CONFIDENTIAL AND PROPRIETARY
Protocol 15-AVP-786-303
Amendment 7, Version 8.0

OPDC
AVP-786

PROTOCOL TITLE:

A Phase 3, Multicenter, Long-term, Extension Study of the Safety and Efficacy of AVP-786 (deuterated [d6] dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type

Protocol: 15-AVP-786-303-Amendment 7

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Date: 26 Jan 2022

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

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Immediately Reportable Event PRA

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alzheimer's Association
AE	Adverse event
AD	Alzheimer's Disease
ADCS	Alzheimer's Disease Cooperative Study
ADWG	Agitation Definition Work Group
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
CitAD	Citalopram study for Agitation in Alzheimer's disease
CGIC	Clinical Global Impression of Change
CGIS-Agitation	Clinical Global Impression of Severity of Illness scale for Agitation
CK	Creatine kinase
CMAI	Cohen-Mansfield Agitation Inventory
COVID-19	Coronavirus Disease 2019
CNS	Central nervous system
CRO	Contract research organization
CSDD	Cornell Scale for Depression in Dementia
CYP	Cytochrome P450
d6-DM	Deuterated (d6)-dextromethorphan hydrobromide (or free base form)
DEMQOL	Dementia Quality of Life
DM	Dextromethorphan hydrobromide
DMP	Data management plan
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
EC	Ethics Committee
ECDEU	Early Clinical Drug Evaluation Unit
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation	Definition
EDC	Electronic data capture
EP	European Pharmacopeia
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ESS	Epworth Sleepiness Scale
EtM	Events to Monitor
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational product
IPA	International Psychogeriatric Association
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
mADCS-CGIC-Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
NF	National Formulary
NIA	National Institute on Aging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory - Nursing Home version
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
OTC	Over–the-counter
PGIC	Patient Global Impression of Change
pH	Potential hydrogen

Abbreviation	Definition
PK	Pharmacokinetics
PR	The P-R interval from an ECG tracing
Q	Quinidine sulfate (or free base form)
QRS	The Q-R-S complex from an ECG tracing
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia's formula
RBC	Red blood cell
RUD	Resource Utilization in Dementia
SAE	Serious adverse event
SAER	Serious Adverse Event Reporting
SDV	Source data verification
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SPCD	Sequential Parallel Comparison Design
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
T3	Triiodothyronine
T4	Thyroxine
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TUG	Timed Up and Go
USP	United States Pharmacopoeia
WBC	White blood cell

PROTOCOL AGREEMENT

Protocol Title:

A Phase 3, Multicenter, Long-term, Extension Study of the Safety and Efficacy of AVP-786 (deuterated [d6] dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type

Protocol Number: 15-AVP-786-303 (Amendment 7, 26 Jan 2022)

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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.
3. The protocol contains all necessary information required to conduct the study, as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board/Ethics Committee (IRB/EC).
4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by OPDC or its representatives, the U.S. Food and Drug Administration (FDA), and other regulatory agencies as applicable.

Principal Investigator Signature Date
Principal Investigator Name:

OPDC Representative Signature Date
OPDC Representative Name: PPD , MD

STUDY SYNOPSIS

Title: A Phase 3, Multicenter, Long-term, Extension Study of the Safety and Efficacy of AVP-786 (deuterated [d6] dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the Treatment of Agitation in Patients with Dementia of the Alzheimer's Type.

Study Objectives

The objectives of the study are to evaluate the long-term safety and maintenance of efficacy of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer's type.

Study Population

Number of Patients: Approximately 1,200 patients will be enrolled at approximately 250 centers globally.

Condition/Disease: Patients with agitation secondary to dementia of the Alzheimer's type. 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.[1] 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.[2]

Key Inclusion Criteria: Patient has successfully completed Studies 15-AVP-786-301, 15-AVP-786-302, 12-AVR-131, or 17-AVP-786-305. Patients may be eligible to delay enrollment (which may include delays associated with coronavirus disease 2019 [COVID-19] restrictions) after receiving Medical Monitor approval, completing the defined screening assessments, and meeting the eligibility criteria. Eligible patients must have a reliable caregiver who is able and willing to comply with all required study procedures, including not administering any prohibited medications during the course of the study.

Key Exclusion Criteria: Patient is currently participating in, or has participated in other interventional (drug or device) clinical study since exiting Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 or within 30 days prior to Baseline for patients who delay enrollment. Patients with co-existent, clinically significant, or unstable systemic diseases that could confound the interpretation of the safety results of the study.

A complete list of inclusion/exclusion criteria is presented in Section 4 of the study protocol.

Study Design

Structure: This is a Phase 3, multicenter, long-term, extension study of the Phase 3 Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 which also allowed patients from the Phase 2 Study 12-AVR-131 to be included. Patients from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 should enroll in the current study within 5 days of the last visit (Visit 6, Day 85) in the preceding study. If enrollment from one of the preceding studies is delayed beyond 5 days, then only patients with Medical Monitor approval will be permitted to undergo screening and assessment for eligibility. Although all patients enrolled will receive AVP-786, the treatment dose assigned will be masked to the patient, investigator, study staff, and the sponsor.

Duration: Patients will be enrolled in the study for approximately 64 weeks. Patients who with Medical Monitor approval delay enrollment will have a screening period of up to 4-weeks.

End of Trial: The end of trial is defined as the "Last Patient Last Visit"; which is the date on which the last patient has his or her last visit or assessment (either for therapeutic or follow-up purposes including a follow-up phone call).

Study Treatment: The investigational product is AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM; INN: deudextromethorphan]/quinidine sulfate [Q]). Three doses of AVP-786 will be used in the study; d6-DM 18 mg/Q 4.9 mg, d6-DM 28 mg/Q 4.9 mg and d6-DM 42.63 mg/Q 4.9 mg, hereafter referred to as AVP-786-18/4.9, AVP-786-28/4.9, and AVP-786-42.63/4.9, respectively.

Control: None

Treatment Assignment: Eligible patients will be assigned to receive either AVP-786-42.63/4.9, AVP-786-28/4.9, or AVP-786-18/4.9 capsules in a masked manner, depending on the last treatment received in the preceding study (15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305). Study medication will be allocated via an interactive web response system (IWRS).

- Patients who received placebo in the preceding studies and patients who with Medical Monitor approval delay enrollment will be started on AVP-786-28/4.9 in the current study and titrated to the AVP-786-42.63/4.9 dose.
- Patients enrolling directly into 15-AVP-786-303 who received AVP-786-18/4.9 previously will continue to receive AVP-786-18/4.9, patients who received AVP-786-28/4.9 will continue to receive AVP-786-28/4.9 and patients who received AVP-786-42.63/4.9 will continue to receive AVP-786-42.63/4.9.

Dose Regimen: Study medication will be administered orally twice daily (BID, 1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart) throughout the study. Patients who received placebo in the preceding studies and patients who delay enrollment will start with AVP-786-28/4.9 once a day for the first 7 days of the study, continue with AVP-786-28/4.9 BID for the next 14 days and from Day 22 (Week 3; between Visit 2 and Visit 2.1) onwards will receive AVP-786-42.63/4.9 BID unless the dose is adjusted (after Day 22).

At the discretion of the investigator, the dose of study medication can be adjusted after Day 22 at any time during the study for safety or efficacy reasons. See Section 5.3.3 for details on dose adjustment during the study.

Assessments and Visits

There are up to 15 scheduled clinic visits in the study. Patients will attend clinic visits at Screening (Day -28 to Day -1, only for patients who delay enrollment), Baseline (Day 1), and on Days 15 (Visit 2; Week 2), 29 (Visit 2.1; Week 4), 43 (Visit 3; Week 6), 85 (Visit 4; Week 12), 127 (Visit 4.1; Week 18), 169 (Visit 5; Week 24), 211 (Visit 5.1; Week 30), 253 (Visit 6; Week 36), 295 (Visit 6.1; Week 42), 337 (Visit 7; Week 48), 365 (Visit 8; Week 52), 395 (Follow-up Visit 1; Week 56), and 455 (Follow-up Visit 2; Week 64). Patients who require

dose-adjustments may have unscheduled visits for safety assessments at the discretion of the investigator. Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1 and Table 2).

Response Measures

Safety and Tolerability

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), Sheehan Suicidality Tracking Scale (S-STS), Mini-Mental State Examination (MMSE), and the Epworth Sleepiness Scale (ESS).

Pregnancy tests will be conducted for patients of childbearing potential.

Efficacy

Efficacy will be assessed using the Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI) agitation/aggression, irritability/lability, and aberrant motor behavior domains, modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change-Agitation (mADCS-CGIC-Agitation), Clinical Global Impression of Severity of Illness scale-Agitation (CGIS-Agitation), Patient Global Impression of Change (PGIC-rated by caregiver), Dementia Quality of Life (DEMQOL), Resource Utilization in Dementia (RUD) and EuroQol 5-Dimension 5-Level (EQ-5D-5L).

General Statistical Methods and Types of Analyses

Analysis Populations

The safety population which includes all patients who received study treatment will be used for all efficacy and safety data summaries. Four treatment groups will be presented for both safety and efficacy: AVP-786-42.63/4.9, AVP-786-28/4.9, AVP-786-18/4.9, and all patients combined. No treatment comparisons will be performed.

Safety Analyses

Safety and tolerability measures including reported AEs, vital signs, clinical laboratory assessments, resting 12-lead ECGs, S-STS, MMSE, and ESS will be summarized using descriptive statistics and/or frequency tables.

Efficacy Analyses

Summary statistics will be provided for observed efficacy data by visit. Observed raw value and change from baseline will be presented where applicable.

Sample Size Calculation

The sample size of approximately 1,200 patients enrolled will provide adequate study medication exposure to satisfy regulatory requirements. The assessment of mADCS-CGIC-Agitation, RUD, and DEMQOL will be performed with approximately 500 patients who completed prior to the implementation of Protocol Amendment 6.

Table 1 Schedule of Evaluations and Visits for Patients Enrolling Directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305

Schedule of Evaluations and Visits for Patients Enrolling Directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305															
	Visit:	**Baseline[1]**	**Visit 2[2,]**	**Visit 2.1[2]**	**Visit 3[2,]**	**Visit 4[2,]**	**Visit 4.1[2]**	**Visit 5[2]**	**Visit 5.1[2]**	**Visit 6[2]**	**Visit 6.1[2]**	**Visit 7[2]**	**Visit 8[2]/ ET[3,4]**	**Follow-up Visit 1[2,3,5]**	**Follow-up Visit 2[2,6]**
	Study Day:	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 85**	**Day 127**	**Day 169**	**Day 211**	**Day 253**	**Day 295**	**Day 337**	**Day 365**	**Day 395**	**Day 455**
Procedure	**End of Study Week**		**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**	**Week 56**	**Week 64**
Sign informed consent forms		X[7]													
Medical history		X[8]													
Risk assessment for falls (worksheet and TUG test[9])		X[8]													
Review of eligibility[10]		X[8]													
Treatment assignment[11]		X													
Physical and neurological exam		X[8]											X		
Vital signs, height, and weight		X[8]	X	X	X	X	X	X[12]	X	X	X	X	X[12]		
CGIS-Agitation		X[8]				X		X		X			X		
mADCS-CGIC-Agitation[13]		X						X					X	X	X
ECG[14]		X[14]	X		X	X		X		X		X	X		
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant: medications, nondrug therapies, and nonpharmacological interventions for agitation		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Evaluations and Visits for Patients Enrolling Directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305

Procedure	Visit:	Baseline[1]	Visit 2[2,]	Visit 2.1[2]	Visit 3[2,]	Visit 4[2,]	Visit 4.1[2]	Visit 5[2]	Visit 5.1[2]	Visit 6[2]	Visit 6.1[2]	Visit 7[2]	Visit 8[2]/ ET[3,4]	Follow-up Visit 1[2,3,5]	Follow-up Visit 2[2,6]
	Study Day:	Day 1	Day 15	Day 29	Day 43	Day 85	Day 127	Day 169	Day 211	Day 253	Day 295	Day 337	Day 365	Day 395	Day 455
	End of Study Week		Week 2	Week 4	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42	Week 48	Week 52	Week 56	Week 64
MMSE		X[8]						X					X		
CMAI		X[8]				X		X		X			X	X	X
NPI agitation/aggression domain		X[8]				X		X		X			X		
NPI irritability/lability and aberrant motor behavior domains		X[8]						X					X		
CSDD[9]		X[8]													
DEMQOL[15]		X[8]						X					X		
EQ-5D-5L[16]		X[8]						X					X		
PGIC[17]		X[8]				X		X		X			X		
RUD[18]		X[8]						X					X		
S-STS		X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
ESS[19]		X[8]						X					X		
Administer morning dose of study medication[20]		X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry, hematology, and urinalysis		X[8]	X		X	X[21]		X[21]		X[21]		X	X[21]		
Urine pregnancy test[22]		X[8]	X		X	X		X		X		X	X		
Dispense study drug and diary card		X	X		X	X	X	X	X	X	X	X			

Schedule of Evaluations and Visits for Patients Enrolling Directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305

Procedure	Visit:	Baseline[1]	Visit 2[2,]	Visit 2.1[2]	Visit 3[2,]	Visit 4[2,]	Visit 4.1[2]	Visit 5[2]	Visit 5.1[2]	Visit 6[2]	Visit 6.1[2]	Visit 7[2]	Visit 8[2]/ ET[3,4]	Follow-up Visit 1[2,3,5]	Follow-up Visit 2[2,6]
	Study Day:	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 85**	**Day 127**	**Day 169**	**Day 211**	**Day 253**	**Day 295**	**Day 337**	**Day 365**	**Day 395**	**Day 455**
	End of Study Week		**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**	**Week 56**	**Week 64**
Review and return unused study medication and diary[20]			X	X	X	X	X	X	X	X	X	X	X		

AE = adverse event; CGIS-Agitation = Clinical Global Impression of Severity of Illness scale for Agitation; CMAI = Cohen-Mansfield Agitation Inventory; CSDD = The Cornell Scale for Depression in Dementia; DEMQOL = Dementia Quality of Life scale; ECG = electrocardiogram; ET = early termination; EQ-5D-5L = EuroQol 5-Dimension 5-Level; mADCS-CGIC-Agitation = modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PGIC = Patient Global Impression of Change rated by the caregiver; RUD = Resource Utilization in Dementia; S-STS = Sheehan Suicidality Tracking Scale; TUG = Timed Up and Go test

1. Baseline visit will occur within 5 days of patient's exit from Studies 15-AVP-786-301, 15-AVP-786-302, or 17-AVP-786-305.
2. Study Visits 2 (Day 15), 2.1 (Day 29), and 3 (Day 43) have a ± 3-day window. All other study visits have a ± 7-day window.
3. Early Termination Visit for patients who withdraw prior to study completion. Follow-up Visit 1 also applies to patients who withdraw prior to study completion (ET patients). See footnote 6 for Follow-up Visit 2.
4. For patients who terminate early from the study, the patient/patient's caregiver will be contacted by telephone for 5 consecutive days following ET Visit to query on the overall well-being of the patient.
5. An on-site follow-up visit (Follow-up Visit 1) will occur approximately 30 days after last dose of study medication for all patients including ET patients.
6. An on-site follow-up visit (Follow-up Visit 2) will occur approximately 3 months after last dose of study medication for all patients, including ET patients.
7. Informed consent can be obtained at the exit visit of Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305.
8. Patient data from the final visit (Visit 6) in the preceding studies will be used as Baseline for the current study, except for medical history which will be obtained from the Screening visit and MMSE which will be obtained from the Baseline visit from the preceding studies. Height should be collected at the Baseline visit only.
9. The TUG test and CSDD should be performed at Baseline only for patients rolling over from Study 17-AVP-786-305.
10. For each patient from any study, the review of inclusion/exclusion criteria will be performed by the investigator.
11. Patients will be assigned to AVP-786-42.63/4.9, AVP-786-28/4.9 or AVP-786-18/4.9 through IWRS.
12. Weight should be measured at Visits 5 and 8 only.
13. Worksheet for mADCS-CGIC-Agitation from the Baseline visit in the preceding studies was to be considered as baseline information for assessing change at Visits 5 and 8 and is no longer required to be performed following the implementation of Protocol Amendment 6.
14. ECG should be performed predose and at least 1 hour after dosing at the Baseline visit. ECGs should be collected at any time during the other visits.
15. The DEMQOL is no longer required to be performed following the implementation of Protocol Amendment 6. The proxy version is to be rated by the caregiver, and the non-proxy version is to be rated only by patients with an MMSE score of ≥ 10 at Baseline.

16. The EQ-5D-5L should be performed only for patients rolling over from Study 17-AVP-786-305.
17. PGIC is to be rated by the caregiver.
18. The RUD is no longer required to be performed following the implementation of Protocol Amendment 6.
19. The ESS is to be rated only by patients with an MMSE score of ≥ 10 at Baseline.
20. The first dose of study medication administered at the Baseline visit should be administered from the blister card in the clinic. All other study medication should be administered from the blister card by the caregiver, family member, nursing home staff, or self-administered with supervision. The time of administration should be recorded on the diary card. The blister card and diary card should be returned to the patient/caregiver at Visits 2 and 2.1 after reviewing for compliance.
21. Glycosylated hemoglobin (HbA1c) test should be performed at Visits 4, 5, 6, and 8.
22. Urine pregnancy test to be performed for patients of childbearing potential only (Section 6.2.5).

Table 2 Schedule of Evaluations and Visits for Patients Who Delay Enrollment

Schedule of Evaluations and Visits for Patients Who Delay Enrollment																
Procedure	**Visit:**	**Screening[1]**	**Baseline**	**Visit 2[2]**	**Visit 2.1[2]**	**Visit 3[2]**	**Visit 4[2]**	**Visit 4.1[2]**	**Visit 5[2]**	**Visit 5.1[2]**	**Visit 6[2]**	**Visit 6.1[2]**	**Visit 7[2]**	**Visit 8[2]/ ET[3,4]**	**Follow-up Visit 1[2,3,5]**	**Follow-up Visit 2[2,6]**
	Study Day:	**-28 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 85**	**Day 127**	**Day 169**	**Day 211**	**Day 253**	**Day 295**	**Day 337**	**Day 365**	**Day 395**	**Day 455**
	End of Study Week			**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**	**Week 56**	**Week 64**
Sign informed consent forms		X														
Medical history		X														
Risk assessment for falls (worksheet and TUG test)		X														
Review of eligibility[7]		X	X													
Treatment assignment[8]			X													
Physical and neurological exam		X												X		
Vital signs, height, and weight		X	X[9]	X	X	X	X	X	X[9]	X	X	X	X	X[9]		
CGIS-Agitation		X	X				X		X		X			X		
mADCS-CGIC-Agitation[10]			X						X					X	X	X
ECG[11]		X[12]	X[13]	X		X	X		X		X		X	X		
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant: medications, nondrug therapies, and nonpharmacological interventions for agitation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Evaluations and Visits for Patients Who Delay Enrollment																
	Visit:	**Screening[1]**	**Baseline**	**Visit 2[2]**	**Visit 2.1[2]**	**Visit 3[2]**	**Visit 4[2]**	**Visit 4.1[2]**	**Visit 5[2]**	**Visit 5.1[2]**	**Visit 6[2]**	**Visit 6.1[2]**	**Visit 7[2]**	**Visit 8[2]/ ET[3,4]**	**Follow-up Visit 1[2,3,5]**	**Follow-up Visit 2[2,6]**
	Study Day:	**-28 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 85**	**Day 127**	**Day 169**	**Day 211**	**Day 253**	**Day 295**	**Day 337**	**Day 365**	**Day 395**	**Day 455**
Procedure	**End of Study Week**			**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**	**Week 56**	**Week 64**
MMSE		X	X						X					X		
CMAI		X	X				X		X		X			X	X	X
NPI agitation/aggression domain		X	X				X		X		X			X		
NPI irritability/lability and aberrant motor behavior domains			X						X					X		
CSDD		X														
DEMQOL[14]			X						X					X		
EQ-5D-5L			X						X					X		
PGIC[15]							X		X		X			X		
RUD[16]			X						X					X		
S-STS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESS[17]			X						X					X		
Administer morning dose of study medication[18]			X[18]	X	X	X	X	X	X	X	X	X	X	X		
Chemistry, hematology, and urinalysis		X[19]	X[19]	X		X	X[19]		X[19]		X[19]		X	X[19]		
Urine pregnancy test[20]		X	X	X		X	X		X		X		X	X		
Dispense study drug and diary card			X	X		X	X	X	X	X	X	X	X			

Schedule of Evaluations and Visits for Patients Who Delay Enrollment

Procedure	Visit:	Screening[1]	Baseline	Visit 2[2]	Visit 2.1[2]	Visit 3[2]	Visit 4[2]	Visit 4.1[2]	Visit 5[2]	Visit 5.1[2]	Visit 6[2]	Visit 6.1[2]	Visit 7[2]	Visit 8[2]/ ET[3,4]	Follow-up Visit 1[2,3,5]	Follow-up Visit 2[2,6]
	Study Day:	**-28 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 85**	**Day 127**	**Day 169**	**Day 211**	**Day 253**	**Day 295**	**Day 337**	**Day 365**	**Day 395**	**Day 455**
	End of Study Week			**Week 2**	**Week 4**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**	**Week 56**	**Week 64**
Review and return unused study medication and diary[18]				X	X	X	X	X	X	X	X	X	X	X		

AE = adverse event; CGIS-Agitation = Clinical Global Impression of Severity of Illness scale for Agitation; CMAI = Cohen-Mansfield Agitation Inventory; CSDD = The Cornell Scale for Depression in Dementia; DEMQOL = Dementia Quality of Life scale; ECG = electrocardiogram; ET = early termination; mADCS-CGIC-Agitation = modified Alzheimer's Disease Cooperative Study- Clinical Global Impression of Change for Agitation; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PGIC = Patient Global Impression of Change rated by the caregiver; RUD = Resource Utilization in Dementia; S-STS = Sheehan Suicidality Tracking Scale; TUG = Timed Up and Go test.

1. Screening visit is applicable only for patients who with Medical Monitor approval delay enrollment from 12-AVR-131 or 17-AVP-786-305. The Screening visit has a + 3-day window and may be extended after discussion with and approval by the Medical Monitor.
2. Study Visits 2 (Day 15) 2.1 (Day 29), and 3 (Day 43) have a ± 3-day window. All other study visits have a ± 7-day window.
3. Early Termination Visit for patients who withdraw prior to study completion. Follow-up visit 1 also applies to patients who withdraw prior to study completion (ET patients). See footnote 6 for Follow-up Visit 2.
4. For patients who terminate early from the study, the patient/patient's caregiver will be contacted by telephone for 5 consecutive days following early termination visit to query on the overall well-being of the patient.
5. An on-site follow-up visit (Follow-up Visit 1) will occur approximately 30 days after last dose of study medication for all patients including ET patients.
6. An on-site follow-up visit (Follow-up Visit 2) will occur approximately 3 months after last dose of study medication for all patients, including ET patients.
7. For each patient, a protocol eligibility form which includes the review of inclusion/exclusion criteria may be requested to be completed by the investigator.
8. Patients will be assigned to study medication through IWRS.
9. Weight should be measured at Baseline, and Visits 5 and 8 only. Height should be measured at the Baseline visit only.
10. The mADCS-CGIC-Agitation baseline evaluation worksheet was to be completed to record baseline information for assessing change at Visits 5 and 8 and is no longer required to be performed following the implementation of Protocol Amendment 6.
11. ECG at the Baseline visit should be performed predose and at least 1 hour after dosing.
12. ECG should be performed in triplicate at the Screening visit.
13. ECG should be performed at any time during the visits after the Baseline visit.
14. The DEMQOL is no longer required to be performed following the implementation of Protocol Amendment 6. The proxy version is to be rated by the caregiver. The non-proxy version is to be rated only by patients with an MMSE score of ≥ 10 at Baseline.
15. PGIC is to be rated by the caregiver.
16. The RUD is no longer required to be performed following the implementation of Protocol Amendment 6.
17. The ESS is to be rated only by patients with an MMSE score of ≥ 10 at Baseline.

18. The first dose of study medication administered at the Baseline visit should be administered from the blister card in the clinic. All other study medication should be administered from the blister card by the caregiver, family member, nursing home staff, or self-administered with supervision. The time of administration should be recorded on the diary card. The blister card and diary card should be returned to the patient/caregiver at Visits 2 and 2.1 after reviewing for compliance.
19. Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) should be performed at the Screening visit only. Glycosylated hemoglobin (HbA1c) test should be performed at Screening, Baseline, and Visits 4, 5, 6, and 8.
20. Urine pregnancy test to be performed for patients of childbearing potential only (Section 6.2.5).

1. BACKGROUND AND CLINICAL RATIONALE

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease eventually leading to death. An estimated 5.4 million Americans have Alzheimer's disease, this number has doubled since 1980 and is expected to be as high as 16 million by 2050.[3] Among US adults over age 65, prevalence estimates of dementia range from 5% to 15%, with AD being the most common type of dementia.[4–6] In the United Kingdom (UK), approximately 850,000 people suffer from dementia of which AD accounts for approximately 62% of the cases.[7]

Agitation is widely recognized as a common and important clinical feature of AD and other forms of dementia.[8] Although readily recognized by clinicians and caregivers, a consensus definition of agitation in dementia was only recently developed by the International Psychogeriatric Association (IPA) Agitation Definition Working Group (ADWG) with the following criteria: "1) occurring in patients with a cognitive impairment or dementia syndrome; 2) exhibiting behavior consistent with emotional distress; 3) manifesting excessive motor activity, verbal or physical aggression; and 4) evidencing behaviors that cause excess disability impairing relationships and/or daily activities and are not solely attributable to another disorder (psychiatric, medical or substance-related)".[2] Agitation and/or aggression are estimated to affect up to approximately 80% of patients with dementia[9,10] with an increase in prevalence as the disease progresses.

Agitation in patients with dementia is associated with increased functional disability,[11] worse quality of life[12] earlier institutionalization,[13] increased caregiver burden,[11] increased healthcare costs,[14] shorter time to severe dementia[15] and accelerated mortality.[15] For these reasons, agitation and aggression are the neuropsychiatric symptoms most likely to require pharmacological intervention in Alzheimer's patients.[8] Currently there is no treatment approved in the United States (US) for the management of agitation in patients with AD. In some countries of the European Union (EU), risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe AD unresponsive to nonpharmacological approaches and when there is a risk of harm to self or others.[16] Clinicians resort to off-label use of antipsychotics, sedatives/hypnotics, anxiolytics, and antidepressants in an attempt to control symptoms.[17] Unfortunately, these treatments have limited utility given a modest efficacy that is offset by relatively poor adherence, safety and tolerability.[8,18,19] Thus a critical need exists to develop a safe and effective pharmacological intervention for the treatment of agitation in dementia. Such a treatment could profoundly impact patient care, reduce caregiver burden and potentially improve overall disease prognosis.

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 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 its CYP2D6 metabolism such that a low dose of quinidine was 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.

The clinical development program for AVP-786 includes 5 Phase 3 studies, patients from 3 of these Phase 3 studies (15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305) that evaluate the safety and efficacy of AVP-786 in patients with dementia of the Alzheimer's type are eligible for enrollment into Study 15-AVP-786-303. Study 15-AVP-786-301 was a multicenter, randomized, double-blind, placebo-controlled study, with 12-week duration of treatment. Approximately 380 patients were planned to be enrolled in the study. Eligible patients were randomized to receive either AVP-786 or matching placebo capsules. Study 15-AVP-786-302 was a multicenter, randomized, double-blind, placebo-controlled study with 12-week duration of treatment. Approximately 470 patients were planned to be enrolled in the study. Eligible patients were randomized to receive either AVP-786 or matching placebo capsules.
Study 17-AVP-786-305 is currently ongoing and is also a multicenter, randomized, double-blind, placebo-controlled study with 12-week duration of treatment. Approximately 550 patients are planned to be enrolled in the study. Eligible patients will be randomized to receive either AVP-786 or matching placebo capsules.

The current study (Study 15-AVP-786-303) is an extension of the three Phase 3 Studies, 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 to evaluate the long-term safety, tolerability and maintenance of efficacy of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer's type. Patients who were enrolled in Study 12-AVR-131 have been allowed to enroll in the current study provided they meet study criteria, as they represent the study population of interest. The doses of AVP-786 evaluated in Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 (AVP-786-42.63/4.9, AVP-786-28/4.9 and AVP-786-18/4.9) will continue to be used in the current study. Patients who, with Medical Monitor approval, delay enrollment into Study 15-AVP-786-303 following completion of the preceding study will start at a dose of AVP-786-28/4.9 BID and titrate up to AVP-786-42.63/4.9 BID. The rationale for the 64-week duration of this study is based on the need to collect long-term safety information on AVP-786 and to meet regulatory requirements for population exposure required to assess clinical safety.

2. STUDY OBJECTIVES

The objectives of the study are to evaluate the long-term safety and maintenance of efficacy of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer's type.

3. STUDY DESIGN

This is a Phase 3, multicenter, long-term, extension study of the Phase 3 Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 of approximately 64 weeks in duration with an additional screening period of up to 4-weeks for patients who, with Medical Monitor approval, have delayed enrollment from a preceding study (may include delays associated with coronavirus disease 2019 [COVID-19] restrictions). Approximately 1,200 patients will be enrolled at approximately 250 centers globally. There are up to 15 scheduled clinic visits in the study including Screening (Day -28 to Day -1, for patients who with Medical Monitor approval delay enrollment), Baseline (Day 1), and on Days 15 (Visit 2; Week 2), 29 (Visit 2.1; Week 4), 43 (Visit 3; Week 6), 85 (Visit 4; Week 12), 127 (Visit 4.1; Week 18), 169 (Visit 5; Week 24), 211 (Visit 5.1; Week 30), 253 (Visit 6; Week 36), 295 (Visit 6.1; Week 42), 337 (Visit 7; Week 48), 365 (Visit 8; Week 52), 395 (Follow-up Visit 1; Week 56), and 455 (Follow-up Visit 2; Week 64).

Eligible patients will be assigned at the Baseline visit to receive AVP-786-42.63/4.9, AVP-786-28/4.9, or AVP-786-18/4.9 in a masked manner, depending on the last treatment received in the preceding study (15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305). Study medication will be administered orally twice daily throughout the study. Patients (or caregivers) will self-administer study medication on all study days except on the specified clinic-visit days when patients will be administered their morning dose of study medication at the clinic in the presence of site personnel, regardless of the time of day. Study medication will be allocated via an interactive web response system (IWRS) and assigned to patients as follows:

- Patients who received placebo in the preceding studies and patients who with Medical Monitor approval delay enrollment will be started on AVP-786-28/4.9 in the current study and titrated to the AVP-786-42.63/4.9 dose.
- Patients enrolling directly into 15-AVP-786-303 who received AVP-786-18/4.9 previously will continue to receive AVP-786-18/4.9, patients who received AVP-786-28/4.9 will continue to receive AVP-786-28/4.9 and patients who received AVP-786-42.63/4.9 will continue to receive AVP-786-42.63/4.9.

Patients who received placebo in the preceding studies and patients who delay enrollment will start with AVP-786-28/4.9 once a day for the first 7 days of the study, continue with AVP-786-28/4.9 BID for the next 14 days and from Day 22 (Week 3; between Visit 2 and Visit 2.1) onwards will receive AVP-786-42.63/4.9 BID unless the dose is adjusted (after Day 22).

At the discretion of the investigator, the dose of study medication can be adjusted after Day 22 at any time during the study for safety or efficacy reasons. Further details on dose adjustments during the study are presented in Section 5.3.3.

4. STUDY POPULATION

The study population includes patients who have successfully completed Studies 15-AVP-786-301, 15-AVP-786-302, or 17-AVP-786-305 and are willing to participate in the current long-term extension study.

In addition, patients from Study 12-AVR-131 who had a diagnosis of probable AD and presented with clinically meaningful, moderate/severe agitation secondary to AD have been allowed to enroll in the study. The diagnosis of probable AD 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.[1] These new criteria were developed based on the review of the NINCDS-ADRDA criteria.[20] Neither AD 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),[2] will be used for selecting study patients. This proposed definition is limited to patients with cognitive impairment and requires: (a) evidence of emotional distress; (b) one 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 are to have otherwise acceptable and stable general health as required by the study protocol, and documented by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory examinations.

Eligible patients must have a caregiver that is able and willing to comply with all required study procedures, ensuring that the patient attends all study visits and takes the study medication as instructed. Caregivers will also be instructed to keep a study diary, to report any changes in patient's status, including adverse events, standard of care setting (e.g., becoming a resident in an assisted living facility) and to provide their impression and assessment regarding the investigational treatment. In order to qualify as a reliable informant (i.e., caregiver) capable of assessing changes in the patient's condition during this study, the individual must spend a minimum of 2 hours per day for 4 days per week with the study patient.

4.1. Inclusion Criteria

1. Patient has successfully completed Studies 15-AVP-786-301, 15-AVP-786-302, 17-AVP-786-305, or 12-AVR-131 and is deemed eligible for enrollment by the investigator after review of the inclusion/exclusion criteria. (Note: A delay in enrollment from a prior study requires Medical Monitor approval and may include delays associated with COVID-19 restrictions.)
2. Males and females; patients who delay enrollment must be 50 to 90 years of age, inclusive.
3. Patients with a diagnosis of probable AD according to the 2011 NIA-AA working group criteria and must be either out-patients or residents of an assisted-living facility or a skilled nursing home.

4. For patients who delay enrollment, they must have clinically significant, moderate/severe agitation at least 2 weeks prior to Baseline, that interferes with daily routine and for which a prescription medication is indicated, in the opinion of the investigator.
5. For patients who delay enrollment, they must have a diagnosis of agitation that meets the IPA provisional definition of agitation.
6. For patients who delay enrollment, they must have a CGIS-Agitation score of ≥ 4 (moderately ill) at Screening and Baseline.
7. For patients who delay enrollment, they must have a MMSE score between 6 and 26 (inclusive) at Screening and Baseline.
8. Patient has stable cardiac, pulmonary, hepatic, and renal function.
9. For patients who delay enrollment, they must have an ECG (obtained at Screening and evaluated by a central ECG reader) with no clinically significant findings.
10. Patients of childbearing potential who are sexually active must use an effective method of birth control for at least 1 month prior to randomization, during participation in the study, and for at least 30 days after the last dose of study drug. The following should be taken into consideration:
    - Patients 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 (e.g., 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.
    - Patients who are sterile (i.e., 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.
    - Patients who are lactating, pregnant, or plan to become pregnant are excluded.
11. For patients who delay enrollment, a stable dose for at least 3 months prior to Baseline of medications for the treatment of AD (e.g., donepezil, rivastigmine, galantamine, memantine) is allowed. During the study, the initiation of approved therapies for the treatment of AD and dose adjustments are allowed for all patients.
12. For patients who delay enrollment, who have been on concomitant antidepressants such as selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, citalopram) and serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, desvenlafaxine, duloxetine), they are allowed provided the dose has been stable for at least 3 months prior to Baseline and within the package insert guidance for that medication. During the study, initiation of new drugs for depression, and dose adjustments are allowed for all patients. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day.

13. For patients who delay enrollment, who have been on concomitant hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 50 mg/day]) for the nighttime treatment of insomnia, they are allowed, provided their dose has been stable for at least 1 month prior to Baseline. During the study, initiation of new drugs for insomnia, and dose adjustments are allowed for all patients.
14. For patients who delay enrollment currently taking allowed medications for the treatment of agitation secondary to AD (e.g., atypical antipsychotics, antidepressants, buspirone) are eligible provided the dose has been stable for at least 1 month prior to Baseline (3 months prior for antidepressants). Dose adjustments are allowed during the study. Initiation of new drugs for the treatment of agitation are not allowed for all patients.
15. For patients who delay enrollment, they must not show current and significant symptoms of a depressive disorder and must have a score <10 in the Cornell Scale for Depression in Dementia (CSDD) at Screening. Patients rolling over from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 with scores greater than 10 in the CSDD at baseline should be evaluated by the investigator for enrollment in the current study.
16. For patients who delay enrollment, they must have no history or current clinical symptoms of schizophrenia, schizoaffective disorder, or bipolar disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).
17. Caregiver must be willing and able to comply with study procedures, including not administering any prohibited medications during the course of the study.
18. 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 (as determined by local regulations) agrees to participation (for patients unable to provide assent) are allowed.

4.2. Exclusion Criteria

1. Patient is currently participating in, or has participated in other interventional (drug or device) clinical study since exiting Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, or within 30 days prior to baseline for patients who delay enrollment.
2. Caregiver is unwilling or unable, in the opinion of the investigator, to comply with study instructions.
3. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (e.g., 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 non-metastatic cancer may be allowed. For patients who delay enrollment, each case to be evaluated individually with the Medical Monitor (MM).

4. Patients determined to have a high imminent risk of falls during the study based on a clinical evaluation by the investigator
5. For patients who delay enrollment, any personal history of complete heart block, QTc prolongation, or *torsades de pointes,*
    a. Screening and Baseline 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 (Screening ECG will be based on central review). Baseline predose ECG will be based on the machine read and investigator's evaluation. If the Baseline predose ECG QTcF result from the machine read is exclusionary, the patient should not be dosed and the Medical Monitor should be contacted.
    b. Presence of premature ventricular contractions (PVCs) as evaluated by a central reader and deemed clinically significant by the investigator.
6. Patients who are currently using or were on NUEDEXTA® in the 2 weeks preceding Baseline.
7. Patients with evidence of serious risk of suicide at Screening (patients who delay enrollment) and Baseline based on the Sheehan Suicidality Tracking Scale (S-STS), i.e., 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.
8. Patients who, in the opinion of the Investigator, Medical Monitor, or sponsor, should not participate in the study.

4.3. Patient Withdrawal From the Study

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, non-compliance, protocol violation, or other administrative reasons. As the study design does not include a specific rescue treatment, based on their medical judgment and a risk/benefit assessment, the Investigator may make a decision about the appropriateness of continuation of the patient in the study. In case of significantly increased agitation and/or significant safety concerns in the judgment of the Investigator, the patient should be withdrawn from the study.

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 investigational product (IP), and follow-up with the patient regarding any unresolved adverse events.

In addition, patients who present 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 at any time after enrollment will be

withdrawn from the study. For patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the post-dose ECG obtained at Visit 6 in the prior study will be used as the predose baseline for calculating change and for patients who delay enrollment, the predose ECG at the Baseline visit will be used. The QTcF values will be assessed for clinical significance and recorded.

Patients who withdraw prior to study completion will be asked to return to the clinic to complete the Visit 8 (end of study) assessments and a follow-up visit, 30 days after last dose of study medication. For all patients who terminate early from the study, patient/patient's caregiver will be contacted by telephone for 5 consecutive days following ET visit to query on the overall well-being of the patient.

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.

5. STUDY TREATMENTS

5.1. Treatments Administered

5.1.1. Description of Study Medications

Clinical study medication will be provided as hard, printed, opaque, blue, gelatin capsules (size 3). Each capsule of the study medication contains 1 of the following (except for the AVP-786 placebo capsules for Days 1 to 7 for patients requiring titration [refer to Section 3]):

- 42.63 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-42.63/4.9
- 28 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-28/4.9
- 18 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-18/4.9

Drug supplies will be provided to the site in individual, pre-labeled blister cards.

All medication used in this study will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

5.1.2. Composition of AVP-786

The qualitative and quantitative compositions of the 3 doses of the IP are listed in Table 3.

Table 3 Composition of Investigational Product

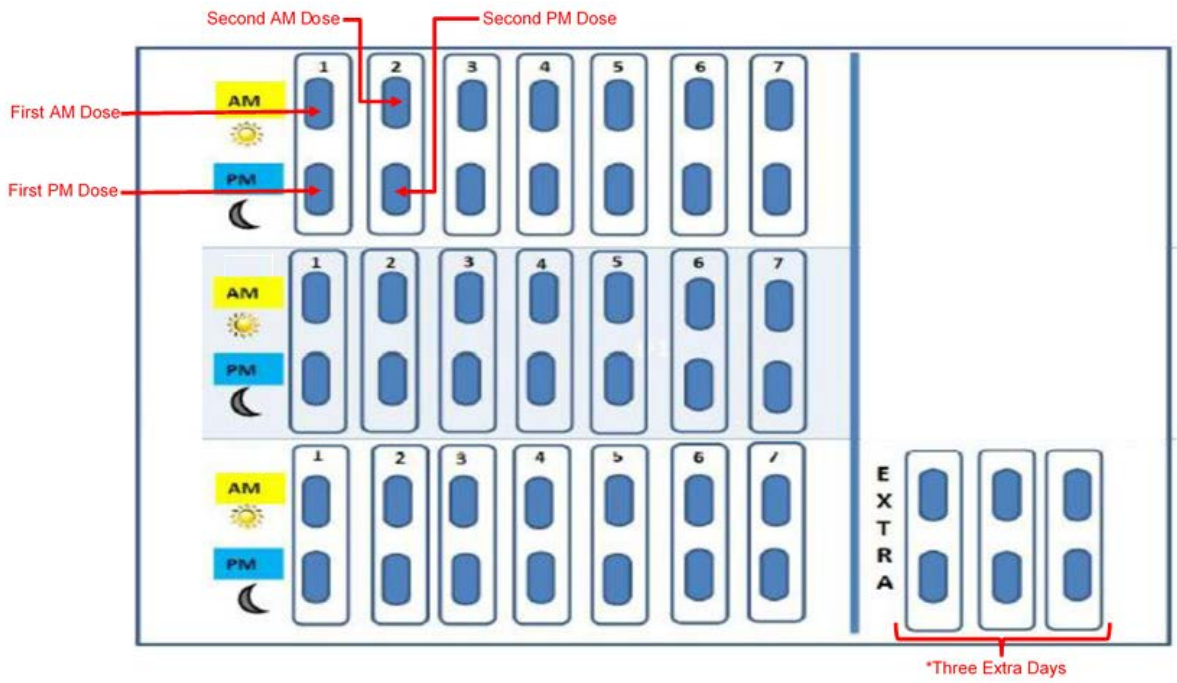
Ingredient (amounts in mg)	AVP-786-42.63/4.9	AVP-786-28/4.9	AVP-786-18/4.9
Deudextromethorphan hydrobromide (*)	42.63 (33)	28.00 (21.67)	18.00 (13.93)
Quinidine sulfate USP, EP (*)	4.9 (4.26)	4.9 (4.26)	4.9 (4.26)
Croscarmellose sodium NF	✓	✓	✓
Microcrystalline cellulose NF	✓	✓	✓
Colloidal silicone dioxide NF	✓	✓	✓
Magnesium stearate NF	✓	✓	✓
Size 3 Blue Opaque capsules	✓	✓	✓

EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary
* Free base equivalent indicated in parenthesis
✓ Indicates inclusion of the excipient.

5.1.3. Packaging

The investigators will be supplied with pre-labeled, individually pre-packaged blister cards. Each panel of the blister card (1 week of study medication) consists of 2 rows of blister strips, one row for the morning dose and one row for the evening dose (Figure 1). Each blister card will contain 3 panels, providing sufficient study medication for 3 weeks of treatment and an additional 3 days of supply (total of 48 capsules).

Figure 1 Sample Configuration of Investigational Product Blister Card



5.1.4. Labeling

All labels will contain protocol number, product name, blister card number, an investigational drug warning, and dosage instructions to take 1 capsule in the morning and 1 capsule in the evening, storage conditions, and company name. The blister card label will consist of either a 2-panel label or booklet label, with a detachable panel that will be removed and affixed to the study medication Dispensing Log page at the time of dispensing.

- The 2-panel label provides space on both panels of the card label to record patient number, visit week, and dispensing date.
- The booklet label does not provide space to record patient number, visit week, and dispensing date. This information will need to be handwritten on the Dispensing Log.

All investigational product labels comply with all applicable federal and local regulations.

5.1.5. Storage of Clinical Supplies

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).

5.1.6. Study Medication Administration

All patients will receive study medication according to the blister card numbers assigned by an IWRS randomization scheme. Designated staff at each site will dispense study medication. The first dose (on Day 1) will be administered at each site by designated staff. For all other days, study medication should be administered to the patient by the caregiver, family member, nursing

home staff, or self-administered with supervision. Patients and caregivers will be instructed that the patient should take the study medication 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.

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

5.2. Accountability of Study Supplies

5.2.1. Receipt of Supplies

The investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. 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 IP supplied is for use only in this study and should not be used for any other purpose. All blister card material ID numbers will also be recorded and tracked at the site using the Drug Accountability Log.

5.2.2. Record of Dispensing

Accurate recording of all IP 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 IP was dispensed; (ii) the date(s) and quantity of the IP dispensed to the patient; and (iii) the blister card material ID number assigned to the patient via IWRS.

Additionally, the detachable panel of the two-panel label on each blister card will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the blister card label to record patient number, the visit week and dispensing date.

5.2.3. Unused Supplies

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

5.3. Methods of Assigning Patients to Treatment Groups

5.3.1. Treatment Assignment

Patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 will maintain the 6-digit patient number assigned to them in the preceding studies. For patients from Study 12-AVR-131, a 6-digit patient number will be assigned where the first 3 digits consist of the center number. The last 3 digits will be assigned sequentially starting with 801. This 6-digit number is the main identifier for patients.

Patients who received placebo in the preceding studies and patients who delay enrollment will be started on AVP-786-28/4.9 in the current study and titrated to the AVP-786-42.63/4.9 dose. For patients directly enrolling from the preceding studies, those patients who received AVP-786-18/4.9 previously will continue to receive AVP-786-18/4.9, those patients who received AVP-786-28/4.9 previously will continue to receive AVP-786-28/4.9 and those patients who received AVP-786-42.63/4.9 will continue to receive AVP-786-42.63/4.9. See Section 5.3.3 for details on dose adjustment during the study.

5.3.2. Blinding/Masking

Eligible patients will be assigned to three different dose levels of AVP-786 as the starting doses via an interactive web response system (IWRS) [refer to Section 3]. 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 un-blinding, 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.

5.3.3. Treatment Dose Adjustment

As indicated in Section 5.3.2 above, the sponsor, patients, caregivers, investigators, or other study personnel will not be aware of the patient's treatment dose assignment at study entry. After Day 22, the dose can be adjusted anytime for safety or efficacy reasons at the discretion of the investigator. A patient can be discontinued from the study at any time for safety reasons, based on the investigator's assessment. Patients will have an unscheduled visit if the dose is adjusted on a non-scheduled visit day.

5.4. Patient Compliance

Patients and caregivers will be instructed to bring any unused study medication and empty blister cards to the clinic at all visits (Visits 2 through 8 [Days 15, 29, 43, 85, 127, 169, 211, 253, 295, 337, and 365]). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses (compliance range 80-120%). 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 at Visits 3 through 8 (Days 43, 85, 127, 169, 211, 253, 295, 337, and 365), or at the time of early study discontinuation. Patients should bring their Diary Card at Visit 2 (Day 15) and Visit 2.1 (Day 29) for compliance review; the Diary Card will be returned to the patient and collected at the next visit.

5.5. Concomitant Medications and Nondrug Therapies

Patients may not take any of the disallowed medications listed in Appendix 1 during the study or 2 weeks or 5 half-lives, whichever is longer, prior to the start of dosing on Day 1. 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.

The conditions of use for allowed concomitant medications and nondrug therapies or prohibited medications do not apply between Visit 8/ET and the Follow-up visits. Any use of medications or nondrug therapies during this period will be at the discretion of the investigator. Patients should allow at least 14 days after stopping study medication before starting an MAOI.

5.5.1. Allowed Concomitant Medications for the Treatment of AD, Agitation, Depression, Insomnia, and Behavioral Disturbances

Drugs for the treatment of AD (e.g., donepezil, rivastigmine, galantamine, memantine), are allowed when administered at a stable dose for at least 3 months prior to Baseline, the dose of these drugs should remain unchanged throughout the study, if possible. However, initiation of approved therapies for the treatment of AD, and dose adjustments are allowed during the study.

Concomitant use of antidepressants such as SSRIs (e.g., fluoxetine, sertraline, citalopram) and SNRIs (e.g., venlafaxine, desvenlafaxine, duloxetine) are allowed provided the dose has been stable for at least 3 months prior to Baseline and within the Package Insert guidance for that medication. During the study, initiation of new drugs for depression, and dose adjustments are allowed. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day. Patients taking SSRIs or SNRIs concomitantly should be monitored for serotonin syndrome which includes altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor.

Concomitant use of hypnotics at bedtime (e.g., eszopiclone, zolpidem, zaleplon, trazodone [up to 50 mg/day]) for the nighttime treatment of insomnia is allowed, provided the dose has been stable for at least 1 month prior to Baseline. During the study, initiation of new drugs for insomnia and dose adjustments are allowed.

The use of drugs for the treatment of agitation secondary to AD (e.g., atypical antipsychotics, antidepressants, buspirone), provided the patient has been on a stable dose at least 1 month prior to Baseline (3 months for antidepressants). Dose adjustments are allowed during the study. Initiation of new drugs for the treatment of agitation are not allowed.

Initiation of new drugs for the treatment of agitation are not allowed. All benzodiazepines are disallowed (See Section 5.5.2).

Short-term use (e.g. 7 days or less) of cold medications containing dextromethorphan are allowed (Appendix 1).

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

5.5.2. Rescue Medication for the Symptoms of Agitation

No rescue medications are allowed. As the study design does not include a specific rescue treatment, in case a patient experiences significantly increased agitation, based on their medical judgment and a risk/benefit assessment, the Investigator may make a decision about the appropriateness of continuation of the patient in the study (Section 4.3).

5.5.3. Prohibited Concomitant Medications

A list of examples of prohibited medications is provided in Appendix 1.

Monoamine oxidase inhibitors (MAOI) are prohibited throughout the study. Patients should allow at least 14 days after stopping study medication before starting an MAOI.

5.5.4. Nondrug Therapies

Information on any prior and concomitant nondrug therapies will be recorded.

5.5.5. Nonpharmacological Interventions for the Treatment of Agitation

Information on any nonpharmacological interventions for the treatment of agitation that were used prior to enrollment or used concomitantly during the study will be collected.

6. STUDY ASSESSMENTS AND PROCEDURES

Whenever possible, each patient and caregiver should have the rating scales administered by the same raters throughout the study, for consistency of ratings. The mADCS-CGIC-Agitation, RUD, and DEMQOL will no longer be required to be performed following the implementation of Protocol Amendment 6, as the requirements for their assessment will have already been met.

6.1. Screening/Baseline Only Procedures

As this is an extension study that includes patients from the double-blind Phase 3 trials (Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305), several assessments performed at the final visit (Visit 6) in the preceding studies are considered as Baseline for the current study for those patients enrolling directly from one of these 3 studies. These assessments include: physical and neurological examination, vital signs, clinical laboratory tests, urine pregnancy test, S-STS, TUG test (except 17-AVP-786-305), ESS, CMAI, NPI agitation/aggression, irritability/lability, and aberrant motor behavior domains, CGIS-Agitation, PGIC, and CSDD (except 17-AVP-786-305). The TUG test and CSDD have to be performed at the Baseline visit for patients from Study 17-AVP-786-305.

For patients who with Medical Monitor approval delay enrollment, procedures to be performed at Baseline are specified in Table 2. The TUG test and CSDD have to be performed only at the Screening visit for these patients.

6.1.1. 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.[21,22]

The TUG test will be performed at Screening (Day -28 to Day -1, for patients who delay enrollment) and Baseline (Day 1, for patients enrolling directly from Study 17-AVP-786-305 only). For patients directly enrolling from Studies 15-AVP-786-301 and 15-AVP-786-302, the TUG assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

6.1.2. Cornell Scale for Depression in Dementia (CSDD)

The CSDD was specifically developed to assess signs and symptoms of major depression in patients with dementia.[23] Because some of these patients may give unreliable reports, the CSDD uses a comprehensive interviewing approach that derives information from the patient and the caregiver. Information is elicited through two semi-structured interviews; an interview with a caregiver and an interview with the patient. The interviews focus on depressive symptoms and signs occurring during the week preceding the assessment. The CSDD takes approximately 20 minutes to administer.

Each item is rated for severity on a scale of 0-2 (0 = absent, 1 = mild or intermittent, 2 = severe). The item scores are added. Scores above 10 indicate a probable major depression, scores above 18 indicate a definite major depression, and scores below 6 as a rule are associated with absence of significant depressive symptoms.

For patients directly enrolling from Studies 15-AVP-786-301 and 15-AVP-786-302, the CSDD assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline. The CSDD will be assessed at Screening (Day -28 to Day -1, for patients who delay enrollment) and Baseline (Day 1, for patients directly enrolling from Study 17-AVP-786-305).

6.2. Safety

6.2.1. Adverse Events

6.2.1.1. Definitions

An AE is any untoward medical occurrence or unintended change (e.g. physical, psychological, or behavioral) from the time ICF is signed, including inter-current illness, whether considered related to treatment 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 medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., 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 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 medication 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 drug administration; and/or follows a known response pattern to the study medication; 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 drug administration; and follows a known response pattern to the study medication; and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

6.2.1.2. Serious Adverse Events

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, i.e., 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 always considered to be 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 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 (i.e., 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 medication 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 childbearing potential of a male patient in the study becomes pregnant within 30 days after his last dose of study medication 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.

6.2.1.3. Reporting Adverse Events

Caregivers will be queried regarding AEs at each clinic visit, including the follow-up visits. The investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication will be followed for at least 30 days after receiving the last dose of study medication.

The sponsor may request additional information on certain events, such as falls. Event to Monitor (EtM) 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 treatment whether considered treatment-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 form (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 medication, action taken regarding the study medication, 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:
FAX: PPD or PPD (North America); PPD (Europe, Pacific, and Africa)
E-mail: CHOSafety@prahs.com **(Europe, Pacific, Africa, and North America)**

SAE hotline (24-hour/7 days a week)
Phone: PPD or PPD (North America), PPD (Europe, Pacific, and Africa)

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

6.2.1.4. Procedures to be followed in the Event of Abnormal Test Values

Any patients with clinically significant abnormal laboratory test results may be required by the MM 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.

6.2.2. Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1, for patients who delay enrollment), and Day 365 (Visit 8). For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final

visit (Visit 6) in the preceding studies will be considered as Baseline. 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.

6.2.3. Vital Signs

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be obtained at all clinic visits except on Follow-up Visit 1 (Day 395) and Follow-up Visit 2 (Day 455). For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline. 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. Weight should be recorded at Baseline (Day 1, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365). For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the respiratory rate, temperature and weight assessments at the final visit (Visit 6) in the preceding studies will be considered as Baseline. Height should be recorded at Baseline (Day 1) for all patients.

6.2.4. Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at Screening (Day -28 to Day -1, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 2 (Day 15), Visit 3 (Day 43), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), Visit 7 (Day 337), and Visit 8 (Day 365) unless specified otherwise. For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen [BUN], serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], creatine kinase [CK], gamma-glutamyl transferase [GGT], triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell [RBC] 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 for patients enrolled who delay enrollment
- Glycosylated hemoglobin (HbA1c) test at the Screening visit (for patients enrolled who delay enrollment), Baseline Visit (for patients enrolled who delay enrollment), and Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), and Visit 8 (Day 365).

Any patients with clinically significant abnormal laboratory test results may be required by the MM 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.

6.2.5. Pregnancy Tests

Urine pregnancy tests are to be performed for patients of childbearing potential at Screening (Day -28 to Day -1, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 2 (Day 15), Visit 3 (Day 43), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), Visit 7 (Day 337), and Visit 8 (Day 365). For patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

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

Patients of childbearing potential who are sexually active, must use an effective method of birth control for at least 1 month prior to Baseline, during the course of the study, and for at least 30 days after the last dose of study drug. The following should be taken into consideration:

- Patients 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 (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, or withdrawal are not acceptable methods of contraception.
- Patients who are sterile (i.e., 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.
- Patients who are lactating, pregnant or plan to become pregnant are excluded.

6.2.6. Electrocardiograms

A resting 12-lead ECG will be performed at the following visits for all patients: Baseline (Day 1), Visit 2 (Day 15), Visit 3 (Day 43), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), Visit 7 (Day 337), and Visit 8 (Day 365). For patients who delay enrollment, ECGs

will be performed in triplicate at the Screening visit (Day -28 to Day -1). At Baseline (Day 1), 2 ECGs will be performed, one predose and one at least 1 hour after dosing. 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 and PR and QTc intervals (milliseconds). Results will be provided by the central reader to the investigators within 1 business day of transmitting the data to the central reader. ECG data will be transferred automatically from the central reader into the eCRF monthly. Any clinically significant abnormal ECG should be discussed with the study Medical Monitor and, if necessary be repeated within a 1-week period.

6.2.7. Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors.[24] 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 Sheehan-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. For the Screening visit (applicable to patients who delay enrollment), the timeframe for the items on the scale will be 'in the past 6 months'. For all other visits the timeframe for the items on the scale will be 'since last visit'.

The S-STS will be assessed at all visits. For patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the S-STS at the final visit (Visit 6) in the preceding studies will be considered as Baseline. Any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to the MM.

6.2.8. 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.[25] 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, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365). For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the MMSE assessment at the Baseline visit in the preceding studies will be considered as Baseline.

6.2.9. 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.[26] 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, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365) for patients with an MMSE score of ≥ 10 at baseline. For patients directly enrolling from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the ESS assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

6.3. Efficacy

6.3.1. Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI 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.[27] These distinct agitation syndromes include: aggressive behavior, physically non-aggressive behavior, and verbally agitated behavior.[28] Scores for the 3 dimensions will be derived based on the factor structure described by Rabinowitz, et al, 2005;[29] further details are provided in the 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 CMAI.

The CMAI (long-form version) will be assessed at Screening (Day -28 to Day -1, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), Visit 8 (Day 365), Follow-up Visit 1 (Day 395), and Follow-up Visit 2 (Day 455). For patients enrolling directly from Studies 15-AVP-786-301 and 15-AVP-786-302, and 17-AVP-786-305 the CMAI assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

6.3.2. Neuropsychiatric Inventory (NPI) Agitation/Aggression, Irritability/Lability, and Aberrant Motor Behavior Domains

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.[30] 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).

Three domains of the NPI will be assessed in this study including: agitation/aggression, irritability/lability and aberrant motor behavior domains. The NPI agitation/aggression domain will be administered to the patient's caregiver at Screening (Day -28 to Day -1, for patients who

delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), and Visit 8 (Day 365).

The NPI irritability/lability and aberrant motor behavior domains will be administered to the patient's caregiver at Baseline (Day 1, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365). For patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786 302, and 17-AVP-786-305, the assessments of the 3 domains of the NPI at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

The NPI domains are generally evaluated for behaviors within the preceding 4 weeks but can be modified according to the needs of the study. In this study, the recall period will be 2 weeks for all the visits.

The NPI nursing-home version (NPI-NH) will be used for patients from in-patient or assisted living facilities. The questions in the NPI-NH were rephrased for professional caregivers who may not know the patients prior to the onset of illness; however, the overall instrument domains and scoring is identical to the NPI except for the caregiver distress section which is replaced with occupational disruptiveness in the NPI-NH version.

6.3.3. Clinical Global Impression of Severity of Illness (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 (ECDEU) 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[31–35] and is easy and quick to administer, provided that the clinician knows the patient well.[36]

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.[37–39]

The CGIS 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 will be assessed at Screening (Day -28 to Day -1, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Visit 4 (Day 85), Visit 5 (Day 169), Visit 6 (Day 253), and Visit 8 (Day 365). For patients enrolling directly from Studies 15-AVP-786-301 and 15-AVP-786-302, and 17-AVP-786-305, the CGIS-Agitation assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

6.3.4. Modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change Rating (mADCS-CGIC-Agitation)

The assessment of mADCS-CGIC-Agitation will no longer be required to be performed following the implementation of Protocol Amendment 6.

The standard ADCS-CGIC instrument was modified to better assess aspects relevant to studying agitation in AD (mADCS-CGIC-Agitation). The mADCS-CGIC-Agitation contains questions related to agitation and an assessment of the Clinician's Impression of Change focused specifically on agitation. It was originally designed for the Citalopram study for Agitation in Alzheimer's disease (CitAD)[40,41] and utilizes a semi-structured interview of both patient and caregiver to determine a baseline level of severity for agitation. Subsequent evaluations assess for change from baseline and also utilize the semi-structured agitation interview of both patient and caregiver.

The baseline mADCS-CGIC-Agitation evaluation will be conducted at the Baseline (Day 1) visit for patients who delay enrollment. The mADCS-CGIC-Agitation will be assessed at Visit 5 (Day 169) and Visit 8 (Day 365) for change from baseline. The Baseline visit of preceding studies for patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302 and 17-AVP-786-305 in agitation syndrome is the baseline for this study. The mADCS-CGIC-Agitation will also be assessed at Follow-up Visit 1 (Day 395) and Follow-up Visit 2 (Day 455) for change from Visit 8/ET (Day 365).

6.3.5. Patient Global Impression of Change (PGIC)

The PGIC is a 7-point (1-7) scale used to assess treatment response, and it is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.[36]

The PGIC will be assessed and rated by the patient's caregiver at Day 85 (Visit 4), Day 169 (Visit 5), Day 253 (Visit 6), and Day 365 (Visit 8).

6.3.6. Dementia Quality of Life (DEMQOL)

The DEMQOL will no longer be required to be performed following the implementation of Protocol Amendment 6.

The DEMQOL is a scale used to evaluate health related quality of life in patients with dementia and their caregivers.[42] There are 2 versions of the DEMQOL, a 28-item version (rated by patient) and a 31-item version (DEMQOL-proxy, rated by caregiver). Both the 28-item and 31-item version are recommended to be used for evaluating patients (and their caregivers) with mild to moderate dementia (MMSE ≥ 10). For patients with severe dementia, only the DEMQOL-proxy (administered to caregiver) is used.

The DEMQOL-proxy (and DEMQOL for patients with MMSE ≥ 10 at baseline) will be assessed at Baseline (Day 1, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365). For patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 the DEM-QOL-proxy (or DEMQOL) assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

6.3.7. Resource Utilization in Dementia (RUD)

The RUD will no longer be required to be performed following the implementation of Protocol Amendment 6.

The RUD is used to calculate healthcare costs associated with dementia.[43] 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.[44]

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 (e.g., hours of caregiver time, visits to doctors, nights in accommodation) by the corresponding unit price vector.

The RUD will be assessed at Baseline (Day 1, for patients who delay enrollment), Visit 5 (Day 169), and Visit 8 (Day 365). For patients enrolling directly from Studies 15-AVP-786-301 and 15-AVP-786-302, and 17-AVP-786-305 the RUD assessment at the final visit (Visit 6) in the preceding studies will be considered as Baseline.

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

The EQ-5D-5L will be assessed only for patients enrolling directly and with delayed enrollment from Study 17-AVP-786-305.

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).[45] 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 from Study 17-AVP-786-305 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, Visit 5 (Day 169), and Visit 8 (Day 365) for patients from Study 17-AVP-786-305. The EQ-5D-5L at the final visit (Visit 6) in the preceding study (17-AVP-786-305) will be considered as Baseline for patients enrolling directly from Study 17-AVP-786-305. For those who delay enrollment following completion of Study 17-AVP-786-305, will have the EQ-5D-5L assessed at the Baseline Visit.

6.4. Schedule of Evaluations and Procedures

A schedule of evaluations and procedures is provided in Table 1 (for patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305) and in Table 2 (for patients who with Medical Monitor approval are permitted to delay enrollment).

6.4.1. 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 pre-defined study assessment results. Further instructions will be provided in the IWRS Site Manual.

6.4.1.1. Screening Visit (Days -28 to -1, + 3-day window)

The Screening visit is applicable only to patients who with Medical Monitor approval delay enrollment. The following procedures will be performed (within 28 days prior to Day 1). The screening period may only be extended after discussion with and approval by the 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. Medical history, including patient demographics, any prior and concomitant medications use (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation will be reviewed and recorded.
3. Review inclusion/exclusion criteria (eligibility form may be requested to be completed).
4. Vital signs will be measured and recorded.
5. Physical and neurological examination will be performed.
6. Risk assessment for falls will be performed (worksheet and TUG test).
7. A resting 12-lead ECG will be performed in triplicate.
8. A blood and urine specimen will be collected for safety laboratory assessments.
9. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
10. The following assessments will be completed:
    - MMSE; a score between 6 and 26 (inclusive) is required for study entry
    - CMAI
    - NPI Agitation/Aggression domain
    - CGIS-Agitation; a score of ≥ 4 is required for study entry
    - S-STS
    - CSDD; a score of < 10 is required for study entry

Following screening procedures for assessment of inclusion and exclusion criteria, the site may be requested to complete a Protocol Eligibility Form (PEF) and submit to the Medical Monitor for review and approval. Patients deemed eligible by the investigator and the Medical Monitor will be randomized into the study should they continue to qualify at the Baseline (Day 1) visit. 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.

6.4.1.2. Baseline Visit (Day 1)

The Baseline visit (Day 1) should occur in the morning, and should be within 5 days of exit from the preceding study for patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 or within 28 days after the Screening visit for those patients who delay enrollment.

The following procedures will be performed.

Before Dosing:

1. Informed consent and/or assent for patients enrolling directly from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 will be obtained if it was not obtained at the final visit (Visit 6) in the preceding study. The investigator will provide the patients, authorized representative 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. Patient eligibility will be reviewed by the investigator for all patients (protocol eligibility form may be requested for patients who delay enrollment).
3. Caregivers will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.

The following procedures performed before dosing are for patients who delay enrollment:

1. Vital signs, height, and weight will be measured and recorded.
2. A resting predose 12-lead ECG will be performed.
3. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. The following assessments will be completed:
   - MMSE
   - CMAI
   - NPI agitation/aggression, irritability/lability, and aberrant motor behavior domains
   - CGIS-Agitation

- S-STS
- ESS (only for patients with an MMSE score of ≥ 10 at baseline)
- EQ-5D-5L (only for patients who delay enrollment from 17-AVP-786-305)

The following procedures performed before dosing are for patients enrolling directly from Study 17-AVP-786-305:

1. Administer the following:
   - TUG test
   - CSDD

Study Medication Dosing:

Patients will be assigned with a study medication kit number via IWRS once it is determined that they satisfy all of the inclusion and none of the exclusion criteria. The first dose of study medication will be administered from the AM strip of blister card, at the clinic regardless of the time of day.

After Dosing:

1. A resting postdose 12-lead ECG will be performed at least 1 hour after taking the morning dose of study medication.
2. The caregiver will be queried regarding AEs.
3. Patient Diary Card and sufficient study medication for a 3-week treatment period will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication 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 medication and patient's Diary Card at each study visit.

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

6.4.1.3. Visit 2 (Day 15 ± 3-day window)

The Visit 2 (Day 15) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected, reviewed for compliance and returned to the patient.
7. The S-STS will be completed.
8. Unused study medication will be accounted for compliance and the blister card returned to the patient.
9. Sufficient study medication for a 3-week treatment period will be dispensed.

Patient/Caregiver Instruction

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

Patients/caregivers will be instructed to finish the study medication from the blister card returned to the patient before starting on the medication from the newly dispensed blister card.

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 medication at each study visit.

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

6.4.1.4. Visit 2.1 (Day 29 ± 3-day window)

The Visit 2.1 (Day 29) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.

3. Patient's Diary Card will be collected, reviewed for compliance and returned to the patient.
4. Unused study medication will be accounted for compliance and the blister card returned to the patient.
5. The S-STS will be completed.

Patient/Caregiver Instruction

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

Patients/caregivers will be instructed to finish the study medication from the blister card returned to the patient.

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 medication at each study visit.

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

6.4.1.5. Visit 3 (Day 43 ± 3-day window)

The Visit 3 (Day 43) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected and reviewed for compliance.
7. Returned, unused study medication will be accounted for compliance.
8. The S-STS will be completed.
9. Patient Diary Card and sufficient study medication for a 6-week treatment period will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.6. Visit 4 (Day 85 ± 7-day window)

The Visit 4 (Day 85) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected and reviewed for compliance.
7. Returned, unused study medication will be accounted for compliance.
8. The following assessments will be completed:
    - CMAI
    - NPI Agitation/Aggression domain
    - CGIS-Agitation
    - S-STS
    - PGIC
9. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.7. Visit 4.1 (Day 127 ± 7-day window)

The Visit 4.1 (Day 127) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. Patient's Diary Card will be collected and reviewed for compliance.
4. Unused study medication will be accounted for compliance.
5. The S-STS will be completed.
6. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.8. Visit 5 (Day 169 ± 7-day window)

The Visit 5 (Day 169) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs and weight will be measured and recorded.
3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected and reviewed for compliance.
7. Returned, unused study medication will be accounted for compliance.
8. The following assessments will be completed:
   - MMSE
   - CMAI
   - NPI agitation/aggression, irritability/lability, and aberrant motor behavior domains
   - CGIS-Agitation
   - S-STS
   - PGIC
   - ESS (only for patients with an MMSE score of ≥ 10 at Baseline)
   - EQ-5D-5L-proxy (and EQ-5D-5L for patients with an MMSE score of ≥ 10 at Baseline) only for Patients from Study 17-AVP-786-305
9. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.9. Visit 5.1 (Day 211 ± 7-day window)

The Visit 5.1 (Day 211) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. Patient's Diary Card will be collected reviewed for compliance.
4. Unused study medication will be accounted for compliance.
5. The S-STS will be completed.
6. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.10. Visit 6 (Day 253 ± 7-day window)

The Visit 6 (Day 253) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.

3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected and reviewed for compliance.
7. Returned, unused study medication will be accounted for compliance.
8. The following assessments will be completed:
    - CMAI
    - NPI Agitation/Aggression domain
    - CGIS-Agitation
    - S-STS
    - PGIC
9. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.11. Visit 6.1 (Day 295 ± 7-day window)

The Visit 6.1 (Day 295) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Vital signs will be measured and recorded.
3. Patient's Diary Card will be collected and reviewed for compliance.

4. Unused study medication will be accounted for compliance.
5. The S-STS will be completed.
6. Patient Diary Card and sufficient study medication will be dispensed for a 6-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 42 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 medication at each study visit.

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

6.4.1.12. Visit 7 (Day 337 ± 7-day window)

The Visit 7 (Day 337) dose of study medication can be administered at home, the time of dosing should be noted by the patient/caregiver. The following procedures will be performed at this visit:

1. Vital signs will be measured and recorded.
2. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
3. A resting 12-lead ECG will be performed.
4. A blood and urine specimen will be collected for safety laboratory assessments.
5. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).
6. Patient's Diary Card will be collected and reviewed for compliance.
7. Returned, unused study medication will be accounted for compliance.
8. The S-STS will be completed.
9. Patient Diary Card and sufficient study medication will be dispensed for a 4-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and

1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 28 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 medication at each study visit.

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

6.4.1.13. Visit 8 (Day 365 ± 7-day window) / Early Termination

Visit 8 (Day 365) should occur in the morning. Patients who withdraw prior to study completion are required to complete study procedures as listed in Visit 8 within 48 hours of the last dose of study medication.

The following procedures will be performed:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. Returned, unused study medication will be accounted for compliance.
3. Patient's Diary Card will be collected and reviewed for compliance.
4. Vital signs and weight will be measured and recorded.
5. Physical and neurological examination will be performed.
6. The following assessments will be completed:
    - MMSE
    - CMAI
    - NPI agitation/aggression, irritability/lability, and aberrant motor behavior domains
    - CGIS-Agitation
    - S-STS
    - PGIC
    - ESS (only for patients with an MMSE score of ≥ 10 at baseline)
    - EQ-5D-5L-proxy (and EQ-5D-5L for patients with an MMSE score of ≥ 10 at Baseline) only for Patients from Study 17-AVP-786-305
7. A resting 12-lead ECG will be performed.
8. A blood and urine specimen will be collected for safety laboratory assessments.
9. A urine pregnancy test will be performed for patients of childbearing potential only (Section 6.2.5).

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 medication.

6.4.1.14. Follow-up Visit 1 (Day 395 ± 7-day window)

A follow-up visit will occur 30 days after the last dose of study medication for all patients including patients who terminate early from the study.

The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. The following assessments will be completed:
   - CMAI
   - S-STS

6.4.1.15. Follow-up Visit 2 (Day 455 ± 7-day window)

A follow-up visit will occur approximately 3 months after the last dose of study medication for all patients, including patients who terminate early from the study.

The following procedures will be performed at this visit:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for treatment of agitation.
2. The following assessments will be completed:
   - CMAI
   - S-STS

6.4.1.16. Follow-up Phone Call

For patients who terminate early from the study, the patient/patient's caregiver will be contacted by telephone for 5 consecutive days following ET visit to query on the overall well-being of the patient.

6.4.1.17. Unscheduled Visits

Patients will have an unscheduled clinic visit if the dose of study medication is adjusted. Dose adjustments can be made any time after Day 22. The safety assessments to be performed at the unscheduled visit will be based on clinical judgment of the investigator.

6.4.2. End of Trial

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

7. DATA MANAGEMENT

7.1. Data Collection

The sponsor or designated representative (e.g., CRO) 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.

Clinical study data will be reported (captured) by study site personnel on eCRFs. An eCRF must be completed for every patient enrolled in the study. The eCRF data will be entered by trained study-site personnel and then reviewed for completeness and accuracy and electronically signed by the investigator or authorized designee. 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.

The clinical monitoring staff will perform source data verification (SDV) of the data recorded in the EDC system with source documents at the clinical study sites 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 Medical Dictionary for Regulatory Activities (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.

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.

8. STATISTICAL METHODS

8.1. Analysis Population

The safety population which includes all patients who received study treatment is the only analysis population that will be used in this study. It will be used for all efficacy and safety data summary. Four treatment groups will be presented for both efficacy and safety: AVP-786-42.63/4.9, AVP-786-28/4.9, AVP-786-18/4.9, and all patients combined. No treatment comparison will be performed.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

8.3. Safety Analysis

Safety and tolerability measures including reported AEs, vital signs, clinical laboratory assessments, resting 12-lead ECGs, S-STS, MMSE, and ESS will be summarized using descriptive statistics and/or frequency tables.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAE). TEAEs are those AEs that occur after the first dose of study medication up until 30 days after last dose.

Summary statistics of absolute values and percentage change from baseline for BP (diastolic and systolic), heart rate, respiratory rate, and ECG parameters will be provided. All values outside a pre-defined normal range will be highlighted in the individual patient data listings.

Laboratory parameters will be summarized via descriptive statistics and via shifts in results in respect to normal ranges between Baseline and end of treatment as increased, decreased, or no change.

8.4. Efficacy Analysis

Efficacy will be assessed using the CMAI, NPI (agitation/aggression, irritability/lability, and aberrant motor behavior domains), CGIS-Agitation, mADCS-CGIC-Agitation, PGIC, RUD, DEMQOL, and EQ-5D-5L. Summary statistics will be provided for observed efficacy data by visit. Observed raw value and change from baseline will be presented where applicable. The assessment of mADCS-CGIC-Agitation, RUD, and DEMQOL will be performed on subjects who enrolled prior to the implementation of Protocol Amendment 6.

8.5. Interim Analysis

Interim analyses may be performed and will be pre-specified in the SAP.

8.6. Sample Size Calculations

The sample size of approximately 1,200 patients enrolled will provide adequate study medication exposure to satisfy regulatory requirements. The assessment of mADCS-CGIC-Agitation, RUD, and DEMQOL will be performed with approximately 500 patients who completed prior to the implementation of Protocol Amendment 6.

9. ADMINISTRATIVE PROCEDURES

9.1. Institutional Review Board/Ethics Committee Approval

Institutional Review Boards/Ethics Committees (IRBs/ECs) must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB/EC approval for the protocol and the signed ICF must be obtained and transmitted to the Sponsor or representative before the study can be initiated. The IRB/EC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with local laws and according to National and State/Provincial laws, GCP, ICH E6 (r2) guidelines, and the World Medical Association Declaration of Helsinki.

9.2. Informed Consent Form

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. For patients that 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 medication. 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.

9.3. Patient's Diary Card

The patient's Diary Card will be reviewed by clinical study personnel at all study treatment visits for confirmation of medication dosage and any rescue medication received. The study personnel are responsible for (i) ensuring that patients and/or caregivers are properly collecting data and recording it into the diaries; and (ii) transcribing the diary recordings into the eCRF. The diary will be collected at all study visits after baseline except Visit 2 (Day 15), wherein the diary will be reviewed and returned to the patient. The originals of all diaries will be maintained at the site as source documents.

9.4. Electronic Case Report Forms

For each patient enrolled who has given informed consent, an eCRF must be completed and electronically signed by the investigator to certify that the data within each eCRF are complete

and correct. This also applies to those patients who fail to complete the study. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome.

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The electronic data capture (EDC) vendor will provide user-specific access to the live (production) eCRF once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

The eCRFs will be reviewed by the study monitor at the study site. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

All investigators will be provided with copies of the eCRFs for their site on a CD-ROM at the end of the study.

9.5. Quality Assurance

9.5.1. 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.

9.5.2. 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. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. 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/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.

9.6. Record Retention

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, e.g., CRFs 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 (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., 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.

9.7. Source Data

The documents that will form the source data for the clinical study (e.g., patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also 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' eCRFs to be monitored.

9.8. Data Handling

Data collected on the eCRFs will be entered into EDC system by trained site staff. Any queries arising from data entry will be checked with the investigator and changes approved.

9.9. Laboratory Procedures

Each individual site laboratory will collect hematology and chemistry blood samples and urine samples for analysis. Instructions for specimen evaluation and transport to a central laboratory will be provided at the time of study initiation.

9.10. Guidelines for Good Clinical Practice

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.

9.11. Conditions for Amending the Protocol

Protocol modification to ongoing studies which could potentially adversely affect the safety of patients or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of patients treated, or patient selection criteria must be made only after appropriate consultation between an appropriate representative of the Sponsor and the investigator.

Protocol modifications must be prepared by a representative of the Sponsor or the investigator, and reviewed and approved by the Sponsor.

All protocol modifications must be reviewed and approved by the appropriate IRB/EC in accordance with local requirements, before the revised edition can be implemented. Modifications which eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB/EC.

9.12. Conditions for Terminating the Study

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.

9.13. Confidentiality of Study Documents and Patient Records

The investigator must assure that the patient's anonymity will be maintained. On eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names but by an identification code.

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.

the Sponsor staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to the Sponsor (or designee) will be identified only by the patient number assigned where applicable.

9.14. 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 the United States Code of Federal Regulations (CFR) Title 21, Part 312.64.

9.15. Publications

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.

9.16. Audits/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 eCRF 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/EC approval(s)
- Study medication 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/EC and the sponsor
- Record retention

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

10. REFERENCES

1. 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.
2. 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.
3. Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement*. 2011;7(1):61-73.
4. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA*. 1989;262(18):2551-6.
5. Losonczy KG, White LR, Brock DB. Prevalence and correlates of dementia: survey of the last days of life. *Public Health Rep*. 1998;113(3):273-80.
6. Kaplan HS. Synopsis of Psychiatry: Behavioral Sciences-Behavioral Sciences. *Clinical Psychiatry*. 1998.
7. ALZHEIMERSUK. 2014a. Dementia 2014 Infographic [Online]. 2014.
8. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol*. 2009;5(5):245-55.
9. Ryu S-H, Katona C, Rive B, Livingston G. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *Am J Geriatr Psychiatry*. 2005;13(11):976-83.
10. Tractenberg RE, Weiner MF, Patterson MB, Teri L, Thal LJ. Comorbidity of psychopathological domains in community-dwelling persons with Alzheimer's disease. *J Geriatr Psychiatry Neurol*. 2003;16(2):94-9.
11. Rabins PV, Schwartz S, Black BS, et al. Predictors of progression to severe Alzheimer's disease in an incidence sample. *Alzheimers Dement*. 2013;9(2):204-7.
12. GonzÃ¡lez-Salvador T, Lyketsos CG, Baker A, et al. Quality of life in dementia patients in long-term care. *Int J Geriatr Psychiatry*. 2000;15(2):181-9.
13. Steele C, Rovner B, Chase GA, Folstein M. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry*. 1990;147(8):1049-51.
14. Murman DL, Chen Q, Powell MC, Kuo SB, Bradley CJ, Colenda CC. The incremental direct costs associated with behavioral symptoms in AD. *Neurology*. 2002;59(11):1721-9.
15. Peters ME, Schwartz S, Han DD, Rabins PV, Tschanz J, Lyketsos CG. Neuropsychiatric symptoms as predictors of progression to severe alzheimers™

dementia and death: the cache county study. *Am J Geriatr Psychiatry*. 2014;22(3):S65-S66.

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

17. 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.

18. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525-38.

19. Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ*. 2012;344:e977.

20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-44.

21. 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.

22. 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.

23. Alexopoulos GS, et al. Cornell scale for depression in dementia. *Biological psychiatry*. 1988;23(3):271-284.

24. 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.

25. 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.

26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-5.

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

28. Cohen-Mansfield J. Agitated behaviors in the elderly. II. Preliminary results in the cognitively deteriorated. *J Am Geriatr Soc*. 1986;34(10):722-7.

29. Rabinowitz J, Davidson M, De Deyn PP, 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. Guy W. ECDEU Assessment Manual for Psychopharmacology. 1976:76-338.

37. 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.

38. 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.

39. 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.

40. Drye LT, Ismail Z, Porsteinsson AP, et al. Citalopram for agitation in Alzheimer's disease: design and methods. *Alzheimers Dement*. 2012;8(2):121-30.

41. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11 Suppl 2:S22-32.

42. Smith SC, Lamping DL, Banerjee S, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess*. 2005;9(10):1-93, iii-iv.

43. Wimo A WA Mastey V, Winblad B. Evaluation of the resource utilization and caregiver time in anti-dementia drug trials â€“ a quantitative battery. *Health economics of dementia*. 1998:465-499.

44. 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.

45. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.

11. SUMMARY OF CHANGES

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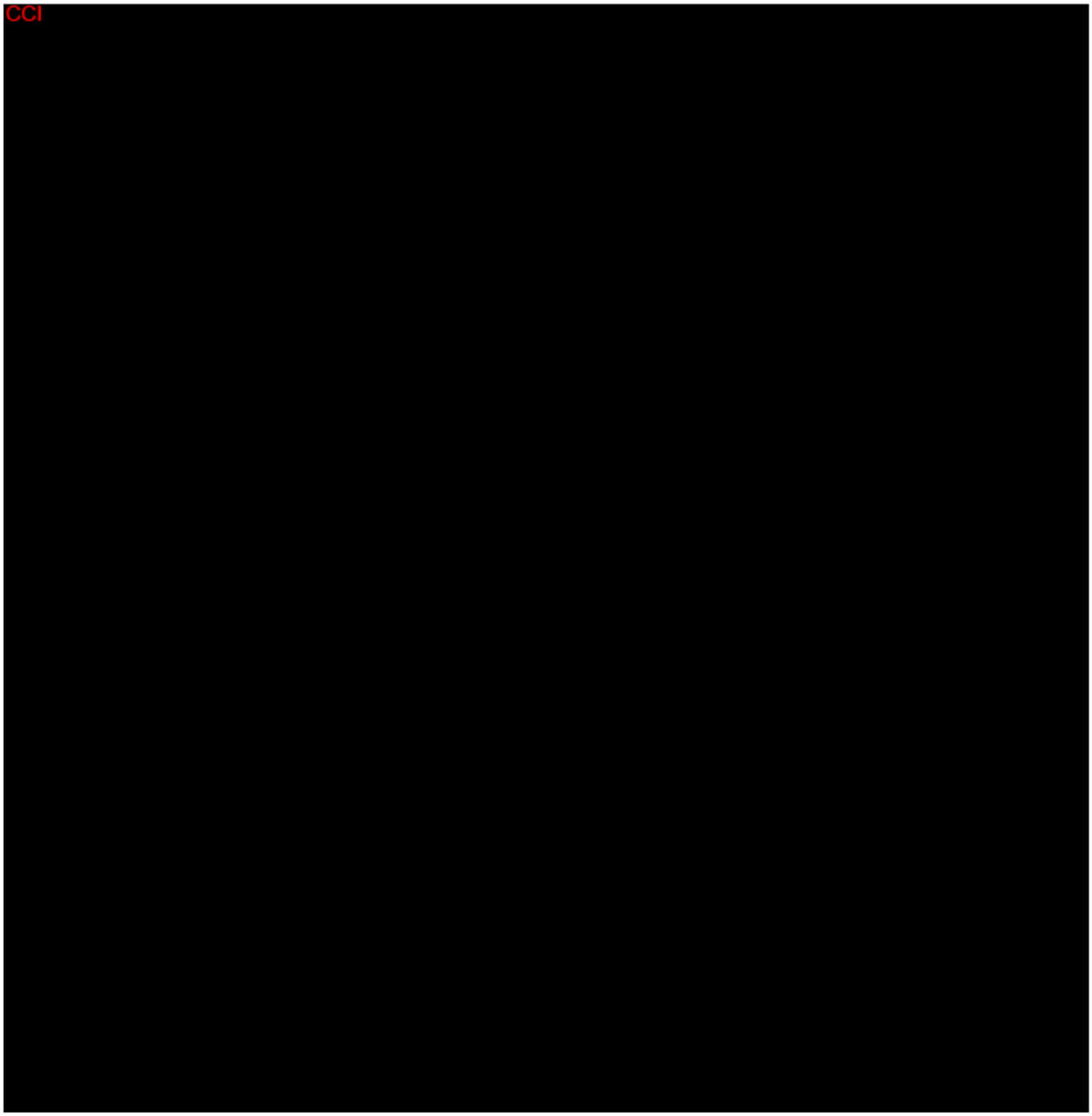

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12. APPENDICES

APPENDIX 1. PROHIBITED CONCOMITANT MEDICATIONS

Patients who are currently taking, or have taken any of the following types of drugs, within **2 weeks or 5 half-lives, whichever is longer,** prior to the initiation of the study medication administration, are to be excluded.

A. Certain drugs that may increase Q levels (exclusion does not include topical medications unless applied under occlusive dressing or other technique that is intended to increase systemic absorption)**:**

- amiodarone
- antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)
- carbonic anhydrase inhibitors (strong inhibitors are prohibited: topiramate is allowed)
- cimetidine
- delavirdine
- diltiazem
- macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin, telithromycin, dirithromycin, roxithromycin)
- mexiletine
- nefazodone
- protease inhibitors (e.g., amprenavir, atazanavir, fosemprenavir, indinavir, ritonavir, saquinavir)
- ranolazine
- verapamil

B. Certain drugs that may have increased plasma levels if co-administered with Q:

- atomoxetine
- tricyclic antidepressants (TCA; e.g., amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline)
- pimavanserin

C. Drugs that are related to Q:

- mefloquine
- quinidine
- quinine

D. Monoamine oxidase inhibitors (MAOIs) (may increase the risk of serotonin syndrome)

Patients should allow at least 14 days after stopping study medication before starting an MAOI.

E. CYP3A4 inducers that may decrease DM or Q plasma levels:

- apalutamide
- carbamazepine
- dexamethasone
- enzalutamide
- fosphenytoin
- lumacaftor
- mitotane
- pentobarbital
- phenobarbital
- phenytoin
- primidone
- rifampicin
- rifamycin
- rifaximin
- St. John's wort

F. Certain drugs that may be prescribed for the treatment of agitation or other indications, but prohibited from this study:

- benzodiazepines (e.g. lorazepam)
- phenothiazines (e.g., chlorpromazine, fluphenazine, levomepromazine, methotrimeprazine, mesoridazine, pencyanzine, perphenazine, prochlorperazine, promazine, thioridazine, thiothixene, trifluoperazine, triflupromazine)
- typical antipsychotics (e.g., droperidol, haloperidol, loxapine, molindone, pimozide, zuclopenthixol)
- clozapine

G. Medications containing dextromethorphan are prohibited, except for intermittent, short-term use (e.g. 7 days or less) of cold medications containing dextromethorphan for the treatment of cold and flu symptoms.