Clinical trial results:
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

Summary

EudraCT number	2017-002455-29
Trial protocol	HU ES FR PL BG CZ IT
Global end of trial date	05 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	15-AVP-786-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02446132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Blvd, Rockville, MD, United States, 20850
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 8446878522, clinicaltransparency@otsuka-us.com
Scientific contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 8446878522, clinicaltransparency@otsuka-us.com

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	05 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2024
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 long-term safety and maintenance of efficacy of AVP-786 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	12 November 2015
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: 1191
Worldwide total number of subjects	1191
EEA total number of subjects	0

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	109
From 65 to 84 years	950
85 years and over	132

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 217 clinical sites in the North America and Europe from 13 November 2015 to 06 September 2024.

Pre-assignment

Screening details:

Of the 1197 subjects who were enrolled for the study, 1191 subjects received the study treatment, and 6 subjects did not receive the study drug. All eligible subjects received AVP-786-42.63/4.9, AVP-786-28/4.9, or AVP-786-18/4.9 depending on the last treatment received in the preceding study 15-AVP-786-301, 15-AVP-786-302, and 17-AVP-786-305.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AVP-786 18 milligrams (mg)

Arm description:

Subjects who received AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-18 (d6-DM 18 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

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

Dosage and administration details:

AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) capsules were administered twice a day for 52-weeks.

Arm title	AVP-786 28 mg

Arm description:

Subjects who received AVP-786-28 (d6-DM 28 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-28 (d6-DM 28 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

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

Dosage and administration details:

AVP-786-28 (d6-DM 28 mg/Q 4.9 mg) capsules were administered twice a day for 52-weeks.

Arm title	AVP-786 42.63 mg

Arm description:

Subjects who received placebo in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) and those who had delayed enrolment,

started AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) in the current study and were eventually titrated to receive AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg) capsules, twice a day for 52 weeks.

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

Dosage and administration details:

AVP-786-42.63 (d6-DM 42.63mg/Q 4.9 mg) capsules were administered twice a day for 52-weeks.

Number of subjects in period 1	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg
Started	166	516	509
Completed	109	332	324
Not completed	57	184	185
Adverse event, serious fatal	2	13	10
Physician decision	1	8	13
Consent withdrawn by subject	11	29	25
Trial Site Terminated by Sponsor	6	4	5
Adverse event, non-fatal	10	27	27
Non-compliance With Study Drug	2	2	3
Study Subject Withdrawal by Parent or Guardian	14	36	22
Study Terminated by Sponsor	4	35	58
Lost to follow-up	2	4	5
Reason not Specified	4	16	10
Lack of efficacy	1	10	6
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AVP-786 18 milligrams (mg)
Reporting group description:	
Subjects who received AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-18 (d6-DM 18 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.	
Reporting group title	AVP-786 28 mg
Reporting group description:	
Subjects who received AVP-786-28 (d6-DM 28 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-28 (d6-DM 28 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.	
Reporting group title	AVP-786 42.63 mg
Reporting group description:	
Subjects who received placebo in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) and those who had delayed enrolment, started AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) in the current study and were eventually titrated to receive AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg) capsules, twice a day for 52 weeks.	

Reporting group values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg
Number of subjects	166	516	509
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74.1	75.6	75.0
standard deviation	± 8.1	± 7.9	± 7.5
Gender categorical Units: Subjects			
Female	95	286	295
Male	71	230	214
Race Units: Subjects			
White	151	473	476
Black or African American	13	29	24
Asian	2	4	2
American Indian or Alaska Native	0	1	0
Native Hawaiian or Other Pacific Islander	0	1	0
Other	0	4	2
Missing	0	4	5
Ethnicity Units: Subjects			
Hispanic or Latino	69	215	278
Not Hispanic or Latino	97	297	226
Missing	0	4	5

Reporting group values	Total		
Number of subjects	1191		
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	676		
Male	515		
Race Units: Subjects			
White	1100		
Black or African American	66		
Asian	8		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	1		
Other	6		
Missing	9		
Ethnicity Units: Subjects			
Hispanic or Latino	562		
Not Hispanic or Latino	620		
Missing	9		

End points

End points reporting groups

Reporting group title	AVP-786 18 milligrams (mg)

Reporting group description:

Subjects who received AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-18 (d6-DM 18 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

Reporting group title	AVP-786 28 mg

Reporting group description:

Subjects who received AVP-786-28 (d6-DM 28 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-28 (d6-DM 28 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

Reporting group title	AVP-786 42.63 mg

Reporting group description:

Subjects who received placebo in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) and those who had delayed enrolment, started AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) in the current study and were eventually titrated to receive AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg) capsules, twice a day for 52 weeks.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE)is any untoward medical occurrence or unintended change (e.g. physical, psychological, or behavioral), including inter-current illness, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including any clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A TEAE is defined as an AE that occurred or worsened after the first dose of study treatment up until 30 days after last dose. Safety population included all subjects who received the study treatment.

End point type	Primary

End point timeframe:

From first dose of study drug (in current study) up to 3 months after last dose of study drug (up to Week 64)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: Subjects	109	304	292	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious TEAE

End point title	Number of Subjects With Serious TEAE[2]

End point description:

A serious adverse event (SAE) is any AE occurring at any dose that results in death, life-threatening experience, persistent or significant disability/incapacity, in-patient hospitalization or prolongation of hospitalization or congenital anomaly/birth defect. A serious TEAE is defined as AE that occurred or worsened after the first dose of study treatment up until 30 days after last dose. Safety population included all subjects who received the study treatment.

End point type	Primary

End point timeframe:

From first dose of study drug (in current study) up to 3 months after last dose of study drug (up to Week 64)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: subjects	22	75	70	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Laboratory Test Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Test Abnormalities[3]

End point description:

Laboratory assessments included clinical chemistry (alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, blood urea nitrogen, calcium, carbon dioxide, cholesterol, creatinine kinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, magnesium, protein, potassium, sodium, triglycerides and uric acid), hematology (basophils, eosinophils/leukocytes, erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, lymphocytes/leukocytes, monocytes, monocytes/leukocytes, neutrophils/leukocytes, platelets). Number of subjects with clinically significant laboratory test abnormalities were reported as per criteria defined in statistical analysis plan (SAP). Safety population included all subjects who received the study treatment. Number of subjects analysed' indicates the unique subjects who were evaluated for this outcome measure. 'n' indicates number of subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

Baseline (current study) up to 52 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: subjects				
Alanine aminotransferase: ≥3X ULN (n=164,510,508)	1	0	1	
Albumin: ≤26 g/L (n=164,510,508)	3	1	2	
Albumin (g/L): ≥60 g/L (n=164,510,508)	1	0	0	
Alkaline Phosphatase: ≥3X ULN (n=164,510,508)	1	0	1	
Aspartate Aminotransferase:≥3XULN (n=164,510,507)	2	0	0	
Bilirubin: 5X ULN (n=164,510,508)	0	2	4	
Blood Urea Nitrogen:≥10.71 mmol/L (n=158,450,398)	19	78	63	
Calcium: ≤1.75 mmol/L (n=164,508,508)	0	1	0	
Calcium: ≥3.0 mmol/L (n=164,508,508)	0	1	0	
Carbon Dioxide: >40 mmol/L (n=164,510,508)	0	0	1	
Cholesterol: ≥7.77 mmol/L (n=164,509,508)	7	19	18	
Creatine Kinase: ≥3X ULN (n=164,507,505)	2	4	4	
Creatinine: >132.6 umol/L (n=164,510,508)	8	53	26	
Gamma Glutamyl Transferase:≥60U/L (n=164,501,488)	13	52	51	
Glucose: ≤2.775 mmol/L (n=164,510,508)	3	9	4	
Glucose: ≥11.1 mmol/L (n=164,510,508)	22	71	79	
Lactate Dehydrogenase: ≥3X ULN (n=164,507,505)	0	1	2	
Magnesium: <0.37 mmol/L (n=164,505,503)	1	1	0	
Magnesium: >1.23 mmol/L (n=164,505,503)	0	0	1	
Potassium: ≤3.0 mmol/L (n=164,510,507)	2	4	2	
Potassium: ≥5.5 mmol/L (n=164,510,507)	6	32	34	
Protein: ≤50 g/L (n=164,510,508)	3	0	4	
Sodium: ≤130 mmol/L (n=164,510,508)	6	13	12	
Sodium: ≥155 mmol/L (n=164,510,508)	0	1	2	
Triglycerides: >3.39 mmol/L (n=164,508,508)	25	61	73	
Uric Acid (Female): ≥505.58 umol/L (n=94,282,295)	3	22	14	
Uric Acid (Male): ≥624.54 umol/L (n=70,226,213)	0	3	3	
Basophils: >0.3 x10^9/L (n=164,510,507)	0	1	1	
Eosinophils/Leukocytes: ≥10 % (n=164,509,505)	12	23	33	

Erythrocytes: ≤2.5 x10^12/L (n=164,510,507)	0	0	1	
Erythrocytes: ≥7.0 x10^12/L (n=164,510,507)	0	1	0	
Hematocrit:<0.3 proportion of 1.0 (n=164,510,507)	4	7	9	
Hematocrit:>0.5 proportion of 1.0 (n=164,510,507)	11	31	44	
Hemoglobin: <100 g/L (n=164,510,507)	5	15	15	
Hemoglobin: >180 g/L(n=164,510,507)	0	1	3	
Leukocytes: ≤2.8 x10^9/L (n=164,510,507)	2	7	3	
Leukocytes: ≥16 x10^9/L (n=164,510,507)	2	4	5	
Lymphocytes: ≤0.5 x10^9/L (n=164,510,507)	0	4	7	
Lymphocytes: >4 x10^9/L (n=164,510,507)	1	8	6	
Lymphocytes/Leukocytes: ≤10 % (n=164,509,505)	6	30	21	
Lymphocytes/Leukocytes: ≥60 % (n=164,509,505)	0	4	6	
Monocytes (10^9/L): >1 x10^9/L (n=164,510,507)	7	27	23	
Monocytes/Leukocytes: ≥15 % (n=164,509,505)	5	24	23	
Neutrophils/Leukocytes: ≤15 % (n=164,509,505)	0	1	1	
Platelets: ≤100 x10^9/L (n=164,510,507)	2	4	6	
Platelets: ≥700 x10^9/L (n=164,510,507)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant 12-lead Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant 12-lead Electrocardiogram (ECG) Abnormalities[4]

End point description:

A resting 12-lead ECG was performed for all the subjects. ECG data included PR interval (milliseconds {msec}) and QTcF (msec) along with change from baseline (CFB) in QTcF. Number of subjects with potentially clinically significant ECG abnormalities was reported as per the criteria defined in SAP. Safety population included all subjects who received the study treatment. 'Number of subjects analysed' indicates the unique subjects who were evaluated for this outcome measure. 'n' indicates number of subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

Baseline (current study) up to 52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: subjects				
PR Interval males,females:>200-≤22(n=162,503,192)	21	66	60	
PR Interval males,females:>220-≤25(n=162,503,192)	13	33	28	
PR Interval males,females:>250msec(n=162,503,1	5	13	9	
QTcF (males):>450 to ≤480 msec (n=68,222,207)	9	28	23	
QTcF (males): >480 to ≤500 msec (n=68,222,207)	2	2	1	
QTcF (females):>470 to ≤485 msec (n=94, 282, 292)	3	12	10	
QTcF (females):>485 to ≤500 msec (n=94, 282, 292)	0	4	2	
QTcF (females): >500 msec (n=94, 282, 292)	0	1	1	
QTcF CFB (male and females):≥30 (n=162, 504, 499)	18	64	66	
QTcF CFB (male and females):≥60 (n=162, 504, 499)	1	5	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Any Abnormal, Clinically Significant Physical and Neurological Examination Finding

End point title	Number of Subjects With Any Abnormal, Clinically Significant Physical and Neurological Examination Finding[5]

End point description:

The physical examination included assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination included assessments of mental status, cranial nerves, motor system, reflexes, coordination, gait and station, and sensory system. Safety population included all subects who received the study treatment.

End point type	Primary

End point timeframe:

Baseline, Week 52

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: subjects	2	4	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities in Vital Signs[6]

End point description:

Vital signs measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Blood pressure (i.e., SBP, DBP) and heart rate were measured in the supine and standing positions after the subject had been in each position for at least 5 and 3 minutes, respectively. Number of subjects with clinically significant vital sign abnormalities were reported as per criteria defined in SAP. The categories with at least one subject with clinically significant vital signs abnormalities are reported here. Safety population included all subjects who received the study treatment. 'Number of subjects analysed' indicates the unique subjects who were evaluated for this outcome measure. 'n' indicates number of subjects evaluable for the specified category.

End point type	Primary

End point timeframe:

Baseline (current study) up to 52 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	516	509	
Units: subjects				
SBP:≤90&≥20 decrease from baseline(n=164,507,509)	5	18	14	
SBP:>180&≥20increase from baseline(n=164,507,509)	0	6	4	
DBP:≤50&≥15decrease from baseline (n=164,507,509)	4	8	8	
DBP:≥105&≥15increase from baseline(n=164,507,509)	2	3	8	
HR:≤50&≥15decrease from baseline (n=164,507,509)	0	7	7	
HR:≥120&≥15increase from baseline (n=164,507,509)	0	4	1	
SBP≥10&HR≥5increase from baseline (n=164,507,509)	53	147	155	
DBP≥5&HR≥5increase from baseline (n=164,507,509)	61	239	225	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in the Sheehan Suicidality Tracking Scale (S-STS) Score at Week 64

End point title	Change From Baseline in the Sheehan Suicidality Tracking Scale (S-STS) Score at Week 64[7]

End point description:

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: 0 = Not at all, 1 = A little, 2 = Moderate, 3 = Very, 4 = Extremely. Higher scores indicate greater severity of suicidal ideation and/or behavior. A negative change from baseline reflects a reduction in suicidal thoughts or behaviors over time. Safety population included all subjects who received the study treatment. 'Subjects analysed' indicates the number of subjects evaluable for the outcome measure at the specified time point.

End point type	Primary

End point timeframe:

Baseline (current study), Week 64

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	276	304	
Units: score on a scale				
arithmetic mean (standard deviation)				
Total Score	-0.0 (± 0.1)	0.0 (± 0.1)	-0.0 (± 0.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in the Mini-Mental State Examination (MMSE) Score at Week 52

End point title	Change From Baseline in the Mini-Mental State Examination (MMSE) Score at Week 52[8]

End point description:

The MMSE is a brief questionnaire that is used to assess 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 subject's cognitive state and are scored as follows: 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 was calculated by summing all of the item scores and ranges from 0 to 30. Higher scores indicate milder cognitive impairment. Negative change from baseline

indicates decline in cognitive performance. Safety population included all subjects who received the study treatment. 'Subjects analysed' indicates the number of subjects evaluable for the outcome measure at the specified time point.

End point type	Primary

End point timeframe:

Baseline (current study), Week 52

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121	372	366	
Units: score on a scale				
arithmetic mean (standard deviation)	-0.8 (± 4.6)	-0.7 (± 4.9)	-0.1 (± 4.1)	

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in the Epworth Sleepiness Scale (ESS) Score at Week 52

End point title	Change From Baseline in the Epworth Sleepiness Scale (ESS) Score at Week 52[9]

End point description:

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 8 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. The scores are summed to give an overall score of 0 to 24 . A total score of 0 to 9 is considered to be normal. Higher score indicates greater daytime sleepiness. Negative change from baseline indicate improvement in daytime sleepiness. Safety population included all subjects who received the study treatment. 'Subjects analysed' indicates the number of subjects evaluable for the outcome measure at the specified time point.

End point type	Primary

End point timeframe:

Baseline (current study), Week 52

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	297	338	
Units: score on a scale				
arithmetic mean (standard deviation)	-0.01 (± 4.43)	0.07 (± 4.39)	0.50 (± 3.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Cohen-Mansfield Agitation Inventory (CMAI) Composite Score at Week 64

End point title	Change From Baseline in the Cohen-Mansfield Agitation Inventory (CMAI) Composite Score at Week 64

End point description:

The CMAI is used to assess the frequency of manifestations of agitated behaviors in elderly persons. It consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. These distinct agitation syndromes include aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior. Each of the 29 items is rated on a 7-point scale of frequency (1 = never, 2 = less than once a week but still occurring, 3 = once or twice a week, 4 = several times a week, 5 = once or twice a day, 6 = several times a day, 7 = several times an hour). The ratings are based on the 2 weeks preceding assessment of the CMAI. Higher scores indicate higher frequency of agitated behaviours while lower scores indicate lower frequency of agitated behaviours.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 64

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[10] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[11] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[12] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Agitation/Aggression, Irritability/Lability, and Aberrant Motor Behavior Domain Scores of the Neuropsychiatric Inventory (NPI) at Week 52

End point title	Change From Baseline in the Agitation/Aggression, Irritability/Lability, and Aberrant Motor Behavior Domain Scores of the Neuropsychiatric Inventory (NPI) at Week 52

End point description:

The NPI is a validated clinical instrument used to assess neuropsychiatric symptoms. It evaluates 12 neuropsychiatric symptom domains including 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. Each symptom domain is rated by the caregiver based on the frequency (1 to 4) and severity (1 to 3) of symptoms, and a composite domain score is calculated by multiplying frequency and severity (range: 1–12). Additionally, caregiver distress for each positive symptom domain is rated on a 6-point scale (0 = not at all distressing, 5 = extremely distressing). In this study, the three NPI domains assessed were agitation/aggression, irritability/lability, and aberrant motor behavior. Higher scores indicate greater severity and frequency of neuropsychiatric symptoms.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[13] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[14] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[15] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change-Agitation (mADCS-CGIC-Agitation) Score at Week 64

End point title	Change From Baseline in the Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change-Agitation (mADCS-CGIC-Agitation) Score at Week 64

End point description:

The mADCS-CGIC-Agitation is used to assess agitation in individuals with Alzheimer's disease. It includes questions focused on agitation and uses a semi-structured interview format involving both the subject and their caregiver. The clinician rates the subject's overall clinical status using a 7-point scale: 1 = marked improvement, 2 = moderate improvement, 3 = minimal improvement, 4 = no change, 5 = minimal worsening, 6 = moderate worsening, and 7 = marked worsening. Lower scores indicate improvement in agitation symptoms, while higher scores indicate worsening.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 64

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[16] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[17] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[18] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Clinical Global Impression of Severity of Illness (CGIS)-Agitation Domain Score at Week 52

End point title	Change From Baseline in the Clinical Global Impression of Severity of Illness (CGIS)-Agitation Domain Score at Week 52

End point description:

The CGIS is an observer-rated scale that measures illness severity. The CGIS-Agitation is a 7-point (1-7) scale (1 = normal, not at all ill; 7 = extremely ill) that assessed the severity of agitation in this study. Higher scores indicate severe agitation, while the lower scores indicate little or no agitation.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[19] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[20] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[21] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Patient Global Impression of Change (PGIC) Score at Week 52

End point title	Change From Baseline in the Patient Global Impression of Change (PGIC) Score at Week 52

End point description:

The PGIC is a 7-point scale used to assess perceived treatment response, as evaluated by the subject's caregiver. The caregiver rates the overall change in the subject's condition since the start of treatment. The PGIC score ranges from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Lower scores reflect greater improvement, while higher scores indicate worsening of the sucondition.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[22] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[23] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[24] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Dementia Quality of Life (DEMQOL) Score at Week 52

End point title	Change From Baseline in the Dementia Quality of Life (DEMQOL) Score at Week 52

End point description:

The DEMQOL is a validated scale used to assess health-related quality of life in individuals with dementia and their caregivers. It includes two versions: a 28-item version completed by the subject (DEMQOL), and a 31-item proxy version completed by the caregiver (DEMQOL-proxy). Each item is rated using a 4-point scale to reflect the frequency or severity of health-related concerns: 1 = A lot, 2 = Quite a bit, 3 = A little, 4 = Not at all. Total score is derived by sum of all item scores, excluding item 29 of DEMQOL and item 32 of DEMQOL-proxy. Lower scores indicate better quality of life.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	0[26]	0[27]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[25] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[26] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[27] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Resource Utilization in Dementia (RUD) Score at Week 52

End point title	Change From Baseline in the Resource Utilization in Dementia (RUD) Score at Week 52

End point description:

The RUD is a standardized tool used to estimate healthcare costs associated with dementia. It assesses the use of both formal and informal (e.g., hospitalizations, doctor visits, living assistance, and unprofessional caregiver time) healthcare resources. The instrument is administered as a semi-structured interview with the subject's primary caregiver. It consists of two main sections: one evaluates the caregiver’s burden, including lost work and leisure time, and the other documents the subjetc's use of healthcare services. Total healthcare costs are calculated by multiplying the quantity of resources used (e.g., number of doctor visits, hours of caregiver, nights in accommodation) by unit costs. Higher estimated totals reflect greater economic impact associated with dementia care.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[28] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[29] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[30] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the EuroQol 5-Dimension 5-Level (EQ-5D-5L) for Subjects From Study 17-AVP-786-305 at Week 52

End point title	Change From Baseline in the EuroQol 5-Dimension 5-Level (EQ-5D-5L) for Subjects From Study 17-AVP-786-305 at Week 52

End point description:

The EQ-5D-5L is a standardized questionnaire used to assess health-related quality of life. It consists of two components: a descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The descriptive

system covers five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-level scale: 1 = No problems, 2 = Slight problems, 3 = Moderate problems, 4 = Severe problems, 5 = Extreme problems. The EQ VAS component allows subjects or caregivers to rate the individual's overall health on a vertical scale from 0 (the worst imaginable health state) to 100 (the best imaginable health state). Only subjects from Study 17-AVP-786-305 with a MMSE score of 10 or higher at the baseline visit were planned to complete the subject-rated version.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 52

End point values	AVP-786 18 milligrams (mg)	AVP-786 28 mg	AVP-786 42.63 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[31]	0[32]	0[33]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[31] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[32] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.
[33] - As AVP-786 development discontinued, no efficacy data was collected, only safety data was analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (in current study) up to 3 months after last dose of study drug (up to Week 64)

Adverse event reporting additional description:

Safety population included all subjects who received the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	AVP-786-18

Reporting group description:

Subjects who received AVP-786-18 (d6-DM 18 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-18 (d6-DM 18 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

Reporting group title	AVP-786-42.63

Reporting group description:

Subjects who received placebo in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) and those who had delayed enrolment, started AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) in the current study and were eventually titrated to receive AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg) capsules, twice a day for 52 weeks.

Reporting group title	AVP-786-28

Reporting group description:

Subjects who received AVP-786-28 (d6-DM 28 mg/Q 4.9 mg) capsules in the previous studies 15-AVP-786-301 (NCT02442765), 15-AVP-786-302 (NCT02442778), or 17-AVP-786-305 (NCT03393520) continued to receive AVP-786-28 (d6-DM 28 mg/Q 4.9 mg), capsules, twice a day for 52 weeks in the current study.

Serious adverse events	AVP-786-18	AVP-786-42.63	AVP-786-28
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 166 (13.25%)	70 / 509 (13.75%)	75 / 516 (14.53%)
number of deaths (all causes)	4	16	22
number of deaths resulting from adverse events	2	11	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Follicular thyroid cancer			

subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Renal cancer			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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	1 / 166 (0.60%)	2 / 509 (0.39%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Femoral artery aneurysm			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Asthenia			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Disease progression			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Inflammation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Acute respiratory failure			
subjects affected / exposed	1 / 166 (0.60%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Pneumothorax			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis aspiration			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Pulmonary oedema			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Respiratory failure			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			

Aggression			
subjects affected / exposed	1 / 166 (0.60%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	4 / 166 (2.41%)	4 / 509 (0.79%)	6 / 516 (1.16%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 166 (0.00%)	4 / 509 (0.79%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance in social behaviour			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphemia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Suicidal ideation			

subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
QRS axis abnormal			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Blood osmolarity increased			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Cervical vertebral fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
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 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	4 / 516 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Femur fracture			
subjects affected / exposed	0 / 166 (0.00%)	3 / 509 (0.59%)	3 / 516 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 166 (1.20%)	5 / 509 (0.98%)	12 / 516 (2.33%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Incisional hernia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Ligament rupture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Intentional medical device removal by patient			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Spinal fracture			

subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Rib fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Skin laceration			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Wound dehiscence			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bundle branch block right			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Bundle branch block left			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 166 (0.60%)	2 / 509 (0.39%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus bradycardia			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary valve stenosis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Nervous system disorders			
Basal ganglia haematoma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Balance disorder			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain hypoxia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Depressed level of consciousness			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dementia Alzheimer's type			
subjects affected / exposed	1 / 166 (0.60%)	1 / 509 (0.20%)	3 / 516 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Dementia			

subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dysstasia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Ischaemic stroke			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Neurodegenerative disorder			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic encephalopathy			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Guillain-Barre syndrome			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 166 (1.81%)	4 / 509 (0.79%)	4 / 516 (0.78%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Leukocytosis			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Thrombocytosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 166 (0.00%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus of small bowel			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Gastric ulcer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Faecaloma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Dysphagia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Melaena			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Inguinal hernia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	3 / 516 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Acute kidney injury			
subjects affected / exposed	1 / 166 (0.60%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract obstruction			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 166 (0.00%)	4 / 509 (0.79%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic bladder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Musculoskeletal stiffness			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Bacteraemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Colonic abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Cellulitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lower respiratory tract infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
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 aspiration			

subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	2 / 516 (0.39%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia viral			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Psoas abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Cystitis			
subjects affected / exposed	1 / 166 (0.60%)	2 / 509 (0.39%)	0 / 516 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyuria			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	2 / 166 (1.20%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	0 / 516 (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
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Necrotising fasciitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
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 / 166 (0.60%)	8 / 509 (1.57%)	3 / 516 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 166 (1.81%)	7 / 509 (1.38%)	5 / 516 (0.97%)
occurrences causally related to treatment / all	0 / 3	0 / 9	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Wound infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	5 / 516 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyponatraemia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 166 (0.00%)	1 / 509 (0.20%)	0 / 516 (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
Lactic acidosis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 509 (0.00%)	1 / 516 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AVP-786-18	AVP-786-42.63	AVP-786-28
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 166 (32.53%)	149 / 509 (29.27%)	150 / 516 (29.07%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 166 (6.02%)	11 / 509 (2.16%)	16 / 516 (3.10%)
occurrences (all)	11	17	23
Fall			
subjects affected / exposed	27 / 166 (16.27%)	60 / 509 (11.79%)	79 / 516 (15.31%)
occurrences (all)	50	99	181
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 166 (6.02%)	17 / 509 (3.34%)	14 / 516 (2.71%)
occurrences (all)	11	20	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 166 (6.02%)	26 / 509 (5.11%)	28 / 516 (5.43%)
occurrences (all)	12	32	31
Psychiatric disorders			
Agitation			
subjects affected / exposed	10 / 166 (6.02%)	39 / 509 (7.66%)	32 / 516 (6.20%)
occurrences (all)	15	56	85
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 166 (7.83%)	43 / 509 (8.45%)	45 / 516 (8.72%)
occurrences (all)	19	56	61

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2015	Revised footnotes to specify that the EQ5D5L, DEMQOL, and ADASCog assessments were to be performed only for subjects with an MMSE score of ≥10 at baseline, rather than at the visit. A new footnote required thyroid function tests (TSH, and reflex T3 and T4 if TSH was abnormal) at the baseline visit for subjects from Study 12AVR131. An exclusion criterion was added for subjects with a serious risk of suicide based on the SSTS. Clarified that study medication was to be administered by a caregiver, family member, nursing staff, or selfadministered under supervision, with dosing times recorded in a diary. Reporting requirements specified that any death during the study or within 30 days after treatment discontinuation had to be reported to the sponsor. Laboratory updates included adding leucocyte esterase and nitrates to urinalysis and reiterating baseline thyroid function testing for eligible subjects . For suicidality monitoring, any change in SSTS score indicating suicidality had to be evaluated and reported. Clarified that DEMQOL was a 28item questionnaire for subjects with MMSE ≥10 at baseline and that the EQ5D5L subject version applied only to subjects meeting this baseline MMSE criterion.
01 October 2015	The CMAI was added as a new efficacy measure, and the CGIC assessment was separated into Overall Clinical Status (ADCSCGICOverall) and agitation syndrome (mADCSCGICAgitation). The EQ5D5L scale was removed from all assessments. For subjects from study 12AVR131, a screening period of up to four weeks was introduced, and the number of scheduled visits was updated to up to nine. The Schedule of Evaluations and Visits was revised, separating tables for Study 12AVR131 from those for studies 15AVP786301 and 302, adding a screening visit for the former, introducing CMAI assessments at specific visits, and deleting certain measures such as ZBI, PGIC, mADCSCGICAgitation, CGIS, NPI, EQ5D5L, and MMSE at Visit 7. Deleted the ZBI at Visits 4 and 6 and EQ-5D-5L at all visits. Inclusion criterion 6 and 9 and exclusion criteria 5 and 7 were updated. Specified that dose can be adjusted after Day 22 at any time during the study. Several scales, including NPI, CGIS Agitation, ADCS CGIC Overall, mADCS CGIC Agitation, ZBI, PGIC, CSDD, and GMHR, had revised schedules, scoring clarifications, or visit changes. Efficacy analyses were updated to reflect the addition of CMAI, the separation of CGIC assessments, and the removal of EQ5D5L.
16 May 2016	Refined the dosing regimen for subjects on placebo in preceding studies and those from Study 12AVR131. The number of clinic visits increased from up to nine to up to thirteen. Additional assessments such as vital signs, SSTS, ESS, drug administration in clinic, and medication/diary review were added. The Epworth Sleepiness Scale (ESS) was added as a safety measure, and the Alzheimer's Disease Cooperative StudyActivities of Daily Living Inventory (ADCSADL) replaced the IADL as an efficacy measure. Inclusion and exclusion criteria were updated, which includes lowering the upper age limit to 90 for certain subjects , adjusting MMSE score requirements, extending stabledose requirements, and clarifying the handling of PVCs. ECG requirements were updated for calculating QTcF changes based on priorstudy or baseline measurements. Concomitant medication rules were revised to allow initiation or adjustment of Alzheimer's disease treatments during the study. Safety procedures were expanded to include orthostatic vital signs, clarified physical/neurological exam elements, revised laboratory and pregnancy testing schedules, and specified ECG timing. The CMAI longform was confirmed for use, and additional caregiver input collected at Visit 4. The visit schedule and order of procedures were updated, and safety analysis plans were updated to incorporate ESS and report laboratory parameter shifts from baseline to end of treatment. Replaced the IADL with the ADCS-ADL

28 February 2017	Revised the planned enrollment to approximately 700 subjects at about 135 centers and updated the study duration to approximately 56 weeks, extending to about 64 weeks for around 100 subjects who had a followup visit three months after their last dose. Added AVP-786-42.63/4.9 dose. Safety procedures were clarified to include vital signs at all visits except Followup Visits and to specify that the Epworth Sleepiness Scale (ESS) would only be administered to subjects with an MMSE score of ≥10 at baseline. Efficacy assessments were expanded to include CMAI and mADCSCGIC at Followup Visits, with mADCSCGIC measuring change from the last treatment visit (Visit 8/ET). The description of the ADCSADL was clarified. Study procedures were updated to align with the revised schedule, adding inclinic followup visits and removing the prior 30day posttreatment followup phone call. The analysis population description was updated to reflect reporting by all four treatment groups, including the newly added AVP78642.63/4.9 arm.
23 October 2017	Increased the planned enrollment to approximately 1,000 subjects at about 250 centers globally and expanded eligibility to include subjects who successfully completed Study 17AVP786305 and were not participating in another study. The amendment clarified that the study was an extension trial also including subjects from Study 17AVP786305. For subjects who had received placebo in preceding studies and subjects from Study 12AVR131, treatment began with AVP78628/4.9 once daily for the first seven days, then twice daily for the next 14 days, and from Day 22 onward transitioned to AVP78642.63/4.9 twice daily unless adjusted after Day 22. Safety and tolerability measures were updated, removing ADAScog and TUG test, while efficacy assessments were updated to NPI, and EQ5D5L added for subjects from Study 17AVP786305. Several assessments including ADCSCGIC, ZBI, CSDD, GMHR, and ADCSADL were removed. Inclusion and exclusion criteria were revised to reflect the expanded population and clarified dose adjustment allowances for all subjects . Safety procedures were updated, including the removal of the "30day AE followup after last dose" rule due to the addition of an inclinic followup visit at that timepoint. The MMSE baseline was defined based on the preceding study, and several ESS visits were removed. Efficacy schedules for mADCSCGIC Agitation, NPI, and CMAI were revised, with the CMAI caregiver questionnaire removed.
01 February 2021	The itemized changes to procedures in the protocol described for each section are intended to decrease the study burden for subjects and their caregivers. To support this objective, as the analysis requirements will be met with the currently enrolled population, the mADCS-CGIC Agitation, RUD, and DEMQOL will no longer be administered following the implementation of Protocol Amendment 6. The amendment includes clarifications throughout the document where the population is described to state that subjects with Medical Monitor prior approval may delay enrollment into Study 15-AVP-786-303 but will be required to meet all screening and eligibility requirements prior to enrollment. As this is applied to more than Study 12-AVR-131, the wording has been simplified in the text to references to subjects who delay enrollment. Clarified throughout the document that pregnancy testing is to be conducted for "subjects " of childbearing potential. The appendices including samples of the study scales (as these are included in the Study Procedures Manual) and Declaration of Helsinki were removed. References were updated to align with changes in the text.
26 January 2022	The protocol was updated to reflect the change in sponsor from Avanir Pharmaceuticals, Inc. to Otsuka Pharmaceutical Development & Commercialization, Inc.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated due to discontinuation of development of the AVP-786 compound.

Notes: