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CONFIDENTIAL
Protocol 20-AVP-786-307
Protocol Amendment 2, Version 3.0

OPDC
AVP-786

PROTOCOL TITLE:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type

Protocol: 20-AVP-786-307 Amendment 2

EU CT No.: 2023-504991-31-00
EudraCT No.: 2020-000799-39
IND: 124099

Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Date: 15 May 2023

Drug: AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q])

Version: 3.0
Supersedes Version: 2.0

Immediately Reportable Event: **Syneos Health**
CCI [redacted]

Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Blvd
Rockville, MD 20850 United States
Phone: 949-389-6700
Fax: 949-643-6891

CONFIDENTIALITY STATEMENT

This document contains confidential and proprietary information of Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC), and it is for the sole information and use of the investigator's research team and the appointed Institutional Review Board/Independent Ethics Committee.

PROTOCOL AGREEMENT

Protocol Title:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type.

Protocol Number: 20-AVP-786-307 Amendment 2 (15 May 2023)

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The signatures of the principal investigator and representative of the sponsor below constitute their approval of this protocol and further provide the necessary assurances that:

1. This study will be conducted according to Good Clinical Practice (GCP) and to all stipulations, as specified in both clinical and administrative sections of the protocol including the Declaration of Helsinki.
2. The conduct and results of this study will be kept confidential, and the electronic case report forms (eCRFs) and other pertinent data will become the property of OPDC Pharmaceuticals.
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_____ _____

Principal Investigator Signature Date

Principal Investigator Name: _____

_____ _____

OPDC Representative Signature Date

OPDC Representative: PPD, MD
PPD Global Clinical Development

SYNOPSIS

Name of Sponsor/Company: Otsuka Pharmaceutical Development & Commercialization, Inc.		
Name of Investigational Product: AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q])		
Name of Active Ingredient(s): deudextromethorphan hydrobromide [d6-DM] and quinidine sulfate [Q]		
Protocol Number: 20-AVP-786-307	**Phase:** 3	**Country:** United States (US), Europe, other global sites
Title of Study: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type		
Study Center(s): Approximately 110 global centers, including the US and Europe		
Studied Period (years): Estimated date first patient enrolled: Sep 2020 Estimated date last patient completed: Dec 2024		**Phase of development:** 3
Objectives: The primary objective is to: • Evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the treatment of agitation in patients with dementia of the Alzheimer's type The secondary objectives are to: • Evaluate the effects of AVP-786 compared to placebo on global assessments of severity and improvement of agitation • Evaluate the effects of AVP-786 compared to placebo on neuropsychiatric symptoms • Evaluate the effects of AVP-786 compared to placebo on measures of quality of life and resource utilization		
Study Design: Phase 3, multicenter, randomized, double-blind, placebo-controlled study **Methodology:** *Screening Period (Days -28 to -1):* A protocol eligibility form will be completed for each patient and reviewed by a Medical Monitor for approval prior to participation in the study. *12-week Double-blind Treatment Period (Days 1-85)*: All eligible patients will be randomly assigned to receive either AVP-786 or placebo (identical in appearance to AVP-786). *30-day Follow-up Period:* All enrolled patients, whether they complete the study or terminate from the study early for any reason, will have a Follow-up visit 30 days after the last dose of study drug for select efficacy and safety assessments. *Assessments and Visits*: Patients will attend clinic visits at Screening, Baseline (Day 1), Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 43), Visit 6 (Day 57), Visit 7 (Day 71), Visit 8/Early Termination (ET) (Day 85), and Follow-up (30 days after the last dose). Study procedures performed at each visit are outlined in the Schedule of Assessments (Table 1).		

Number of Patients (planned): Approximately 750 patients
Diagnosis and Main Criteria for Inclusion: Patients with agitation secondary to Alzheimer's dementia; the diagnosis of probable Alzheimer's disease will be based on the '2011 Diagnostic Guidelines for Alzheimer's Disease' issued by the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups. Diagnosis of agitation will be based on the provisional consensus definition of agitation in patients with cognitive disorders developed by the International Psychogeriatric Association (IPA) Agitation Definition Work Group. **Key Inclusion Criteria:** Patients 50 to 90 years of age (inclusive) with clinically significant, moderate-to-severe agitation for at least 2 weeks prior to Screening that interferes with daily routine per the Investigator's judgment, and who require pharmacotherapy for the treatment of agitation per the Investigator's judgment after an evaluation of reversible factors and a course of nonpharmacological interventions. A Neuropsychiatric Inventory Agitation/Aggression (NPI-AA) score of ≥ 4 and Mini Mental State Examination (MMSE) score of 8 to 24 (inclusive) at Screening and Baseline are required for study participation. Patients must meet an additional predetermined blinded eligibility criterion, which will remain blinded to the clinical study site Investigators and staff. Eligible patients must have a reliable caregiver who is able and willing to comply with all study procedures, including adherence to administering study drug and not administering any prohibited medications during the course of the study, and who spends a minimum of 2 hours per day for 4 days per week with the patient. **Key Exclusion Criteria:** Patients with dementia predominantly of the non-Alzheimer's type (eg, vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia) and patients with symptoms of agitation that are not secondary to Alzheimer's dementia (eg, secondary to pain, other psychiatric disorder, or delirium) are not eligible.
Investigational Product, Dosage and Mode of Administration: AVP-786 capsule will be administered orally BID up to a maximum dose of d6-DM 42.63 mg and Q 4.9 mg.
Duration of Treatment: Patients will be enrolled in the study for approximately 20 weeks, which includes: • Up to a 28-day Screening Period • 12-week Double-blind Treatment Period • 30-day Follow-up Period
Reference Therapy, Dosage and Mode of Administration: Matching placebo capsule (identical appearance to AVP-786 capsule) will be administered orally BID.
Criteria for Evaluation: **Efficacy:** **Primary Efficacy Measure:** Cohen-Mansfield Agitation Inventory (CMAI) **Key Secondary Efficacy Measure:** Clinical Global Impression of Severity of Illness for Agitation (CGIS-Agitation) **Other Efficacy Measures:** Other efficacy measures include, Clinical Global Impression of Change (CGIC-Agitation), NPI-AA, NPI total, EuroQol 5-Dimension 5-Level (EQ-5D-5L), and Resource Utilization in Dementia-Lite (RUD-Lite).

Pharmacokinetics: Plasma concentrations of d6-DM, its metabolites d3-dextrorphan (d3-DX) and d3-3-methoxymorphinan (d3-3-MM), and Q will be measured. Urine concentrations of d6-DM and its metabolite d3-DX will be measured.

Safety: Safety and tolerability of AVP-786 will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), MMSE, the Epworth Sleepiness Scale (ESS), and the Sheehan Suicidality Tracking Scale (S-STS).

Statistical Methods: Complete details of the planned statistical analysis will be presented in the Statistical Analysis Plan (SAP).

Efficacy Analyses: The primary efficacy endpoint is the change from Baseline to the end of the efficacy period in the CMAI total score.

All efficacy analyses will be based on the intent-to-treat analysis set, defined as all patients in the randomized population who take at least 1 dose of study drug (AVP-786 or placebo), have a Baseline, and at least 1 post-Baseline evaluation for the CMAI total score. Descriptive statistics will be provided for all efficacy 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 mixed-effect model repeat measures (MMRM). The primary statistical comparison of interest is AVP-786 versus placebo. The null hypothesis of this comparison is that there is no difference between the AVP-786 treatment group and placebo in change from Baseline to the end of the efficacy period in the CMAI total score. This comparison will be tested for statistical significance at a 0.05 (2-sided) significance level. Details of sensitivity analyses under the assumption of missing not at random will be provided in the SAP.

Pharmacokinetic Analyses: Plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be summarized descriptively. Urine concentrations of d6-DM and its metabolite d3-DX will be summarized descriptively.

Safety Analyses: Safety analyses will be based on safety population defined as all patients who are randomized and take at least one dose of study drug. It will consist of data summaries for biological parameters and AEs. Descriptive statistics will be provided for all safety variables in general. Continuous variables will be summarized by tabulations of mean, median, range, and SD. Tabulations of frequency distributions will be provided for categorical variables. Safety analyses will be tabulated by treatment. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary statistics of absolute values and percentage change from baseline for blood pressure (systolic and diastolic), heart rate, respiratory rate, and ECG parameters will be provided. All values outside a predefined normal range will be highlighted in the individual patient data listings. Laboratory parameters will be summarized via descriptive statistics and via shifts in results with respect to normal ranges between Baseline and end of treatment as increased, decreased, or no change. The S-STS, MMSE, and ESS will be summarized via descriptive statistics.

Sample Size: Approximately 750 patients. Statistical assumptions and additional details are provided in the SAP.

Interim Analysis: An interim analysis may be performed and will be prespecified in the Interim Analysis Plan (IAP).

Table 1: Schedule of Assessments and Visits

			12-WEEK DOUBLE-BLIND TREATMENT PERIOD								
	Visit:	**Screening[a]**	**Baseline**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 (or ET)**	**Follow-up Visit [b]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8 (±3days)**	**Day 15 (±3days)**	**Day 29 (±3days)**	**Day 43 (±3days)**	**Day 57 (±3days)**	**Day 71 (±3days)**	**Day 85 (±3days)**	**30 (+7) days Post Last Dose**
Procedure	**End of Study Week:**			**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
ELIGIBILITY and HISTORY											
Signed informed consent forms		X									
Inclusion and exclusion criteria		X	X								
Medical, psychiatric, and neurological history		X									
Risk assessment for falls (worksheet and TUG)		X									
Hachinski Ischemic Scale (Rosen Modification)		X									
Protocol eligibility form[c]		X									
EFFICACY											
CMAI		X	X	X	X	X	X	X	X	X	X
CGIS-Agitation		X	X	X	X	X	X	X	X	X	X
CGIC-Agitation				X	X	X	X	X	X	X	
NPI[d]		X[d]	X	X	X[d]	X[d]	X	X[d]	X	X	
EQ-5D-5L			X							X	
RUD-Lite			X							X	
SAFETY											
Vitals signs		X	X	X	X	X	X	X	X	X	
Weight and height[e]			X[e]							X[e]	
Physical and neurological examination		X								X	
ECG		X[f]	X[g]	X[g]			X[h]			X[h]	

			12-WEEK DOUBLE-BLIND TREATMENT PERIOD								
	Visit:	**Screening[a]**	**Baseline**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 (or ET)**	**Follow-up Visit [b]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8 (±3days)**	**Day 15 (±3days)**	**Day 29 (±3days)**	**Day 43 (±3days)**	**Day 57 (±3days)**	**Day 71 (±3days)**	**Day 85 (±3days)**	**30 (+7) days Post Last Dose**
Procedure	**End of Study Week:**			**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	
Chemistry, hematology, urinalysis		X[i]					X			X[i]	
Urine pregnancy test[j]		X	X							X	
Adverse events			X	X	X	X	X	X	X	X	X
Prior and concomitant medications, non-drug therapies, nonpharmacological interventions for agitation		X	X	X	X	X	X	X	X	X	X
MMSE		X	X							X	
ESS[k]			X							X	
S-STS		X	X							X	
OTHER PROCEDURES											
PK blood sample[l]				X			X		X		
PK urine sample[m]				X							
CYP2D6 blood sample				X							
Amyloid β blood sample				X							
Administer morning dose of study drug in clinic			X	X			X				
Dispense blister card and diary cards			X	X	X	X	X	X	X		
Review blister card and diary cards				X	X	X	X	X	X	X	

AE = adverse event; CGIC-Agitation = Clinical Global Impression of Change for Agitation; CGIS-Agitation = Clinical Global Impression of Severity of Illness for Agitation; CMAI = Cohen-Mansfield Agitation Inventory; ECG = electrocardiogram; EQ-5D-5L= EuroQol 5-Dimension 5-Level; ESS = Epworth Sleepiness Scale; ET = early termination; MMSE = Mini Mental State Examination; NPI = Neuropsychiatric Inventory; PK= Pharmacokinetics; RUD-Lite = Resource Utilization in Dementia-Lite; S-STS = Sheehan Suicidality Tracking Scale; TUG= Timed Up and Go

[a] The Screening period may be extended after discussion with and approval by a Medical Monitor.

[b] All enrolled patients will have an in-clinic Follow-up visit 30 (+7) days after last dose of study drug for selected safety and efficacy assessments.

[c] For each patient, a protocol eligibility form will be completed by the site and reviewed by a Medical Monitor for approval prior to participation in the study.
[d] Only the Agitation/Aggression domain of the NPI will be performed at Screening, and at Visit 3, Visit 4, and Visit 6 (ie, Days 15, 29, and 57).
[e] Height and weight will be measured at Baseline (Day 1); only weight will be measured at Visit 8 (Day 85/ET).
[f] At Screening, 3 ECGs will be performed (eg, one after the other).
[g] ECG will be performed predose and 1 to 1.5 hours postdose at Baseline (Day 1) and Visit 2 (Day 8).
[h] ECG will be performed at any time at Visit 5 (Day 43) and Visit 8 (Day 85/ET).
[i] Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) will be performed at Screening. Glycosylated hemoglobin (HbA1c) test will be performed at Screening and Visit 8 (Day 85/ET).
[j] Urine pregnancy test will be performed for women of child-bearing potential only.
[k] ESS will be rated only by patients who have a MMSE score of ≥ 10 at Baseline.
[l] At Visit 2 (Day 8), the PK blood sample will be collected 1 to 4 hours postdose. At Visit 5 (Day 43), the PK blood sample will be collected predose. At Visit 7 (Day 71), the PK blood sample will be collected at any time. The time of the last 2 doses of study drug prior to collection of the PK blood sample will be recorded in the clinical database.
[m] At Visit 2 (Day 8), the PK urine sample will be collected 1 to 4 hours postdose.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation	Definition
ADWG	Agitation Definition Working Group
ANCOVA	analysis of covariance
AVP-786	d6-DM and Q
BP	blood pressure
CFR	US Code of Federal Regulations
CGIC-Agitation	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CGIS-Agitation	Clinical Global Impression of Severity of Illness scale for Agitation
CMAI	Cohen-Mansfield Agitation Inventory
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CYP	cytochrome P450
d6-DM	deudextromethorphan hydrobromide (or deudextromethorphan)
DEMQOL	Dementia Quality of Life
DMP	data management plan
DSMB	Data and Safety Monitoring Board
DSM-V-TR	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EP	European Pharmacopoeia
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation	Definition
HbA1c	glycosylated hemoglobin
HR	heart rate
IAP	interim analysis plan
ICF	informed consent form
ICH	International Council for Harmonisation
IEC/EC	Independent Ethics Committee
ITT	intent-to-treat
IRB	Institutional Review Board
IWRS	interactive web-response system
LOCF	last observation carried forward
mADCS-CGIC-Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale for Agitation
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effect model for repeated measures
MMSE	Mini Mental State Examination
MNAR	missing data being missing not at random
NIA-AA	National Institute on Aging – Alzheimer's Association
NPI	Neuropsychiatric Inventory
NPI-AA	Neuropsychiatric Inventory Agitation/Aggression
NPI-NH	Neuropsychiatric Inventory – Nursing Home
OC	observed case
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
OTC	over-the-counter
PK	pharmacokinetic
PVC	premature ventricular contractions
Q	quinidine sulfate (or quinidine)
QOL	quality of life
QTcF	QTc by Fridericia's formula
RUD-Lite	Resource Utilization in Dementia-Lite

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitors
S-STS	Sheehan Suicidality Tracking Scale
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TUG	Timed Up and Go
UN	unstructured variance covariance structure
US	United States
USP	United States Pharmacopoeia

1. INTRODUCTION

Alzheimer's disease, the most common form of dementia, is a progressive neurodegenerative disease that eventually leads to death. There are an estimated 5.8 million people in the United States (US) with Alzheimer's dementia and this number is expected to reach 14 million by the year 2050 [1]. National estimates of the prevalence of all dementias from population-based studies including the Aging, Demographics, and Memory Study (ADAMS), a nationally representative sample of older adults, show that 14 percent of people age 71 and older in the US have dementia [2,3].

Agitation is widely recognized by clinicians as a common and important clinical feature of Alzheimer's disease and other forms of dementia [4,5,6,7,8]. Agitation, aggression, depression, hallucinations, and delusions are estimated to affect up to approximately 90% of patients with Alzheimer's disease with an increase in prevalence as the disease progresses [4,9]. In a meta analyses of data from 55 studies, overall prevalence of agitation ranged from 5% to 88% across all studies, with 23 studies reporting the prevalence of at least one neuropsychiatric syndrome with a range of 40% to 100%. Agitation in patients with dementia is associated with increased functional disability, worse quality of life [10,11,12], earlier institutionalization [13], increased caregiver burden [14,5,15,16,17,18], increased healthcare costs [19,20,13,21], shorter time to severe dementia [22,23], and accelerated mortality [23,24]. Currently, there is no approved treatment in the US to manage agitation in patients with Alzheimer's disease [25]. Pharmacologic treatments for patients with agitation in Alzheimer's disease include off-label use of atypical antipsychotics, selective serotonin reuptake inhibitors, benzodiazepines, and anticonvulsants [26,27,28]; however, these treatments provide only modest efficacy that is offset by relatively poor adherence, safety, and tolerability [29,30]. It is widely recognized that a safe and effective treatment for patients with agitation in Alzheimer's disease represents a significant unmet need [31]. Such a treatment could profoundly impact patient care, potentially reduce caregiver burden, and improve overall disease prognosis.

1.1. Rationale for Investigating AVP-786 for Treatment of Agitation in Dementia

AVP-786 is a combination product of deudextromethorphan hydrobromide (d6-DM), a central nervous system (CNS)-active agent, and quinidine sulfate (Q), used as an inhibitor of d6-DM metabolism via the cytochrome P450 (CYP) liver isoenzyme 2D6 (CYP2D6). AVP-786 is being developed by Otsuka Pharmaceutical Development & Commercialization, Inc (OPDC, or Sponsor) for the treatment of neuropsychiatric conditions.

The demonstrated receptor pharmacology of d6-DM supports a potential clinical benefit for agitation in patients with dementia of the Alzheimer's type. d6-DM binds to receptors responsible for modulation of glutamate and monoamines, and also binds to the sigma-1 receptor; these interactions may be key to CNS therapeutics. Pharmacology studies conducted by the Sponsor with d6-DM have demonstrated that deuteration does not alter the basic pharmacology of DM. Pharmacokinetic (PK) and drug metabolism studies indicate that d6-DM is metabolized by the same metabolic pathways as DM, but that deuteration results in a decreased rate of metabolism by CYP2D6.

Studies conducted by the Sponsor have shown that d6-deuterium modification of dextromethorphan reduces the rate of CYP2D6 metabolism such that a low dose of quinidine is sufficient to achieve pharmacologically relevant plasma concentrations of d6-DM. The low levels of Q in AVP-786 may minimize the risk of interactions with other CYP2D6 substrates, limit Q levels even in the presence of CYP3A4 inhibitors, and minimize the risk of effects on cardiac repolarization and QTc interval.

Based on the above, further clinical investigation is warranted to explore the potential efficacy and safety of AVP-786.

The current study (Study 20-AVP-786-307) is designed to evaluate the efficacy, safety, and tolerability of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer's type.

1.2. Rationale for the Study Design

The randomized, placebo-controlled, double-blind design reduces sources of bias that are inherent in less well-controlled designs. The safety assessments used are standard in clinical research and are generally recognized as reliable, accurate, and relevant. The rating scales used to assess efficacy are well-established instruments that are widely used in clinical studies of agitation in Alzheimer's disease.

1.3. Rationale for AVP-786 Dose

Based on the collective efficacy, safety, and tolerability data in the completed Phase 3 studies, doses of up to a maximum of 42.63 mg of d6-DM and 4.9 mg of Q administered BID will be evaluated in this Phase 3 study. The doses given in the previous AVP-786 studies were within this dose range and were generally well tolerated.

1.4. Rationale for the Duration of AVP-786 Dosing

A drug being developed for treatment of a chronic condition needs to show some evidence of persistence of acute effects. A 12-week treatment duration is generally considered by experts and regulators as a reasonable time frame to assess efficacy and safety of a compound for chronic use.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Primary Objective

The primary objective is to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo for the treatment of agitation in patients with dementia of the Alzheimer's type.

2.2. Secondary Objectives

The secondary objectives are to:

- Evaluate the effects of AVP-786 compared to placebo on global assessments of severity and improvement of agitation
- Evaluate the effects of AVP-786 compared to placebo on neuropsychiatric symptoms
- Evaluate the effects of AVP-786 compared to placebo on measures of quality of life and resource utilization

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study with a 12-week treatment duration. The study consists of a 4-week Screening period, a 12-week double-blind treatment period, and a 30-day Follow-up period. Approximately 750 patients with agitation of the Alzheimer's type will be enrolled at approximately 110 centers including the United States [US] and Europe.

Screening Period (Day -28 to Day -1)

Patient eligibility will be determined during the Screening visit, which will occur within 4 weeks of the Baseline visit. A protocol eligibility form will be completed for each patient and reviewed by a Medical Monitor for approval prior to participation in the study.

Double-blind, Treatment Period (12 Weeks)

During the double-blind treatment period, all eligible patients will be randomly assigned to receive either AVP-786 or matching placebo. Randomization will be stratified by site and baseline concomitant antipsychotic use (yes/no). Study drug will be administered twice daily (BID; morning and evening) starting from the Baseline visit (Day 1) through Visit 8 (Day 85).

Follow-up Period

All enrolled patients, whether they complete the study or terminate from the study early for any reason, will have a Follow-up visit 30 days after the last dose of study drug for select efficacy and safety assessments.

Assessments and Visits:

Patients will attend clinic visits at Screening (Day -28 to -1), Baseline (Day 1), Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 43), Visit 6 (Day 57), Visit 7 (Day 71), Visit 8 (Day 85; or Early Termination [ET] Visit), and 30 days after the last dose of study drug (Follow-up visit).

Study assessments and procedures will be performed at each visit as outlined in the Schedule of Assessments and Visits (Table 1). The primary efficacy measure is the Cohen-Mansfield Agitation Inventory (CMAI). Secondary efficacy measures include Clinical Global Impression of Severity of Illness for Agitation (CGIS-Agitation), Clinical Global Impression of Change for Agitation (CGIC-Agitation), Neuropsychiatric Inventory Agitation/Aggression (NPI-AA), NPI total, EuroQol 5-Dimension 5-Level (EQ-5D-5L), and Resource Utilization in Dementia-Lite (RUD-Lite).

Pharmacokinetic (PK) measurements of plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be measured from blood samples collected at Visit 2 (Day 8), Visit 5 (Day 43), and Visit 7 (Day 71). PK measurements of urine concentrations of d6-DM and its metabolite d3-DX will be measured from a urine sample collected at Visit 2 (Day 8).

The safety and tolerability of AVP-786 will be assessed by reported AEs, physical and neurological examination, vital signs, clinical laboratory measures, resting 12-lead

electrocardiograms (ECG), and the following safety scales: Mini-Mental State Examination (MMSE), Epworth Sleepiness Scale (ESS), and Sheehan Suicidality Tracking Scale (S-STS).

3.2. Study Assessments and Procedures

A tabular summary of the schedule of study assessments and procedures by visit is provided in the Schedule of Assessments and Visits (Synopsis Table 1). A more detailed description of the assessments at each visit is provided in Section 9, Schedule of Evaluations and Procedures.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Patients enrolled in this study must have a diagnosis of probable Alzheimer's disease and must present with clinically significant, moderate-to-severe agitation secondary to Alzheimer's disease. The diagnosis of probable Alzheimer's disease will be based on the '2011 Diagnostic Guidelines for Alzheimer's Disease' issued by the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups [32]. Neither Alzheimer's disease nor agitation should be explainable by delirium, substance use and/or major psychiatric disorders.

The provisional consensus definition of agitation in patients with cognitive disorders developed by the Agitation Definition Work Group (ADWG) from the International Psychogeriatric Association (IPA)[33] will be used to select study patients. This proposed definition is limited to patients with cognitive impairment and requires: (a) evidence of emotional distress; (b) 1 of 3 observable types of behaviors: excessive motor activity, verbal aggression, or physical aggression; (c) that the behavior causes excess disability; and (d) that the behaviors cannot be solely attributable to a suboptimal care environment or other disorder such as a psychiatric illness, a medical illness, or effects of a substance.

Eligible patients must have clinically significant, moderate-to-severe agitation for at least 2 weeks prior to Screening that interferes with daily routine per the Investigator's judgment, and who require pharmacotherapy for the treatment of agitation per the Investigator's judgment after an evaluation of reversible factors and a course of nonpharmacological interventions.

An NPI-AA score of ≥ 4 and MMSE score of 8 to 24 (inclusive) at Screening and Baseline are required for study participation. Patients must meet an additional predetermined blinded eligibility criterion, which will remain blinded to the clinical study site Investigators and staff.

Eligible patients are to have otherwise acceptable and stable general health as required by the study protocol and documented by medical history, physical and neurological examination, ECG, and clinical laboratory examinations.

Eligible patients must have a caregiver who is able and willing to comply with all required study procedures, ensuring that the patient attends all study visits and takes the study drug as instructed, including adherence to not administering any prohibited medications during the course of the study. Caregivers will also be instructed to record the daily number of capsules taken and the time of administration in the patient Diary Card. In addition, caregivers are responsible for reporting any changes in patient's status, including adverse events and standard of care setting (eg, becoming a resident in an assisted living facility), as well as providing their impression and assessment regarding the investigational treatment to the study team at the Investigator's site. A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process. In order to qualify as a reliable informant (ie, caregiver) capable of assessing changes in the patient's condition during this study, the individual must spend a minimum of 2 hours with the patient per day for 4 days per week. In addition, this individual should remain as the patient's caregiver throughout the study.

The complete list of inclusion and exclusion criteria for this study are provided in the following sections.

4.1. Patient Inclusion Criteria

1. Males and females 50 to 90 years of age (inclusive) at the time of informed consent.
2. Diagnosis of probable Alzheimer's disease according to the 2011 NIA-AA working groups criteria. Either outpatients or residents of an assisted living facility, a skilled nursing home, a dementia unit, or any other type of facility providing long-term care.
3. MMSE score between 8 and 24 (inclusive) at Screening and Baseline.
4. Patient has clinically significant, moderate-to-severe agitation for at least 2 weeks prior to Screening that interferes with daily routine per the Investigator's judgment.
5. Patients who require pharmacotherapy for the treatment of agitation per the Investigator's judgment, after:
   - An evaluation of reversible factors (eg, pain, infection, or polypharmacy), and
   - A course of nonpharmacological interventions (eg, redirecting behavior, group activities, music therapy).
6. Diagnosis of agitation must meet the International Psychogeriatric Association (IPA) provisional definition of agitation.
7. NPI-AA total score (frequency × severity) must be ≥ 4 at Screening and Baseline.
8. Patient must meet an additional predetermined blinded eligibility criterion.
9. Patient has stable cardiac, pulmonary, hepatic, and renal function per the Investigator's judgment.
10. No clinically significant findings on the Screening ECGs based on central review and on the Baseline predose ECG based on the machine read and Investigator's evaluation.
11. Women who are of childbearing potential and are sexually active must use an effective method of birth control for at least 1 month prior to the Baseline, during participation in the study, and for at least 30 days after the last dose of study drug. The following requirements must be met:
    - Women who are of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, or condom with spermicide or sponge with spermicide. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception.
    - Women who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause), or practice true abstinence (when this method is in line with the preferred and usual lifestyle of the patient) are exempt from this requirement.

- Women who are lactating, pregnant, or plan to become pregnant are not eligible for participation in the study.

12. For restricted and prohibited concomitant medications, patients willing and able to meet all protocol requirements for duration of stability or washout prior to study entry and during the study (see Table 3 Restricted and Prohibited Concomitant Medications and Appendix 1 Prohibited Concomitant Medications).
13. Caregiver must be willing and able to comply with all study procedures, including adherence to administering study drug and not administering any prohibited medications during the study. The caregiver must spend a minimum of 2 hours with the patient per day for at least 4 days per week to qualify as caregiver.
14. Patient/caregiver must be willing to sign and receive a copy of patient/caregiver informed consent form (ICF) after the nature and risks of study participation have been fully explained. Patients who are not capable of signing the ICF but are able to provide assent, or the patient's authorized representative agrees to participation (for patients unable to provide assent) are allowed.

4.2. Patient Exclusion Criteria

1. Caregiver is unwilling or unable, in the opinion of the Investigator, to comply with study instructions.
2. Patient has dementia predominantly of non-Alzheimer's type (eg, vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia).
3. Patients with symptoms of agitation that are not secondary to Alzheimer's dementia (eg, secondary to pain, other psychiatric disorder, or delirium).
4. Patients who have been diagnosed with an Axis 1 disorder (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision [DSM-5] criteria) including, but not limited to:
   - Schizophrenia, schizoaffective disorder, or other psychotic disorders not related to dementia
   - Bipolar I or II disorder, bipolar disorder not otherwise specified
   - Current Major Depressive Episode: Patients with a history of major depressive disorder, that is currently not symptomatic, are eligible. Patients currently on a stable dose(s) of allowed antidepressant medication(s) for at least 3 months prior to the Screening visit are eligible.
5. Patients with myasthenia gravis (contraindication for quinidine).
6. Patients with any personal history of complete heart block, QTc prolongation, or *torsades de pointes*.
   a. Screening and Baseline predose QT interval corrected for heart rate using the Fridericia's formula (QTcF) of > 450 msec for males and > 470 msec for females unless due to ventricular pacing (See Section 8.1.5).

Screening ECGs will be based on central review. Baseline predose ECG will be based on the machine read and Investigator's evaluation; if the QTcF result from the machine read is exclusionary, do not administer study drug and please contact a Medical Monitor.

b. Presence of premature ventricular contractions (PVCs) as evaluated by a central reader and deemed clinically significant by the Investigator.

7. Patients with any family history of congenital QT interval prolongation syndrome.
8. Patients with known hypersensitivity to DM, Q, opiate drugs (codeine, etc), or any other ingredient of the study drug.
9. Patients who have ever received DM co-administered with Q or d6-DM co-administered with Q.
10. Patients who would be likely to require a prohibited concomitant medication during the study (see Table 3, Restricted and Prohibited Concomitant Medications and Appendix 1 Prohibited Concomitant Medications).
11. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (eg, malignancy [except skin basal-cell carcinoma], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease). Certain other nonmetastatic cancer may be allowed. Each case is to be evaluated individually with a Medical Monitor.
12. Patients who are currently participating in or who have participated in other interventional (drug or device) clinical study, or found to be a "Virtually Certain" match in Clinical Trial Subject Database (CTSdatabase) with a patient who has participated in another interventional drug or device study within 30 days of Baseline.
13. Patients with history of postural syncope or any history of unexplained syncope (evaluated on a case-by-case basis) within 12 months of Baseline.
14. Patients with a history of substance and/or alcohol abuse within 12 months of Baseline.
15. Patients determined to have a high imminent risk of falls during the study based on a clinical evaluation by the Investigator.
16. Patients with evidence of serious risk of suicide at Screening and Baseline based on the Sheehan Suicidality Tracking Scale (S-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.
17. Patients who, in the opinion of the Investigator, Medical Monitor, or sponsor, should not participate in the study.

4.3. Patient Withdrawal Criteria

Patients and caregivers will be advised verbally and in the written ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are

otherwise entitled. The Investigator or sponsor may discontinue a patient from the study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, noncompliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Regardless of the circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the caregiver return all unused study drug, and follow-up with the patient regarding any unresolved adverse events.

In addition, patients who present at any time after the Baseline visit (Day 1) with a persistent QTc interval (QTcF) > 500 msec (unless due to ventricular pacing) or a persistent QTcF interval change from the predose Baseline ECG of > 60 msec, that is confirmed by the central ECG reader, will be withdrawn from the study after consultation with a Medical Monitor. The QTcF values will be assessed for clinical significance and recorded.

Patients who terminate early from the study will have an ET visit to complete the Visit 8 (Day 85/ET) assessments and a Follow-up visit 30 days after the last dose of study drug for select efficacy and safety assessments. If a patient terminates early from the study, the investigator and site personnel should make every effort to have the patient and caregiver return to the clinic for the ET visit and the Follow-up visit.

If the patient withdraws from the study, and consent is withdrawn by the caregiver and/or patient's representative for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. Patients who withdraw from the study will not be replaced.

4.4. CTSdatabase and Subject Database Authorization

Clinical trial registries, such as CTSdatabase, seek to reduce duplicate enrollment by identifying duplicates before randomization. At the time of providing the Informed Consent for the study, the Investigator or designee will explain the IRB/IEC/EC-approved Subject Database Authorization to the patient and witness the signature.

During Screening, site staff who have received training and login information access to www.ctsdatabase.com will enter the patient study ID and authorized patient identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days, or (3) the subject matches with a subject who has prescreened at another site.

At the last patient contact, site staff will access CTSdatabase, enter the patient Study ID and nature of the last contact (ie, early termination, completed study).

5. TREATMENT OF PATIENTS

5.1. Description of Study Drug

Study drug will be provided as opaque hard gelatin capsules with a purple cap and white body. Each capsule contains one of the following:

- **AVP-786 capsules**
- **Placebo capsules:** matching AVP-786 in appearance

Drug supplies will be provided to the site in double-blind, individual, prelabeled blister cards.

5.2. Concomitant Medications and Nondrug Therapies

At each visit, caregivers will be queried as to whether or not the patient has taken any concomitant medications and, if so, the Investigator will record the medications taken and the reasons for their use.

AVP-786 contains quinidine which is a P-glycoprotein inhibitor. Concomitant administration of quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. Plasma digoxin concentrations should be closely monitored in patients taking digoxin concomitantly and dose reduced, as necessary.

In cases of prodrugs whose actions are mediated by the CYP2D6-produced metabolites (for example, codeine and hydrocodone, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in the presence of AVP-786 due to quinidine-mediated inhibition of CYP2D6. Alternative treatment should be considered.

For patients who terminate early, the conditions of use for allowed concomitant medications and nondrug therapies or prohibited medications do not apply between the ET visit and the Follow-up visit. Any use of medications during this period will be at the discretion of the Investigator. Patients should allow at least 14 days after stopping study drug before starting a monoamine oxidase inhibitor (MAOI).

5.2.1. Restricted and Prohibited Concomitant Medications

Psychotropic concomitant medications that are either allowed with certain restrictions or prohibited are listed in Table 3. A detailed list of prohibited concomitant medications that may result in significant drug-drug interactions is provided in Appendix 1.

Due to differences in the commercial availability of allowed concomitant medications in the specific country, please contact a Medical Monitor to discuss any alternative medications not listed below.

Table 3: Restricted and Prohibited Concomitant Medications

	Medication	Prior to Study Entry	During Double-Blind Treatment Period
1.	Medications to treat Alzheimer's disease (eg, cholinesterase inhibitors, memantine, or other cognitive enhancers approved in the respective country)	Allowed provided that the dose has been stable for at least 3 months prior to the Screening visit, AND there is no change in dose or discontinuation within the same time period	Should remain on the same dose throughout the duration of the study, except when medically indicated due to a change in the underlying medical condition
2.	Atypical Antipsychotics • except clozapine • except brexpiprazole	Allowed provided that the dose has been stable for at least 1 month prior to the Screening visit, AND there is no change in dose or discontinuation within the same time period	Should remain on the same dose throughout the duration of the study
	Clozapine	Not allowed within 1 month prior to the Screening visit	Prohibited
	Typical Antipsychotics	Not allowed within 1 month prior to the Screening visit	Prohibited
	Brexpiprazole	Not allowed within 1 month prior to the Screening visit	Prohibited
3.	Antidepressants • select antidepressants listed below are restricted or prohibited	Allowed provided that the dose has been stable for at least 3 months prior to the Screening visit and is within the range specified in the prescribing information for that medication, AND there is no change in dose or discontinuation within the same time period	Should remain on the same dose throughout the duration of the study
	Paroxetine	Allowed with a maximum dose of 10 mg/day	Should remain on the same dose throughout the duration of the study
	Trazodone	Allowed with a maximum dose of 50 mg/day	Should remain on the same dose throughout the duration of the study
	Nefazodone	Not allowed within 3 months prior to the Screening visit	Prohibited
	Tricyclic Antidepressants	Not allowed within 3 months prior to the Screening visit	Prohibited
	Monoamine Oxidase Inhibitors (MAOI)	Not allowed within 3 months prior to the Screening visit	Prohibited Patients should allow at least 14 days after stopping study drug before starting an MAOI
4.	Benzodiazepines	Not allowed within 1 month prior to the Screening visit	Prohibited

Medication		Prior to Study Entry	During Double-Blind Treatment Period
5.	Hypnotic Sleep Agents (eg, zolpidem, zaleplon, zopiclone, eszopiclone, or other sleep agent approved in the respective country)	Allowed if the dose of the sleep agent for insomnia was taken on a regular basis for at least 1 month prior to the Screening visit, AND there is no change in dose or frequency, or discontinuation in the same time period	Should remain on the same dose and at the same frequency throughout the duration of the study
6.	Other allowed psychotropic medications that may impact agitation (eg, mood stabilizers, antiepileptics) • select medications listed below are prohibited	Allowed provided that the dose has been stable for at least 1 month prior to the Screening visit, AND there is no change in dose or discontinuation within the same time period	Should remain on the same dose throughout the duration of the study
	Atomoxetine, carbamazepine, fosphenytoin, pentobarbital, phenobarbital, phenytoin, primidone	Not allowed within 1 month prior to the Screening visit	Prohibited
7.	Other prohibited concomitant medications (see Appendix 1)	Not allowed within 2 weeks or 5 half-lives (whichever is longer) prior to the Baseline visit	Prohibited

5.3. Treatment Compliance

Patients and caregivers will be instructed to return all dispensed study drug, including unused and used empty blister cards, to the clinic on Visits 2 through 8 (Days 8, 15, 29, 43, 57, 71, and 85/ET). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses (compliance range 80% to 120%). Caregivers will be provided with diary cards and will be instructed to record daily the number of capsules taken and the time of administration. Diary cards will be reviewed for compliance and collected on Visits 2 through 8, or at the time of early study discontinuation. Patients should bring their Diary Card to each of these visits for compliance review; the Diary Card will be returned to the patient and collected at the next visit, if applicable.

5.4. Randomization and Blinding

Eligible patients will be randomized to either treatment with AVP-786 or placebo according to a randomization scheme devised by the Sponsor or its representative and managed within an interactive web response system (IWRS). The randomization will be stratified by site and baseline concomitant antipsychotic use (yes/no).

If in the Investigator's judgement, it becomes medically necessary to identify which treatment a patient has received, the blind can be broken by the Investigator. If identification of the study treatment is required for emergency therapeutic measures, the investigator or designee can immediately obtain the current treatment assignment electronically through the IWRS. In any situation requiring unblinding, ideally the Investigator should contact the study Medical Monitor

to discuss the unmasking of a patient. If this is not possible, the study Medical Monitor should be notified as soon as possible.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug Composition

Each capsule of study drug will contain one of the following:

- AVP-786
- Matching Placebo: identical in appearance to AVP-786 capsules; containing inactive ingredients only

The inactive ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal silicone dioxide, and magnesium stearate.

Study drug will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Council on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

6.2. Study Drug Packaging and Labeling

The investigators will be supplied with prelabeled, individually prepackaged blister cards (1-week and 2-week blister cards). The panel of the 1-week blister card (1 week of study drug) consists of 3 rows of 7 capsules; one row for the morning dose, one row for the evening dose, and one row for extra supplies. The panel of the 2-week blister card (2 weeks of study drug) consists of 5 rows of 7 capsules; one row for the morning and one row for the evening dose for the first week and second week, and one row for extra supplies.

All labels will contain the protocol number, product name, blister card kit number (Med ID No.), an investigational drug warning, dosage instructions to take one capsule in the morning (AM) and one capsule in the evening (PM), storage conditions, and company name. The blister card label will consist of either a 2-panel label or booklet label. Both will have a detachable panel that will be removed and affixed to the study drug Dispensing Log page at the time of dispensing.

6.3. Study Drug Storage

Clinical supplies must be stored in compliance with label requirements in a secure place and kept at room temperature: 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F-86°F).

6.4. Study Drug Administration

All patients will receive study drug according to the blister card kit numbers assigned by an IWRS randomization scheme. Designated staff at each site will dispense study drug. Study drug should be administered to the patient by the caregiver, family member, nursing home staff, or self-administered with supervision, except on applicable clinic visit days when patients will be administered their dose of study drug at the clinic in the presence of site personnel, regardless of the time of day; the morning dose of study drug will be administered in the clinic at Baseline (Day 1), Visit 2 (Day 8), and Visit 5 (Day 43). For the remaining visits (Visit 3 [Day 15], Visit 4 [Day 29], Visit 6 [Day 57], Visit 7 [Day 71], and Visit 8 [Day 85]/ET), the

morning dose of study drug can be administered at home prior to the clinic visit; the time of the morning dosing should be noted by the patient/caregiver.

Patients and caregivers will be instructed that the patient should take the study drug orally with water approximately every 12 hours ± 4 hours (morning and evening). The time the patient takes each dose of medication should be recorded in the diary card. Patient's missed doses will be noted in the electronic case report form (eCRF).

All study drug will be supplied and administered in a double-blind manner throughout the entire duration of the study.

6.5. Study Drug Accountability

6.5.1. Receipt of Drug Supplies

The investigator is responsible for maintaining an inventory of each shipment of study drug received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form, as well as completing the receipt verification in IWRS. The investigator will verify the accuracy of the information on the form, sign and date it, and return the form to the sponsor or its representative. All study drug supplied is for use only in this study and should not be used for any other purpose. All blister card kit numbers will also be recorded and tracked at the site using the Drug Accountability Log.

6.5.2. Record of Dispensing

Accurate recording of all study drug dispensing for individual patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: (i) patient number to whom the study drug was dispensed; (ii) the date(s) and quantity of the study drug dispensed to the patient; and (iii) the blister card kit number assigned to the patient via IWRS.

Additionally, the detachable panel of the label on each blister card will be removed and affixed to the study drug Dispensing Log page at the time of dispensing. The detachable panel contains the study number and kit number (Med ID No.). Space is provided on the affixed part of the label to record patient number, the visit week and dispense date.

6.6. Study Drug Handling and Disposal

At the end of the study, all unused investigational supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or its representative, along with a completed and signed Drug Accountability Report/Material Shipping Form. Any study drug returns will be reported in IWRS. If any study drug is lost or damaged, it should be indicated on the form and should be reported in IWRS.

7. ASSESSMENT OF EFFICACY

Whenever possible, each patient and caregiver should have the rating scales administered by the same raters throughout the study, for consistency of ratings. The following scales MUST be administered by the same rater at each visit: CMAI, CGIS-Agitation, CGIC-Agitation, and NPI.

7.1. Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI will be used as the primary efficacy measure in this study. The CMAI (long-form version) is used to assess the frequency of manifestations of agitated behaviors in elderly persons. It consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation [34]. These distinct agitation syndromes include: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior [35]. Scores for the 3 dimensions will be derived based on the factor structure described by Rabinowitz, et al, 2005 [36]; further details are provided in the statistical analysis plan (SAP). Each of the 29 items is rated on a 7-point scale of frequency (1 = never, 2 = less than once a week but still occurring, 3 = once or twice a week, 4 = several times a week, 5 = once or twice a day, 6 = several times a day, 7 = several times an hour). The ratings are based on the 2 weeks preceding assessment of the CMAI.

The CMAI will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 43), Visit 6 (Day 57), Visit 7 (Day 71), Visit 8 (Day 85/ET), and the Follow-up visit (30 days postdose). The CMAI must be administered by the same rater at each visit.

7.2. Clinical Global Impression of Severity of Illness-Agitation (CGIS-Agitation)

The CGIS is an observer-rated scale that measures illness severity and is one of the most widely used brief assessment tools in psychiatry research.

The Early Clinical Drug Evaluation Unit version of the CGIS is the most widely used format of this validated tool, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. The CGIS has proved to be a robust measure of efficacy in many clinical drug trials [37,38,39,40,41] and is easy and quick to administer, provided that the clinician knows the patient well [42].

Reliability and validity of CGI have been tested in multiple studies, including patients with dementia, schizophrenia and affective disorders. Overall, CGI showed high correlation (r: ~90%) with other assessment instruments and it has also shown positive significant relationships and concurrent validity with other clinician's rating. In addition, the scale has good sensitivity to change over time [43,44,45].

The CGIS-Agitation is a 7-point (1-7) scale (1 = normal, not at all ill; 7 = among the most extremely ill patients) and assesses severity of agitation in this study. The CGIS-Agitation will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 43), Visit 6 (Day 57), Visit 7 (Day 71), Visit 8

(Day 85/ET), and the Follow-up visit (30 days postdose). The CGIS-Agitation must be administered by the same rater at each visit.

7.3. Clinical Global Impression of Change-Agitation (CGIC-Agitation)

The CGIC-Agitation is a 7-point (1-7) scale (1 = very much improved; 7 = very much worse) that assesses the change in the severity of agitation in this study [42]. The CGIC-Agitation evaluation will be conducted at Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 43), Visit 6 (Day 57), Visit 7 (Day 71), and Visit 8 (Day 85/ET). The CGIC-Agitation must be administered by the same rater at each visit.

7.4. Neuropsychiatric Inventory (NPI)

The NPI is a validated clinical instrument for evaluating psychopathology in a variety of disease settings, including dementia. The NPI is a retrospective caregiver-informant interview covering 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavioral disorders, and appetite/eating disorders [46]. Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of both frequency (1 to 4) and severity (1 to 3), yielding a composite symptom domain score (frequency x severity). Caregiver distress is rated for each positive neuropsychiatric symptom domain on a scale anchored by scores of 0 (not distressing at all) to 5 (extremely distressing).

The NPI will be administered to the patient's caregiver at Baseline (Day 1), Visit 2 (Day 8), Visit 5 (Day 43), Visit 7 (Day 71), and Visit 8 (Day 85/ET). Only the Agitation/Aggression domain of the NPI (NPI-AA) will be administered to the patient's caregiver at Screening (Day -28 to Day -1), Visit 3 (Day 15), Visit 4 (Day 29), and Visit 6 (Day 57). The recall period will be 2 weeks for all the visits. The NPI must be administered by the same rater at each visit. The NPI nursing-home version (NPI-NH) will be used for patients from in-patient or assisted living facilities.

7.5. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L is a generic questionnaire measuring health-related quality of life and consists of a descriptive system and the EuroQol Visual Analogue Scale (EQ VAS) [47]. The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. There are 2 versions of the EQ-5D-5L, a version rated by the patient and a version (EQ-5D-5L-proxy) rated by caregiver. The patient version will be rated only by patients with an MMSE score of ≥ 10 at the Baseline visit.

The EQ-5D-5L-proxy (and EQ-5D-5L for patients with MMSE ≥ 10) will be assessed at Baseline (Day 1) and Visit 8 (Day 85/ET).

7.6. Resource Utilization in Dementia (RUD) Lite

The RUD is used to calculate healthcare costs associated with dementia [48]. It evaluates dementia patients' utilization of formal and informal healthcare resources, including hospitalizations and doctor visits, living assistance, and time spent by nonprofessional caregivers. Within the context of clinical trials, the RUD is often used to determine the cost effectiveness of new pharmaceutical treatments [49].

The RUD is administered as a semi-structured interview with the patient's primary caregiver, and contains 2 sections; one focusing on caregiver impact (loss of work and leisure time incurred by caregiver) and the other focusing on the patient's use of healthcare resources. The total healthcare costs associated with the patient's dementia can be estimated by multiplying the number of units used (eg, hours of caregiver time, visits to doctors, nights in accommodation) by the corresponding unit price vector.

The RUD-Lite (RUD 5.0) is a shorter version of the RUD developed to reduce the interview burden on caregivers. Questions related to caregiver resource use (eg, work status, respite or hospital care, social services, day care, or drug use), which in general is low for caregivers, have been removed from the RUD-Lite [50].

The RUD-Lite will be assessed at Baseline (Day 1) and Visit 8 (Day 85/ET).

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

8.1.1. Adverse and Serious Adverse Events

8.1.1.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence or unintended change (eg, physical, psychological, or behavioral), including inter-current illness, whether considered related to study drug or not. An AE can therefore be any unfavorable and unintended sign (including any clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (eg, onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (eg, cold or seasonal allergies, instead of runny nose).

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome, even if toxic effects were not observed.

AEs will be graded on a 3-point severity scale and reported in detail as indicated on the eCRF:

Mild:	easily tolerated, causing minimal discomfort and not interfering with normal everyday activities
Moderate:	sufficiently discomforting to interfere with normal everyday activities
Severe:	incapacitating and/or preventing normal everyday activities

The relationship of each AE to study drug should be determined by the investigator using the following explanations:

Not related:	the event is clearly related to other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient
Unlikely related:	the event is most likely produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient; and does not follow a known response pattern to the study medication
Possibly related:	the event follows a reasonable temporal sequence from the time of study drug administration; and/or follows a known response pattern to the study drug; but could have been produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

Related: the event follows a reasonable temporal sequence from the time of study drug administration; and follows a known response pattern to the study drug; and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

8.1.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening experience (one that places the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, ie, it does not include an AE that, had it occurred in a more severe form, might have caused death)
3. Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
4. In-patient hospitalization or prolongation of hospitalization
5. Congenital anomaly/birth defect

Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The terms "cancer" and "overdose" are not necessarily considered SAEs, but if a patient experiences cancer or overdose, they are still reportable as AEs.

Pregnancy is not considered to be an AE or an SAE, but all reported pregnancies occurring during the study will be reported on the Pregnancy and Breastfeeding Exposure Form (PBEF). The site should follow-up each trimester with the patient/partner until the final outcome is known (ie, normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). Should a complication occur that meets the requirements for an AE or SAE, it must be reported within 24 hours of awareness. Patients who are pregnant or likely to become pregnant are excluded from this study. In the event a patient becomes pregnant during the study, study drug must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of awareness.

A pregnancy report form must also be completed in the event that the partner of child-bearing potential of a male patient in the study becomes pregnant within 30 days after his last dose of study drug or study completion, whichever is greater.

The term 'severe' is a measure of intensity; thus, a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe but may not be clinically serious.

8.1.1.3. Reporting Adverse Events

Caregivers will be queried regarding AEs at each clinic visit after the Screening visit (Baseline [Day 1], Visits 2-8 [Days 8, 15, 29, 43, 57, 71, and 85/ET], and Follow-up visit). Only treatment emergent adverse events (TEAE) that occur after administration of the first dose of study drug will be captured for the purposes of the study. Any intercurrent AEs that occur after the signing of the informed consent and prior to the patient's first dose of study drug will be captured as medical history. In the instance that the site becomes aware of any such intercurrent adverse events subsequent to confirmation and approval of eligibility for an enrolled patient, the site should update the medical history records to reflect this updated information and ensure that the updated information is provided to the Medical Monitor. Any AE newly reported after receiving the last dose of study drug and up until 30 days after receiving the last dose of study drug will be followed.

The Sponsor may request additional information on certain events, such as falls. Event to Monitor data collection forms and completion guidelines will be provided for the Investigator to complete for such events. These forms should be submitted to the Sponsor as specified on the form.

A death occurring during the study, or which comes to the attention of the Investigator within 30 days after stopping the study drug whether considered drug-related or not, must be reported to the sponsor.

For all SAEs the investigator should consult with the Sponsor's Medical Monitor or designated representative as needed and report any SAE via the Serious Adverse Event Reporting (SAER) Form by fax/email (as detailed below) no later than 24 hours after becoming aware of the event. The SAE must be assessed for the following details: seriousness criteria of the event, SAE start date, SAE stop date, severity, relationship to study drug, action taken regarding study drug, and outcome to date. The narrative section of the form may be used to detail any treatment information.

SAE and Events to Monitor reporting by FAX or e-mail correspondence:

E-mail: CCI [redacted]

Preliminary (initial) reports will be followed by detailed descriptions, which may include copies of hospital records/discharge summaries, autopsy reports, death certificates, and other related documents as requested.

The Institutional Review Board/Independent Ethics Committee (IRB/IEC/EC) will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

8.1.2. Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1) and Visit 8 (Day 85/ET). The physical examination will include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination will include assessments of mental status, cranial nerves, motor system, reflexes, coordination, gait and station, and sensory

system. The physical and neurological examinations should be performed by the same person each time, whenever possible.

Physical and neurological examination abnormalities determined by the investigator to be clinically significant at Screening should be recorded as medical history.

Any clinically significant changes in physical and neurological examination findings from the screening examination should be recorded as AEs.

8.1.3. Vital Signs

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed at all clinic visits, except the Follow-up visit. Supine BP and HR will be measured after a patient has rested for at least 5 minutes in the supine position. Each measurement will be taken twice in the same position and recorded. After the measurement of supine BP and HR, the patient will stand still for up to 3 minutes and a single measurement of standing BP and HR will be recorded within 1 to 3 minutes of standing.

Respiratory rate (breaths/minute) and body temperature (ºF/ºC) will be assessed at all clinic visits.

8.1.4. Weight and Height

Height and weight will be measured at Baseline (Day 1); only weight will be measured at Visit 8 (Day 85/ET).

8.1.5. Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at Screening, Baseline, Visit 2 (Day 8), Visit 5 (Day 43), and Visit 8 (Day 85/ET). At Screening, 3 ECGs will be performed (eg, one after the other). At Baseline (Day 1) and Visit 2 (Day 8), 2 ECGs will be performed; one predose and one postdose 1 to 1.5 hours after study drug dosing. An ECG will be performed at any time at Visit 5 (Day 43) and Visit 8 (Day 85/ET).

ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute), QRS complex, PR and QTc intervals (milliseconds). Results will be provided by the central reader to the investigators within 24 hours. ECG abnormalities present at Screening will be recorded as medical history. Any changes from the ECG status at Screening visit that are deemed to be clinically significant by the investigator should be captured as AEs. Any clinically significant abnormal ECG should be discussed with a Medical Monitor and, if necessary, be repeated within a 1-week period.

For eligibility to enroll in the study, the QTcF assessment of the 3 ECGs conducted at Screening will be based on the central review. A patient will be excluded if 2 of the 3 Screening ECGs have a QTcF > 450 msec in males and > 470 msec in females, unless due to ventricular pacing. If only 1 Screening ECG has a QTcF > 450 msec in males and > 470 msec in females, which is not reproduced in either of the other 2 Screening ECGs, then the patient may be eligible for the study. The assessment of ECGs conducted at Baseline will be based on the machine read and

investigator evaluation of the read. If the Baseline predose ECG QTcF result from the machine read is exclusionary, the patient should not be dosed and a Medical Monitor should be consulted.

8.1.6. Clinical Laboratory Assessments

Unless otherwise specified, the following clinical laboratory assessments are to be performed at Screening (Day -28 to Day -1), Visit 5 (Day 43), and Visit 8 (Day 85/ET):

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, creatine kinase, gamma-glutamyl transferase, triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell count, hemoglobin, hematocrit, white blood cell [WBC] count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
- Urinalysis (pH, specific gravity, protein, glucose, ketones, blood, leucocyte esterase, nitrates, and microscopic appearance)
- Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) at Screening visit only
- Glycosylated hemoglobin (HbA1c) test at the Screening visit and Visit 8 (Day 85) only
- CYP2D6 genotyping at Visit 2 (Day 8) only
- Amyloid β biomarker at Visit 2 (Day 8) only

Any patients with clinically significant abnormal laboratory test results may be required by a Medical Monitor to have a repeat test 1 week later or earlier, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry.

8.1.7. Pregnancy Tests

Urine pregnancy tests are to be performed for women of childbearing potential at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Day 85/ET).

All female patients of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study drug.

Women of childbearing potential who are sexually active must use an effective method of birth control for at least 1 month prior to randomization, during the course of the study, and for at least 30 days after the last dose of study drug. The following requirements must be met:

- Women of childbearing potential must use 2 of the following precautions in order to minimize the risk of failure of 1 method of birth control: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, or condom with spermicide or sponge with

spermicide. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception.

- Women who are sterile (ie, had an oophorectomy and/or hysterectomy), postmenopausal (defined as 12 months with no menses without an alternative medical cause), or practice true abstinence (when this method is in line with the preferred and usual lifestyle of the patient) are exempt from this requirement.
- Women who are lactating, pregnant, or plan to become pregnant are not eligible for participation in the study.

8.1.8. Mini Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. It is also used to estimate the severity of cognitive impairment at a specific time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate the patient's cognitive state [51]. The MMSE total score ranges from 0 to 30, with higher scores indicating better cognitive function. It requires only 5 to 10 minutes for a trained rater to administer it.

The MMSE will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Day 85).

8.1.9. Epworth Sleepiness Scale (ESS)

The ESS is an 8-item questionnaire that is used to measure sleepiness by rating the probability of falling asleep on 8 different situations that most people engage in during the day [52]. The questions are rated on a 4-point scale (0 to 3) where 0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, and 3 = high chance of dozing. A total score of 0 to 9 is considered to be normal.

The ESS will be assessed at Baseline (Day 1) and Visit 8 (Day 85/ET) for patients with an MMSE score of ≥ 10 at the Baseline visit.

8.1.10. Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors [53]. Each item of the S-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). The S-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. For the Screening visit, the timeframe for the items on the scale will be 'in the past 6 months' and for all other visits it will be 'since last visit'.

The S-STS will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), and Visit 8 (Day 85/ET). Any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to a Medical Monitor.

8.1.11. Assessment of Risk of Falls for Eligibility

8.1.11.1. Timed Up and Go (TUG) Test

The TUG test measures the time (in seconds) taken for an individual to stand up from a standard armchair, walk 3 meters, turn, walk back to the chair and sit down. It is a commonly used scale for measuring functional mobility and risk of falls [54,55]. The TUG test will be performed only at Screening (Day -28 to Day -1) to assess the risk of falls for the purpose of eligibility for the study.

8.1.12. Hachinski Ischemic Scale (Rosen Modification)

The Rosen-modified Hachinski Ischemic Scale assesses whether a patient'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 [56]. The total score ranges from 0 to 12, with higher scores indicating a greater risk of vascular dementia. The Rosen-modified Hachinski Ischemic Scale will be completed at the Screening visit to assess the risk of vascular dementia and eligibility for the study by the same physician who performs the neurological examination.

9. SCHEDULE OF EVAUATIONS AND PROCEDURES

A schedule of evaluations and procedures by visit is provided in Table 1.

9.1. Description of Study Procedures

At each visit throughout the study, site staff will be required to enter information into the IWRS regarding patient data and predefined study assessment results. Further instructions will be provided in the IWRS Site Manual.

9.1.1. Screening Visit (Days -28 to -1)

The following procedures will be performed at Screening (within 28 days prior to Day 1). The screening period may be extended after discussion with and approval by a Medical Monitor. In the event that a patient is rescreened for enrollment, new informed consent and/or assent documents must be signed, new patient number assigned, and all screening procedures repeated.

1. The Investigator will provide the patients, authorized representatives, and/or their caregivers with informed consent and/or assent documents and will explain the rationale for the study, providing ample time for participants, authorized representatives, and/or caregivers to ask questions.
2. Review inclusion/exclusion criteria (protocol eligibility form completed by site).
3. Medical, psychiatric, and neurological history will be reviewed and recorded, including patient demographics, any prior and concomitant medications (including over-the-counter [OTC], vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
4. Risk assessment for falls will be performed (worksheet and TUG test).
5. Vital signs will be measured and recorded.
6. Physical and neurological examination will be performed.
7. Three resting 12-lead ECGs will be performed.
8. A blood and urine specimen will be collected for safety laboratory assessments (including thyroid function tests and Hb A1c).
9. A urine pregnancy test will be performed for women of childbearing potential only (Section 8.1.7).
10. The following assessments will be completed (the CMAI and NPI-AA should be administered before the CGIS-Agitation):
    - CMAI
    - NPI-AA domain; a score of ≥ 4 is required for study entry
    - CGIS-Agitation
    - MMSE; a score between 8 and 24 (inclusive) is required for study entry

- S-STS

11. Register the Screening visit in IWRS.

Following screening procedures for assessment of inclusion and exclusion criteria, the site will complete a protocol eligibility form to be reviewed by a Medical Monitor for approval prior to participation in the study. Patients deemed eligible by the Investigator and a Medical Monitor will proceed to the Baseline visit of the study.

Patients who have ECG or laboratory test results outside of the reference normal range that the investigator considers to be clinically significant and may put the patient at a higher risk for study participation, will not be enrolled.

9.1.2. Baseline Visit (Day 1)

The Baseline visit (Day 1) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. Review inclusion/exclusion criteria.
2. Vital signs will be measured and recorded.
3. Weight and height will be measured and recorded.
4. A resting 12-lead ECG will be performed (predose).
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 8.1.7).
6. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
7. The following assessments will be completed (the CMAI and NPI should be administered before the CGIS-Agitation):
   - CMAI
   - NPI
   - CGIS-Agitation
   - EQ-5D-5L
   - RUD-Lite
   - MMSE
   - ESS (only for patients with an MMSE score of ≥ 10 at Baseline)
   - S-STS

Patients will proceed with the Baseline visit once it is determined that they satisfy all of the inclusion and none of the exclusion criteria (on the basis of the Screening and Baseline assessments described above) and will be assigned with a blister card kit number via IWRS.

Study Drug Dosing:

The first dose of study drug will be administered at the clinic regardless of the time of day from the AM strip of the blister card (1-week blister card) after predose assessments are completed; note the time of dosing.

After Dosing:

1. A resting 12-lead ECG will be performed (1 to 1.5 hours postdose).
2. The caregiver will be queried regarding AEs.
3. Patient Diary Card and a blister card (1-week blister card) will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 7 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and patient's Diary Card at each study visit. For the next scheduled visit (Visit 2, Day 8), caregivers will be advised that the patient's morning dose of study drug will be administered at the clinic.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.3. Visit 2 (Day 8 ± 3-day window)

Visit 2 (Day 8) should occur in the morning prior to the morning dose of study drug. The following procedures will be performed.

Before Dosing:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. A resting 12-lead ECG will be performed (predose).

4. The following assessments will be completed (the CMAI and NPI should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI
    - CGIS-Agitation
    - CGIC-Agitation
5. Register the study visit in IWRS and a blister card kit number will be assigned to patient (1-week blister card).

Study Drug Dosing:

The morning dose of study drug will be administered at the clinic from the AM strip of the new blister card (1-week blister card) after predose assessments are completed; note the time of dosing.

After Dosing:

1. A resting 12-lead ECG will be performed (1 to 1.5 hours postdose).
2. A blood and urine sample will be collected for PK assessments (1 to 4 hours postdose).
3. A blood sample will be collected for CYP2D6 genotyping.
4. A blood sample will be collected for amyloid β biomarker.
5. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (1-week blister card).
6. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 7 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and the patient's Diary Card at each study visit. For the next scheduled visit (Visit 3, Day 15), caregivers will be advised to administer the morning dose of study drug to the patient prior to the clinic appointment and note the time of dosing.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.4. Visit 3 (Day 15 ± 3-day window)

Visit 3 (Day 15) should occur in the morning. The morning dose of study drug can be administered at home any time prior to the visit; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed at Visit 3:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. The following assessments will be completed (the CMAI and NPI-AA should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI-AA
    - CGIS-Agitation
    - CGIC-Agitation
4. Register study visit in IWRS and a blister card kit number will be assigned to patient (2-week blister card).
5. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (2-week blister card).
6. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and the patient's Diary Card at each study visit. For the next scheduled visit (Visit 4, Day 29), caregivers will be advised to administer the morning dose of study drug to the patient prior to the clinic appointment and note the time of dosing.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.5. Visit 4 (Day 29 ± 3-day window)

Visit 4 (Day 29) should occur in the morning. The morning dose of study drug can be administered at home any time prior to the clinic visit; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed at Visit 4:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. The following assessments will be completed (the CMAI and NPI-AA should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI-AA
    - CGIS-Agitation
    - CGIC-Agitation
4. Register study visit in IWRS and a blister card kit number will be assigned to patient (2-week blister card).
5. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (2-week blister card).
6. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and the patient's Diary Card at each study visit. For the next scheduled visit (Visit 5, Day 43), caregivers will be advised that the patient's morning dose of study drug will be administered at the clinic.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.6. Visit 5 (Day 43 ± 3-day window)

Visit 5 (Day 43) should occur in the morning prior to the morning dose of study drug. The following procedures will be performed at Visit 5.

Before Dosing:

1. A blood sample will be collected for safety laboratory assessments and PK assessments.

The following procedures may be performed at any time:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. A resting 12-lead ECG will be performed (at any time during this visit).
4. The following assessments will be completed (the CMAI and NPI should be administered before the CGIS-Agitation and CGIC-Agitation):
   - CMAI
   - NPI
   - CGIS-Agitation
   - CGIC-Agitation
5. Register study visit in IWRS and a blister card kit number will be assigned to patient (2-week blister card).
6. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (2-week blister card).
7. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Study Drug Dosing:

The morning dose of study drug will be administered at the clinic from the AM strip of the new blister card (2-week blister card) after predose assessments are completed; note the time of dosing.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and the patient's Diary Card at each study visit. For the next scheduled

visit (Visit 6, Day 57), caregivers will be advised to administer the morning dose of study drug to the patient prior to the clinic appointment and note the time of dosing.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.7. Visit 6 (Day 57 ± 3-day window)

Visit 6 (Day 57) should occur in the morning. The morning dose of study drug can be administered at home any time prior to the clinic visit; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed at Visit 6:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. The following assessments will be completed (the CMAI and NPI-AA should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI-AA
    - CGIS-Agitation
    - CGIC-Agitation
4. Register study visit in IWRS and a blister card kit number will be assigned to patient (2-week blister card).
5. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (2-week blister card).
6. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study drug and the patient's Diary Card at each study visit. For the next scheduled

visit (Visit 7, Day 71), caregivers will be advised to administer the morning dose of study drug to the patient prior to the clinic appointment and note the time of dosing.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.8. Visit 7 (Day 71 ± 3-day window)

Visit 7 (Day 71) should occur in the morning. The morning dose of study drug can be administered at home any time before the clinical visit; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed at Visit 7:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
3. A blood sample will be collected for PK assessments (at any time during this visit).
4. The following assessments will be completed (the CMAI and NPI should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI
    - CGIS-Agitation
    - CGIC-Agitation
5. Register study visit in IWRS and a blister card kit number will be assigned to patient (2-week blister card).
6. Unused study drug will be accounted for compliance, and a new blister card will be dispensed (2-week blister card).
7. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study drug twice-daily (1 capsule of study drug from the top row [AM] of blister card in the morning and 1 capsule of study drug from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or study coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic

any unused study drug and patient's Diary Card at each study visit. For the next scheduled visit (Visit 8, Day 85/ET), caregivers will be advised to administer the morning dose of study drug to the patient prior to the clinic appointment and note the time of dosing.

A CMAI caregiver diary will be provided to be used by the caregiver to support reporting of behaviors during the CMAI interview process.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

9.1.9. Visit 8 (Day 85 ± 3-day window) / Early Termination

Visit 8 (Day 85/ET) should occur in the morning. The morning dose of study drug can be administered at home any time prior to the clinic visit; the time of dosing should be noted by the patient/caregiver.

Patients who withdraw prior to study completion are required to complete study procedures as listed for Visit 8/ET within 48 hours of the last dose of study drug.

The following procedures will be performed at Visit 8 (or ET):

1. Vital signs will be measured and recorded.
2. Weight will be measured and recorded.
3. Physical and neurological examination will be performed.
4. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
5. A resting 12-lead ECG will be performed (any time during this visit).
6. A blood and urine specimen will be collected for safety laboratory assessments.
7. A urine pregnancy test will be performed for women of childbearing potential only (Section 8.1.7).
8. The following assessments will be completed (the CMAI and NPI should be administered before the CGIS-Agitation and CGIC-Agitation):
    - CMAI
    - NPI
    - CGIS-Agitation
    - CGIC-Agitation
    - EQ-5D-5L
    - RUD-Lite
    - MMSE
    - ESS (only for patients with an MMSE score of ≥ 10 at Baseline)

- S-STS

9. Register study visit in IWRS.
10. Any unused study drug will be returned and accounted for compliance.
11. Patient's Diary Card will be reviewed for compliance.
12. Any previously reported and not yet resolved AE and any newly reported AE at the time of this visit will be followed-up for up to 30 days after the last dose of study drug.
13. If ET, site staff will access CTSdatabase, enter the patient Study ID and nature of the last contact (ie, early terminated).

Caregivers and patients will be instructed to return to the clinic for a Follow-up visit 30 days after the last dose of study drug.

9.1.10. Follow-up Visit (30 days post last dose; + 7-day window)

The Follow-up visit should occur 30 days (+ 7-day window) after the last dose of study drug.

The following procedures will be performed:

1. The caregiver will be queried regarding AEs, concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation.
2. The following assessments will be completed:
   - CMAI (completed first)
   - CGIS-Agitation
3. Site staff will access the CTSdatabase and enter the patient Study ID and nature of the last contact (ie, completed study).

9.2. End of Trial

The end of the trial is defined as the "Last Patient Last Visit", which is the date on which the last patient has his or her last visit (ie, the Follow-up visit) or assessment, either for therapeutic or follow-up purposes.

10. STATISTICS

10.1. Sample Size Calculations

The planned sample size for this trial is approximately 750 randomized patients. Statistical assumptions and additional details are provided in the SAP.

10.2. Analysis Populations

The following analysis population are defined for this study:

- Enrolled: all patients enrolled in this study
- Randomized: all patients who are randomized into this study
- Safety: all patients who are randomized in this study and take at least one dose of study drug
- Efficacy: all patients in the randomized population who take at least 1 dose of study drug, have a baseline CMAI total score, and at least 1 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 patient is randomized.

The core dataset for all efficacy analyses is based on the ITT population, which is defined in the efficacy analysis set 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 analyses.

10.3. Handling of Missing Data

In general, missing data will be handled by analysis of mixed-effect model repeated measures (MMRM) methodology based on observed-case (OC) data from protocol specified visits in the ITT population under the assumption of missing at random. Details of sensitivity analyses under the assumption of missing data being missing not at random (MNAR) will be provided in the SAP as well as additional sensitivity analyses, as applicable.

The OC dataset consists of actual observations recorded at each visit during the double-blind treatment period, and no missing data will be imputed.

10.4. Efficacy Analysis

10.4.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the change from baseline to the end of the efficacy period in the CMAI total score. The change from baseline to the end of the efficacy period in the CMAI total score will be analyzed using a MMRM analysis with an unstructured variance covariance structure (UN). The model will include fixed class effect terms for treatment, study site, baseline concomitant antipsychotic use (yes/no), visit week, and an interaction term of treatment by visit

week, and will include the interaction term of baseline values of the CMAI total score and NPI-AA score by visit week as a covariate. All scheduled visits after baseline during the double-blind treatment period will be included in the model.

Complete details of the planned statistical analysis will be presented in the SAP. Details of sensitivity analyses for MNAR, as well as additional sensitivity analyses will be prespecified in the SAP.

10.4.2. Key Secondary Analysis

The key secondary efficacy variable is the change from baseline to end of efficacy period 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. The procedure to control the overall type I error rate for this key secondary efficacy analysis will be described in the SAP.

10.4.3. Other Efficacy Endpoint Analysis

Other efficacy variables include the following:

- Change from baseline to each study visit in efficacy period in CMAI Total score
- Change from baseline to each study visit in efficacy period in CGIS-Agitation score
- CGIC-Agitation score at each study visit in the efficacy period
- Change from baseline to each study visit in efficacy period in NPI-AA score
- Change from baseline to each study visit in efficacy period in NPI total score
- CMAI Response Rate at each study visit in efficacy period, where response is defined as ≥ 30% reduction in CMAI Total Score from baseline
- CMAI Response Rate at each study visit in efficacy period, where response is defined as ≥ 50% reduction in CMAI Total Score from baseline
- Change from baseline to each study visit in efficacy period in the EQ-5D-5L total score
- Change from baseline to each study visit in efficacy period in the RUD-Lite

Change from baseline will be evaluated using the same MMRM model described in the primary analysis.

Change from baseline for the endpoints with one postbaseline assessment will be evaluated using analysis of covariance (ANCOVA) with baseline value, study site and baseline concomitant antipsychotic use (yes/no) as a covariate and treatment as main factor.

The response variables will be evaluated by the Cochran-Mantel-Haenszel (CMH) General Association Test controlling, in last-observation-carried-forward (LOCF) analyses, for study site and baseline concomitant antipsychotic use (yes/no). The OC analysis will not control for stratification factors.

The CGIC-Agitation score will be evaluated by the Cochran–Mantel–Haenszel row mean score differ test (van Eltern), controlling for study site and baseline concomitant antipsychotic use (yes/no) in the LOCF analysis. The OC analysis will not control for stratification factors.

Further details and analysis methods will be described in the SAP.

10.4.4. Control of Experiment-wise Type 1 Error

Control of experiment-wise Type 1 error is described in the SAP.

10.4.5. Other Efficacy Endpoint Analyses

Additional analyses of efficacy endpoints are described in the SAP.

10.5. Interim Analysis

One interim analysis may be performed; the details of the interim analysis will be provided in an interim analysis plan (IAP).

10.6. Analysis of Demographic and Baseline Characteristics

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

10.7. Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, and physical and neurological examination. In addition, data from the following safety scales will be evaluated: MMSE, ESS, and S-STS. Safety analysis will be conducted based on the Safety Population. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of study drug, unless specified otherwise. Prospectively defined criteria will be used to identify potentially clinically relevant abnormal values for clinical laboratory tests, vital signs, ECGs. Details of safety analyses will be provided in the SAP.

10.7.1. 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:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the study drug
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the study drug

The above summaries will also be prepared for TEAEs potentially causally related to the study drug.

10.7.2. Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements will be provided. In addition, the incidence of potentially clinically relevant values identified using prospectively defined criteria for laboratory tests will be summarized.

10.7.3. Physical and Neurological Examination and Vital Sign Data

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

10.7.4. Electrocardiogram 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.

The analysis of QT and corrected QT interval (QTc) data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used:

- QTcF is the length of the QT interval corrected for heart rate by the Fridericia's formula: $QTcF = QT/(RR)0.33$

Results will be summarized by visit.

10.7.5. Other Safety Data

Change from baseline in scores for the MMSE and ESS will be evaluated using ANCOVA with baseline value as a covariate and treatment as main factors. The analyses will be based on the OC and LOCF datasets of the Safety Population.

The suicidality (eg, S-STS) will be summarized by treatment group based on the OC dataset of the Safety Population. Details will be described in SAP.

10.7.6. Data and Safety Monitoring Board

The Sponsor will appoint a Data and Safety Monitoring Board (DSMB) for the periodic review of available study data.

The DSMB is an independent group of experts that advises the sponsor and the study Investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study.

The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking, and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

10.8. Other Analyses

10.8.1. Pharmacokinetic Analysis

No PK analysis is planned, as only sparse samples will be obtained. Plasma concentrations of d6-DM, its metabolites d3-DX and d3-3-MM, and Q will be summarized using descriptive statistics by dose and timepoint. Urine concentrations of d6-DM and its metabolite d3-DX will be summarized using descriptive statistics by dose and timepoint.

10.8.2. Pharmacodynamic Analysis

No pharmacodynamic (PD) analysis is planned.

10.8.3. Pharmacokinetic/Pharmacodynamic Analysis

A population or PK/PD modeling may be performed using the data from this study and other studies and would be reported separately.

10.8.4. Pharmacogenomic Analysis

CYP2D6 genotype and predicted phenotype will be listed for all patients by treatment group.

10.8.5. Exploratory Endpoint Analysis

Exploratory endpoint analysis will be described in the SAP.

11. ETHICS

11.1. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS); and will be consistent with GCP, ICH Guidelines, and the United States (US) Food and Drug Administration (FDA) CFR (21 CFR Parts 50 and 56) for the protection of the rights and welfare of human patients participating in biomedical research, and the applicable regulatory requirements.

11.2. Institutional Review Board - Ethics Review

All Institutional Review Boards/Independent Ethics Committee (IRBs/IECs/ECs) must meet the requirements as described in Part 56, Title 21 of the Code of Federal Regulations (CFR) and conform to local laws and customs where appropriate. Written IRB/IEC/EC approval for the protocol and the signed ICF must be obtained and transmitted to the Sponsor or its representative before the study can be initiated.

The protocol, the protocol amendments, and the sample ICF must be reviewed and approved by an IRB/IEC/EC of the participating study center in accordance with the CFR, the International Conference on Harmonisation (ICH), and Good Clinical Practice (GCP) before initiation of the study at their respective center. All protocol amendments and any changes to the ICF that occurred during the study must be approved by the Sponsor and the IRB/IEC/EC.

The Investigator will ensure that this study is conducted in full conformance with local laws and according to National and State laws of the US (Investigator Responsibilities [57] and the World Medical Association Declaration of Helsinki). The Principal Investigator is responsible for informing the IRB/IEC/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC/EC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/IEC/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB/IEC/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC/EC according to local regulations and guidelines.

11.3. Written Informed Consent

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed consent will be obtained from the patient (if the patient is capable in the judgment of the investigator to provide informed consent) or the authorized representative as determined by local regulations. For patients who are not capable of providing informed consent, but are capable of providing assent, the patient will be asked to provide assent. If the patient is not capable of providing assent, the investigator will

document the reasons why and maintain that documentation with the other informed consent documents. The patient's caregiver will also be asked to provide informed consent as they will be providing data on themselves and the patient, as well as, being responsible for ensuring compliance from the patient between study visits.

The patients and/or patient's authorized representative and the caregiver will be properly informed of the purpose of the study. The patients and/or patient's authorized representative and the caregiver will be alerted to any anticipated AE that may be encountered with the study drug. A signed ICF will be obtained from all patients and/or patient's authorized representative and the caregiver prior to patient entry into this study. Patients and/or patient's authorized representative and the caregiver will be provided with a copy of their signed and dated ICF.

The Investigators or designee will also explain the IRB/IEC/EC-approved Subject Database Authorization to the patient and witness the signature. All participants will also be informed that their medical records will be kept confidential except for review by the Sponsor or its representatives, the US FDA, or other regulatory agencies if applicable.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Standards for GCP and the ethical requirements equivalent to the provisions of Directive 2001/20/EC (Clinical Trials Directive) must be adhered to for all study-based procedures.

12.1. Documentation

For each process, evaluation, or test that generates study data but is not described in the protocol or eCRF, a written description of the data generation procedures shall be retained in the quality assurance section of the study files. In the case of routine clinical diagnostic procedures, only a copy of the relevant certification document is required.

12.2. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative and the caregiver for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB/IEC/EC. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

12.3. Direct Access to Source Data/Documents for Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from the Sponsor or to health authority inspectors after appropriate notification. The verification of the data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

The inspector from the regulatory authority will be especially interested in the following items:

- Visits from the sponsor's representatives
- IRB/IEC/EC approval(s)
- Study drug accountability

- Study protocol and amendments
- ICFs of the patient (if capable of providing ICF, according to the investigator) or patient's authorized representatives and caregivers
- Assent of the patients (if capable of providing assent, according to the investigator)
- Medical records supportive of eCRF data
- Reports to the IRB/IEC/EC and the sponsor
- Record retention

The sponsor will be available to help investigators prepare for an inspection.

13. DATA HANDLING AND RECORDKEEPING

13.1. Data Management and Collection

The sponsor or designated representative (eg, contract research organization) will perform the data management activities in accordance with the data management plan (DMP). The DMP will outline the systems and procedures to be used in the study.

Source documents and source data will be captured electronically (where permitted by local regulation) in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated according to 21 CFR Part 11. Changes to the data will be captured by an automatic audit trail.

Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application, rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified per the monitoring plan and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, wrong data right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or their designee.

Another exception will be safety laboratory [or central ECG data], where the official source documentation will be considered the report issued by the analyzing laboratory.

Designated trial site staff will not be given access to the electronic source system until they have been appropriately trained. All study-site personnel must use a password-protected user account to enter, review, or correct study data. Electronic signature procedures shall comply with the CFR Title 21 Part 11. Passwords will be strictly confidential.

All eCRF data will be exported from the electronic data capture (EDC) system and transferred to the sponsor or representative. The sponsor or representative will also receive electronic transfers of non-eCRF data such as laboratory data from the central laboratory, ECG data from the central ECG reader, as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the sponsor or representative and documented in the DMP or vendor data transfer requirements document as appropriate.

Remote monitoring of the original electronic source records will take place; however, on site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol

adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

The clinical monitoring staff will perform source data verification of the data recorded in the EDC system according to the data management plan and clinical monitoring plan. The data will be subjected to consistency and validation checks within the EDC system with supplemental data reviews performed outside of the EDC system.

Medical history and adverse events will be coded using a current version of MedDRA, and concomitant medications using a current version of the WHO Drug Dictionary. The sponsor or representative will perform a medical safety review of the coding.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data. Completed eCRF images with a date- and time-stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the investigator's site and at the sponsor's site.

13.2. Source Data

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications.

Data will be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' data to be monitored.

13.3. Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records should be retained by the Investigator according to International Conference on Harmonization standards, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable by the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13.4. Confidentiality of Study Documents and Patient Records

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission.

Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, 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 unique subject ID. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

The Investigator should keep a separate log of patient's codes, names, and addresses. Documents not for submission to the Sponsor, for example, patients' signed ICFs, should be maintained by the Investigator in strict confidence.

13.5. Reports

At the completion of the study, the investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study as described in CFR Title 21, Part 312.64.

14. CRITERIA FOR STUDY TERMINATION

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at the site at any time. Should this be necessary, the procedures to effect study termination will be arranged after review and consultation by both parties. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

15. PUBLICATION POLICY

It is anticipated that a report of this study will be published in the scientific literature by the sponsor. The investigator will not seek to arrange for publication of any of the information or results from the study in any scientific journal, or other publication or by way of lecture without the Sponsor's prior review and written consent.

16. LIST OF REFERENCES

Reference List

1. https://www.alz.org/alzheimers-dementia/facts-figures . 2019.
2. Plassman BL LK Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*. 2007;29(1-2):125-32.
3. Wilson RS WD Leurgans SE, Evans DA, Hebert LE, Langa KM, et al. Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement*. 2011;7(1):74-9.
4. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2008;23(2):170-7.
5. Fauth EB, Gibbons A. Which behavioral and psychological symptoms of dementia are the most problematic? Variability by prevalence, intensity, distress ratings, and associations with caregiver depressive symptoms. *Int J Geriatr Psychiatry*. 2014;29(3):263-71.
6. Borsje P, Wetzels RB, Lucassen PL, Pot AM, Koopmans RT. The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review. *Int Psychogeriatr*. 2015;27(3):385-405.
7. Wetzels RB, Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *Am J Geriatr Psychiatry*. 2010;18(12):1054-65.
8. Gauthier S, Lopez OL, Waldemar G, et al. Effects of donepezil on activities of daily living: integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease. *Int Psychogeriatr*. 2010;22(6):973-83.
9. Anatchkova M, Brooks A, Swett L, et al. Agitation in patients with dementia: a systematic review of epidemiology and association with severity and course. *Int Psychogeriatr*. 2019;11:1-14.
10. Conde-Sala JL, Turro-Garriga O, Pinan-Hernandez S, et al. Effects of anosognosia and neuropsychiatric symptoms on the quality of life of patients with Alzheimer's disease: a 24-month follow-up study. *Int J Geriatr Psychiatry*. 2016;31(2):109-19.
11. Laybourne A, Livingston G, Cousins S, et al. Carer coping and resident agitation as predictors of quality of life in care home residents living with dementia: Managing Agitation and Raising Quality of Life (MARQUE) English national care home prospective cohort study. *Int J Geriatr Psychiatry*. 2019;34(1):106-113.
12. Livingston G, Barber J, Marston L, et al. Prevalence of and associations with agitation in residents with dementia living in care homes: MARQUE cross-sectional study. *BJPsych Open*. 2017;3(4):171-178.

13. Knapp M, Chua K-C, Broadbent M, et al. Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. *BMJ Open*. 2016;6(11):e013591.
14. Senanarong V, Jamjumras P, Harmphadungkit K, et al. A counseling intervention for caregivers: effect on neuropsychiatric symptoms. *Int J Geriatr Psychiatry*. 2004;19(8):781-8.
15. Ismail MS, Dagerman K, Tariot PN, Abbott S, Kavanagh S, Schneider LS. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD): baseline characteristics. *Curr Alzheimer Res*. 2007;4(3):325-35.
16. Huis In Het Veld J, Verkaik R, van Meijel B, et al. Self-management by family caregivers to manage changes in the behavior and mood of their relative with dementia: an online focus group study. *BMC Geriatr*. 2016;16:95.
17. de Mauleon A, Soto M, Ousset PJ, Nourhashemi F, Lepage B, Vellas B. Potentially modifiable factors associated with agitation and aggression in Alzheimer's disease: results of the ICTUS study. *Int Psychogeriatr*. 2019;31(10):1509-1516.
18. Shin H-Y, Chung E-K, Rhee J-A, Yoon J-S, Kim J-M. [Prevalence and related factors of dementia in an urban elderly population using a new screening method]. *J Prev Med Public Health*. 2005;38(3):351-8.
19. Costa N, Wubker A, De Mauleon A, et al. Costs of Care of Agitation Associated With Dementia in 8 European Countries: Results From the RightTimePlaceCare Study. *J Am Med Dir Assoc*. 2018;19(1):95.e1-95.e10.
20. Yu X, Chen S, Chen X, et al. Clinical management and associated costs for moderate and severe Alzheimer's disease in urban China: a Delphi panel study. *Transl Neurodegener*. 2015;4:15.
21. Vossius C, Selbaek G, Saltyte Benth J, Wimo A, Bergh S. The use of direct care in nursing home residents: A longitudinal cohort study over 3 years. *Int J Geriatr Psychiatry*. 2019;34(2):337-351.
22. Zahodne LB, Ornstein K, Cosentino S, Devanand DP, Stern Y. Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. *Am J Geriatr Psychiatry*. 2015;23(2):130-40.
23. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am J Psychiatry*. 2015;172(5):460-5.
24. Sampson EL, White N, Lord K, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. *Pain*. 2015;156(4):675-83.

25. Ahmed M, Malik M, Teselink J, Lanctot KL, Herrmann N. Current Agents in Development for Treating Behavioral and Psychological Symptoms Associated with Dementia. *Drugs Aging*. 2019;36(7):589-605.
26. Seitz DP, Gill SS, Herrmann N, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. *Int Psychogeriatr*. 2013;25(2):185-203.
27. Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. *The Institute of Psychiatry*. 2009.
28. McDermott CL, Gruenewald DA. Pharmacologic Management of Agitation in Patients with Dementia. *Curr Geriatr Rep*. 2019;8(1):1-11.
29. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359-69.
30. Panel A. Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674-694.
31. Garay RP, Citrome L, Grossberg GT, Cavero I, Llorca P-M. Investigational drugs for treating agitation in persons with dementia. *Expert Opin Investig Drugs*. 2016;25(8):973-83.
32. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-9.
33. Cummings J, Mintzer J, Brodaty H, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr*. 2015;27(1):7-17.
34. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol*. 1989;44(3):M77-84.
35. Cohen-Mansfield J. Agitated behaviors in the elderly. II. Preliminary results in the cognitively deteriorated. *J Am Geriatr Soc*. 1986;34(10):722-7.
36. Rabinowitz J, Davidson M, De DPP, Katz I, Brodaty H, Cohen-Mansfield J. Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. *American Journal of Geriatric Psychiatry*. 2005;13(11):991-998.
37. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry*. 1998;155(1):54-61.
38. Laks J, Engelhardt E, Marinho V, et al. Efficacy and safety of risperidone oral solution in agitation associated with dementia in the elderly. *Arq Neuropsiquiatr*. 2001;59(4):859-64.

39. Ravina B, Putt M, Siderowf A, et al. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry*. 2005;76(7):934-9.
40. Cakir S, Kulaksizoglu IB. The efficacy of mirtazapine in agitated patients with Alzheimer's disease: A 12-week open-label pilot study. *Neuropsychiatr Dis Treat*. 2008;4(5):963-6.
41. Lesem MD, Tran-Johnson TK, Riesenberg RA, et al. Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. *Br J Psychiatry*. 2011;198(1):51-8.
42. Guy W. ECDEU Assessment Manual for Psychopharmacology. 1976:76-338.
43. Dahlke F, Lohaus A, Gutzmann H. Reliability and clinical concepts underlying global judgments in dementia: implications for clinical research. *Psychopharmacol Bull*. 1992;28(4):425-32.
44. Leon AC, Shear MK, Klerman GL, Portera L, Rosenbaum JF, Goldenberg I. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *J Clin Psychopharmacol*. 1993;13(5):327-31.
45. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159-71.
46. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-14.
47. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
48. Wimo A WA Mastey V, Winblad B. Evaluation of the resource utilization and caregiver time in anti-dementia drug trials – a quantitative battery. *Health economics of dementia*. 1998:465-499.
49. Gustavsson A, Cattelin F, Jonsson L. Costs of care in a mild-to-moderate Alzheimer clinical trial sample: key resources and their determinants. *Alzheimers Dement*. 2011;7(4):466-73.
50. Wimo A, Gustavsson A, Jonsson L, Winblad B, Hsu M-A, Gannon B. Application of Resource Utilization in Dementia (RUD) instrument in a global setting. *Alzheimers Dement*. 2013;9(4):429-435.e17.
51. 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.
52. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-5.
53. Sheehan DV, Giddens JM, Sheehan IS. Status Update on the Sheehan-Suicidality Tracking Scale (S-STS) 2014. *Innov Clin Neurosci*. 2014;11(9-10):93-140.

54. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-8.

55. Shumway-Cook a, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. *Phys Ther*. 1997;77(8):812-9.

56. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol*. 1980;7(5):486-8.

57. INTERNATIONAL CFH. https://www.ich.org/page/efficacy-guidelines. November 2016.

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