Statistical Analysis Plan

Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Protocol No:	15-AVP-786-303
Protocol Version No./ Date	Amendment 7 26-Jan-2022
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
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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Otsuka Pharmaceutical Development & Commercialization, Inc. Protocol 15-AVP-786-303.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the Protocol Amendment 7 dated 26-Jan-2022 and CRF dated 22-April-2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

1.1 Changes from Protocol

Due to the decision to terminate AVA-786 Program, Otsuka decided to proceed with abbreviated clinical study report. However, previously planned analyses are still kept in this analysis plan.

2.0 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.

3.0 Study Design

3.1 General Description

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 preceding study (may include delays associated with coronavirus disease 2019 restrictions). 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.

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 (Visit2; 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).

Table 1. Schedule of Events and Visits for Patients from Studies 15-AVP-786-301,15-AVP-786-302, and 17-AVP-786-305

Schedule of Evaluations and Visits for Patients 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		X[8]													
Review of eligibility[10]		X[8]													
Treatment assignment[11]		X													
Physical and neurological exam		X[8]											X		
Vital signs 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		X[13]						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		X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMSE		X[8]						X					X		
CMAI		X[8]				X		X		X			X	X	X
NPI agitation/aggression		X[8]				X		X		X			X		

Schedule of Evaluations and Visits for Patients 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
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		X[8]						X					X		
S-STS		X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
ESS[18]		X[8]						X					X		
Administer morning dose of study medication in		X	X[19]	X[19]	X	X	X	X	X	X	X	X	X[19]		
Chemistry, hematology, and urinalysis		X[8]	X		X	X[20]		X[20]		X[20]		X	X[20]		
Urine pregnancy test[21]		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			
Review and return unused study medication and diary			X[19]	X[19]	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 the 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 will 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, 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 females of child bearing potential only.

Table 2. Schedule of Events 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 [2,]	Visit 5[2]	Visit [2]	Visit 6[2]	Visit 6.1[2]	Visit 7[2]	Visit 8[2]/	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		X												X		
Vital signs 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[11]	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		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMSE		X	X						X					X		
CMAI		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 [2]	Visit 5[2]	Visit [2]	Visit 6[2]	Visit 6.1[2]	Visit 7[2]	Visit 8[2]/	Follow-up Visit	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
NPI agitation/aggression		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			
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 the 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 will 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, 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 dairy 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 females of child bearing potentialonly.

3.2 Treatment Assignments

All patients will receive active treatment in Study 15-AVP-786-303. The sponsor, patients, caregivers, investigators, or other study personnel will be masked to the patient's treatment dose assignment. Patients will be assigned to treatments using the following rules:

Treatment Groups:
Eligible patients will be assigned to receive either:

(1) AVP-786-42.63/4.9,
(2) AVP-786-28/4.9, or
(3) 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 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 (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 in the presence of site personnel, regardless of the time of day.
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.

Treatment Adjustment during the study:
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.

3.3 Sample Size Considerations

The sample size of 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 implementation of Protocol Amendment 6.

3.4 Randomization

All patients will receive study medication according to the blister card numbers assigned by an IWRS randomization scheme. All study medication will be supplied and administered in a double-blind manner throughout the entire duration of the study.

4.0 Study Endpoints and Covariates

4.1 Baseline for Scales and Questionnaires

Patient data from the final visit (Visit 6) from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305 will be used as the Baseline data for all applicable efficacy variables for the current study, except for patients who with Medical Monitor approval delay enrollment, procedures to be performed at Baseline are specified in Table 2.

4.1.1 Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI is used to assess the frequency of manifestations of agitated behaviors in elderly persons. 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), Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36) Day 365 (Week 52), Day 395 (Follow-up Visit 1, Week 56) and Day 455 (Follow-up Visit 2, Week 64). For patients 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, Week 12) in the preceding studies will be considered as Baseline.
The CMAI consists of 29 agitated behaviors that are further categorized into 3 distinct agitation syndromes, also known as CMAI factors of agitation. These distinct agitation syndromes include: aggressive behavior, physically non-aggressive behavior, and verbally agitated behavior. Scores for the 3 dimensions will be derived based on the factor structure described by Rabinowitz, et al, 2005.

The distinct agitation dimensions consist of the following:

- **Factor 1 - Aggressive Behavior (12 items)**: hitting, kicking, pushing, scratching, tearing things, cursing or verbal aggression, grabbing (biting, spitting), throwing things, screaming, hurt self or others.
- **Factor 2 - Physically Nonaggressive Behavior (6 items)**: pacing, inappropriate robing or disrobing, trying to get to a different place, handling things inappropriately, general restlessness, repetitious mannerisms
- **Factor 3 - Verbally Agitated Behavior (4 items)**: complaining, constant requests for attention, negativism, repetitious sentences or questions

Each of the 29 items is rated on a 7-point scale of frequency consisting of the following:

CMAI Item Scores
- 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 CMAI total score is calculated as the sum of ratings for all 29 items and range from 29 to 203. The CMAI total score will be unevaluable if less than 24 of the 29 items have recorded responses. If 24 to 28 items are recorded, then the total score will be the mean of the recorded items multiplied by 29 rounded to the first decimal place. The CMAI factor scores are calculated as the sum of each item in the factor when all items included in that factor are recorded.

In addition, for each factor, a patient's agitated/not agitated status is defined based on the below criteria (CMAI manual):

F1 - Aggressive behavior occurring at least several times a week, i.e.,
at least one aggressive behavior occurring at a frequency of 4 or higher
or at least two aggressive behaviors occurring at a frequency of 3

or at least three aggressive behaviors occurring at a frequency of 2
or two aggressive behaviors occurring at a frequency of 2 and one at a frequency of 3

F2 - Physically nonaggressive behavior occurring at least once a day, i.e.,
at least one physically nonaggressive behavior occurring at a frequency of 5 or higher
or least two physically nonaggressive behaviors occurring at a frequency of 4
or least three physically nonaggressive behaviors occurring at a frequency of 3
or least four physically nonaggressive behaviors occurring at a frequency of 2

F3 - Verbally agitated behavior occurring at least once a day, i.e.,
at least one verbally agitated behavior occurring at a frequency of 5 or higher
or least two verbally agitated behaviors occurring at a frequency of 4
or least three verbally agitated behaviors occurring at a frequency of 3
or least four verbally agitated behaviors occurring at a frequency of 2

4.1.2 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. 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 of 0 (not distressing at all) to 5 (extremely distressing).

The three domains of the NPI assessed in this study are: 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), Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36), and Day 365 (Week 52).

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), Day 169 (Week 24), and Day 365 (Week 52). For patients 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, Week 12) 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 in this version are rephrased for professional caregivers who may not know the patients prior to the onset of illness. The overall instrument domains and scoring are identical to the NPI except for the caregiver distress section which is replaced with occupational disruptiveness in the NPI-NH version.

The scripted NPI interview includes a compound screening question for each symptom domain, followed by a list of interrogatives about domain-specific behaviors that is administered when a positive response to a screening question is elicited. Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of frequency and severity, yielding a domain score. Domain scores range from 1 to 12 and are calculated using the following formula:

domain score = frequency x severity

where, frequency and severity are rated according to the following scales:

Frequency	Severity
• 1 = Rarely – less than once per week • 2 = Sometimes – about once per week • 3 = Often – several times per week but less than every day • 4 = Very often – once or more per day	• 1 = Mild – produces little distress in the patient • 2 = Moderate – more disturbing to the patient but can be redirected by the caregiver • 3 = Severe – very disturbing to the patient and difficult to redirect

Frequency and severity rating scales have defined anchor points to enhance the reliability of caregiver responses. Caregiver distress is also rated for each positive neuropsychiatric symptom domain using the following anchored scores:

- 0 = Not at all
- 1 = Minimally (almost no change in work routine)
- 2 = Mildly (some change in work routine but little time rebudgeting required)
- 3 = Moderately (disrupts work routine, requires time rebudgeting)
- 4 = Severely (disruptive, upsetting to staff and other residents, major time infringement)
- 5 = Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

There will not be total scores derived as the instrument is not validated for modified NPI.

4.1.3 Clinical Global Impression of Severity of Illness-Agitation (CGIS-Agitation)

The CGIS-Agitation is an observer-rated scale that measures illness severity and is one of the most widely used brief assessment tools in psychiatry research. Reliability and validity of CGI have been tested in multiple studies, including patients with dementia, schizophrenia and affective disorders. Overall, CGI showed high correlation (ρ: ~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.

In the CGIS, a clinician is asked to rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. The CGIS-Agitation is a 7-point scale and will be assessed for severity of agitation. A value of 0 is given to patients who are not assessed. The 7-point scale for CGIS-Agitation is the following:

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

The CGIS-Agitation will be assessed at Screening (Day -28 to Day -1, for patients who delay enrollment), Baseline (Day 1, for patients who delay enrollment), Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36), and Day 365 (Week 52). For patients 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, Week 12) in the preceding studies will be considered as Baseline.

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

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) 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 also utilize the semi-structured agitation interview of both patient and caregiver.

The response for the mADCS-CGIC-Agitation will consist of one of the following:

Overall Clinical Status Responses
- 1 = Marked Improvement
- 2 = Moderate Improvement
- 3 = Minimal Improvement
- 4 = No Change
- 5 = Minimal Worsening
- 6 = Moderate Worsening
- 7 = Marked Worsening

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 Day 169 (Week 24) and Day 365 (Week 52) for change from baseline (Baseline visit of preceding studies for patients from Studies 15-AVP-786-301, 15-AVP-786-302 and 17-AVP-786-305) in agitation syndrome. The mADCS-CGIC-Agitation will also be assessed at Day 395 (Follow-up Visit 1, Week 56) and Day 455 (Follow-up Visit 2, Week 64) for change from Day 365 (Week 52/ET).

4.1.5 Patient Global Impression of Change (PGIC)

The PGIC is a 7-point scale used to assess treatment response and will be assessed and rated by the patient's caregiver at Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36), and Day 365 (Week 52).

The response values for the PGIC are provided below:

Patient Global Impression of Change Scale
- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

4.1.6 Dementia Quality of Life (DEMQOL)

The DEMQOL is a scale used to evaluate health related quality of life in patients with dementia and their caregivers. 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), Day 169 (Week 24), and Day 365 (Week 52). For patients 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, Week 12) in the preceding studies will be considered as Baseline.

The following provides the response categories for the individual DEMQOL questions and the overall quality of life question:

DEMQOL Responses for Individual Questions	Overall Quality of Life Question
• 1 = A lot • 2 = Quite a bit • 3 = A little • 4 = Not at all	• 1 = Very good • 2 = Good • 3 = Fair • 4 = Poor

Scores for DEMQOL Item 1, 3, 5, 6, 10, 29, DEMQOL-proxy item 1, 4, 6, 8, 11, 32, need to be reversed for analysis, i.e., 4=A lot, 3=Quite a bit, 2=A little, 1=Not at all. Total score is derived by sum of all item scores with item 29 in DEMQOL and item 32 in DEMQOL-proxy being excluded. Missing item handling for DEMQOL, 1) count the number of missing item for question 1 to 28, 2) if the number < 15, set the missing item values to the mean of the non-missing item 1 to 28, then add them up; if the number of missing >= 15, then the total is missing. Missing item handling for DEMQOL-proxy, 1) count the number of missing item for question 1 to 31, 2) if the number < 16, set the missing item values to the mean of the non-missing item 1 to 31, then add them up; if the number of missing ≥ 16, then the total is missing. In addition, DEMQOL Item 29 and DEMQOL-proxy Item 32 will be summarized separately.

4.1.7 Resource Utilization in Dementia (RUD)

The RUD is used to calculate healthcare costs associated with dementia and will be assessed at Baseline (Day 1, for patients who delay enrollment), Day 169 (Week 24), and Day 365 (Week 52). For patients 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, Week 12) in the preceding studies will be considered as Baseline.

The RUD is used to calculate healthcare costs associated with dementia. 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.

The RUD evaluates dementia patients' utilization of formal and informal healthcare resources, including hospitalizations and doctor visits, living assistance, and time spent by nonprofessional caregivers. The RUD is administered as a semi-structured interview with the patient's primary caregiver. One section focuses on caregiver impact (loss of work and leisure time incurred by the caregiver) and the other section focuses on the patient's use of healthcare resources. The total healthcare costs associated with the patient's dementia is 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.

4.1.8 EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L will be assessed only for patients 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). 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.

EQ-5D-5L Dimensions	Responses for Each Dimension
• Mobility • Self-care • Usual activities • Pain/Discomfort	• Slight Problems • Moderate Problems • Severe Problems • Extreme Problems

• Anxiety/Depression	

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale (VAS) 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, Day 169 (Week 24), and Day 365 (Week 52) for patients from Study17-AVP-786-305. The EQ-5D-5L at the final visit (Visit 6, Week 12) in the preceding study (17-AVP-786-305) will be considered as Baseline.

4.2 Efficacy Endpoints

Efficacy endpoints will include the CMAI (Total Score, Factor 1 Aggressive Behavior, Factor 2 Physically Non-aggressive Behavior and Factor 3 Verbally Agitated), mADCS-CGIC-Agitation, NPI (only three domains agitation/aggression, irritability/lability, and aberrant motor behavior domains at Week 24 and Week 52), CGIS-Agitation, PGIC-rated by caregiver, EQ-5D-5L (which is applicable only for patients from Study 17-AVP-786-305), DEMQOL, and RUD.

4.3 Safety Endpoints

Safety and tolerability measurements of AVP-786 will include: adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), Sheehan Suicidality Tracking Scale (S-STS), MMSE, the Time Up and Go (TUG) test, and the Epworth Sleepiness Scale (ESS).

5.0 Analysis Populations

The safety population which includes all patients who received study treatment is the only analysis population that will be used in this study.

5.1 Safety Population

The Safety population 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. Patients will be included in the treatment group based on the actual treatment received.

Since patient's dose can be adjusted anytime (> Day 22), a dose summary table will be presented which will include % of time a patient is exposed to each dose group.

6.0 Definitions

Age

The following SAS® code will be used to calculate patient age (years):

Age = floor ([intck{'month', birth date, screen date} - {day(informed consent date) < day(birth date)}] / 12), where intck is a SAS® function counting integer days.

Baseline
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, Week 12) 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, ECGs, 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.

Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

If a baseline value has not been recorded for a parameter, then CFB will not be calculated for that parameter. Patients with missing CFB values will be excluded from analyses in which CFB is the endpoint.

Percent CFB, when needed, will be calculated by dividing CFB by the baseline value multiplied by 100. Patients with a value of 0 at baseline will not have a percent CFB calculated.

Concomitant medications
Concomitant medications are defined as any medications taken on or after the date of first dose of study drug in Study 15-AVP-786-303 or that are ongoing concomitant medications from Studies 15-AVP-786-301, 15-AVP-786-302, 17-AVP-786-305, and 12-AVR-131.

Discontinuation of study
A patient will be considered discontinued from the study when a Study Exit CRF page is completed indicating primary reason for discontinuation.

End of Treatment (EOT)

EOT is defined as the last dosing date for a given patient, whenever it occurred.

Enrolled patient
An enrolled patient is one with a record in the database that is not a screen failure.

Prior medication
Prior medications are defined as any medications with start and stop dates prior to the date of first dose of study drug in Study 15-AVP-786-303. Medications are defined as prior or concomitant, but not both (see also definition of concomitant medication in this section).

Protocol deviation
Potential planned or unplanned protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion criteria, exclusion criteria, study drug, safety assessment, efficacy assessment, visit window, informed consent, prohibited medication, and other). All deviations will be reviewed, categorized, and finalized prior to database lock.

Relationship to study treatment
AEs related to study treatment will be defined as those entered as possibly related or related. Unlikely related or not related entries will be considered not related to study treatment. If relationship is missing, then it will be considered as related to study treatment.

Study day
Study day is defined relative to the date of the first dose of study drug. For assessments that occur after this visit date, study day is calculated as (assessment date – study drug first dose date + 1). For assessments that occur prior to study drug first dose date, study day will be calculated as (assessment date –study drug first dose date); there is no Study Day 0.

Treatment-emergent adverse event
An AE will be considered to be a treatment-emergent AE (TEAE) if it begins or worsens on or after the first dose date in Study 15-AVP-786-303 and before the last dose date + 30 days.

Incidence Rate
Incidence is defined as the number of events. Incidence per 100 subject years rate is calculated as follow:

Exposure Duration = last dose date - first dose date +1;

Incidence per 100 subject years = ((Incidence × 365.25) / Total Exposure Duration in days) × 100.

7.0 Interim Analyses

The planned interim analyses have been canceled due to termination of the AVP-786 program.

8.0 Data Handling and Review

8.1 Visit Windows

Data at scheduled visits will be assigned to analysis visits as defined in the Visit Window tables below. Visit Windows will be used to classify unscheduled and early termination visits. If 2 or more visits occur within the same analysis window, then the values closest to the target day will be summarized. If the assessment is the same distance from the target day, then the latest one will be used.

TABLE 4.1. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT WEEKS 2, 4, 6, 12, 18, 24, 30, 36, 42, 48, 52, 56, AND 64

Week/Visit	Target Day	Study Days
Week 2/Visit 2	15	2, 22
Week 4/Visit 2.1	29	23, 36
Week 6/Visit 3	43	37, 64
Week 12/Visit 4	85	65, 106
Week 18/Visit 4.1	127	107, 148
Week 24/Visit 5	169	149, 190
Week 30/Visit 5.1	211	191, 232
Week 36/Visit 6	253	233, 274
Week 42/Visit 6.1	295	275, 316
Week 48/Visit 7	337	317, 351
Week 52/Visit 8	365	352, 380
Week 56/Follow-up Visit 1	395	381, 425
Week 64/Follow-up Visit 2	455	426, day of last visit

Note: for S-STS.

TABLE 4.2. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT WEEKS 2, 4, 6, 12, 18, 24, 30, 36, 42, 48, AND 52

Week/Visit	Target Day	Study Days
Week 2/Visit 2	15	2, 22
Week 4/Visit 2.1	29	23, 36
Week 6/Visit 3	43	37, 64
Week 12/Visit 4	85	65, 106

Week 18/Visit 4.1	127	107, 148
Week 24/Visit 5	169	149, 190
Week 30/Visit 5.1	211	191, 232
Week 36/Visit 6	253	233, 274
Week 42/Visit 6.1	295	275, 316
Week 48/Visit 7	337	317, 351
Week 52/Visit 8	365	352, day of last visit

Note: for Vital signs, height and weight.

TABLE 4.3. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT DAY 1, WEEKS 2, 6, 12, 24, 36, 48, AND 52

Week/Visit	Target Day	Study Days
Day 1/Visit 1	1	1
Week 2/Visit 2	15	2, 29
Week 6/Visit 3	43	30, 64
Week 12/Visit 4	85	65, 127
Week 24/Visit 5	169	128, 211
Week 36/Visit 6	253	212, 295
Week 48/Visit 7	337	296, 351
Week 52/Visit 8	365	352, day of last visit

Note: for ECG and Laboratory test.

TABLE 4.4. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT WEEKS 24 AND 52

Week/Visit	Target Day	Study Days
Week 24/Visit 5	169	149, 190
Week 52/Visit 8	365	191, day of last visit

Note: for MMSE, NPI irritability/lability and aberrant motor behavior domains, DEMQOL, EQ-5D-5L, ESS, RUD.

TABLE 4.5. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT WEEK 52.

Week/Visit	Target Day	Study Days
Week 52/Visit 8	365	352, day of last visit

Note: for Physical and neurological exam.

TABLE 4.6. VISIT WINDOWS FOR ASSESSMENTS ON-TREATMENT AT WEEKS 2, 6, 12, 18, 24, 30, 36, 42, AND 48.

Week/Visit	Target Day	Study Days
Week 2/Visit 2	15	2, 29
Week 6/Visit 3	43	30, 64
Week 12/Visit 4	85	65, 106
Week 18/Visit 4.1	127	107, 148
Week 24/Visit 5	169	149, 190
Week 30/Visit 5.1	211	191, 232
Week 36/Visit 6	253	233, 274
Week 42/Visit 6.1	295	275, 316
Week 48/Visit 7	337	317, day of last visit

Note: for Dispense of study drug.

8.2 Missing Data Conventions

Missing data will be handled differently depending on the parameter and analysis. Analyses that are done on 'observed cases' will not follow any imputation rules below. Imputation rules are as follows:

- Missing baseline values will not be imputed in any situation.

- Any assessments for patients without a Week 52 value will use the last non-missing post-baseline observation prior to Week 52 as EOT. For summary purposes, for patients with a Week 52 value, an EOT record is also created using the Week 52 value.
- Missing post-baseline values for by-visit efficacy and safety data will be summarized using the Visit Windows from Section 8.1. If a value is not available within a given window, then no imputation will be done.
- Missing data for AE relationship will be imputed as "Related".
- Rules for partial dates are provided in Appendices 2 and 3. These rules will apply to adverse events and medications.

8.3 Treatment Misallocations

Efficacy and safety data will be summarized, "as treated", according to the treatment the patient actually received on Day 22. If a patient early discontinued prior to Day 22, this patient will be summarized under the last treatment received.

8.4 Data Handling and Transfer

Data will be entered by investigational sites into a clinical database built with Bioclinica and exported as SAS® version 9.4 or higher datasets (SAS Institute, Inc., Cary, NC). Converted datasets are created using SAS® and following Clinical Data Interchange Standards Consortium (CDISC) Standard Data Tabulation Model conventions (v3.1.3 implementation guide v1.3). Derived analysis datasets are generated using SAS® and following standard CDISC Analysis Dataset Model conventions (implementation guide v1.0). Data analyses including summary tables, figures, and listings (TFLs) are produced using SAS®.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 to assign a system organ class (SOC) and preferred term (PT) to each AE. AEs severity will be graded on a 3-point scale and reported in detail as indicated on the eCRF.

Prior and concomitant medications are coded to preferred drug names using the World Health Organization Drug Dictionary Enhanced (WHODRUG GLOBAL B3 MAR 2024).

8.5 Data Screening

The ICON programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word "Problem" and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run (Dry Run#1) on clean patients allows for further data screening prior to database lock (DBL). The post-freeze TFLs will be discussed with Otsuka in a data review meeting to identify any final data issues and seek corrections prior to DBL. The ICON statistician and Otsuka must approve database lock.

8.6 Data Safety Monitoring Board (DSMB)

This study is monitored on an ongoing basis by an external data safety monitoring board (DSMB). Safety analyses will be provided to the DSMB approximately every 3 months. Select efficacy results may be included, although no p-values will be provided. Details of the DSMB can be found in the DSMB charter and DSMB SAP.

9.0 Overall Statistical Considerations

9.1 Summary Statistics

All analyses will use SAS® version 9.4 or higher. Summary tables will be organized by actual treatment group on Day 22 (AVP-786 18 mg, AVP-786 28 mg, AVP-786 42.63 mg, and all patients combined), or the last treatment received for patients who early discontinued prior to Day 22.

Unless otherwise noted, categorical data will be presented using counts and percentages, with the number of patients in the analysis population by treatment group as the denominator for percentages. Percentages are rounded to one decimal place except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous data, unless otherwise noted, will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The mean and median will be rounded to 1 decimal place greater than the precision of the original value, up to a maximum of 3 decimal places. The SD will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

Supporting figures may be used for some efficacy or safety analyses in addition to the summary tables.

9.2 Hypothesis Testing and Multiplicity of Endpoints

There will be no treatment comparisons performed for efficacy or safety data for this study.

10.0 Efficacy Statistical Analysis Methods

No analysis for efficacy will be performed resulting from termination of the AVP-786 program.

11.0 Safety Statistical Analysis Methods

Safety will be assessed through the analysis of AEs, clinical laboratory assessments, ECGs, vital signs, physical and neurological examinations, S-STS, MMSE, TUG, and the ESS. All safety analyses will be completed on the Safety population. Unless otherwise specified, safety analyses will be displayed by treatment groups as indicated in Section 5.1.

11.1 Adverse Events

AE tables (except the AE Overview table) will only include summaries of TEAEs. AEs occurred in prior studies (15-AVP-786-301, 15-AVP-786-302, or 17-AVP-786-305) and continued in this study without worsening will not be included.

An overview table containing the number and percentage of the following will be included:

- Number of total AEs, TEAEs, and deaths
- Incidence of patients with at least one TEAE, drug-related TEAE, non-serious AEs, serious TEAEs, drug-related serious TEAEs, and death
- Incidence of patients who discontinued due to TEAE, drug-related TEAE, serious TEAEs, and drug-related serious TEAEs
- Incidence of deaths and deaths due to drug-related TEAE

TEAEs will be summarized by system organ class (SOC) and preferred term (PT), descending frequency of PT, and by maximum severity. Summaries of PTs will also be done for those occurring in at least 5% of patients in any treatment group.

TEAEs leading to discontinuation will be summarized by SOC and PT. Drug-related TEAEs will be summarized by SOC and PT and in descending frequency of PT.

Time to onset for common TEAEs (as defined below) will be summarized descriptively for each of these events. In addition, summary statistics for the duration and percentage of total study days will be provided for each AE. The n (%) of patients with recurrences will also be given.

Serious TEAEs will be summarized by SOC and PT and will include a summary of drug-related events.

Non-SAEs will be summarized by SOC and PT with incidence and incidence rate presented.

Below are the rules to follow for AE summaries:

- If a patient has multiple AEs within the same SOC or PT, the patient will only be counted once within a level of MedDRA.
- A drug-related AE is defined as an AE with an assigned relationship of "possibly related," "related," or missing.
- When assessing severity, if a patient has 2 or more TEAEs, the TEAE with the worst severity will be chosen. AEs with missing severity will be excluded from summaries of AE by severity.
- A common TEAE is defined as a TEAE an incidence of ≥3% in any AVP-786 treatment group.
- Time to onset will be calculated in days as (AE start date – first dose date).
- Duration of AE is generally defined as (AE end date – AE start date + 1). Below are some additional considerations for AE duration:
    - If the patient has an AE that has not ended when the patient ends the study, AE end date is defined as the last dose of study drug.
    - If the same AE occurs more than once, duration will be the sum of the individual AE durations.
- For a given patient, percentage of total study days is defined as total duration (as defined above) divided by (last dose date – first dose date + 1) x 100.
- Recurrence is defined as a new report of the same TEAE with a new AE start date.

AEs will be coded using MedDRA version 27.0.

11.2 Clinical Laboratory Assessments

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), Day 15 (Week 2), Day 43 (Week 6), Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36), Day 337 (Week 48), and Day 365 (Week 52) unless specified otherwise. For patients from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6, Week 12) in the preceding studies will be considered as Baseline.

The following parameters will be summarized descriptively through change from baseline and percent change from baseline.

- 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: (thyroid stimulating hormone [TSH], and reflex T3 and T4 if TSH is abnormal) at Screening visit only for patients who delay enrollment and will only be provided in a data listing.
- Glycosylated hemoglobin (HbA1c) test at the Screening visit (for patients who delay enrollment), Baseline Visit (for patients who delay enrollment), and Day 85 (Week 12), Day 169 (Week 24), Day 253 (Week 36), and Day 365 (Week 52).

Out-of-range values will be assessed through shift tables of baseline to EOT. Each lab value will be assessed as low, normal or high based on the normal ranges provided by the central lab. Frequencies of each combination of shifts will be provided by treatment group.

The denominator for the percentages will be the total number of patients in the treatment group with a baseline and post-baseline value. Lab tests without normal ranges will be excluded from the shift tables.

Potentially clinically significant (PCS) tables will also be used to summarize out-of-range values. PCS values are found in Table 5. The number and percentage of patients meeting the criteria below will be summarized by treatment group. Summaries will be given for any time post-baseline. The denominator for the percentages will be the number of patients who had a post-baseline assessment for each parameter.

TABLE 5. LAB PCS CRITERIA

Laboratory Parameter	Unit	Low PCS Criteria	High PCS Criteria		Laboratory Parameter	Unit	Low PCS Criteria	High PCS Criteria
Chemistry								
Albumin	g/L	≤26	≥60		GGT	U/L	None	≥ 60
Alkaline Phosphatase	U/L	None	≥3X ULN		Glucose	mmol/L	≤2.775	≥11.1
ALT (SGPT)	U/L	None	≥3X ULN		LDH	U/L	None	≥3X ULN
AST (SGOT)	U/L	None	≥3X ULN		Magnesium	mmol/L	<0.37	>1.23
Bilirubin	umol/L	None	≥1.5 ULN		Phosphate	mmol/L	≤0.4522	>3.88
BUN	mmol/L	None	≥10.71		Potassium	mmol/L	≤3.0	≥5.5
Calcium	mmol/L	≤1.75	≥3.0		Protein	g/L	≤50	≥100
Carbon Dioxide	mmol/L	≤ 9	>40		Sodium	mmol/L	≤130	≥155
Chloride	mmol/L	≤85	≥120		Triglycerides	mmol/L	None	>3.39
Cholesterol	mmol/L	None	≥7.77		Urate (Male)	umol/L	None	≥624.54
Creatine Kinase	U/L	None	≥3 ULN		Urate (Female)	umol/L	None	≥505.58
Creatinine	umol/L	None	>132.6					
Hematology								
Hemoglobin	g/L	<100	>180		Monocytes	x10^9/L	None	>1
Hematocrit	proportion of 1.0	<0.3	>0.5		Monocytes/ Leukocytes	%	None	≥15
Basophils	x10^9/L	None	>0.3		Neutrophils/ Leukocytes	%	≤15	None

Laboratory Parameter	Unit	Low PCS Criteria	High PCS Criteria		Laboratory Parameter	Unit	Low PCS Criteria	High PCS Criteria
Eosinophils/Leukocytes	%	None	≥10		Leukocytes	x10^9/L	≤2.8	≥16
Lymphocytes	x10^9/L	≤0.5	>4		Erythrocytes	x10^12/L	≤2.5	≥7.0
Lymphocytes/Leukocytes	%	≤10	≥60		Platelet Count	x10^9/L	≤100	≥700

Over the course of the study, there may be some lab tests performed that are not mentioned in the protocol. These tests will not be summarized but will be included in the listings and flagged as non-protocol tests.

11.3 ECGs

A resting 12-lead ECG will be performed 2 to 3 hours (±15 minutes) after dosing at the following visits:

- Screening (Day -28 to Day -1, for patients who delay enrollment)
- Baseline (Day 1)
- Day 15 (Week 2)
- Day 43 (Week 6)
- Day 85 (Week 12)
- Day 169 (Week 24)
- Day 253 (Week 36)
- Day 337 (Week 48)
- Day 365 (Week 52).

For patients who delay enrollment, ECG will be performed in triplicate at the Screening visit and will be performed both pre-dose and post-dose at the Baseline visit.

ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute) QRS complex, PR interval, and QTc intervals (milliseconds).

Change from baseline and percent change from baseline will be calculated for each parameter and summarized by the treatment groups mentioned in Section 5.1.

In addition, since ECGs are recorded pre- and post-dose at Baseline, change from pre- to post-dose will be summarized at these visits for patients who delay enrollment.

PR interval and Fridericia's Correction (QTcF) will be further investigated through PCS tables, for which the criteria are found in Table 6 below. The number and percentage of patients meeting the criteria below will be summarized by treatment group. Summaries will be given for both overall (i.e., any time post-baseline) and by visit. For QTcF, males and females will be assessed separately. Patients will be included in all categories for which they qualify. For criteria on the "Actual" values, the denominator for the percentages is the number of patients who had a post-baseline assessment for each parameter. For criteria on the change, the denominator is the number of patients who had a baseline and post-baseline assessment.

TABLE 6. ECG PCS CRITERIA

ECG parameter	Sex	Actual or Change	PCS Criteria

PR Interval (msec)	Both	Actual	>200 to ≤220, >220 to ≤250, >250
QTcF (msec)	Males	Actual	>450 to ≤480, >480 to ≤500, >500
	Females	Actual	>470 to ≤485, >485 to ≤500, >500
	Both	Change from baseline (increase)	≥30, ≥60

ECG overall interpretations will be summarized by the number and percentage that were normal or abnormal. The interpretations by the cardiologist (i.e., central ECG) will be used for these summaries. The listings will provide all interpretations and corresponding details.

11.4 Vital Signs

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be obtained at all clinic visits except on Day 395 (Follow-up Visit 1, Week 56) and Day 455 (Follow-up Visit 2, Week 64). For patients from Studies 15-AVP-786- 301 and 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6, Week 12) 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. The average of the measurements will be presented. 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 (°F/ °C) will be assessed at all clinic visits. Weight should be recorded at Baseline (Day 1, for patients who delay enrollment), Day 169 (Week 24), and Day 365 (Week 52). For patients from Studies 15-AVP-786-301 and 15-AVP-786-302, and 17-AVP 786- 305, the respiratory rate, temperature and weight assessments at the final visit (Visit 6, Week 12) in the preceding studies will be considered as Baseline.
The following parameters will be summarized: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and temperature. These parameters will be summarized through change from baseline and percent change from baseline in similar fashion as the ECG parameters.

Vital signs will also be assessed through PCS criteria, which are given in Table 7. Patients will be counted if they meet the criteria below at any time post-baseline. The definition of baseline is consistent with those for ECG parameters. The denominators are the number of patients with both a baseline and post-baseline assessment.

TABLE 7. VITAL SIGN PCS CRITERIA

Vital Sign Parameter	High values	Low values
SBP (mmHg)	>180 AND ≥20 increase from baseline	≤90 AND ≥20 decrease from baseline
DBP (mmHg)	≥105 AND ≥15 increase from baseline	≤50 AND ≥15 decrease from baseline
Heart rate (bpm)	≥120 AND ≥15 increase from baseline	≤50 AND ≥15 decrease from baseline
SBP and heart rate	SBP ≥10 increase from baseline AND heart rate ≥5 increase from baseline	
DBP and heart rate	DBP ≥5 increase from baseline AND heart rate ≥5 increase from baseline	

Orthostatic changes in blood pressure and heart rate from supine to standing will also be summarized. Additionally, patients meeting orthostatic hypotension or postural tachycardia PCS criteria at any time post-baseline will be summarized according to the criteria in Table 8.

TABLE 8. ORTHOSTATIC HYPOTENSION AND POSTURAL TACHYCARDIA PCS CRITERIA

Category	PCS Criterion
Orthostatic hypotension	≥ 20 mmHg decrease in SBP or ≥ 10 mmHg decrease in DBP from supine to standing
Postural tachycardia	≥ 30 bpm increase in heart rate from supine to standing or a standing heart rate ≥ 120 bpm

11.5 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 (Week 52). For patients from Studies 15-AVP-786-301 and 15-AVP-786-302, and 17-AVP-786-305, the assessment at the final visit (Visit 6, Week 12) 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. Physical and neurological examination data will be provided in a data listing.

11.6 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors. Each item of the S-STS is scored on a 5-point Likert scale as shown below:

S-STS Item Scale

- 0 = Not at all
- 1 = A little
- 2 = Moderate
- 3 = Very
- 4 = Extremely

The S-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, and a 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 from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the S-STS at the final visit (Visit 6, Week 12) in the preceding studies will be considered as Baseline.

The S-STS will be assessed at all clinic visits. Any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to the Medical Monitor (MM). Scores, CFB in scores, and percent CFB in scores will be summarized descriptively by visit and treatment group for each subscale and total score. S-STS suicidal ideation subscale score, suicidal behavior subscale score, and a total score will be calculated as follow:

Parameter	Description of Derivation	Programming Algorithm	Missing Data Handling
Suicidal Ideation	Sum of: Questions 2 - 11; Questions are on a 0-4 scale	Sum of: SSTS102, SSTS103, SSTS104, SSTS105, SSTS106, SSTS107, SSTS108, SSTS109, SSTS110, SSTS111	if any missing for Questions 2 - 11, then score will be missing
Suicidal Behavior	If Question 1b=Yes, then use the following algorithm: Sum of: Questions 1a, highest score of (Q12 or any row of Q16), highest score of (Q14 or any row of Q15), 17, and 20 If Question 1a is not present, then use the following algorithm: Sum of: highest score of (Q12 or any row of Q16), highest score of (Q14 or any row of Q15), 17, and 20 Notes: Questions 15, 16, 17, and 20 are optional and only included in the QS datasets if populated with data. Scores should still be calculated if these Q15, Q16, Q17, Q20 are missing.	If SSTS101B=Yes (looks like this is only present in data if =Yes, then do: Sum of: SSTS101A, max(SSTS112 or SSTSQ16C or SSTSQ16D), max(SSTS114 or SSTSQ15C or SSTSQ15D), SSTS17=Yes add 100, SSTS20=Yes add 4 If SSTS101B not present or No, then do: Sum of: max(SSTS112 or SSTSQ16C or SSTSQ16D), max(SSTS114 or SSTSQ15C or SSTSQ15D), SSTS17=Yes add 100, SSTS20=Yes add 4	if Questions 12 or 14 are missing, then score will be missing
Total Scale Score	If Question 1b=Yes, then use the following algorithm: Sum of: Questions 2 - 11, Questions 1a, highest score of (Q12 or any row of Q16), highest score of (Q14 or any row of Q15), 17, and 20 If Question 1a is not present, then use the following algorithm: Sum of: Questions 2 - 11, highest score of (Q12 or any row of Q16), highest score of (Q14 or any row of Q15), 17, and 20 Notes: Questions 15, 16, 17, and 20 are optional and only	If SSTS101B=Yes (looks like this is only present in data if =Yes, then do: Sum of: SSTS102, SSTS103, SSTS104, SSTS105, SSTS106, SSTS107, SSTS108, SSTS109, SSTS110, SSTS111, SSTS101A, max(SSTS112 or SSTSQ16C or SSTSQ16D), max(SSTS114 or SSTSQ15C or SSTSQ15D), SSTS17=Yes add 100, SSTS20=Yes add 4 If SSTS101B not present or No, then do: Sum of: SSTS102, SSTS103, SSTS104, SSTS105, SSTS106, SSTS107, SSTS108, SSTS109, SSTS110, SSTS111, max(SSTS112 or SSTSQ16C or SSTSQ16D), max(SSTS114 or SSTSQ15C or SSTSQ15D), SSTS17=Yes add 100, SSTS20=Yes add 4	if any missing for Questions 2 - 12, 14, then score will be missing

	included in the QS datasets if populated with data. Scores should still be calculated if these Q15, Q16, Q17, Q20 are missing.		

11.7 Mini Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire test that is used to screen for cognitive impairment and severity of cognitive impairment. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate a patient's cognitive state and are scored according to the following ranges:

Item	Score Range
• Orientation to Time	• 0 to 5
• Orientation to Place	• 0 to 5
• Registration	• 0 to 3
• Attention and Calculation	• 0 to 5
• Recall	• 0 to 3
• Naming	• 0 to 2
• Repetition	• 0 to 1
• Comprehension	• 0 to 3
• Reading	• 0 to 1
• Writing	• 0 to 1
• Drawing	• 0 to 1

The total score is calculated by summing all of the item scores and ranges from 0 to 30. Higher scores indicate milder cognitive impairment.

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), Day 169 (Week 24), and Day 365 (Week 52). For patients 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. The MMSE total score, CFB in total score, and percent CFB in total score will be summarized descriptively by visit and treatment group.

11.8 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.

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 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. The TUG test data will be provided in a data listing.

11.9 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. 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), Day 169 (Week 24), and Day 365 (Week 52) for patients with an MMSE score of ≥ 10 at baseline. For patients from Studies 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305, the ESS assessment at the final visit (Visit 6, Week 12) in the preceding studies will be considered as Baseline. The total score, CFB in total score, and percent CFB in total will be summarized descriptively by visit and treatment group.

12.0 Additional Summaries

12.1 Patient Disposition

Patient enrollment will provide the number of patients screened along with the reason for screen failures. Patient status will be summarized by the following:

- Enrolled
- Took study medication
- Discontinued
- Completed study

Primary reasons for discontinuation will be provided based on the number of patients in the treatment group. The number of patients in the Safety population will be provided.

12.2 Protocol Deviations

Protocol deviations (see definition in Section 6) for patients will be reported by category for each treatment group and overall. Categories include inclusion criteria, exclusion criteria, study drug, safety assessment, efficacy assessment, visit window, informed consent, prohibited medication, and other.

Protocol deviations will be listed and summarized.

12.3 Demographic and Baseline Characteristics

Demographics will be summarized by treatment group and overall for the following characteristics:

- Sex (male/female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age
- Age group (<65, ≥65)
- Weight
- Body mass index
- Use of concomitant antipsychotic medications (yes/no)

For categorical parameters, the denominators for the percentages are the number of patients who had the parameter assessed.

12.4 Medical History

Medical history will be summarized by SOC and PT and will be provided in data listings.

12.5 Exposure

Duration of exposure will be summarized quantitatively using the number of days on study medication for each patient, displayed by treatment group and overall. Duration will be calculated as (last dose date – first dose date + 1).

An additional summary of exposure will be provided by dose taken for patients who took AVP-786 at any time during the study. The number of days at the specified dose level will be summarized. Doses summarized will be 18 mg QD, 18 mg BID, 28 mg BID, and 42.63 mg BID.

12.6 Compliance

Overall treatment compliance will be calculated as a percentage using the total number of capsules that were taken. Patients will be grouped into categories of <80%, 80% to 120%, >120%. Counts will be summed over the visits for each patient to calculate an overall compliance value.

Compliance will be summarized as described above and using descriptive statistics by treatment group. The number of doses taken and number of doses should have taken are necessary to calculate compliance. The 3 steps for calculating compliance are shown here:

1. Doses taken = actual amount taken
2. Doses should have taken: 2 * (last dose date – first dose date) + 1
3. Compliance = (doses taken / doses should have taken) * 100

The formula is based on the assumption that patients take 2 capsules per day except for the last day, in which they only take 1.

12.7 Prior and Concomitant Medications

The number and percentage of prior and concomitant medications will be provided by the treatment group. Summaries will be provided by anatomical therapeutic chemical (ATC) and preferred term for the Safety population.

In addition, below information will be summarized:

- At baseline, number and % patients who used medications for AD (donepezil, donamem, rivastigmine, galantamine, memantine), medications for agitation secondary to AD (atypical antipsychotics, antidepressants, buspirone).
- Cumulative number and % patients who used short term rescue medication lorazepam by visit.

12.8 Pharmacokinetics and Pharmacodynamics

Not applicable since there are no planned Pharmacokinetics/Pharmacodynamics data in this study.

13.0 Validation

ICON's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

14.0 References

1. 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.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:

AD	Alzheimer's disease
ADCS	Alzheimer's Disease Cooperative Study
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AR1	First-order autoregressive
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
ATC	Anatomic therapeutic classification
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFB	Change from baseline
CGIC	Clinical Global Impression of Change
CGIS-Agitation	Clinical Global Impression of Severity of Illness-Agitation
CK	Creatinine kinase
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DEMQOL	Dementia Quality of Life
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOT	End of treatment
ESS	Epworth Sleepiness Scale
GGT	Gamma-glutamyl transferase
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
mADCS-CGIC-Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Rating for Agitation
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory Nursing-Home version
PCS	Potentially clinically significant
PGIC	Patient Global Impression of Change

pH	Potential hydrogen
PR	The P-R interval from an ECG tracing
PT	Preferred term
QD	Once daily
QRS	The Q-R-S complex from an ECG tracing
QT	QT interval from an ECG tracing
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett's formula
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
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
S-STS	Sheehan Suicidality Tracking Scale
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
TSH	Thyroid stimulating hormone
TUG	Timed Up and Go
VAS	Visual analog scale
WBC	White blood cells
WHODRUG DDE	World Health Organization Drug Dictionary Enhanced

Appendix 2 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 3 Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

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