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

Summary

EudraCT number	2017-001339-38
Trial protocol	HU ES FR GB CZ BG PL IT
Global end of trial date	14 December 2023

Results information

Result version number	v1 (current)
This version publication date	09 March 2025
First version publication date	09 March 2025

Trial information

Trial identification

Sponsor protocol code	17-AVP-786-305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03393520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Blvd, Rockville, United States, 2085
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 8446878522 ,
Scientific contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 8446878522 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo, for the treatment of agitation in subjects with dementia of the Alzheimer's type.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 288
Country: Number of subjects enrolled	South Africa: 36
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Bulgaria: 54
Country: Number of subjects enrolled	Czechia: 80
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Italy: 9
Worldwide total number of subjects	601
EEA total number of subjects	258

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	68
From 65 to 84 years	480
85 years and over	53

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at investigational sites in the United States, United Kingdom, South Africa, France, Italy, Spain, Hungary, Czech Republic, Poland, and Bulgaria from 27 March 2018 to 14 December 2023.

Pre-assignment

Screening details:

Of the total 1143 subjects screened, 601 subjects were randomized to receive AVP-786-28 milligrams (mg) (deudextromethorphan hydrobromide [d6-DM] 28 mg/quinidine sulfate [Q] 4.9 mg), AVP-786-42.63 mg (d6-DM 42.63 mg/Q 4.9 mg) or placebo in 3:3:4 ratio in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matched AVP-786 placebo capsules, orally, twice daily (BID) for the 12-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matched AVP-786 placebo capsules BID for the 12-week treatment period

Arm title	AVP-786-28 mg

Arm description:

Following a 3-week titration schedule, subjects received AVP-786-18/4.9 capsules, orally, once a day (QD) for the first 7 days of the study, followed by AVP-786-18/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-28/4.9, capsules, BID for 9 weeks.

Arm type	Experimental
Investigational medicinal product name	AVP-786-28
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

AVP-786-18/4.9 capsule, orally, QD for 7 days followed by AVP-786-18/4.9 capsule, BID for next 14 days, and then AVP-786-28/4.9 capsule, BID for the 9 weeks.

Arm title	AVP-786-42.63 mg

Arm description:

Following a 3-week titration schedule, subjects received AVP-786-28/4.9 capsules, orally, QD for the first 7 days of the study, followed by AVP-786-28/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-42.63/4.9, capsules, BID for 9 weeks.

Arm type	Experimental
Investigational medicinal product name	AVP-786-42.63
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

AVP-786-28/4.9 capsule, orally, QD for 7 days followed by AVP-786-28/4.9 capsule, BID for next 14 days, and then AVP-786-42.63/4.9 capsule BID for 9 weeks.

Number of subjects in period 1	Placebo	AVP-786-28 mg	AVP-786-42.63 mg
Started	217	198	186
Modified Intent to Treat (mITT)	164 [1]	148 [2]	149 [3]
Safety	216	197	186
Completed	191	173	163
Not completed	26	25	23
End of Study Form Not Completed	1	-	-
Study subject withdrawal by parent or guardian	3	2	3
Physician decision	-	1	1
Trial site terminated by sponsor	-	1	-
Death	3	1	-
Adverse event	3	3	6
Non-compliance with study drug	-	1	-
Reason not specified	4	6	2
Lost to follow-up	1	2	1
Withdrawal by subject	10	8	9
Protocol deviation	1	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are the number of subjects for the specified milestone.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are the number of subjects for the specified milestone.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are the number of subjects for the specified milestone.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matched AVP-786 placebo capsules, orally, twice daily (BID) for the 12-week treatment period.	
Reporting group title	AVP-786-28 mg
Reporting group description:	
Following a 3-week titration schedule, subjects received AVP-786-18/4.9 capsules, orally, once a day (QD) for the first 7 days of the study, followed by AVP-786-18/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-28/4.9, capsules, BID for 9 weeks.	
Reporting group title	AVP-786-42.63 mg
Reporting group description:	
Following a 3-week titration schedule, subjects received AVP-786-28/4.9 capsules, orally, QD for the first 7 days of the study, followed by AVP-786-28/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-42.63/4.9, capsules, BID for 9 weeks.	

Reporting group values	Placebo	AVP-786-28 mg	AVP-786-42.63 mg
Number of subjects	217	198	186
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74.1	74.2	75.1
standard deviation	± 7.61	± 7.68	± 7.99
Gender categorical Units: Subjects			
Female	129	120	99
Male	88	78	87
Ethnicity Units: Subjects			
Hispanic or Latino	69	60	64
Not Hispanic or Latino	145	134	118
Not Reported	3	4	4
Race Units: Subjects			
White	198	175	161
Black or African American	15	16	19
Asian	0	0	1
Other	1	3	1
Not Reported	3	4	4
CMAI - Total Score			
CMAI is used to assess frequency of manifestations of agitated behaviors categorized into 3 distinct agitation factors (CMAI factors of agitation): Factor 1-Aggressive Behavior, Factor 2-Physically Nonaggressive Behavior, Factor 3-Verbally Agitated Behavior. Each of 29 items was rated on a 7-point scale of frequency ranging from 1=Never to 7=Several times an hour. CMAI total score was sum of ratings for all 29 items, ranged from 29 to 203. Higher score indicate greater frequency of manifestations of agitated behaviour.			
Units: Score on a scale			

arithmetic mean standard deviation	± ±	± ±	± ±
CGIS-Agitation Score			
The CGIS is an observer-rated scale that measures illness severity on a 7-point scale (score range: 1-7, where 1 = normal, not at all ill; 7 = among the most extremely ill subjects).			
Units: Score on a scale arithmetic mean standard deviation	 ±	 ±	 ±

Reporting group values	Total		
Number of subjects	601		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female Male	348 253		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Reported	193 397 11		
Race Units: Subjects			
White Black or African American Asian Other Not Reported	534 50 1 5 11		
CMAI - Total Score			
CMAI is used to assess frequency of manifestations of agitated behaviors categorized into 3 distinct agitation factors (CMAI factors of agitation): Factor 1-Aggressive Behavior, Factor 2-Physically Nonaggressive Behavior, Factor 3-Verbally Agitated Behavior. Each of 29 items was rated on a 7-point scale of frequency ranging from 1=Never to 7=Several times an hour. CMAI total score was sum of ratings for all 29 items, ranged from 29 to 203. Higher score indicate greater frequency of manifestations of agitated behaviour.			
Units: Score on a scale arithmetic mean standard deviation	 -		
CGIS-Agitation Score			
The CGIS is an observer-rated scale that measures illness severity on a 7-point scale (score range: 1-7, where 1 = normal, not at all ill; 7 = among the most extremely ill subjects).			
Units: Score on a scale arithmetic mean standard deviation	 -		

Subject analysis sets	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation Cohen-Mansfield Agitation Inventory (CMAI) total score during treatment period.

Subject analysis set title	AVP-786-28 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation CMAI total score during treatment period.

Subject analysis set title	AVP-786-42.63 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation CMAI total score during treatment period.

Reporting group values	Placebo	AVP-786-28 mg	AVP-786-42.63 mg
Number of subjects	164	148	149
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Not Reported			
Race Units: Subjects			
White Black or African American Asian Other Not Reported			
CMAI - Total Score			
CMAI is used to assess frequency of manifestations of agitated behaviors categorized into 3 distinct agitation factors (CMAI factors of agitation): Factor 1-Aggressive Behavior, Factor 2-Physically Nonaggressive Behavior, Factor 3-Verbally Agitated Behavior. Each of 29 items was rated on a 7-point scale of frequency ranging from 1=Never to 7=Several times an hour. CMAI total score was sum of ratings for all 29 items, ranged from 29 to 203. Higher score indicate greater frequency of manifestations of agitated behaviour.			
Units: Score on a scale			

arithmetic mean	77.0	73.5	75.0
standard deviation	± 18.61	±	±
CGIS-Agitation Score			
The CGIS is an observer-rated scale that measures illness severity on a 7-point scale (score range: 1-7, where 1 = normal, not at all ill; 7 = among the most extremely ill subjects).			
Units: Score on a scale			
arithmetic mean	4.6	4.7	4.6
standard deviation	± 0.68	± 0.69	± 0.66

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received matched AVP-786 placebo capsules, orally, twice daily (BID) for the 12-week treatment period.

Reporting group title	AVP-786-28 mg

Reporting group description:

Following a 3-week titration schedule, subjects received AVP-786-18/4.9 capsules, orally, once a day (QD) for the first 7 days of the study, followed by AVP-786-18/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-28/4.9, capsules, BID for 9 weeks.

Reporting group title	AVP-786-42.63 mg

Reporting group description:

Following a 3-week titration schedule, subjects received AVP-786-28/4.9 capsules, orally, QD for the first 7 days of the study, followed by AVP-786-28/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-42.63/4.9, capsules, BID for 9 weeks.

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation Cohen-Mansfield Agitation Inventory (CMAI) total score during treatment period.

Subject analysis set title	AVP-786-28 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation CMAI total score during treatment period.

Subject analysis set title	AVP-786-42.63 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population included all randomised subjects who took at least one dose of double-blind medication in double-blind treatment period, were CMAI Factor 1 Aggressive Behavior agitated at baseline & who had a baseline & at least one post-randomisation CMAI total score during treatment period.

