

**Clinical trial results:****A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-arm Study to Assess the Efficacy, Safety, and Tolerability of AVP-786 (Deudextromethorphan hydrobromide [d6-DM]/Quinidine sulfate [Q]) for the Treatment of Negative Symptoms of Schizophrenia****Summary**

EudraCT number	2021-001352-33
Trial protocol	BG PL ES
Global end of trial date	23 May 2023

Results information

Result version number	v1 (current)
This version publication date	15 June 2024
First version publication date	15 June 2024

Trial information**Trial identification**

Sponsor protocol code	18-AVP-786-207
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03896945
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 124525

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Blvd, Rockville, United States, 20850
Public contact	Agitation Project Team, Otsuka Pharmaceutical Development & Commercialization, Inc., 585 319 7969, chirag.savla@otsuka-us.com
Scientific contact	Agitation Project Team, Otsuka Pharmaceutical Development & Commercialization, Inc., 585 319 7969, chirag.savla@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	23 May 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and tolerability of AVP-786, as compared with placebo, for the treatment of negative symptoms of schizophrenia.

Protection of trial subjects:

Each subject signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Bulgaria: 27
Country: Number of subjects enrolled	United States: 104
Country: Number of subjects enrolled	Puerto Rico: 1
Worldwide total number of subjects	136
EEA total number of subjects	31

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)	136
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in this study at 65 investigative sites in Bulgaria, Poland, and the United States including Puerto Rico from 15 February 2019 to 23 May 2023.

Pre-assignment

Screening details:

Subjects with schizophrenia were enrolled in Phase A: Placebo run-in period. On completing Phase A, subjects were randomised in a 1:1 ratio in Phase B: Double-blind treatment (DBT) period to receive AVP-786/placebo. In Phase A, subjects were classified as placebo responders & non-responders. Placebo responders were excluded from efficacy analysis.

Period 1

Period 1 title	Phase A: Placebo Run-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Arm title	Placebo (Run-in Period)
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Arm description:

Subjects received AVP-786 matching placebo capsules, orally, twice a day (BID) over a 3-week run-in period.

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

Dosage and administration details:

Oral capsules, BID during 3-week run-in period.

Number of subjects in period 1	Placebo (Run-in Period)
Started	136
Placebo Responders	10 ^[1]
Placebo Non-Responders	115 ^[2]
Completed	125
Not completed	11
Non-compliance	1
Withdrawal by Subject	4
Lost to follow-up	2
Reason not Specified	3
Protocol deviation	1

Notes:

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

Justification: The participants who completed the Placebo Run-in Period (Phase A) were only classified as placebo responder or non-responders. Hence, the number reported for this milestone is less than the total number of participants who were enrolled in the study.

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

Justification: The participants who completed the Placebo Run-in Period (Phase A) were only classified as placebo responder or non-responders. Hence, the number reported for this milestone is less than the total number of participants who were enrolled in the study.

Period 2

Period 2 title	Phase B: Double-blind Treatment Period
Is this the baseline period?	Yes ^[3]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	AVP-786

Arm description:

Subjects received AVP-786-28/4.9 (deudextromethorphan hydrobromide (d6-DM) 28 milligrams (mg)/quinidine sulfate (Q) 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, once daily (QD) for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.

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:

Oral capsules, QD for 3 days followed by BID for the next 4 days. Following 1 week titration, BID for the remaining 11 weeks of the DBT period.

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

Dosage and administration details:

Oral capsules, QD for 3 days.

Arm title	Placebo
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Arm description:

Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.

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

Dosage and administration details:

Oral capsules, BID during 12-week DBT period.

Notes:

[3] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Participants who completed the Placebo run-in period (Phase A) were considered to be randomized in the study. All participants completing Phase A started the DBT period (Phase B). Hence, Phase B was considered to be the baseline period.

Number of subjects in period 2^[4]	AVP-786	Placebo
Started	65	60
Completed	57	52
Not completed	8	8
Noncompliance with Study Drug	-	2
Physician decision	1	-
Adverse Event	2	-
Withdrawal by Subject	3	4
Study Terminated by Sponsor	-	1
Protocol deviation	2	-
Lack of efficacy	-	1

Notes:

[4] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only the subjects randomized in the Double-blind Treatment Period were analyzed for baseline characteristics.

Baseline characteristics

Reporting groups

Reporting group title	AVP-786
Reporting group description:	
Subjects received AVP-786-28/4.9 (deudextromethorphan hydrobromide (d6-DM) 28 milligrams (mg)/quinidine sulfate (Q) 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, once daily (QD) for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.	
Reporting group title	Placebo
Reporting group description:	
Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.	

Reporting group values	AVP-786	Placebo	Total
Number of subjects	65	60	125
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	44.8	44.0	
standard deviation	± 9.54	± 10.25	-
Gender categorical			
Units: Subjects			
Female	20	24	44
Male	45	36	81
Ethnicity			
Units: Subjects			
Hispanic or Latino	6	7	13
Not Hispanic or Latino	42	40	82
Unknown or Not Reported	17	13	30
Race			
Units: Subjects			
White	14	12	26
Black or African American	33	34	67
Asian	1	0	1
Other	0	1	1
Missing	17	13	30

Patient Global Impression of Change (PGI-C) Score			
The PGI-C is 7-point (1-7) subject-rated scale used to assess treatment response with respect to schizophrenia as follows: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, or 7=very much worse. Missing PGI-C rating was not imputed. Modified Intent-To-Treat (mITT) population included all subjects who were placebo run-in nonresponders, randomised in Phase B and in the safety population with both Phase B baseline and at least 1 postbaseline PANSS measurement.			
Units: score on a scale arithmetic mean standard deviation		±	±

Subject analysis sets

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

Subject analysis set description:

Subjects received AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, QD for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.

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

Subject analysis set description:

Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.

Reporting group values	AVP-786	Placebo	
Number of subjects	61	54	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

Race			
Units: Subjects			
White			
Black or African American			
Asian			
Other			
Missing			
Patient Global Impression of Change (PGI-C) Score			
<p>The PGI-C is 7-point (1-7) subject-rated scale used to assess treatment response with respect to schizophrenia as follows: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, or 7=very much worse. Missing PGI-C rating was not imputed. Modified Intent-To-Treat (mITT) population included all subjects who were placebo run-in nonresponders, randomised in Phase B and in the safety population with both Phase B baseline and at least 1 postbaseline PANSS measurement.</p>			
Units: score on a scale			
arithmetic mean	3.3	3.5	
standard deviation	± 0.91	± 0.86	

End points

End points reporting groups

Reporting group title	Placebo (Run-in Period)
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Reporting group description:

Subjects received AVP-786 matching placebo capsules, orally, twice a day (BID) over a 3-week run-in period.

Reporting group title	AVP-786
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Reporting group description:

Subjects received AVP-786-28/4.9 (deudextromethorphan hydrobromide (d6-DM) 28 milligrams (mg)/quinidine sulfate (Q) 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, once daily (QD) for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.

Reporting group title	Placebo
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Reporting group description:

Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.

Subject analysis set title	AVP-786
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Subjects received AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, QD for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.

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

Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.

Primary: Change From Baseline (Week 3) to Week 15 in the Positive and Negative Syndrome Scale (PANSS) Marder Negative Factors Score

End point title	Change From Baseline (Week 3) to Week 15 in the Positive and Negative Syndrome Scale (PANSS) Marder Negative Factors Score
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End point description:

PANSS consists of 3 subscales: a total of 30 disparate items. Each item's severity was rated on 7-point scale, with 1=absence of symptoms & 7=extremely severe symptoms. PANSS marder negative factors score comprises 7 items of 30-item PANSS: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity & flow of conversation, motor retardation & active social avoidance. PANSS Negative Subscale score range is 7=absence of symptoms to 49=extremely severe symptoms. PANSS total score range=30-210, higher scores=more severe symptoms. Negative change from baseline=improvement. Baseline=end of placebo run-in period (Week 3) & the last assessment prior to first dose of study drug. mITT population=all subjects who were placebo run-in nonresponders, randomised in Phase B & in safety population with both Phase B baseline & at least 1 postbaseline PANSS measurement.

End point type	Primary
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End point timeframe:

Baseline (Week 3); Week 15

End point values	AVP-786	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	54		
Units: score on a scale				
least squares mean (standard error)	-2.3 (\pm 0.47)	-2.5 (\pm 0.49)		

Statistical analyses

Statistical analysis title	PANSS Marder Negative Factors Score
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768 ^[1]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.47

Notes:

[1] - The MMRM analysis included fixed effects for treatment, trial centre, visit, treatment-by-visit interaction, and baseline-by-visit interaction. An unstructured covariance model was used.

Secondary: Change From Baseline (Week 3) to Week 15 in the Negative Symptom Assessment-16 (NSA-16) Global Negative Symptom Score

End point title	Change From Baseline (Week 3) to Week 15 in the Negative Symptom Assessment-16 (NSA-16) Global Negative Symptom Score
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End point description:

NSA-16 consists of 16 items & uses 5-factor model to describe negative symptoms: communication(1-4)range=4-24, emotional/affective(5-7)range=3-18, social involvement(8-10)range=3-18, motivational(11-14)range=4-24, & retardation(15&16)range=3-18, & Global Negative Symptom Rating. Items are rated on 6-point scale, 1=behaviour is normal to 6=behaviour severely reduced. Each item admits score of 9 if item is not ratable. Global Negative Symptom Rating range is 1=no evidence of symptoms to 7=extremely severe symptoms. 16 items total score range=16-96, higher score=greater clinical severity of symptoms & global rating scale range=1-7, higher score=extremely severe symptoms. If >3 items were not ratable, total score unevaluable & was regarded as missing. Negative change from baseline=improvement. mITT population=all placebo run-in nonresponders, randomised in Phase B (safety population), had Phase B baseline & at least 1 postbaseline PANSS.

End point type	Secondary
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End point timeframe:

Baseline (Week 3); Week 15

End point values	AVP-786	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	54		
Units: score on a scale				
least squares mean (standard error)	-0.4 (± 0.10)	-0.5 (± 0.10)		

Statistical analyses

Statistical analysis title	NSA-16 Global Negative Symptom Score
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443 [2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.37

Notes:

[2] - The MMRM analysis included fixed effects for treatment, trial centre, visit, treatment-by-visit interaction, and baseline-by-visit interaction. An unstructured covariance model was used.

Secondary: Change From Baseline (Week 3) to Week 15 in the Patient Global Impression of Severity (PGI-S) Score

End point title	Change From Baseline (Week 3) to Week 15 in the Patient Global Impression of Severity (PGI-S) Score
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End point description:

The severity of subjects' illness with respect to their schizophrenia was rated using a 7-point PGI-S. PGI-S scores range from 1 to 7, where 1= normal, not at all ill, 2= borderline ill, 3=mildly ill, 4=moderately ill, 5= markedly ill, 6=severely ill, 7=extremely ill. Missing PGI-S rating were not imputed. Negative change from baseline indicates improvement. Baseline is defined as the end of the placebo run-in period (Week 3), and to be the last assessment prior to the first dose of study drug. mITT population included all subjects who were placebo run-in nonresponders, randomised in Phase B and in the safety population with both Phase B baseline and at least 1 postbaseline PANSS measurement.

End point type	Secondary
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End point timeframe:

Baseline (Week 3); Week 15

End point values	AVP-786	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	54		
Units: score on a scale				
least squares mean (standard error)	-0.3 (± 0.16)	-0.4 (± 0.16)		

Statistical analyses

Statistical analysis title	PGI-S Score
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59 [3]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.54

Notes:

[3] - The MMRM analysis included fixed effects for treatment, trial centre, visit, treatment-by-visit interaction, and baseline-by-visit interaction. An unstructured covariance model was used.

Secondary: Patient Global Impression of Change (PGI-C) Score

End point title	Patient Global Impression of Change (PGI-C) Score
End point description:	
<p>The PGI-C is a 7-point (1-7) subject-rated scale used to assess treatment response with respect to schizophrenia as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, or 7 = very much worse. Missing PGI-C rating will not be imputed. mITT population included all subjects who were placebo run-in nonresponders, randomised in Phase B and in the safety population with both Phase B baseline and at least 1 postbaseline PANSS measurement.</p>	
End point type	Secondary
End point timeframe:	
At Weeks 6, 9, 12 and 15	

End point values	AVP-786	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	54		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6	3.1 (± 1.07)	3.0 (± 1.05)		
Week 9	2.8 (± 1.10)	2.9 (± 0.98)		
Week 12	2.9 (± 1.15)	2.9 (± 1.05)		
Week 15	2.8 (± 1.20)	2.9 (± 1.00)		

Statistical analyses

Statistical analysis title	Comparison at Week 6
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6377 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.51

Notes:

[4] - P-value and treatment difference (CI) were derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Statistical analysis title	Comparison at Week 9
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4827 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.24

Notes:

[5] - P-value and treatment difference (CI) were derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Comparison at Week 12
Comparison groups	AVP-786 v Placebo

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8662 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.36

Notes:

[6] - P-value and treatment difference (CI) were derived from CMH row mean scores statistics controlling for study center.

Statistical analysis title	Comparison at Week 15
Comparison groups	AVP-786 v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6062 ^[7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.3

Notes:

[7] - P-value and treatment difference (CI) were derived from CMH row mean scores statistics controlling for study center.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of the study drug to end of follow up period (Up to Week 19)

Adverse event reporting additional description:

Safety population included all subjects who were randomised in Phase B and took at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Placebo (Run-in Period)
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Reporting group description:

Subjects received AVP-786 matching placebo capsules, orally, BID over a 3-week run-in period.

Reporting group title	AVP-786
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Reporting group description:

Subjects received AVP-786-28/4.9 (d6-DM 28 mg/Q 4.9 mg) capsule, along with AVP-786 matching placebo capsule, orally, QD for 3 days followed by AVP-786-28/4.9 capsule, orally, BID for the next 4 days of titration period. Following the 1-week titration period, subjects received AVP-786-42.63/4.9 (d6-DM 42.63 mg/Q 4.9 mg), orally, BID for the remaining 11 weeks of the DBT period.

Reporting group title	Placebo
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Reporting group description:

Subjects received AVP-786 matching placebo capsules, orally, BID over a 12-week DBT period.

Serious adverse events	Placebo (Run-in Period)	AVP-786	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 136 (0.00%)	2 / 65 (3.08%)	0 / 60 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (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
Pneumonia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo (Run-in Period)	AVP-786	Placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 136 (14.71%)	25 / 65 (38.46%)	14 / 60 (23.33%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	2 / 65 (3.08%) 2	0 / 60 (0.00%) 0
General disorders and administration site conditions Decreased activity subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1 1 / 136 (0.74%) 1 0 / 136 (0.00%) 0	0 / 65 (0.00%) 0 0 / 65 (0.00%) 0 1 / 65 (1.54%) 1	0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Reproductive system and breast disorders Ejaculation delayed subjects affected / exposed occurrences (all) Retrograde ejaculation subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0 0 / 136 (0.00%) 0	0 / 65 (0.00%) 0 0 / 65 (0.00%) 0	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion	0 / 136 (0.00%) 0 0	0 / 65 (0.00%) 0 0	1 / 60 (1.67%) 1 1

subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Psychiatric disorders			
Agitation			
subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Alcohol use disorder			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Insomnia			
subjects affected / exposed occurrences (all)	2 / 136 (1.47%) 2	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Schizophrenia			
subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Suspiciousness			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Blood pressure increased			
subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Gamma-glutamyltransferase increased			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	2 / 65 (3.08%) 2	0 / 60 (0.00%) 0
Glucose urine present			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Hepatic enzyme increased			
subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Urine protein/creatinine ratio abnormal			

subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	2 / 65 (3.08%) 2	0 / 60 (0.00%) 0
Injury, poisoning and procedural complications			
Accidental overdose subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	2 / 65 (3.08%) 2	0 / 60 (0.00%) 0
Overdose subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Skin abrasion subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Skin laceration subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Congenital, familial and genetic disorders			
Type V hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 136 (1.47%) 2	2 / 65 (3.08%) 2	1 / 60 (1.67%) 1
Extrapyramidal disorder			

subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	3 / 136 (2.21%) 3	2 / 65 (3.08%) 2	2 / 60 (3.33%) 2
Hyperresponsive to stimuli subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	2 / 136 (1.47%) 2	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Syncope subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Sedation subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Blood and lymphatic system disorders			
Eosinophilia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Leukopenia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Neutropenia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Gastrointestinal disorders			
Dry mouth subjects affected / exposed occurrences (all)	2 / 136 (1.47%) 2	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Nausea			

subjects affected / exposed occurrences (all)	2 / 136 (1.47%) 2	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	1 / 136 (0.74%) 1	0 / 65 (0.00%) 0	0 / 60 (0.00%) 0
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	2 / 65 (3.08%) 2	1 / 60 (1.67%) 1
Back pain subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	2 / 60 (3.33%) 2
Bursitis subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Muscle spasms subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	0 / 65 (0.00%) 0	1 / 60 (1.67%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 136 (0.00%) 0	1 / 65 (1.54%) 1	0 / 60 (0.00%) 0
Infections and infestations			

Bacterial vaginosis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Corona virus infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 136 (0.74%)	2 / 65 (3.08%)	0 / 60 (0.00%)
occurrences (all)	1	2	0
Pharyngitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 65 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 65 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	1 / 60 (1.67%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			

subjects affected / exposed	0 / 136 (0.00%)	1 / 65 (1.54%)	0 / 60 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2020	The following changes were made as part of Amendment 1: 1. Increased number of sites. 2. Updated inclusion and exclusion criteria.
27 May 2021	The following changes were made as part of Amendment 2: 1. Increased number of sites to include European sites. 2. Expanded trial sites to include all of North America. 3. Updated estimated date of last subject completed. 4. Added secondary efficacy objective. 5. Updated inclusion and exclusion criteria.
31 March 2022	The following changes were made as per Amendment 3: 1. Updated sponsor information. 2. Updated inclusion and exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 May 2023	The study was terminated based on the Interim Analysis outcome and recommendation by the DMC, based on futility.	-

Notes:

Limitations and caveats

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

Not applicable

Notes: