <u>3</u> 2-211, the 30-day safety follow-up visit for Trial 331-12-284 will occur as a clinic visit at <i>either</i> the <i>investigator's site or</i> residential facility, <i>if institutionalized</i> . If the <i>institutionalized</i> subject has left the residential facility where he or she participated in the trial, the 30-day safety follow-up visit will occur as a clinic visit at the investigator's site.
Synopsis Subject Population	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential area facility.	The subject population will include male and female subjects between 55 and 90 years of age (inclusive), who are <u>living in either an</u> <u>institutionalized setting (e.g.,</u> nursing home, domentia unit
	or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the NINCDS- ADRDA criteria. Subjects must have a previous magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain, which was performed after the onset of symptoms of dementia, with	nursing nome, dementia unit, assisted living facility, or any other residential care facility providing long term care) or in a non- institutionalized setting where the subject is not living alone. In both the institutionalized and non- institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per

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	findings consistent with a diagnosis of	day for 4 days per week with the
	Alzheimer's disease. Additionally, at	subject in order to assess changes in
	both the screening and baseline visits,	the subject's condition in a
	subjects must have a Mini-Mental	dementia unit, nursing home,
	State Examination (MMSE) score of	assisted living facility, or any other
	5 to 22, inclusive, and a total score	residential care facility providing
	(frequency x severity) of $\geq 4$ on the	long-term care, All subjects must
	agitation/aggression item of the	havewith a diagnosis of probable
	Neuropsychiatric Inventory—Nursing	Alzheimer's disease according to the
	Home (NPI-NH)	NINCDS-ADRDA criteria. Subjects
		must have a previous magnetic
	Subjects must have been residing at	resonance imaging (MRI) or computed
	their current facility for at least 1	tomography (CT) scan of the brain,
	month before screening and be	which was performed after the onset
	expected to remain at the same facility	of symptoms of dementia, with
	for the duration of the trial. Subjects	findings consistent with a diagnosis of
	may receive supervised day passes at	Alzheimer's disease. <i>If a previous</i>
	the discretion of the investigator.	MRI or CT scan of the brain
	Overnight passes will not be allowed	performed after the onset of the
	for this trial.	symptoms of dementia is not
		available, then an MRI/CT scan
	A caregiver who is usually assigned to	should be performed during
	care for the subject on a regular basis,	screening. Additionally, at both the
	has sufficient contact to describe the	screening and baseline visits, subjects
	subject's symptoms, and has direct	must have a Mini-Mental State
	observation of the subject's behavior	Examination (MMSE) score of 5 to
	must be identified during the	22, inclusive, and a total score
	screening period for participation in	(frequency x severity) of $\geq 4$ on the
	the interview for the CMAI, NPI-NH,	agitation/aggression item of the
	and other applicable trial assessments.	Neuropsychiatric Inventory—Nursing
	The identified caregiver will be a	Home (NPI-NH). <i>The NPI-NH will</i>
	member of the residential facility or	be used for both institutionalized and
	other individual (e.g., family member,	non-institutionalized subjects;
	family friend, hired professional	however, the Occupational
	caregiver) who meets the caregiver	Disruptiveness questions will not be
	requirements. The recommended	answered for non-institutionalized
	minimum level of contact between the	subjects. Instead, the Distress
	caregiver and the subject is 2 nours	questions from the Neuropsychiatric
	per day for 4 days per week.	Inventory (NPI) will replace the
		Occupational Disruptiveness
		questions for non-institutionalized
		subjects. This neuropsychiatric
		assessment for non-institutionalized
		subjects based on the NPI/NPI-NH
		will hereafter be referred to as
		~ <i>INPI/INPI-INH</i> ~
		Subjects must have been residing -t
		their current location facility for at
		least 14 days 1 month hafara
		screening and he avagated to remain at
		the same location facility for the
		duration of the trial <b>Subjects from a</b>

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		non-institutionalized setting who at
		any point during the double-blind
		treatment phase require permanent
		placement to a nursing home or
		assisted living facility will be
		withdrawn from the trial. Subjects
		who at any point during the double-
		blind treatment phase transfer from
		an institutionalized setting to a
		non-institutionalized setting will also
		be withdrawn from the trial. In case
		of a change in the
		non-institutionalized address or
		institutionalized address, the
		investigator should consult with the
		medical monitor on a case-by-case
		basis. In case of a brief
		hospitalization, determination of
		subject eligibility to stay in the trial
		must be made based on subject safety
		by the investigator and INC Research
		medical monitor. Subjects in an
		institutionalized setting subjects
		may receive supervised day passes at
		the discretion of the investigator;
		however, overnight passes will not be
		allowed for this trial.
		A caregiver who is usually assigned
		to care for the subject on a regular
		basis, has sufficient contact to
		describe the subject's symptoms,
		and has direct observation of the
		subject's behavior must be
		identified during the screening
		period for participation in the
		interview for the CMAI, NPI-NH,
		and other applicable trial
		assessments. Subjects in a non-
		institutionalized setting may have a
		caretaker as well as a caregiver. The
		subject's caretaker is the person who
		lives with and cares for the subject on
		a regular basis. The caretaker may
		be supported in providing care to the
		subject by a professional(s), friend(s),
		or family member(s). Tthe subject's
		caregiver is the person who has
		sufficient contact to describe the
		subject's symptoms and who has
		direct observation of the subject's
		behavior in order to participate in the
		interview for the CMAI, NPI-NH,

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		NPI/NPI-NH, and other applicable
		trial assessments. For subjects in an
		institutionalized setting, there is only
		one role defined and that is the role
		of caregiver. The identified caregiver
		can be a staff member of the
		institutionalized setting will be a
		member of the residential facility or
		<b>an</b> other individual (e.g., family
		member, family friend, hired
		professional caregiver) who meets the
		<del>caregiver requirements</del> who has
		sufficient contact to describe the
		subject's symptoms and who has
		direct observation of the subject's
		behavior in order to participate in
		the interview for the CMAL NPI-
		NH NPI/NPI-NH and other
		applicable trial assessments The
		recommended minimum level of
		contact between the caregiver and the
		subject is 2 hours per day for 4 days
		ner week in both the institutionalized
		and non-institutionalized settings
Synopsis	It is planned that approximately 330	It is planned that approximately 330
Trial Sites	subjects will be screened at	subjects will be screened at
	approximately 30 trial centers	approximately 4630 trial centers
	worldwide so that 230 subjects will be	worldwide so that 230 subjects will be
	randomized to treatment	randomized to treatment
Synopsis	All doses of brevpiprazole and	All doses of brevninrazole and
Investigational	matching placebo will be taken orally	matching placebo will be taken orally
Medicinal Product	once daily preferably in the morning	once daily preferably in the morning
Dose Formulation	and can be administered without	and can be administered without
Mode of Administration	regard to meals. Breyninrazole should	regard to meals. Breypiprazole should
Wode of Administration	be taken at the same time each day	be taken at annrovimataly the same
	particularly prior to visits with	time each day particularly prior to
	pharmacokinetic sampling	visits with pharmacokinetic sampling
	pharmaeoknetic sampling.	visits with pharmacokinetic sampling.

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Location	Current Text	Revised Text
		CCI
Synopsis Criteria for Evaluation Safety Variables	Pharmacokinetic samples for determination of brexpiprazole and its major metabolite, DM-3411, will be collected at the baseline visit and at the Week 8 and Week 12/ET trial visits, at the same time as the sample collection for the clinical laboratory tests. For those subjects who have a separate signed ICF for the optional pharmacogenomic testing for determination of CYP2D6 metabolism status and other drug metabolizing enzymes and transporters, as necessary, a pharmacogenomic sample will be collected at the baseline visit.	Pharmacokinetic samples for determination of brexpiprazole and its major metabolite, DM-3411, will be collected at the baseline visit and at the Week 8 and Week 12/ET trial visits, at the same time as the sample collection for the clinical laboratory tests. For those subjects who have a separate signed ICF for the optional pharmacogenomic testing for determination of <i>cytochrome P450</i> (CYP) 2D6 metabolism status and other drug metabolizing enzymes and transporters <del>,</del> as necessary, <i>as well as</i> <i>banking for potential future analysis,</i> a pharmacogenomic sample will be collected at the baseline visit.
Synopsis Statistical Methods	Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. The primary endpoint will be analyzed using a mixed-effect model repeated measure (MMRM) methodology. The model will include fixed class effect terms	Descriptive statistics will be provided for all efficacy and safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation (SD). Tabulations of frequency distributions will be provided for categorical variables. The primary endpoint will be analyzed using a mixed-effect model repeated measure (MMRM) methodology. The model will include fixed class effect terms

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	for treatment, trial center, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline by visit week as a covariate. The primary efficacy outcome measure is the mean change from baseline to the endpoint in the CMAI total score. COL The resulting sample size is 103 subjects/arm. To account for a portion of subjects who discontinue prematurely and whose data may potentially dilute the treatment effect, approximately an additional 10% of subjects was added to the sample size, resulting in a sample size of 115 subjects/arm, which means the total sample size is 230 subjects.	for treatment, trial center, visit week, and an interaction term of treatment by visit week and include the interaction term of baseline by visit week as a covariate. The primary efficacy outcome measure is the mean change from baseline ( <i>Day 0 Visit</i> ) to the <b>endpoint</b> end of the double-blind treatment period (Week 12 visit) in the CMAI total score. <b>CO</b> The resulting sample size is 103 subjects/arm. After allowance of 10% non-evaluable subjects, To account for a portion of subjects who discontinue prematurely and whose data may potentially dilute the treatment effect, approximately an additional 10% of subjects was added to the sample size, <i>it</i> result <u>sing</u> in a sample size of 115 subjects/arm.
Synopsis Trial Duration	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4.5 years, of which approximately 4 years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP.	which means the total sample size of 115 subjects and, which means the total sample size is 230 subjects. The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4 <u>3</u> years are allotted for recruitment of subjects. Individual participation for subjects who complete the trial will range from 16 to 22 weeks, consisting of a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day follow-up period. All subjects will be followed up at a clinic visit or via telephone contact 30 (+ 2) days after the last dose of the IMP. <i>In</i> <i>addition, for all subjects who</i> <i>terminate early from the study, all</i> <i>attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> 16. <i>ACR Albumin-to-creatinine ratio</i>
and Definition of Terms		NPI Neuropsychiatric Inventory

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Section 1.3 Known and Potential Risks and BenefitsAs of 20 Sep 2012, brexpiprazole has been studied in 33 clinical trials (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.As of 20 Sep 2012, brexpiprazole has been studied in 33 clinical trials (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.As of 20 Sep 2012, brexpiprazole has been studied in 33 clinical trial (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
Known and Potential Risks and Benefitsbeen studied in 33 clinical trials (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.has been studied in 33 clinical trial (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.has been studied in 33 clinical trial (25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
Risks and Benefitscompleted and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.(25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.(25 completed and 8 ongoing) conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.conducted under US INDs for 3 indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
(schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.indications (schizophrenia or schizoaffective disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder (above the trials (3 completed and 2 ongoing) conducted outside of the US.
disorder, major depressive disorder [MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US. disorder, major depressive disorder, major depressive disorder [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
[MDD], and adult attention- deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.depressive disorder [MDD], and adult attention-deficit/hyperactivit disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.adult attention deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
[ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US. disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.
completed and 2 ongoing) conducted outside of the US.trials (3 completed and 2 ongoing) conducted outside of the US.
outside of the US. conducted outside of the US.
Brexpiprazole has been well tolerated Brexpiprazole has been well
by healthy volunteers at single doses tolerated by healthy volunteers at
up to 6 mg and at multiple doses up to single doses up to 6 mg and at
2 mg/day. In trials, brexpiprazole has multiple doses up to 2 mg/day. In
been well tolerated at multiple doses trials, brexpiprazole has been well
up to 12 mg/day in subjects with tolerated at multiple doses up to
schizophrenia or schizoaffective <b>12 mg/day in subjects with</b>
disorder, up to 4 mg/day in subjects schizophrenia or schizoaffective
with MDD who received concomitant disorder, up to 4 mg/day in subject
ADT, and up to 4 mg/day in adults with MDD who received
with ADHD who received <b>concomitant ADT, and up to</b>
concomitant stimulant therapy. 4 mg/day in adults with ADHD wh
Recently completed phase 2 clinical received concomitant stimulant
trials evaluated multiple oral doses up therapy. Recently completed phase
to 6 mg/day in subjects with <b>2 clinical trials evaluated multiple</b>
schizophrenia; up to 2 mg/day when oral doses up to 6 mg/day in
coadministered with marketed ADT in subjects with schizophrenia; up to
subjects with MDD; and up to <b>2 mg/day when coadministered with</b>
2 mg/day when coadministered with marketed ADT in subjects with
marketed stimulant therapy in subjects MDD; and up to 2 mg/day when
with ADHD. coadministered with marketed
stimulant therapy in subjects with
In the 25 completed brexpiprazole ADHD.
trials conducted under US
(ND) (10 where 1 twists 1 where 1h
(IND) (19 phase 1 trials, 1 phase 10 trials conducted under US
1772 (67 0%) subjects who received Application (IND) (10 phase 1 twis
hrowning and 5 phase 2
or expipitazore entief afone of another marketed trials 1204 of 1772 (67.09/)
mediantion reported at least
1 treatment emergent adverse event
(TEAE) compared with 325 of 520
(62.5%) subjects who received reported at least 1 treatment
nlacebo either alone or coadministered amargant advarse event (TEAE)
with another marketed medication
The most frequently reported TFAFs subjects who received placebo aith
(incidence $> 5\%$ of the total
brexpiprazole group and more than another markated medication. The
total placebo group) in all subjects
who received brexpiprazole were (incidence > 5% of the total

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Location	dizziness (8.7%) insomnia (7.0%)	brevninrazole group and more than
	nausea $(6.2\%)$ , and akathisia $(5.8\%)$ .	total placebo group) in all subjects
	In the total placebo group, headache	who received brevninrazole were
	(9.8%) was the most frequently	dizziness (8.7%), insomnia (7.0%).
	reported TEAE (incidence $> 5\%$ of	nausea (6.2%), and akathisia
	subjects) In the total brexpiprazole	(5.8%) In the total placebo group
	group 67 of 1773 (3.8%) subjects	hoadacha (0.8%) was the most
	discontinued the study due to 1 or	frequently reported TFAF
	more TEAE compared with 12 of 520	(incidence > 5% of subjects) In the
	(2, 3%) of subjects in the total placebo	total browning zolo group 67 of
	(2.576) of subjects in the total placebo	1773 (3.8%) subjects discontinued
	group.	the study due to 1 or more TEAE
	One death has been reported in the 25	compared with 12 of $520(2.3\%)$ of
	trials completed under the US NDs as	subjects in the total pleashe group
	of the 20 Sep 2012 sutoff date. This	subjects in the total placebo group.
	death accurred 12 days after the	
	subject received the last does of	<b>One usatin has been reported in the</b>
	browning and in the phase 2 double	1 23 trais completed under the US
	blind ashizonbronic trial (Trial 221	data This death 12 data
	07 202) and the death must	date. This death occurred 12 days
	0/-203), and the death was not	after the subject received the last
	considered by the investigator to be	dose of prexpiprazoie in the phase 2,
	not related to the INIP. One additional	double-blind schizophrenia trial
	death was reported in the ongoing,	(1 rial 331-07-203), and the death
	phase 2, open-label MDD trial	was not considered by the
	(Irial 331-08-212). The subject was	investigator to be not related to the
	reported to have died from progressive	IMP. One additional death was
	metastatic disease approximately 2	reported in the ongoing, phase 2,
	months after the initial onset of the	open-label MDD trial (Trial 331-08-
	event (81 days after the last dose of	<b>212).</b> The subject was reported to
	the IMP). The event was assessed as	have died from progressive
	not related to the IMP by the	metastatic disease approximately 2
	investigator.	months after the initial onset of the
		event (81 days after the last dose of
	Serious TEAEs have been reported in	the IMP). The event was assessed as
	20 of 1773 (1.1%) subjects who	not related to the IMP by the
	received brexpiprazole (either alone or	<del>investigator.</del>
	coadministered with another	
	medication) and 9 of 520 (1.7%)	Serious TEAEs have been reported
	subjects who received placebo (either	in 20 of 1773 (1.1%) subjects who
	alone or coadministered with another	received brexpiprazole (either alone
	medication) in combined	or coadministered with another
	brexpiprazole trials completed under	medication) and 9 of 520 (1.7%)
	the US INDs as of the 20 Sep 2012	subjects who received placebo
	cutoff date. Treatment with	either alone or coadministered with
	brexpiprazole does not appear to	another medication) in combined
	promote suicidal behavior in subjects	brexpiprazole trials completed
	with MDD or schizophrenia.	under the US INDs as of the 20 Sep
		2012 cutoff date. Treatment with
	Brexpiprazole did not result in any	brexpiprazole does not appear to
	consistent, clinically relevant changes	promote suicidal behavior in
	in laboratory values, vital signs (blood	subjects with MDD or
	pressure or heart rate), or ECG	schizophrenia.
	parameters in the completed phase 1	

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	and 2 clinical trials in subjects with MDD or schizophrenia. Statistically significant increases in weight were observed with brexpiprazole relative to placebo in both sample populations. Brexpiprazole exhibited a favorable profile with respect to movement disorders in subjects with MDD at doses up to 3 mg/day (Trial 331-09- 221) and in subjects with schizophrenia at doses up to 12 mg/day (Trial 331-08-205). In the dose-ranging trial that enrolled subjects who were experiencing an acute exacerbation of schizophrenia (Trial 331-07-203), an increase in the incidence of EPS was observed at the highest dose (i.e., brexpiprazole $5.0 \pm 1.0$ mg/day).	Based on the Investigator's Brochure, <sup>16</sup> combined data from the completed phase 1 clinical trials indicate that brexpiprazole is safe and well tolerated in healthy subjects at single oral doses of 0.2 to 6 mg and at multiple oral doses up to 2 mg/day. Data from the completed multiple-dose clinical trials indicate brexpiprazole is well tolerated at multiple oral doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder; up to 4 mg/day when coadministered with marketed ADT in subjects with MDD; and up to 4 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD.
	Refer to the current Investigator's Brochure for a summary of available nonclinical and clinical safety data. <sup>16</sup>	<ul> <li>Based on data from the 18 completed phase 1 clinical trials in healthy subjects or special populations (including healthy subjects from 2 phase 1 trials conducted in special populations) (15 in the US, 2 in Japan, and 1 in Korea), the most frequently reported TEAEs (incidence ≥ 5% or more of all healthy subjects who received brexpiprazole and more than placebo, administered either alone or with another marketed drug) were:</li> <li>Healthy subjects (N = 15 trials conducted in the US): dizziness, headache, postural dizziness, nausea, somnolence, constipation, and diarrhoea</li> <li>Healthy subjects (N = 3 trials conducted in Japan and Korea): nausea, orthostatic hypotension, somnolence, and dizziness</li> </ul>
		By indication, the most frequently reported TEAEs (incidence $\geq$ 5% or more of all subjects who received brexpiprazole and more than placebo, administered either alone or with another marketed therapy or drug (i.e., ADT, stimulant therapy, or antibiotic) in completed phase 1, phase 1b, and/or phase 2 double- blind patient trials (excluding

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		subjects enrolled in phase 2 open-
		label extension trials) conducted
		Annlications (INDs) were:
		<ul> <li>Schizophrenia or schizoaffective</li> </ul>
		disorder ( $N = 4$ trials):
		headache, anxiety, akathisia,
		nausea, increased weight, and
		dizziness
		• <i>MDD</i> ( <i>N</i> = 3 trials): akathisia,
		Increased weight, insomnia,
		and nasopharyngitis
		<ul> <li>ADHD (N = 2 trials): insomnia</li> </ul>
		In the single completed phase 1 trial
		in subjects with schizophrenia
		conducted in Japan, TEAEs reported
		In 5 or more subjects who received
		were.
		• Schizophrenia (N = 1 trial):
		increased serum prolactin and
		increased serum creatine
		phosphokinase
		Brexpiprazole did not result in any
		consistent, clinically relevant changes
		in laboratory values, vital signs (blood
		pressure or heart rate), or ECG
		and 2 clinical trials in subjects with
		MDD or schizophrenia. Statistically
		significant increases in weight were
		observed with brexpiprazole relative
		to placebo in both sample populations.
		Brexpiprazole exhibited a favorable
		disorders in subjects with MDD at
		doses up to 3 mg/day (Trial 331-09-
		221) and in subjects with
		schizophrenia at doses up to
		12 mg/day (Trial 331-08-205). In the
		dose-ranging trial that enrolled
		acute exacerbation of schizophrenia
		(Trial 331-07-203), an increase in the
		incidence of EPS was observed at the
		highest dose (i.e., brexpiprazole
		$5.0 \pm 1.0$ mg/day).
		Two deaths have been reported in the
		30 completed clinical trials. One