Primary: Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Total Score

End point title	Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Total Score

End point description:

CMAI is used to assess frequency of manifestations of agitated behaviors categorized into 3 distinct agitation factors (CMAI factors of agitation): Factor 1-Aggressive Behavior, Factor 2-Physically Nonaggressive Behavior, Factor 3-Verbally Agitated Behavior. Each of 29 items was rated on a 7-point scale of frequency ranging from 1=Never to 7=Several times an hour. CMAI total score was sum of ratings for all 29 items, ranged from 29 to 203. Higher score indicate greater frequency of manifestations of agitated behaviour. Negative change from baseline indicates improvement in condition. mITT population was used. Subjects analysed' signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Placebo	AVP-786-28 mg	AVP-786-42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	127	126	
Units: score on a scale				
least squares mean (standard error)	-18.0 (± 1.25)	-20.7 (± 1.32)	-19.7 (± 1.27)	

Statistical analyses

Statistical analysis title	Change from Baseline in CMAI Total Score
Comparison groups	Placebo v AVP-786-28 mg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.096
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	0.5

Notes:

[1] - MMRM model included fixed class-effect terms for treatment, site, baseline concomitant antipsychotic use, visit week; an interaction term of treatment by visit week; covariates-interaction term of baseline values of CMAI Total Score, Neuropsychiatric Inventory - agitation/aggression (NPI-AA) score by visit week, baseline CMAI Total Score, & NPI-AA score. Heterogeneous Toeplitz (TOEPH) variance-covariance was used.

Statistical analysis title	Change from Baseline in CMAI Total Score
Comparison groups	Placebo v AVP-786-42.63 mg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.302
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	1.5

Notes:

[2] - MMRM model included fixed class-effect terms for treatment, site, baseline concomitant antipsychotic use, visit week; an interaction term of treatment by visit week; covariates-interaction term of baseline values of CMAI Total Score, NPI-AA score by visit week, baseline CMAI Total Score, & NPI-AA score. Heterogeneous Toeplitz (TOEPH) variance-covariance was used.

Secondary: Change From Baseline to Week 12 in the Clinical Global Impression of Severity of Illness Scale for Agitation (CGIS-Agitation Score)

End point title	Change From Baseline to Week 12 in the Clinical Global Impression of Severity of Illness Scale for Agitation (CGIS-Agitation Score)

End point description:

The CGIS is an observer-rated scale that measures illness severity on a 7-point scale (score range: 1-7, where 1 = normal, not at all ill; 7 = among the most extremely ill subjects). A negative change from baseline indicates improvement in condition. mITT population was used. 'Subjects analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	AVP-786-28 mg	AVP-786-42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	127	125	
Units: score on a scale				
least squares mean (standard error)	-0.9 (± 0.09)	-1.3 (± 0.09)	-1.1 (± 0.09)	

Statistical analyses

Statistical analysis title	Change From Baseline in the CGIS-Agitation score
Comparison groups	Placebo v AVP-786-28 mg
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1

Notes:

[3] - MMRM included fixed class-effect terms for treatment, site, baseline CGIS-Agitation, NPI-AA Score, baseline concomitant antipsychotic use, visit week; an interaction term of treatment by visit week; covariates: interaction term of baseline values of CGIS-Agitation, Score NPI-AA score by visit week. Compound Symmetry (CS) variance-covariance was used.

Statistical analysis title	Change From Baseline in the CGIS-Agitation score

Comparison groups	Placebo v AVP-786-42.63 mg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.056
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0

Notes:

[4] - MMRM included fixed class-effect terms for treatment, site, baseline CGIS-Agitation, NPI-AA Score, baseline concomitant antipsychotic use, visit week; an interaction term of treatment by visit week; covariates: interaction term of baseline values of CGIS-Agitation, Score NPI-AA score by visit week. Compound Symmetry (CS) variance-covariance was used.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of the study drug up to 30 days after last dose of study drug (up to Week 16)	
Adverse event reporting additional description:	
Safety population included all randomised subjects who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matched AVP-786 placebo capsules twice daily (BID) for the 12-week treatment period.	
Reporting group title	AVP-786-28 mg
Reporting group description:	
Following a 3-week titration schedule, subjects received AVP-786-18/4.9 capsules, orally, once a day (QD) for the first 7 days of the study, followed by AVP-786-18/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-28/4.9, capsules, BID for 9 weeks.	
Reporting group title	AVP-786-42.63 mg
Reporting group description:	
Following a 3-week titration schedule, subjects received AVP-786-28/4.9 capsules, orally, QD for the first 7 days of the study, followed by AVP-786-28/4.9, capsules, BID for the next 14 days. Beginning on Day 22, subjects received AVP-786-42.63/4.9, capsules, BID for 9 weeks.	

