- **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**
- **Date of the document: 10 September 2015**
- **NCT number: NCT01922258**

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

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850, United States
Sponsor Representatives:	
Director, Global Clinical Development	PPD Phone: PPD Fax: PPD E-mail: PPD PPD Phone: PPD Fax: PPD E-mail: PPD
Director, Clinical Management	PPD Phone: PPD Fax: PPD E-mail: PPD
Associate Director, Clinical Management	PPD Phone: PPD Fax: PPD E-mail: PPD
Immediately Reportable Event:	INC Research (see Appendix 2)

Protocol 331-12-284

Issue Dates:

Original Protocol:	06 May 2013
Date of Amendment 1:	16 Dec 2013
Date of Amendment 2:	07 Jul 2014
Date of Amendment 3:	10 Sep 2015

Protocol 331-12-284

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, 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
Clinical Phase:	3
Treatment Indication:	Agitation associated with dementia of the Alzheimer's type
Objective(s):	*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 Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment. *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.
Trial Design:	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 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. CCI [redacted]

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.

The trial is organized as follows:

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.

The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. Determinations by the investigator of the capacity of 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.

CCI [redacted]

An interactive voice response system (IVRS) or 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. 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.

CCI [redacted]

CCI [redacted]

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:

Dosing Scheme				
	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[a]	2 mg/day[b]
Placebo	<----------			---------->

[a] 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).

[b] 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.

	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]). 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). 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. 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). 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 Treatment Period). 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 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 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. *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. CCI [redacted] 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

	total score (frequency x severity) of ≥ 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

	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 [redacted]
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.

	• 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.

Protocol 331-12-284

Criteria for Evaluation:	*Primary Efficacy Variable*: The primary efficacy variable is the change from baseline to Week 12/ET in the CMAI total score. *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. CCI [redacted] CCI [redacted]

	• CCI [redacted] *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 CCI [redacted] 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. CCI [redacted]
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 and include the interaction term of baseline by visit week as a covariate. 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. CCI [redacted] The alpha used in the analysis of the 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. 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. CCI [redacted]
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. CCI [redacted]

Protocol 331-12-284

Table of Contents

Protocol 331-12-284

Protocol 331-12-284

Protocol 331-12-284

List of In-text Tables

List of In-text Figures

Protocol 331-12-284

List of Appendices

Protocol 331-12-284

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-HT_{1A}	Serotonin type 1A receptor
5-HT_{2A}	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 [redacted]	[redacted]
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)
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
CCI [redacted]	[redacted]
BMI	Body mass index
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
CAARS-O:SV	Conners' Adult ADHD Rating Scale-Observer: Screening Version
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
CGI-S	Clinical Global Impression-Severity of Illness scale
CHO-K1	Chinese hamster ovary cells
CMAI	Cohen-Mansfield Agitation Inventory
CMH	Cochran-Mantel-Haenszel
C_{max}	Maximum (peak) plasma concentration
CNS	Central nervous system
CPK	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

Abbreviation	Definition
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_{1c}	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_2EDTA	Potassium ethylenediaminetetraacetic acid
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LOCF	Last-observation-carried-forward

Abbreviation	Definition
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 [redacted]	[redacted]
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 [redacted]	[redacted]
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 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 [redacted]	[redacted]
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
RBC	Red blood cell
CCI [redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SD	Standard deviation
CCI [redacted]	[redacted]

Abbreviation	**Definition**
T_4	Thyroxine
TEAE	Treatment-emergent adverse event
t_{max}	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

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

Protocol 331-12-284

1. Introduction

Dementia is a term that describes disorders that cause cognitive decline. The most common type of dementia is Alzheimer's disease.[1] 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.[1] In the United States, among adults older than age 65, prevalence estimates of dementia range from 5% to 15%, with Alzheimer's disease being the most common type of dementia.[2,3,4] 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.[5]

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.[5] These neuropsychiatric symptoms contribute to subject and caregiver distress[6] and increased healthcare costs[7] and even may lead to institutionalization.[8]

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.[9] 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.[10,11] 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[11]

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 ($5\text{-}HT_{1A}$) receptors and an antagonist at serotonin type 2A ($5\text{-}HT_{2A}$) 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,[12,13,14,15] brexpiprazole may have the potential to exhibit improved safety compared with other agents. The more potent antagonism at $5\text{-}HT_{2A}$ 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_1-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).[16]

Protocol 331-12-284

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.[16]

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^{2+}) 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_{2A} receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT_{2A} 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_{1A} 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

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 1.17×10^{-7} mol/L. The mechanism for the blood pressure decreasing effect of brexpiprazole was suggested to result from a blockade of the α_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

t (AUC_t), 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 ^{14}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 (≥ 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.

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.[16]

Protocol 331-12-284

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 ± 0.25 mg/day, 1.5 ± 0.50 mg/day, or matching placebo. In this trial, adjunctive brexpiprazole dosed at 1.5 ± 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 ± 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 (≥ 50% decrease MADRS Total Score) and remission rate (MADRS Total Score ≤ 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

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 compared with 9.6% of subjects in the placebo 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®)-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 tolerability of multiple ascending oral doses of brexpiprazole as adjunctive therapy in the treatment of elderly subjects (70 to 85 years) with MDD.

Protocol 331-12-284

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 ± 0.5 mg/day and 5.0 ± 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 ≥ 30% from baseline in PANSS total score or CGI-I score of 1 [very much improved] or 2 [much

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%])

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,[16] 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 ≥ 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 ≥ 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

- 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 ± 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.[16]

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. CCI [redacted]

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

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.[17,18,19] However, the occupancy associated with effective doses of another partial dopamine agonist, aripiprazole, are greater than 80%[20,21] 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.

CCI [redacted]

CCI [redacted] 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®), have been conducted to investigate its benefit in the treatment of psychosis in subjects with Alzheimer's dementia.[21,22,23] 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.[21,22,24] 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.

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. CCI [redacted]

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

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.

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

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 CCI [redacted] on a routine basis in order to corroborate information recorded on the CMAI. Since the diary data is a tool to assist CCI [redacted] 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

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. CCI [redacted]

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.

Protocol 331-12-284

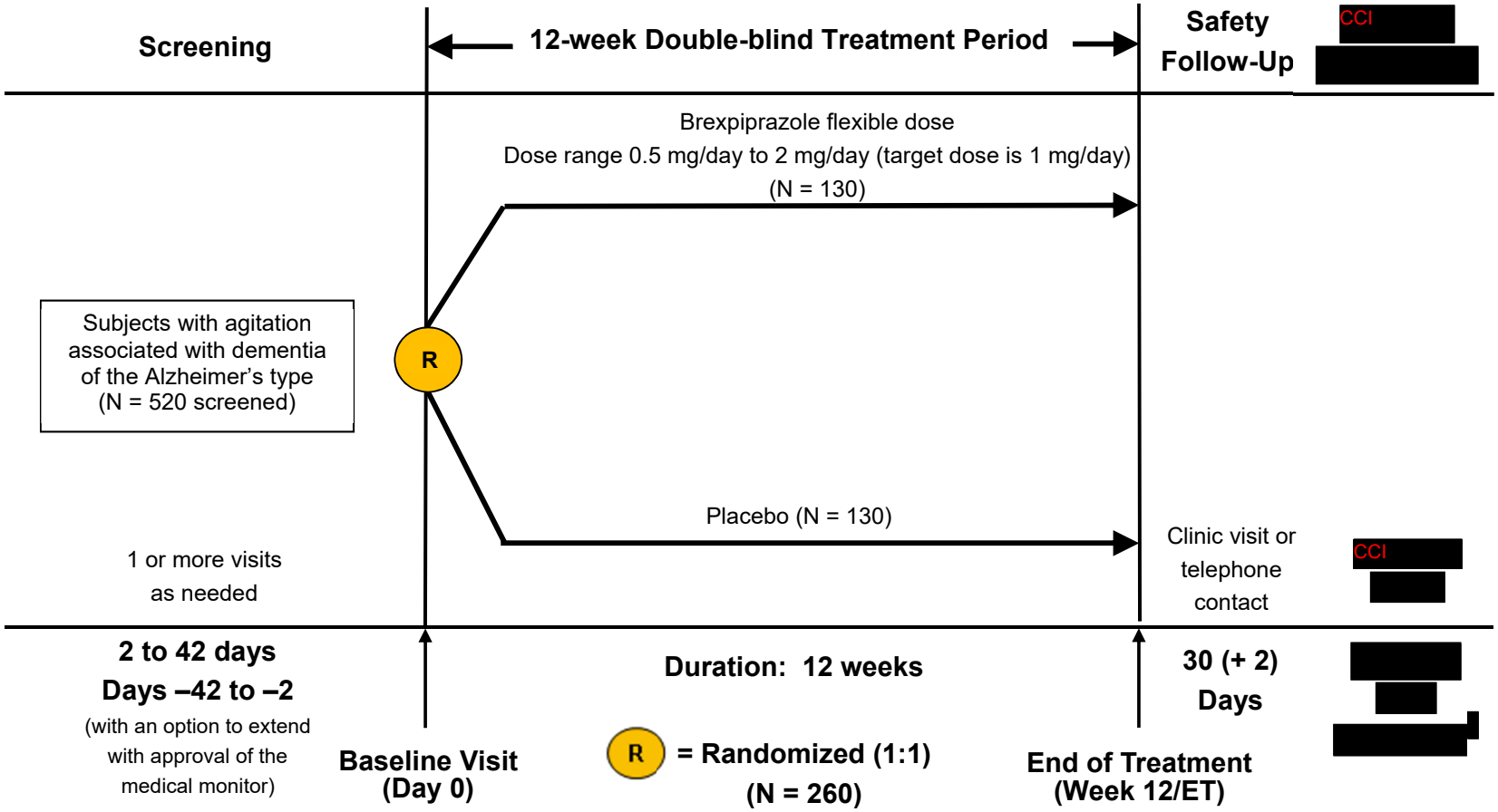


Figure 3.1-1 Trial Design Schematic

CCI

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 Scheme

Treatment Group	Recommended Daily Dose Administered			
	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[a]	2 mg/day[b]
Placebo	<----------			---------->

[a] 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).

[b] 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]).

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).

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.

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).

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

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 ≥ 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.

CCI [redacted]

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

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.

Protocol 331-12-284

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[25] 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 subject understand and freely have 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

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.

CCI [redacted]

Protocol 331-12-284

3.4.2. Inclusion Criteria

Subjects are required to meet the following inclusion criteria:

Table 3.4.2-1 Inclusion Criteria

1.	The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the trial. Once this determination is made by the investigator, the options for obtaining informed consent from 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 ≥ 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.

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.

Protocol 331-12-284

3.4.3. Exclusion Criteria

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

Table 3.4.3-1 Exclusion Criteria	
Target Disease	
1.	Subjects with dementia or other memory impairment not due to Alzheimer's disease, such as mixed or vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, frontotemporal dementia, substance-induced dementia, HIV-dementia, traumatic brain injury, normal pressure hydrocephalus, or any other specific non-Alzheimer's-type dementia; subjects with a diagnosis of Down syndrome.
2.	Subjects with a previous MRI or CT scan of the brain, which was performed after the onset of 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.
Medical 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.

Table 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 ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure, OR development of symptoms. Abnormal vital signs results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.
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_4 at screening. Eligibility of subjects excluded based on an abnormal free T_4 result can be discussed with the medical monitor if, in the investigator's judgment, the subject is a suitable candidate for the trial.
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 kg/m^2.
16.	Subjects who have met *Diagnostic and Statistical Manual of Mental Disorders*, 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.
Physical 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.

Table 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 ≤ 75,000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 • Aspartate transaminase (AST) > 2 x 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_{1c} ≥ 8% • Abnormal T_4, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if the result for thyroid-stimulating hormone [TSH] is abnormal.) • QTcF ≥ 450 msec in men and ≥ 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 and 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.
Prohibited 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®).
Allergies 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.

Table 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_{1c} = 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_4 = 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.

Protocol 331-12-284

3.5.3. CCI [redacted]

[redacted]

3.5.4. CCI [redacted]

[redacted]

3.5.5. CCI [redacted]

[redacted]

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, CCI [redacted]

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_{1c}), 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

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. CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

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.

Table 3.7-1 Schedule of Assessments

Assessment	Visit										
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	FU[c]	[redacted]
ENTRANCE/HISTORY											
Informed consent[e]	X										
Inclusion/exclusion criteria[f]	X	X									
Demography	X										
Medical history	X										
Psychiatric history	X										
Neurological history[g]	X										
Prior medication washout[h]	X										
NINCDS-ADRDA	X										
Hachinski Ischemic Scale (Rosen Modification)[g]	X										
HBsAg and anti-HCV	X										
[redacted]	[redacted]										
EFFICACY											
CMAI	X	X		X	X	X	X	X	X		
CGI-S[j]	X	X		X	X	X	X	X	X		
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]				X	X	X	X	X	X		
NPI-NH (for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects)	X	X		X	X	X	X	X	X		

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments

Assessment	Visit										
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	FU[c]	[redacted]
OTHER											
CCI [redacted]		[redacted]							[redacted]		
[redacted]		[redacted]							[redacted]		
[redacted]		[redacted]							[redacted]		
[redacted]		[redacted]							[redacted]		
SAFETY											
Physical examination[k]	X								X		
Neurological examination[l]	X								X		
Vital signs[m]	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[n]	X	X[o]			X[p]		X[p]		X		
Prolactin (blinded)[n]	X								X		
TSH with reflex to free T_4 if abnormal[n]	X								X		
HbA_{1c}[n]	X								X		
PT, aPTT, and INR[n]	X								X		
ACTH and cortisol[n]	X								X		
Urine pregnancy test (women of childbearing potential) only[q]	X								X		
ECG[r]	X	X			X		X		X		
Blood alcohol[s,t]	X										
Urine drug screen[s,t]	X										
MMSE	X	X							X		
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments

Assessment	Visit										
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	FU[c]	[redacted]
[redacted]											
[redacted]											
[redacted]											
Adverse events[v]	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic sampling[w]		X					X		X		
[redacted]											
Concomitant medications[y]	X	X	X	X	X	X	X	X	X	X	
[redacted]											
OTHER PROCEDURES											
Register trial visit in IVRS/IWRS	X	X	X	X	X	X	X	X	X		
Randomize eligible subjects via IVRS/IWRS		X									
IMP dispensing[aa]		X	X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X	X		
Telephone contact[bb]											
ADDITIONAL ENTRANCE/HISTORY											
MRI/CT scan[cc]	X[cc]										

ACTH = adrenocorticotropic hormone; AIMS = Abnormal Involuntary Movement Scale; anti-HCV = hepatitis C antibodies; aPTT = activated partial thromboplastin time [redacted]; CGI-S = Clinical Global Impression-Severity of Illness; CMAI = Cohen-Mansfield Agitation Inventory; [redacted] CT = computed tomography; ECG = electrocardiogram; ET = early termination; FU = follow up; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; IAP = Independent Adjudication Panel; ICF = informed consent form; IMP = investigational medicinal product; INR = International Normalized Ratio; IVRS = interactive voice response system; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; [redacted]; MRI = magnetic resonance imaging; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; [redacted]; NPI-NH = Neuropsychiatric Inventory-Nursing Home rating scale; NPI/NPI-NH = Neuropsychiatric Assessment for Non-Institutionalized Patients based on the NPI/NPI-NH; PT = prothrombin time; [redacted]

CCI ; CCI ; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] 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.

[b] 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.

[c] 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.

[d] CCI

[e] 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.

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

[g] 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.

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

[i] CCI

[j] CCI CGI-S, CCI are based on agitation.

[k] Physical examination includes measurement of height and waist circumference at screening and waist circumference at Week 12/ET.

[l] 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.

[m] 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.

[n] 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.

[o] 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.

[p] Urinalysis is not required at Week 4 or Week 8.

[q] 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.

[r] 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.

[s] 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.

[t] 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.

[u] CCI [redacted]

[v] Adverse events will be recorded, starting after the ICF has been signed.

[w] 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.

[x] CCI [redacted]

[y] 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.

[z] CCI [redacted]

[aa] Subjects will start taking IMP from the new blister card the day after the clinic visit.

[bb] 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.

[cc] 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 [redacted] in order to confirm eligibility.

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 CCI [redacted] 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.

- 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_{1c}, ACTH, cortisol, and TSH with reflex to free T_4 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.
- CCI [redacted]
- AEs will be recorded, beginning with the signing of the ICF.
- Concomitant medications will be recorded.
- CCI [redacted]
- 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 [redacted]
- 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.
- CCI [redacted]

- CCI [redacted]
- An adequately trained and experienced clinician will administer the MMSE.
- CCI [redacted]
- 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.
- CCI [redacted]
- AEs and concomitant medications will be recorded.

- 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.

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 ± 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 [redacted] 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.
- CCI [redacted]
- 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:

- CCI [redacted]
- 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.

- 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.
- CCI [redacted]
- 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 (± 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 [redacted]
- CCI [redacted]
- CCI [redacted]

Protocol 331-12-284

- CCI [redacted]
- An adequately trained and experienced clinician will administer the MMSE.
- CCI [redacted]
- CCI [redacted]
- 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_{1c}, ACTH, cortisol, and TSH with reflex to free T_4 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.
- CCI [redacted]
- 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.

- 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.

CCI [redacted]

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 [redacted] CCI [redacted] 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

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. CCI [redacted] The CMAI was developed to assess the frequency of agitated behaviors in elderly persons and was originally used in nursing home residents. It consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation.[11] As initially described by Cohen-Mansfield[11] and outlined in the Instruction Manual for the CMAI,[26] 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.[27] To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the subject at this time?" Response choices are 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects. A sample of the CGI-S is provided in Appendix 7.

3.7.2.3. CCI [redacted]

Protocol 331-12-284

3.7.2.4. CCI

[redacted]

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.[28,29] 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.[29] 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.[30]

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.[31] The NPI/NPI-NH differs from the NPI-NH in that questions referring to "Occupational Disruptiveness" from the NPI-NH

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

3.7.3.1. CCI

[redacted]

Protocol 331-12-284

3.7.3.2. CCI

[redacted]

3.7.3.3. CCI

[redacted]

3.7.3.4. CCI

[redacted]

Protocol 331-12-284

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.[37] 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.[38] 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.

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 CCI [redacted] 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.

Table 3.7.4.2-1 Clinical Laboratory Assessments

Hematology	Serum Chemistry
WBC count with differential	ALP
RBC count	ALT (SGPT)
Hematocrit	AST (SGOT)
Hemoglobin	BUN
Platelet count	CPK
	Creatinine
Urinalysis	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 the urinalysis is not negative)	Insulin
	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
	Urine pregnancy (women of childbearing potential)[a]
Other	
Blood alcohol	TSH, with reflex to free T_4 if TSH is abnormal
	PT, aPTT, and INR
Additional Tests (Screening Only)	ACTH
HBsAg	Cortisol
Anti-HCV	HbA_{1c}
Urine albumin (only for subjects with IDDM)	
Urine creatinine (only for subjects with IDDM)	

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_{1c} = 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_4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

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

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 ≤ 75,000/mm^3
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/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_{1c} ≥ 8%
- Abnormal free thyroxine (T_4), unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if the result for 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.

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.[39]

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.

Protocol 331-12-284

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 ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP within 3 minutes of standing compared to the previous supine blood pressure or development of symptoms (see Table 3.7-1). In addition, subjects should be excluded if they have any other vital sign measurement at screening 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.

Protocol 331-12-284

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.

Protocol 331-12-284

3.7.4.5. CCI

[redacted]

3.7.4.5.1. CCI

[redacted]

3.7.4.5.2. CCI

[redacted]

Protocol 331-12-284

CCI

3.7.4.5.3. CCI

3.7.4.5.4. CCI

Protocol 331-12-284

CCI [redacted]

3.7.4.5.5. Mini-Mental State Examination (MMSE)

The MMSE[43] 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.

3.7.6. CCI [redacted]

Protocol 331-12-284

CCI

[redacted]

3.7.6.1. CCI [redacted]

[redacted]

Protocol 331-12-284

3.7.6.2. CCI

[redacted]

3.7.7. End of Trial

The end-of-trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up 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

3.7.9. CCI

[redacted]

Protocol 331-12-284

CCI

[redacted]

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

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.

CCI [redacted]

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. CCI [redacted] 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 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 followed for non-institutionalized subjects who are lost to follow-up.

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.

Protocol 331-12-284

Table 4.1-1 List of Restricted and Prohibited Medications

All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.

	Medication	Prior to Randomization	During Double-Blind Treatment Period
1.	Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, 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)[a,b]	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

Table 4.1-1 List of Restricted and Prohibited Medications

All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.

	Medication	Prior to Randomization	During Double-Blind Treatment Period
7.	Nonbenzodiazepine sleep agents[c]	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[d]	7-day washout	Prohibited
10.	Propranolol[e]	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.

Protocol 331-12-284

Table 4.1-1 List of Restricted and Prohibited Medications			
All other psychotropic agents not listed in the below table are prohibited and must be discontinued at least 24 hours before the first dose of IMP.			
	Medication	**Prior to Randomization**	**During Double-Blind Treatment Period**
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

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

[b] 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.

[c] 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 is not feasible, the 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.

[d] Anticholinergic treatment of extrapyramidal symptoms (eg, benztropine) is not permitted within the 7 days prior to randomization and for the duration of the trial.

[e] 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.

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

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

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

[a]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.

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

4.2. Other Restrictions

The following restrictions apply:

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

- The investigator may request a blood or urine drug screen 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 immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
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.

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.)

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 ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 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

- 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.

5.7.4. CCI

[redacted]

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). CCI

[redacted]

Protocol 331-12-284

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

CCI

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.

CCI [redacted]

The primary analysis CCI [redacted] 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.

Protocol 331-12-284

7.4.3. CCI

[redacted]

7.4.4. CCI

[redacted]

7.4.5. CCI

[redacted]

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.

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, CCI [redacted] 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_{1c}, 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.

Protocol 331-12-284

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: $QTcF=QT/(RR)^{0.33}$
3) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

Results will be summarized by visit.

7.6.5. CCI

[redacted]

7.7. CCI

[redacted]

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.

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 PPD

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.

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, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

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.

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

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.

14. References

1 Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, et al. Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. JAMA. 1997;278(16):1363-71.

2 Kaplan HI, Sadock BJ. Synopsis of psychiatry. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 329.

3 Evans DA, Funkenstein H, Albert MS, Schen PA, Cook NR, Chown MJ, et al. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. JAMA. 1989;262(18):2551-6.

4 Losonczy KG, White LR, Brock DB. Prevalence and correlates of dementia: survey of the last days of life. Public Health Rep. 1998;113(3):273-80.

5 Costa PT Jr, Williams TF, Somerfield M, et al. Clinical Practice Guideline Number 19: Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias. Rockville, MD: US Dept Health Human Services, Agency for Health Care Policy and Research; 1996. AHCRP publication 97-0702.

6 Schultz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. Gerontologist. 1995;35(6):771-91.

7 CCI [redacted]

8 Stern Y, Tang M-X, Albert MS, Brandt J, Jacobs DM, Bell K, et al. Predicting time to nursing home care and death in individuals with Alzheimer's disease. JAMA. 1997;277(10):806-12.

9 Risperdal (risperidone) [Summary of Product Characteristics, Labeling, and Package Leaflet]. European Medicines Agency.

10 Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly, I: a conceptual review. J Am Geriatr Soc. 1986;34(10):711-21.

11 Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. J Gerontol. 1989;44(3):M77-84.

12 Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment - pharmacological mechanisms. Pharmacol Ther. 2010;125(1):169-79.

13 Sharpley AL, Attenburrow ME, Hafizi S, Cowen PJ. Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients. J Clin Psychiatry. 2005;66(4):450-4.

14 Miller DD. Atypical antipsychotics: Sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry. 2004;6(Suppl 2):3-7.

15 Ohno Y. New insight into the therapeutic role of 5-HT1A receptors in central nervous system disorders. Cent Nerv Syst Agents Med Chem. 2010;10(2):148-57.

[16] Brexpiprazole (OPC-34712) Investigator's Brochure, Otsuka Pharmaceutical Development & Commercialization, Inc. Version No. 9, 09 Sep 2013.

[17] Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry. 1988;45(1):71-6.

[18] Nordström AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatr. 1993;33(4):227-35.

[19] Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatr. 2000;157(4):514-20.

[20] Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. Am J Psychiatry. 2007;164(9):1411-7.

[21] Yokoi F, Gründer G, Biziere K, Stephane M, Dogan AS, Dannals RF,et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [11C]raclopride. Neuropsychopharmacology. 2002;27:248-59.

[22] Mintzer JE, Tune LE, Breder CD, Swanink R, Marcus RN, McQuade RD, et al. Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. Am J Geriatr Psychiatry. 2007;15(11):918-31.

[23] Streim JE, Porsteinsson AP, Breder CD, Swanink R, Marcus R, McQuade R, et al. A randomized, double-blind, placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer disease. Am J Geriatr Psychiatry. 2008;16(7):537-50.

[24] De Deyn P, Jeste DV, Swanink R, Kostic D, Breder C. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease. J Clin Psychopharmacol. 2005;25:463-7.

[25] International Conference on Harmonisation (ICH) [homepage on the Internet]. E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2005 Dec 6]. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

[26] Instruction Manual for the Cohen Mansfield Agitation Inventory (CMAI). Rockville, MD. The Research Institute of the Hebrew Home of Greater Washington; 1991.

[27] Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

[28] Iverson GL, Hopp GA, DeWolfe K, Solomons K. Measuring change in psychiatric symptoms using the Neuropsychiatric Inventory: Nursing Home version. Int J Geriatr Psychiatry. 2002;17:438-43.

29 Cummings JL. Neuropsychiatric Inventory Nursing Home Version (NPI-NH): Comprehensive assessment of psychopathology in patients with dementia residing in nursing homes. 2009.

30 Lange RT, Hopp GA, Kang N. Psychometric properties and factor structure of the Neuropsychiatric Inventory Nursing Home version in an elderly neuropsychiatric population. Int J Geriatr Psychiatry. 2004;19:440-8.

31 Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology. 1997;48:S10-6.

32 CCI

33 CCI

34 CCI

35 CCI

36 Gustavsson A, Cattelin F, Jönsson L. Costs of care in a mild-to-moderate Alzheimer clinical trial sample: key resources and their determinants. Alzheimers Demen. 2011;7(4):466-73.

37 Knopman DS, DeKosky ST, Cummings JL, Chuit H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Neurology. 2001;56:1143-53.

38 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.

39 The Practical Guide: Identification, evaluation, and treatment of overweight and obesity in adults. Developed by National Institutes of Health National Heart, Lung and Blood Institute. North American Association for the Study of Obesity. NIH Publication Number 00-4084, October 2000.

40 CCI

41 CCI

42 CCI

[43] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

Protocol 331-12-284

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

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

Compound Director

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

Clinical Contact

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

Protocol 331-12-284

Appendix 2 Institutions 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

Protocol 331-12-284

Europe:
PPD

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

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

Central Laboratory
Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
USA

Bioanalytical Laboratory
Covance Laboratories
3301 Kinsman Boulevard
Madison, WI 53704
USA

CCI

CCI

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

Protocol 331-12-284

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

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

Central IRB
PPD

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

Protocol 331-12-284

Appendix 3 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

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

ULN = upper limit of normal

Protocol 331-12-284

Appendix 4 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic blood pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic blood pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic hypotension	≥ 20 mmHg decrease in systolic blood pressure and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not applicable (baseline status not considered)
Weight	–	≥ 7% increase ≥ 7% decrease

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

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

Protocol 331-12-284

Appendix 5 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

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

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

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

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

Protocol 331-12-284

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:

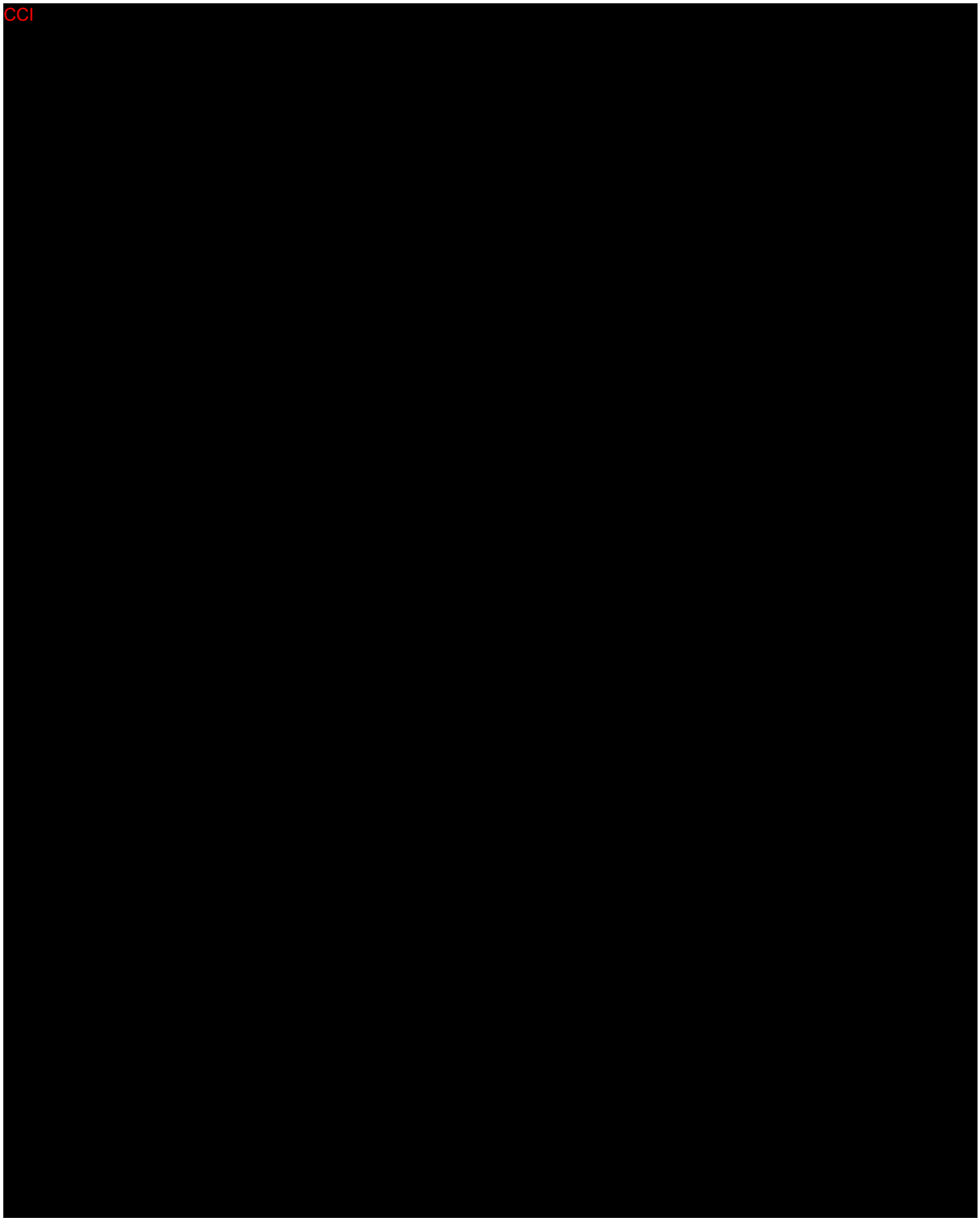
	Never 1	Less than once a week 2	Once or twice a week 3	Several times a week 4	Once or twice a day 5	Several times a day 6	Several times an hour 7
1. Pace, aimless wandering	1	2	3	4	5	6	7
2. Inappropriate dress or disrobing	1	2	3	4	5	6	7
3. Spitting (include at meals)	1	2	3	4	5	6	7
4. Cursing or verbal aggression	1	2	3	4	5	6	7
5. Constant unwarranted request for attention or help	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

22

	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
16. Trying to get to a different place (e.g., out of the room, building)	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

23

Protocol 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

Protocol 331-12-284

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

Protocol 331-12-284

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 trying to harm him/her or steal from him/her. Has he/she said that family members or staff are not who they say they are or that his/her spouse is having an affair? Has the resident had any other unusual beliefs?

☐ 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/her is in danger – that others are planning to hurt him/her or have been hurting him/her?	☐ Yes	☐ No
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 say they are?	☐ 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
6. Does he/she believe any other unusual things that I haven't asked about?	☐ Yes	☐ 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 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 amount of unusual or strange behavior.

Occupational 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)

8

Protocol 331-12-284

B. HALLUCINAIONS **(NA)**

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)
☐ No (if no, please proceed to next screening question) ☐ N/A

1. Does the resident act as if he/she hears voices or describe hearing voices?	☐ Yes	☐ No
2. Does the resident talk to people who are not there?	☐ Yes	☐ No
3. Does the resident see things that are not present or act like he/she sees things that are not present (people, animals, lights, etc)?	☐ Yes	☐ No
4. Does the resident smell things that others cannot smell?	☐ Yes	☐ No
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).

Occupational 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)

9

Protocol 331-12-284

C. AGITATION/AGGRESSION **(NA)**

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

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?	☐ Yes	☐ No

Comments: _____

_____

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 – 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 by the caregiver.
☐ 2. Moderate – 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.

Occupational 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)

10

Protocol 331-12-284

D. DEPRESSION/DYSPHORIA **(NA)**

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

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

1. Does the resident cry at 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 like a failure?	☐ Yes	☐ No
4. Does the resident say that he/she is a bad person or deserves to be punished?	☐ Yes	☐ No
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 about killing him/herself?	☐ Yes	☐ No
8. Does the resident show any other signs of depression or sadness?	☐ Yes	☐ No

Comments: _____

_____

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.

Occupational 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)

11

Protocol 331-12-284

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 for no apparent reason other than being nervous?	☐ Yes	☐ No
4. 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)	☐ Yes	☐ No
5. Does the resident avoid certain places or situations that make him/her more nervous such as 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.

Occupational 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)

12

Protocol 331-12-284

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) ☐ N/A

1. Does the resident appear to feel too good or to be too happy?	☐ Yes	☐ No
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 inappropriately (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
5. Does the resident show any other signs of feeling too good or being too happy?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

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 – 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.

Occupational 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)

13

Protocol 331-12-284

G. APATHY/INDIFFERENCE **(NA)**

Does the resident sit quietly without paying attention to things going on around 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 group activities.

☐ 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 around him/her?	☐ Yes	☐ No
2. Does the resident fail to start conversation? (score only if conversation is possible)	☐ 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 around him/her?	☐ Yes	☐ No
7. Does the resident show any other signs that he/she doesn't care about doing new things?	☐ Yes	☐ No

Comments: _____

_____

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

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 change in their behavior or participation in activities.
☐ 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.

Occupational 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)

14

Protocol 331-12-284

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 resident act impulsively without thinking of the consequences?	☐ Yes	☐ No
2. Does the resident talk to total strangers as if he/she knew them?	☐ Yes	☐ No
3. Does the resident say things to people that are insensitive or hurt their feelings?	☐ Yes	☐ No
4. Does the resident say crude things or make inappropriate sexual remarks?	☐ Yes	☐ No
5. Does the resident talk openly about very personal or private matters not usually discussed in public?	☐ Yes	☐ No
6. Does the resident fondle, touch or hug others in way that is not appropriate?	☐ Yes	☐ No
7. Does the resident show any other signs of loss of control of his/her impulses?	☐ Yes	☐ No

Comments: _____

_____

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.

Occupational 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)

15

Protocol 331-12-284

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) ☐ N/A

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 anger?	☐ 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. 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 /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.

Occupational 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)

16

Protocol 331-12-284

J. ABERRANT MOTOR BEHAVIOR **(NA)**

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) ☐ N/A

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.

Occupational 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)

17

Protocol 331-12-284

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 up once or twice per night only 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?

☐ 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
6. Does the resident have any other nighttime behaviors that we haven't talked about?	☐ Yes	☐ No

Comments: _____

_____

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.

Occupational 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)

18

Protocol 331-12-284

L. APPETITE AND EATING CHANGES **(NA)**

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 (if no, please proceed to next screening question) ☐ N/A

1. Does he/she have a poor appetite?	☐ Yes	☐ No
2. Does he/she have an unusually good appetite?	☐ Yes	☐ No
3. Has he/she lost weight?	☐ Yes	☐ No
4. Has he/she gained weight?	☐ Yes	☐ No
5. Does he/she have unusual eating behavior such as putting too much food in his/her mouth at 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?	☐ Yes	☐ No

Comments: _____

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

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 – 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.

Occupational 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)

(06/01/09: JLC)

19

Protocol 331-12-284

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 people are trying to harm him/her or steal from him/her. Has he/she said that family members or staff are not who they say they are or that his/her spouse is having an affair? Has the resident had any other unusual beliefs?

☐ 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?	☐ Yes	☐ No
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 say they are?	☐ 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
6. Does he/she believe any other unusual things that I haven't asked about?	☐ Yes	☐ 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 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 amount of unusual or strange behavior.

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

B. HALLUCINATIONS **(NA)**

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)

☐ No (If no, please proceed to next screening question) ☐ N/A

1. Does the resident act as if he/she hears voices or describe hearing voices?	☐ Yes	☐ No
2. Does the resident talk to people who are not there?	☐ Yes	☐ No
3. Does the resident see things that are not present or act like he/she sees things that are not present (people, animals, lights, etc)?	☐ Yes	☐ No
4. Does the resident smell things that others cannot smell?	☐ Yes	☐ No
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. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

☐ 4. Severely

☐ 5. Very severely or extremely

C. AGITATION/AGGRESSION (NA)

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

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? ☐ Yes ☐ No

Comments:_____

_____

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 – 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 by the caregiver.

☐ 2. Moderate – 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?

☐ 0. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

☐ 4. Severely

☐ 5. Very severely or extremely

D. DEPRESSION/DYSPHORIA (NA)

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

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

1. Does the resident cry at 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 like a failure? ☐ Yes ☐ No
4. Does the resident say that he/she is a bad person or deserves to be punished? ☐ Yes ☐ No

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 about killing him/herself? ☐ Yes ☐ No

8. Does the resident show any other signs of depression or sadness? ☐ Yes ☐ No

Comments:_____

_____

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. Not at all

☐ 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 re sident 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 for no apparent reason other than being nervous? ☐ Yes ☐ No

4. 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) ☐ Yes ☐ No

5. Does the resident avoid certain places or situations that make him/her more nervous such as

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) ☐ N/A

1. Does the resident appear to feel too good or to be too happy? ☐ Yes ☐ No

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 inappropriately (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

5. Does the resident show any other signs of feeling too good or being too happy? ☐ Yes ☐ No

Comments:_____

_____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

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 – 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. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

☐ 4. Severely

☐ 5. Very severely or extremely

G. APATHY/INDIFFERENCE (NA)

Does the resident sit quietly without paying attention to things going on around 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 group activities?

☐ 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 around him/her?	☐ Yes	☐ No
2. Does the resident fail to start conversation? (score only if conversation is possible)	☐ 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 around him/her?	☐ Yes	☐ No
7. Does the resident show any other signs that he/she doesn't care about doing new things?	☐ Yes	☐ No

Comments:_____

_____

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

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 causes little change in their behavior or participation in activities.

☐ 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. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

☐ 4. Severely

☐ 5. Very severely or extremely

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 resident act impulsively without thinking of the consequences?	☐ Yes	☐ No
2. Does the resident talk to total strangers as if he/she knew them?	☐ Yes	☐ No
3. Does the resident say things to people that are insensitive or hurt their feelings?	☐ Yes	☐ No
4. Does the resident say crude things or make inappropriate sexual remarks?	☐ Yes	☐ No
5. Does the resident talk openly about very personal or private matters not usually discussed in public?	☐ Yes	☐ No
6. Does the resident fondle, touch or hug others in way that is not appropriate?	☐ Yes	☐ No
7. Does the resident show any other signs of loss of control of his/her impulses?	☐ Yes	☐ No

Comments:_____

_____

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.

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

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) ☐ N/A

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 anger?	☐ 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?	☐ Yes	☐ No

Comments:_____

_____

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. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

☐ 4. Severely

☐ 5. Very severely or extremely

J. ABERRANT MOTOR BEHAVIOR **(NA)**

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) ☐ N/A

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. Not at all

☐ 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 only 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?

☐ 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
6. Does the resident have any other nighttime behaviors that we haven't talked about?	☐ Yes	☐ No

Comments:_____

_____

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 (NA)

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

1. Does he/she have a poor appetite?	☐ Yes	☐ No
2. Does he/she have an unusually good appetite?	☐ Yes	☐ No
3. Has he/she lost weight?	☐ Yes	☐ No
4. Has he/she gained weight?	☐ Yes	☐ No
5. Does he/she have unusual eating behavior such as putting too much food in his/her mouth at		

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?	☐ Yes	☐ No

Comments:_____

_____

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

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 – 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.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all

☐ 1. Minimally

☐ 2. Mildly

☐ 3. Moderately

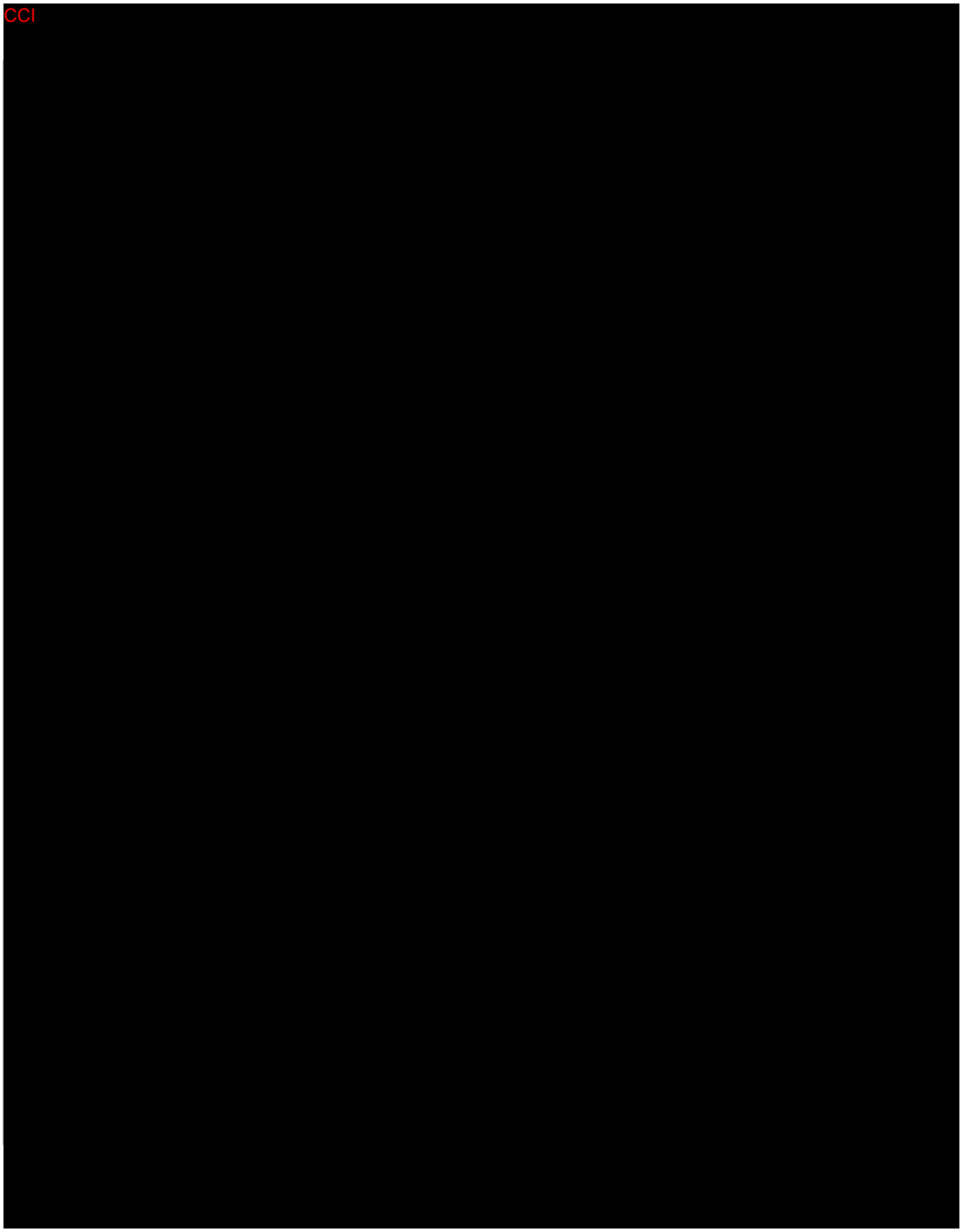
☐ 4. Severely

☐ 5. Very severely or extremely

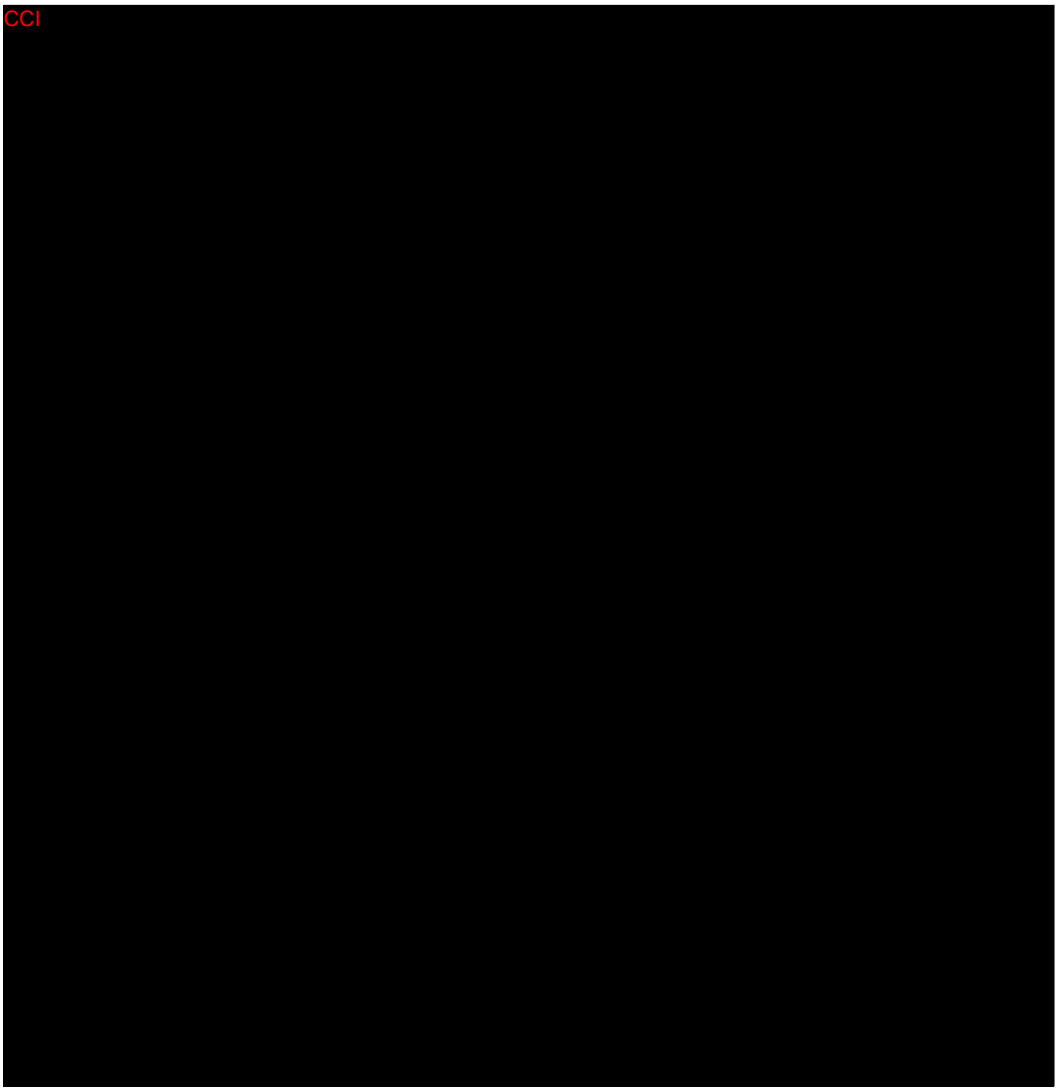
Completed by:	Signature
	Printed Name

NPI-NH - United States/English - Mapi.
ID8281 / NPI-NH_TS2.0_eng-USori.doc

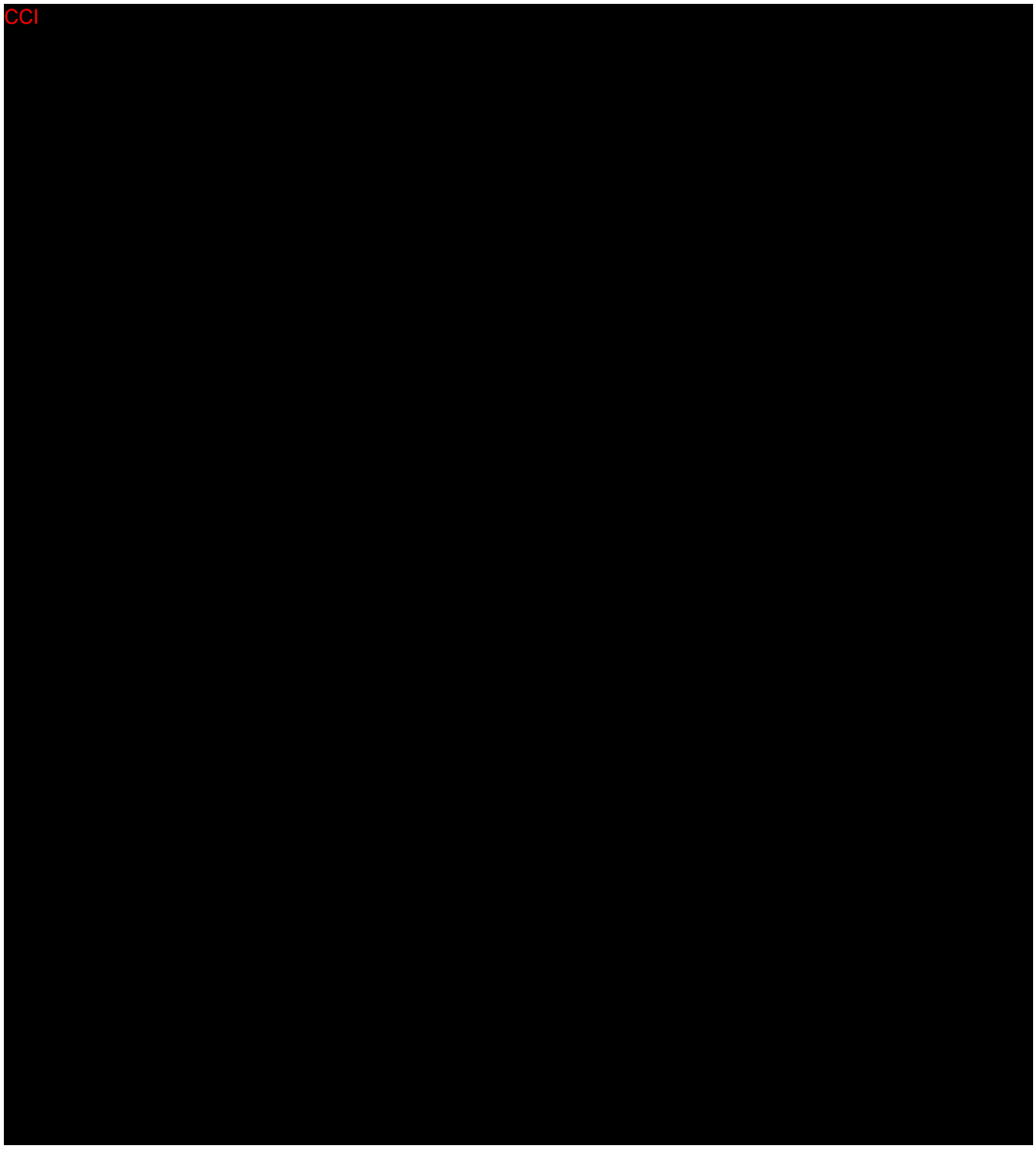
Protocol 331-12-284



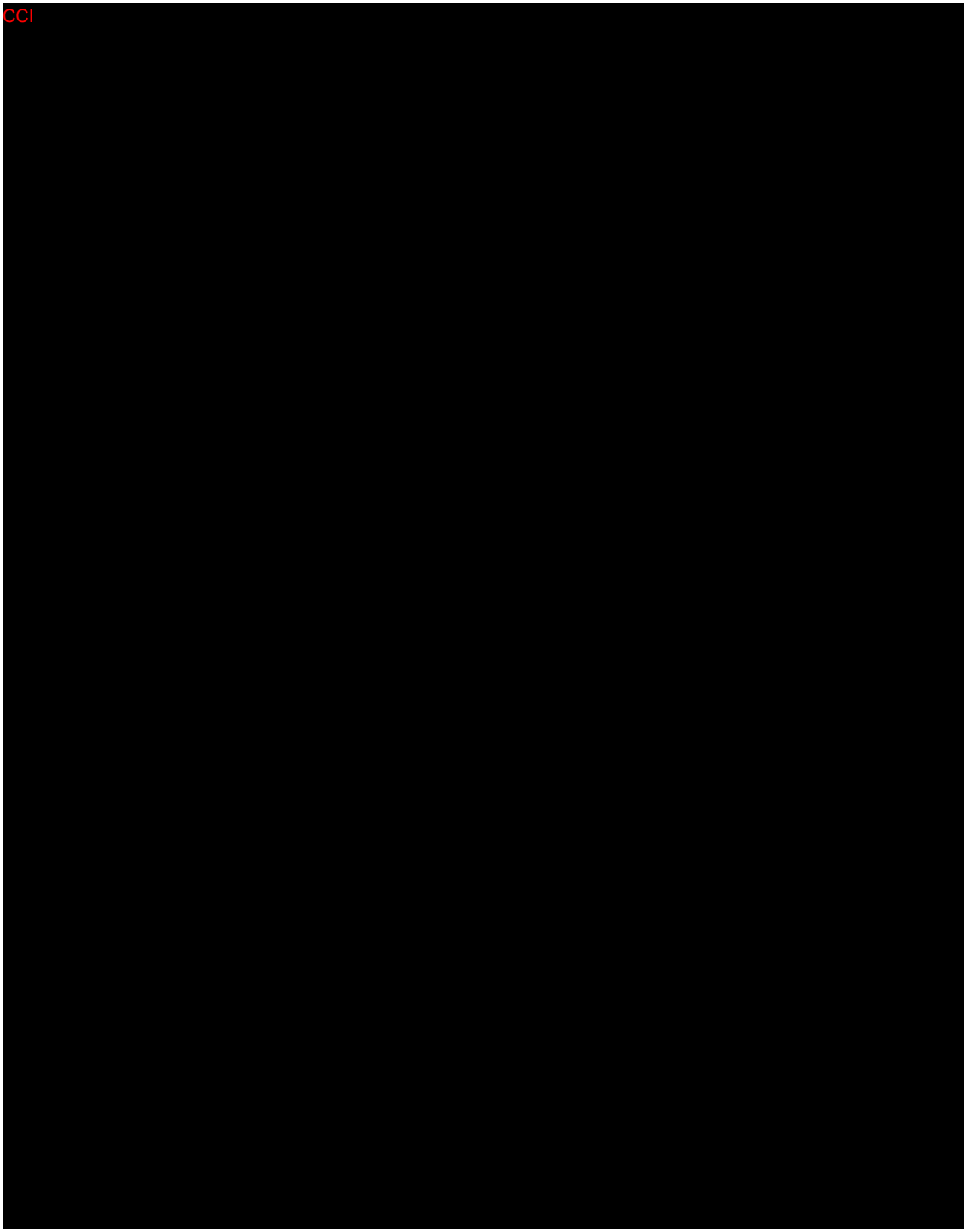
Protocol 331-12-284



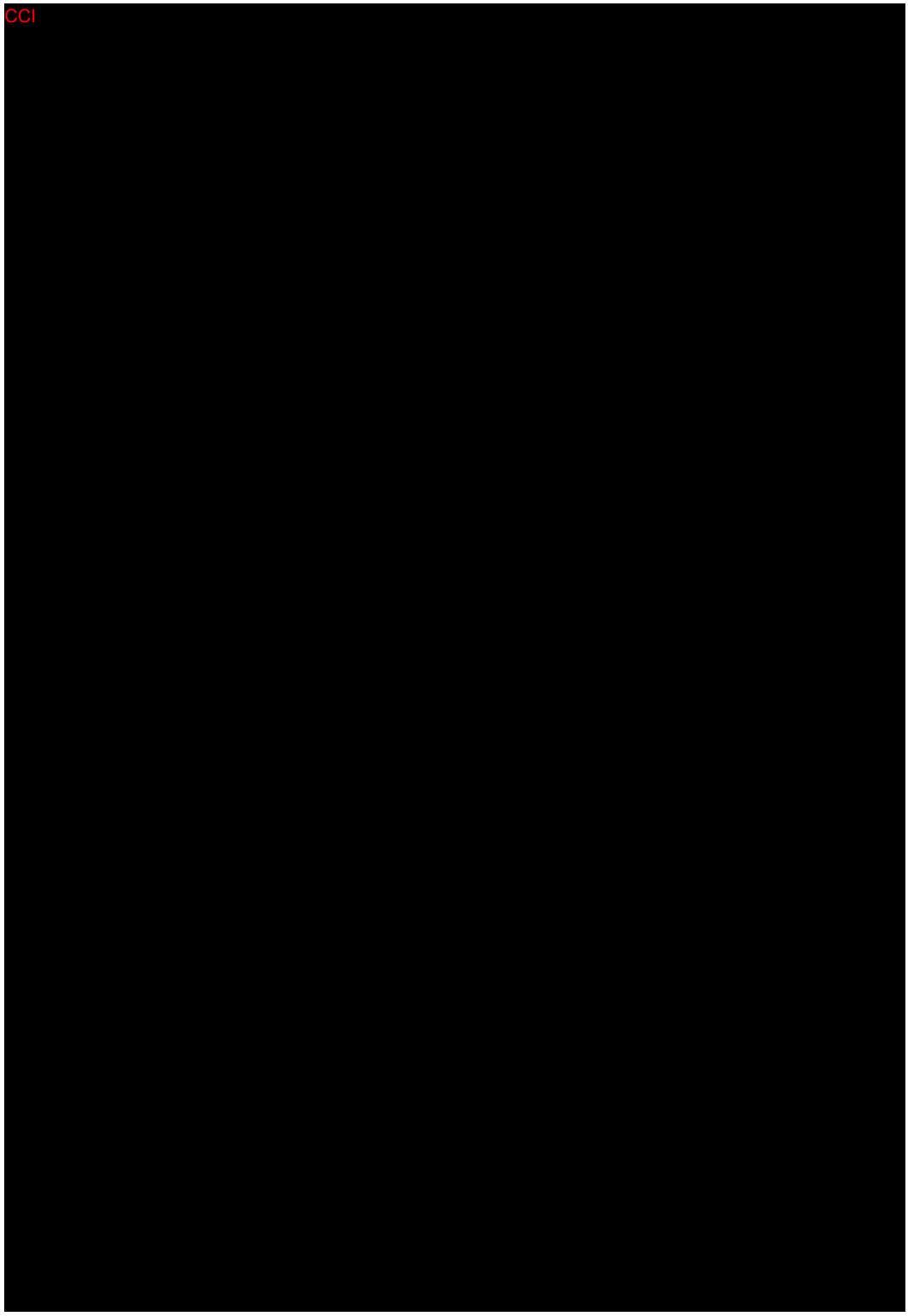
Protocol 331-12-284



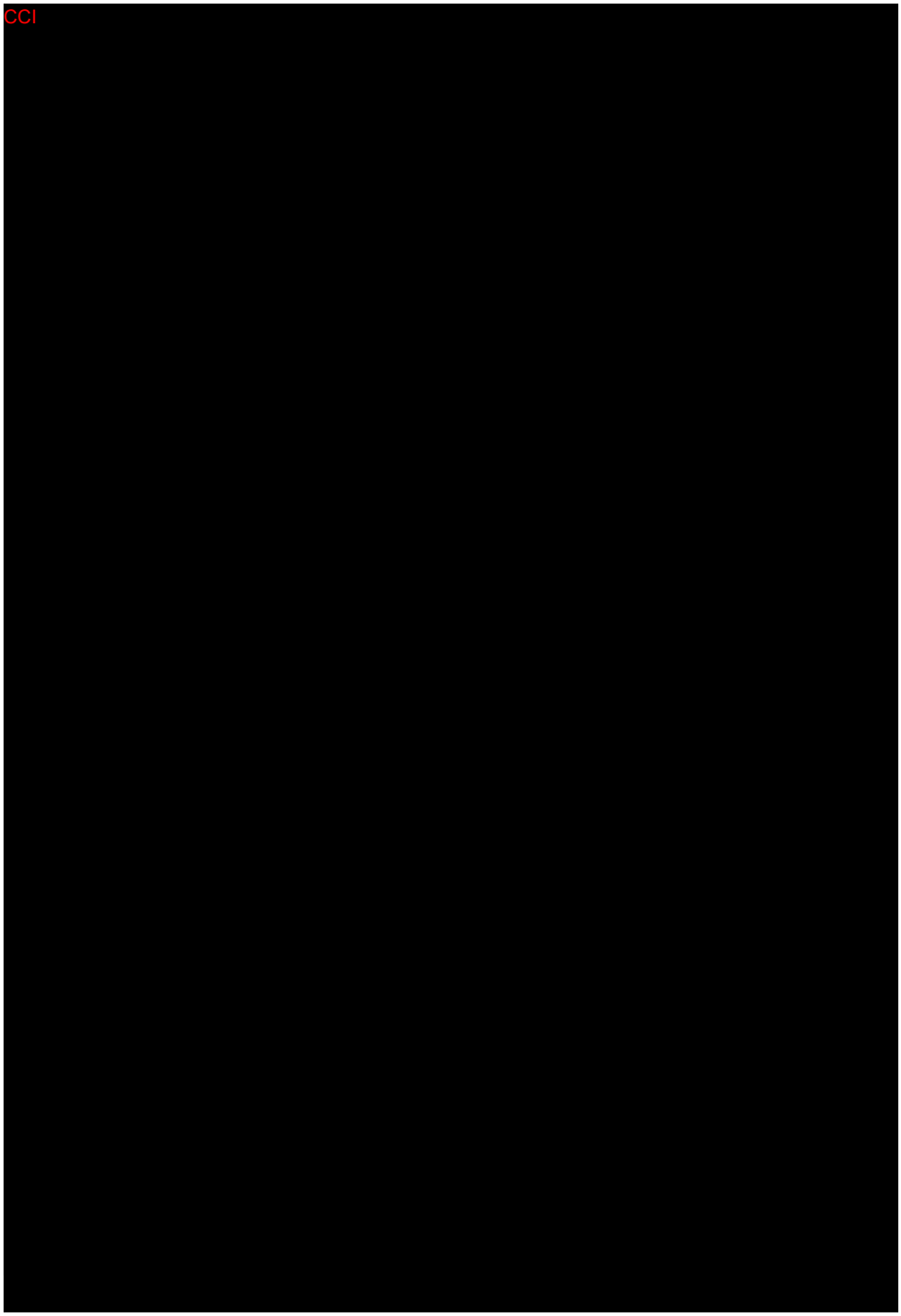
Protocol 331-12-284



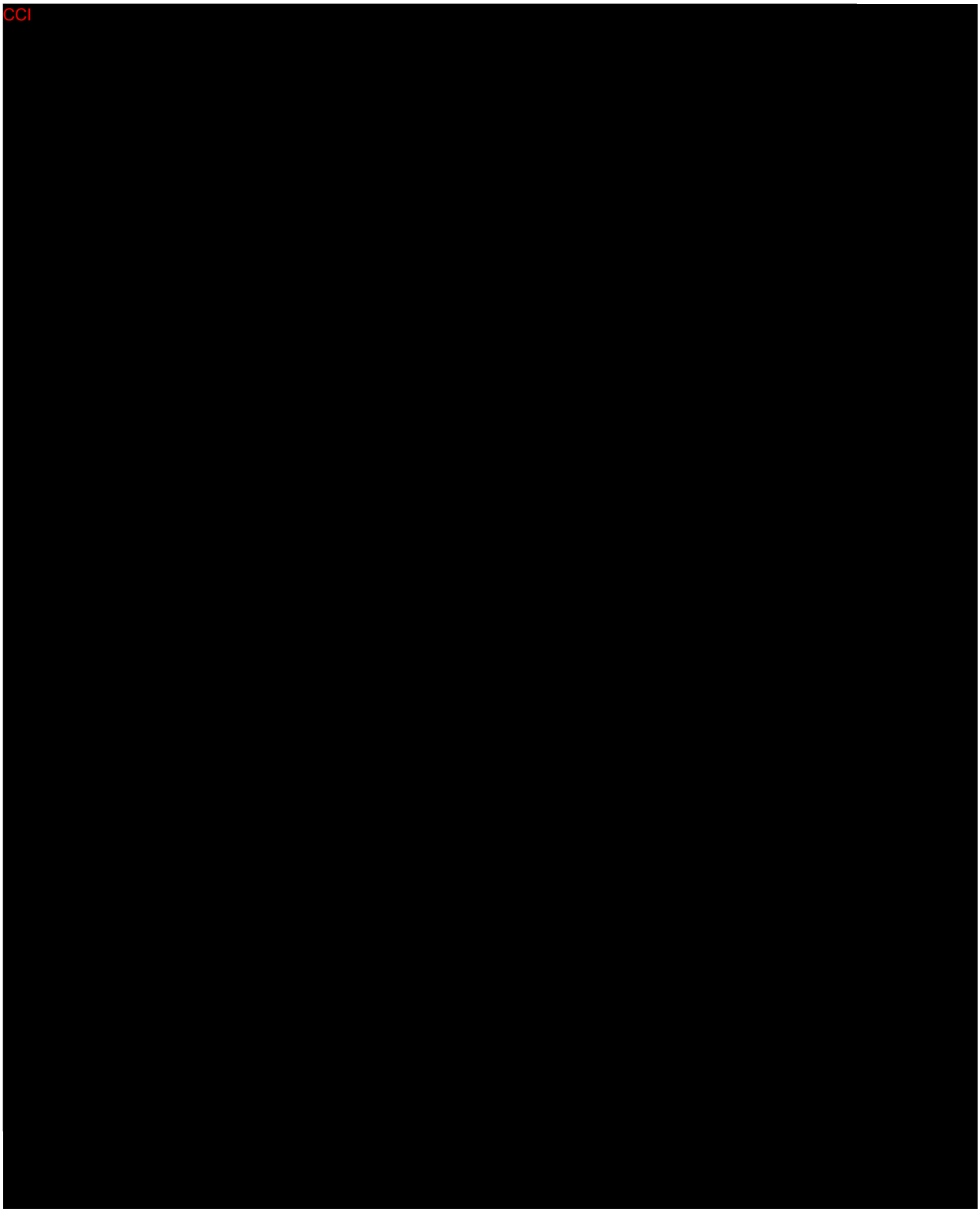
Protocol 331-12-284



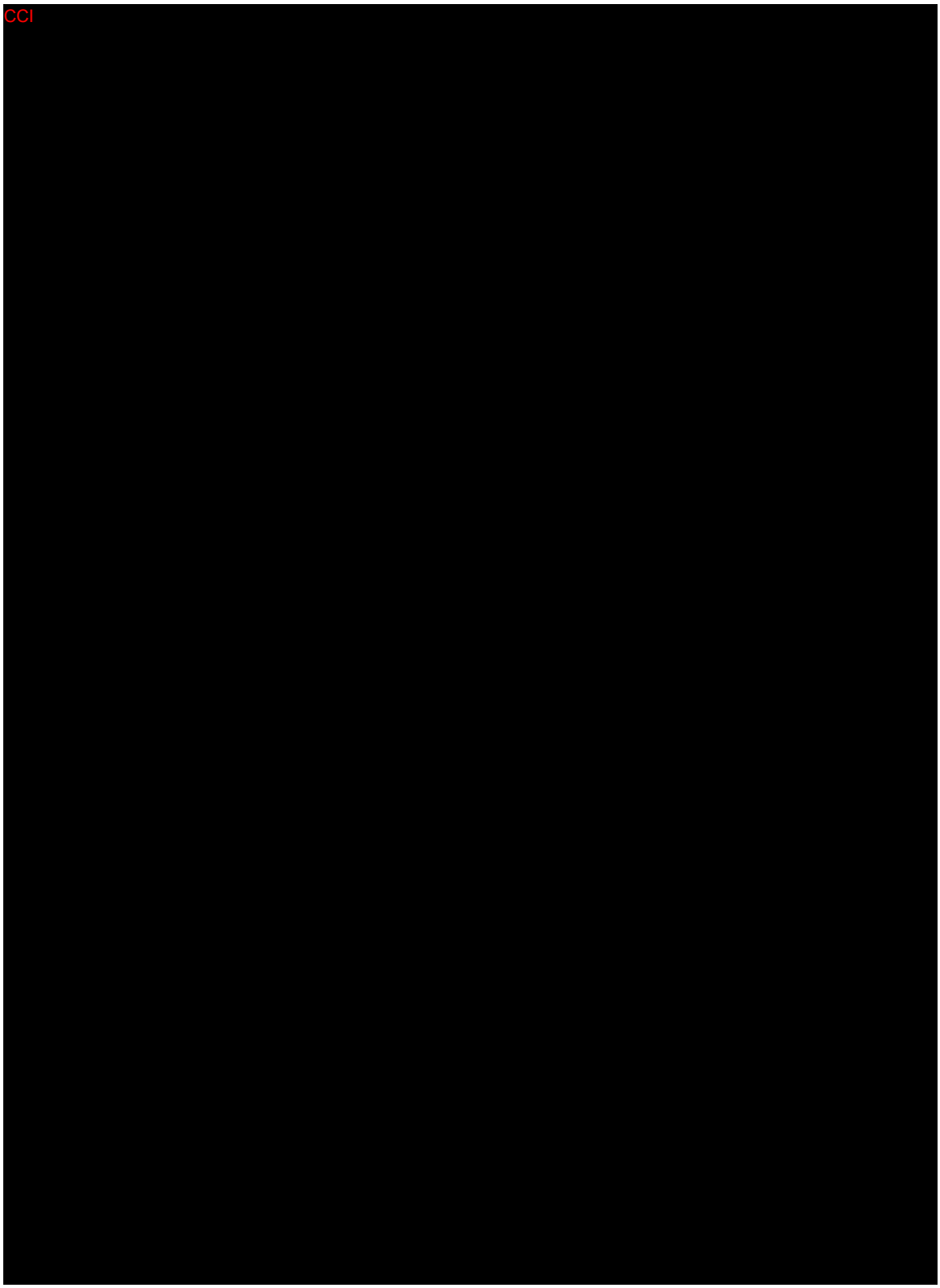
Protocol 331-12-284



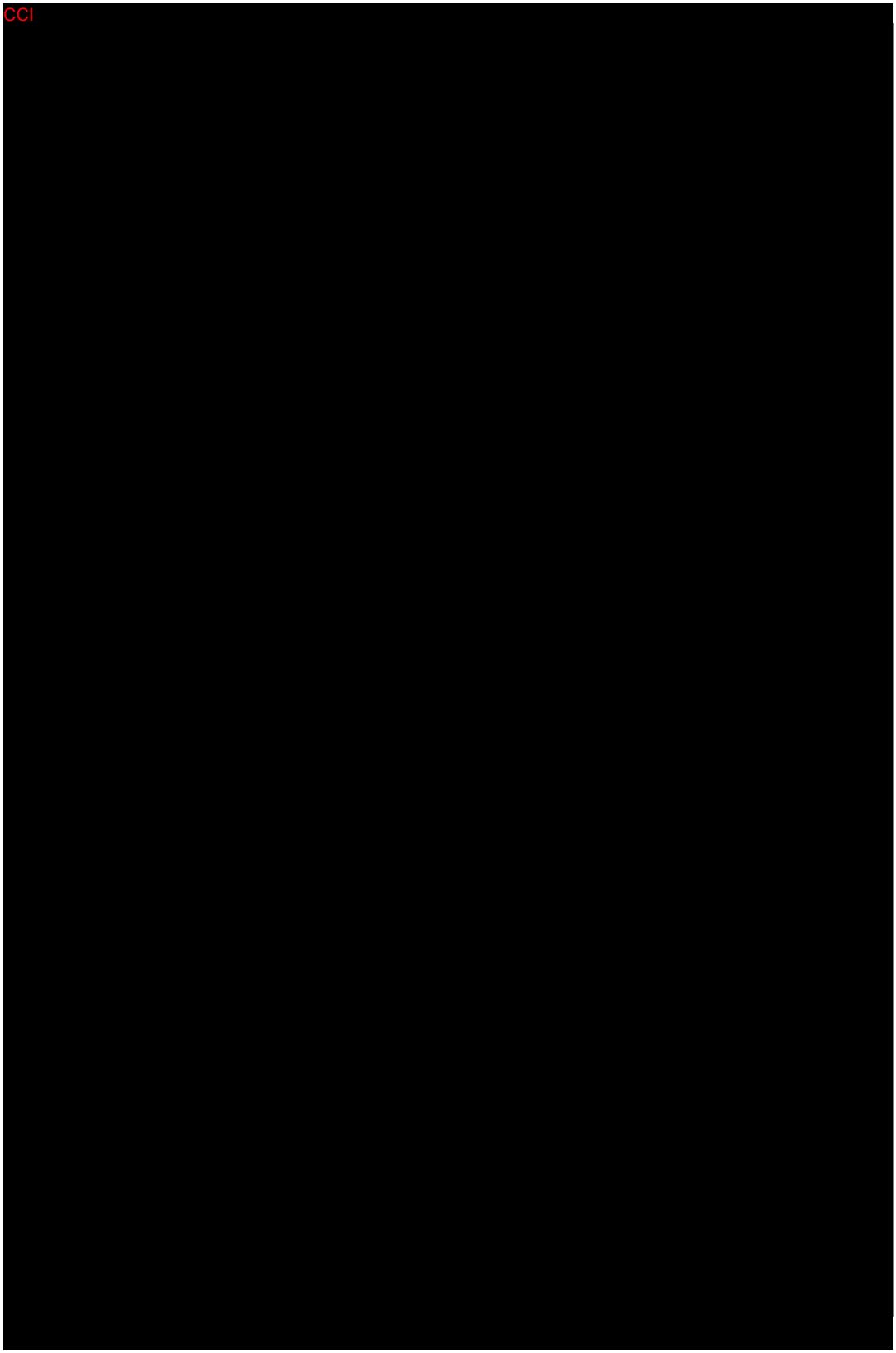
Protocol 331-12-284



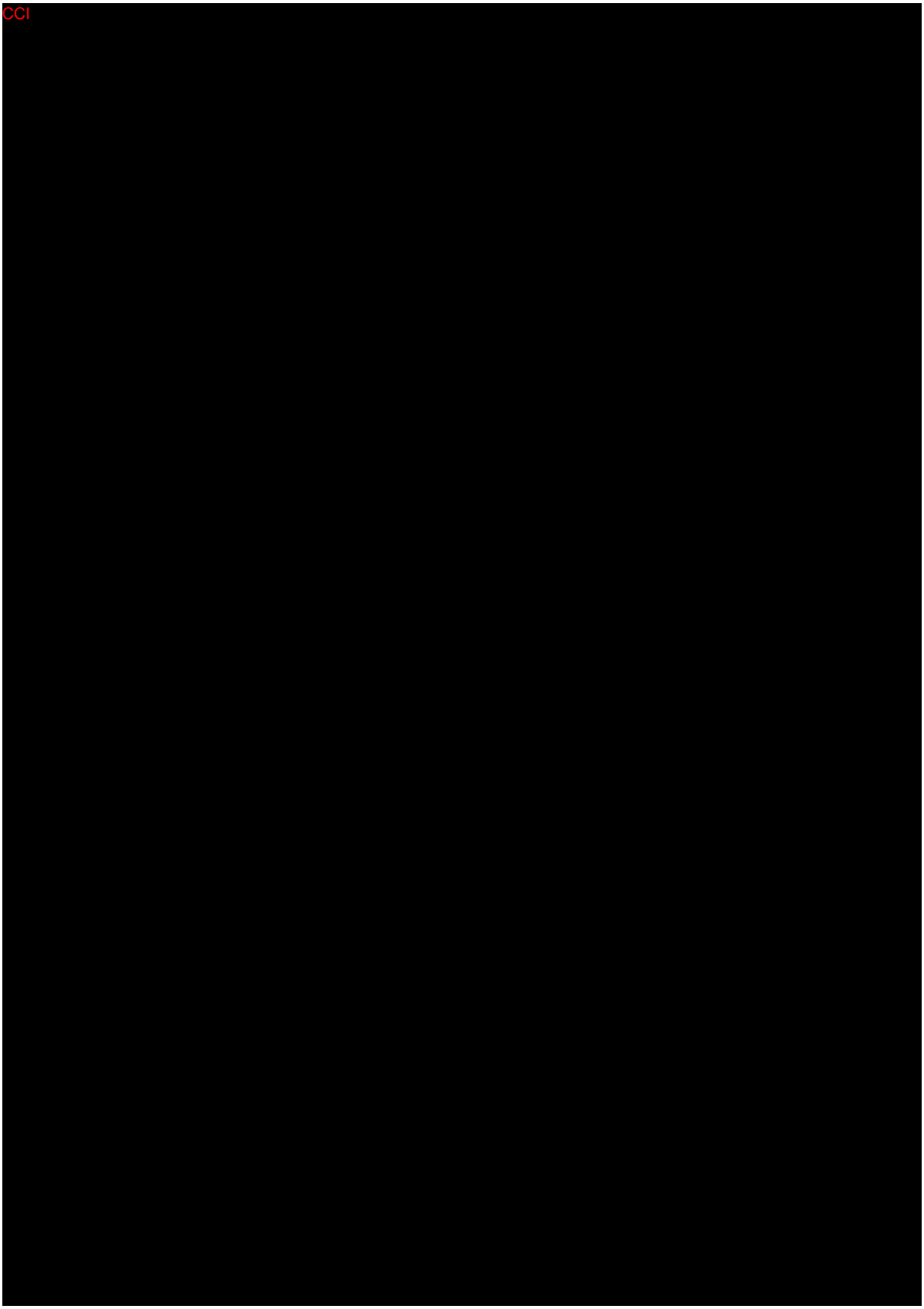
Protocol 331-12-284



Protocol 331-12-284

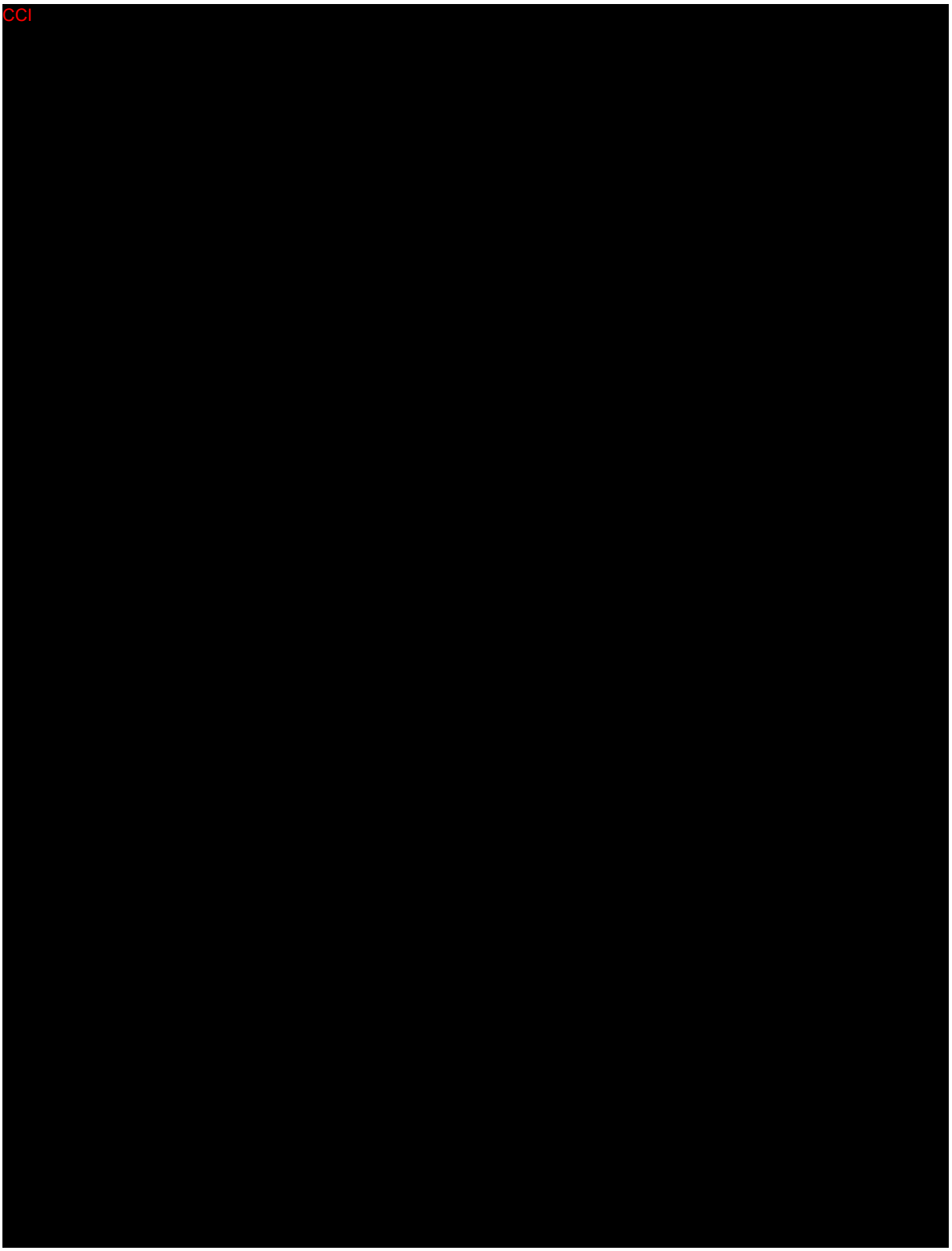


Protocol 331-12-284



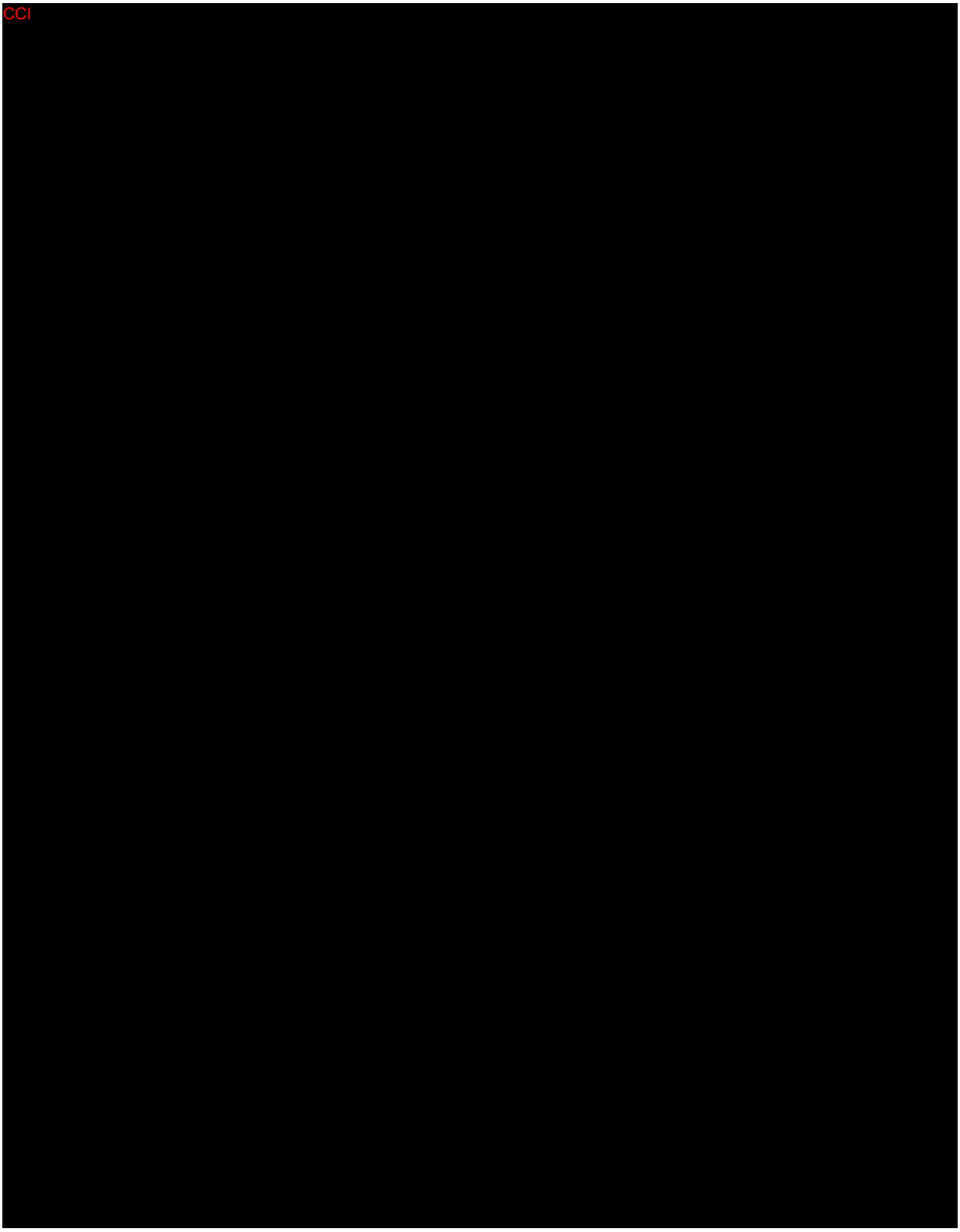
Protocol 331-12-284

Protocol 331-12-284

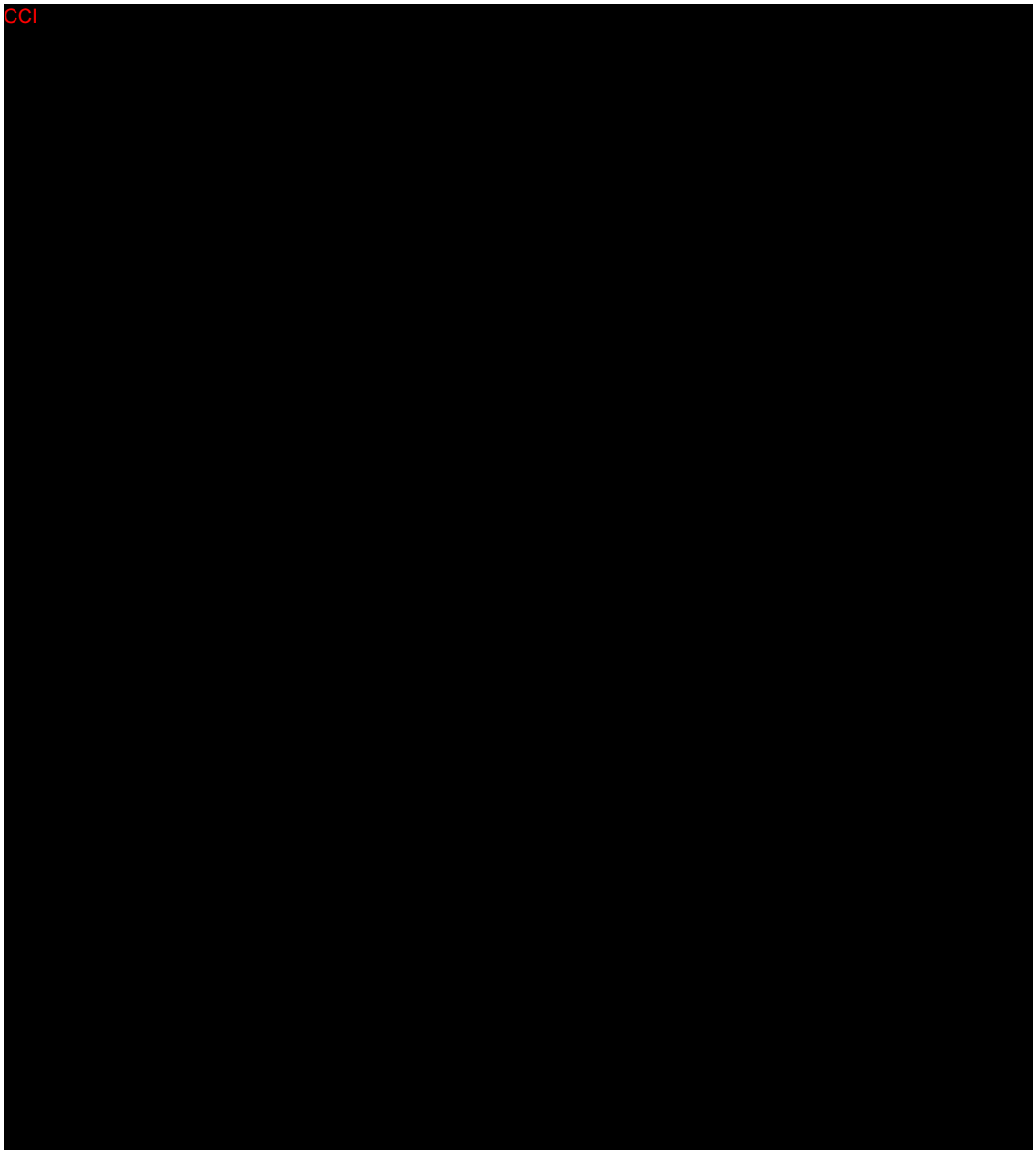


Protocol 331-12-284

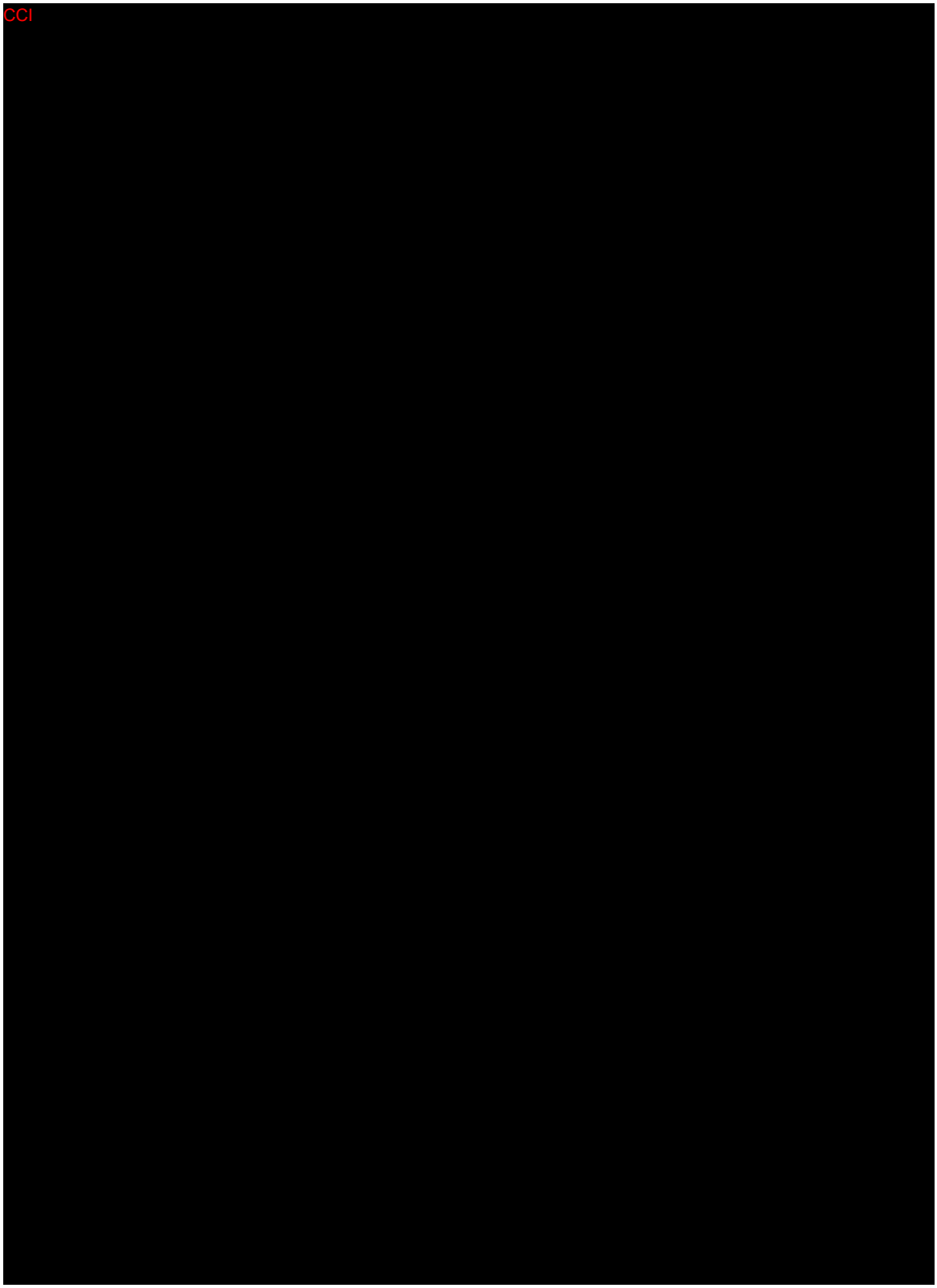
CCI



Protocol 331-12-284

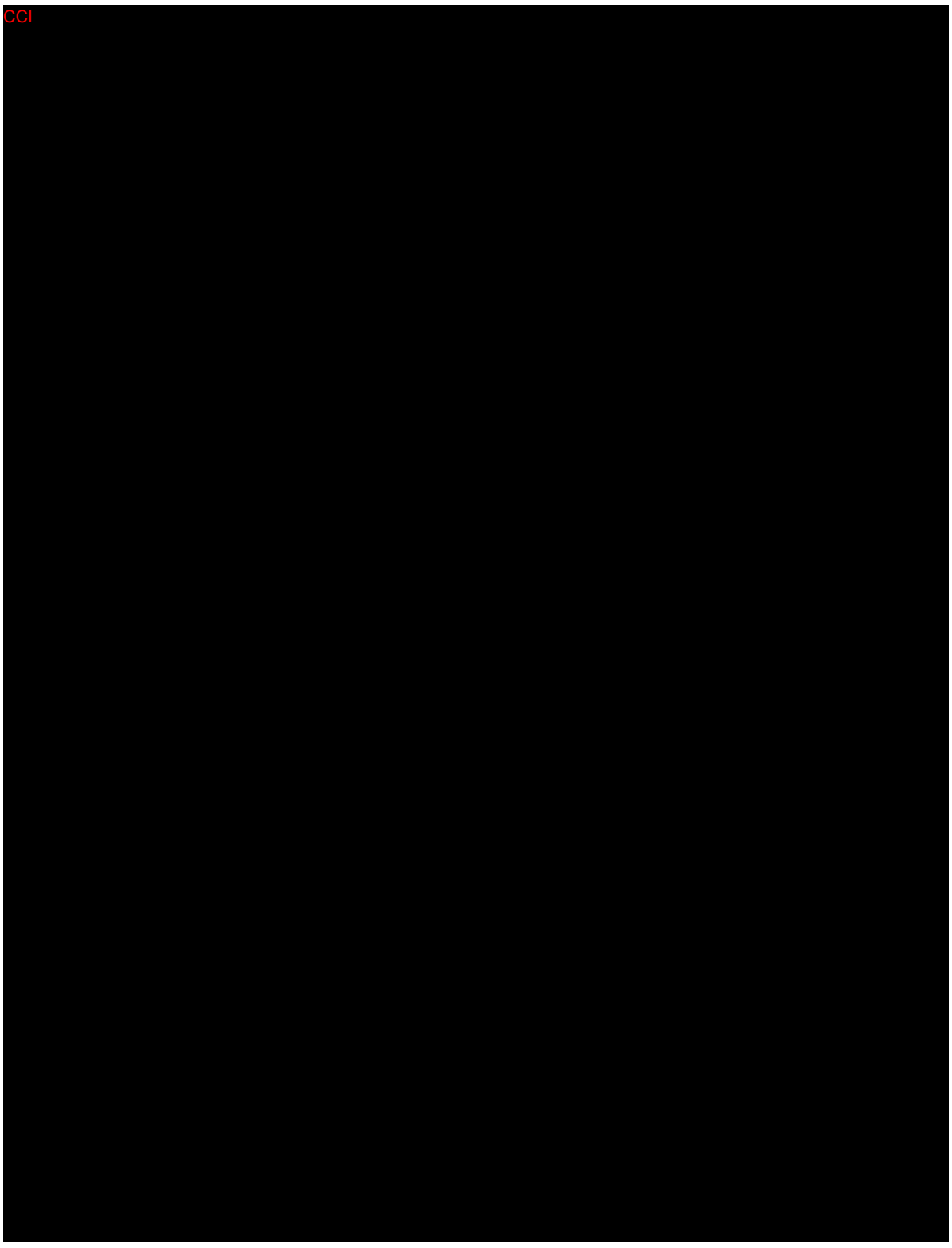


Protocol 331-12-284

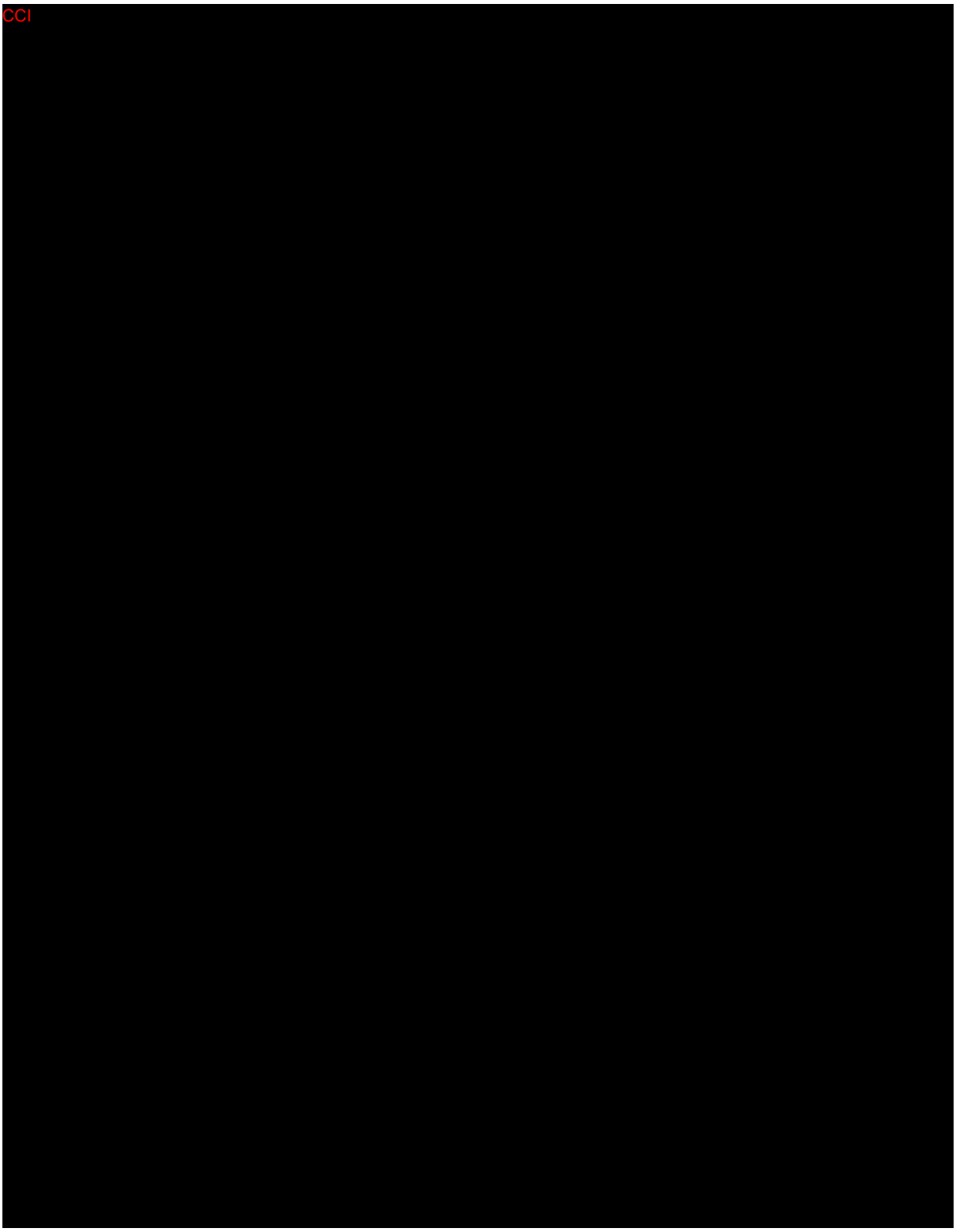


Protocol 331-12-284

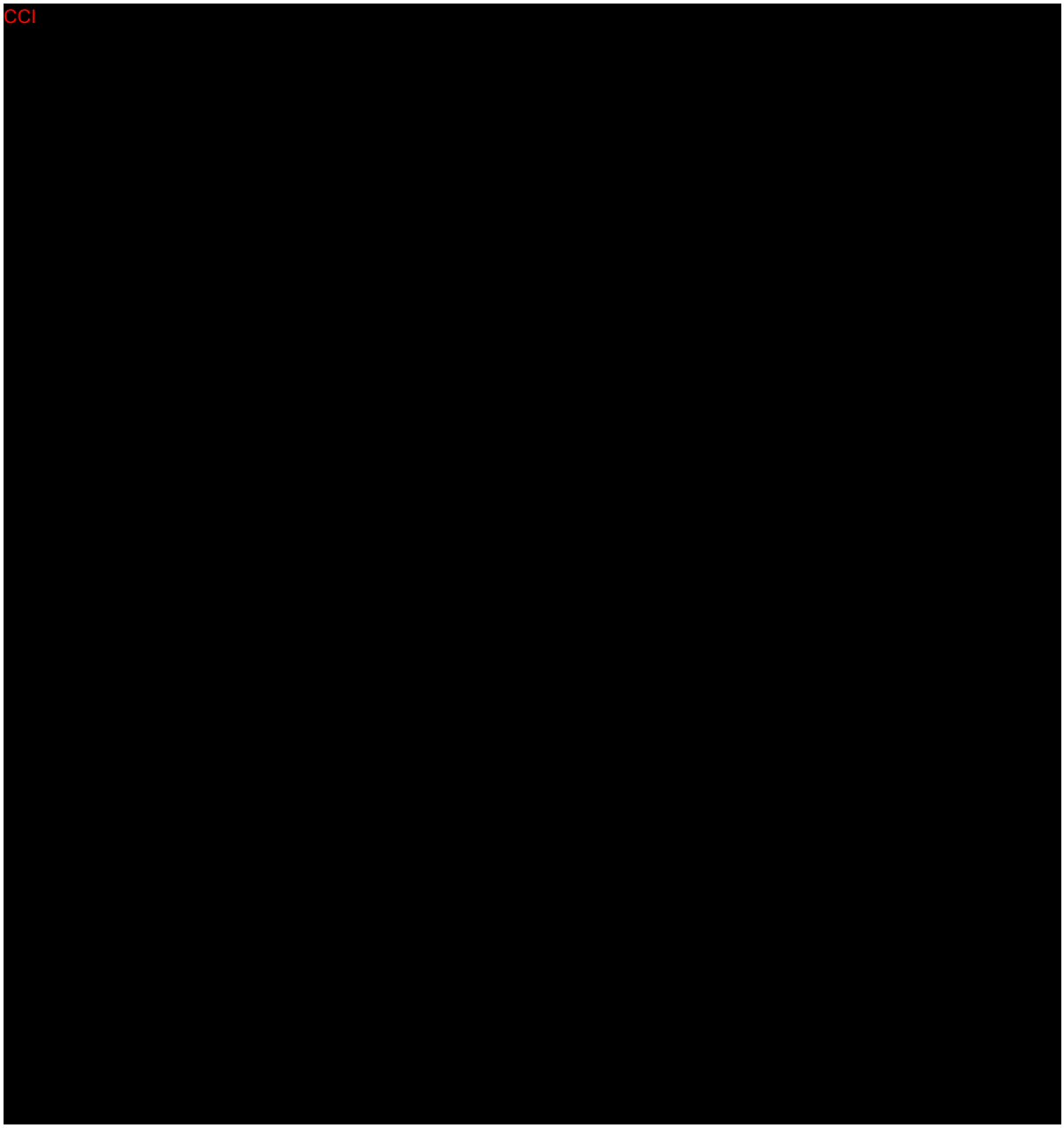
Protocol 331-12-284



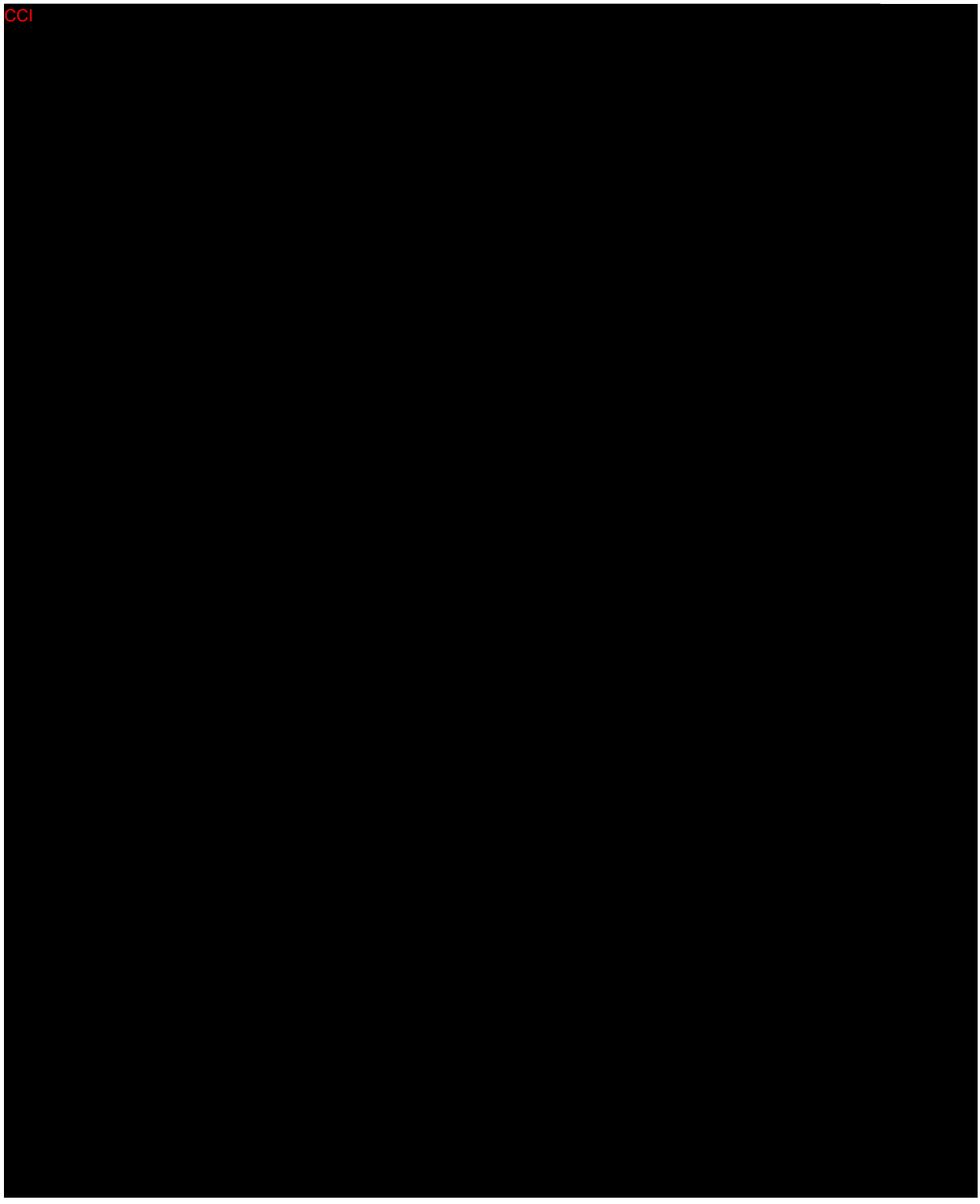
Protocol 331-12-284



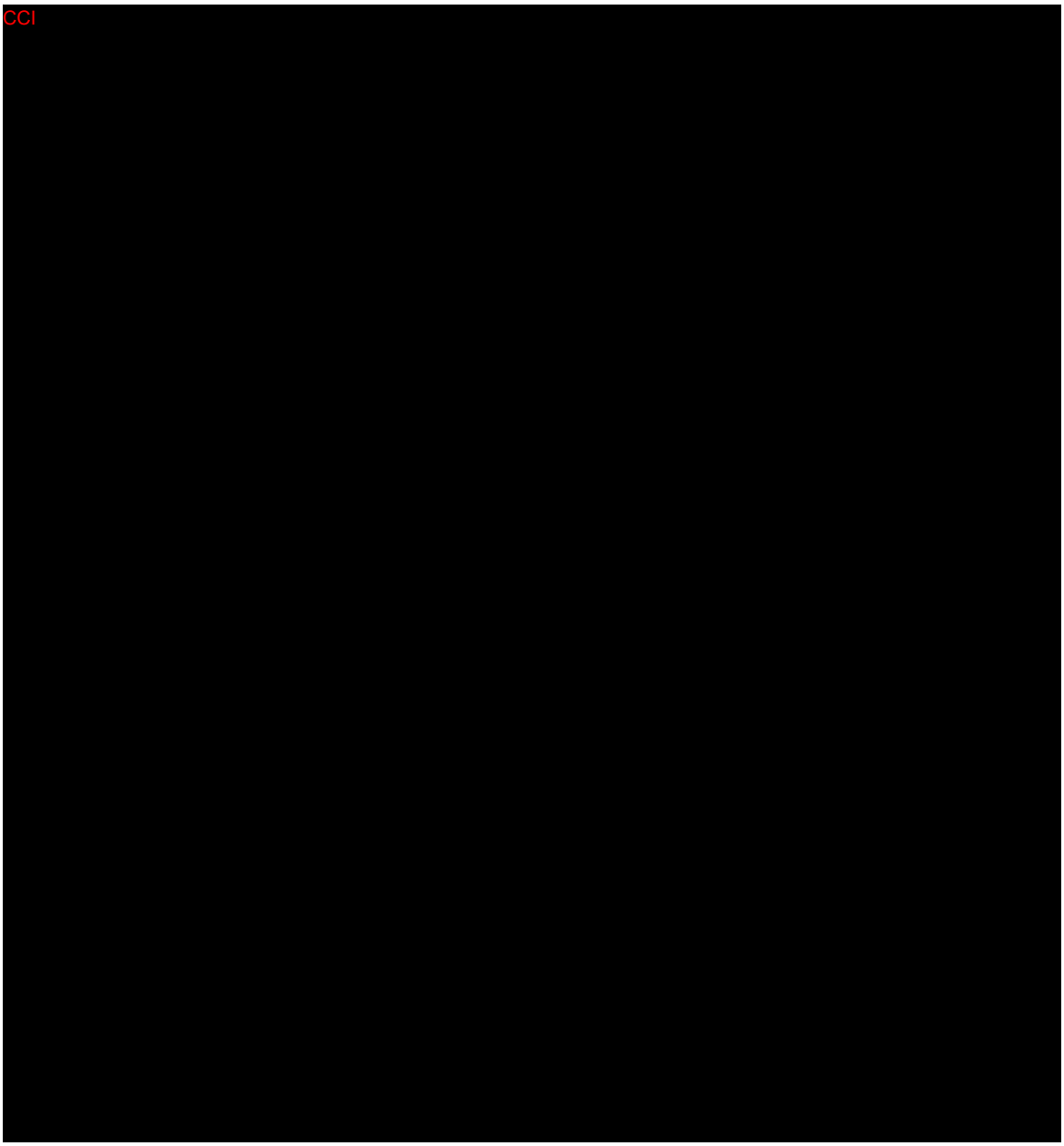
Protocol 331-12-284



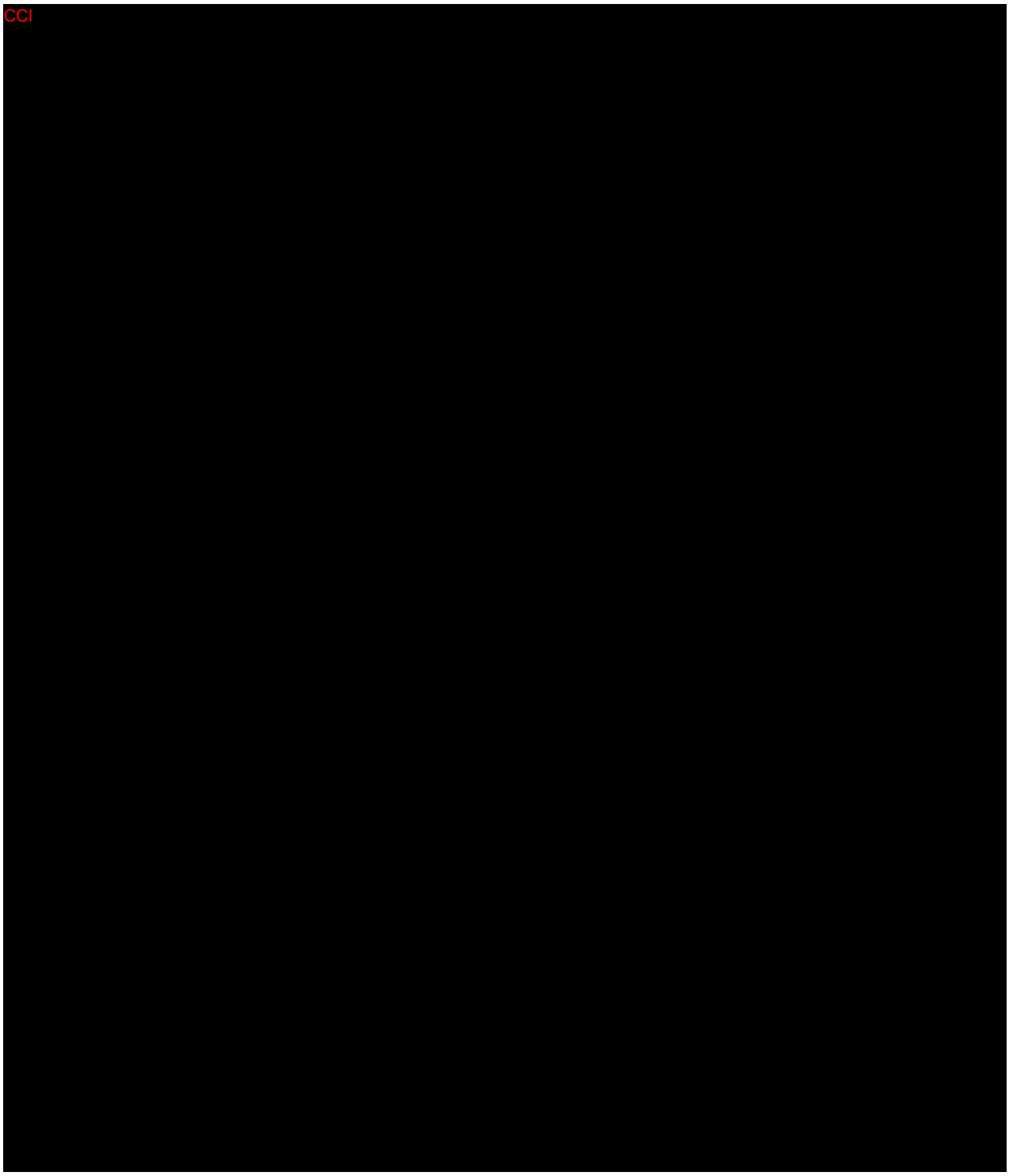
Protocol 331-12-284



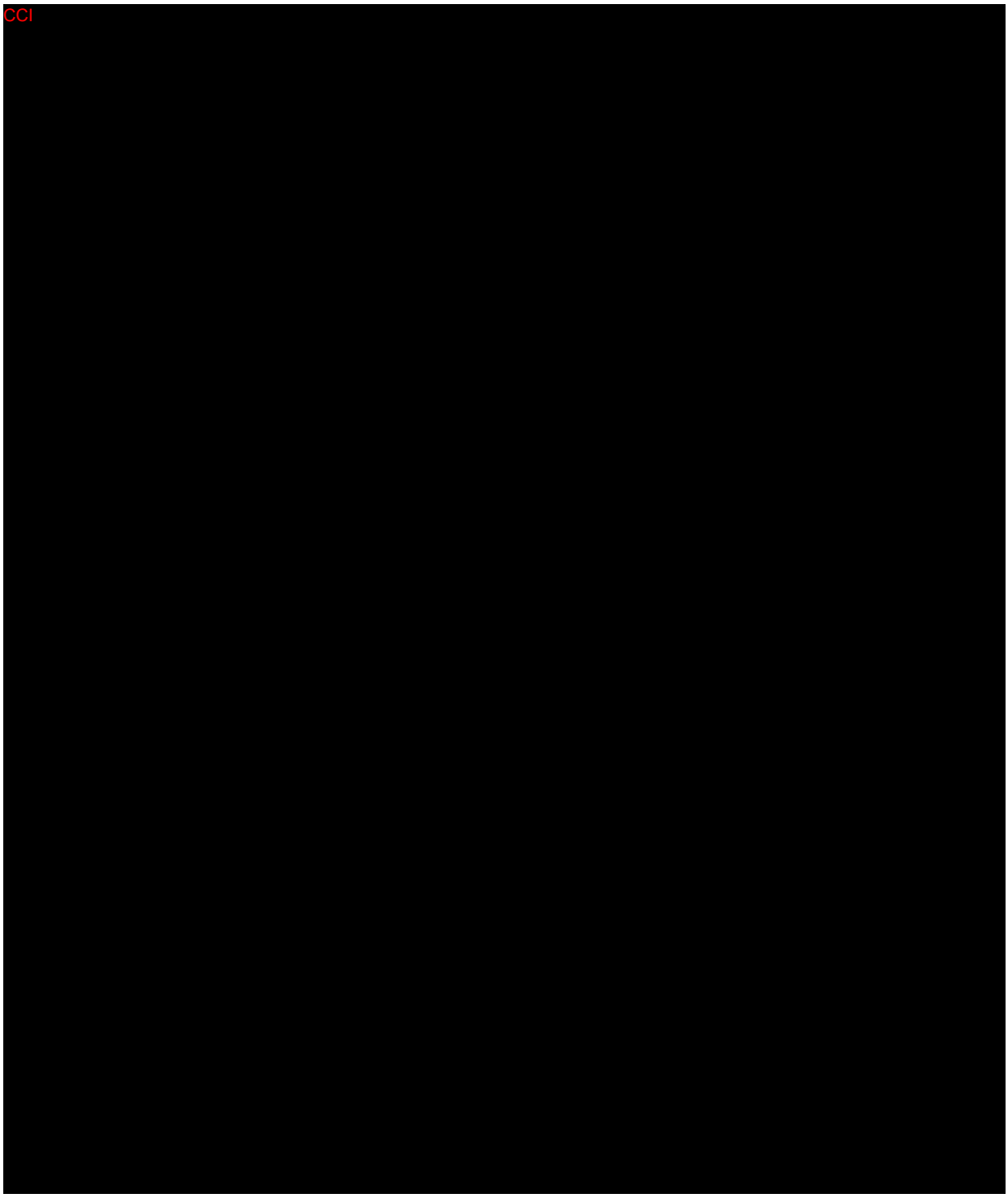
Protocol 331-12-284



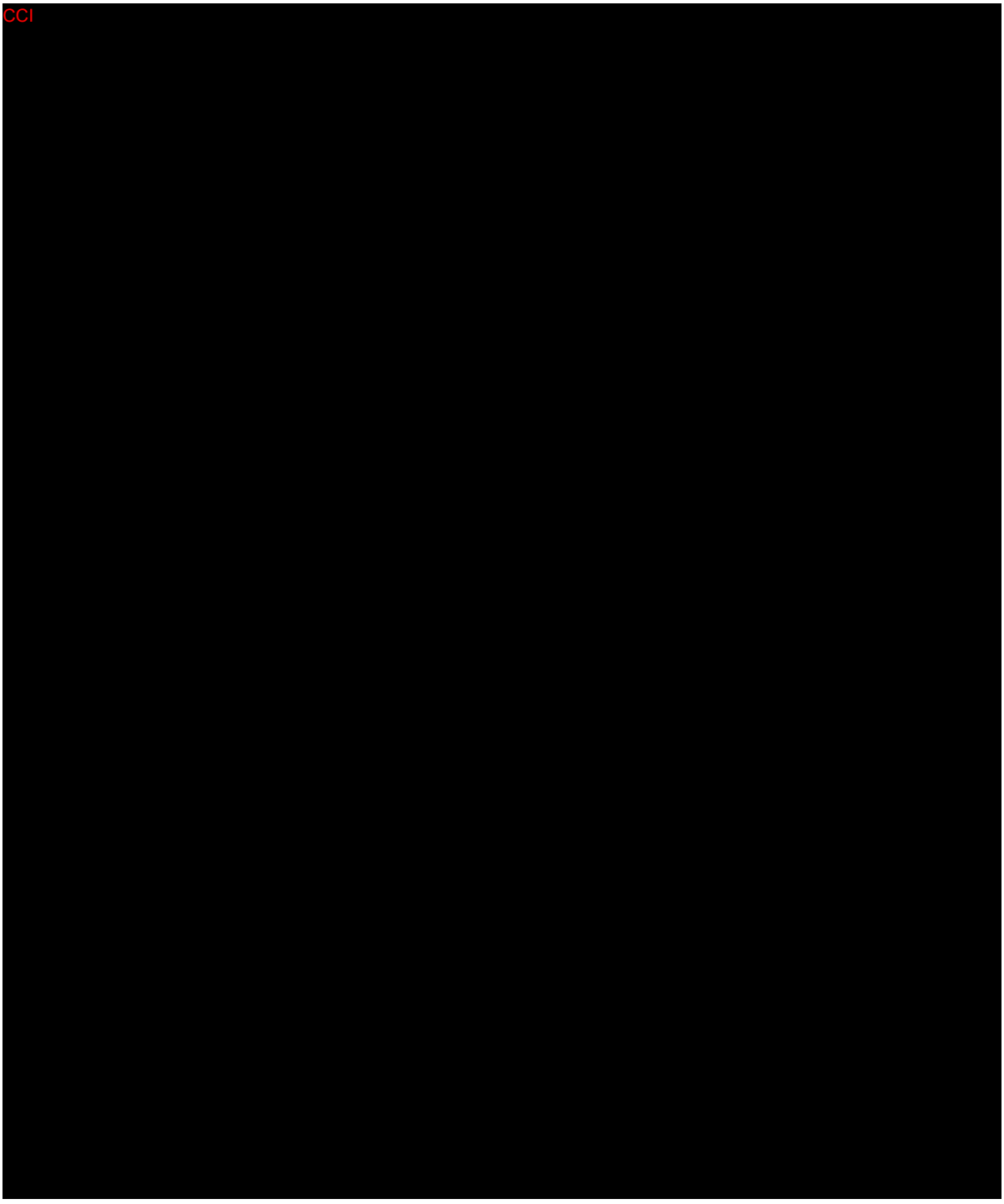
Protocol 331-12-284



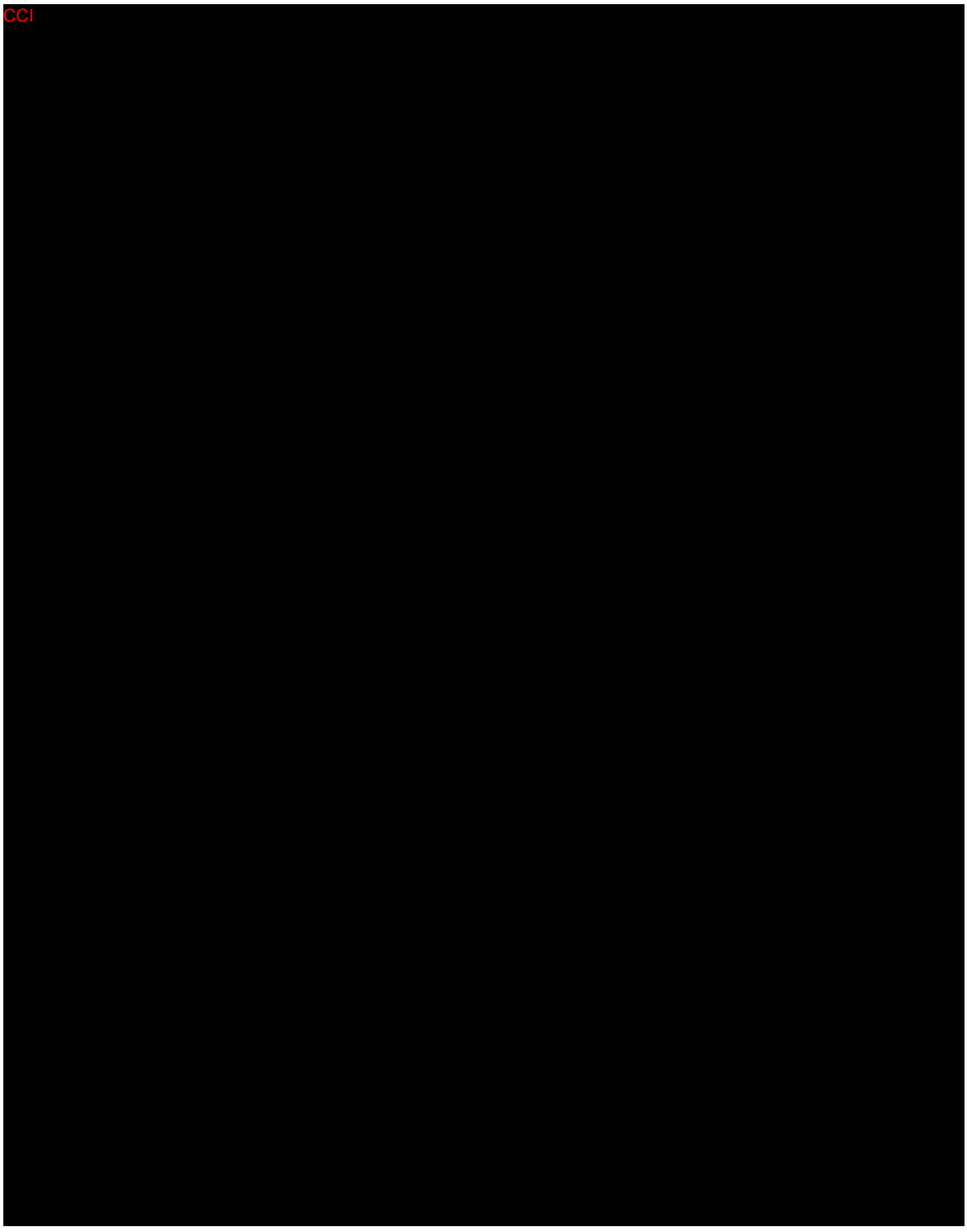
Protocol 331-12-284



Protocol 331-12-284

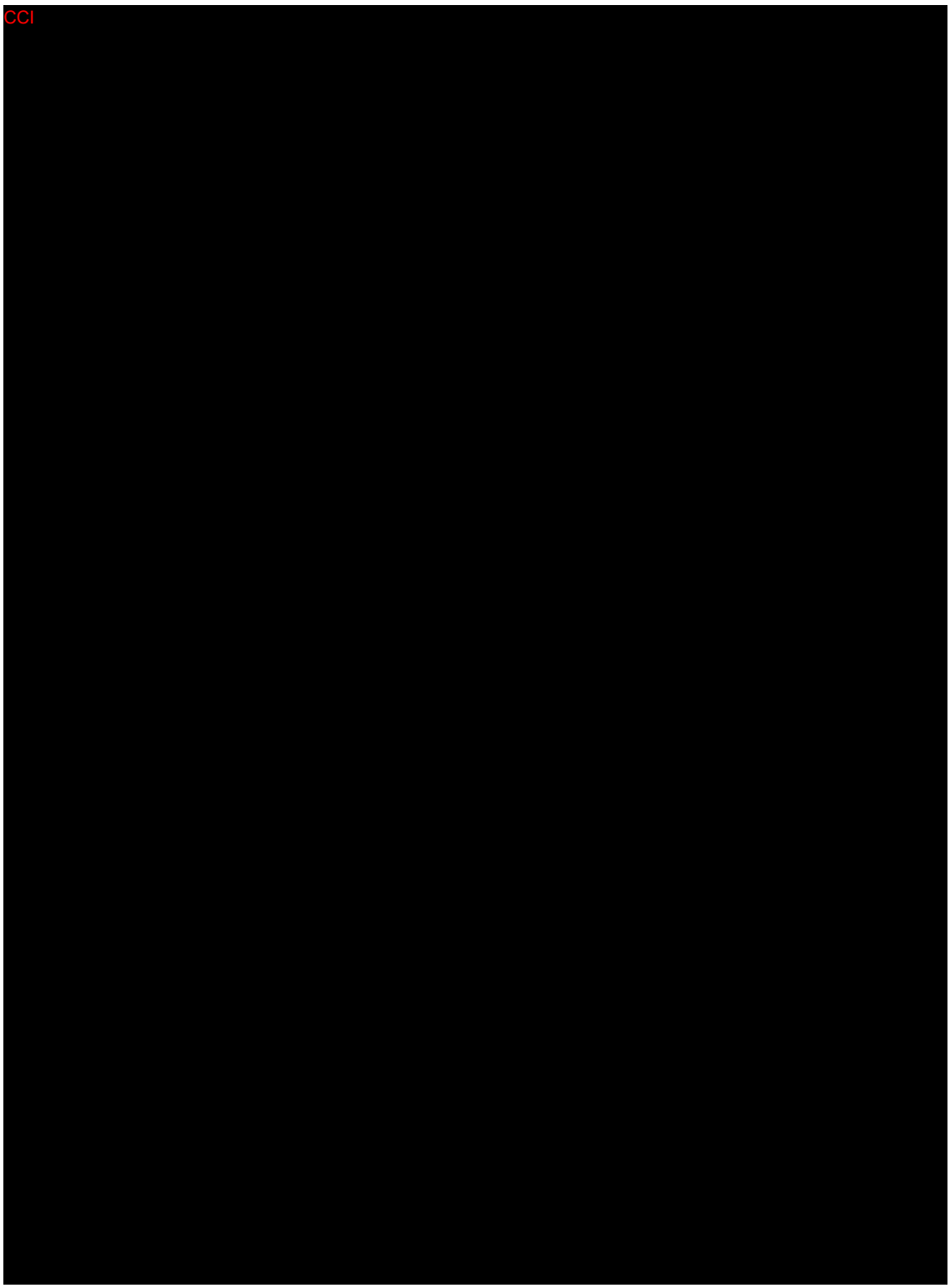


Protocol 331-12-284

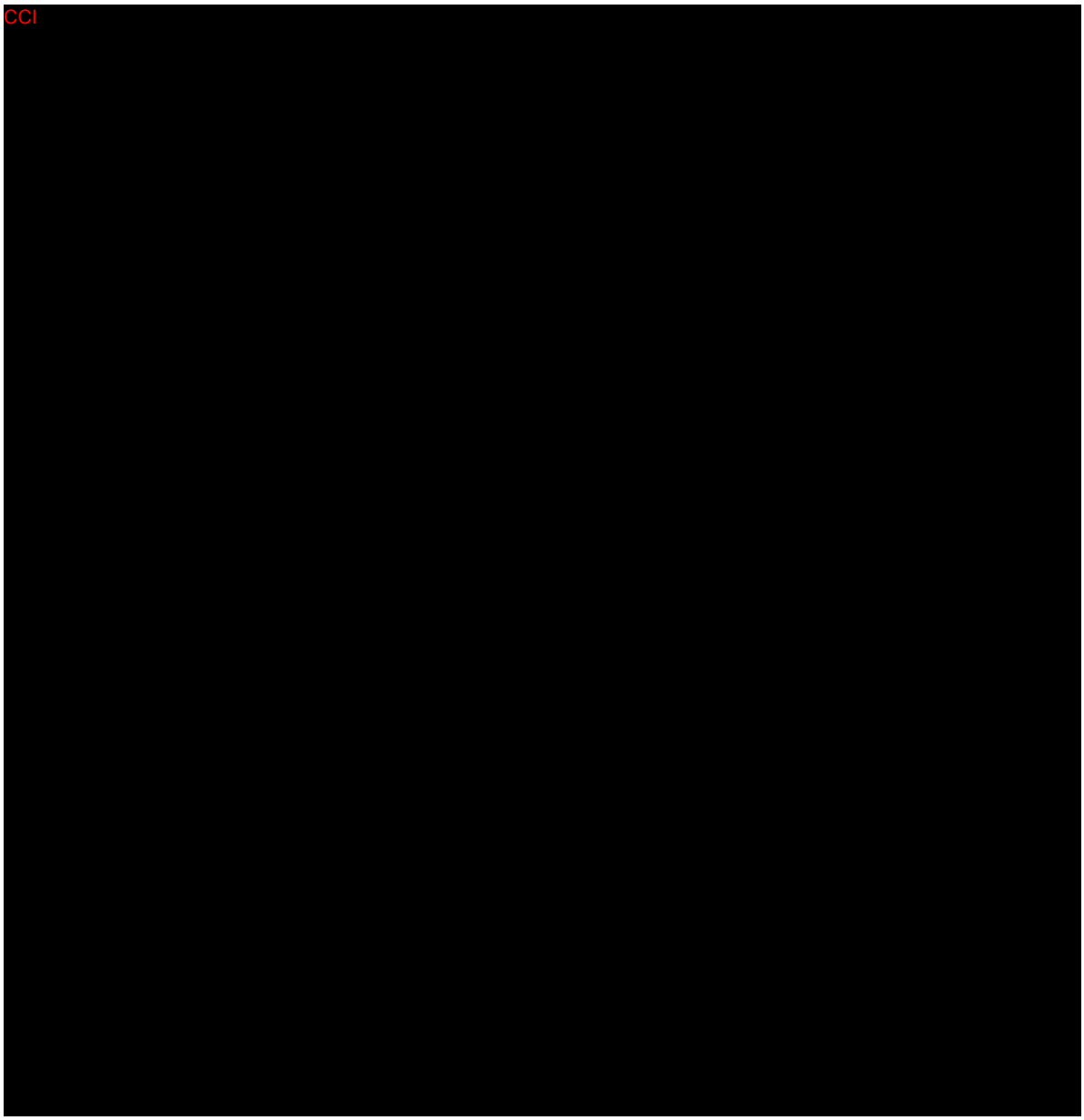


Protocol 331-12-284

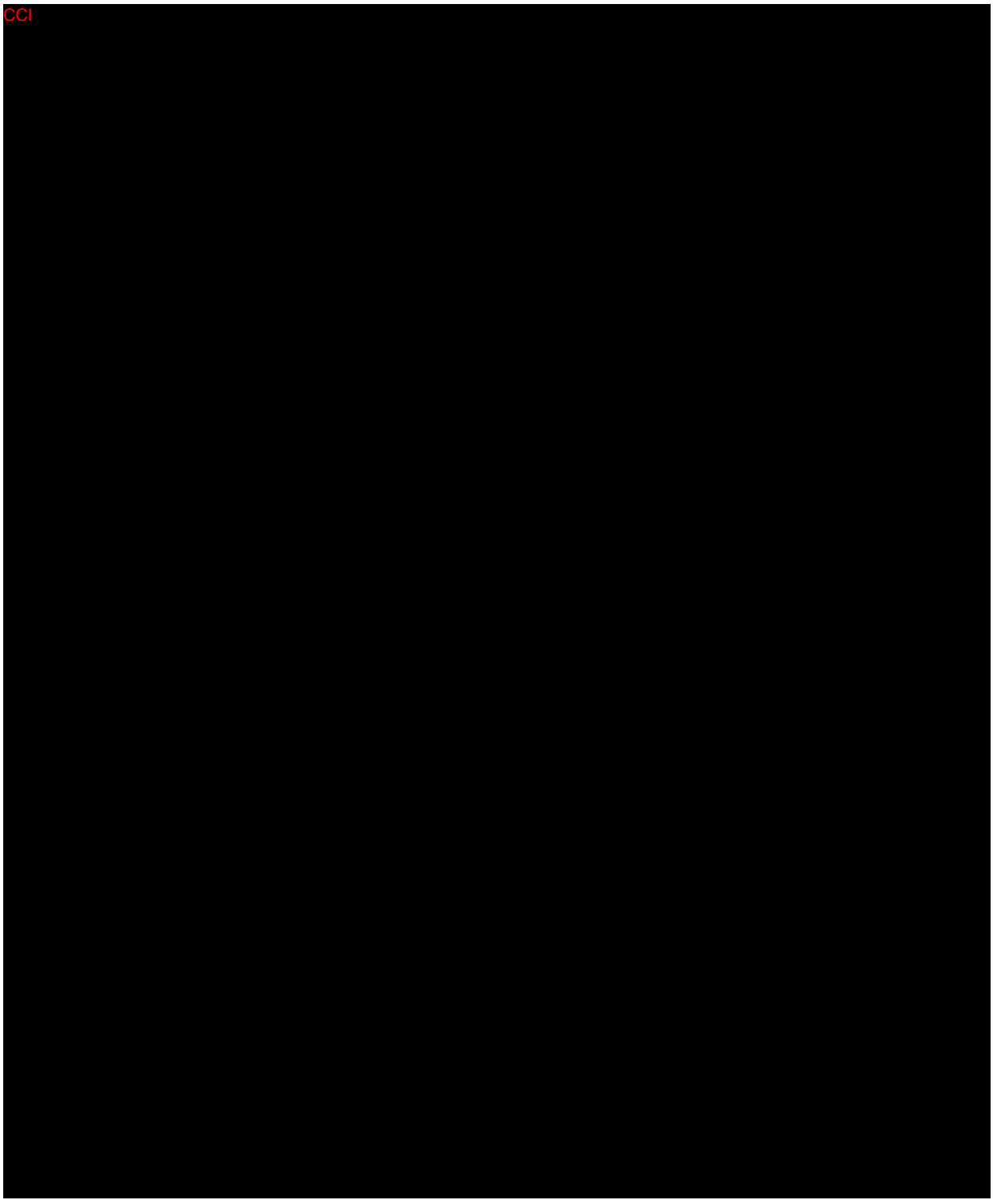
Protocol 331-12-284



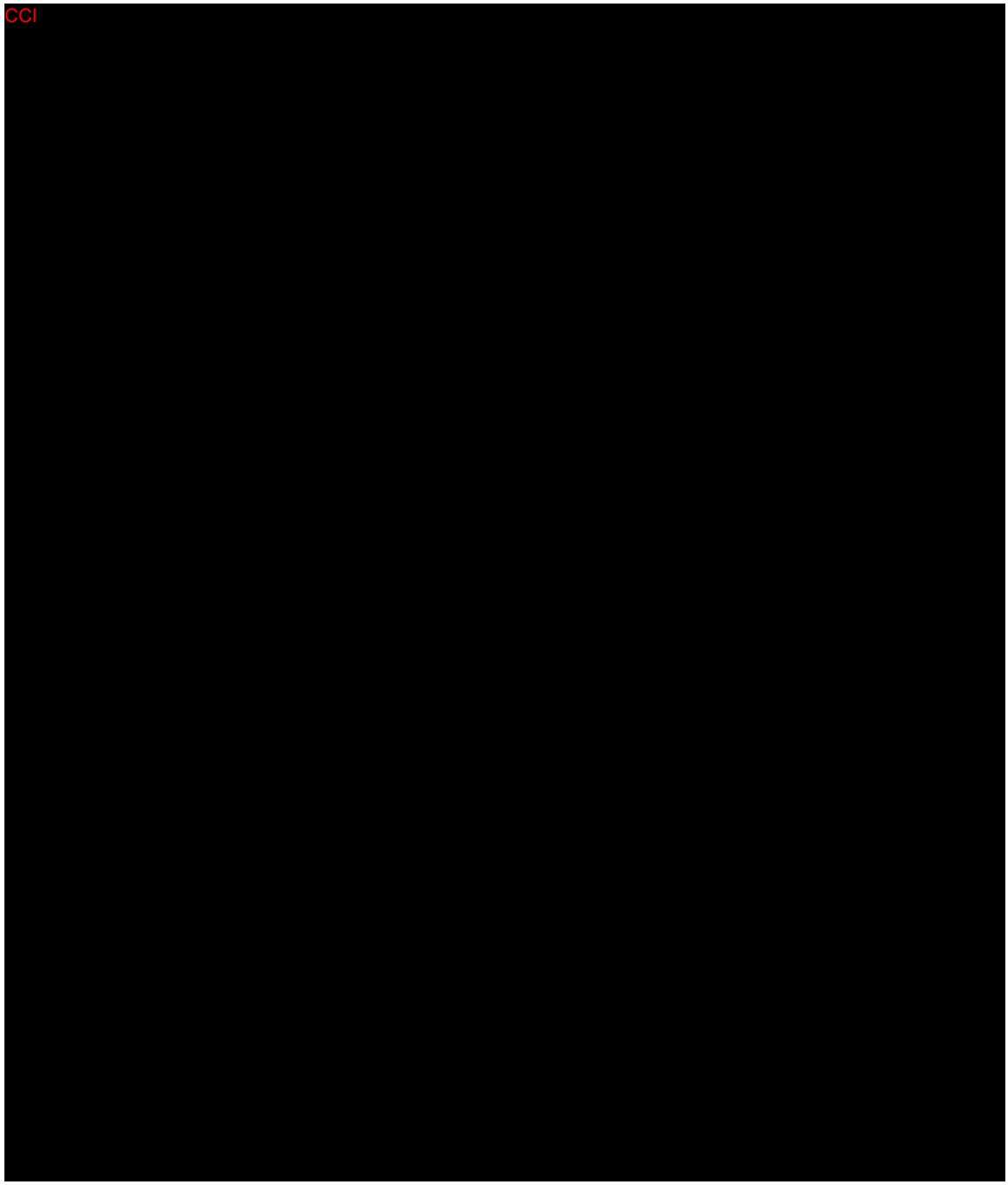
Protocol 331-12-284



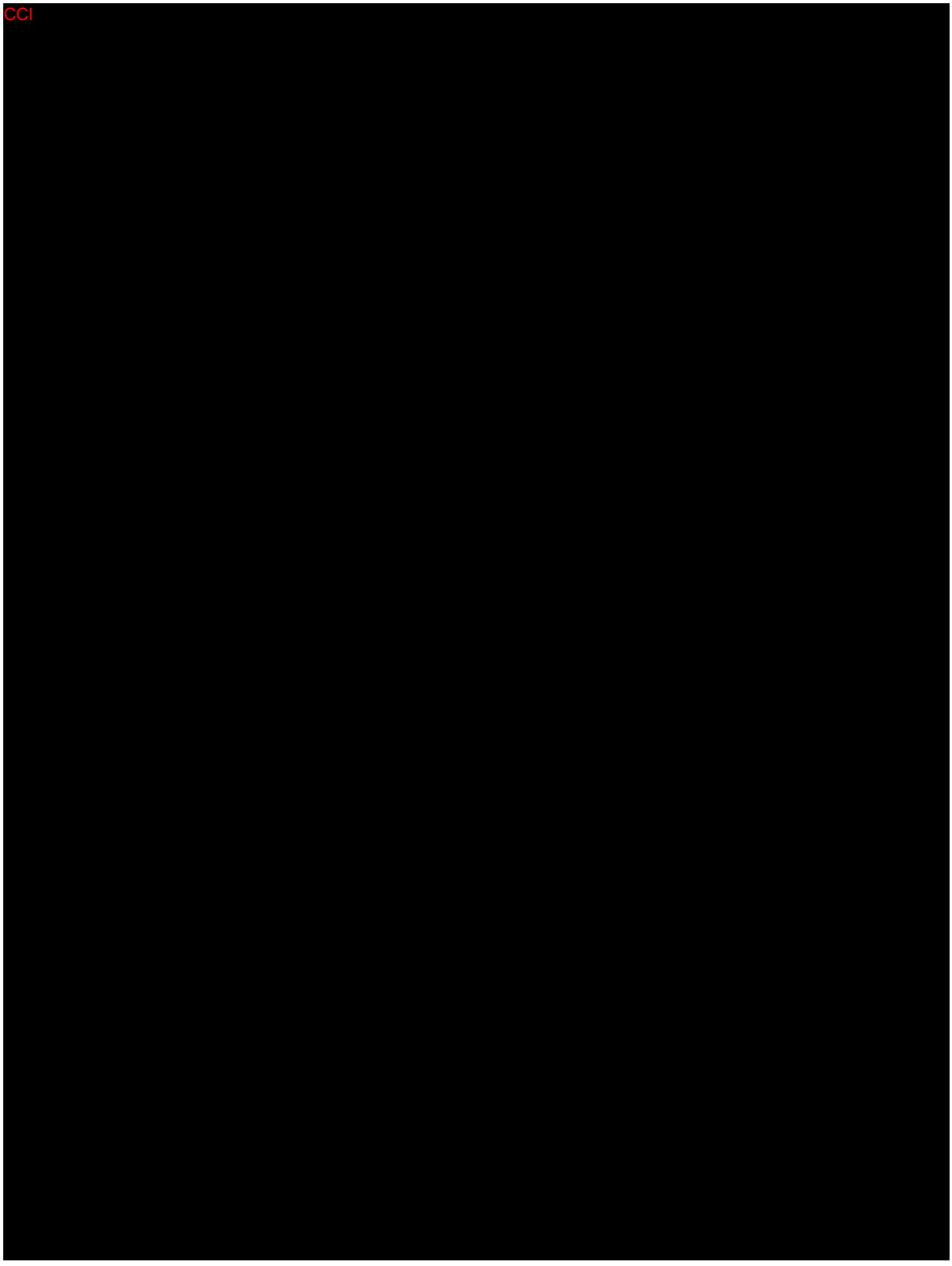
Protocol 331-12-284



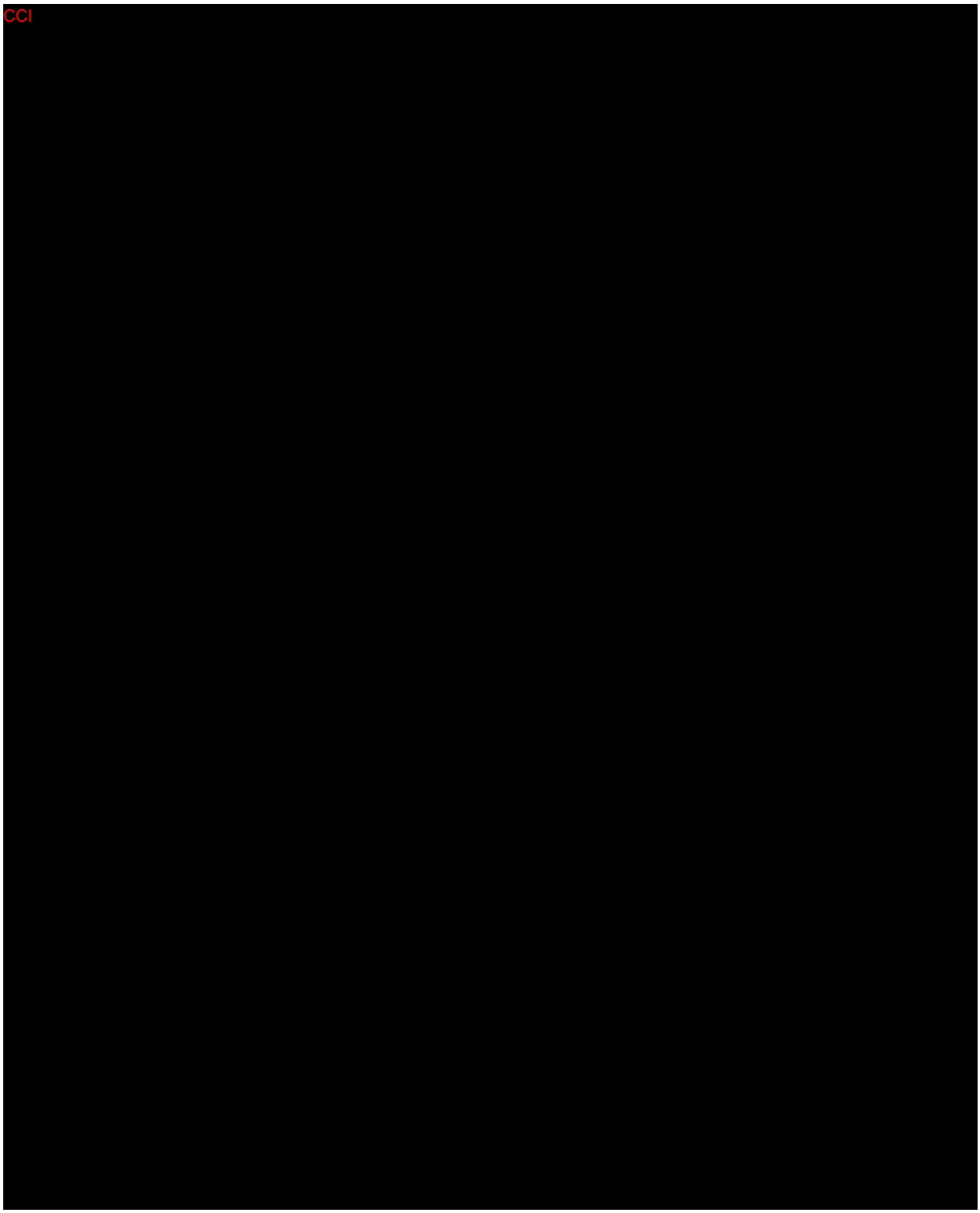
Protocol 331-12-284



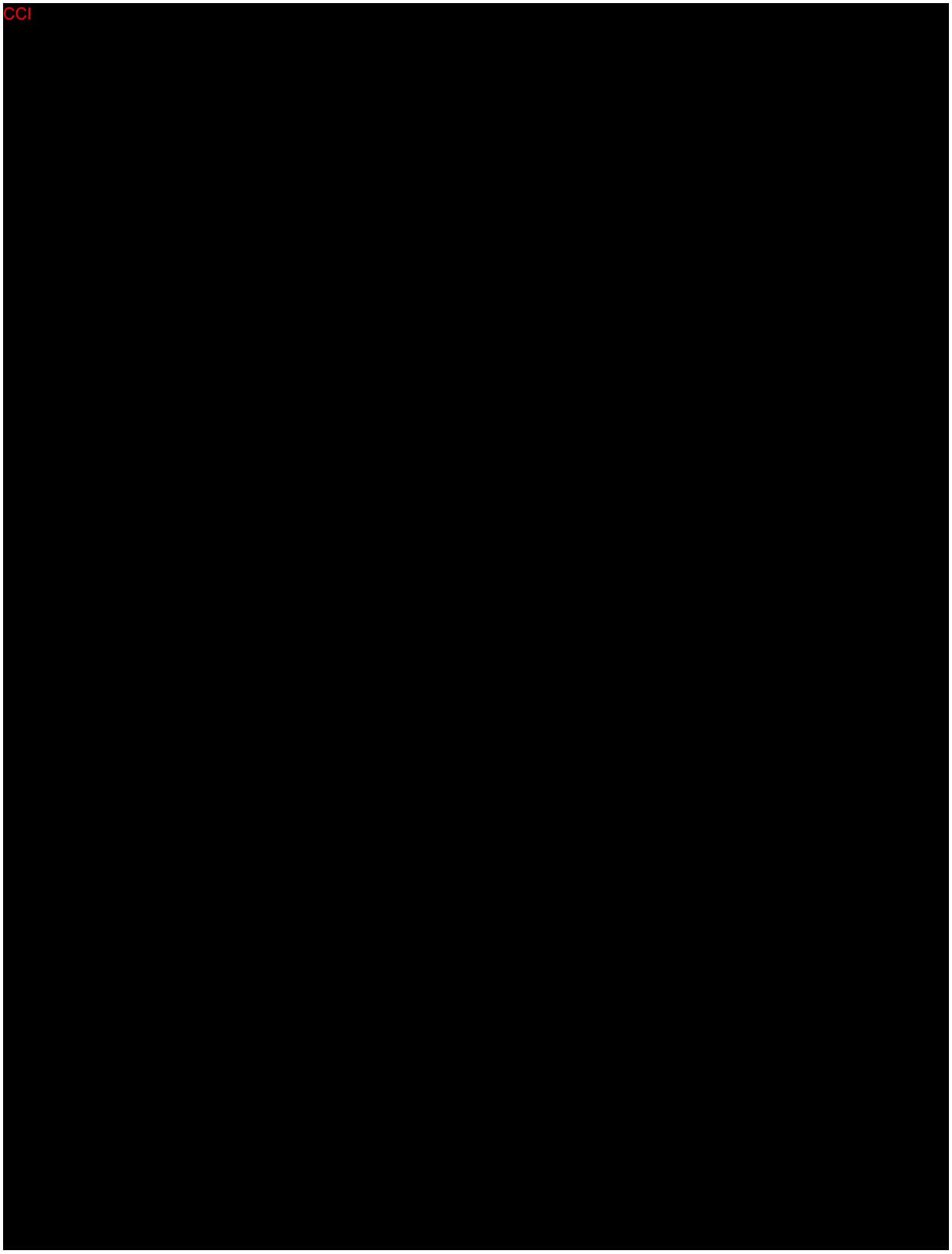
Protocol 331-12-284



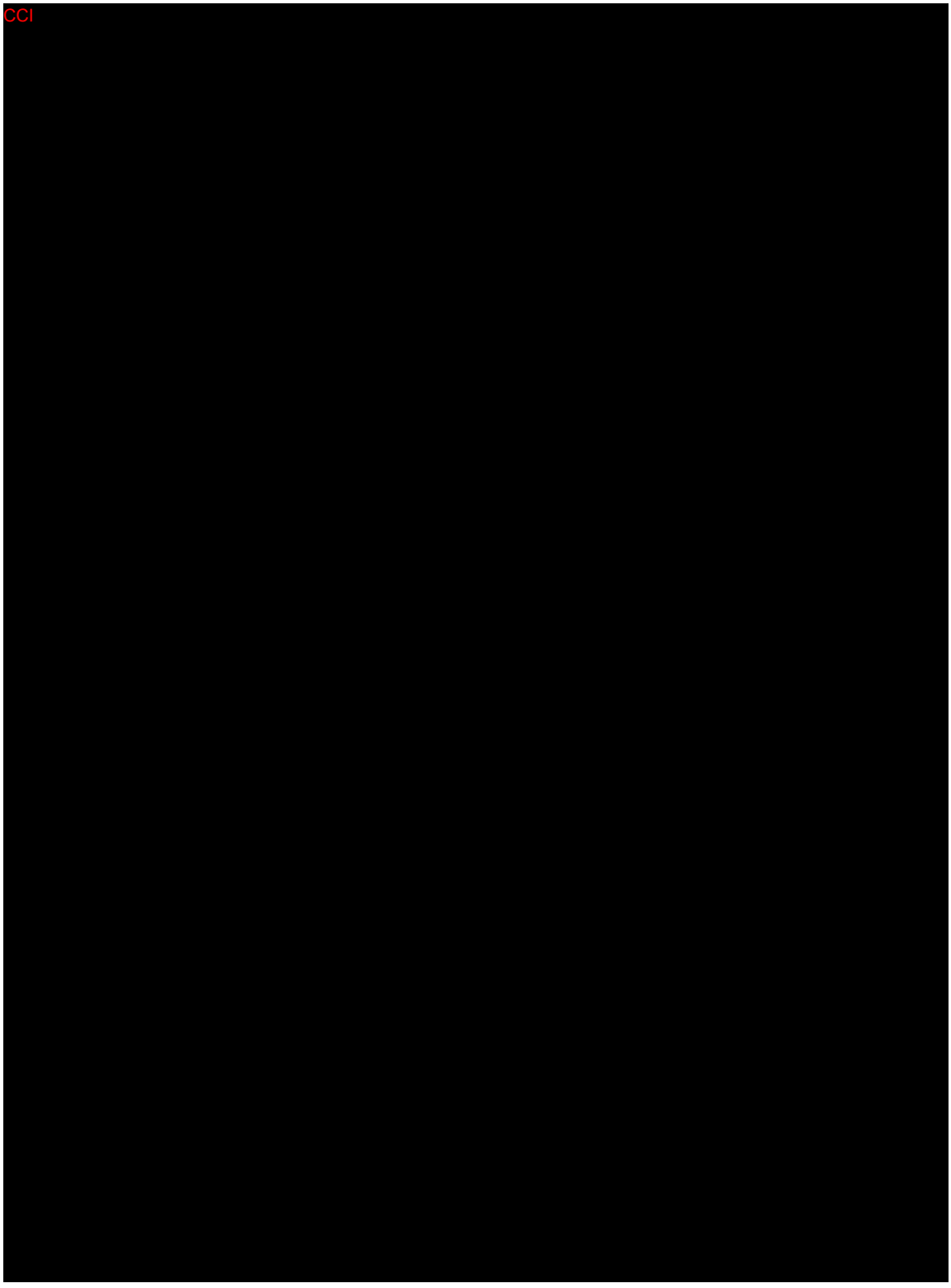
Protocol 331-12-284



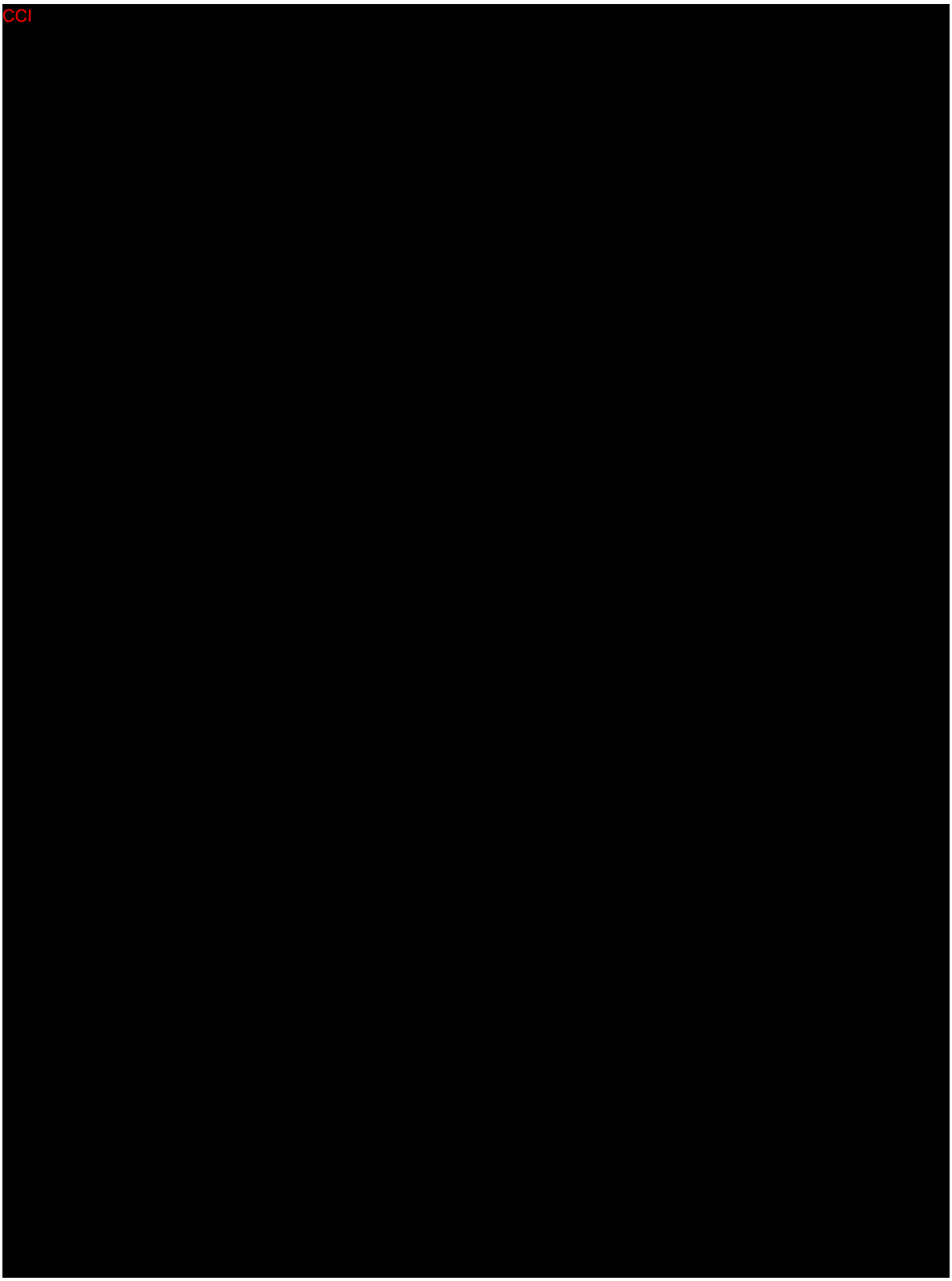
Protocol 331-12-284



Protocol 331-12-284



Protocol 331-12-284



Protocol 331-12-284

Appendix 14 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related 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.

Protocol 331-12-284

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.

Appendix 15 Hachinski Ischemic Scale (Rosen Modification)

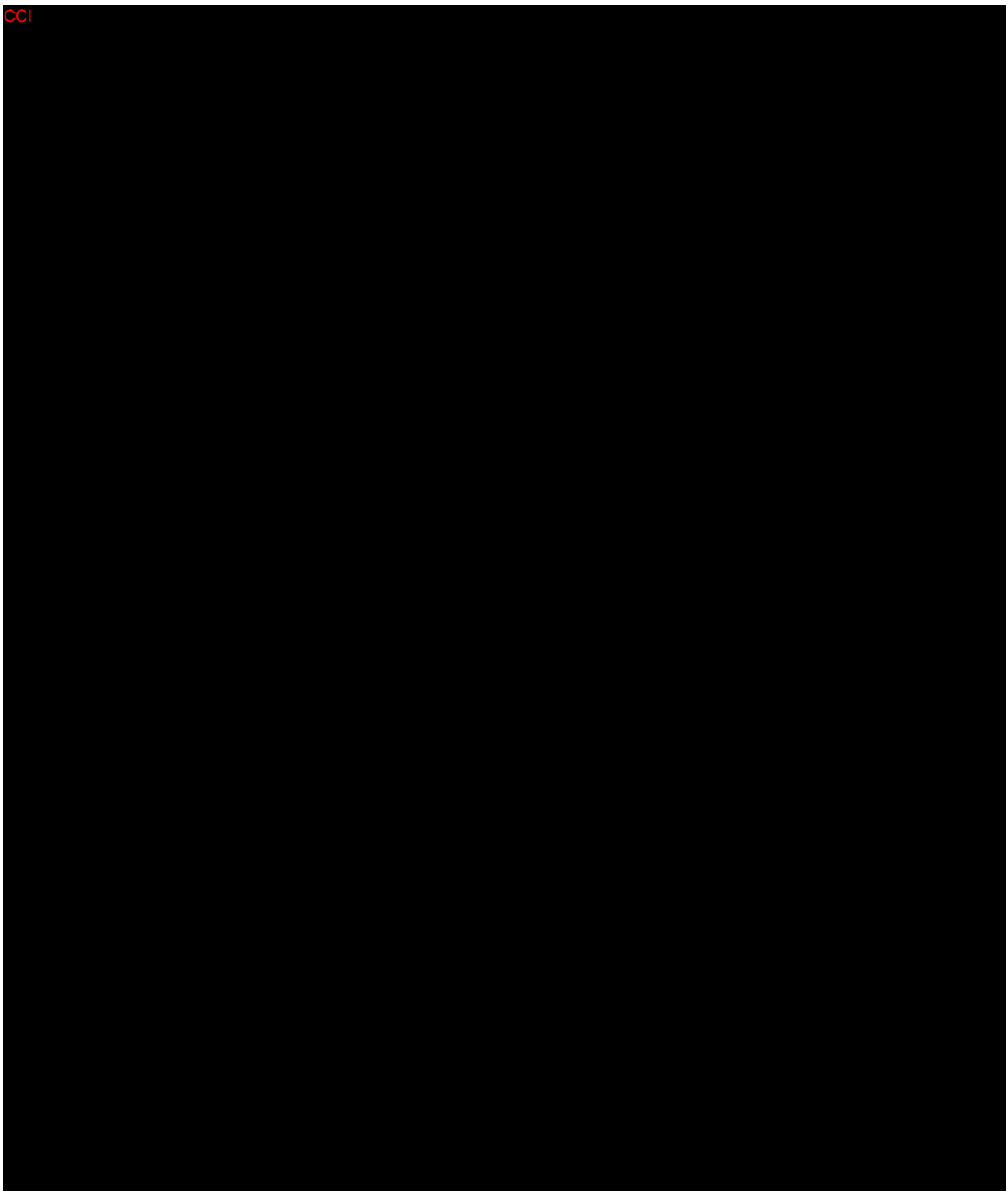
Please complete the following scale using information obtained from the subject's history and neurological examination. Indicate if a clinical feature is present or absent by selecting the appropriate score.

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

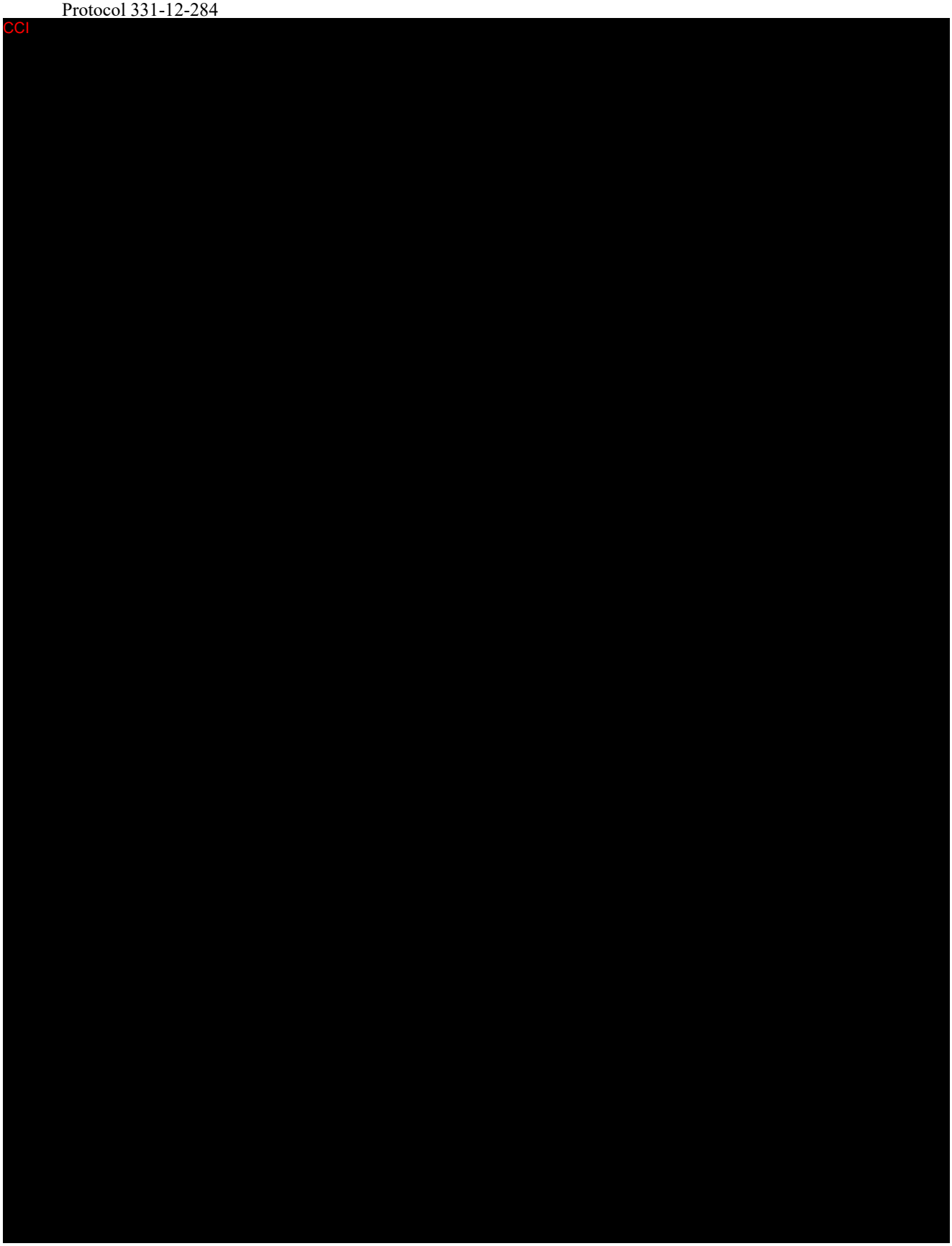
Total Score: _____

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.

Protocol 331-12-284

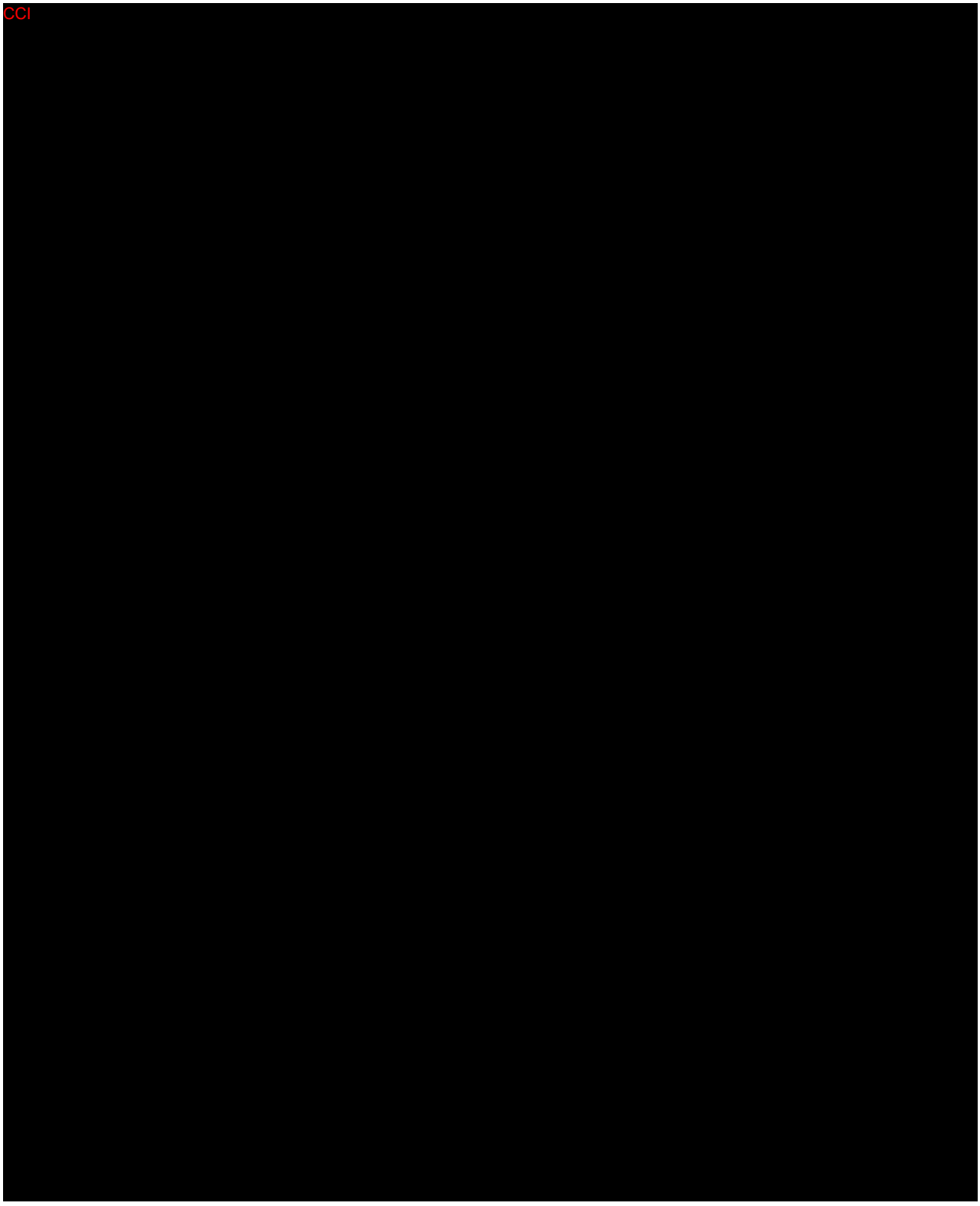


Protocol 331-12-284

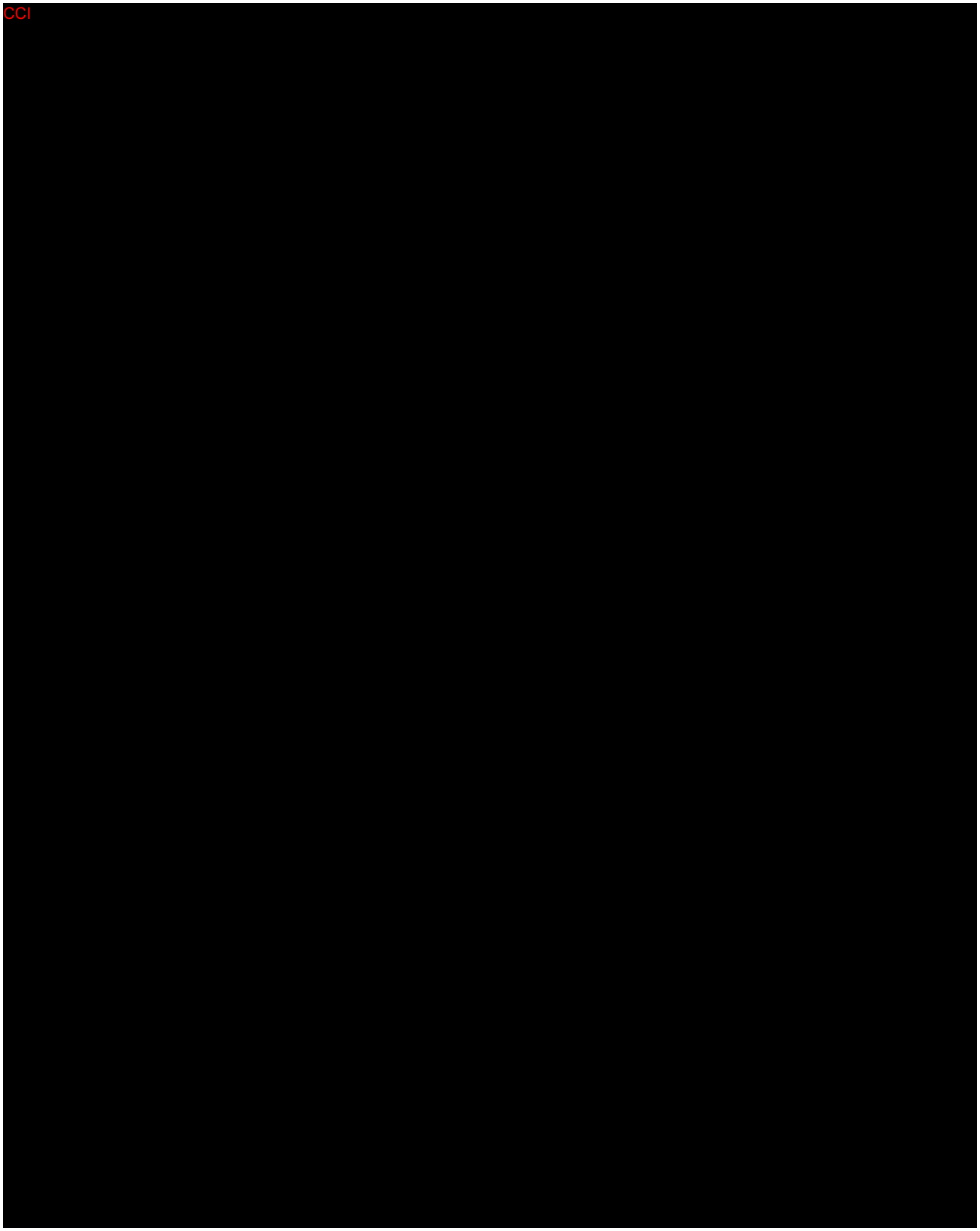


Protocol 331-12-284

Protocol 331-12-284

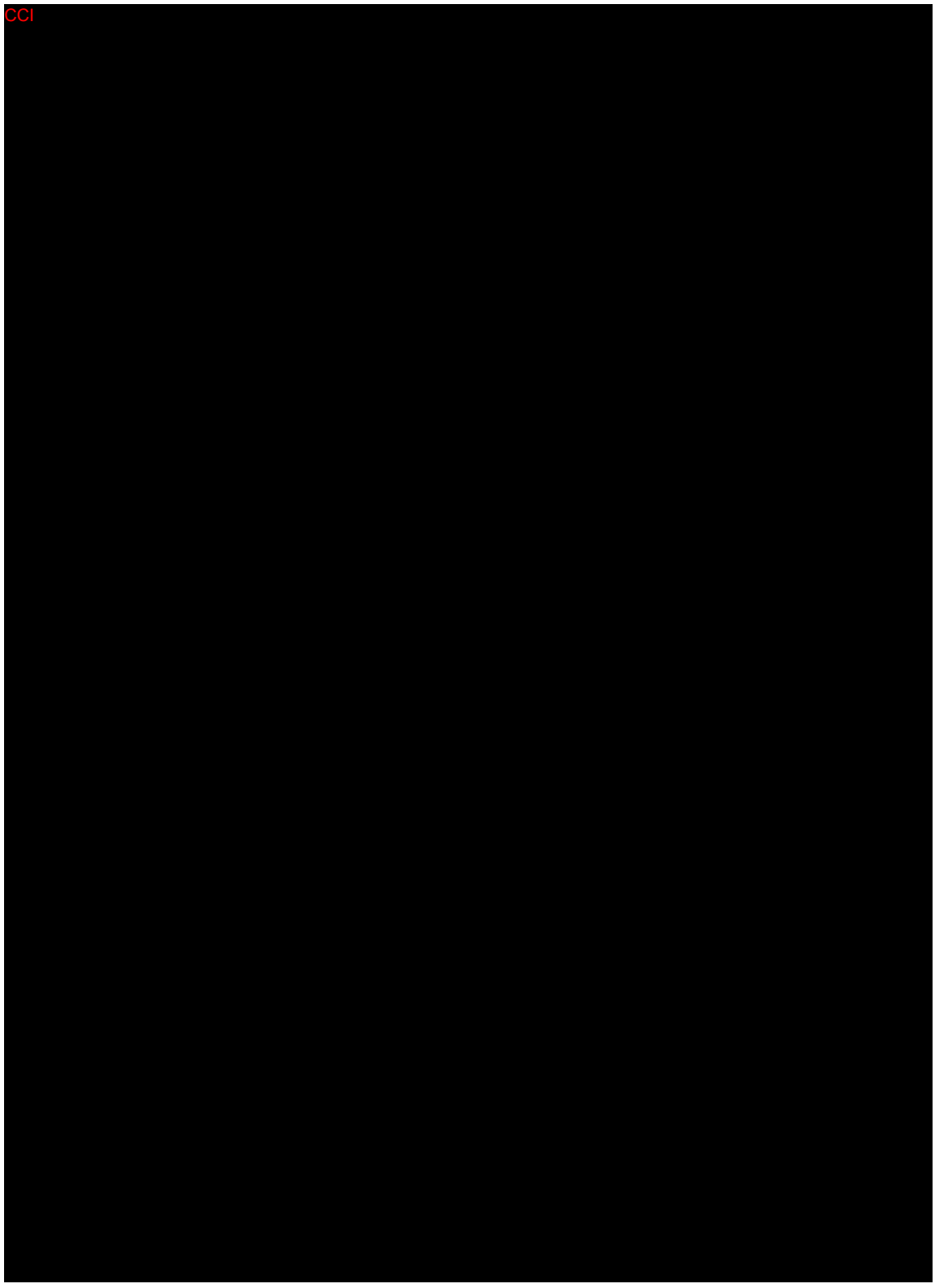


Protocol 331-12-284

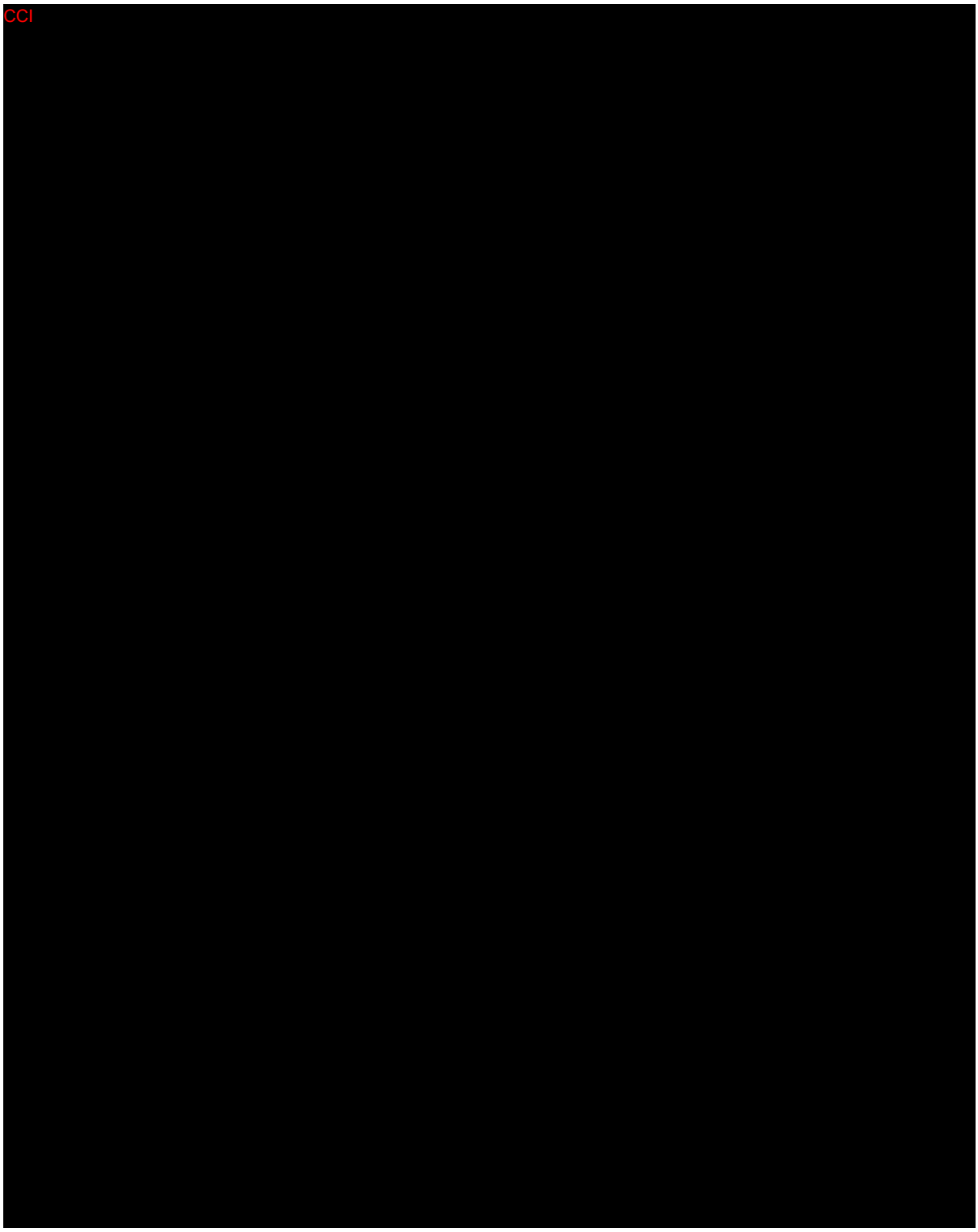


Protocol 331-12-284

Protocol 331-12-284



Protocol 331-12-284



Protocol 331-12-284

Protocol 331-12-284

Appendix 20 Mini-Mental State Examination (MMSE)

Mini-Mental State Examination (MMSE)

Name: _____ **Age:** _____ **Years of School Completed:** _____

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 (circle 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 (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.

Protocol 331-12-284

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 (circle 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 (circle one)	
APPLE		0	1
PENNY		0	1
TABLE		0	1

NAMING*

	Response	Score (circle 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.

Protocol 331-12-284

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 (circle 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 (circle 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 (circle 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)	
0	1

DRAWING

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

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

Score (circle one)	
0	1

Assessment of level of consciousness.

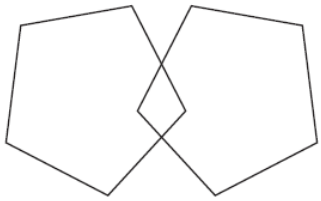
Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive

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

Protocol 331-12-284

CLOSE YOUR EYES

Protocol 331-12-284



Protocol 331-12-284

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

If neither a −70°C nor −20°C freezer is available, the primary and backup pharmacokinetic samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.

CCI [redacted]

Pharmacokinetic [redacted] Sample Shipment

Plasma [redacted] 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.

Protocol 331-12-284

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

Amendment Number: 1

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.

Protocol 331-12-284

- 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 [redacted] 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:

- **<u>Bold and underlined text:</u>** 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.

Protocol 331-12-284

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~~ ~~**Phone:** 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 capable of providing informed 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***

Location	Current Text	Revised Text
		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.
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 follows:***

Protocol 331-12-284

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 *(Day 4 [+2 days]*)**	**Day ~~15(day~~ after *the* Week 2 visit *(Day 15 [±2 days]*)**	**Day ~~29(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***[a]	2 mg/***day***[b]
Placebo	<---------->			

[a] ***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).***

[b] ***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 Trial Design 12-week, Double-blind Treatment Period	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 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. 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 first dose of IMP will be administered on the day after the Baseline visit (i.e., 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 (i.e., Day 4 [+2 days]).*** ***The dose will then be increased to 1 mg/day starting on the day after the Week 2 visit (i.e., 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). ~~**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***

Location	Current Text	Revised Text
		visit (i.e., 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 (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. ***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 (***or matching placebo***) will be discontinued from the trial. If a subject is ***discontinued from the trial~~withdrawn~~***, every effort will be made to complete all of the Week 12/***Early termination*** (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 a	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~~may~~*** be seen in the investigator's clinic or (if a clinic visit is not possible) assessed by telephone contact with the subject and

Protocol 331-12-284

Location	Current Text	Revised Text
	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.	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.*** ~~**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 ≥ 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 ***of the brain,*** which was performed after the onset of symptoms of dementia, ***with findings*** 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 ≥ 4 on the agitation/aggression item of the ***Neuropsychiatric Inventory-Nursing Home (***NPI-NH***)***.

Location	Current Text	Revised Text
	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, ***polypharmacy***) 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 ***pulmonary or cerebral*** 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 **30** 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. 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	~~**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**~~

Protocol 331-12-284

Location	Current Text	Revised Text
	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.~~
CCI [redacted]	[redacted]	[redacted]
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 **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. **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**

Protocol 331-12-284

Location	Current Text	Revised Text
		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 Pharmacokinetics and Pharmacodynamics	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 recently was 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.	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 ~~**recentlywas**~~***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.
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. 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 the subject's capacity to provide informed consent 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 subject. An interactive voice response system (IVRS) or interactive web response	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. ***Additional requirements for obtaining informed consent from this vulnerable subject population are provided in Section 3.4.1.*** ~~**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 the subject's capacity to provide informed consent during the screening period and throughout the course of the study; if the subject is no longer deemed capable**~~

Protocol 331-12-284

Location	Current Text	Revised Text
	system (IWRS) will be used to obtain the subject study identification number for each subject with a signed ICF.	~~**of providing informed consent, informed consent must be obtained 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 Type/Design of Trial Screening Period	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 patient's daily behavior will be logged into an eDiary by the caregiver.	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 patient's daily behavior will be logged into an eDiary by the caregiver ***and/or facility staff.***
Section 3.1 Type/Design of Trial 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 (refer to Table 3.2-1). 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 in vestigator's clinical evaluation of the subject's efficacy and tolerability.	***Subjects will follow a titration schedule to gradually increase their dose of the IMP to the target dose (refer to Table 3.2-1).*** ~~**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 (refer to Table 3.2-1). 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.**~~

Protocol 331-12-284

Location	Current Text	Revised Text
Section 3.1 Type/Design of Trial 12-week, Double-blind Treatment Period	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 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. 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.	~~**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 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. 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.**~~ ***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.***
Section 3.1 Type/Design of Trial 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 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.	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***~~**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. ~~**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***

Protocol 331-12-284

Location	Current Text	Revised Text
		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**~~

Treatment Group	**Recommended Daily Dose Administered**			
	Day ~~1(day~~ after *the* Baseline visit *(Day 1*)	**Day ~~4 (day~~ after *the* Day 3 visit *(Day 4 [+2 days]*)**	**Day ~~15(day~~ after *the* Week 2 visit *(Day 15 [±2 days]*)**	**Day ~~29(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***[a]	2 mg***/day***[b]
Placebo	<---------->			

[a] ~~**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).***

[b] ***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.***

Protocol 331-12-284

Location	Current Text	Revised Text
Section 3.2 Treatments	The first dose of the IMP will be administered on Day 1, i.e., the day after the Baseline visit. On Day 4, i.e., the day after the Day 3 visit, the dose will be increased to 0.5 mg/day of brexpiprazole (or matching placebo) for all subjects; and on Day 15 i.e., the day after the Week 2 visit, the dose will be increased to 1 mg/day of brexpiprazole (or matching placebo) for all subjects. 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 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. 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 first dose of IMP will be administered on the day after the Baseline visit (i.e., 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 (i.e., Day 4 [+2 days]).*** ***The dose will then be increased to 1 mg/day starting on the day after the Week 2 visit (i.e., 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). 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 (i.e., 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 (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. 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).***

Protocol 331-12-284

Location	Current Text	Revised Text
		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*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.**~~
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 ≥ 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 reversible factors (e.g., pain, infection) and trial of nonpharmacological interventions.	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 ***of the brain,*** which was performed after the onset of symptoms of dementia, ***with findings*** 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 ≥ 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 reversible factors (e.g., pain, infection, ***polypharmacy***) and trial of nonpharmacological interventions.
Section 3.4.1 Informed Consent	Written informed consent will be obtained from the subject, if deemed capable by the investigator, and acknowledgement from the subject's legally acceptable representative, in accordance with state and/or local regulations, prior to initiation of any study protocol-required procedures. Alternatively, if the subject is deemed incapable of providing consent by the	***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 study. Once these determinations are made by the investigator, the following options for obtaining informed consent from***

Protocol 331-12-284

Location	Current Text	Revised Text
	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 study 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 subject.	***and/or on behalf of the subject must be followed:*** ~~**Written informed consent will be obtained from the subject, if**~~ ***If the subject is*** deemed capable by the investigator, ***written informed consent will be obtained from the subject prior to the initiation of any study protocol-required procedures. In such cases,*** ~~**and**~~ 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***~~**,**~~ 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**~~***f*~~ the subject ***was initially deemed capable*** of providing informed consent ***but*** is no longer deemed ***so***, informed consent must be obtained from the legally acceptable representative, and assent ~~***from the subject, if possible, will***~~**must** be ***confirmed***~~**obtained from the subject in accordance with state and/or local regulations prior to the initiation of any study protocol-required procedures.**~~ ***I*~~**i**~~***f*~~ the subject is deemed incapable ***by the investigator*** of providing consent ***(e.g.,*** ~~**minors,**~~ ***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***, if possible,*** will be ***confirmed***~~**obtained**~~ ***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***

Location	Current Text	Revised Text
		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 study entry, but subsequent dissents to participate in the trial, the subject will be early terminated from the trial.***
Section 3.4.1 Informed Consent	Consent will be documented on a written ICF. The ICF will be approved by the same IRB/IEC that approves this protocol. Each ICF will comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline 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). When a study includes subjects who may not have the capacity to provide informed consent, the investigator will be required to assess capacity. If the subject is deemed capable of providing informed consent, then the subject can be enrolled with the consent of the subject. If the subject is deemed to not have the capacity to provide informed consent (e.g., minors, subjects with severe dementia), then the subject can only be enrolled with the consent of the subject's legally acceptable	***Section 3.4.1.2 Documentation of Informed Consent*** Consent will be documented on a written ICF. The ICF will be approved by the same IRB/IEC that approves this protocol. Each ICF will comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guideline 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). ~~**When a study includes subjects who may not have the capacity to provide informed consent, the investigator will be required to assess capacity. If the subject is deemed capable of providing informed consent, then the subject can be enrolled with the consent of the subject. If the subject is deemed to not have the capacity to provide informed consent (e.g., minors, subjects with severe dementia), then**~~

Protocol 331-12-284

Location	Current Text	Revised Text
	representative and the subject must be informed about the study 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.	~~**the subject can only be enrolled with the consent of the subject's legally acceptable representative and *T*t**~~he subject must be informed about the study 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.
Table 3.4-1 Inclusion Criteria	#1 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.	#1 ~~**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.**~~ ***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.***
Table 3.4-1 Inclusion Criteria	#5 Subjects must have a previous MRI or CT scan, which was performed after the onset of symptoms of dementia, consistent with a diagnosis of Alzheimer's disease.	#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.
Table 3.4-1 Inclusion Criteria	#10 Subjects who require 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.	# 10 Subjects who require pharmacotherapy for the treatment of agitation per the investigator's judgment, after an evaluation for reversible factors (e.g., pain, infection, ***polypharmacy***) and trial of nonpharmacological interventions.
Table 3.4-2 Exclusion Criteria	#2 Subjects with a previous MRI or CT scan performed after the onset of symptoms of dementia with findings consistent with a clinically significant	#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

Protocol 331-12-284

Location	Current Text	Revised Text
	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 ***pulmonary or cerebral*** 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 ***~~two~~2 or more*** previous antipsychotic medications for the treatment of agitation associated with Alzheimer's disease.
Table 3.4-2 Exclusion Criteria	#8 • Bipolar I or II disorder, bipolar disorder not otherwise specified • 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 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications). • Eating disorder (including anorexia nervosa or bulimia)--unless resolved with no symptoms for at least 1 year prior to screening	#8 • Bipolar I or II disorder, bipolar disorder not otherwise specified • 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). • Eating disorder (including anorexia nervosa or bulimia)--unless resolved with no symptoms for at least 1 year prior to screening
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	#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.*** Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not

Protocol 331-12-284

Location	Current Text	Revised Text
	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 ***chronic*** ~~**renal**~~***kidney*** disease ~~**(glomerular filtration rate < 60 mL/min/1.73 m^2)**~~.
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***; subjects with clinically relevant dysphagia***.
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 visits***~~**in 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-~~**283**~~***284***.
Table 3.4-2 Exclusion Criteria	#34 Subjects who are being treated with anticoagulants.	#34 Subjects who ***have a medical condition that requires treatment with an***~~**are being treated with**~~ anticoagulant~~**s**~~.
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.

Protocol 331-12-284

Location	Current Text	Revised Text
	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, a new 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 ***retested*** ~~rescreened~~ ***(or the evaluation may be repeated within the screening period) 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, a new screening number assigned, and all screening procedures repeated.
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 **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.

Protocol 331-12-284

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	X	X	X	X	X	X	X	X	X		
Randomize eligible subjects via IVRS/IWRS		X									
IMP dispensing[aa]		X	X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X	X		
ADDITIONAL ENTRANCE/HISTORY											
MRI/CT scan[bb]	***X[bb]***										

Abbreviations: ACTH = adrenocorticotropic hormone; CCI anti-HCV = hepatitis C antibodies; aPTT = activated partial thromboplastin time CCI CGI-S = Clinical Global Impression-Severity of Illness; CMAI = Cohen-Mansfield Agitation Inventory; CCI ***CT = computed tomography;*** ECG = electrocardiogram; ET = early termination; FU = follow up; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; ***IAP = Independent Adjudication Panel;*** ICF = informed consent form; IMP = investigational medicinal product; INR = International Normalized Ratio IVRS = interactive voice response system; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; CCI ***MRI = magnetic resonance imaging;*** NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; CCI ; NPI-NH = Neuropsychiatric Inventory-Nursing Home rating scale; PT = prothrombin time; CCI ; CCI CCI T_4 = thyroxine; TSH = thyroid-stimulating hormone.

.
.
.

d ~~**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***

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.

. . .

e ~~**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 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.***

. . .

g The neurological history and Hachinski Ischemic Scale (Rosen Modification) will be completed to assess eligibility for the trial by the same ~~**neurologist**~~***physician*** 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.***

. . .

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

. . .

n 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.

. . .

bb ***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***.

Protocol 331-12-284

Location	Current Text	Revised Text
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 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.	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 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	• Psychiatric and neurological history will be recorded. • Medications taken within 30 days of screening (signing of ICF/assent) will be recorded.	• 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*** CCI [redacted] ***in order to confirm eligibility***. • Medications taken within 30 days of screening (signing of ICF/assent) will be recorded.
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 a~~**neurologist**~~***physician***. Vital sign measurements (body

Location	Current Text	Revised Text
	pressure, and heart rate) will be recorded...	weight, body temperature, blood 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 ~~**neurologist**~~***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 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 ***and/or facility staff*** 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

Protocol 331-12-284

Location	Current Text	Revised Text
	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.	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 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 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 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**~~ ***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: A complete physical examination (including waist circumference) will be performed at *Week 6 only*. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial	The following additional evaluations will be performed at the designated visits: A complete physical examination (including waist circumference) will be performed at *Week 6 only*. A detailed neurological examination, which will consist of an evaluation of the subject's mental status, cranial

Protocol 331-12-284

Location	Current Text	Revised Text
	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 *Week 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 ~~**neurologist**~~***physician*** at *Week 6* 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 ~~**neurologist**~~***physician***.
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***

Protocol 331-12-284

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 provided in Appendix 13.	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**~~***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 13.
Section 3.7.3.7 Electronic Diary	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.	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 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 [redacted] ***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

Protocol 331-12-284

Location	Current Text	Revised Text
	examination, he or she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Whenever possible, the same individual should perform all physical examinations.	examination, he or she must be permitted by local regulations and his/her name must be included on the ***Form*** FDA ~~**Form**~~1572. Whenever possible, the same individual should perform all physical examinations.
Section 3.7.4.3.2 Neurological Examination	A detailed neurological examination will be performed 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. The neurologist is responsible for performing the neurological examination and must be included on the FDA Form 1572. Whenever possible, the same neurologist should perform all neurological examinations. Any condition present at the post-treatment neurological examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.	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. The ~~**neurologist**~~***physician*** is responsible for performing the neurological examination and must be included on the **Form** FDA ~~**Form**~~1572. Whenever possible, the same ~~**neurologist**~~***physician*** should perform all neurological examinations. Any condition present at the post-treatment neurological 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 Independent Data Monitoring Committee	The data monitoring committee (DMC) will monitor safety in subjects who participate in the trial. The DMC meetings will occur every 6 months, 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 data monitoring committee (DMC) will monitor safety in subjects who participate in the trial. The DMC meetings will occur ***as outlined in the DMC Charter*** ~~**every 6 months**~~, 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.
Section 3.8.3 Individual Subject	The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week	The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 12 must complete the Week

Protocol 331-12-284

Location	Current Text	Revised Text
	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 ***should*~~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.
4.1. Prohibited 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. ***The required duration of washout for selected prohibited medications is provided in Table 4.1-1***. All ***other*** psychotropic agents, ~~**including but 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. ***The oral benzodiazepine therapy permitted during the trial is summarized in Table 4.1-3.***
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.***

Protocol 331-12-284

Location	Current Text	Revised Text
Table 4.1-1 Prohibited Medications	#3 Prior to Randomization Allowed provided that the dose has been stable for 30 days prior to randomization. Antidepressant medications that are CYP2D6 inhibitors are prohibited (see Table 4.1-2 for prohibited antidepressant medications).	#3 Prior to Randomization 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*** During Double-Blind Treatment Period ***Antidepressant medications that are CYP2D6 or CYP3A4 inhibitors are prohibited.*** (see Table 4.1-2 for prohibited antidepressant medications).
Table 4.1-1 Prohibited Medications	Added text	***#5 Anticonvulsants, 7-day washout, prohibited***
Table 4.1-1 Prohibited Medications	#11 Medication Medications to treat other medical conditions, such as hypertension	#11 Medication Medications to treat other medical conditions, such as hypertension***, hypercholesterolemia, etc., and anti-platelet agents.***
Section 5.1 Definitions	***Nonserious adverse events*** are AEs that do not meet the criteria for an SAE.	***Nonserious adverse events*** are AEs that do not meet the criteria for an SAE. ***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: dyskinesia, generalized rigidity, 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.***
Section 5.1 Definitions	**Immediately Reportable Event (IRE)**	**Immediately Reportable Event (IRE)**

Protocol 331-12-284

Location	Current Text	Revised Text
	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 or screening value with an increase in total bilirubin ≥ 2 times the ULN or screening value)	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 ~~**or screening value**~~ with an increase in total bilirubin ≥ 2 times the ULN ~~**or screening value**~~)
Section 5.4 Potential Hy's Law Cases	For subjects that experience an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, 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.	~~**For subjects that experience an elevation in AST or ALT that is ≥ 3 times the upper normal limit, a total bilirubin level should also be evaluated. If the total bilirubin is > 2 times the upper normal limit, confirmatory repeat labs should be drawn within 48 to 72 hours of the initial draw. If these values are confirmed, study 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 study with nonexclusionary elevated transaminase levels at baseline, please discuss any potential drug-induced liver injury events with the medical monitor.**~~ ***For subjects that experience an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, 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.***
Section 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	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

Protocol 331-12-284

Location	Current Text	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.	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.
Section 8.1 Packaging and Labeling	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 cannot be dispensed to another 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.
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 ***or other unique identifier as appropriate)*** and date of each clinician (or designee) who made an entry in the progress notes
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. ***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.
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.~~**Version No.**~~

Protocol 331-12-284

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

Protocol 331-12-284

Appendix 2

Institutions Concerned With the Trial

Safety Reporting

Revised Text

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

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

.
.
.

Medical Monitors

North America:

PPD

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

Protocol 331-12-284

Appendix 9

Clinical Global Impression (CGI)

Revised Text

CCI [redacted]

[redacted]

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.

Protocol 331-12-284

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 [redacted]
- 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.
- CCI [redacted]
- 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.

Protocol 331-12-284

MODIFICATIONS TO PROTOCOL:

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

General Revisions:

All changes by section are provided below.

Sectional Revisions:

Location	Current Text	Revised Text
Title Page	Director, Global Clinical Development PPD Phone: PPD Fax: PPD E-mail: PPD ... Original Protocol: 06 May 2013 Date of Amendment 1: 16 December 2013	Director, Global Clinical Development PPD Phone: PPD Fax: PPD E-mail: PPD PPD ***Phone:*** PPD ***Fax:*** PPD PPD ... Original Protocol: 06 May 2013 Date of Amendment 1: 16 Dec~~ember~~ 2013 ***Date of Amendment 2: 07 Jul 2014***
Synopsis Trial Design	... 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 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 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. 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** ~~**in a 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

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. ***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 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 ***required*** per the local guidelines of **the institutionalized setting or according to the discretion of the principal investigator** ~~**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

Location	Current Text	Revised Text
	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 ***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 ~~**at**~~**in** the investigator's **site**~~**.clinic or (if**~~ **If** a clinic visit is not possible~~**)**~~***, the subject should be*** assessed by telephone contact with the subject and a caregiver. ***For all subjects who terminate early from the 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**3**~~2~~-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 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 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 of the brain, which was performed after the onset of symptoms of dementia, with	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 (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. In both the institutionalized and non-institutionalized settings, the subject must have a caregiver who can spend a minimum of 2 hours per**

Protocol 331-12-284

Location	Current Text	Revised Text
	findings 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 ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory—Nursing Home (NPI-NH). ... Subjects must have been residing at their current facility for at least 1 month before screening and be expected to remain at the same facility for the duration of the trial. Subjects may receive supervised day passes at the discretion of the investigator. 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 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.	**day for 4 days per week with the subject in order to assess changes in the 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 have**~~**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 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 total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory—Nursing Home (NPI-NH). ***The NPI-NH will be used for both institutionalized and non-institutionalized subjects; however, the Occupational Disruptiveness questions will not be answered for non-institutionalized subjects. Instead, the Distress questions from the Neuropsychiatric 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 "NPI/NPI-NH".***... Subjects must have been residing at their current **location** ~~**facility**~~ for at least **14 days**~~**1 month**~~ before screening and be expected to remain at the same **location** ~~**facility**~~ for the duration of the trial. ***Subjects from a***

Protocol 331-12-284

Location	Current Text	Revised Text
		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, o**vernight 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,***

Protocol 331-12-284

Location	Current Text	Revised Text
		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 **an**other individual (e.g., family member, family friend, hired professional caregiver) ~~**who meets the caregiver requirements**~~ **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**. 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***.
Synopsis Trial Sites	It is planned that approximately 330 subjects will be screened at approximately 30 trial centers worldwide so that 230 subjects will be randomized to treatment.	It is planned that approximately 330 subjects will be screened at approximately **46**~~**30**~~ trial centers worldwide so that 230 subjects will be randomized to treatment.
Synopsis Investigational Medicinal Product, Dose, Formulation, Mode of Administration	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 the same time each day, particularly prior to visits with pharmacokinetic sampling.	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.
CCI [redacted]	[redacted]	[redacted]

Protocol 331-12-284

Location	Current Text	Revised Text
		CCI
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 ***cytochrome P450 (***CYP***)*** 2D6 metabolism status and other drug metabolizing enzymes and transporters~~,~~ as necessary, ***as well as banking for potential future analysis,*** 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

Protocol 331-12-284

Location	Current Text	Revised Text
	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. CCI [redacted] ... 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 ***(Day 0 Visit)*** to the ~~**endpoint**~~ ***end of the double-blind treatment period (Week 12 visit)*** in the CMAI total score. CCI [redacted] ... 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,**~~ ***it*** result~~**ing**~~ in a sample size of 115 subjects/arm, which means the total sample size is 230 subjects.
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.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately **4** **3**.5 years, of which approximately **4** **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. ***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.***
List of Abbreviations and Definition of Terms	-- -- --	***ACR Albumin-to-creatinine ratio*** ***NPI Neuropsychiatric Inventory*** CCI [redacted]

Protocol 331-12-284

Location	Current Text	Revised Text
Section 1.3 Known and Potential Risks and Benefits	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 [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US. Brexpiprazole has been well tolerated by healthy volunteers at single doses up to 6 mg and at multiple doses up to 2 mg/day. In trials, brexpiprazole has been well tolerated at multiple doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder, up to 4 mg/day in subjects with MDD who received concomitant ADT, and up to 4 mg/day in adults with ADHD who received concomitant stimulant therapy. Recently completed phase 2 clinical trials evaluated multiple oral doses up to 6 mg/day in subjects with schizophrenia; up to 2 mg/day when coadministered with marketed ADT in subjects with MDD; and up to 2 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD. In the 25 completed brexpiprazole trials conducted under US Investigational New Drug Application (IND) (19 phase 1 trials, 1 phase 1b trial, and 5 phase 2 trials), 1204 of 1773 (67.9%) subjects who received brexpiprazole either alone or coadministered with another marketed medication reported at least 1 treatment-emergent adverse event (TEAE) compared with 325 of 520 (62.5%) subjects who received placebo either alone or coadministered with another marketed medication. The most frequently reported TEAEs (incidence ≥ 5% of the total brexpiprazole group and more than total placebo group) in all subjects who received brexpiprazole were	~~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 [MDD], and adult attention-deficit/hyperactivity disorder [ADHD]) and 5 clinical trials (3 completed and 2 ongoing) conducted outside of the US.~~ ~~Brexpiprazole has been well tolerated by healthy volunteers at single doses up to 6 mg and at multiple doses up to 2 mg/day. In trials, brexpiprazole has been well tolerated at multiple doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder, up to 4 mg/day in subjects with MDD who received concomitant ADT, and up to 4 mg/day in adults with ADHD who received concomitant stimulant therapy. Recently completed phase 2 clinical trials evaluated multiple oral doses up to 6 mg/day in subjects with schizophrenia; up to 2 mg/day when coadministered with marketed ADT in subjects with MDD; and up to 2 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD.~~ ~~In the 25 completed brexpiprazole trials conducted under US Investigational New Drug Application (IND) (19 phase 1 trials, 1 phase 1b trial, and 5 phase 2 trials), 1204 of 1773 (67.9%) subjects who received brexpiprazole either alone or coadministered with another marketed medication reported at least 1 treatment-emergent adverse event (TEAE) compared with 325 of 520 (62.5%) subjects who received placebo either alone or coadministered with another marketed medication. The most frequently reported TEAEs (incidence ≥ 5% of the total~~

Location	Current Text	Revised Text
	dizziness (8.7%), insomnia (7.0%), nausea (6.2%), and akathisia (5.8%). In the total placebo group, headache (9.8%) was the most frequently reported TEAE (incidence ≥ 5% of subjects). In the total brexpiprazole group, 67 of 1773 (3.8%) subjects discontinued the study due to 1 or more TEAE, compared with 12 of 520 (2.3%) of subjects in the total placebo group. One death has been reported in the 25 trials completed under the US INDs as of the 20 Sep 2012 cutoff date. This death occurred 12 days after the subject received the last dose of brexpiprazole in the phase 2, double-blind schizophrenia trial (Trial 331-07-203), and the death was not considered by the investigator to be not related to the IMP. One additional death was reported in the ongoing, phase 2, open-label MDD trial (Trial 331-08-212). The subject was reported to have died from progressive metastatic disease approximately 2 months after the initial onset of the event (81 days after the last dose of the IMP). The event was assessed as not related to the IMP by the investigator. Serious TEAEs have been reported in 20 of 1773 (1.1%) subjects who received brexpiprazole (either alone or coadministered with another medication) and 9 of 520 (1.7%) subjects who received placebo (either alone or coadministered with another medication) in combined brexpiprazole trials completed under the US INDs as of the 20 Sep 2012 cutoff date. Treatment with brexpiprazole does not appear to promote suicidal behavior in subjects with MDD or schizophrenia. 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	~~brexpiprazole group and more than total placebo group) in all subjects who received brexpiprazole were dizziness (8.7%), insomnia (7.0%), nausea (6.2%), and akathisia (5.8%). In the total placebo group, headache (9.8%) was the most frequently reported TEAE (incidence ≥ 5% of subjects). In the total brexpiprazole group, 67 of 1773 (3.8%) subjects discontinued the study due to 1 or more TEAE, compared with 12 of 520 (2.3%) of subjects in the total placebo group.~~ ~~One death has been reported in the 25 trials completed under the US INDs as of the 20 Sep 2012 cutoff date. This death occurred 12 days after the subject received the last dose of brexpiprazole in the phase 2, double-blind schizophrenia trial (Trial 331-07-203), and the death was not considered by the investigator to be not related to the IMP. One additional death was reported in the ongoing, phase 2, open-label MDD trial (Trial 331-08-212). The subject was reported to have died from progressive metastatic disease approximately 2 months after the initial onset of the event (81 days after the last dose of the IMP). The event was assessed as not related to the IMP by the investigator.~~ ~~Serious TEAEs have been reported in 20 of 1773 (1.1%) subjects who received brexpiprazole (either alone or coadministered with another medication) and 9 of 520 (1.7%) subjects who received placebo (either alone or coadministered with another medication) in combined brexpiprazole trials completed under the US INDs as of the 20 Sep 2012 cutoff date. Treatment with brexpiprazole does not appear to promote suicidal behavior in subjects with MDD or schizophrenia.~~

Protocol 331-12-284

Location	Current Text	Revised Text
	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 ± 1.0 mg/day). Refer to the current Investigator's Brochure for a summary of available nonclinical and clinical safety data.[16]	***Based on the Investigator's Brochure,[16] 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 ≥ 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 ≥ 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***

Location	Current Text	Revised Text
		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*** • ***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 (i.e., brexpiprazole 5~~.0~~ ± 1~~.0~~ mg/day). ***Two deaths have been reported in the 30 completed clinical trials. One***

Protocol 331-12-284

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 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.[16]
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 **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**

Protocol 331-12-284

Location	Current Text	Revised Text
	may contribute to the risk of increased death.	**days per week with the subject in order to assess changes in the subject's condition ~~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 may contribute to the risk of increased death.~~**
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 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.	... 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. 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 ~~in a 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 16.*** **~~Subjects may receive supervised~~**

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 Type/Design of Trial Screening Period	The patient's daily behavior will be logged into an eDiary by the caregiver and/or facility staff.	The ~~**patient's**~~ **subject's** ~~**daily**~~ behavior will be logged into an eDiary by the caregiver and/or facility staff.
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 per the local guidelines of the facility. Subjects will be evaluated at Baseline and at Day 3 and Weeks 2, 4, 6, 8, 10, and 12 during the double-blind treatment period. Beginning at Week 3, the subject's identified 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. Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1).	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** ~~**the facility**~~. Subjects will be evaluated at Baseline~~**, and at**~~ 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 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.*** Trial-related efficacy and safety assessments will be performed as outlined in the Schedule of Assessments (Table 3.7-1).
Section 3.1 Type/Design of Trial 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 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.	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 ~~**atin**~~ the investigator's **site**~~**.clinic or (if**~~ **If** a

Protocol 331-12-284

Location	Current Text	Revised Text
	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.	clinic visit is not possible~~)~~***, the subject should be*** assessed by telephone contact with the subject and a caregiver. ***For all subjects who terminate early from the 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**3**~~2~~-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*** 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 Trial Design Schematic	--	
Section 3.2 Treatments	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 the same time each day, particularly prior to visits with pharmacokinetic sampling.	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.
Section 3.3	The subject population will include	The subject population will include

Protocol 331-12-284

Location	Current Text	Revised Text
Trial Population	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 of the brain, which was performed after the onset of symptoms of dementia, with findings 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 ≥ 4 on the agitation/aggression item of the NPI-NH. ... Subjects must have been residing at their current facility for at least 1 month before screening and be expected to remain at the same facility for the duration of the trial. Subjects may receive supervised day passes at the discretion of the investigator. 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 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 30 trial centers	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. 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.** ~~**in a 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 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 total score (frequency x severity) of ≥ 4 on the agitation/aggression item of the NPI-NH. ***The NPI-NH will be used for both institutionalized and non-institutionalized subjects; however, the Occupational Disruptiveness questions will not be answered for non-institutionalized subjects. Instead, the Distress questions from the Neuropsychiatric Inventory (NPI) will replace the Occupational Disruptiveness questions for non-***

Protocol 331-12-284

Location	Current Text	Revised Text
	worldwide in order to randomize 230 subjects.	***institutionalized subjects. This 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 days**~~**1 month**~~ before screening and be expected to remain at the same **location** ~~**facility**~~ for the duration of the trial. ***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** ~~**subjects**~~ may receive supervised day passes at the discretion of the investigator**; however, o**vernight 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**~~

Protocol 331-12-284

Location	Current Text	Revised Text
		~~**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 ~~**30**~~**46** trial centers worldwide in order to randomize 230 subjects.
Section 3.3.1 Caregiver Requirements	Null (new section)	***3.3.1.1 Non-institutionalized Subjects*** ***In a non-institutionalized setting, the subject's caretaker is the person who lives with and cares for the subject on a regular basis. For example, caring for a subject on a regular basis may include the following activities: assisting with dispensing of IMP; observing the subject's general medical condition, including nutrition and hydration intake; reducing the chance of fall; and assisting the subject if emergency medical care is needed by contacting appropriate emergency services, the subject's primary physician, or the principal investigator, whatever is warranted. The caretaker may be supported in providing care to the subject by a professional(s), friend(s), or family 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 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. 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***

Location	Current Text	Revised Text
		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 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, 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 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 (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.***

Protocol 331-12-284

Location	Current Text	Revised Text
Section 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 study. 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 study 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 in accordance with state and/or local regulations prior to initiation of any study protocol-required procedures. • 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 of any study protocol-required procedures. ... • If the subject initially provided assent at study entry, but subsequent dissents to participate in the trial, the subject will be early terminated from the trial.	The investigator must assess the capacity of the subject to provide informed consent during the screening period and throughout the course of the study. ***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 study 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 study protocol-required procedures. • ~~**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 of any study protocol-required procedures.**~~ ... • If the subject initially provided assent at study entry, but subsequent***ly*** dissents to participate in the trial, the subject will be early terminated from the trial. • ***If the subject was initially deemed capable of providing***

Protocol 331-12-284

Location	Current Text	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.
Table 3.4.2-1 Inclusion Criteria	#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 expected to remain at the same facility for the duration of the trial.	#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 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 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.	#7 ***Institutionalized*** ~~**S**~~**s**ubjects **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 subject's behavior. The identified caregiver **can be a staff member of the institutionalized setting** ~~**will be a member of the residential facility**~~ or **an**other individual (e.g., 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.***
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: ...	#8 Subjects who have been diagnosed with an Axis I disorder (DSM-IV-TR criteria) including, but not limited to: ...

Protocol 331-12-284

Location	Current Text	Revised Text
	Current major depressive episode —unless on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization.	Current major depressive **disorder** ~~**episode**~~ —unless on a stable dose(s) of antidepressant medication(s) for the 30 days prior to randomization.
	#13 Subjects with insulin-dependent diabetes mellitus (IDDM) (i.e., any subjects using insulin) are 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: ...	#13 Subjects with insulin-dependent diabetes mellitus (IDDM) (i.e., any subjects using insulin) **may be eligible for the trial if their condition is well controlled and if they do not have current microalbuminuria** ~~**are 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 chronic kidney disease.	#14 Subjects with **clinically significant**~~**stage 3 or higher**~~ chronic kidney disease ***based on the investigator's judgment***.
	#27 Subjects who have significant risk of death within the next 6 months based on the investigator's judgment.	~~**#27 Subjects who have significant risk of death within the next 6 months based on the investigator's judgment.**~~
	#31 ... In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: ... • QTcF ≥ 450 msec	#**30** ~~**31**~~ ... In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: ... • ***ACR > 30 mg/g (calculated as urine albumin [mg/dL] / urine creatinine [g/dL])*** ... • QTcF ≥ 450 msec ***in men and ≥ 470 msec in women (refer to Section 3.7.4.4 for further details)***
	#32 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	#**31** ~~**32**~~ 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

Protocol 331-12-284

Location	Current Text	Revised Text
	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 ***with spermicide***, 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.	#**39** ~~**40**~~ 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.
CCI		
CCI		

Protocol 331-12-284

Location	Current Text	Revised Text
Section 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 approximately4 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. ... CCI [redacted] the CST will perform regular quality reviews of CMAI data and will compare these data against other sources of behavioral information, including patterns of movement using actigraphy technology (refer to Section 3.7.3.6), daily behavior logs collected by caregivers through electronic diaries (refer to Section 3.7.3.7), and investigator progress notes. Trial assessment time points are summarized in Table 3.7-1.	The time from enrollment of the first subject to the last subject's last trial visit will be approximately **3.5** ~~**4.5**~~ years, of which approximately **4** **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. ***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.*** ... CCI [redacted], the CST will perform regular quality reviews of CMAI data and will compare these data against other sources of behavioral information, including patterns of movement using actigraphy technology (refer to Section 3.7.3.~~6~~**7**), ~~**daily**~~ behavior logs collected by caregivers through electronic diaries (refer to Section 3.7.3.~~7~~**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 institutionalized subjects).*** Trial assessment time points are summarized in Table 3.7-1.

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments (truncated)

Assessment	Visit											
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	~~Between clinic visit phone call~~[e]	FU~~/dc~~	*Wk 16*[d]
EFFICACY												
...												
NPI-NH ***(for institutionalized subjects) or NPI/NPI-NH (for non-institutionalized subjects)***	X	X		X	X	X	X	X	X			
OTHER												
CCI [redacted]		[redacted]				[redacted]			[redacted]			
[redacted]		[redacted]				[redacted]			[redacted]			
[redacted]		[redacted]				[redacted]			[redacted]			
[redacted]		[redacted]				[redacted]			[redacted]			
...												
SAFETY												
...												
Adverse events[w]	X	X	X	X	X	X	X	X	X	~~X~~	X	
...												
Concomitant medications[z]	X	X	X	X	X	X	X	X	X	~~X~~	X	
Mortality assessment[aa]												***X***

Table 3.7-1 Schedule of Assessments (truncated)

Assessment	Visit											
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	~~Between clinic visit phone call~~[e]	FU~~dc~~	*Wk 16*[d]
OTHER PROCEDURES												
Register trial visit in IVRS/IWRS	X	X	X	X	X	X	X	X	X			
Randomize eligible subjects via IVRS/IWRS		X										
IMP dispensing~~aa~~bb		X	X	X	X	X	X	X				
IMP accountability			X	X	X	X	X	X	X			
Telephone contact[cc]												
ADDITIONAL ENTRANCE/HISTORY												
MRI/CT scan~~bb~~dd	X~~bb~~dd											

Abbreviations: ... ***NPI = Neuropsychiatric Inventory;*** ... [redacted]

~~c~~d 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 ~~at~~in the investigator's site~~.clinic or (if~~ 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 331-12-283. For those subjects who plan to enroll into Trial 331-13~~2~~-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 clinic visit at the investigator's site.

[d] ***Note that this visit is 16 weeks postbaseline.***

...

k 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*** ~~A~~a~~a~~ctigraph ~~must~~ be checked daily to ensure that the subject is wearing it and that it continues to be operational.

...

[p]Subjects **should** ~~**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.

...

[v]CCI [redacted]

[x]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.

...

[z]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.***

[aa]***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.***

~~aa~~[bb]Subjects will start taking IMP from the new blister card the day after the clinic visit.

[cc]***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.***

~~bb~~[dd]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 [redacted] in order to confirm eligibility.

Protocol 331-12-284

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. 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 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. ... • A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver. ... • 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.	~~**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.**~~ 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.*** ... • 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. ... • ***Albumin-to-creatinine ratio (ACR) will be determined (must be < 30 mg/g; calculated as urine albumin [mg/dL] / urine creatinine [g/dL]).*** ... • A qualified and certified rater will administer the CMAI***,*** ~~**and**~~ NPI-NH***, and NPI/NPI-NH*** to the caregiver. ... • After the ICF is signed during the screening visit, an actigraphy

Protocol 331-12-284

Location	Current Text	Revised Text
	• 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.	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*** t~~T~~he **actigraph~~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.**~~ • ~~**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.**~~ • ***The subject's caregiver and/or facility staff will complete an electronic diary (eDiary) daily (if possible) after the ICF is signed, continuing through ~~the~~ 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. CCI … [redacted] … • Daily eDiary recording will continue. • 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.	• A qualified and certified rater will administer the CMAI***, ~~and~~*** NPI-NH***, and NPI/NPI-NH*** to the caregiver. … • CCI [redacted] … • ~~**Daily**~~ eDiary recording will continue. • The subject will take the first dose of the IMP from the assigned

Protocol 331-12-284

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 ***approximately*** the same time each day, preferably in the morning, without regard to meals
Section 3.7.1.3.1 Day 3	• 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. ... • Daily eDiary recording will continue.	• 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. ... • ~~**Daily**~~ eDiary recording will continue.
Section 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 ± 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. ... • A qualified and certified rater will administer the CMAI and NPI-NH to the caregiver. ... • Daily eDiary recording will continue. ... • 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. CCI [redacted]	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. ... • A qualified and certified rater will administer the CMAI~~**, and**~~ NPI-NH***, and NPI/NPI-NH*** to the caregiver. ... • ~~**Daily**~~ eDiary recording will continue. ... • 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. CCI [redacted]

Protocol 331-12-284

Location	Current Text	Revised Text
		CCI [redacted] ... ***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)	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 to the caregiver. ... • CCI [redacted]	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***, and NPI/NPI-NH*** to the caregiver. ... • CCI [redacted]
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 ~~**at**~~**in** the investigator's **site**~~**.clinic or (if**~~ **If** a clinic visit is not possible~~**),**~~ ***the subject should be*** assessed by telephone with the subject and a caregiver. All AEs and concomitant medications will be recorded. ***For all subjects who terminate early from the 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, CCI [redacted]	It is required that adequately trained and experienced clinicians administer the CMAI, NPI-NH, ***NPI/NPI-NH,***

Protocol 331-12-284

Location	Current Text	Revised Text
	and CCI In addition, the raters must be certified for this trial to administer the CMAI and 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 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 recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week. 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. 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. 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. 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. The recommended minimum level of	CGI S, CCI [redacted] In addition, the raters must be certified for this trial to administer the CMAI, ~~and~~ 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 ~~**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, ***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 per week. The identified caregiver will be a member of the residential facility staff or other individual (e.g., family member, family friend, hired professional caregiver) who meets the caregiver requirements.**~~ 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,*** ~~**T**~~t**h**e identified caregiver will gather information from several informants, including staff from the day, afternoon, and night shifts, as well as from reliable family members or friends, in order to provide an accurate and comprehensive overview of the subject's behavioral symptoms and condition. ***If the subject is in a non-institutionalized setting, the identified caregiver can gather information from the caretaker (if different than the identified caregiver) or from other informants who are in a position to observe the subject and provide information regarding behavioral symptoms and activities of***

Protocol 331-12-284

Location	Current Text	Revised Text
	contact between the caregiver and the subject is 2 hours per day for 4 days per week.	***daily living. Details on the caregiver requirements can be found in Section 3.3.1*** ~~**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. The recommended minimum level of contact between the caregiver and the subject is 2 hours per day for 4 days per week.**~~
Section 3.7.2.6 Neuropsychiatric Inventory (NPI)	Null (new section)	***The NPI is a structured caregiver interview designed to obtain information on the presence of psychopathology in subjects with brain disorders, including Alzheimer's disease and other dementias.[31] 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 behavioral and two neurovegetative symptom domains comprise the NPI (including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behavior disorders, and appetite/eating disorders). Caregivers are instructed to indicate the frequency of a given behavior (on a scale of 1 to 4), its severity (on a scale of 1 to 3), and how much distress that behavior causes for him or her (on a scale of 0 to 5). Each domain produces 4 scores: frequency, severity, total (frequency x severity), and distress. A total NPI 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***

Protocol 331-12-284

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.***
CCI [redacted]	[redacted]	[redacted]
Section 3.7.3.7 Actigraphy	3.7.3.6 Actigraphy The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including patterns of movement using	3.7.3.~~6~~7 Actigraphy The CST will perform ongoing reviews of CMAI raters by reviewing CMAI data relative to other sources of behavioral information, including patterns of movement using actigraphy

Protocol 331-12-284

Location	Current Text	Revised 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.	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**~~ ***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 actigraph data.*** ... 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.
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. ...	3.7.3.~~7~~**8** 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. ***For subjects in a non-institutionalized***

Location	Current Text	Revised Text
	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.	***setting, one of the responsibilities of the caregiver is to complete the eDiary 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 made available to site personnel, and**~~ will not be statistically analyzed.
Table 3.7.4.2-1 Clinical Laboratory Assessments	--	Addition of albumin and creatinine under Urinalysis
Section 3.7.4.2 Clinical Laboratory Assessments	The following laboratory test results at screening are exclusionary:	The following laboratory test results at screening are exclusionary: ... • ***Urine albumin-to-creatinine ratio (ACR) > 30 mg/g (calculated as urine albumin [mg/dL] / urine creatinine [g/dL])***
Section 3.7.4.3.1 Physical Examination	Waist circumference will be measured at each physical examination (screening, Week 6 and Week 12/ET).	Waist circumference will be measured at each physical examination (screening, Week 6**,** and Week 12/ET)**,** ***using the provided measuring tape***.
Section 3.7.4.4 ECG Assessments	A screening ECG finding of QTcF ≥ 450 msec is exclusionary (see Table 3.4.3-1). 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 ECG with	~~**A screening ECG finding of QTcF ≥ 450 msec is exclusionary (see Table 3.4.3-1).**~~ ***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 study results) or meets an exclusion criterion (see Table 3.4.3-1), the subject should be excluded from the***

Protocol 331-12-284

Location	Current Text	Revised Text
	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 Appendix 5 for a list of potentially clinically relevant ECG abnormalities.	***study. 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 ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done. If only 1 ECG time point has a QTcF of ≥ 450 msec in men and ≥ 470 msec in women, and this is not reproduced at either of the other 2 time points, the subject can be included in the 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 ECG 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 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***.
Section 3.7.5.1 Blood Collection Times	... 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 the same	... 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

Protocol 331-12-284

Location	Current Text	Revised Text
	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.	***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.
CCI		

Protocol 331-12-284

Location	Current Text	Revised Text
		CCI [redacted]
Section 3.8.3 Individual Subject	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 ... CCI [redacted] 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 residential facility. If the subject has left the residential facility where	In addition, subjects meeting any of the following criteria must be withdrawn from the trial: ... 4) At the request of the subject, ***caregiver, legally acceptable representative,*** investigator, sponsor, or regulatory authority ... ***10) 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 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.***

Protocol 331-12-284

Location	Current Text	Revised Text
	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 [redacted] 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 the ***institutionalized*** subject has left the residential facility where he or she participated in the trial, the subject should be seen ~~**atin**~~ the investigator's **site**. ~~**clinic or (i**~~**I**f a clinic visit is not possible~~**)**~~***, the subject should be*** assessed by telephone contact with the subject and a caregiver. ***In addition, for all subjects who terminate early from the 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***

Protocol 331-12-284

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 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 (e.g., withdrew consent or AE) will be classified as "lost to follow-up." If a subject leaves the residential facility in which he/she was residing before completion of the study, 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.	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 (e.g., withdrew consent or AE) will be classified as "lost to follow-up." If a***n institutionalized*** subject leaves the residential facility in which he/she was residing before completion of the study, 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 followed for non-institutionalized subjects who are lost to follow-up.***
Section 3.12 Subject Compliance	Responsible trial personnel will dispense the IMP (i.e., brexpiprazole or matching placebo). Accountability and compliance verification should be documented in the subject's trial records.	Responsible trial personnel will dispense the IMP (i.e., 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.***
Section 5.7.4 Follow-up Mortality Assessment	Null (new section)	***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***

Location	Current Text	Revised Text
		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 Sample Size	... 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.	... 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,**~~ ***it*** result~~**sing**~~ in a sample size of 115 subjects/arm, which means the total sample size is 230 subjects.
Section 7.4.1 Primary Efficacy Analysis	The primary endpoint will be analyzed using a mixed-effect model repeated measure (MMRM) model. The primary efficacy outcome measure is the mean change from baseline to the endpoint in the CMAI total score. CCI [redacted] 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 the MMRM analysis with an unstructured variance covariance matrix for the repeated measures in which the change from baseline to endpoint in CMAI total score 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 and include the interaction term of baseline by visit week as a covariate.	The primary endpoint will be analyzed using a mixed-effect model repeated measure (MMRM) model. The primary efficacy outcome measure is the mean change from baseline ***(Day 0 Visit)*** to the~~**-endpoint**~~ ***end of the double-blind treatment period (Week 12 visit)*** in the CMAI total score. CCI [redacted] 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 ~~**the**~~ ***fitting a*** MMRM analysis with an unstructured variance covariance matrix ~~**for the repeated measures**~~ in which the change from baseline ~~**to endpoint**~~ ***(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 and include**~~

Protocol 331-12-284

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 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.*
CCI		
CCI		

Protocol 331-12-284

<table>
<tr><th>Location</th><th>Current Text</th><th>Revised Text</th></tr>
<tr><td>Appendix 1
Names of Sponsor Personnel</td><td>Primary Medical Contact
PPD
PPD
Development
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, NJ 08540
Phone: PPD
Fax: PPD</td><td>Primary Medical Contacts
PPD
PPD
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, NJ 08540
Phone: PPD
Fax: PPD

PPD
PPD
Otsuka Pharmaceutical Development & Commercialization, Inc.
1 University Square Drive, Suite 500
Princeton, NJ 08540
Phone: PPD
Fax: PPD</td></tr>
<tr><td>Appendix 2
Institutions Concerned With the Trial
Medical Monitors</td><td><table><tr><th>Country</th><th>Safety Fax Line</th></tr><tr><td>United States</td><td rowspan="5">PPD</td></tr><tr><td>Canada</td></tr><tr><td>United Kingdom</td></tr><tr><td>France</td></tr><tr><td>Ukraine</td></tr><tr><td colspan="2">Additional countries being considered for participation</td></tr><tr><td>Slovenia</td><td rowspan="6">PPD</td></tr><tr><td>Lithuania</td></tr><tr><td>Sweden</td></tr><tr><td>Austria</td></tr><tr><td>Finland</td></tr><tr><td>Ireland</td></tr></table>* Please note that this is a partner CRO number, not INC.

Europe:
PPD
PPD
INC Research, LLC
UI. Emaus 5
30-201 Kraków, Poland
Office: PPD
Mobile: PPD
Fax: PPD</td><td><table><tr><th>Country</th><th>Safety Fax Line</th></tr><tr><td>United States</td><td rowspan="5">PPD</td></tr><tr><td>Canada</td></tr><tr><td>United Kingdom</td></tr><tr><td>France</td></tr><tr><td>Ukraine</td></tr><tr><td colspan="2"><s>Additional countries being considered for participation</s></td></tr><tr><td>Slovenia</td><td rowspan="6">PPD</td></tr><tr><td><s>Lithuania</s></td></tr><tr><td><s>Sweden</s></td></tr><tr><td><s>Austria</s></td></tr><tr><td>Finland</td></tr><tr><td><s>Ireland</s></td></tr></table>* Please note that this is a partner CRO number, not INC.

Europe:
PPD
PPD
PPD
INC Research, LLC
UI. Emaus 5
30-201 Kraków, Poland
Office: PPD
Mobile: PPD
Fax: PPD</td></tr>
<tr><td>Appendix 5
Criteria for Identifying ECG Measurements of Potential Clinical Relevance</td><td>Increase in QTc | QTcF ≥ 450 msec (men and women)</td><td>Increase in QTc | QTcF ≥ 450 msec (men <s>and women</s>)
<u>QTcF ≥ 470</u></td></tr>
</table>

Protocol 331-12-284

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 [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]

Protocol 331-12-284

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 [redacted]
- Add the AIMS at Weeks 2, 4, and 8 and remove the AIMS at Week 6.
- Remove CCI [redacted], physical examination, and neurological examination at Week 6.
- Change telephone contact to Weeks 3, 5, and 7 during the double-blind treatment period.

Protocol 331-12-284

- 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.
- CCI [redacted]

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 PPD Phone: PPD Fax: PPD E-mail: PPD PPD ...	Associate Director, Clinical Management PPD Phone: PPD Fax: PPD E-mail: PPD PPD

Protocol 331-12-284

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 Trial Design	...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. ... *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. ... *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. *Follow-up Period:* All subjects, whether they complete the trial or are withdrawn prematurely for any reason, will be followed up for a	...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. ... *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. ... *12-week, Double-blind Treatment Period:* ... 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. *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

Protocol 331-12-284

Location	Old Text	Updated Text
	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 institutionalized. 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. ... ... 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 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.	last dose of IMP during a clinic visit at either the investigator's site or residential facility, if applicable. ... ... 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.
Synopsis 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 (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. ... 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 × severity) of ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory—Nursing Home (NPI-NH). The NPI-NH will be used for both institutionalized and non-institutionalized subjects; however, the Occupational Disruptiveness questions will not be answered for non-institutionalized subjects. Instead, the Distress questions from the Neuropsychiatric 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 "NPI/NPI-NH".	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. ... 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 ≥ 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. ... 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

Protocol 331-12-284

Location	Old Text	Updated 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 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.	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 order to participate in the interview for the CMAI, NPI-NH, and other applicable trial assessments.
Synopsis Inclusion/Exclusion Criteria	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,	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

Protocol 331-12-284

Location	Old Text	Updated Text
	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. ... • Subjects with a history of stroke, transient ischemic attack, or pulmonary or cerebral embolism. • Subjects with a history of clinically relevant traumatic brain injury with neurological sequelae. • Subjects with a history of a deep venous thrombosis within the 5 years prior to the screening visit. • Subjects with delirium, unless resolved with no symptoms for at least 30 days prior to the screening visit. ... • Subjects considered in poor general health based on the investigator's judgment.	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 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 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.
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.
CCI [redacted]	[redacted]	CCI [redacted] CCI [redacted]

Protocol 331-12-284

Location	Old Text	Updated Text
	CCI *Other Outcome Variables:* ... *Safety Variables:* ... Other safety variables will include the MMSE score CCI and adverse events of interest (e.g., falls, sedation, diabetes, weight changes, QTc prolongation, or deaths). 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. CCI	• CCI : ... *Safety Variables:* ... Other safety variables will include the MMSE score CCI 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. CCI
Synopsis Statistical Methods	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 80% power at a 2-sided alpha level of 0.05. The resulting sample size is 103 subjects/arm.	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

Protocol 331-12-284

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

Protocol 331-12-284

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).

Protocol 331-12-284

Location	Old Text	Updated Text
	prior to administering additional medications for the treatment of agitation or other prohibited medications.	
Section 3.1 Type/Design of Trial 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 institutionalized. 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. ... 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 either at 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.	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. ... 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 either at the investigator's site or residential facility, if applicable.
Figure 3.1-1 Trial Design Schema	Screening Subjects with agitation associated with dementia of the Alzheimer's type (N = 330) 2 to 42 days Days –42 to –2 12-week Double-blind Treatment Period Brexpiprazole flexible dose Dose range 0.5 mg/day to 2 mg/day (target dose is 1 mg/day) (N = 115) Placebo (N = 115) Randomized (1:1) (N = 230)	Screening Subjects with agitation associated with dementia of the Alzheimer's type (N = 520 screened) 2 to 42 days Days –42 to –2 (with an option to extend with approval of the medical monitor) 12-week Double-blind Treatment Period Brexpiprazole flexible dose Dose range 0.5 mg/day to 2 mg/day (target dose is 1 mg/day) (N = 130) Placebo (N = 130) Randomized (1:1) (N = 260)
Section 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 (e.g., nursing home, dementia unit, assisted living facility, or any other	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

Protocol 331-12-284

Location	Old Text	Updated Text
	residential care facility providing long term care) or in a non-institutionalized setting where the subject is not living alone. ... 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 ≥ 4 on the agitation/aggression item of the NPI-NH. The NPI-NH will be used for both institutionalized and non-institutionalized subjects; however, the Occupational Disruptiveness questions will not be answered for non-institutionalized subjects. Instead, the Distress questions from the Neuropsychiatric 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 "NPI/NPI-NH". 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 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.	alone. ... 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 ≥ 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. 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.

Protocol 331-12-284

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 ≥ 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 ≥ 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	1. 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. 3. Subjects with a history of stroke, transient ischemic attack, or pulmonary or cerebral embolism. 4. Subjects with a history of clinically relevant traumatic brain injury with neurological sequelae. 5. Subjects with a history of a deep venous thrombosis within the 5 years prior to the screening visit.	1. 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. 3. Subjects with a history of stroke, well-documented transient ischemic attack, or pulmonary or cerebral embolism. (this exclusion criterion was removed) (this exclusion criterion was removed)

Protocol 331-12-284

Location	Old Text	Updated Text
	7. Subjects with delirium, unless resolved with no symptoms for at least 30 days prior to the screening visit. 8. 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 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). • Eating disorder (including anorexia nervosa or bulimia)—unless resolved with no symptoms for at least 1 year prior to screening • Obsessive-compulsive disorder—unless resolved with no symptoms for at least 1 year prior to screening • Panic disorder—unless resolved with no symptoms for at least 1 year prior to screening • Posttraumatic stress disorder—unless resolved with no symptoms for at least 1 year prior to screening 9. Subjects with an Axis II (DSM-IV-TR criteria) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder.	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). (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.

Protocol 331-12-284

Location	Old Text	Updated Text
	13. Subjects with insulin-dependent diabetes mellitus (IDDM) (i.e., any subjects using insulin) may be eligible for the trial if their condition is well-controlled and if they do not have current microalbuminuria. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying **ALL** of the following criteria: • Glycosylated hemoglobin (HbA_{1c}) < 8.0%, **AND** • Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non-fasting screening glucose is ≥ 200 mg/dL, subjects must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, **AND** • Urine albumin-to-creatinine ratio (ACR) must be < 30 mg/g (calculated), **AND** • Subject has been maintained on a stable regimen of oral anti-diabetic 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, **AND** • Subject has not had any hospitalizations within the 3 months prior to screening due to diabetes or complications related to diabetes. Subjects with newly diagnosed diabetes during screening are excluded.	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 (non-fasting). If the non-fasting 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.
	14. Subjects with clinically significant chronic kidney disease based on the investigator's judgment.	(this exclusion criterion was removed)
	17. Subjects with a clinical history consistent with a hypercoagulable state and/or evidence of a hypercoagulable state based on laboratory tests.	(this exclusion criterion was removed)
	18. Subjects with human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, or chronic hepatitis B or C.	13. Subjects with seropositive status for hepatitis B (ie, HBsAg positive) or hepatitis C (ie, anti-HCV positive).

Protocol 331-12-284

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)
	23. Subjects with weight < 40 kilograms.	15. Subjects with a BMI < 18.5 kg/m^2.
	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.	(this exclusion criterion was removed)
	25. Subjects who are bedridden.	(this exclusion criterion was removed)
	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.	(this exclusion criterion was removed)
	27. Subjects who are known to be poor CYP2D6 metabolizers.	(this exclusion criterion was removed)
	30. ... Tests with abnormal results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: • Platelets ≤ 120,000/mm^3 • Hemoglobin ≤ 10 g/dL for women, 11 g/dL for men • Neutrophils, absolute ≤ 1500/mm^3 • ... • ACR > 30 mg/g (calculated as urine	18. ... In addition, subjects with the following laboratory test and ECG results at screening must be excluded from the trial: • Platelets ≤ 75,000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 • ... • QTcF ≥ 450 msec in men and ≥ 470 msec in women (see Section 3.7.4.4 for further details), unless due to ventricular pacing Tests with exclusionary results should

Protocol 331-12-284

Location	Old Text	Updated Text
	albumin [mg/dL] / urine creatinine [g/dL]) • ... • QTcF ≥ 450 msec in men and ≥ 470 msec in women (see Section 3.7.4.4 for further details) 33. Subjects who have a medical condition that requires treatment with an anticoagulant. 36. Subjects who received brexpiprazole in any prior clinical trial. 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.	be repeated (if ECG, 3 consecutive recordings) to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. 21. Subjects who have a current medical condition that requires treatment with an anticoagulant. 24. Subjects who received brexpiprazole in any prior clinical trial or commercially available brexpiprazole (Rexulti®). 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.
CCI [redacted]	[redacted]	[redacted]

Protocol 331-12-284

Location	Old Text	Updated Text
	CCI [redacted]	
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	...
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. ... CCI [redacted] 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 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. ... CCI [redacted] the CST will perform regular quality reviews of CMAI data and will compare these data against other sources of behavioral information, including behavior logs

Protocol 331-12-284

Location	Old Text	Updated Text
	movement using actigraphy technology (refer to Section 3.7.3.7), behavior logs collected by caregivers through electronic diaries (refer to Section 3.7.3.8), 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 institutionalized subjects).	collected by caregivers through paper diaries and investigator progress notes. 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.
Table 3.7-1 Schedule of Assessments	The changes to the Schedule of Assessments are presented below. **<u>Bold and underlined text:</u>** Changed or added text ~~**Bold and strikethrough text:**~~ Deleted text	

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments

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

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments

Assessment	Visit										
	Screening[a]	Baseline (Day 0)	Day 3	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ ET[b]	FU[c]	[redacted]
OTHER											
CCI [redacted]											
[redacted]											
[redacted]											
[redacted]											
~~Actigraphy~~[k]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		
~~Electronic diaries~~[l]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		
SAFETY											
Physical examination[~~m~~k]	X					~~X~~			X		
Neurological examination[~~n~~l]	X					~~X~~			X		
Vital signs[~~o~~m]	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[~~p~~n]	X	X[~~q~~o]			X[~~p~~]		X[~~p~~]		X		
Prolactin (blinded)[~~p~~n]	X				~~X~~		~~X~~		X		
TSH with reflex to free T_4 if abnormal[~~p~~n]	X								X		
HbA_{1c}[~~p~~n]	X								X		
PT, aPTT, and INR[~~p~~n]	X								X		
ACTH and cortisol[~~p~~n]	X								X		
Urine pregnancy test (women of childbearing potential) only[~~r~~q]	X				~~X~~		~~X~~		X		
ECG[~~s~~r]	X	X			X		X		X		
Blood alcohol[~~t,u~~s,t]	X										
Urine drug screen[~~t,u~~s,t]	X										

Protocol 331-12-284

Table 3.7-1 Schedule of Assessments

	Visit										
Assessment	**Screening[a]**	**Baseline (Day 0)**	**Day 3**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12/ ET[b]**	**FU[c]**	**Wk 16[d]**
MMSE	X	X							X		
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Adverse events[~~w~~v]	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic sampling[~~x~~w]		X					X		X		
[redacted]		[redacted]									
Concomitant medications[~~z~~y]	X	X	X	X	X	X	X	X	X	X	
[redacted]											[redacted]
OTHER PROCEDURES											
Register trial visit in IVRS/IWRS	X	X	X	X	X	X	X	X	X		
Randomize eligible subjects via IVRS/IWRS		X									
IMP dispensing[~~bb~~aa]		X	X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X	X		
Telephone contact[~~ee~~bb]											
ADDITIONAL ENTRANCE/HISTORY											
MRI/CT scan[~~dd~~cc]	X[~~dd~~cc]										

Protocol 331-12-284

Location	Old Text	Updated Text
Table 3.7-1 Schedule of Assessments, footnotes	[a]Screening begins when the ICF is signed. Screening procedures must be initiated between Day −42 and Day −2.	[a]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.
	[c]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 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. ... 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 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.	[c]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. ... 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.
	[k]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 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 footnote was removed)
	[l]Electronic diary (eDiary) information will be entered by the caregiver and/or facility staff after the ICF is signed.	(this footnote was removed)
	[m]Physical examination includes measurement of height and waist circumference at screening and waist circumference at Weeks 6 and 12/ET.	[k]Physical examination includes measurement of height and waist circumference at screening and waist circumference at Week 12/ET.

Protocol 331-12-284

Location	Old Text	Updated Text
	[n]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) [s]... Any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the trial. [cc]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.	[l]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. [p]Urinalysis is not required at Week 4 or Week 8. [r]... 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. [bb]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	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. ... 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 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). ... • 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). ... • Albumin-to-creatinine ratio (ACR) will be determined (must be < 30 mg/g; calculated as urine albumin [mg/dL] / urine creatinine [g/dL]). ... • A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver.	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 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). ... • Blood samples will be drawn for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C (anti-HCV). ... • 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]). ...

Protocol 331-12-284

Location	Old Text	Updated Text
	... • 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. • 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.	• 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. ... • 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.
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 [redacted]	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. ... • CCI [redacted]

Protocol 331-12-284

Location	Old Text	Updated Text
	... • Actigraphy recording will continue. • eDiary recording will continue.	CCI [redacted] ... • Diary recording will continue.
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 continue. • eDiary recording will continue.	This visit is to occur within + 2 days of the target visit date. At the Day 3 visit the following evaluations will be performed: ... • Diary recording will continue.
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. ... • A qualified and certified rater will administer the CMAI, NPI-NH, and NPI/NPI-NH to the caregiver. ... • CCI [redacted] ... • 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. • eDiary recording will continue. ... The following additional evaluations will be performed at the designated visits: • A complete physical examination	... The following evaluations will be performed at the Weeks 2, 4, 6, 8, and 10 visits. ... • 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. ... • Diary recording will continue. ... The following additional evaluations will be performed at the designated visits: • CCI [redacted] • 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

Protocol 331-12-284

Location	Old Text	Updated Text
	(including waist circumference) will be performed at *Week 6 only*. • A detailed neurological 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 *Week 6* only. • CCI • 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. ... • Women of childbearing potential will be given a urine pregnancy test at *Weeks 4 and 8 only*. 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.	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.

Protocol 331-12-284

Location	Old Text	Updated Text
	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)	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, NPI-NH, and NPI/NPI-NH to the caregiver. • An adequately trained and experienced clinician will administer the CGI-S, CCI [redacted] ... • The actigraphy device will be taken off, the data will be downloaded to the computer, and the actigraphy monitoring will be stopped. • eDiary recording will be stopped.	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 [redacted] ... • Diary recording will be stopped.

Protocol 331-12-284

Location	Old Text	Updated Text
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 30 (+ 2) days after the last dose of IMP during a clinic visit at either the 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 subject should be seen at the investigator's site. ... 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 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.	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. ... 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 applicable.
Section 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. CCI [redacted]	The primary efficacy variable is the change from baseline to Week 12/ET in the CMAI total score. CCI [redacted]
Section 3.7.2.5 Neuropsychiatric Inventory-Nursing Home (NPI-NH)	The NPI-NH questionnaire is used to interview the caregiver about the subject's possible neuropsychiatric symptoms (i.e., 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 (1 to 4), severity (1 to 3), and occupational disruption (0 to 5) of each of the 12 separate behavioral domains.	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.

Protocol 331-12-284

Location	Old Text	Updated Text
Section 3.7.2.6 Neuropsychiatric Inventory (NPI)	Section 3.7.2.6 Neuropsychiatric Inventory (NPI) The NPI is a structured caregiver interview designed to obtain information on the presence of psychopathology in subjects with brain disorders, including Alzheimer's disease and other dementias.[31] 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 behavioral and two neurovegetative symptom domains comprise the NPI (including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behavior disorders, and appetite/eating disorders). Caregivers are instructed to indicate the frequency of a given behavior (on a scale of 1 to 4), its severity (on a scale of 1 to 3), and how much distress that behavior causes for him or her (on a scale of 0 to 5). Each domain produces 4 scores: frequency, severity, total (frequency x severity), and distress. A total NPI 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 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 3.7.2.6 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.[31] The NPI/NPI-NH differs from the NPI-NH in that questions referring to "Occupational Disruptiveness" from the NPI-NH 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.
CCI [redacted]	[redacted]	[redacted]

Protocol 331-12-284

Location	Old Text	Updated Text
CCI		
CCI		
CCI		
CCI		

Protocol 331-12-284

Location	Old Text	Updated Text
Section 3.7.3.7 Actigraphy	The CST will perform ongoing 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 actigraph 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	(this section was removed)

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 Electronic Diary (eDiary)	3.7.3.8 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	(this section was removed)

Location	Old Text	Updated 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 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>Additional Tests (Screening Only)</u> HIV HBsAg Anti-HCV	<u>Urinalysis</u> (these asessments were removed) <u>Additional Tests (Screening Only)</u> HBsAg Anti-HCV Urine albumin (only for subjects with IDDM) Urine creatinine (only for subjects with IDDM)

Protocol 331-12-284

Location	Old Text	Updated Text
Section 3.7.4.2 Clinical Laboratory Assessments	Urine will be collected and blood will be drawn from each subject during screening prior to treatment with the IMP. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. ... Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Subjects should be fasting for a minimum of 8 hours prior to the blood draws, if possible. ... The following laboratory test results at screening are exclusionary: • Platelets ≤ 120,000/mm^3 • Hemoglobin ≤ 10 g/dL for women, 11 g/dL for men • Neutrophils, absolute ≤ 1500/mm^3 ... • Urine albumin-to-creatinine ratio (ACR) > 30 mg/g (calculated as urine albumin [mg/dL] / urine creatinine [g/dL])	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. ... Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. ... The following laboratory test results at screening are exclusionary: • Platelets ≤ 75,000/mm^3 • Hemoglobin ≤ 9 g/dL • Neutrophils, absolute ≤ 1000/mm^3 ... • 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).
Section 3.7.4.3.1 Physical Examination	... Repeat measurement of height is not required at the physical examinations scheduled for the Weeks 6 and 12/ET visits. Waist circumference will be measured at each physical examination (screening, Week 6, and Week 12/ET), using the provided measuring 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.
Section 3.7.4.3.2 Neurological Examination	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.	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.
Section 3.7.4.4 ECG Assessments	... 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 ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done.	... 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 ≥ 450 msec in men and ≥ 470 msec in women for 2 of the 3 time points of the ECGs done, unless due to ventricular pacing.

Protocol 331-12-284

Location	Old Text	Updated Text
CCI [redacted]	[redacted]	[redacted]
Section 3.8.3 Individual Subject	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 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. ... ... 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. ...	9) 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. ... ... 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. ...
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

Protocol 331-12-284

Location	Old Text	Updated Text
	use of prescription or OTC 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.	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.
Table 4.1-1 List of Restricted and Prohibited Medications	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 3. Antidepressants Subject will remain on the same dose throughout the duration of the trial. 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.	1. Medications to treat Alzheimer's disease (cholinesterase inhibitors, memantine, and/or other cognitive enhancers) Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition. 3. Antidepressants Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition. 12. Medications to treat other medical conditions, such as hypertension, hypercholesterolemia, etc., and anti-platelet agents Subject should remain on the same dose throughout the duration of the trial, except when medically indicated due to a change in the underlying medical condition.
Section 6 Pharmacokinetic Analysis	Pharmacokinetic samples will be analyzed for brexpiprazole (OPC-34712) and its major metabolite, DM-3411, and descriptive statistics will be calculated.	Pharmacokinetic samples will be analyzed for brexpiprazole (OPC-34712) and its metabolite(s) and descriptive statistics will be calculated.
Section 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 80% power at a 2-sided alpha level of 0.05. The resulting sample size is 103 subjects/arm. 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.	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.

Protocol 331-12-284

Location	Old Text	Updated Text
CCI	[redacted]	CCI [redacted]

Protocol 331-12-284

Location	Old Text	Updated Text
CCI [redacted]	[redacted]	[redacted]
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)
CCI [redacted]	[redacted]	[redacted] ...
Appendix 1 Names of Sponsor Personnel	(address change for all sponsor contacts) Otsuka Pharmaceutical Development & Commercialization, Inc. 1 University Square Drive, Suite 500 Princeton, NJ 08540	(address change for all sponsor contacts) Otsuka Pharmaceutical Development & Commercialization, Inc. 508 Carnegie Center Princeton, NJ 08540

Protocol 331-12-284

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

Protocol 331-12-284

Location	Old Text	Updated Text
	eDiary 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	(these vendors were removed)
Appendix 9 Neuropsychiatric Assessment for Non-Institutionalized Patients Based on the NPI/NPI-NH	Appendix 9 Neuropsychiatric Inventory (NPI)	Appendix 9 Neuropsychiatric Assessment for Non-Institutionalized Patients Based on the NPI/NPI-NH
Appendix 16 Actigraphy Description	Actigraphy utilizes a portable device (actigraph) that records movement with a piezoelectric accelerometer over extended periods of time and is worn most commonly on the nondominant wrist. 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 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 being worn. The actigraphy data will be downloaded from the device, verified, and transferred to Clinilabs' core laboratory at each study visit	(this appendix was removed)

Protocol 331-12-284

Location	Old Text	Updated Text
	(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 evaluate the diurnal activity patterns, the activity counts for one-hour blocks at 8:00 am, 12:00 pm, 4:00 pm, and 8:00 pm will be provided. This will provide for the possibility of measuring "time of day" specific activity related to agitation. Since actigraphy will be collected twenty four hours per day for extended periods of time, sleep parameters will be evaluated as a continuous evaluation of these multiple day indices. Sleep-wake patterns 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	

Protocol 331-12-284

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)

Location	Old Text	Updated Text
	21) –Trying to get to a different place 22) –Complaining 23) –Constant unwarranted request for attention or help 24) –Cursing or verbal aggression 25) –Making verbal sexual advances 26) –Negativism 27) –Repetitive sentences or questions 28) –Screaming 29) –Making strange noises If the caregivers click on "Help", they will be able to view the definitions of the behaviors within their selected category. After the caregivers select a behavior, they will be taken to a screen where they can enter the time the behavior occurred.	
Appendix 23 Handling and Shipment of Bioanalytical Samples	Pharmacokinetic Sample Collection ... The sample must be stored at −70°C, if available, or −20°C or below. One tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab. If neither a −70°C nor −20°C freezer is available, the primary pharmacokinetic sample should be shipped on dry ice to the central laboratory on the day of collection. The backup sample can be refrigerated (2 to 8°C) for up to 48 hours prior to shipment on dry ice to the central laboratory.	Pharmacokinetic Sample Collection ... The sample must be stored at −70°C, if available, or −20°C or below. If only a −20°C freezer is available, samples must be shipped within 30 days of collection. Primary and backup samples may be shipped together. If samples are stored in a −70°C freezer, then one tube (primary sample) will be shipped on dry ice to the central lab as soon as possible after collection. Following confirmation that the first tube arrived safely, the second tube (backup sample) can also be shipped to the central lab. If neither a −70°C nor −20°C freezer is available, the primary and backup pharmacokinetic samples must be shipped on dry ice in the same box to the central laboratory on the day of collection.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 331-12-284

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

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically captured signature

OPC-34712

SIGNATURE PAGE

Document Name: Protocol_331-12-284_Amend 3

Document Number: 0001191988

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Approval	11-Sep-2015 03:33 GMT+00
	Clinical Approval	11-Sep-2015 13:38 GMT+00
	Clinical Pharmacology	11-Sep-2015 13:51 GMT+00