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Location	Current Text	Revised Text death was reported in the completed phase 2 double-blind trial in adult subjects with acute schizophrenia (Trial 331-07-203). The second death was reported in the completed phase 2 open-label MDD trial (Trial 331-08-212). None of these subjects were taking IMP at the time of death and none of these fatal events were considered by the investigator to be related to IMP. Additionally, 4 deaths have been reported in 2 ongoing phase 3 open-label trials of brexpiprazole. One death was reported in an ongoing schizophrenia trial (331-10-237) and 3 deaths were reported in an ongoing MDD trial (331-10-238). One of the deaths (completed suicide in Trial 331-10- 238) was considered by the investigator to be possibly related to IMP. Serious TEAEs have been reported for 64 subjects who received havening on on the 20 source of the
		brexpiprazole in the 30 completed trials. In ongoing trials of brexpiprazole, 120 subjects receiving brexpiprazole had reported serious TEAEs. Refer to the current Investigator's Brochure for a summary of available
S 21		nonclinical and clinical safety data. <sup>10</sup>
Section 2.1 Trial Rationale	In light of the Food and Drug Administration (FDA) boxed warning of increased mortality with the use of antipsychotics in elderly subjects with dementia-related psychosis and similar caution advised by other regulatory authorities, the clinical trial will be conducted in an environment that allows for close safety monitoring, specifically in subjects who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care. The settings will provide the type of medically supervised environment needed to closely monitor trial participants, particularly for events related to cardiac and pulmonary disease that	In light of the Food and Drug Administration (FDA) boxed warning of increased mortality with the use of antipsychotics in elderly subjects with dementia-related psychosis and similar caution advised by other regulatory authorities, the clinical trial will be conducted in an environment that allows for close safety monitoring, specifically in subjects who are <u>living</u> in either an institutionalized setting (e.g., nursing home, dementia unit, assisted living facility, or any other residential care facility providing long term care) or in a non- institutionalized setting where the subject is not living alone and has a caregiver who can spend a minimum of 2 hours per day for 4

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London       may contribute to the risk of increased death.       days per week with the subject in order to assess changes in the subject in order to assess changes in the subject is not the risk of increased direct second time, in-ar-adementia unit, nersing home, assisted living facility, or any other residential care facility providing long term care, and 90 years of age (inclusive), who are resident in a dementia unit, mursing home, assisted living facility, or any other residential care facility providing long term care, with the subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, mursing home, assisted living facility, or any other residential care facility providing long term care, or in a non-institutionalized setting (e.g., nursine home, dementia unit, arestide living facility, or any other residential care facility, or any other residential care facility providing long to the National linstitute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.       The trial comprises a 2- to 42-day sorter energing period, a 12-week double-blind treatment follow-up period, Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.         Nue trial comprises a 2- to 42-day screening period, Subjects may receive super subjects in a non-institutionalized and non-institutionalised secting the providing long term earce,	Location	Current Text	Revised Text
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usani.       Interpretation in the institutionalized setting the institutionalized setting in the institutionalized in theory instheases and institutine of Neurological and C		death	arder to assess changes in the
Section 3.1       The trial population will include male and female subjects between 55         Section 3.1       The trial population will include male and female subjects between 55         Section 3.1       The trial population will include male and female subjects between 55         and 90 years of age (inclusive), who are residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.         The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive swill not be allowed for this trial.         The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive swill not be allowed for this trial.         The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive swill not be allowed for this trial.		death.	order to assess changes in the
section 3.1       The trial population will include         Type/Design of Trial       The trial population will include         male and female subjects between 55       and 90 years of age (inclusive), who are residential care facility or any other residential care facility providing long tevens 55         and 90 years of age (inclusive), who are residential care facility providing long tevens 55         and 90 years of age (inclusive), who are residential care facility providing long tevens 55         and 90 years of age (inclusive), who are residential care facility providing long tevens 55         and 90 years of age (inclusive), who are residential care facility providing long tevens 55         isease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), alteria.         The trial comprises a 2- to 42-day screening period. Subjects may receive supervised day passes at the discretion of the investigator. Overnigh passes will not be allowed for this trial.         Side line in order to assoss collation of the investigator. Overnigh passes will not be allowed for this trial.       The trial comprises a 2- to 42-day screening period. All 2/beimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.         The trial comprises a 2- to 42-day screening period. The subject's must have a caregiver who can greater where the subject's condition in + 4         double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects may cook and the Alzheimer's Disease and Related Disorders Associatio			<u>subject's condition</u> in a dementia
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Section 3.1 The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day bases at the discretion of the investigator. Overnight passes will not be allowed for this trial.The existing subjects here the institutionalized setting where the custific is not living alone. In both the institutionalized and non- institutionalized and non- institutionalized setting, the subject's condition is a domention int, nursing home, assisted living facility, providing long term caree, All subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects must hayewith a diagnosis of probable Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2-to 42-day screening period, a 12-week double-blind treatment perio			facility providing long-term care.
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are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		and 90 years of age (inclusive), who	and 90 years of age (inclusive), who
<ul> <li>nursing home, assisted living facility, or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.</li> <li>The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.</li> <li>The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.</li> </ul>		are residing in a dementia unit,	are <u>living in either an</u>
or any other residential care facility providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		nursing home, assisted living facility,	institutionalized setting (e.g.,
providing long-term care, with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.assisted living facility, or any other residential care facility providing long term care) or in a non- institutionalized setting, where the subject is not living alone. In both the institutionalized and non- institutionalized setting, the subject must have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject's condition in-+ dementia unit, nursing home, assisted living facility, or any other residential care facility providing long term care, All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period.serier care, All subjects must havewith a diagnosis of probable Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.		or any other residential care facility	<u>nursing home, dementia unit,</u>
diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. Havewith a diagnosis of probable Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. Havewith a diagnosis of probable Alzheimer's Disease and Related Disorders and Stroke and the Alzheimer's Disease and Related Disorders and Stroke and the subject's caregiver at Week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		providing long-term care, with a	assisted living facility, or any other
disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. In the subject's condition is an dementia unit, nursing home, assisted living facility, or any other residential care facility providing long term care, All subjects must have with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		diagnosis of probable Alzheimer's	residential care facility providing
Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. Hat trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		disease according to the National	long term care) or in a non-
Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.subject is not living alone. In both the institutionalized and non- institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per dav for 4 days per week with the subject is condition in n dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term eare, All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		Institute of Neurological and	institutionalized setting where the
and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. He subject's condition in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care, All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		Communicative Disorders and Stroke	subject is not living alone. In both
Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. Have a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject's condition in + dementia unit, nursing home, assisted living facility, or any other residential care facility providing long term care, All subjects must have with a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		and the Alzheimer's Disease and	the institutionalized and non-
(NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. Will not be allowed for this trial. Hereitaunit, nursing home, assisted living facility, or any other residential care facility providing long term care, All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		Related Disorders Association	institutionalized settings the subject
The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		(NINCDS-ADRDA) criteria	must have a caregiver who can
The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		(ININCEDS-ADICEA) cincina.	snond a minimum of 2 hours nor
The that comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial. <b>auty tor 4 days per week with the subject's condition in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long term care, <u>All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment follow-up period. <i>In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subject's caregiver at Week</i></u></b>		The trial communication of 2 to 42 days	day for 4 days per week with the
screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		The trial comprises a 2- to 42-day	day for 4 days per week with the
double-bind treatment period, and a 30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.<		screening period, a 12-week	subject in order to assess changes in
30-day post-treatment follow-up period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		double-blind treatment period, and a	the subject's condition in a
period. Subjects may receive supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		30-day post-treatment follow-up	dementia unit, nursing home,
supervised day passes at the discretion of the investigator. Overnight passes will not be allowed for this trial.		period. Subjects may receive	assisted living facility, or any other
of the investigator. Overnight passes will not be allowed for this trial.long term care, All subjects must havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised		supervised day passes at the discretion	residential care facility providing
will not be allowed for this trial.havewith a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised		of the investigator. Overnight passes	long-term care, <u>All subjects must</u>
Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week		will not be allowed for this trial.	havewith a diagnosis of probable
National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week			Alzheimer's disease according to the
Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			National Institute of Neurological and
and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			Communicative Disorders and Stroke
Related Disorders Association (NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			and the Alzheimer's Disease and
(NINCDS-ADRDA) criteria. The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			Related Disorders Association
The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> <i>who terminate early from the study,</i> <i>all attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> 16 Subjects may receive supervised			(NINCDS ADDDA) aritaria
The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> <i>who terminate early from the study,</i> <i>all attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> 16 Subjects may receive supervised			(ININCEDS-ADICEA) cilicita.
The trial comprises a 2- to 42-day screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> <i>who terminate early from the study,</i> <i>all attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> 16 Subjects may receive supervised			
screening period, a 12-week double-blind treatment period, and a 30-day post-treatment follow-up period. <i>In addition, for all subjects</i> <i>who terminate early from the study,</i> <i>all attempts will be made to collect</i> <i>mortality data by telephone contact</i> <i>with the subject's caregiver at Week</i> 16 Subjects may receive supervised			The trial comprises a 2- to 42-day
double-blind treatment period, and a 30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			screening period, a 12-week
30-day post-treatment follow-up period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			double-blind treatment period, and a
period. In addition, for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			30-day post-treatment follow-up
who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			period. In addition, for all subjects
all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			who terminate early from the study,
mortality data by telephone contact with the subject's caregiver at Week 16 Subjects may receive supervised			all attempts will be made to collect
with the subject's caregiver at Week			mortality data by telephone contact
16 Subjects may receive supervised			with the subject's caregiver at Week
			16. Subjects may receive supervised

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Location	Current Text	Revised Text
		day passes at the discretion of the
		investigator. Overnight passes will
		not be allowed for this trial.
Section 3.1	The patient's daily behavior will be	The <b>patient's subject's daily</b>
Type/Design of Trial	logged into an eDiary by the caregiver	behavior will be logged into an eDiary
Screening Period	and/or facility staff.	by the caregiver and/or facility staff.
Section 3.1	The subjects' condition will be	The subjects' condition will be
Type/Design of Trial	evaluated routinely, including vital	evaluated routinely, including vital
12-week, Double-blind	signs assessments, as per the local	signs assessments, as <i>required</i> per the
Treatment Period	guidelines of the facility. Subjects	local guidelines of <u>the</u>
	will be evaluated at Baseline and at	institutionalized setting or according
	Day 3 and Weeks 2, 4, 6, 8, 10, and 12	to the discretion of the principal
	during the double-blind treatment	investigator the facility. Subjects
	period. Beginning at Week 3, the	will be evaluated at Baseline, and at
	subject's identified caregiver at the	Day 3, and <i>at</i> Weeks 2, 4, 6, 8, 10, and
	residential facility or other individual	12 during the double-blind treatment
	(e.g., family member, family friend,	period. All study visits will take place
	hired professional caregiver) will be	as a clinic visit at either the
	contacted by telephone between the	investigator's site (for non-
	scheduled visits. Trial-related	institutionalized subjects) or
	efficacy and safety assessments will	residential facility (for
	be performed as outlined in the	institutionalized subjects). Beginning
	Schedule of Assessments (Table 3.7-	at Week 3, the subject's identified
	1).	caregiver at the residential facility
		or other individual (e.g., family
		member, family friend, hired
		professional caregiver) will be
		contacted by telephone between the
		scheduled visits. In addition, the
		subject's identified caregiver will be
		contacted by telephone every odd
		numbered week after Week 2 (i.e.,
		Weeks 3, 5, 7, 9, 11) to assess
		compliance with IMP, confirm any
		changes to concomitant medications,
		and assure the subject's well-being.
		I rial-related efficacy and safety
		assessments will be performed as
		A gaggements (Table 2.7.1)
Section 2.1	All subjects whether they complete	Assessments (Table 5.7-1).
Tume/Degign of Trial	the trial or are withdrawn promotivaly	the trial or are with drawn promoturaly
Follow up Period	for any reason will be followed up for	for any reason will be followed up for
Follow-up Fellou	a safety evaluation at a clinic visit at	To any reason, will be followed up for a safety evaluation $30 (\pm 2)$ days after
	the residential facility 20 $(\pm 2)$ days	the last dose of IMP during at a clinic
	after the last dose of the IMP. If the	visit at aither the investigator's site or
	subject has left the residential facility	residential facility if institutionalized
	where he or she participated in the	$30 (\pm 2) \text{ days after the last days of}$
	trial the subject should be seen in the	the IMD If the institutionalized
	investigator's clinic or (if a clinic visit	subject has left the residential facility
	is not nossible) assessed by telephone	where he or she participated in the
	contact with the subject and a	trial the subject should be seen <b>atin</b>
	careoiver	the investigator's site clinic or (if If a
	001051001.	and involugator b site chine of (IFII a

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Location	Current Text	Revised Text
Location		clinic visit is not possible) the subject
	Subjects who complete both the 12-	<i>should be</i> assessed by telephone
	week double-blind treatment period	contact with the subject and a
	and the 30-day safety follow-up visit	caregiver For all subjects who
	are eligible to enroll into Trial 331-13-	terminate early from the study all
	211 which is a 2-month	attempts will be made to collect
	observational rollover trial to evaluate	mortality data by telephone contact
	the safety of subjects with agitation	with the subject's caregiver at Week
	associated with Alzheimer's disease	wan the subject's caregiver at week
	who previously participated in Trial	10.
	331 12 284 For those subjects who	Subjects who complete both the 12
	plan to enroll into Trial 331 12 211	week double blind treatment period
	the 30 day safety follow up visit for	and the 30 day safety follow up visit
	Trial 331 12 284 will occur as a clinic	and the 50-day safety follow-up visit
	visit at the residential facility. If the	211 which is a 2 month
	subject has left the residential facility	observational rollover trial to evaluate
	where he or she participated in the	the safety of subjects with agitation
	trial the 30-day safety follow-up visit	associated with Alzheimer's disease
	will occur as a clinic visit at the	who previously participated in Trial
	investigator's site	331-12-284 For those subjects who
	investigator s site.	plan to enroll into Trial 331-1 <b>32</b> -211
		the 30-day safety follow-up visit for
		Trial 331-12-284 will occur as a clinic
		visit <i>aithor</i> at the <i>investigator's site</i> or
		residential facility. If the
		institutionalized subject has left the
		residential facility where he or she
		participated in the trial, the 30-day
		safety follow-up visit will occur as a
		clinic visit at the investigator's site.
Figure 3.1-1		CCI
Trial Design Schematic		
Section 3.2	Neither the investigator nor the subject	Neither the investigator nor the subject
Treatments	will be aware of the treatment	will be aware of the treatment
	assignment. All doses of	assignment. All doses of
	brexpiprazole and matching placebo	brexpiprazole and matching placebo
	should be taken orally once daily,	should be taken orally once daily,
	preferably in the morning, and can be	preferably in the morning, and can be
	administered without regard to meals.	administered without regard to meals.
	Brexpiprazole should be taken at the	Brexpiprazole should be taken at
	same time each day, particularly prior	<i>approximately</i> the same time each
	to visits with pharmacokinetic	day, particularly prior to visits with
~	sampling.	pharmacokinetic sampling.
Section 3.3	The subject population will include	The subject population will include

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Location	Current Text	Revised Text
Trial Population	male and female subjects between 55	male and female subjects between 55
	and 90 years of age (inclusive), who	and 90 years of age (inclusive), who
	are residing in a dementia unit,	are <u>living in either an</u>
	nursing home, assisted living facility,	institutionalized setting (e.g.,
	or any other residential care facility	<u>nursing home, dementia unit,</u>
	providing long-term care, with a	assisted living facility, or any other
	diagnosis of probable Alzheimer's	residential care facility providing
	disease according to the NINCDS-	long term care) or in a non-
	ADRDA criteria. Subjects must have	institutionalized setting where the
	a previous magnetic resonance	subject is not living alone. In both
	imaging (MRI) or computed	the institutionalized and non-
	tomography (C1) scan of the brain,	institutionalized settings, the subject
	of symptoms of demontia, with	must have a caregiver who can spond a minimum of 2 hours por
	findings consistent with a diagnosis of	day for 4 days per week with the
	Alzheimer's disease Additionally at	subject in order to assess changes in
	both the screening and baseline visits	the subject's condition in a
	subjects must have a Mini-Mental	dementia unit nursing home
	State Examination (MMSE) score of	assisted living facility, or any other
	5 to 22, inclusive, and a total score	residential care facility providing
	(frequency x severity) of $\geq 4$ on the	long-term care, All subjects must
	agitation/aggression item of the	havewith a diagnosis of probable
	NPI-NH	Alzheimer's disease according to the
		NINCDS-ADRDA criteria. Subjects
	Subjects must have been residing at	must have a previous magnetic
	their current facility for at least 1	resonance imaging (MRI) or computed
	month before screening and be	tomography (CT) scan of the brain,
	expected to remain at the same facility	which was performed after the onset
	for the duration of the trial. Subjects	of symptoms of dementia, with
	may receive supervised day passes at	findings consistent with a diagnosis of
	the discretion of the investigator.	Alzheimer's disease. If a previous
	Overnight passes will not be allowed	MRI or CT scan of the brain
	for this trial.	performed after the onset of the
	A corregiver who is usually assigned to	symptoms of dementials not available then an MPL/CT sean
	care for the subject on a regular basis	available, then an MKI/CI Scan should be performed during
	has sufficient contact to describe the	screening Additionally at both the
	subject's symptoms and has direct	screening and baseline visits subjects
	observation of the subject's behavior	must have a Mini-Mental State
	must be identified during the	Examination (MMSE) score of 5 to
	screening period for participation in	22, inclusive, and a total score
	the interview for the CMAI, NPI-NH,	(frequency x severity) of $\geq 4$ on the
	and other applicable trial assessments.	agitation/aggression item of the
	The identified caregiver will be a	NPI-NH. The NPI-NH will be used
	member of the residential facility or	for both institutionalized and non-
	other individual (e.g., family member,	institutionalized subjects; however,
	family friend, hired professional	the Occupational Disruptiveness
	caregiver) who meets the caregiver	questions will not be answered for
	requirements.	non-institutionalized subjects.
		Instead, the Distress questions from
	It is planned that approximately 330	the Neuropsychiatric Inventory (NPI)
	subjects will be screened at	will replace the Occupational
	approximately 30 trial centers	Disruptiveness questions for non-

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Location	Current Text	Revised Text						
	worldwide in order to randomize 230	institutionalized subjects. This						
	subjects.	neuropsychiatric assessment for non-						
		institutionalized subjects based on the						
		NPI/NPI-NH will hereafter be						
		referred to as "NPI/NPI-NH"						
		Subjects must have been residing at						
		their current location facility for at						
		least 14 days1 month before						
		sereening and he expected to remain at						
		the same location facility for the						
		duration of the trial <b>Subjects from a</b>						
		non institutionalized setting who at						
		any point during the double blind						
		treatment phase require permanent						
		placement to a nursing home or						
		assisted living facility will be						
		withdrawn from the trial Subjects						
		who at any point during the double-						
		blind treatment phase transfer from						
		an institutionalized setting to a						
		non-institutionalized setting will also						
		he withdrawn from the trial In case						
		of a change in the						
		non-institutionalized address or						
		institutionalized address the						
		investigator should consult with the						
		medical monitor on a case-by-case						
		basis. In case of a brief						
		hospitalization. determination of						
		subject eligibility to stay in the trial						
		must be made based on subject safety						
		by the investigator and INC Research						
		medical monitor. Subjects in an						
		institutionalized setting subjects						
		may receive supervised day passes at						
		the discretion of the investigator:						
		however, overnight passes will not be						
		allowed for this trial.						
		A caregiver who is usually assigned						
		to care for the subject on a regular						
		basis, has sufficient contact to						
		describe the subject's symptoms.						
		and has direct observation of the						
		subject's behavior must be						
		identified during the screening						
		period for participation in the						
		interview for the CMAI, NPI-NH,						
		and other applicable trial						
		assessments. The identified						
		caregiver will be a member of the						
		residential facility or other						

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		individual (e.g., family member,
		family friend, hired professional
		caregiver) who meets the caregiver
		requirements.
		It is planned that approximately 330
		subjects will be screened at
		approximately <b>3046</b> trial centers
		worldwide in order to randomize 230
		subjects.
Section 3.3.1 Caregiver	Null (new section)	3.3.1.1 Non-institutionalized
Requirements		Subjects
requirements		Subjects
		In a non-institutionalized setting, the
		subject's caretaker is the person who
		lives with and cares for the subject on
		a regular basis For example caring
		for a subject on a regular basis may
		include the following activities.
		assisting with dispensing of IMP.
		assisting with dispensing of 1111, observing the subject's general
		medical condition including
		nutrition and hydration intaka
		reducing the chance of falls and
		assisting the subject if amorgancy
		ussisting the subject if emergency madical care is needed by contacting
		appropriate emergency services the
		subject's primary physician or the
		subject s primary physician, or the
		principal investigator, whatever is
		supported in providing care to the
		supported in providing cure to the subject by a professional(s) friend(s)
		subject by a projessional(s), jriena(s),
		or jumily member(s).
		The subject's caregiver is defined as
		the person who has sufficient contact
		to describe the subject's symptoms
		and has direct observation of the
		and has affect observation of the subject's behavior in order to
		subject s benuvior in order to narticinate in the interview for the
		CMAI NDI_NH NDI/NDI NH and
		other applicable trial assessments
		including completion of the a Diam
		A caroaiver must be identified during
		the seventing period for participation
		ine screening period jor purucipation in the interview of the applicable trial
		in the interview of the applicable is an and the applicable is a set the stime of the
		ussessments. At the time of the
		subject s screening visit, the
		curegiver will be provided a
		aucument inat witt outline all
		curegiver responsibilities. The
		curegiver snoula acknowledge and
		agree to undertake all the tasks

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		designated by this protocol at the time					
		of the informed consent process. The					
		caregiver role in the non					
		institutionalized setting may or may					
		not be the same individual who					
		fulfills the role of caretaker					
		depending on the circumstances of					
		the subject. The recommended					
		minimum level of contact between the					
		caregiver and the subject is 2 hours					
		per day for 4 days per week. The					
		caregiver is the person who should					
		accompany the subject to all visits					
		where the CMAI and NPI-NH are					
		aaministerea uniess other					
		by the sponsor					
		by the sponsor.					
		3.3.1.2 Institutionalized Subjects					
		To distant and shared and discout					
		In the institutionalized setting, there					
		is only one role defined and that is					
		the institutionalized setting is an					
		ine insulutionalized setting is an individual who has sufficient contact					
		to describe the subject's symptoms					
		and who has direct observation of the					
		subject's behavior in order to					
		participate in the interview for the					
		CMAI, NPI-NH, NPI/NPI-NH, and					
		other applicable trial assessments. A					
		caregiver must be identified during					
		the screening period for participation					
		in the interview of the applicable trial					
		ussessments. At the time of the					
		subject s screening visu, the					
		document that will outline all					
		caregiver responsibilities. The					
		caregiver should acknowledge and					
		agree to undertake all the tasks					
		designated by this protocol at the time					
		of the informed consent process. The					
		identified caregiver can be a staff					
		member of the institutionalized					
		setting or another individual (e.g.,					
		family member, family friend, hired					
		professional caregiver) who meets the					
		caregiver requirements. The					
		recommended minimum level of					
		contact between the caregiver and the					
		subject is 2 hours per day for 4 days					
		per week.					

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Location	Current Text	Revised Text
Section 3.4.1.1	The investigator must assess the	The investigator must assess the
Determinations of	capacity of the subject to provide	capacity of the subject to provide
Capacity	informed consent during the screening	informed consent during the screening
	period and throughout the course of	period and throughout the course of
	the study. Once these determinations	the study. This assessment will be
	are made by the investigator, the	made in accordance with the
	following options for obtaining	investigator's standard practice.
	informed consent from and/or on	Once these determinations are made
	behalf of the subject must be followed:	by the investigator, the following
	• If the subject is deemed capable	options for obtaining informed consent
	by the investigator, written	from and/or on behalf of the subject
	informed consent will be obtained	must be followed:
	from the subject prior to the	• If the subject is deemed capable
	initiation of any study protocol-	by the investigator, written
	required procedures. In such	informed consent will be obtained
	cases, acknowledgement from the	from the subject prior to the
	subject's legally acceptable	initiation of any study protocol-
	indicial or other hody, authorized	required procedures. In such
	under applicable law to consent to	subject's legally accentable
	the subject's participation in the	representative (an individual or
	clinical trial on behalf of that	iudicial or other body authorized
	prospective subject) will also be	under applicable law to consent to
	obtained in accordance with state	the subject's participation in the
	and/or local regulations prior to	clinical trial on behalf of that
	initiation of any study protocol-	prospective subject) will also be
	required procedures.	obtained, <i>if required</i> , in
	• If the subject was initially deemed	accordance with state and/or local
	capable of providing informed	regulations prior to initiation of
	consent but is no longer deemed	any study protocol-required
	so, informed consent must be	procedures.
	obtained from the subject's	<ul> <li>If the subject was initially</li> </ul>
	legally acceptable representative,	deemed capable of providing
	and assent from the subject, if	informed consent but is no
	possible, will be confirmed in	longer deemed so, informed
	accordance with state and/or local	consent must be obtained from
	regulations prior to the initiation	the subject's legally acceptable
	of any study protocol-required	representative, and assent from
	procedures.	the subject, if possible, will be
		state and/or local regulations
	• If the subject initially provided	nrior to the initiation of any
	subsequent dissents to participate	study protocol required
	in the trial, the subject will be	nrocoduros
	early terminated from the trial	procedures.
		• If the subject initially provided
		• If the subject initially provided
		subsequent <i>by</i> dissents to
		narticinate in the trial the subject
		will be early terminated from the
		trial.
		• If the subject was initially
		deemed capable of providing

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Location	Current Text	Revised Text
Location Table 3.4.2-1 Inclusion Criteria	Current Text #6 Subjects who are residing in a dementia unit, nursing home, assisted living facility, or any other residential care facility providing long-term care. Subjects who have been residing at their current facility for at least 1 month before screening and are	Revised Text           informed consent but is no longer deemed so, informed consent must be obtained from the subject's legally acceptable representative, and assent from the subject, if possible, will be confirmed in accordance with state and/or local regulations prior to the initiation or continuation of any study protocol-required procedures.           #6         Subjects who are residing at their current location for at least 14 days before screening and are expected to remain at the same location for the duration of the trial. Subjects who are residing in a domentia unit, nursing home
	month before screening and are expected to remain at the same facility for the duration of the trial. #7 Subjects must have an identified caregiver who is usually assigned to care for the subject on a regular basis, has sufficient contact to describe the subject's symptoms, and has direct observation of the subject's behavior. The identified caregiver will be a member of the residential facility or other individual (e.g., family member, family friend, hired professional caregiver) who meets the caregiver requirements.	dementia unit, nursing home, assisted living facility, or any other residential care facility providing long term care. Subjects who have been residing at their current facility for at least 1 month before screening and are expected to remain at the same facility for the duration of the trial. #7 Institutionalized Sgubjects with must have an identified caregiver who is usually assigned to care for the subject on a regular basis, has sufficient contact to describe the subject's symptoms, and has direct observation of the institutionalized setting will be a member of the residential facility or <u>an</u> other individual (e.g., family member, family friend, hired professional caregiver) who meets the caregiver requirements.
Table 3.4.3-1 Exclusion Criteria	#8 Subjects who have been diagnosed with an Axis I disorder (DSM-IV-TR criteria) including, but not limited to:	Non-institutionalized subjects may not be living alone (see Section 3.3.1.1 for caretaker definition) and must have an identified caregiver who has sufficient contact to describe the subject's symptoms and has direct observation of the subject's behavior. #8 Subjects who have been diagnosed with an Axis I disorder (DSM-IV-TR criteria) including, but not limited to:

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	Current major depressive episode	Current major depressive disorder					
	—unless on a stable dose(s) of	episode unless on a stable dose(s)					
	antidepressant medication(s) for the 30	of antidepressant medication(s) for the					
	days prior to randomization.	30 days prior to randomization.					
	#13 Subjects with insulin-dependent	#13 Subjects with insulin-dependent					
	diabetes mellitus (IDDM) (i.e., any	diabetes mellitus (IDDM) (i.e., any					
	subjects using insulin) are excluded.	subjects using insulin) may be eligible					
	Subjects with non-IDDM may be	for the trial if their condition is well					
	eligible for the trial if their condition	<u>controlled and if they do not have</u>					
	is stable as determined by satisfying	<u>current microalbuminuria</u> <del>are</del>					
	ALL of the following criteria:	excluded. Subjects with non-IDDM					
		may be eligible for the trial if their					
		condition is stable as determined by					
		satisfying ALL of the following					
		criteria:					
		• Urine albumin-to-creatinine					
		ratio (ACR) must be < 30 mg/g					
		(calculated), AND					
	#14 Subjects with stage 3 or higher	#14 Subjects with <u>clinically</u>					
	chronic kidney disease.	significantstage 3 or higher chronic					
		kidney disease based on the					
		investigator's judgment.					
	#27 Subjects who have significant	#27 Subjects who have significant					
	risk of death within the next 6 months	risk of death within the next 6					
	based on the investigator's judgment.	months based on the investigator's					
	#21						
	#51	# <u>30 <del>31</del></u> In addition, subjects with the					
	following laboratory test and ECG	following laboratory test and ECG					
	results at screening must be excluded	results at screening must be excluded					
	from the trial:	from the trial:					
	nom die dial.						
	$\sim$ OT $\sim$ 150 mass	• ACR > 30 mg/g (calculated as					
	• Q1cF $\geq$ 450 lisec	urine albumin [mg/dL] / urine					
		creatinine [9/dL])					
		• OTcF $\geq$ 450 msec <i>in men and</i>					
		$\geq$ 470 msec in women (refer to					
		Section 3.7.4.4 for further					
		details)					
	#32 Sexually active females of	# <u>31</u> 32 Sexually active females of					
	childbearing potential (see Section	childbearing potential (see Section					
	5.5) and male subjects who are not	5.5) and male subjects who are not					
	practicing 2 different methods of birth	practicing 2 different methods of birth					
	control with their partner during the	control with their partner during the					
	trial and for 30 days after the last dose	trial and for 30 days after the last dose					
	of trial medication or who will not	of trial medication or who will not					
	remain abstinent during the trial and	remain abstinent during the trial and					
	for 30 days after the last dose. If	for 30 days after the last dose. If					
	employing birth control, each couple	employing birth control, each couple					
	must use 2 of the following	must use 2 of the following					
	precautions: vasectomy, tubal	precautions: vasectomy, tubal					

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	ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide.	ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, birth control depot injections, condom <i>with</i> <i>spermicide</i> , or sponge with spermicide.						
	#40 Subjects who participated in a clinical trial within the last 180 days or who participated in more than 2 clinical trials within the past year.	# <u>39</u> 40 Subjects who participated in a clinical trial within the last 180 days or who participated in more than 2 <i>interventional</i> clinical trials within the past year.						

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Location	Current Text	Revised Text
Section 3.7	The time from enrollment of the first	The time from enrollment of the first
Trial Procedures	subject to the last subject's last trial	subject to the last subject's last trial
	of which approximately 4.5 years,	visit will be approximately <u>3.5</u> 4.5
	allotted for recruitment of subjects	years are allotted for recruitment of
	Individual participation for subjects	subjects. Individual participation for
	who complete the trial will range from	subjects who complete the trial will
	16 to 22 weeks, consisting of a 2- to	range from 16 to 22 weeks, consisting
	42-day screening period, a 12-week	of a 2- to 42-day screening period, a
	double-blind treatment period, and a	12-week double-blind treatment
	30-day follow-up period. All subjects	period, and a 30-day follow-up period.
	will be followed up at a clinic visit or $v_{i}$ taken being contact 20 (1 2) down	All subjects will be followed up at a
	via telephone contact $50 (+2)$ days	(+2) days after the last dose of the
	after the last dose of the livit.	IMP In addition for all subjects
	CCI	who terminate early from the study.
	the CST	all attempts will be made to collect
	will perform regular quality reviews of	mortality data by telephone contact
	CMAI data and will compare these	with the subject's caregiver at Week
	data against other sources of	16.
	behavioral information, including	
	tachnology (refer to Section 2.7.2.6)	the CST
	daily behavior logs collected by	, the CST will perform regular quality reviews of
	caregivers through electronic diaries	CMAI data and will compare these
	(refer to Section 3.7.3.7), and	data against other sources of
	investigator progress notes.	behavioral information, including
		patterns of movement using actigraphy
	Trial assessment time points are	technology (refer to Section 3.7.3.67),
	summarized in Table 3.7-1.	daily behavior logs collected by
		caregivers through electronic diaries
		(refer to Section $3./.3.+\underline{8}$ ), and
		investigator progress notes.
		All study visits will take place as a
		clinic visit at either the investigator's
		site (for non-institutionalized
		subjects) or residential facility (for
		<i>institutionalized subjects)</i> . Trial
		assessment time points are
		summarized in Table 3.7-1.

Table 3.7-1   Schedule of As	ssessments (t	runcated)										
	Visit											
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	<del>Between</del> <del>clinic visit</del> <del>phone call<sup>e</sup></del>	FU <sup>d</sup> c	Wk 16 <sup>d</sup>
EFFICACY												
NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects)	X	Х		Х	Х	Х	Х	х	Х			
OTHER		1	1						1			_L
CCI												
SAFETY					1							4
Adverse events <sup>w</sup>	Х	Х	Х	Х	Х	X	Х	Х	Х	X	X	
7												-
Concomitant medications <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	Х	
aa Mortality assessment												X

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Table 3.7-1       Schedule of Assessments (truncated)												
		Visit										
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	<del>Between</del> <del>clinic visit</del> <del>phone call<sup>e</sup></del>	FU <sup>đ</sup> c	Wk 16 <sup>d</sup>
OTHER PROCEDURES												
Register trial visit in IVRS/IWRS	Х	Х	Х	Х	Х	Х	Х	Х	Х			
Randomize eligible subjects via IVRS/IWRS		Х										
IMP dispensing		Х	X	Х	Х	Х	Х	Х				
IMP accountability			Х	Х	Х	Х	Х	Х	Х			
Telephone contact <sup>cc</sup>												
ADDITIONAL ENTRANCE/HIST	ORY											
MRI/CT scan	X <sup>bb<u>dd</u></sup>											
Abbreviations: NPI = Neuropsychiatric Inventory; Bel												

<sup>cd</sup>All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at-30 (+ 2) days after the last dose of IMP during a clinic visit at either the investigator's site or residential facility 30 (+ 2) days after the last dose of IMP. If the institutionalized subject has left the residential facility where he or she participated in the trial, the subject should be seen atim the investigator's <u>site schere</u> contact with the subject and a caregiver. Subjects who complete both the 12-week double-blind treatment period and the 30-day safety follow-up visit are eligible to enroll into Trial 331-13-211, which is a 2-month, observational, rollover trial to evaluate the safety of subjects with agitation associated with Alzheimer's disease who previously participated in Trial 331-12-283. For those subjects who plan to enroll into Trial 331-13-211, the 30-day safety follow-up visit for Trial 331-12-283 will occur as a clinic visit at either the investigator's site or residential facility. If the institutionalized subject has left the residential facility. If the institutionalized subject has left the residential facility where he or she participated in the trial, the 30-day safety follow-up visit for Trial 331-12-283 will occur as a clinic visit at either the investigator's site or residential facility. If the institutionalized subject has left the residential facility where he or she participated in the trial, the 30-day safety follow-up visit will occur as a clinic visit at the investigator's site.

<sup>d</sup>Note that this visit is 16 weeks postbaseline.

<sup>k</sup>After the ICF is signed during the screening visit, the actigraphy device will be put on the subject's nondominant wrist and worn daily until Week 12/ET. *It is recommended that the* <u>Aa</u>ctigraph <u>must</u> be checked daily to ensure that the subject is wearing it and that it continues to be operational.

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<sup>p</sup>Subjects <u>should</u> must be fasting for a minimum of 8 hours prior to blood draws for screening laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial.

<sup>x</sup>Pharmacokinetic samples will be obtained at baseline and at any time during the Week 8 and Week 12/ET visits. If blood samples for clinical laboratory tests are not collected at the baseline visit, pharmacokinetic samples do not need to be obtained at baseline. Every possible effort should be made to collect samples at the same time at each visit. The subject should be advised to take the IMP at *approximately* the same time each day throughout the trial, but most importantly, prior to each pharmacokinetic sampling. The date and time of the last 2 doses prior to each pharmacokinetic blood draw will be recorded on the electronic case report form (eCRF). Vital sign and ECG assessments should be completed before any blood samples are collected.

<sup>Z</sup>All medications taken within 30 days of screening (signing of ICF/assent) will be recorded. In addition, all prescription and nonprescription medications taken during the trial will be recorded as concomitant medications. Details of prohibited and restricted medications are provided in the protocol (refer to Section 4.1). During the first 4 weeks of the randomized phase (baseline to Week 4 visit), benzodiazepines are allowed but limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam (or equivalent) or less depending on dose-limiting side effects. Benzodiazepines must not be administered within 12 hours prior to the efficacy and safety scales. After the Week 4 visit, benzodiazepines are prohibited.

<sup>aa</sup> For all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16.

and boost start taking IMP from the new blister card the day after the clinic visit.

<sup>cc</sup> The subject's identified caregiver will be contacted by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.

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

Location	Current Text	Revised Text		
Section 3.7.1.1 Screening	At the time of subject's screening visit, the caregiver will be provided a document which will outline all caregiver responsibilities and their role in this study. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.	At the time of subject's screening visit, the caregiver will be provided a document which will outline all caregiver responsibilities and their role in this study. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.		
	<ul> <li>Screening evaluations will include the following:</li> <li>A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Subjects with screening QTcF ≥ 450 msec will be excluded from the trial (see Section 3.7.4.4). The ECG is to be completed before any blood is drawn.</li> </ul>	Screening evaluations will include the following: • At the time of the subject's screening visit, the caregiver will be provided a document that will outline all caregiver responsibilities and their role in this study. The caregiver should acknowledge and agree to undertake all the tasks designated by this protocol at the time of the informed consent process.		
	<ul> <li>A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.</li> <li>After the ICF is signed during the screening visit, an actigraphy device will be put on the subject's nondominant wrist. The actigraph will be worn continuously throughout the double-blind treatment period. The device must be checked daily to ensure that the subject is wearing it and that it continues to be operational. At every study visit (except the Day 3 visit), subjects will take off the device so that site personnel can download the data stored in the device, and the device battery will be changed. Once the download is complete, the device will be placed back on the subject. If the screening period extends beyond 4 weeks, the battery will need to be replaced once. Once the download is complete, the device will be placed back on the subject.</li> </ul>	<ul> <li>A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Subjects with screening QTcF ≥ 450 msec (males) or ≥ 470 msec (females) will be excluded from the trial (see Section 3.7.4.4). Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject. The ECG is to be completed before any blood is drawn.</li> <li>Albumin-to-creatinine ratio (ACR) will be determined (must be &lt; 30 mg/g; calculated as urine albumin [mg/dL] / urine creatinine [g/dL]).</li> <li>A qualified and certified rater will administer the CMAI, and NPI/NPI-NH to the caregiver.</li> <li>After the ICF is signed during the screening visit, an actigraphy</li> </ul>		

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Location	Current Text	Revised Text		
Location	<ul> <li>Current Text</li> <li>After the ICF has been signed, the caregiver and/or facility staff will enter daily into the electronic diary (eDiary) information regarding the subject's behavior.</li> </ul>	<ul> <li>Revised Text         <ul> <li>device will be put on the subject's nondominant wrist. The actigraph will be worn continuously throughout the double-blind treatment period. It is recommended that <u>t</u>The <u>actigraphdevice must</u> be checked daily to ensure that the subject is wearing it and that it continues to be operational. At every study visit (except the Day 3 visit), subjects will take off the device so that site personnel can download the data stored in the device, and the device battery will be changed. Once the download is complete, the device will be placed back on the subject. If the screening period extends beyond 4 weeks, the battery will need to be replaced once. Once the download is complete, the divide the device will be placed back on the subject.</li> <li>After the ICF has been signed, the caregiver and/or facility staff will enter daily into the electronic diary (eDiary) information regarding the subject's behavior.</li> </ul></li></ul>		
		electronic diary (eDiary) daily (if possible) after the ICF is signed, continuing through <del>the</del> -Week 12/ET.		
Section 3.7.1.2 Baseline (Day 0)	• A qualified and certified rater will administer the CMAI and NPI- NH to the caregiver.	• A qualified and certified rater will administer the CMAI, and NPI-NPI-NH, and NPI/NPI-NH to the caregiver.		
	<ul> <li>Daily eDiary recording will</li> </ul>	• CCI		
	<ul> <li>continue.</li> <li>The subject will take the first dose of the IMP from the assigned blister card on Day 1 (i.e., the day after the baseline visit). The subject should take the IMP at the same time each day, preferably in the morning, without regard to meals.</li> </ul>	<ul> <li></li> <li>Daily eDiary recording will continue.</li> <li>The subject will take the first dose of the IMP from the assigned</li> </ul>		

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Location	Current Text	Revised Text
		blister card on Day 1 (i.e., the day after the baseline visit). The subject should take the IMP at <i>approximately</i> the same time each day, preferably in the morning, without regard to meals
Section 3.7.1.3.1 Day 3	<ul> <li>The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at the same time each day, preferably in the morning, without regard to meals.</li> <li>Daily eDiary recording will</li> </ul>	<ul> <li>The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at <i>approximately</i> the same time each day, preferably in the morning, without regard to meals.</li> <li>Daily eDiary recording will</li> </ul>
Section 3.7.1.3.2 Weeks 2, 4, 6, 8, and 10	<ul> <li>All subjects will be evaluated at Weeks 2, 4, 6, 8, and 10. Visits are to occur within ± 2 days of the target visit date. Beginning at Week 3, the subject's identified caregiver will be contacted by telephone between the scheduled visits. The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.</li> <li>A qualified and certified rater will administer the CMAI and NPI- NH to the caregiver.</li> <li>Daily eDiary recording will continue.</li> <li>The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at the same time each day, preferably in the morning, without regard to meals.</li> </ul>	<ul> <li>All subjects will be evaluated at Weeks 2, 4, 6, 8, and 10. Visits are to occur within ± 2 days of the target visit date. Beginning at Week 3, the subject's identified caregiver will be contacted by telephone between the scheduled visits. The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.</li> <li>A qualified and certified rater will administer the CMAI, and NPI-NH. to the caregiver.</li> <li>Daily eDiary recording will continue.</li> <li>The subject will start taking the IMP from the assigned blister card the day after the clinic visit. The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.</li> </ul>

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		 In addition, the subject's identified caregiver will be contacted by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.
Section 3.7.1.4 End of Treatment (Week 12/ET)	<ul> <li>The following activities and assessments will occur at Week 12 (or at the ET visit, if applicable):</li> <li>A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver.</li> <li>CCI</li> </ul>	The following activities and assessments will occur at Week 12 (or at the ET visit, if applicable): • A qualified and certified rater will administer the CMAI, <b>and</b> -NPI- NH, <b>and NPI/NPI-NH</b> to the caregiver.  • CCI
Section 3.7.1.5 Follow-up	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation at a clinic visit at the residential facility 30 (+ 2) days after the last dose of the IMP. If the subject has left the residential facility where he or she participated in the trial, the subject should be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone with the subject and a caregiver. All AEs and concomitant medications will be recorded.	All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a safety evaluation 30 (+ 2) days after the last dose of IMP during at a clinic visit at either the investigator's site or residential facility, if institutionalized 30 (+ 2) days after the last dose of the IMP. If the institutionalized subject has left the residential facility where he or she participated in the trial, the subject should be seen atim the investigator's <u>site.elinie or (if If a</u> clinic visit is not possible), the subject should be assessed by telephone with the subject and a caregiver. All AEs and concomitant medications will be recorded. For all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16.
Section 3.7.2 Efficacy Assessments	It is required that adequately trained and experienced clinicians administer the CMAI, NPI-NH, CGI S, CC	It is required that adequately trained and experienced clinicians administer the CMAI, NPI-NH, <i>NPI/NPI-NH</i> ,

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	and <b>CC</b> In addition, the raters	CGI S, CCI In addition,
	must be certified for this trial to	the raters must be certified for this trial
	administer the CMAI and NPI-NH.	to administer the CMAI, <del>and NPI-NH,</del>
	Notations in the subject's trial records	and NPI/NPI-NH. Notations in the
	should substantiate the ratings.	subject's trial records should
	Training, certification, and materials	substantiate the ratings. Training,
	for rating will be provided by a rater	certification, and materials for rating
	training group.	will be provided by a rater training
		group.
	A caregiver who is usually assigned to	
	care for the subject on a regular basis,	A caregiver who is usually assigned to
	has sufficient contact to describe the	<del>care for the subject on a regular</del>
	subject's symptoms, and has direct	<del>basis, has sufficient contact to</del>
	observation of the subject's behavior,	describe the subject's symptoms, and
	must be identified during the	has direct observation of the
	screening period for participation in	subject's behavior, must be identified
	the interview for the CMAI, NPI-NH,	during the screening period for
	and other applicable trial assessments.	participation in the interview for the
	The recommended minimum level of	CMAI, NPI-NH, <i>NPI/NPI-NH</i> , and
	contact between the caregiver and the	other applicable trial assessments. The
	subject is 2 hours per day for 4 days	<del>recommended minimum level of</del>
	per week. The identified caregiver	contact between the caregiver and
	will be a member of the residential	the subject is 2 hours per day for 4
	facility or other individual (e.g.,	days per week. The identified
	family member, family friend, hired	<del>caregiver will be a member of the</del>
	professional caregiver) who meets the	residential facility staff or other
	caregiver requirements. In addition to	individual (e.g., family member,
	providing responses to trial	family friend, hired professional
	questionnaires, the identified caregiver	caregiver) who meets the caregiver
	will be interviewed by the trial	requirements. In addition to providing
	personnel regarding the subject's	responses to trial questionnaires, the
	general medical condition, behavioral	identified caregiver will be interviewed
	symptoms, and activities of daily	by the trial personnel regarding the
	living. The identified caregiver will	subject's general medical condition,
	gather information from several	behavioral symptoms, and activities of
	informants, including staff from the	daily living. If the subject is in an
	day, afternoon, and night shifts, as	institutionalizea setting, +tne
	well as from reliable family members	information from an 11 f
	or intends, in order to provide an	information from several informants,
	accurate and comprehensive overview	including stall from the day, afternoon,
	of the subject's benavioral symptoms	and night shifts, as well as from reliable
	and condition.	ianni members or iriends, in order to
	At the time of subject's comming	provide an accurate and comprehensive
	At the time of subject's screening	overview of the subject's benavioral
	document which will cutling all	symptoms and condition. If the subject
	area iver responsibilities and their	is in a non-institutionalized setting, the
	role in this study. The corregiver	information from the equators of
	should asknowledge and agree to	injormation from the caretaker (If
	undertake all the tasks designated by	aujjereni inan ine menujiea caregiver)
	this protocol at the time of the	or from other informants who are in a
	informed consent process. The	position to observe the subject and
	recommonded minimum level of	provide information regarding
	recommended minimum level of	denavioral symptoms and activities of

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Location	Current Text	Revised Text
Location	contact between the caregiver and the	daily living Details on the caregiver
	subject is 2 hours per day for 4 days	requirements can be found in Section
	ner week	2 2 1
	per week.	5.5.1
		At the time of subject's sereening
		visit the approximation will be provided a
		visit, the caregiver will be provided a
		document which will outline an
		caregiver responsibilities and their
		role in this study. The caregiver
		should acknowledge and agree to
		undertake all the tasks designated by
		this protocol at the time of the
		informed consent process. The
		recommended minimum level of
		contact between the caregiver and
		the subject is 2 hours per day for 4
		<del>days per week.</del>
Section 3.7.2.6	Null (new section)	The NPI is a structured caregiver
Neuropsychiatric		interview designed to obtain
Inventory (NPI)		information on the presence of
• • •		psychopathology in subjects with brain
		disorders, including Alzheimer's
		disease and other dementias. <sup>31</sup> The
		NPI differs from the NPI-NH in that it
		is tailored for use in non-institutional
		settings (as opposed to the nursing
		home). Item domains are identical
		between the two scale versions. Ten
		hehavioral and two neurovegetative
		symptom domains comprise the NPI
		(including delusions hallucinations
		agitation/aggression
		denression/dysnharia anviety
		alation/aunhoria anathy/indiffaranca
		disinhibition irritability abarrant
		motor behavior nighttime behavior
		disordars and appatita/agting
		disordars) Caraginars are instructed
		to indicate the frequency of a given
		behavior (on a scale of 1 to 4) its
		benavior (on a scale of 1 to 4), as
		severily (on a scale of 1 to 5), and now
		much distress that behavior causes for
		nim or ner (on a scale of 0 to 5). Each
		aomain produces 4 scores: frequency,
		severity, total (jrequency x severity),
		ana distress. A total NPI score is
		calculatea by adding the first 10
		aomain total scores (frequency x
		severity scores) together. All 12
		aomain total scores can be summed in
		special circumstances where the
		neurovegetative symptoms are of
		particular importance. Administering

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Location	Current Text	Revised Text
		the NPI generally takes about 15 minutes. The psychometric properties and factor structure of the NPI have been shown to have internal consistency, reliability, convergent validity, and discriminant validity. A sample of the NPI is provided in Appendix 9
Section 3.7.3.7	3.7.3.6 Actigraphy	3.7.3.6 <u>7</u> Actigraphy
Acugraphy	The CST will perform ongoing	The CST will perform ongoing reviews
	reviews of CMAI raters by reviewing	of CMAI raters by reviewing CMAI
	CMAI data relative to other sources of behavioral information including	data relative to other sources of
	patterns of movement using	patterns of movement using actigraphy

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Location	Current Text	Revised Text
Location	Current Text actigraphy technology. Motion will be collected through an actigraphy device resembling a wristwatch worn by the subject on their nondominant wrist for 24 hours/day during the screening and treatment periods. If the subject decides not to wear the actigraph at any time after the consent is obtained, the assessment may be discontinued and continued study participation will not be affected. Study staff will be responsible for uploading actigraphy data from the device to the actigraphy vendor at regular intervals corresponding to the date of the CMAI.  Since actigraphy data are tools to assist the CST in monitoring CMAI rater training, actigraphy information will not be made available to site personnel, and will not be statistically analyzed.	<b>Revised Text</b> technology. Motion will be collected through an actigraphy device resembling a wristwatch worn by the subject on their nondominant wrist for 24 hours/day during the screening and treatment periods. If the subject decides not to wear the actigraph at any time after the consent is obtained, the assessment may be discontinued and continued study participation will not be affected. <b>Study staff will be</b> <b>responsible for uploading</b> <i>The</i> actigraphy data <i>will be downloaded</i> from the device to the actigraphy vendor at regular intervals corresponding to the date of the CMAI. <i>For non-institutionalized subjects, the</i> <i>caregiver will not be expected to</i> <i>change the actigraph watch battery or</i> <i>download the actigraph data; these</i> <i>duties will be completed by the site</i> <i>staff. For institutionalized subjects,</i> <i>the caregiver or site staff may be</i> <i>responsible for changing the actigraph</i> <i>watch battery or downloading the</i> <i>actigraph data.</i>  Since actigraphy data are tools to assist the CST in monitoring CMAI rater training, actigraphy information will not be <del>made available to site</del> <b>personnal and will not be statictically</b>
Section 3.7.3.8 Electronic Diary (eDiary)	3.7.3.7 Electronic Diary (eDiary) The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including daily behavior logs collected by caregivers and/or facility staff through eDiaries (refer to Appendix 17). Caregivers will record occurrence of the 29 behaviors listed in the CMAI as they occur using an eDiary. All 29 behaviors will be listed, and the caregiver will check the box next to the behavior when it occurs; there is no free text in the eDiary. Observations recorded using the eDiary will be transmitted wirelessly to the eDiary vendor. 	analyzed. 3.7.3.78 Electronic Diary (eDiary) The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including <b>daily</b> behavior logs collected by caregivers and/or facility staff through eDiaries (refer to Appendix 17). Caregivers will record occurrence of the 29 behaviors listed in the CMAI as they occur using an eDiary. All 29 behaviors will be listed, and the caregiver will check the box next to the behavior when it occurs; there is no free text in the eDiary. Observations recorded using the eDiary will be transmitted wirelessly to the eDiary vendor. For subjects in a non-institutionalized

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	Since eDiary data are tools to assist	setting, one of the responsibilities of
	the CST in monitoring CMAI rater	the caregiver is to complete the eDiary
	training, eDiary information will not	by noting the subject's symptoms of
	be made available to site personnel,	agitation. While it is preferred that
	and will not be statistically analyzed.	eDiary data are collected 7 days a
		week, it is realized that eDiary use for
		7 days a week may not be possible
		because the minimum amount of time
		that the caregiver is required to
		observe the subject is 4 days a week.
		The caretaker may provide
		information to the caregiver to
		complete the eDiary on a daily basis,
		but this is not a requirement. The
		responsibility of the caregiver for
		logging behaviors in the eDiary
		remains the same for subjects in an
		institutionalized setting. However,
		more than one caregiver may use the
		eDiary for any given subject; whoever
		is providing care for the subject at a
		given time can log behaviors in the
		eDiary.
		Since eDiary data are tools to assist the
		CST in monitoring CMAI rater training,
		eDiary information will not be made
		available to site personnel, and will
		not be statistically analyzed.
Table 3.7.4.2-1		Addition of albumin and creatinine
Clinical Laboratory		under Urinalysis
Assessments		
Section 3.7.4.2	The following laboratory test results at	The following laboratory test results at
Clinical Laboratory	screening are exclusionary:	screening are exclusionary:
Assessments		
		• Urine albumin-to-creatinine ratio
		(ACR) > 30  mg/g (calculated as
		urine albumin [mg/aL] / urine
Section 37431	Waist circumference will be measured	Waist circumference will be measured
Physical Examination	at each physical examination	at each physical examination
T frystear Examination	(screening Week 6 and Week 12/FT)	(screening Week 6 and Week 12/FT)
	(sereening, week o and week 12/11).	using the provided measuring tane
Section 3744	A screening ECG finding of OTcF	A screening ECC finding of OTcF
ECG Assessments	> 450 msec is exclusionary (see Table	> 450 msec is evclusionary (see Table
	3 4 3-1) In addition subjects should	$\frac{2}{3}$ $\frac{1}{3}$ $\frac{1}{1}$ If according to the
	be excluded if they have any other	investigator's judgment, any abnormal
	abnormal ECG finding at screening	ECG finding is deemed medically
	that, in the investigator's judgment, is	significant (impacting the safety of the
	medically significant in that it would	subject and/or the interpretation of the
	impact the safety of the subject or the	study results) or meets an exclusion
	interpretation of the trial results.	criterion (see Table 3.4.3-1), the
	However, any screening ECG with	subject should be excluded from the

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Location	Current Text	Revised Text
Location	abnormal result(s) considered to be	study Abnormal results for ECCs
	abinically significant should be	should be repeated once at severating
	repeated to confirm the finding(c)	snould be repeated once at screening
	he for a service of the service of former the	with 5 consecutive ECG recordings to
	before excluding the subject from the	ensure reproducibility of the
	trial. Refer to Appendix 5 for a list of	abnormality before excluding a subject
	potentially clinically relevant ECG	based on the criteria noted
	abnormalities.	above. Each ECG recording should be
		taken approximately 5 minutes apart
		(the ECG result reported will be
		evaluated at each time point). The
		central ECG service will provide the
		corrections for the 3 ECGs performed.
		Based on the OT interval as corrected
		by Fridericia's formula (OTcF)
		reported by the central service, $a$
		subject will be excluded if the
		corrections are > 150 msec in men and
		> 470 msag in woman for 2 of the 3
		$\geq 470$ msec in women joi 2 oj ine 5
		<i>ume points of the ECGs uone. If only</i>
		$1 ECG time point has a QICF of \geq 450$
		msec in men and $\geq 4/0$ msec in
		women, and this is not reproduced at
		either of the other 2 time points, the
		subject can be included in the study.
		In addition, subjects should be
		excluded if they have any other
		abnormal ECG finding at screening
		that, in the investigator's judgment,
		is medically significant in that it
		would impact the safety of the subject
		or the interpretation of the trial
		results. However, any screening
		ECC with abnormal result(s)
		considered to be clinically significant
		should be repeated to confirm the
		finding(s) before excluding the
		subject from the trial Refer to
		Amondia 5 for a list of notantially
		Appendix 5 for a list of potentially
		clinically relevant ECG abnormalities
		to guiae investigators for the
		assessment of potential ECG
		abnormalities for clinical significance
		postrandomization. Exclusion criteria
		for screening do not apply as
		mandatory discontinuation criteria for
		subjects who are already randomized.
		Please consult the medical monitor in
		case of questions.
Section 3.7.5.1	Every possible effort should be	Every possible effort should be made
Blood Collection	made to collect pharmacokinetic	to collect pharmacokinetic samples at
Times	samples at the same time at each visit.	the same time at each visit.
	Furthermore, the subject should be	Furthermore, the subject should be
	advised to take the IMP at the same	advised to take the IMP at

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Location	Current Text	Revised Text	
	time each day throughout the trial, but	approximately the same time each day	
	most importantly, prior to each	throughout the trial, but most	
	pharmacokinetic sampling. The date	importantly, prior to each	
	and time of the last 2 doses of IMP	pharmacokinetic sampling. The date	
	prior to each sample draw, and the	and time of the last 2 doses of IMP	
	date and time of the actual blood draw	prior to each sample draw, and the date	
	will be recorded on the eCKF.	he recorded on the cCPE	
CCI		be recorded on the eCKr.	

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	Location	Revised Text	Current Text
Section 3.8.3 Individual SubjectIn addition, subjects meeting any of the following criteria must be withdrawn from the trial:  4) At the request of the subject, investigator, sponsor, or regulatory authorityIn addition, subjects meeting any of following criteria must be withdrawn from the trial:  4) At the request of the subject, caregiver, legally acceptable representative, investigator, sponsor regulatory authority Image: The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week 12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at the regridentia focility. If the aubidetIn addition, subjects meeting any of following criteria must be withdrawn following criteria must be withdrawn from the trialImage: The investigator of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safe by the investigator and INC Researd meter and inter	Location	Revised Text         SCI         SCI         In addition, subjects meeting any of the       In addition, subjects meeting any of the following criteria must be withdrawn from the trial:         bject, gulatory       In addition, subjects meeting any of the following criteria must be withdrawn from the trial:         bject, gulatory       In addition, subjects meeting any of the following criteria must be withdrawn from the trial:         In       At the request of the subject, caregiver, legally acceptable representative, investigator, sponsor, or regulatory authority         In       IO       Subject from a non- institutionalized setting requires permanent placement to a nursing home or assisted living facility, or subject transfers from an institutionalized setting. In case of a change in the non-institutionalized address or institutionalized address or institutionalized address or institutionalized address or institutionalized address or should consult with the medical monitor on a case-by-case basis. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and INC Research madiael monitor	Current Text         In addition, subjects meeting any of the following criteria must be withdrawn from the trial:            4) At the request of the subject, investigator, sponsor, or regulatory authority            The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week 12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at the regidential focility. If the subject

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	he or she participated in the trial, the subject should be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and a caregiver.	CCI The investigator will notify the sponsor
		promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week 12/ET evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at
		a clinic visit at <i>either the investigator's</i> <i>site or</i> residential facility. If the <i>institutionalized</i> subject has left the residential facility where he or she participated in the trial, the subject should be seen <del>atin</del> the investigator's <u>site</u> . <i>elinie or (iI</i> f a clinic visit is not possible), <i>the subject should be</i> assessed by telephone contact with the while and a consciour. In addition
		for all subjects who terminate early from the study, all attempts will be made to collect mortality data by telephone contact with the subject's caregiver at Week 16. Three attempts will be made to contact the subject's caregiver by telephone; in the event the site is unable to reach the subject's caregiver by telephone, the site will
		attempt to contact the subject's caregiver via certified mail or an alternative similar method where appropriate. Any subject who withdraws
		prematurely from the trial will not be eligible to roll-over into Trial 331-13- 211.
		Meeting a screening exclusion criterion postrandomization does not require an automatic discontinuation of the subject. The investigator should assess the change for clinical significance, determine if an AE

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<b>x</b>	<b>a</b>	
Location	Current Text	Revised Text
		should be reported, and make a
		determination of subject continuation
		based on subject safety. The
		investigator could consult with the
		medical monitor to determine subject
		continuation in the study.
Section 3.11	Subjects who cannot be contacted on	Subjects who cannot be contacted on or
Definition of Subjects	or before the Week 12 visit during the	before the Week 12 visit during the
Lost to Follow-up	treatment period and who do not have	treatment period and who do not have a
Lost to Follow up	a known reason for discontinuation	known reason for discontinuation (e.g.
	(e.g. withdrew consent or AE) will be	withdrew consent or AE) will be
	classified as "lost to follow up". If a	alossified as "lost to follow up". If an
	subject leaves the residential facility	institutionalized subject leaves the
	in which he/she was residing hefere	residential facility in which ha/she was
	In which he/she was residing before	residential facility in which he/she was
	completion of the study, the site will	residing before completion of the study,
	make 3 attempts to contact the subject	the site will make 3 attempts to contact
	by telephone; in the event the site is	the subject by telephone; in the event
	unable to reach the subject by	the site is unable to reach the subject by
	telephone, the site will attempt to	telephone, the site will attempt to
	contact the subject via certified mail	contact the subject via certified mail or
	or an alternative similar method where	an alternative similar method where
	appropriate.	appropriate. A similar procedure will
		be followed for non-institutionalized
		subjects who are lost to follow-up.
Section 3.12	Responsible trial personnel will	Responsible trial personnel will
Subject Compliance	dispense the IMP (i.e., brexpiprazole	dispense the IMP (i.e., brexpiprazole or
	or matching placebo). Accountability	matching placebo) <i>according to the</i>
	and compliance verification should be	visits outlined in the Schedule of
	documented in the subject's trial	Assessments (Table 3.7-1).
	records.	Accountability and compliance
		verification should be documented in
		the subject's trial records.
		5
		For non-institutionalized subjects, the
		caretaker or caregiver may administer
		IMP to the subject as long as the
		subject is compliant with IMP dosing
		roquiromonts
		requirements.
		For institutionalized subjects the
		aragivar will be responsible for
		administering IMP to the subject. It
		may be possible that there is more than
		may be possible that there is more than
		one caregiver for a subject. The
		caregiver(s) should be appropriately
		instructed to ensure that the subject is
		compliant with IMP dosing
		requirements.
Section 5.7.4	Null (new section)	For all subjects who terminate early
Follow-up Mortality		from the study, all attempts will be
Assessment		made to collect mortality data by
		telephone contact with the subject's
		caregiver at Week 16. Three attempts

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		will be made to contact the subject's
		caregiver by telephone; in the event
		the site is unable to reach the subject's
		caregiver by telephone, the site will
		attempt to contact the subject's
		caregiver via certified mail or an
		alternative similar method where
		appropriate.
Section 7.1	The resulting sample size is 103	The resulting sample size is 103
Sample Size	subjects/arm. To account for a portion	subjects/arm. <i>After allowance of 10%</i>
	of subjects who discontinue	non-evaluable subjects, <del>To account</del>
	prematurely and whose data may	for a portion of subjects who
	potentially dilute the treatment effect,	discontinue prematurely and whose
	approximately an additional 10% of	data may potentially dilute the
	subjects was added to the sample size,	treatment effect, approximately an
	resulting in a sample size of 115	additional 10% of subjects was added
	subjects/arm, which means the total	to the sample size, it resultsing in a
	sample size is 230 subjects.	sample size of 115 subjects/arm, which
		means the total sample size is 230
		subjects.
Section 7.4.1	The primary endpoint will be analyzed	The primary endpoint will be analyzed
Primary Efficacy	using a mixed-effect model repeated	using a mixed-effect model repeated
Analysis	measure (MMRM) model. The	measure (MMRM) model. The primary
	primary efficacy outcome measure is	efficacy outcome measure is the mean
	the mean change from baseline to the	change from baseline (Day 0 Visit) to
	endpoint in the CMAI total score.	the endpoint end of the double-blind
		treatment period (Week 12 visit) in the
		CMAI total score.
	I ne null nypothesis for the	The
	does worsus placebo is that there is no	hypothesis for the comparison of
	difference between the browning	hypothesis for the comparison of
	treatment group and placebo in change	placebo is that there is no difference
	from baseline to endpoint in CMAI	between the brevpiprezole treatment
	total score. The comparison will be	group and placebo in change from
	made at the significance level of alpha	baseline to endpoint in CMAI total
	= 0.05	score. The comparison will be made at
	0.03.	the significance level of $alpha = 0.05$
	The statistical comparison will be	
	performed by the MMRM analysis	The statistical comparison will be
	with an unstructured variance	performed by the <i>fitting a</i> MMRM
	covariance matrix for the repeated	analysis with an unstructured variance
	measures in which the change from	covariance matrix for the repeated
	baseline to endpoint in CMAI total	measures in which the change from
	score will be the dependent variable	baseline to endpoint (Day 0 Visit) in
	based on the OC dataset. The model	CMAI total score (at Weeks 2, 4, 6, 8,
	will include fixed class-effect terms	10, and 12) will be the dependent
	for treatment, trial center, visit week	variable based on the OC dataset. The
	and an interaction term of treatment	model will include fixed class-effect
	by visit week and include the	terms for treatment, trial center, visit
	interaction term of baseline by visit	week and an interaction term of
	week as a covariate.	treatment by visit week and include

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Location	Current Text	Revised Text
		the interaction term of baseline by
		visit week as a covariate. The model
		will also include a random effect for
		subject and the interaction term of
		baseline (Day 0 visit) by visit week as
		covariates. The primary comparison
		between the brexpiprazoie and the
		placebo groups al week 12 will be
		estimuted as the afference between the least squares (IS) means utilizing the
		computing software SAS procedure
		PROC MIXED.
CCI		

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Location	Curre	ent Text	Revis	ed Text
Appendix 1	Primary Medical C	Contact	Primary Medical Contacts	
Names of Sponsor	PPD		PPD	
Personnel	PPD		PPD	
	Development		Otsuka Pharmaceutical Development & Commercialization, Inc. 1 University Square Drive, Suite 500 Princeton, NJ 08540 Phone: PPD	
	Otsuka Pharmaceu	tical Development		
	& Commercializat	ion, Inc.		
	1 University Squar	re Drive, Suite 500		
	Princeton, NJ 0854	40		
	Phone: PPD		Fax: PPD	
	Fax: PPD			
			PPD	
			PPD	
			Otsuka Pharmaceu	tical Development
			& Commercializati	on, Inc.
			1 University Squar	e Drive, Suite 500
			Princeton, NJ 0854	40
			Phone: PPD	
			Fax: PPD	
Appendix 2	Country	Safety Fax Line	Country	Safety Fax Line
Institutions Concerned	United States	PPD	United States	PPD
With the Trial	Canada		Canada	
Medical Monitors	United		United Kingdom	
	Kingdom		France	
	France	+ -	Ukraine	-
	Ukraine	+ -	Additional count	ries being
	Additional count	ries being	considered for no	rticination
	considered for pa	rticipation	Slovenia	
	Slovenia		Slovenia	FFU
		110	Lithuania	-
	Lithuania	۲ ۲	Swodon	-
	Sweden		Austria	-
	Austria		Figles 4	-
			Finland	
	Finland	,	Ireland	
	Ireland		* Please note that the	nis is a partner
	* Please note that	this is a partner	CRO number, no	ot INC.
	CRO number, n	ot INC.	Г	
	Г		Europe:	
	Europe:		PPD	- All and a second s
	PPD		PPD	
	PPD		PPD INC Decembration	7
	INC Research, LL	C	INC Research, LLC	<i>.</i>
	30-201 Kraków, Poland Office: PPD		01. Emaus 3 20.201 Knolvány Do	land
			30-201 Krakow, Po	land
			Office: PPD	
	Mobile: PPD		Mobile: PPD	-
Annondiy 5	rax: PPD		rax: PPD	
Appendix 3 Criteria for Identifying	Increase in	OT = E > 450	Inoracasin	OT - E > 450
FCG Measurements of	OT-	Q1CF ≥ 450	oT <sub>c</sub>	Q1CF ≥ 450
Dotential Clinical	QIC	msec	QIC	msec
Polevonce		(men and		(men and
Relevance		women)		women)
				$QTcF \ge 470$

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Location	Current Text	Revised Text
		msec
		(women)
Appendix 9 Neuropsychiatric Inventory (NPI)	Null (new appendix)	Added NPI for subjects in a non-institutionalized setting (this resulted in renumbering of the subsequent appendices).
CCI		

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## Amendment Number: 3

Issue Date: 10 Sep 2015

# **PURPOSE:**

The sponsor has determined the need for a third formal amendment. This amendment serves to reflect clarifications and changes to trial procedures intended to enhance subject safety and accuracy of data, as well as to streamline the exclusion criteria. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency, and changes to correct typographical, punctuation, and formatting errors. These changes were minor and do not change the design or content of the protocol, and therefore, are not summarized in this appendix.

The purpose of amending Protocol 331-12-284, issued 07 Jul 2014, was to:

- Increase the number of screened subjects from 330 to 520 and the number of trial sites from 46 to 65.
- Change the power from 80% to 85% and the resulting sample size from 103 subjects/arm to 117 subjects/arm.
- Increase the total sample size from 230 subjects to 260 subjects (from 115 subjects/arm to 130 subjects/arm).
- Increase the time from enrollment of first subject to last subject's last trial visit from 3.5 to 4.5 years and the time for recruitment from 3 to 4 years.
- Broaden the definition of subjects in an institutionalized setting and add overnight passes (at the investigator's discretion) for these subjects.
- Broaden the location of trial visits.
- Add that the screening period can be extended or that subjects can be rescreened more than once with the approval of the medical monitor.
- Modify inclusion criterion #8.
- Modify exclusion criteria #1, 3, 7, 8, 11, 13, 18, 21, 23, 30, 33, 36, and 39, and remove exclusion criteria #4, 5, 9, 14, 17, 19, 20, 22, and 24-27. These modifications resulted in the renumbering of the exclusion criteria.
- Remove HIV testing at screening.
- Remove urinalysis, prolactin, and urine pregnancy testing at Week 4 and Week 8.
- CCI
- Add the AIMS at Weeks 2, 4, and 8 and remove the AIMS at Week 6.
- Remove CCI , physical examination, and neurological examination at Week 6.
- Change telephone contact to Weeks 3, 5, and 7 during the double-blind treatment period.

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- Change electronic diaries to paper diaries, as well as remove the diary line item from Table 3.7-1 (Schedule of Assessments), remove Section 3.7.3.8 (Electronic Diary), and remove Appendix 17 (Electronic Diary).
- Remove actigraphy from the trial.
- Modify the criteria during the double-blind treatment period for restricted/prohibited medications #1, 3, and 12 in Table 4.1-1.
- Modify the other efficacy variables and add a section for exploratory efficacy variables.
- Remove adverse events of interest from the safety variables.
- Change the sponsor clinical contact and the North American medical monitor.
- Update the address for all sponsor contacts, electronic data capture, and IVRS/IWRS.
- Remove the eDiary, actigraphy, and rater surveillance vendors.
- Add Bulgaria and Russia as participating countries and update the safety fax numbers.
- Replace the NPI assessment with the NPI/NPI-NH assessment for non-institutionalized subjects.
- • •

# **BACKGROUND:**

These changes to Protocol 331-12-284 Amendment 2 were made on the basis of adjustments considered important to ensure the safety of the subjects enrolled and to facilitate appropriate trial implementation and communication.

# **MODIFICATIONS TO PROTOCOL:**

## **General Revisions:**

All changes by section are provided below.

### **Sectional Revisions:**

Note that the tabular format below follows the new protocol template and differs from the tabular format used for the previous 331-12-284 protocol amendments.

Location	Old Text	Updated Text
Title Page	Manager, Clinical Management	Associate Director, Clinical
		Management
	PPD	
	Phone: PPD	PPD
	Fax: PPD	Phone: PPD
	E-mail: PPD	Fax: PPD
	PPD	E-mail: PPD
		PPD

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Location	Old Text	Updated Text
	Issue Dates:	
	Date of Amendment 2: 07 Jul 2014	Issue Dates:
		Date of Amendment 2: 07 Jul 2014
~ .		Date of Amendment 3: 10 Sep 2015
Synopsis	The trial population will include male	The trial population will include male
Trial Design	and female subjects between 55 and	and female subjects between 55 and
	90 years of age (inclusive), who are	90 years of age (inclusive), who are
	living in either an institutionalized setting	living in either an institutionalized
	(e.g., nursing nome, dementia unit,	setting where the subject is not living
	residential care facility providing long	alone
	term care) or in a non-institutionalized	alone.
	setting where the subject is not living	 Screening Period
	alone	The screening period will range from 2
	uione.	days to 42 days and will begin when the
	 Screening Period	informed consent form (ICF) is signed
	The screening period will range from a	prior to the initiation of any procedures.
	minimum of 2 days to a maximum of 42	The screening period may be extended
	days and will begin when the informed	after discussion with and approval by
	consent form (ICF) is signed, prior to the	the medical monitor.
	initiation of any procedures.	
		12-week, Double-blind Treatment
	12-week, Double-blind Treatment	Period:
	Period:	
		Subjects will be evaluated at Baseline,
	The subjects' condition will be evaluated	Day 3, and at Weeks 2, 4, 6, 8, 10, and
	routinely, including vital signs	12 during the double-blind treatment
	assessments, as required per the local	period. All trial visits will take place as
	guidelines of the institutionalized setting	a clinic visit at either the investigator's
	or according to the discretion of the	site or residential facility, if applicable.
	avaluated at Pagalina, Day 2, and at	All attempts should be made to
	Weaks 2 4 6 8 10 and 12 during the	with regard to physician appointments
	double blind treatment period. All study	Individual aircumstances that fall
	visits will take place as a clinic visit at	outside this general convention should
	either the investigator's site (for	be discussed with the medical monitor
	non-institutionalized subjects) or	in order to determine appropriateness
	residential facility (for institutionalized	to proceed. In addition, the subject's
	subjects). In addition, the subject's	identified caregiver will be contacted by
	identified caregiver will be contacted by	telephone at Weeks 3, 5, and 7 to assess
	telephone every odd numbered week	compliance with IMP, confirm any
	after Week 2 (i.e., Weeks 3, 5, 7, 9, 11)	changes to concomitant medications,
	to assess compliance with IMP, confirm	and assure the subject's well-being.
	any changes to concomitant medications,	Trial-related efficacy and safety
	and assure the subject's well-being.	assessments will be performed as
	Trial-related efficacy and safety	outlined in the Schedule of
	assessments will be performed as	Assessments.
	outlined in the Schedule of Assessments.	
		Follow-up Period:
	Follow-up Period:	All subjects, whether they complete the
	All subjects, whether they complete the	trial or are withdrawn prematurely for
	trial or are withdrawn prematurely for	any reason, will be followed up for a
	any reason, will be followed up for a	satety evaluation $30 (+2)$ days after the

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Location	Old Text	Updated Text	
	safety evaluation $30 (+2)$ days after the	last dose of IMP during a clinic visit at	
	last dose of IMP during a clinic visit at	either the investigator's site or	
	either the investigator's site or residential	residential facility, if applicable	
	facility, if institutionalized. If the		
	institutionalized subject has left the	For those subjects who plan to enroll	
	residential facility where he or she	into Trial 331-13-211, the 30-day safety	
	participated in the trial, the subject	follow-up visit for Trial 331-12-284 will	
	should be seen at the investigator's site.	occur as a clinic visit at either the	
		investigator's site or residential facility,	
		if applicable.	
	For those subjects who plan to enroll		
	follow up visit for Trial 221, 12, 284 will		
	follow-up visit for final 551-12-264 will		
	investigator's site or residential facility		
	if institutionalized If the		
	institutionalized subject has left the		
	residential facility where he or she		
	participated in the trial, the 30-day safety		
	follow-up visit will occur as a clinic visit		
	at the investigator's site.		
Synopsis	The subject population will include male	The subject population will include	
Subject Population	and female subjects between 55 and	male and female subjects between	
	90 years of age (inclusive), who are	55 and 90 years of age (inclusive), who	
	living in either an institutionalized setting	are living in either an institutionalized	
	(e.g., nursing home, dementia unit,	setting or in a non-institutionalized	
	assisted living facility, or any other	setting where the subject is not living	
	residential care facility providing long	alone Additionally, at both the	
	term care) or in a non-institutionalized	screening and baseline visits, subjects	
	setting where the subject is not living	must have a Mini-Mental State	
	alone Additionally, at both the	Examination (MIVISE) score of 5 to 22,	
	must have a Mini Mental State	$\frac{1}{2}$ severity) of > 1 on the	
	Examination (MMSE) score of 5 to 22	agitation/aggression item of the	
	inclusive and a total score (frequency $\times$	Neuropsychiatric Inventory—Nursing	
	severity) of $> 4$ on the	Home (NPI-NH) or the	
	agitation/aggression item of the	Neuropsychiatric Assessment for	
	Neuropsychiatric Inventory—Nursing	Non-institutionalized Patients based on	
	Home (NPI-NH). The NPI-NH will be	the NPI/NPI-NH (hereafter referred to	
	used for both institutionalized and	as "NPI/NPI-NH"). The NPI-NH will	
	non-institutionalized subjects; however,	be used for institutionalized subjects and	
	the Occupational Disruptiveness	the NPI/NPI-NH will be used for	
	questions will not be answered for non-	non-institutionalized subjects.	
	institutionalized subjects. Instead, the		
	Distress questions from the	Subjects who at any point during the	
	Neuropsychiatric Inventory (NPI) will	double-blind treatment phase transfer	
	replace the Occupational Disruptiveness	Irom an institutionalized setting to a	
	questions for non-institutionalized	non-institutionalized setting, or vice	
	assessment for non-institutionalized	In case of a brief hospitalization	
	subjects based on the NPI/NPLNH will	determination of subject eligibility to	
	hereafter be referred to as "NPI/NPI-	stay in the trial must be made based on	
	NH".	subject safety by the investigator and	
	I	jj - j m. congator and	

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Location	Old Text	Updated Text	
Location	Old Text Subjects from a non-institutionalized setting who at any point during the double-blind treatment phase require permanent placement to a nursing home or assisted living facility will be withdrawn from the trial. Subjects who at any point during the double-blind treatment phase transfer from an institutionalized setting to a non-institutionalized setting will also be withdrawn from the trial. In case of a change in the non-institutionalized address or institutionalized address, the investigator should consult with the medical monitor on a case-by-case basis. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and INC Research medical monitor. Subjects in an institutionalized setting may receive supervised day passes at the discretion of the investigator; however, overnight passes will not be allowed for this trial. The subject's caregiver is the person who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in	Updated Text medical monitor. All attempts should be made to maintain the subjects' normal routine with regard to appointments with physicians and overnight accommodations. Subjects in an institutionalized setting may receive supervised day passes at the discretion of the investigator and may also receive supervised overnight passes at the discretion of the investigator as long as such overnight stays are part of the subjects' normal routine. For purposes of this trial, the subject's caregiver is the person who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI/NPI-NH, and other applicable trial assessments. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in	
	observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, NPI/NPI-NH, and other applicable trial assessments. The identified caregiver can be a staff member of the institutionalized setting or another individual (eg, family member, family friend, hired professional caregiver) who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, NPI/NPI-NH, and other applicable trial assessments	observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, and other applicable trial assessments.	
Synopsis	Key exclusion criteria include the	Key exclusion criteria include the	
Inclusion/Exclusion	following:	following:	
Criteria	• Subjects with dementia or other	• Subjects with dementia or other	
	Alzheimer's disease such as mixed	Alzheimer's disease such as mixed	
	or vascular dementia. dementia with	or vascular dementia. dementia	
	Lewy bodies, Parkinson's disease	with Lewy bodies, Parkinson's	
	dementia, frontotemporal dementia,	disease dementia, frontotemporal	

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Location	Old Text	Updated Text
	<ul> <li>substance-induced dementia, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects 55 years or older with a diagnosis of Down syndrome.</li> <li>Subjects with a history of stroke, transient ischemic attack or</li> </ul>	dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.
	<ul> <li>Subjects with a history of clinically relevant traumatic brain injury with neurological sequelae.</li> <li>Subjects with a history of a deep venous thrombosis within the 5 years prior to the screening visit.</li> </ul>	<ul> <li>Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism.</li> <li>Subjects with delirium or history of delirium within the 30 days prior to the screening visit.</li> </ul>
	<ul> <li>Subjects with delirium, unless resolved with no symptoms for at least 30 days prior to the screening visit.</li> <li>Subjects considered in poor general health based on the investigator's judgment.</li> </ul>	<ul> <li>Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.</li> </ul>
Synopsis Trial Sites	It is planned that approximately 330 subjects will be screened at approximately 46 trial centers worldwide so that 230 subjects will be randomized to treatment.	It is planned that approximately 520 subjects will be screened at approximately 65 trial sites worldwide so that 260 subjects will be randomized to treatment.

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Location	Old Text	Updated Text
	After allowance of 10% non-evaluable subjects, it results in a sample size of 115 subjects/arm, which means the total sample size is 230 subjects.	117 subjects/arm. After allowance of 10% non-evaluable subjects, it results in a sample size of 130 subjects/arm, which means the total sample size is 260 subjects.
Synopsis Trial Duration	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 3.5 years, of which approximately 3 years are allotted for recruitment of subjects.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4.5 years, of which approximately 4 years are allotted for recruitment of subjects.
Section 2.1 Trial Rationale	In light of the Food and Drug Administration (FDA) boxed warning of increased mortality with the use of antipsychotics in elderly subjects with dementia-related psychosis and similar caution advised by other regulatory authorities, the clinical trial will be conducted in an environment that allows for close safety monitoring, in subjects who are living in either an institutionalized setting (e.g., nursing home, dementia unit, assisted living facility, or any other residential care facility providing long term care) or in a non-institutionalized setting where the subject is not living alone and has a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition.	In light of the Food and Drug Administration (FDA) boxed warning of increased mortality with the use of antipsychotics in elderly subjects with dementia-related psychosis and similar caution advised by other regulatory authorities, the clinical trial will be conducted in an environment that allows for close safety monitoring, in subjects who are living in either an institutionalized setting or in a non- institutionalized setting where the subject is not living alone and has a caregiver who can spend a minimum of 2 hours per day for 4 days per week with the subject in order to assess changes in the subject's condition.
Section 3.1 Type/Design of Trial	The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting (e.g., nursing home, dementia unit, assisted living facility, or any other residential care facility providing long term care) or in a non-institutionalized setting where the subject is not living alone.	The trial population will include male and female subjects between 55 and 90 years of age (inclusive), who are living in either an institutionalized setting or in a non-institutionalized setting where the subject is not living alone.
Section 3.1 Type/Design of Trial Screening Period	The screening period will range from a minimum of 2 days to a maximum of 42 days and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures.  In addition, the subject will be monitored through actigraphy and eDiary assessments as a means of corroborating information recorded on the CMAI. Both assessments will be initiated after the ICF is signed during the screening visit and followed through	The screening period will range from 2 days to 42 days and will begin when the informed consent form (ICF) is signed, prior to the initiation of any procedures. The screening period may be extended after discussion with and approval by the medical monitor.  In addition, starting at screening and continuing throughout the 12-week double-blind treatment period, the subject's behavior will be logged into a diary by the caregiver and/or facility

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Location	Old Text	Updated Text
	Week 12/Early Termination (ET). The subjects will be given an actigraph, which will record their physical activity, to wear on their nondominant wrist for 24 hours/day. If the subject decides not to wear the actigraph at any time after the consent is obtained, the assessment may be discontinued and study participation will not be affected. The subject's behavior will be logged into an eDiary by the caregiver and/or facility staff.	staff. This diary data along with the collection of progress notes will be sent to the CST group on a routine basis in order to corroborate information recorded on the CMAI. Since the diary data is a tool to assist the CST in monitoring CMAI rater training, the diary data will not be statistically analyzed. While it is preferred that diary data are collected 7 days a week, it is realized that diary use for 7 days a week may not be possible because the minimum amount of time that the caregiver is required to observe the subject is 4 days a week. Every effort should be put forth by the sites to encourage the caregivers to collect and submit as much data as possible. Caretakers, facility personnel, and/or family members may provide information to the caregiver to complete the diary, but this is not a requirement. Details around this procedure can be found in the operations manual.
Section 3.1 Type/Design of Trial 12-week, Double-blind Treatment Period	The subjects' condition will be evaluated routinely, including vital signs assessments, as required per the local guidelines of the institutionalized setting or according to the discretion of the principal investigator. Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. All study visits will take place as a clinic visit at either the investigator's site (for non- institutionalized subjects) or residential facility (for institutionalized subjects). In addition, the subject's identified caregiver will be contacted by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. Trial- related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1). If a subject discontinues the trial prematurely, every effort will be made to complete the Week 12/ET evaluations	Subjects will be evaluated at Baseline, Day 3, and at Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. All trial visits will take place as a clinic visit at either the investigator's site or residential facility, if applicable. All attempts should be made to maintain the subjects' normal routine with regard to physician appointments. Individual circumstances that fall outside this general convention should be discussed with the medical monitor in order to determine appropriateness to proceed. In addition, the subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1).

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Location	Old Text	Updated Text
	prior to administering additional	
	medications for the treatment of agitation	
Section 2.1	or other prohibited medications.	
Section 5.1 Type/Design of	All subjects, whether they complete the	All subjects, whether they complete the
Trial	any reason, will be followed up for a	any reason, will be followed up for a
Follow-up Period	safety evaluation $30 (+2)$ days after the	safety evaluation $30 (+2)$ days after the
1	last dose of IMP during a clinic visit at	last dose of IMP during a clinic visit at
	either the investigator's site or residential	either the investigator's site or
	facility, if institutionalized. If the	residential facility, if applicable.
	institutionalized subject has left the	
	residential facility where he or she	For those subjects who plan to enroll
	should be seen at the investigator's site	follow up visit for Trial 331, 12, 283 will
	should be seen at the investigator's site.	occur as a clinic visit either at the
	For those subjects who plan to enroll	investigator's site or residential facility.
	into Trial 331-13-211, the 30-day safety	if applicable.
	follow-up visit for Trial 331-12-283 will	**
	occur as a clinic visit either at the	
	investigator's site or residential facility.	
	If the institutionalized subject has left the	
	participated in the trial, the 30 day safety	
	follow-up visit will occur as a clinic visit	
	at the investigator's site.	
Figure 3.1-1	Screening	Screening
Trial Design		
Schema	Subjects with agitation associated with	Subjects with agitation associated with
	dementia of the Alzheimer's type $(N - 220)$	dementia of the Alzheimer's type $(N = 520 \text{ screened})$
	(11 - 350)	(N – 520 screened)
	2 to 42 days	2 to 42 days
	Days -42 to -2	Days -42 to -2
		(with an option to extend with approval
		of the medical monitor)
	12-week Double-blind Treatment Period	12-week Double-blind Treatment Period
	Brexpiprazole flexible dose	Brexpiprazole flexible dose
	Dose range 0.5 mg/day to 2 mg/day	Dose range 0.5 mg/day to 2 mg/day
	(target dose is 1 mg/day)	(target dose is 1 mg/day)
	(N = 115)	(N = 130)
	Placebo	Placebo
	(N = 115)	(N = 130)
	Randomized (1:1)	Randomized (1:1)
	(N = 230)	(N = 260)
Section 3.3	The subject population will include male	The subject population will include
I mai Population	and remain subjects between 55 and 90 years of age (inclusive), who are	male and remain subjects between
	living in either an institutionalized setting	are living in either an institutionalized
	(e.g., nursing home, dementia unit,	setting or in a non-institutionalized
	assisted living facility, or any other	setting where the subject is not living

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Location	Old Text	Updated Text
	residential care facility providing long	alone Additionally, at both the
	term care) or in a non-institutionalized	screening and baseline visits, subjects
	setting where the subject is not living	must have a Mini-Mental State
	alone Additionally, at both the	Examination (MMSE) score of 5 to 22,
	screening and baseline visits, subjects	inclusive, and a total score (frequency x
	must have a Mini-Mental State	severity) of $\geq 4$ on the
	Examination (MMSE) score of 5 to 22,	agitation/aggression item of the NPI-NH
	inclusive, and a total score (frequency x	or the Neuropsychiatric Assessment for
	severity) of $\geq 4$ on the	Non-institutionalized Patients based on
	agitation/aggression item of the NPI-NH.	the NPI/NPI-NH (hereafter referred to
	The NPI-NH will be used for both	as "NPI/NPI-NH"). The NPI-NH will
	institutionalized and non-institutionalized	be used for institutionalized subjects and
	subjects; however, the Occupational	the NPI/NPI-NH will be used for
	Disruptiveness questions will not be	non-institutionalized subjects.
	answered for non-institutionalized	
	subjects. Instead, the Distress questions	Subjects must have been residing at
	from the Neuropsychiatric Inventory	their current location for at least 14 days
	(NPI) will replace the Occupational	before screening and be expected to
	Disruptiveness questions for non-	remain at the same location for the
	institutionalized subjects. This	duration of the trial. Subjects who at
	neuropsychiatric assessment for non-	any point during the double-blind
	institutionalized subjects based on the	treatment phase transfer from an
	NPI/NPI-NH will hereafter be referred to	institutionalized setting to a
	as "NPI/NPI-NH".	non-institutionalized setting, or vice
		versa, will be withdrawn from the trial.
	Subjects must have been residing at their	In case of a brief hospitalization,
	current location for at least 14 days	determination of subject eligibility to
	before screening and be expected to	stay in the trial must be made based on
	remain at the same location for the	subject safety by the investigator and
	duration of the trial. Subjects from a	medical monitor. All attempts should
	non-institutionalized setting who at any	be made to maintain the subjects'
	point during the double-blind treatment	normal routine with regard to
	phase require permanent placement to a	appointments with physicians and
	nursing home or assisted living facility	overnight accommodations. Subjects
	will be withdrawn from the trial.	in an institutionalized setting may
	Subjects who at any point during the	receive supervised day passes at the
	double-blind treatment phase transfer	discretion of the investigator and may
	iron an institutionalized setting to a	also receive supervised overnight passes
	non-institutionalized setting will also be	at the discretion of the investigator as
	withdrawn from the trial. In case of a	the subjects' normal stays are part of
	change in the non-institutionalized	the subjects normal routine.
	investigator should consult with the	 It is planned that approximately 520
	investigator should consult with the	it is planned that approximately 520
	In cose of a brief hearitalization	subjects will be screened at
	determination of subject of sibility to	approximately of that sites worldwide
	stay in the trial must be made based or	in order to randomize 200 subjects.
	stay in the trial must be made based on	
	NC Pasagrah madical monitor Subjects	
	in an institutionalized setting may receive	
	supervised day passes at the discretion of	
	the investigator: however, overnight	
	nasses will not be allowed for this trial	
	Passes will not be anowed for this trial.	

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Location	Old Text	Updated Text
	 It is planned that approximately 330 subjects will be screened at approximately 46 trial centers worldwide in order to randomize 230 subjects.	
Section 3.3.1.1 Non- institutionalized Subjects	The subject's caregiver is defined as the person who has sufficient contact to describe the subject's symptoms, and has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, NPI/NPI-NH, and other applicable trial assessments, including completion of the eDiary The caregiver is the person who should accompany the subject to all visits where the CMAI and NPI-NH are administered unless other arrangements are made and approved by the sponsor.	For purposes of this trial, the subject's caregiver is defined as the person who has sufficient contact to describe the subject's symptoms, and has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI/NPI-NH, and other applicable trial assessments, including completion of the diary The caregiver is the person who should accompany the subject to all visits where the CMAI and NPI/NPI-NH are administered unless other arrangements are made and approved by the sponsor.
Section 3.3.1.2 Institutionalized Subjects	A caregiver in the institutionalized setting is an individual who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, NPI/NPI-NH, and other applicable trial assessments.	A caregiver in the institutionalized setting is an individual who has sufficient contact to describe the subject's symptoms and who has direct observation of the subject's behavior in order to participate in the interview for the CMAI, NPI-NH, and other applicable trial assessments.
Table 3.4.2-1 Inclusion Criteria	8. Subjects with a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the NPI-NH at the screening and baseline visits.	8. Subjects with a total score (frequency x severity) of $\geq$ 4 on the agitation/aggression item of the NPI-NH (for institutionalized subjects) or the NPI/NPI-NH (for non-institutionalized subjects) at the screening and baseline visits.
Table 3.4.3-1 Exclusion Criteria	<ol> <li>Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as substance-induced dementia, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects aged 55 years or older with a diagnosis of Down syndrome.</li> <li>Subjects with a history of stroke, transient ischemic attack, or pulmonary or cerebral embolism.</li> <li>Subjects with a history of clinically relevant traumatic brain injury with neurological sequelae.</li> <li>Subjects with a history of a deep venous thrombosis within the 5 years prior to the screening visit.</li> </ol>	<ol> <li>Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as substance-induced dementia, HIV- dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.</li> <li>Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism. (this exclusion criterion was removed)</li> <li>(this exclusion criterion was removed)</li> </ol>

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Location	Old Text	Updated Text
	7. Subjects with delirium, unless resolved	5. Subjects with delirium or history of
	with no symptoms for at least 30 days	delirium within the 30 days prior to the
	prior to the screening visit.	screening visit.
	8. Subjects who have been diagnosed	6. Subjects who have been diagnosed
	with an Axis I disorder (DSM-IV-IR	with an Axis I disorder (DSM-IV-IR
	criteria) including, but not limited to:	criteria) including, but not limited to:
	<ul> <li>Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia</li> <li>Bipolar I or II disorder, bipolar disorder not otherwise specified</li> <li>Current major depressive disorder—unless on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).</li> <li>Eating disorder (including anorexia nervosa or bulimia)—unless resolved with no symptoms for at least 1 year prior to screening</li> <li>Obsessive-compulsive disorder—unless resolved with no symptoms for at least 1 year prior to screening</li> </ul>	<ul> <li>Schizophrenia, schizoaffective disorder, or other psychotic disorder not related to dementia</li> <li>Bipolar I or II disorder, bipolar disorder not otherwise specified</li> <li>Current major depressive episode. Subjects with major depressive disorder are eligible provided that they have been on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization. Please note: antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).</li> </ul>
	<ul> <li>Panic disorder—unless resolved with no symptoms for at least 1 year prior to screening</li> <li>Posttraumatic stress</li> </ul>	
	<ul> <li>disorder—unless resolved with no symptoms for at least 1 year prior to screening</li> <li>9. Subjects with an Axis II (DSM-IV-TR criteria) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder</li> </ul>	(this exclusion criterion was removed)
	11. Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders.	8. Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, gastrointestinal, or psychiatric disorders.

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	13. Subjects with insulin-dependent	10. Subjects with diabetes mellitus may
	diabetes mellitus (IDDM) (i.e., any	be eligible for the trial if their condition
	subjects using insulin) may be eligible	is stable and well-controlled as
	for the trial if their condition is	determined by satisfying ALL of the
	well-controlled and if they do not have	Ioliowing criteria:
	non IDDM may be eligible for the trial if	• $HDA_{1c} < 8.0\%$ , AND
	their condition is stable as determined by	• Screening glucose must be
	satisfying ALL of the following criteria:	$\leq 125$ mg/dL (lasting) or $\leq 200$ mg/dL (non fasting). If the
	<ul> <li>Glycosylated hemoglobin (HbA<sub>10</sub>) </li> </ul>	> 200 mg/dL (non-fasting). If the non-fasting screening glucose is
	8.0%, <b>AND</b>	> 200  mg/dL subjects must be
	• Screening glucose must be	retested in a fasted state and the
	$\leq 125 \text{ mg/dL}$ (fasting) or	retest value must be $< 125 \text{ mg/dL}$
	< 200 mg/dL (non-fasting). If the	AND
	non-fasting screening glucose is	• Subject has not had any
	$\geq$ 200 mg/dL, subjects must be	hospitalizations within the 3 months
	retested in a fasted state and the	prior to screening due to diabetes or
	retest value must be $\leq 125 \text{ mg/dL}$ ,	complications related to diabetes.
	AND	Subjects with non-IDDM (ie, any
	• Urine albumin-to-creatinine ratio	subjects not using insulin) must also
	(ACR) must be $< 30 \text{ mg/g}$	satisfy the below criterion:
	(calculated), AND	• Subject has been maintained on a
	• Subject has been maintained on a	stable regimen of oral antidiabetic
	madiantian(a) for at least 28 days	medication(s) for at least 28 days
	prior to screening or diabetes has	been well controlled by diet for at
	been well-controlled by diet for at	least 28 days prior to screening
	least 28 days prior to screening.	Subjects with IDDM (ie. any subjects
	AND	using insulin) must also satisfy the
	• Subject has not had any	below criterion:
	hospitalizations within the 3 months	• No current microalbuminuria; ie,
	prior to screening due to diabetes or	urine ACR must be < 30 mg/g
	complications related to diabetes.	(calculated).
	Subjects with newly diagnosed diabetes	Subjects with newly diagnosed diabetes
	during screening are excluded.	during screening are excluded.
	14. Subjects with clinically significant	(this exclusion criterion was removed)
	chronic kidney disease based on the	
	Investigator's judgment.	(this avaluation aritarian was removed)
	consistent with a hypercoagulable state	(this exclusion chierion was removed)
	and/or evidence of a hypercoagulable	
	state based on laboratory tests.	
	18. Subjects with human	13. Subjects with seropositive status for
	immunodeficiency virus (HIV)	hepatitis B (ie, HBsAg positive) or
	seropositive status/acquired	hepatitis C (ie, anti-HCV positive).
	immunodeficiency syndrome, or chronic	· · · · · · · · · · · · · · · · · · ·
	hepatitis B or C.	

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Location	Old Text	Updated Text
	19. Subjects with clinically relevant sensory impairments such as visual or hearing loss that would limit subjects' participation in the trial and ability to comply with the protocol requirements based on the investigator's judgment.	(this exclusion criterion was removed)
	20. Subjects with significant swallowing difficulties that would preclude taking oral medications in tablet form; subjects with clinically relevant dysphagia.	(this exclusion criterion was removed)
	21. Subjects considered in poor general health based on the investigator's judgment.	14. Subjects considered in poor general health based on the investigator's judgment. Examples include subjects who have a recent clinically significant weight loss, chronic dehydration or hypovolemia, poor fluid or nutritional intake, or a recent clinically significant infection, as per the investigator's judgment.
	22. Subjects with weight loss of more than 5% in the7 days prior to the baseline visit or more than 10% between the screening and baseline visits.	(this exclusion criterion was removed)
	<ul> <li>23. Subjects with weight &lt; 40 kilograms.</li> <li>24. Subjects with dehydration or hypovolemia, or a consistent or chronic pattern of poor fluid and/or nutritional intake, or with recent need for supplemental fluid via intravenous solution or supplemental nutrition via gastric tube.</li> </ul>	15. Subjects with a BMI < 18.5 kg/m <sup>2</sup> . (this exclusion criterion was removed)
	<ul><li>25. Subjects who are bedridden.</li><li>26. Subjects with recent clinically significant infection, as evidenced by treatment with intravenous antibiotics or hospitalization, within the 2 weeks prior to the screening visit.</li></ul>	(this exclusion criterion was removed) (this exclusion criterion was removed)
	27. Subjects who are known to be poor CYP2D6 metabolizers.	(this exclusion criterion was removed)
	be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. In addition, subjects with the following	In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial:
	<ul> <li>laboratory test and ECG results at screening must be excluded from the trial:</li> <li>Platelets ≤ 120,000/mm<sup>3</sup></li> <li>Hemoglobin ≤ 10 g/dL for women</li> </ul>	<ul> <li>Platelets ≤ 75,000/mm<sup>3</sup></li> <li>Hemoglobin ≤ 9 g/dL</li> <li>Neutrophils, absolute ≤ 1000/mm<sup>3</sup></li> <li></li> <li>OTeE &gt; 450 meas in men and &gt; 470</li> </ul>
	$11 \text{ g/dL for men}$ Neutrophils, absolute $\leq 1500/\text{mm}^3$ $ACR > 30 \text{ mg/g} \text{ (calculated as units)}$	<ul> <li>QTCF 2 430 insect in men and 2 470 msec in women (see Section 3.7.4.4 for further details), unless due to ventricular pacing</li> <li>Tests with avaluation or results should</li> </ul>
l	- $ACK > 50 \text{ mg/g}$ (calculated as urme	1 csts with exclusionary results should

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Location	Old Text	Updated Text
	<ul> <li>albumin [mg/dL] / urine creatinine [g/dL])</li> <li></li> <li>QTcF ≥ 450 msec in men and ≥ 470 msec in women (see Section 3.7.4.4 for further details)</li> </ul>	be repeated (if ECG, 3 consecutive recordings) to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
	<ul><li>33. Subjects who have a medical condition that requires treatment with an anticoagulant.</li><li>36. Subjects who received brexpiprazole in any prior clinical trial.</li></ul>	<ul> <li>21. Subjects who have a current medical condition that requires treatment with an anticoagulant.</li> <li>24. Subjects who received brexpiprazole in any prior clinical trial or commercially available brexpiprazole (Rexulti®).</li> </ul>
	39. Subjects who participated in a clinical trial within the last 180 days or who participated in more than 2 interventional clinical trials within the past year.	27. Subjects who participated in a clinical trial within the last 30 days.
Section 3.4.3 Exclusion Criteria	In the event that a screen failure is rescreened after the 42-day screening period expires, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.	A subject may be rescreened more than once after discussion with and approval by the medical monitor. In the event that a screen failure is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

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Location	Old Text	Updated Text
Section 3.5.6 Pharmacokinetic/ Pharmacodynamic Variables	Plasma concentrations will be determined for brexpiprazole and its major metabolite, DM-3411, and descriptive statistics will be calculated.	Plasma concentrations will be determined for brexpiprazole and its metabolite(s) and descriptive statistics will be calculated.
Section 3.7 Trial Procedures	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 3.5 years, of which approximately 3 years are allotted for recruitment of subjects.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately 4.5 years, of which approximately 4 years are allotted for recruitment of subjects.
	t, the CST will perform regular quality reviews of CMAI data and will compare these data against other sources of behavioral information, including patterns of	the CST will perform regular quality reviews of CMAI data and will compare these data against other sources of behavioral information, including behavior logs

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	movement using actigraphy technology	collected by caregivers through paper
	(refer to Section 3.7.3.7), behavior logs	diaries and investigator progress notes.
	collected by caregivers through	
	electronic diaries (refer to Section	All trial visits will take place as a clinic
	3.7.3.8), and investigator progress notes.	visit at either the investigator's site or
		residential facility, if applicable. All
	All study visits will take place as a clinic	attempts should be made to maintain the
	visit at either the investigator's site (for	subjects' normal routine with regard to
	non-institutionalized subjects) or	physician appointments. Individual
	residential facility (for institutionalized	circumstances that fall outside this
	subjects).	general convention should be
		discussed with the medical monitor in
		order to determine appropriateness to
		proceed.
Table 3.7-1	The changes to the Schedule of Assessments are presented below.	
Schedule of	Bold and underlined text: Changed or added text	
Assessments	Bold and strikethrough text: Deleted text	

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	Visit										
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	<mark>CC</mark> I
ENTRANCE/HISTORY	·										
Informed consent <sup>e</sup>	Х										
Inclusion/exclusion criteria <sup>f</sup>	Х	Х									
Demography	Х										
Medical history	X										
Psychiatric history	Х										
Neurological history <sup>g</sup>	Х										
Prior medication washout <sup>h</sup>	Х										
NINCDS-ADRDA	Х										
Hachinski Ischemic Scale (Rosen Modification) <sup>g</sup>	Х										
HIV, HBsAg, and anti-HCV	Х										
Pre-Baseline Packet <sup>i</sup>	Х										
EFFICACY	·		•		•						
CMAI	Х	Х		Х	Х	Х	Х	Х	Х		
CGI-S <sup>J</sup>	Х	Х		Х	Х	X	Х	Х	Х		
NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects)	X	Х		Х	X	Х	Х	Х	Х		

Table 3.7-1 Schedule of Assessments	5										
	Visit										
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	CCI
OTHER	Servering	(Duj 0)	Dayo	*** K 2		W K U	WK O	*****	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
CCI											T
Actigraphy k					X						
Electronic diaries					<u> </u>						
SAFETY											
Physical examination mk	Х					X			Х		
Neurological examination <sup><b>n</b>]</sup>	Х					X			Х		
Vital signs <sup><b>0</b><u>m</u></sup>	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Clinical laboratory tests (hematology, serum chemistry, urinalysis) <sup><b>Pn</b></sup>	Х	Х <sup><b>9</b><u>0</u></sup>			Х <sup><u>р</u></sup>		х <u></u>		Х		
Prolactin (blinded) <sup><b>P</b><u>n</u></sup>	X				X		X		Х		
TSH with reflex to free $T_4$ if abnormal <sup>PD</sup>	Х								Х		
HbA <sub>1c</sub> <sup>pn</sup>	Х								Х		
PT, aPTT, and INR <sup>₱</sup>	Х								Х		
ACTH and cortisol <sup>Pn</sup>	Х								Х		
Urine pregnancy test (women of childbearing potential) only <sup><b>Fg</b></sup>	X				X		X		Х		
ECG <sup><u>sr</u></sup>	Х	Х			Х		Х		Х		
Blood alcohol	Х										
Urine drug screen <sup>t,us_t</sup>	X			]							

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Table 3.7-1 Schedule of Assessments	S										
	Visit										
Assessment	Screening <sup>a</sup>	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET <sup>b</sup>	FU <sup>c</sup>	Wk 16 <sup>d</sup>
MMSE	Х	Х							Х		
Adverse events <sup>#</sup>	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	
Pharmacokinetic sampling		Х					Х		Х		
Concomitant medications <sup>ZV</sup>	X	Х	X	Х	Х	X	X	Х	Х	Х	
OTHER PROCEDURES											<u>.</u>
Register trial visit in IVRS/IWRS	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Randomize eligible subjects via IVRS/IWRS		Х									
IMP dispensing		Х	Х	Х	Х	Х	Х	Х			
IMP accountability			Х	Х	Х	Х	Х	Х	Х		
Telephone contact											
ADDITIONAL ENTRANCE/HISTORY											
MRI/CT scan	X <sup>dd<u>cc</u></sup>										

Location	Old Text	Updated Text
Table 3.7-1	<sup>a</sup> Screening begins when the ICF is	<sup>a</sup> Screening begins when the ICF is
Schedule of	signed. Screening procedures must be	signed. Screening procedures must be
Assessments, footnotes	initiated between Day -42 and Day	initiated between Day -42 and Day -2.
	-2.	The screening period may be extended
		after discussion with and approval by
		the medical monitor.
	<sup>c</sup> All subjects, whether they complete	<sup>c</sup> All subjects, whether they complete
	the trial or are withdrawn prematurely	the trial or are withdrawn prematurely
	for any reason, will be followed up for	for any reason, will be followed up for
	a safety evaluation $30 (+2)$ days after	a safety evaluation 30 (+ 2) days after
	the last dose of IMP during a clinic	the last dose of IMP during a clinic visit
	visit at either the investigator's site or	at either the investigator's site or
	residential facility. If the	residential facility, if applicable For
	institutionalized subject has left the	those subjects who plan to enroll into
	residential facility where he or she	Trial 331-13-211, the 30-day safety
	participated in the trial, the subject	follow-up visit for Trial 331-12-284
	should be seen at the investigator's	will occur as a clinic visit at either the
	site For those subjects who plan to	investigator's site or residential facility,
	enroll into Trial 331-13-211, the	if applicable.
	30-day safety follow-up visit for Trial	
	331-12-284 will occur as a clinic visit	
	at either the investigator's site or	
	residential facility. If the	
	institutionalized subject has left the	
	residential facility where he of she	
	safety follow up visit will occur as a	
	clinic visit at the investigator's site	
	$^{k}$ After the ICE is signed during the	(this footnote was removed)
	screening visit the actigraphy device	(inis footnote was femoved)
	will be put on the subject's	
	nondominant wrist and worn daily	
	until Week12/ET. It is recommended	
	that the actigraph be checked daily to	
	ensure that the subject is wearing it	
	and that it continues to be operational.	
	At every study visit (except the Day 3	
	visit), subjects will take off the watch	
	so that site personnel can download	
	the data stored in the device, and the	
	device battery will be changed. If the	
	screening period extends beyond	
	4 weeks, the battery will need to be	
	replaced once. Once the download is	
	complete, the device will be placed	
	back on the subject.	(this facture to was as 1)
	will be entered by the conscience of $\frac{1}{2}$	(uns toomote was removed)
	will be entered by the caregiver and/or	
	<sup>m</sup> Physical examination includes	<sup>k</sup> Physical examination includes
	measurement of height and waist	measurement of height and waist
	circumference at screening and waist	circumference at screening and waist
	circumference at Weeks 6 and 12/ET	circumference at Week 12/ET.
I	incomposition at the berg 0 and 12/E1.	encamerence at wook 12/12/1.

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Location	Old Text	Updated Text
	<sup>n</sup> A detailed neurological examination will be performed by a physician at screening, Week 6, Week 12/ET, and as needed during the trial for new onset neurological symptoms. (new footnote)	<sup>1</sup> A detailed neurological examination will be performed by a physician at screening, Week 12/ET, and as needed during the trial for new onset neurological symptoms. <sup>p</sup> Urinalysis is not required at Week 4 or Week 8.
	<sup>cc</sup> The subject's identified caregiver will be contacted by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.	<sup></sup> Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated (with 3 consecutive ECG recordings) to confirm the finding(s) before excluding the subject from the trial. <sup>bb</sup> The subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.
Section 3.7.1.1 Screening	<ul> <li>The screening period begins after written informed consent has been obtained. Subjects will participate in screening activities for a minimum of 2 days and a maximum of 42 days</li> <li>Screening evaluations will include the following:</li> <li>A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Subjects with screening OTcF ≥ 450 msec</li> </ul>	The screening period begins after written informed consent has been obtained. Subjects will participate in screening activities for 2 days to 42 days. The screening period may be extended after discussion and approval of the medical monitor Screening evaluations will include the following:  • A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least
	<ul> <li>(males) or ≥ 470 msec (females) will be excluded from the trial (see Section 3.7.4.4)</li> <li>Blood samples will be drawn for human immunodeficiency virus (HIV) serology and the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C (anti-HCV).</li> <li></li> <li>Albumin-to-creatinine ratio (ACR) will be determined (must</li> </ul>	<ul> <li>5 minutes. Subjects with screening QTcF ≥ 450 msec (males) or ≥ 470 msec (females) will be excluded from the trial, unless due to ventricular pacing (see Section 3.7.4.4)</li> <li>Blood samples will be drawn for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C (anti-HCV).</li> <li>Urine albumin-to-creatinine ratio</li> </ul>
	<ul> <li>be &lt; 30 mg/g; calculated as urine albumin [mg/dL] / urine creatinine [g/dL]).</li> <li>A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver.</li> </ul>	(ACR) will be determined only for subjects with insulin-dependent diabetes mellitus (IDDM) (must be < 30 mg/g; calculated as urine albumin [mg/dL]/urine creatinine [g/dL]).

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Location	Old Text	Updated Text
	<ul> <li>After the ICF is signed during the screening visit, the actigraphy device will be put on the subject's nondominant wrist. The actigraph will be worn continuously throughout the double-blind treatment period. It is recommended that the actigraph be checked daily to ensure that the subject is wearing it and that it continues to be operational. At every study visit (except the Day 3 visit), subjects will take off the device so that site personnel can download the data stored in the device, and the device battery will be changed. Once the download is complete, the device will be placed back on the subject. If the screening period extends beyond 4 weeks, the battery will need to be replaced once.</li> <li>The subject's caregiver and/or facility staff will complete an electronic diary (eDiary) daily (if possible) after the ICF is signed, continuing through Week 12/ET</li> </ul>	<ul> <li>A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.</li> <li>The subject's caregiver and/or facility staff will complete a paper diary daily (if possible) after the ICF is signed, continuing through Week 12/ET.</li> </ul>
Section 3.7.1.2 Baseline (Day 0)	If the subject is found to be eligible for the trial during the screening period, the following procedures will be performed at the baseline visit:  • A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver.  • CCI	If the subject is found to be eligible for the trial during the screening period, the following procedures will be performed at the baseline visit:  • A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non- institutionalized subjects) to the identified caregiver.  • CC

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Location	Old Text	Updated Text
	<ul> <li>Actigraphy recording will continue.</li> <li>eDiary recording will continue.</li> </ul>	<ul> <li>Diary recording will continue</li> </ul>
Section 3.7.1.3.1 Day 3	This visit is to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be performed:  • Actigraphy recording will	<ul> <li>Diary recording will continue.</li> <li>This visit is to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be performed:</li> <li>Diary recording will continue.</li> </ul>
	<ul> <li>eDiary recording will continue</li> </ul>	
Section 3.7.1.3.2 Weeks 2, 4, 6, 8, and 10	<ul> <li>eDiary recording will continue.</li> <li> The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.</li> <li>A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver.</li> <li>CCI</li> <li>At each visit, subjects will take off the actigraph so that site personnel can download the data stored in the device, and the device battery will be changed. Once the download is complete, the device will be placed back on the subject.</li> <li>eDiary recording will continue.</li> <li>The following additional evaluations will be performed at the designated visits:</li> <li>A complete physical examination</li> </ul>	<ul> <li> The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits.</li> <li>A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.</li> <li>Diary recording will continue.</li> <li>The following additional evaluations will be performed at the designated visits:</li> <li>CCI</li> <li>A fasting blood draw for clinical laboratory tests (hematology and serum chemistry) will be obtained at Weeks 4 and 8 only. Vital sign and ECG assessments should be completed before any blood</li> </ul>

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Location	Old Text	Updated Text
Location	<ul> <li>Old Text <ul> <li>(including waist circumference)</li> <li>will be performed at <i>Week 6 only</i>.</li> </ul> </li> <li>A detailed neurological <ul> <li>examination, which will consist of an evaluation of the subject's mental status, cranial nerves, motor system (e.g., motor strength, muscle tone, reflexes), cerebellar system (e.g., coordination), gait and station, and sensory system, will be performed by a physician at <i>Week 6</i> only.</li> </ul> </li> <li>CCI</li> </ul>	Updated Text samples are collected.  In addition, the subject's identified caregiver will be contacted by telephone at Weeks 3, 5, and 7 to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being.
	<ul> <li>A fasting blood draw for clinical laboratory tests (hematology and serum chemistry, including prolactin [blinded]) will be obtained and urine will be collected for urinalysis at Weeks 4 and 8 only. Vital sign and ECG assessments should be completed before any blood samples are collected.</li> </ul>	
	<ul> <li>Women of childbearing potential will be given a urine pregnancy test at <i>Weeks 4 and 8 only</i>. Any positive result must be confirmed by a serum pregnancy test. Subjects with positive urine and serum test results must discontinue trial medication and be withdrawn from the trial.</li> </ul>	

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Location	Old Text	Updated Text
Section 3.7.1.4 End of Treatment (Week 12/ET)	In addition, the subject's identified caregiver will be contacted by telephone every odd numbered week after Week 2 (i.e., Weeks 3, 5, 7, 9, 11) to assess compliance with IMP, confirm any changes to concomitant medications, and assure the subject's well-being. The following activities and assessments will occur at Week 12 (or at the ET wight if applicable):	The following activities and assessments will occur at Week 12 (or at the ET vicit, if applicable):
(Week 12/ET)	<ul> <li>at the ET visit, if applicable):</li> <li>A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver.</li> <li>An adequately trained and experienced clinician will administer the CGI-S, GCI</li> <li></li> <li>The actigraphy device will be taken off, the data will be downloaded to the computer, and the actigraphy monitoring will be stopped.</li> <li>eDiary recording will be stopped.</li> </ul>	<ul> <li>at the ET visit, if applicable):</li> <li>A qualified and certified rater will administer the CMAI and NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects) to the identified caregiver.</li> <li>An adequately trained and experienced clinician will administer the CGI-S, CGI</li> <li>Image: Comparison of the comparison of the</li></ul>

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Location	Old Text	Updated Text
Section 3.7.1.5	All subjects, whether they complete	All subjects, whether they complete the
Follow-up	the trial or are withdrawn prematurely	trial or are withdrawn prematurely for
	for any reason, will be followed up for	any reason, will be followed up for a
	a safety evaluation $30 (+2)$ days after	safety evaluation $30 (+2)$ days after the
	the last dose of IMP during a clinic	last dose of IMP during a clinic visit at
	visit at either the investigator's site or	either the investigator's site or
	If the institutionalized subject has left	residential facility, if applicable.
	the residential facility where he or she	For these subjects who plan to oppoll
	narticipated in the trial the subject	into Trial 331 13 211 the 30 day safety
	should be seen at the investigator's	follow-up visit for Trial 331-12-283
	site	will occur as a clinic visit at either the
	Site.	investigator's site or residential facility.
	For those subjects who plan to	if applicable.
	enroll into Trial 331-13-211, the 30-	
	day safety follow-up visit for Trial	
	331-12-283 will occur as a clinic visit	
	at either the investigator's site or	
	residential facility. If the	
	institutionalized subject has left the	
	residential facility where he or she	
	participated in the trial, the 30-day	
	safety follow-up visit will occur as a	
Section 2721	Clinic visit at the investigator's site.	The minute office of the line of the
Section 3.7.2.1 Cohon Manafield	The primary efficacy variable is the	The primary efficacy variable is the
A gitation Inventory	in the CMAI total score	the CMAL total score
(CMAI)	In the CMAT total score.	
(CIVITIT)		
Section 3.7.2.5	The NPI-NH questionnaire is used to	The NPI-NH questionnaire is used to
Neuropsychiatric	interview the caregiver about the	interview the identified caregiver about
Inventory-Nursing	subject's possible neuropsychiatric	the institutionalized subject's possible
Home (NPI-NH)	symptoms (i.e., delusions,	neuropsychiatric symptoms (ie,
	hallucinations, agitation/aggression,	delusions, hallucinations,
	depression/dysphoria, anxiety,	agitation/aggression,
	elation/euphoria, apathy/indifference,	depression/dysphoria, anxiety,
	disinhibition, irritability, aberrant	elation/euphoria, apathy/indifference,
	motor benavior, nighttime benaviors,	disinhibition, irritability, aberrant motor
	NDL NH gives on insight into the	benavior, nightlime benaviors, and
	frequency $(1 \text{ to } 4)$ severity $(1 \text{ to } 2)$	NH gives an insight into the frequency
	and occupational disruption $(0 \text{ to } 5)$ of	(on a scale of 1 to 4) severity (on a
	each of the 12 separate behavioral	scale of 1 to 3) and occupational
	domains.	disruption (on a scale of 0 to 5) of each
		of the 12 separate behavioral domains.

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Location	Old Text	Undated Text
Section 3.7.2.6	Section 3.7.2.6 Neuropsychiatric	Section 3.7.2.6 Neuropsychiatric
Neuropsychiatric	Inventory (NPI)	Assessment for Non-institutionalized
Inventory (NPI)		Patients Based on the NPI/NPI-NH
• • •	The NPI is a structured caregiver	(NPI/NPI-NH)
	interview designed to obtain	
	information on the presence of	The NPI/NPI-NH is a structured
	psychopathology in subjects with	caregiver interview designed to obtain
	brain disorders, including Alzheimer's	information on the presence of
	disease and other dementias. <sup>31</sup> The	psychopathology in non-
	NPI differs from the NPI-NH in that it	institutionalized subjects with brain
	is tailored for use in non-institutional	disorders, including Alzheimer's
	settings (as opposed to the nursing	disease and other dementias. <sup>31</sup> The
	home). Item domains are identical	NPI/NPI-NH differs from the NPI-NH
	between the two scale versions.	in that questions referring to
	I en behavioral and two	"Occupational Disruptiveness" from the
	accomprise the NPL (including	NPI-NH have been replaced with
	delugiong hellugingtions	the Neuropsychiatric Inventory (NIPI)
	agitation/aggression	Item domains are identical between the
	depression/dysphoria_anxiety	NPI/NPI-NH and NPI-NH
	elation/euphoria, apathy/indifference.	Ten behavioral and two neurovegetative
	disinhibition, irritability, aberrant	symptom domains comprise the
	motor behavior, nighttime behavior	NPI/NPI-NH (ie. delusions.
	disorders, and appetite/eating	hallucinations, agitation/aggression,
	disorders). Caregivers are instructed	depression/dysphoria, anxiety,
	to indicate the frequency of a given	elation/euphoria, apathy/indifference,
	behavior (on a scale of 1 to 4), its	disinhibition, irritability, aberrant motor
	severity (on a scale of 1 to 3), and how	behavior, nighttime behavior disorders,
	much distress that behavior causes for	and appetite/eating disorders). The
	him or her (on a scale of 0 to 5). Each	identified caregivers are instructed to
	domain produces 4 scores: frequency,	indicate the frequency (on a scale of 1
	severity, total (frequency x severity),	to 4), severity (on a scale of 1 to 3), and
	and distress. A total NPI score is	distress (on a scale of 0 to 5) of each of
	calculated by adding the first	the 12 separate behavioral domains. $T_{1}$
	10 domain total scores (frequency x	Therefore, for each benavioral domain,
	sevenity scores) together. All	total (frequency x coverity) and
	in special circumstances where the	distress A total NPI/NPI NH score is
	neurovegetative symptoms are of	calculated by adding the first 10 domain
	neurovegetative symptoms are of	total scores (frequency x severity
	the NPI generally takes about 15	scores) together All 12 domain total
	minutes The psychometric properties	scores can be summed in special
	and factor structure of the NPI have	circumstances where the
	been shown to have internal	neurovegetative symptoms are of
	consistency, reliability, convergent	particular importance. Administering
	validity, and discriminant validity.	the NPI/NPI-NH generally takes about
		15 minutes.
	A sample of the NPI is provided in	
	Appendix 9.	A sample of the NPI/NPI-NH is
		provided in Appendix 9.
CCI		

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Location	Old Text	Updated Text
Section 3.7.3.7	The CST will perform ongoing	(this section was removed)
Actigraphy	reviews of CMAI raters by reviewing	
	CMAI data relative to other sources of	
	behavioral information, including	
	patterns of movement using	
	actigraphy technology. Motion will	
	be collected through an actigraphy	
	device resembling a wristwatch worn	
	by the subject on their nondominant	
	wrist for 24 hours/day during the	
	screening and treatment periods. If	
	the subject decides not to wear the	
	actigraph at any time after the consent	
	is obtained, the assessment may be	
	discontinued and continued study	
	participation will not be affected. The	
	actigraphy data will be downloaded	
	from the device to the actigraphy	
	vendor at regular intervals	
	corresponding to the date of the	
	CMAI. For non-institutionalized	
	subjects, the caregiver will not be	
	expected to change the actigraph	
	watch battery or download the	
	actigraph data; these duties will be	
	completed by the site staff. For	
	institutionalized subjects, the	
	caregiver or site staff may be	
	responsible for changing the actigraph	
	watch battery or downloading the	
	acugraph data.	
	Actigraphy uses a portable	
	Motionlogger device (actigraph) that	
	records movement over extended	
	periods of time and that most	
	commonly is worn on the wrist (refer	
	to Appendix 16). The actigraph	
	accelerometers samples physical	
	activity 32 times a second to detect	
	wrist movement. These data are	
	stored within the actigraph for up to	
	several weeks. The length of time the	
	actigraph is able to record data is	
	typically dependent on the actigraph's	
	epoch length (15 seconds, in this	
	study). The subject is advised to wear	
	the actigraph continuously all times,	
	including during sleep. If the subject	
	must remove the device for any	
	reason, the subject is instructed to	
	place it back on the wrist as soon as	
	possible. The device is able to detect	

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Location	Old Text	Updated Text
	when it is not on the subject's wrist,	
	and it tracks the time that it is not	
	being worn. An event marker on the	
	device can be used to mark the	
	occurrence of significant events such	
	as bedtime, or the time of a rating	
	(e.g., such as the CMAI). The	
	actigraphy data will be downloaded,	
	verified, and transferred to Clinilabs'	
	core laboratory at each study visit	
	(except the Day 3 visit) from the	
	device by attaching it to a docking	
	station connected to a computer that	
	allows communication with the	
	software program on the computer.	
	The computer program summarizes	
	these data and can display and print a	
	histogram (called an actogram), which	
	shows the subject's activity levels for	
	each epoch during successive 24-hour	
	periods. The computer program	
	provides validated algorithms that	
	summarize activity data. The data are	
	then reviewed for active periods and	
	rest periods. The actigraph will be put	
	on the subject after the ICF/assent is	
	signed and taken off at the Week	
	12/ET visit.	
	Investigator progress notes as well as	
	other efficacy data will be reviewed	
	by the CST as part of this in-trial	
	CMAI data quality oversight method	
	Any clinically relevant findings	
	generated by this review suggesting	
	rater training or other issues will be	
	discussed with the sites and measures	
	may be taken to enhance training	
	when needed. Details of this CMAI	
	quality review may be found in the	
	Operations Manual	
	Since actigraphy data are tools to	
	assist the CST in monitoring CMAI	
	rater training, actigraphy information	
	will not be statistically analyzed.	
Section 3.7.3.8	3.7.3.8 Electronic Diary (eDiary)	(this section was removed)
Electronic Diary		
(eDiary)	The CST will perform ongoing	
	reviews of CMAI raters by reviewing	
	CMAI data relative to other sources of	
	behavioral information, including	
	behavior logs collected by caregivers	

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Location	Old Text	Updated Text
Location	Old Text and/or facility staff through eDiaries (refer to Appendix 17). Caregivers will record occurrence of the 29 behaviors listed in the CMAI as they occur using an eDiary. All 29 behaviors will be listed, and the caregiver will check the box next to the behavior when it occurs; there is no free text in the eDiary. Observations recorded using the eDiary will be transmitted wirelessly to the eDiary vendor. For subjects in a non-institutionalized setting, one of the responsibilities of the caregiver is to complete the eDiary by noting the subject's symptoms of	Updated Text
	by noting the subject's symptoms of agitation. While it is preferred that eDiary data are collected 7 days a week, it is realized that eDiary use for 7 days a week may not be possible because the minimum amount of time that the caregiver is required to observe the subject is 4 days a week. The caretaker may provide information to the caregiver to complete the eDiary on a daily basis, but this is not a requirement. The responsibility of the caregiver for logging behaviors in the eDiary remains the same for subjects in an institutionalized setting. However, more than one caregiver may use the eDiary for any given subject; whoever is providing care for the subject at a given time can log behaviors in the eDiary.	
	 Since eDiary data are tools to assist the CST in monitoring CMAI rater training, eDiary information will not be statistically analyzed.	
Table 3.7.4.2-1 Clinical Laboratory Assessments	<u>Urinalysis</u> Albumin Creatinine	<u>Urinalysis</u> (these asessments were removed)
	Additional Tests (Screening Only) HIV HBsAg Anti-HCV	Additional Tests (Screening Only) HBsAg Anti-HCV Urine albumin (only for subjects with IDDM) Urine creatinine (only for subjects with IDDM)

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Location	Old Text	Updated Text
Section 3.7.4.2	Urine will be collected and blood will	Urine will be collected and blood will
Clinical Laboratory	be drawn from each subject during	be drawn from each subject during
Assessments	screening prior to treatment with the	screening prior to treatment with the
	IMP. If fasting blood samples are not	IMP. Subjects should be fasting for a
	feasible at screening, nonfasting blood	minimum of 8 hours prior to the blood
	determining aligibility for the trial	draws, il possible. Il fasting blood
	Additional uring and blood samples	samples are not leasible at screening,
	may be collected for further	obtained initially for determining
	evaluation of safety as warranted by	eligibility for the trial Additional
	the investigator's judgment. Subjects	urine and blood samples may be
	should be fasting for a minimum of 8	collected for further evaluation of
	hours prior to the blood draws, if	safety as warranted by the
	possible.	investigator's judgment.
	The following laboratory test results at	The following laboratory test results at
	screening are exclusionary:	screening are exclusionary:
	• Platelets $\leq 120,000/\text{mm}^3$	• Platelets $\leq 75,000/\text{mm}^3$
	• Hemoglobin $\leq 10 \text{ g/dL}$ for	• Hemoglobin $\leq 9 \text{ g/dL}$
	women, 11 g/dL for men	• Neutrophils, absolute $\leq 1000/\text{mm}^3$
	• Neutrophils, absolute $\leq 1500/\text{mm}^3$	
		• Subjects with IDDM (ie, any
	• Office aroundine-to-creatinine ratio (ACR) > 30 mg/g (calculated as	satisfy the following criterion: no
	urine albumin [mg/dL] / urine	current microalbuminuria: ie urine
	creatinine [g/dL])	ACR must be $< 30 \text{ mg/g}$
		(calculated).
Section 3.7.4.3.1	Repeat measurement of height is	Repeat measurement of height is not
Physical Examination	not required at the physical	required at the physical examinations
	examinations scheduled for the Weeks	scheduled for the Week 12/ET visits.
	6 and 12/ET visits. Waist	Waist circumference will be measured
	circumference will be measured at	at each physical examination (screening
	each physical examination (screening,	and Week 12/E1), using the provided
	week 6, and week 12/E1), using the	measuring tape.
Section 37432	A detailed neurological examination	A detailed neurological examination
Neurological	will be performed by a physician at	will be performed by a physician at
Examination	screening Week 6 Week 12/ET and	screening Week 12/ET and as needed
2	as needed during the trial for new	during the trial for new onset
	onset neurological symptoms.	neurological symptoms.
Section 3.7.4.4	Based on the QT interval as	Based on the QT interval as corrected
ECG Assessments	corrected by Fridericia's formula	by Fridericia's formula (QTcF) reported
	(QTcF) reported by the central	by the central service, a subject will be
	service, a subject will be excluded if	excluded if the corrections are $\geq$ 450
	the corrections are $\geq$ 450 msec in men	msec in men and $\geq$ 470 msec in women
	and $\geq$ 470 msec in women for 2 of the	for 2 of the 3 time points of the ECGs
	3 time points of the ECGs done.	done, unless due to ventricular pacing.

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Location	Old Text	Updated Text
Section 3.8.3 Individual Subject	<ul> <li>9) Subject from a non-institutionalized setting requires permanent placement to a nursing home or assisted living facility, or subject transfers from an institutionalized setting to a non-institutionalized setting. In case of a change in the non-institutionalized address, the investigator should consult with the medical monitor on a case-by-case basis. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and INC Research medical monitor.</li> <li></li> <li> In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at either the investigator's site or residential facility. If the institutionalized subject has left the residential facility where he or she participated in the trial, the subject should be seen at the investigator's site. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver</li> </ul>	<ul> <li>9) Subject transfers from an institutionalized setting, or vice versa. In case of a brief hospitalization, determination of subject eligibility to stay in the trial must be made based on subject safety by the investigator and medical monitor.</li> <li></li> <li> In addition, all subjects who withdraw prematurely from the trial will be assessed 30 (+2) days after the last dose of the IMP for evaluation of safety. This assessment can be accomplished at a clinic visit at either the investigator's site or residential facility, if applicable. If a clinic visit is not possible, the subject should be assessed by telephone contact with the subject and a caregiver</li> </ul>
Section 3.9 Screen Failures	If a subject fails to qualify for the trial during the 42-day screening period for a reason other than a positive screen for cocaine, marijuana, or other illicit drugs, the subject is permitted to be rescreened once at a later date. The medical monitor must be contacted before rescreening any subjects who initially failed screening due to a positive blood alcohol test or positive drug screens resulting from	If a subject fails to qualify for the trial during the 42-day screening period for a reason other than a positive screen for cocaine, marijuana, or other illicit drugs, the subject is permitted to be rescreened at a later date. A subject may be rescreened more than once after discussion with and approval by the medical monitor. The medical monitor must be contacted before rescreening any subjects who initially failed

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Location	Old Text	Undated Text
Loomin	use of prescription or OTC	screening due to a positive blood
	medications or products. In the event that the subject is rescreened for trial participation after the 42-day screening period expires, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.	alcohol test or positive drug screens resulting from use of prescription or OTC medications or products. In the event that the subject is rescreened for trial participation, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.
Table 4.1-1	1. Medications to treat Alzheimer's	1. Medications to treat Alzheimer's
List of Restricted and Prohibited Medications	disease (cholinesterase inhibitors, memantine, and/or other cognitive enhancers)	disease (cholinesterase inhibitors, memantine, and/or other cognitive enhancers)
	Allowed provided that the dose has been stable for 90 days prior to randomization	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.
	3. Antidepressants	3. Antidepressants
	Subject will remain on the same dose throughout the duration of the trial.	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition
	12. Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and antiplatelet agents	12. Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and anti- platelet agents
	Subject will remain on the same dose throughout the duration of the trial.	Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.
Section 6	Pharmacokinetic samples will be	Pharmacokinetic samples will be
Pharmacokinetic Analysis	analyzed for brexpiprazole (OPC- 34712) and its major metabolite, DM-3411, and descriptive statistics will be calculated.	analyzed for brexpiprazole (OPC- 34712) and its metabolite(s) and descriptive statistics will be calculated.
Section 7.1	The sample size was calculated based	The sample size was calculated based
Sample Size	on the treatment effect of 6.5 points	on the treatment effect of 6.5 points
	with a standard deviation of 16.5 in	with a standard deviation of 16.5 in the
	the change from baseline to the	change from baseline to the endpoint in
	endpoint in the CMAI total score, to	the CMAI total score, to achieve 85%
	achieve 80% power at a 2-sided alpha	power at a 2-sided alpha level of 0.05.
	level of 0.05. The resulting sample	I he resulting sample size is
	size is 105 subjects/arm. After	11 / subjects/arm. After allowance of 10% non-evaluable subjects, it results
	subjects it results in a sample size of	in a sample size of 130 subjects/arm
	115 subjects/arm, which means the	which means the total sample size is
	total sample size is 230 subjects.	260 subjects.

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Location	Old Text	Updated Text
Section 7.6.1 Adverse Events	The incidence of AEs of interest (e.g., falls, sedation, diabetes, weight changes, QTc prolongation, or deaths) will be summarized by treatment group.	(this text was deleted)
Appendix 1 Names of Sponsor Personnel	<ul> <li>(address change for all sponsor contacts)</li> <li>Otsuka Pharmaceutical Development &amp; Commercialization, Inc.</li> <li>1 University Square Drive, Suite 500</li> <li>Princeton, NJ 08540</li> </ul>	 (address change for all sponsor contacts) Otsuka Pharmaceutical Development & Commercialization, Inc. 508 Carnegie Center Princeton, NJ 08540

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Location	Old Text	Updated Text
	Primary Medical Contact:	Primary Medical Contact:
	PPD	PPD
	PPD	PPD
	PPD	PPD
	Clinical Contact:	Clinical Contact:
	PPD	PPD
	PPD	PPD
	Otsuka Pharmaceutical Development	PPD
	& Commercialization, Inc.	Otsuka Pharmaceutical Development &
	1 University Square Drive, Suite 500	Commercialization, Inc.
	Princeton, NJ 08540	2440 Research Blvd
	Phone: PPD	Rockville, MD 20850
	Mobile: PPD	Phone: PPD
		Fax: PPD
Appendix 2	United States PPD	United States PPD or
Institutions Concerned		PPD
With the Trial	United Kingdom PPD	
		United Kingdom PPD
	Slovenia PPD	
	Finland PPD	Slovenia PPD
		Finland PPD
		Bulgaria PPD
		Russia PPD
	Medical Monitors	Medical Monitors
	North America:	North America
	PPD	PPD
	PPD	PPD
	INC Research, LLC	INC Research, LLC
	3201 Beechleaf Court, Suite 600	3201 Beechleaf Court, Suite 600
	Raleigh, NC 27604 USA	Raleigh, NC 27604 USA
	Phone: PPD	Office: PPD
	Mobile: PPD	Mobile: PPD
		Fax: PPD
	Europe:	
	PPD	Europe:
	PPD	PPD
		PPD
	Plasma Sample Storage Facility	Plasma Sample Storage Facility
	FBS.customer.service@thermofisher.c	(email address was removed)
	om	
	Electronic Data Capture	Electronic Data Capture
	Medidata Solutions Worldwide	Medidata Solutions, Inc.
	79 Fifth Avenue, 8 <sup>th</sup> Floor	350 Hudson Street, 9 <sup>th</sup> Floor
	New York, NY 10003	New York, NY 10014
	USA	USA
	IVKS/IWKS	IVKS/IWRS
	S-Clinica Inc.	S-Clinica Inc.
	33 Wood Avenue South	41 University Drive
	Suite 600	Suite 400
	Iselin, NJ 08830	Newtown, PA 18940
	USA	USA

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Location	Old Text	Updated Text
	<u>eDiary</u>	(these vendors were removed)
	eResearch Technology	
	1818 Market Street, Suite 1000	
	Philadelphia, PA 19103	
	USA	
	Actigraphy	
	Clinilabs, Inc.	
	423 West 55th Street	
	New York, NY 10019	
	USA	
	Rater Surveillance	
	CROnos	
	1800 East State Street	
	Suite 144B	
	Hamilton, NJ 08609	
	USA	
Appendix 9	Appendix 9 Neuropsychiatric	Appendix 9 Neuropsychiatric
Neuropsychiatric	Inventory (NPI)	Assessment for Non-Institutionalized
Assessment for Non-		Patients Based on the NPI/NPI-NH
Institutionalized		
Patients Based on the		
NPI/NPI-NH		
Appendix 16	Actigraphy utilizes a portable device	(this appendix was removed)
Actigraphy	(actigraph) that records movement	
Description	with a piezoelectric accelerometer	
	over extended periods of time and is	
	worn most commonly on the	
	nondominant wrist. The actigraph	
	accelerometers samples physical	
	wrist movement. These data are	
	stored within the actigraph for up to	
	several weeks. The length of time the	
	actigraph is able to record data are	
	typically dependent on the actigraph's	
	epoch length (15 seconds, in this	
	study). The subject is advised to wear	
	the actigraph continuously, at all	
	times, including during sleep	
	beginning after the informed consent	
	is signed to Week 12/ET. If the	
	subject must remove the device for	
	any reason, the subject is instructed to	
	place it back on the wrist as soon as	
	possible. The device is able to detect	
	when it is not on the subject's wrist,	
	and it tracks the time that it is not	
	be downloaded from the dowice	
	verified and transferred to Clinilaba'	
	core laboratory at each study visit	
	core laboratory at each study visit	

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	(except the Day 3 visit) by attaching	•
	it to a docking station connected to a	
	computer that allows communication	
	with the software program on the	
	computer. A computer program	
	summarizes these data and can display	
	and print a histogram (called an	
	actogram), which shows the subject's	
	activity levels for each epoch over	
	successive 24-hour periods. The	
	computer program provides validated	
	algorithms that summarize activity	
	data. The data are then reviewed for	
	active periods and rest periods.	
	In addition, activity will be analyzed	
	over each 24-hour period ("Daily"	
	intervals) for maximum, total and	
	average activity levels to understand	
	the amount of day time movement	
	from the subject and to evaluate	
	restlessness, agitation, and increased	
	random movements like those seen in	
	akathisia. Raw activity data will also	
	be generated that allows the total	
	number of epochs with zero activity	
	counts to be calculated during baseline	
	and treatment period for both groups	
	over each 24-hour period. In addition,	
	for non-zero epochs, the mean activity	
	can be calculated over each 24-hour	
	period.	
	To contract the dimensional estimites	
	To evaluate the diurnal activity	
	hour blocks at 8.00 are 12.00 rm	
	hour blocks at $8:00 \text{ am}$ , $12:00 \text{ pm}$ , $4:00 \text{ pm}$ and $8:00 \text{ pm}$ will be	
	4:00 pm, and 8:00 pm will be	
	provided. This will provide for the	
	possibility of measuring time of day	
	Since actionary vill be collected	
	twenty four hours per day for	
	extended periods of time sleep	
	narameters will be evaluated as a	
	continuous evaluation of these	
	multiple day indices Sleep-wake	
	natterns are estimated from periods of	
	activity and inactivity based on this	
	movement during the rest period.	
	Actigraphy is based on the principle	
	that there is reduced movement during	
	sleep and increased movement during	
	wake. The computer programs can	

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Location	Old Text	Updated Text
	estimate sleep and wake based upon computer algorithm-defined thresholds of activity. Thus, the estimated sleep-wake parameters such as sleep latency, total sleep time, number and frequency of awakenings, sleep efficiency can be derived. Circadian rhythm parameters, such as the amplitude (peak-to-nadir difference) or acrophase (time of peak activity), can also be typically obtained.	
	Source: Littner M, Kushida C, Anderson WM, Bailey D, Berry RB, Davila DG, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep. 2003;26(3): 337-41.	
Appendix 17 Electronic Diary (eDiary)	Once caregivers and/or facility staff log in, they will be prompted to select from the 29 behaviors listed in the CMAI: 1) –Biting 2) –Grabbing onto people or things inappropriately 3) –Hitting (including self) 4) –Hurting self or other 5) –Kicking 6) –Making physical sexual advances or exposing genitals 7) –Pushing 8) –Scratching 9) –Spitting (including while feeding) 10) –Tearing things or destroying property 11) –Throwing things 12) –Eating or drinking inappropriate substances 13) –General restlessness 14) –Handling things inappropriately (e.g., playing with food, fecal smearing) 15) –Hiding things 16) –Hoarding things 17) –Inappropriate dressing or disrobing 18) –Intentional falling 19) –Pacing and aimless wandering 20) –Performing repetitious mannerisms	(this appendix was removed)

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# **ADDITIONAL RISK TO THE SUBJECT:**

There is no additional risk to the subjects.

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#### 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 Research Agreement.

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

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

I agree to await IRB/IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.

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

Principal or Coordinating Investigator Signature and Date

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# Otsuka Pharmaceutical Development & Commercialization, Inc.

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**OPC-34712** 

**SIGNATURE PAGE** 

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