Serious adverse events	Placebo	AVP-786-28 mg	AVP-786-42.63 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 216 (2.31%)	7 / 197 (3.55%)	8 / 186 (4.30%)
number of deaths (all causes)	3	1	0
number of deaths resulting from adverse events	3	1	0
Investigations			
Streptococcus test positive			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer recurrent			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 216 (0.00%)	2 / 197 (1.02%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 216 (0.46%)	0 / 197 (0.00%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 216 (0.46%)	0 / 197 (0.00%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			

subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	1 / 216 (0.46%)	0 / 197 (0.00%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aggression			
subjects affected / exposed	1 / 216 (0.46%)	0 / 197 (0.00%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 216 (0.00%)	1 / 197 (0.51%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 216 (0.00%)	0 / 197 (0.00%)	1 / 186 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 197 (0.00%)	0 / 186 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	AVP-786-28 mg	AVP-786-42.63 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 216 (8.33%)	19 / 197 (9.64%)	22 / 186 (11.83%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 216 (2.78%)	16 / 197 (8.12%)	15 / 186 (8.06%)
occurrences (all)	7	22	20
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	14 / 216 (6.48%)	4 / 197 (2.03%)	10 / 186 (5.38%)
occurrences (all)	16	5	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2017	1. Removed the following secondary efficacy endpoints: change from baseline to week 12 in Zarit Burden Interview (ZBI), Cornell Scale for Depression in Dementia (CSDD), and General Medical Health Rating (GMHR). 2. Removed the Time Up and Go (TUG) test from the safety assessments. 3. Clarified that the CSDD and TUG test administered only at the Screening visit and not at follow-up visits. 4. The CSDD used as a screening tool for major depression and the TUG test as a tool for assessing risk of falls. 5. Removed the ADAS-cog, MMSE, ADCS-CGIC Overall, CSDD, and TUG test assessment at Visit 4 (Week 6). 6. Also, removed the ADCS-CGIC Overall assessment at Visit 4 (Week 6) and clarified that change from baseline will be assessed only at Visit 6 (Week 12).
17 July 2018	1. Provided a single, global protocol for use in all countries. 2. The number of study centers was revised from 70 centers outside the US to 90 centers worldwide (including North America). 3. Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) removed as secondary efficacy measure. 4. Removed reference to Study 12-AVR-131. 5. Inclusion criteria updated to include clarification that a subject's authorized representative was based on the applicable local regulations.
05 October 2018	1. The study objectives were clarified with descriptions of primary and secondary objectives. 2. Added clarification defining the end of trial as the date of the last patient last visit. 3. Country removed from randomization stratification due to potential randomization unbalance among treatment groups. 4. Updated to remove reference to study 15-AVP-786-303 and included a reference to a potential long-term extension study for some subjects. 5. Inclusion Criterion: #9 was updated to include a full definition of women of childbearing potential and clarify acceptable forms of birth control. A specific statement was also added to clarify that women who were lactating, pregnant or plan to become pregnant were excluded. 6. Exclusion Criteria: #6 and #7 were clarified as sub-bullets under Exclusion Criteria #5. In addition, the information about the review of the electrocardiogram (ECG) for screening and baseline were updated to define how the reviews will be performed to determine eligibility for study enrollment.

30 March 2020	1.Removed secondary endpoints: Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Rating (mADCS-CGIC-Agitation), Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Rating (ADCS-CGIC Overall), Dementia Quality of Life (DEMQOL), Resource Utilization in Dementia (RUD). 2. Sample size calculations have been updated to address an increase in the dropout and non-evaluable rate from 15% to 20%. 3. Removed the mADCS-CGIC-Agitation, DEMQOL,RUD, and ADCS-CGIC-Overall assessments. 4. Removed 'in clinic' requirement for administration of study medication at visits other than Baseline. 5. Clarified terminology for the development of AVP-786 for the treatment of neuropsychiatric conditions. 6. Updated the number of subjects enrolled to 550. 7. Randomization/Stratification updated to reduce and optimize the type and number of stratification factors. 8. Inclusion Criteria and exclusion criteria were updated. 9. Removed information indicating that concomitant use of short acting benzodiazepines was allowed, as these were no longer permitted. 10. Removed the allowance to use rescue medication (lorazepam).
27 January 2022	1. Sponsor information was updated from Avanir Pharmaceuticals, Inc. to Otsuka Pharmaceutical Development & Commercialization, Inc. 2. Summary of Changes table was added.
11 May 2023	1. Brexpiprazole was added to the list of Prohibited Concomitant Medications. 2. The definition of the mITT population was updated for consistency with the statistical analysis plan (SAP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported