



Clinical trial results:

A Phase 2, Double-blind, Randomized, Placebo-controlled, Four-arm, Multicenter, Dose-finding Study to Assess the Safety and Efficacy of Three Dose Levels of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Central Neuropathic Pain in Patients with Multiple Sclerosis

Summary

EudraCT number	2011-002178-22
Trial protocol	ES CZ PL GB
Global end of trial date	26 September 2013

Results information

Result version number	v1 (current)
This version publication date	02 January 2021
First version publication date	02 January 2021

Trial information

Trial identification

Sponsor protocol code	11-AVR-130
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01324232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Avanir Pharmaceuticals, Inc.
Sponsor organisation address	30 Enterprise, Suite 400, Aliso Viejo, California, United States, 92656
Public contact	Clinical Trial Information Desk, Avanir Pharmaceuticals, Inc., 1 949-268-1167, study11AVR130@avanir.com
Scientific contact	Clinical Trial Information Desk, Avanir Pharmaceuticals, Inc., 1 949-268-1167, study11AVR130@avanir.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	01 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study are to evaluate the safety, tolerability, and efficacy of 3 doses of AVP-923 capsules containing either 45 mg DM and 10 mg Q (AVP-923-45) or 30 mg DM 10 mg Q (AVP-923-30) or 20 mg DM and 10 mg Q (AVP-923-20) compared to placebo, for the treatment of central neuropathic pain in a population of patients with multiple sclerosis (MS) over a 12-week period.

Protection of trial subjects:

Ethics committees met the guidelines set out by the Food and Drug Administration (FDA) and conformed to local laws and customs where appropriate. Written institutional review board (IRB) approval for the protocol and the signed informed consent form (ICF) were obtained and transmitted to Avanir Pharmaceuticals, Inc. or their representative before the study was initiated. The IRB was informed of and approved all protocol amendments. Modifications that eliminated an apparent immediate hazard to patients did not require preapproval by the IRB/IEC.

Standards for Good Clinical Practice, as outlined by regional regulations, were adhered to for all study-based procedures. The investigator ensured that this study was conducted in full conformance with the laws and regulations of the United States.

Informed consent followed the principles outlined in the current version of the Helsinki Declaration. Each patient found to be eligible for the study was properly informed of the purpose of the study. The patient was alerted to any anticipated adverse event (AE) that may be encountered with the study drug. A signed ICF was obtained from all patients (or their authorized representative if enrolled prior to Amendment 2 of the protocol) prior to patient entry into this study. Patients were provided with a copy of their signed ICF (except for patients enrolled prior to Amendment 1 of the protocol).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2011
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: 31
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	United States: 112
Country: Number of subjects enrolled	Argentina: 8
Worldwide total number of subjects	209
EEA total number of subjects	89

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)	198
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After screening procedures, participants underwent a 1-week washout period for all analgesic medications, with the exception of ibuprofen in doses that did not exceed 800 milligrams per day (mg/day).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received one matching placebo capsule in the morning during the first 7 days of the study. Participants then received one matching placebo capsule twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

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 capsule; once daily and twice daily

Arm title	AVP-923-20
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Arm description:

Participants received one capsule containing 20 milligrams (mg) dextromethorphan (DM) and 10 mg quinidine (Q) (AVP-923-20) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-20 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	AVP-923
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral capsule; once daily and twice daily

Arm title	AVP-923-30
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Arm description:

Participants received one capsule containing 30 mg DM and 10 mg Q (AVP-923-30) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Arm type	Experimental
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Investigational medicinal product name	AVP-923
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Oral capsule; once daily and twice daily	
Arm title	AVP-923-45

Arm description:

Participants received one capsule containing 45 mg DM and 10 mg Q (AVP-923-45) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	AVP-923
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral capsule; once daily and twice daily

Number of subjects in period 1	Placebo	AVP-923-20	AVP-923-30
Started	49	53	54
Completed	44	42	41
Not completed	5	11	13
Consent withdrawn by subject	-	3	4
Adverse event, non-fatal	2	5	6
Other	2	2	2
Intercurrent illness	-	-	-
Patient refused medication	-	1	-
Lost to follow-up	1	-	-
Missing	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	AVP-923-45
Started	53
Completed	42
Not completed	11
Consent withdrawn by subject	-
Adverse event, non-fatal	6
Other	2
Intercurrent illness	1
Patient refused medication	-

Lost to follow-up	-
Missing	-
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received one matching placebo capsule in the morning during the first 7 days of the study. Participants then received one matching placebo capsule twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-20
Reporting group description:	
Participants received one capsule containing 20 milligrams (mg) dextromethorphan (DM) and 10 mg quinidine (Q) (AVP-923-20) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-20 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-30
Reporting group description:	
Participants received one capsule containing 30 mg DM and 10 mg Q (AVP-923-30) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-45
Reporting group description:	
Participants received one capsule containing 45 mg DM and 10 mg Q (AVP-923-45) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	

Reporting group values	Placebo	AVP-923-20	AVP-923-30
Number of subjects	49	53	54
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	49.7	47.2	49.1
standard deviation	± 8.41	± 9.20	± 11.21
Gender categorical			
Units: Subjects			
Female	40	46	42
Male	9	7	12
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	43	46	49
Black or African American	3	4	5
Asian	1	0	0
Hispanic or Latino	2	3	0

Reporting group values	AVP-923-45	Total	
Number of subjects	53	209	
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	48.1 ± 13.04	-	
Gender categorical Units: Subjects			
Female	41	169	
Male	12	40	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	48	186	
Black or African American	4	16	
Asian	0	1	
Hispanic or Latino	1	6	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received one matching placebo capsule in the morning during the first 7 days of the study. Participants then received one matching placebo capsule twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-20
Reporting group description: Participants received one capsule containing 20 milligrams (mg) dextromethorphan (DM) and 10 mg quinidine (Q) (AVP-923-20) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-20 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-30
Reporting group description: Participants received one capsule containing 30 mg DM and 10 mg Q (AVP-923-30) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Reporting group title	AVP-923-45
Reporting group description: Participants received one capsule containing 45 mg DM and 10 mg Q (AVP-923-45) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants received one matching placebo capsule containing in the morning during the first 7 days of the study. Participants then received one matching placebo capsule twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	AVP-923-20
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants received one capsule containing 20 milligrams (mg) dextromethorphan (DM) and 10 mg quinidine (Q) (AVP-923-20) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-20 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	AVP-923-30
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants received one capsule containing 30 mg DM and 10 mg Q (AVP-923-30) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	AVP-923-45
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants received one capsule containing 45 mg DM and 10 mg Q (AVP-923-45) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	Total
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All participants receiving placebo, AVP-923-20, AVP-923-30, or AVP-923-45.	

Subject analysis set title	AVP-923-20 and AVP-923-30
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received either AVP-923-20 or AVP-923-30 in the morning during the first 7 days of the study. Participants then received one capsule of AVP-20 or AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	AVP-923-30 and AVP-923-45
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received either AVP-923-30 or AVP-923-45 in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 or AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.	
Subject analysis set title	All AVP-923
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants receiving AVP-923-20, AVP-923-30, or AVP-923-45.	

Primary: Association between the Dextromethorphan (DM) Plasma Concentration and the Change from Baseline Pain Rating Scale Score to the Average Pain Rating Scale Score during Days 57 through 84

End point title	Association between the Dextromethorphan (DM) Plasma Concentration and the Change from Baseline Pain Rating Scale Score to the Average Pain Rating Scale Score during Days 57 through 84
End point description:	
The association between the DM plasma concentration and the change from Baseline (BL) PRS score to the average PRS score during Days 57 through 84 was measured. The PRS requires participants (par.) to rate their pain over the past 12 hours on a scale of 0 to 10 (0=no pain; 10=worst possible pain) by circling the number that best describes their pain on average over the past 12 hours. Baseline (BL) PRS was defined as the average of the PRS scores in the last 7 days collected prior to the BL visit. Post-BL PRS is the average of the Day 57 through 84 values. For par. who did not have any PRS scores during Days 57 through 84, the average of the last 7 available post-BL PRS scores was used. Change from BL was calculated as the post-BL score minus the BL score. Modified Intention-To-Treat (MITT) Population: all par. in the ITT Population (randomized participants) who received ≥1 dose of study drug, provided a BL PRS score, and had ≥1 post-BL PRS assessment. 999=data not available.	
End point type	Primary
End point timeframe:	
Baseline; Days 57 through 84	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[1]	53 ^[2]	54 ^[3]	53 ^[4]
Units: units on a scale				
median (full range (min-max))				
Change from BL in PRS Scores, n=49,53,54,53,209	-1.821 (-7.86 to 2.06)	-2.143 (-7.60 to 5.71)	-2.650 (-6.54 to 3.00)	-1.679 (-6.79 to 2.00)
DM Plasma Concentration, n=0,43,35,45,133	999 (999 to 999)	4.019 (2.38 to 4.84)	4.493 (3.27 to 5.55)	4.758 (-1.61 to 5.81)

Notes:

[1] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[2] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[3] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

received)

[4] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	209 ^[5]			
Units: units on a scale				
median (full range (min-max))				
Change from BL in PRS Scores, n=49,53,54,53,209	-2.000 (-7.86 to 5.71)			
DM Plasma Concentration, n=0,43,35,45,133	4.394 (-1.61 to 5.81)			

Notes:

[5] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The null hypothesis was that the true correlation between the change from Baseline PRS scores and the DM plasma concentration was equal to zero and was tested using a 2-sided test at the 5% level of significance within active treatment groups.	
Comparison groups	AVP-923-20 v AVP-923-30 v Placebo v AVP-923-45
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9827
Method	t-test, 2-sided

Secondary: Comparison of the Change From Baseline PRS Score to the Average PRS Score During Days 57 Through 84

End point title	Comparison of the Change From Baseline PRS Score to the Average PRS Score During Days 57 Through 84
End point description:	
The PRS requires participants to rate their pain over the past 12 hours on a scale of 0 to 10 (0=no pain; 10=worst possible pain) by circling the number that best describes their pain on average over the past 12 hours. Baseline PRS was defined as the average of the PRS scores in the last 7 days collected prior to the Baseline visit. If participants did not have at least 4 PRS scores during the last 7 days prior to the Baseline visit, then the average of up to 7 of the most recent PRS scores available prior to the Baseline visit was used. Post-Baseline PRS is the average of the Day 57 through 84 values. For participants who did not have any PRS scores during Days 57 through 84, the average of the last 7 available post-Baseline PRS scores was used. Change from Baseline was calculated as the post-Baseline score minus the Baseline score. PRS score change from baseline to Days 57-84 was the dependent variable, treatment group was a fixed effect, and the baseline PRS score was a covariate.	
End point type	Secondary
End point timeframe:	
Baseline; Days 57 through 84	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[6]	53 ^[7]	54 ^[8]	53 ^[9]
Units: units on a scale				
least squares mean (standard error)	-2.04 (± 0.332)	-2.07 (± 0.319)	-2.41 (± 0.316)	-2.00 (± 0.319)

Notes:

[6] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[7] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[8] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[9] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

End point values	AVP-923-20 and AVP-923-30	AVP-923-30 and AVP-923-45	All AVP-923	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	107 ^[10]	107 ^[11]	160 ^[12]	
Units: units on a scale				
least squares mean (standard error)	-2.24 (± 0.224)	-2.21 (± 0.225)	-2.16 (± 0.184)	

Notes:

[10] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[11] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[12] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Overall P value tested the hypothesis of no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8869
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9381
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	0.46

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4128
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.46

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9427
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	0.461

Statistical analysis title	Statistical Analysis 5
Comparison groups	Placebo v AVP-923-20 and AVP-923-30

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6075
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.401

Statistical analysis title	Statistical Analysis 6
Comparison groups	Placebo v AVP-923-30 and AVP-923-45
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.669
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.402

Statistical analysis title	Statistical Analysis 7
Comparison groups	Placebo v All AVP-923
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7394
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.62

Variability estimate	Standard error of the mean
Dispersion value	0.38

Secondary: Change From Baseline in Fatigue Severity Scale (FSS) Scores

End point title	Change From Baseline in Fatigue Severity Scale (FSS) Scores
End point description:	
<p>The FSS questionnaire contains 9 statements that attempt to explore the severity of fatigue symptoms in participants with MS and other conditions, including chronic fatigue immune dysfunction syndrome and systemic lupus erythematosus, and is designed to differentiate fatigue from clinical depression because both share some of the same symptoms. Participants were asked to respond to each statement on a scale of 1 to 7, with 1 indicating "Strongly Disagree" and 7 indicating "Strongly Agree." The total score is computed as the sum of the sub-scores for all 9 statements; a higher score indicates increasing fatigue. Baseline (BL) is defined as last non-missing measurement prior to dosing. Change from BL is calculated as the post-BL value minus the BL value. Only participants with a value at both the BL visit and the specific post-BL visit have been included in the analysis. FSS change from BL was the dependent variable, treatment group was a fixed effect, and the BL FSS was a covariate.</p>	
End point type	Secondary
End point timeframe:	
Baseline; Days 57 through 84	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48 ^[13]	52 ^[14]	54 ^[15]	53 ^[16]
Units: units on a scale				
least squares mean (standard error)	-3.32 (± 1.742)	-2.00 (± 1.680)	-6.32 (± 1.642)	-2.12 (± 1.662)

Notes:

[13] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[14] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[15] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[16] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9731
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	6.09
Variability estimate	Standard error of the mean
Dispersion value	2.42

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.72
upper limit	1.72
Variability estimate	Standard error of the mean
Dispersion value	2.394

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	5.95
Variability estimate	Standard error of the mean
Dispersion value	2.408

Secondary: Change From Baseline in Expanded Disability Status Scale (EDSS) Scores

End point title	Change From Baseline in Expanded Disability Status Scale (EDSS) Scores
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End point description:

The EDSS is a method of quantifying disability in participants with MS. It is based on neurological examination of 8 functional systems (FS) (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other) that allows neurologists to assign a FS score to each of these systems. Neurological findings in each FS are scored on a scale of 0 (low level of problems) to 5 (high level of problems). The "other" category is not rated numerically but measures disability related to a particular issue, like motor loss. A total EDSS score is then calculated on a scale of 0 (normal) to 10 (death from MS). The total EDSS score is determined by 2 factors: gait and FS scores. A higher score indicates greater disability. Baseline (BL) is defined as last non-missing measurement prior to dosing. Change from BL is calculated as the post-BL value minus the BL value. Only participants with a value at both the BL visit and the specific post-BL visit were included in the analysis.

End point type	Secondary
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End point timeframe:

Baseline; Days 22 and 85

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[17]	54 ^[18]	53 ^[19]	53 ^[20]
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 22, n=46, 41, 42, 45, 174	-0.1 (± 0.35)	-0.1 (± 0.56)	-0.2 (± 0.67)	-0.0 (± 0.63)
Day 85, n=48, 51, 49, 52, 200	-0.1 (± 0.75)	-0.1 (± 0.67)	-0.1 (± 0.46)	0.0 (± 0.58)

Notes:

[17] - Safety Population: all participants who received at least 1 dose of study drug

[18] - Safety Population: all participants who received at least 1 dose of study drug

[19] - Safety Population: all participants who received at least 1 dose of study drug

[20] - Safety Population: all participants who received at least 1 dose of study drug

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	209 ^[21]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 22, n=46, 41, 42, 45, 174	-0.1 (± 0.56)			
Day 85, n=48, 51, 49, 52, 200	-0.1 (± 0.62)			

Notes:

[21] - Safety Population: all participants who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis Impact Scale-29 (MSIS-29) Scores

End point title	Change From Baseline in Multiple Sclerosis Impact Scale-29 (MSIS-29) Scores
End point description:	
The MSIS-29 is an instrument measuring the physical (20 items) and psychological (9 items) impact of MS from the participant' perspective and is used to evaluate therapeutic effectiveness from the participants' perspective. Participants were asked to circle the response that best described the impact of MS on daily life on a scale of 0 (not at all) to 5 (extremely). The total MSIS-29 score is calculated as the sum of the sub-scores for all 29 questions, with lower scores indicating better quality of life. Baseline is defined as last non-missing measurement prior to dosing. Change from Baseline is calculated as the post-Baseline value minus the Baseline value. For participants with missing data at Day 85, the last available value has been used. MSIS change from Baseline to Day 85 was the dependent variable, treatment group was a fixed effect, and the Baseline MSIS was a covariate.	
End point type	Secondary
End point timeframe:	
Baseline; Day 85	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[22]	53 ^[23]	54 ^[24]	53 ^[25]
Units: units on a scale				
least squares mean (standard error)	-4.84 (± 2.651)	-4.34 (± 2.551)	-6.50 (± 2.526)	-1.41 (± 2.550)

Notes:

[22] - mITT Population: Analysis was based on the randomized treatment assigned

[23] - mITT Population: Analysis was based on the randomized treatment assigned

[24] - mITT Population: Analysis was based on the randomized treatment assigned

[25] - mITT Population: Analysis was based on the randomized treatment assigned

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4778
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.76
upper limit	7.74
Variability estimate	Standard error of the mean
Dispersion value	3.676

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.89
upper limit	5.56
Variability estimate	Standard error of the mean
Dispersion value	3.663

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.83
upper limit	10.68
Variability estimate	Standard error of the mean
Dispersion value	3.681

Secondary: Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) Scores	
End point title	Change From Baseline in Pittsburgh Sleep Quality Index (PSQI) Scores

End point description:

The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. A total of 19 individual items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and

daytime dysfunction. Each component is scored from 0 (no difficulty) to 3 (severe difficulty). The sum of the scores for the 7 components yields 1 global score (from 0 to 21). A higher PSQI score indicates worse quality of sleep. Baseline (BL) is defined as last non-missing measurement prior to dosing. Change from BL is calculated as the post-BL value minus the BL value. Only participants with a value at both the BL visit and the specific post-BL visit were included in the analysis. For participants with missing data at Day 85, the last available value was used. PSQI change from BL was the dependent variable, treatment group was a fixed effect, and the BL PQIS was a covariate.

End point type	Secondary
End point timeframe:	
Baseline; Day 85	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[26]	53 ^[27]	54 ^[28]	53 ^[29]
Units: units on a scale				
least squares mean (standard error)	-0.51 (± 0.490)	-1.02 (± 0.471)	-1.36 (± 0.467)	-1.71 (± 0.472)

Notes:

[26] - mITT Population: Analysis was based on the randomized treatment assigned

[27] - mITT Population: Analysis was based on the randomized treatment assigned

[28] - mITT Population: Analysis was based on the randomized treatment assigned

[29] - mITT Population: Analysis was based on the randomized treatment assigned

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0685
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	0.83

Variability estimate	Standard error of the mean
Dispersion value	0.68

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.677

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.681

Secondary: Change From Baseline in MS Neuropsychological Screening Questionnaire (MSNQ) Scores

End point title	Change From Baseline in MS Neuropsychological Screening Questionnaire (MSNQ) Scores
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End point description:

The MSNQ is a self-reporting, 15-item questionnaire developed to screen for cognitive impairment in participants with MS. Participants (or their informants) scored each item on a scale from 0 (not at all) to 4 (often and greatly interferes with life). The total MSNQ score is calculated as the sum of the sub-scores for all 15 questions and thus ranges from 0 to 60. A higher score indicates greater impairment. Baseline is defined as last non-missing measurement prior to dosing. Change from Baseline is calculated as the post-Baseline value minus the Baseline value. Only participants with a value at both the Baseline visit and the specific post-Baseline visit have been included in the analysis. For participants with missing data at Day 85, the last available value has been used. MSNQ change from Baseline to Day 85 was the

dependent variable, treatment group was a fixed effect, and the Baseline MSNQ was a covariate.

End point type	Secondary
End point timeframe:	
Baseline; Day 85	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48 ^[30]	52 ^[31]	54 ^[32]	53 ^[33]
Units: units on a scale				
least squares mean (standard error)	-0.99 (± 1.058)	-1.48 (± 1.020)	-1.88 (± 0.998)	0.47 (± 1.006)

Notes:

[30] - mITT Population: Analysis was based on the randomized treatment assigned

[31] - mITT Population: Analysis was based on the randomized treatment assigned

[32] - mITT Population: Analysis was based on the randomized treatment assigned

[33] - mITT Population: Analysis was based on the randomized treatment assigned

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	AVP-923-20 v Placebo v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4201
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	1.473

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	1.97
Variability estimate	Standard error of the mean
Dispersion value	1.454

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	4.34
Variability estimate	Standard error of the mean
Dispersion value	1.46

Secondary: Change From Baseline in Beck Depression Inventory (BDI-II) Scores

End point title	Change From Baseline in Beck Depression Inventory (BDI-II) Scores
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End point description:

The BDI-II is a 21-item, self-reported instrument intended to assess the existence and severity of symptoms of depression. Each item corresponds to a symptom of depression and is scored on a 4-point scale, ranging from 0 to 3. Participants are asked to consider each statement as it relates to the way they have felt for the past 2 weeks. Each of the 21 items is summed to give a single score (ranging from 0 to 63). A total score of 0 to 13 indicates minimal depression, a score of 14 to 19 indicates mild depression, a score of 20 to 28 indicates moderate depression, and a score of 29 to 63 indicates severe depression. Baseline (BL) is defined as last non-missing measurement prior to dosing. Change from BL is calculated as the post-BL value minus the BL value. Only participants with a value at both the BL visit and the specific post-BL visit have been included in the analysis. For participants with missing data at Day 85, the last available value has been used.

End point type	Secondary
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End point timeframe:

Baseline; Day 85

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49 ^[34]	53 ^[35]	54 ^[36]	53 ^[37]
Units: units on a scale				
least squares mean (standard error)	0.83 (± 0.868)	-0.26 (± 0.835)	0.21 (± 0.828)	1.15 (± 0.837)

Notes:

[34] - mITT Population: Analysis was based on the randomized treatment assigned

[35] - mITT Population: Analysis was based on the randomized treatment assigned

[36] - mITT Population: Analysis was based on the randomized treatment assigned

[37] - mITT Population: Analysis was based on the randomized treatment assigned

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8068
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	1.28
Variability estimate	Standard error of the mean
Dispersion value	1.205

Statistical analysis title	Statistical Analysis 3
Comparison groups	Placebo v AVP-923-30

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	1.74
Variability estimate	Standard error of the mean
Dispersion value	1.2

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	2.69
Variability estimate	Standard error of the mean
Dispersion value	1.207

Secondary: Change From Baseline in Symbol Digit Modalities Test (SDMT) Scores

End point title	Change From Baseline in Symbol Digit Modalities Test (SDMT) Scores
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End point description:

The SDMT assesses organic cerebral dysfunction in both children (8 years and older) and adults. The SDMT involves a simple substitution task that normal participants can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. The SDMT score is the total correct response (not counting errors) in 90 seconds and ranges from 0 to 110. Lower scores indicate increased dysfunction. Baseline is defined as last non-missing measurement prior to dosing. Change from Baseline is calculated as the post-Baseline value minus the Baseline value. Only participants with a value at both the Baseline visit and the specific post-Baseline visit have been included in the analysis. For participants with missing data at Day 85, the last available value has been used. SDMT change from Baseline to Day 85 was the dependent variable, treatment group was a fixed effect, and the Baseline SDMT was a covariate.

End point type	Secondary
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End point timeframe:

Baseline; Day 85

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48 ^[38]	52 ^[39]	54 ^[40]	53 ^[41]
Units: units on a scale				
least squares mean (standard error)				
Total correct responses, oral; n=11, 13, 20, 14	0.59 (± 2.045)	2.96 (± 1.881)	1.91 (± 1.525)	2.06 (± 1.809)
Total correct responses, written; n=37, 39, 34, 39	1.85 (± 1.111)	3.62 (± 1.086)	0.16 (± 1.158)	0.20 (± 1.083)

Notes:

[38] - mITT Population: Analysis was based on the randomized treatment assigned

[39] - mITT Population: Analysis was based on the randomized treatment assigned

[40] - mITT Population: Analysis was based on the randomized treatment assigned

[41] - mITT Population: Analysis was based on the randomized treatment assigned

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect. Oral responses.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6315
Method	ANCOVA

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Oral responses	
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	7.93
Variability estimate	Standard error of the mean
Dispersion value	2.772

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Oral responses

Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.83
upper limit	6.45
Variability estimate	Standard error of the mean
Dispersion value	2.562

Statistical analysis title	Statistical Analysis 4
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	6.94
Variability estimate	Standard error of the mean
Dispersion value	2.728

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
P-value presented tests the hypothesis for overall treatment effect versus no treatment effect. Written responses.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1485
Method	ANCOVA

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:	
Written responses	
Comparison groups	Placebo v AVP-923-20
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	4.85
Variability estimate	Standard error of the mean
Dispersion value	1.558

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Written responses	
Comparison groups	Placebo v AVP-923-30
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.86
upper limit	1.49
Variability estimate	Standard error of the mean
Dispersion value	1.605

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Written responses	
Comparison groups	Placebo v AVP-923-45
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	1.41
Variability estimate	Standard error of the mean
Dispersion value	1.549

Secondary: Mean Numerical Rating Scale (NRS) Scores

End point title	Mean Numerical Rating Scale (NRS) Scores
End point description:	
The NRS is an 11-point scale for participant self-reporting of pain. Scores range from 0 (no spasticity) to 10 (worst possible spasticity). Only participants with a value at both the Baseline visit and the specific post-Baseline visit have been included in the analysis. For participants with missing data at Day 85, the last available value has been used.	
End point type	Secondary
End point timeframe:	
Baseline; Days 22, 50, and 85	

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45 ^[42]	49 ^[43]	49 ^[44]	47 ^[45]
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 22, n=42, 39, 37, 40, 158	3.29 (± 2.717)	3.56 (± 3.016)	3.41 (± 2.723)	3.90 (± 2.649)
Day 50, n=42, 37, 36, 37, 152	3.24 (± 2.721)	2.89 (± 2.633)	4.06 (± 2.888)	3.54 (± 2.364)
Day 85, n=44, 48, 46, 47, 185	3.66 (± 2.869)	3.13 (± 3.085)	3.87 (± 2.825)	3.36 (± 2.666)

Notes:

[42] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[43] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[44] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[45] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	190 ^[46]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 22, n=42, 39, 37, 40, 158	3.54 (± 2.762)			
Day 50, n=42, 37, 36, 37, 152	3.42 (± 2.666)			
Day 85, n=44, 48, 46, 47, 185	3.50 (± 2.857)			

Notes:

[46] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The null hypothesis is that the true correlation between NRS scores and DM plasma concentration is equal to zero. Only 158 of the 209 participants in the mITT Population were analyzed at Day 22.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1404 ^[47]
Method	t-test, 2-sided
Notes: [47] - Day 22	

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: The null hypothesis that the true correlation between NRS scores and DM plasma concentration is equal to zero. Only 152 of the 209 participants in the mITT Population were analyzed at Day 50.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0805 ^[48]
Method	t-test, 2-sided
Notes: [48] - Day 50	

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: The null hypothesis that the true correlation between NRS scores and DM plasma concentration is equal to zero. Only 185 of the 209 participants in the mITT Population were analyzed at Day 85.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0551 ^[49]
Method	t-test, 2-sided
Notes: [49] - Day 85	

Secondary: Summary of Patient Global Impression of Change (PGIC) Scores

End point title	Summary of Patient Global Impression of Change (PGIC) Scores
End point description: The PGIC is a standard, validated 7-point categorical scale. The participant was asked to assess the overall change in his or her central neuropathic pain symptoms since entry into the study on a scale of 0 to 7 (0=much better; 7=much worse). Only participants with a value at the specific post-Baseline visit have been included in the analysis. For participants with missing data at Day 85, the last available value has been used.	
End point type	Secondary

End point timeframe:

Day 85

End point values	Placebo	AVP-923-20	AVP-923-30	AVP-923-45
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43 ^[50]	45 ^[51]	46 ^[52]	45 ^[53]
Units: units on a scale				
arithmetic mean (standard deviation)	3.58 (± 1.842)	4.42 (± 2.398)	3.70 (± 2.346)	3.64 (± 2.298)

Notes:

[50] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[51] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[52] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

[53] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	179 ^[54]			
Units: units on a scale				
arithmetic mean (standard deviation)	3.84 (± 2.244)			

Notes:

[54] - mITT Population: Analysis was based on the randomized treatment assigned (not treatment received)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The p-value presented tests the hypothesis for overall treatment effect versus no treatment effect.	
Comparison groups	Placebo v AVP-923-20 v AVP-923-30 v AVP-923-45
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9207
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (AEs) are defined as those events with an onset that was anytime during the study and while on treatment, following the first dose of study drug on Day 1. AEs were collected up to Week 12.

Adverse event reporting additional description:

AEs are reported for members of the Safety Population, comprising all participants who received at least one dose of study drug. Safety analyses were performed based on the treatment participants actually received.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received one matching placebo capsule containing in the morning during the first 7 days of the study. Participants then received one matching placebo capsule twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Reporting group title	AVP-923-20
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Reporting group description:

Participants received one capsule containing 20 milligrams (mg) dextromethorphan (DM) and 10 mg quinidine (Q) (AVP-923-20) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-20 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Reporting group title	AVP-923-30
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Reporting group description:

Participants received one capsule containing 30 mg DM and 10 mg Q (AVP-923-30) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-30 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Reporting group title	AVP-923-45
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Reporting group description:

Participants received one capsule containing 45 mg DM and 10 mg Q (AVP-923-45) in the morning during the first 7 days of the study. Participants then received one capsule of AVP-923-45 twice daily (approximately every 12 hours) during the remaining 11 weeks of the study to complete 12 weeks of treatment.

Serious adverse events	Placebo	AVP-923-20	AVP-923-30
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (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 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AVP-923-45		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	AVP-923-20	AVP-923-30
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 49 (67.35%)	40 / 54 (74.07%)	43 / 53 (81.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Fibroadenoma of breast subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Vascular disorders			
Flushing subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Haematoma subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Hot flush subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Peripheral coldness subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Venous insufficiency subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	2 / 54 (3.70%) 3	1 / 53 (1.89%) 1
Chest discomfort subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	1 / 53 (1.89%) 3
Chills subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	3 / 54 (5.56%) 3	3 / 53 (5.66%) 4
Feeling cold			

subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Feeling jittery			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	2 / 53 (3.77%)
occurrences (all)	0	1	2
Oedema peripheral			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	1
Product taste abnormal			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Metrorrhagia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Bronchial hyperreactivity subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	1 / 54 (1.85%) 1	1 / 53 (1.89%) 3
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Sinus congestion subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Anxiety subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	1 / 54 (1.85%) 1	3 / 53 (5.66%) 4
Bruxism subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Depression subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	3 / 53 (5.66%) 3
Hallucination subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Insomnia			

subjects affected / exposed	1 / 49 (2.04%)	3 / 54 (5.56%)	2 / 53 (3.77%)
occurrences (all)	1	3	2
Libido decreased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Stress			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 49 (0.00%)	2 / 54 (3.70%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	2 / 53 (3.77%)
occurrences (all)	0	1	2
Blood sodium decreased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	2 / 54 (3.70%)	2 / 53 (3.77%)
occurrences (all)	1	2	2
Heart rate irregular			

subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	1
Urine analysis abnormal			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Burns second degree			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Excoriation			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	1	0	2
Fall			
subjects affected / exposed	2 / 49 (4.08%)	2 / 54 (3.70%)	2 / 53 (3.77%)
occurrences (all)	2	2	3
Hand fracture			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Laceration			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Overdose			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Bundle branch block left			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Palpitations			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Balance disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Burning sensation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	1
Cervical cord compression			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Clumsiness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Demyelination			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	4 / 49 (8.16%)	4 / 54 (7.41%)	9 / 53 (16.98%)
occurrences (all)	4	6	13
Dysgeusia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Extensor plantar response			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	6 / 49 (12.24%)	11 / 54 (20.37%)	14 / 53 (26.42%)
occurrences (all)	9	20	22
Hemiparesis			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Hyperreflexia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Hypertonia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 49 (0.00%)	2 / 54 (3.70%)	2 / 53 (3.77%)
occurrences (all)	0	2	2
Lethargy			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Loss of consciousness			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Mental impairment			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 49 (0.00%)	2 / 54 (3.70%)	3 / 53 (5.66%)
occurrences (all)	0	2	3
Muscle spasticity			
subjects affected / exposed	2 / 49 (4.08%)	1 / 54 (1.85%)	2 / 53 (3.77%)
occurrences (all)	3	1	2
Neuralgia			
subjects affected / exposed	4 / 49 (8.16%)	2 / 54 (3.70%)	3 / 53 (5.66%)
occurrences (all)	5	2	3
Paraesthesia			

subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Sinus headache			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Somnolence			
subjects affected / exposed	2 / 49 (4.08%)	5 / 54 (9.26%)	3 / 53 (5.66%)
occurrences (all)	2	6	3
Syncope			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Trigeminal neuralgia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Uhthoff's phenomenon			
subjects affected / exposed	2 / 49 (4.08%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	0 / 49 (0.00%)	2 / 54 (3.70%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Tinnitus			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	2
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Uveitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Vitreous floaters			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	1	0	2
Abdominal distension			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 49 (2.04%)	3 / 54 (5.56%)	0 / 53 (0.00%)
occurrences (all)	1	3	0
Crohn's disease			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 49 (2.04%)	2 / 54 (3.70%)	2 / 53 (3.77%)
occurrences (all)	1	2	3
Dry mouth			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Duodenitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	1	1	1
Dysphagia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Faecal incontinence			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	7 / 49 (14.29%)	12 / 54 (22.22%)	10 / 53 (18.87%)
occurrences (all)	7	16	10
Periodontitis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	0 / 49 (0.00%)	5 / 54 (9.26%)	2 / 53 (3.77%)
occurrences (all)	0	6	2
Chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	2	1	0
Decubitus ulcer			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Ecchymosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	1 / 53 (1.89%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	1	1	0

Rash subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Renal pain subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Urinary retention subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Endocrine disorders Early menarche subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 3	1 / 54 (1.85%) 1	1 / 53 (1.89%) 1
Back pain subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	2 / 53 (3.77%) 2
Bone pain subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 2	0 / 53 (0.00%) 0
Costochondritis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4	1 / 54 (1.85%) 1	5 / 53 (9.43%) 6

Muscle tightness			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Musculoskeletal chest pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Musculoskeletal discomfort			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	1	0	4
Neck pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	4 / 49 (8.16%)	0 / 54 (0.00%)	2 / 53 (3.77%)
occurrences (all)	4	0	2
Pain in jaw			
subjects affected / exposed	1 / 49 (2.04%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	1	1	0
Plantar fasciitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Rotator cuff syndrome			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
occurrences (all)	0	1	0

Sensation of heaviness subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	2 / 53 (3.77%) 2
Infections and infestations			
Asymptomatic bacteriuria subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	1 / 53 (1.89%) 1
Cellulitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Cystitis subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Ear infection subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Fungal infection subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Gastrointestinal viral infection subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Herpes zoster subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	1 / 54 (1.85%) 1	3 / 53 (5.66%) 3
Laryngitis			

subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 49 (4.08%)	1 / 54 (1.85%)	7 / 53 (13.21%)
occurrences (all)	2	1	7
Oral candidiasis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 49 (6.12%)	1 / 54 (1.85%)	2 / 53 (3.77%)
occurrences (all)	3	1	2
Urinary tract infection			
subjects affected / exposed	3 / 49 (6.12%)	4 / 54 (7.41%)	5 / 53 (9.43%)
occurrences (all)	3	5	5
Viral infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	1 / 53 (1.89%) 1
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Increased appetite subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0

Non-serious adverse events	AVP-923-45		
Total subjects affected by non-serious adverse events subjects affected / exposed	40 / 53 (75.47%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Fibroadenoma of breast subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
Vascular disorders			
Flushing subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Haematoma subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 4		
Hot flush subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Hypotension subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Peripheral coldness subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Venous insufficiency			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Chest discomfort			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Feeling cold			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Feeling jittery			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Product taste abnormal			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) Metrorrhagia subjects affected / exposed occurrences (all) Ovarian cyst subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0 1 / 53 (1.89%) 1 0 / 53 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Bronchial hyperreactivity subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0 2 / 53 (3.77%) 2 0 / 53 (0.00%) 0 0 / 53 (0.00%) 0 1 / 53 (1.89%) 1		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		

Anxiety			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Bruxism			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Hallucination			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Libido decreased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Stress			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Blood sodium decreased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Heart rate irregular			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Urine analysis abnormal			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
White blood cells urine positive			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Burns second degree			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Contusion			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Excoriation			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Hand fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Overdose			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Post-traumatic pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		

Bradycardia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Bundle branch block left			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Balance disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Burning sensation			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Cervical cord compression			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Clumsiness			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Cognitive disorder			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Demyelination			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Disturbance in attention			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	22		
Dysgeusia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Extensor plantar response			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	8 / 53 (15.09%)		
occurrences (all)	23		
Hemiparesis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Hyperreflexia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Hypertonia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Loss of consciousness			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Memory impairment			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Mental impairment			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	3		
Multiple sclerosis relapse			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Muscle spasticity			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Neuralgia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Sinus headache			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Syncope			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Trigeminal neuralgia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Uhthoff's phenomenon</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 53 (0.00%)</p> <p>0</p> <p>0 / 53 (0.00%)</p> <p>0</p>		
<p>Blood and lymphatic system disorders</p> <p>Lymphadenopathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 53 (1.89%)</p> <p>1</p> <p>0 / 53 (0.00%)</p> <p>0</p>		
<p>Ear and labyrinth disorders</p> <p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 53 (0.00%)</p> <p>0</p> <p>3 / 53 (5.66%)</p> <p>3</p> <p>5 / 53 (9.43%)</p> <p>5</p>		
<p>Eye disorders</p> <p>Diplopia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eye irritation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eye pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eyelid oedema</p>	<p>2 / 53 (3.77%)</p> <p>2</p> <p>0 / 53 (0.00%)</p> <p>0</p> <p>0 / 53 (0.00%)</p> <p>0</p> <p>0 / 53 (0.00%)</p> <p>0</p>		

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Uveitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	3		
Vitreous floaters			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Crohn's disease			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Duodenitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		

Dyspepsia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Faecal incontinence			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 53 (15.09%)		
occurrences (all)	11		
Periodontitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Decubitus ulcer			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Ecchymosis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Renal pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Urinary retention			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Early menarche			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Costochondritis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

Neck pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Plantar fasciitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Sensation of heaviness			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Fungal infection			

subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Gastrointestinal viral infection			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Oral candidiasis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Tonsillitis			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2011	<ul style="list-style-type: none">• Text was added to further clarify the diagnosis of and the eligibility criteria for central neuropathic pain.• Participants with a resting respiratory rate of >20 breaths/minute were ineligible for the study.• A posttreatment, safety follow-up visit was added to the study at Week 13 (Visit 6 [Day 92]).• Early termination was added as 1 of the time points when participants were to return unused study drug to the clinic.• Text was added to clarify the timing, calculation, and review of Pain Rating Scale (PRS) scores in the participants' diaries.• It was clarified that patient diaries would be reviewed to determine eligibility.• The Expanded Disability Status Scale (EDSS) was changed from an efficacy assessment to a safety assessment.• The Symbol Digit Modalities Test (SDMT) was added as an efficacy assessment.• It was clarified that participants must complete a 1-week washout period for analgesic medications (when applicable), except for acetaminophen in doses up to 2600 milligrams per day.• Text was added to inclusion criteria to specify that dose adjustment may be needed for selective serotonin reuptake inhibitors SSRIs that are CYP2D6 substrates when coadministered with quinidine.• "Physical, psychological, and behavioral" were added as descriptors of unintended change to the definition of an adverse event.• Text was added specifying that any newly reported adverse experience, after receiving the last dose of study drug and up until 30 days after receiving the last dose of study drug, would be followed up until resolved.• Pregnancy was added to the list of reasons why participants may be withdrawn from the study.• It was specified that follow-up of laboratory test results should continue until test values return to the participant's normal baseline (pretreatment) range.• The process and procedures for monitoring compliance with the study protocol and the overall quality of data collected was clarified.

15 December 2011	<ul style="list-style-type: none"> • The total number of sites was increased from approximately 65 sites to approximately 90 sites. • Eligibility criteria were updated. • Text was added stating that a sponsor may withdraw a participant from the study for administrative reasons. • The Modified Ashworth Scale (MAS), Patient Global Impression of Change (PGIC), and Numerical Rating Scale (NRS) were added as efficacy assessments. • A definition for compliance was added. • A modified Intent-to-Treat (MITT) population was added to the analysis populations. • An additional pharmacokinetic sample collection was added to Visit 4 (Day 50). • Text was removed stating that the study drug could be administered by the caregiver and that the caregiver could complete the participant's diaries. • The stabilization period for multiple sclerosis (MS) disease-modifying therapy was reduced to at least 2 months before randomization from at least 3 months before randomization. • Text was added stating that oral steroids at a stable dose prior to randomization were allowed as long as the dose remained unchanged during the study. • Acetaminophen up to 2600 mg/day was replaced with ibuprofen up to 800 mg/day as a permitted rescue pain medication. • It was clarified that participants should not begin recording their daily pain score until the 1-week washout period was completed, if applicable. • Informants (i.e., a person having contact with the participant at least 3 times a week) could not complete the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ). • It was clarified that an MS relapse or acute exacerbation was defined as symptoms causing significant change in functional ability or in sensory function. • Randomization was stratified by geographic region instead of by center. • Dynamic allocation was handled by interactive voice response system (IVRS). • Text in the introduction was reorganized, deleted, and added. • Records of all investigational product dispensing were in the eCRF.
24 April 2013	<ul style="list-style-type: none"> • The sample size was updated to 200 patients from 400 participants. • Due to the decreased sample size, the primary efficacy endpoint was updated from the change from baseline PRS scores to an assessment of the correlation between DM Cmax and change from baseline PRS scores. The key secondary efficacy endpoint changed from change in Fatigue Severity Scores (FSS) to the change from baseline PRS scores. The change in FSS scores was still included as an additional secondary endpoint. • Participants who participated in an interventional clinical study within the past 30 days were excluded from participating in the study; the previous version stated that participating in any clinical study was exclusionary. • Participants with evidence of uncontrolled diabetes based on HbA1c >53 millimoles/mole (mmol/mol) (>7.0%) were excluded from the study; in previous versions, participants with HbA1c <53 mmol/mol (>7.0%) were excluded from participating. • Height and weight were added to the vital sign measurements. • It was clarified that AEs reported after receiving the last dose of study drug would be followed up until resolution or until stabilization of the event had occurred. • Text stating that participant instructions would be reviewed in person and that written instructions would be provided to the participant or their caregiver was removed. • It was clarified that concomitant medication use should not be entered in the patient diary card, as this information was captured in the electronic Case Report Form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported