# 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 |

### 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) |

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 |

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<br>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<br>Units: years | | | |
| arithmetic mean | 44.8 | 44.0 | |
| standard deviation | ± 9.54 | ± 10.25 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 20 | 24 | 44 |
| Male | 45 | 36 | 81 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 6 | 7 | 13 |
| Not Hispanic or Latino | 42 | 40 | 82 |
| Unknown or Not Reported | 17 | 13 | 30 |
| Race<br>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<br>arithmetic mean<br>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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | ± | ± | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino<br>Not Hispanic or Latino<br>Unknown or Not Reported | | | |

| | | | |
|---|---|---|---|
| Race<br>Units: Subjects | | | |
| White<br>Black or African American<br>Asian<br>Other<br>Missing | | | |
| 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 | 3.3 | 3.5 | |
| standard deviation | ± 0.91 | ± 0.86 | |

## End points

### End points reporting groups

| Reporting group title | Placebo (Run-in Period) |
|---|---|
| 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 |
| 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. | |
| 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. | |

### 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 |
|---|---|
| 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 |
| 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 (± 0.47) | -2.5 (± 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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:

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, = 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.

| 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo (Run-in Period) |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | AVP-786 |

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 |

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 | 0 / 136 (0.00%) | 2 / 65 (3.08%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Decreased activity | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 65 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 136 (0.74%) | 0 / 65 (0.00%) | 0 / 60 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 65 (1.54%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 1 / 65 (1.54%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Ejaculation delayed | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 65 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Retrograde ejaculation | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 65 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 136 (0.00%) | 0 / 65 (0.00%) | 1 / 60 (1.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |

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

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

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

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